THYROID HORMONES AND CARDIAC ARRHYTHMIA

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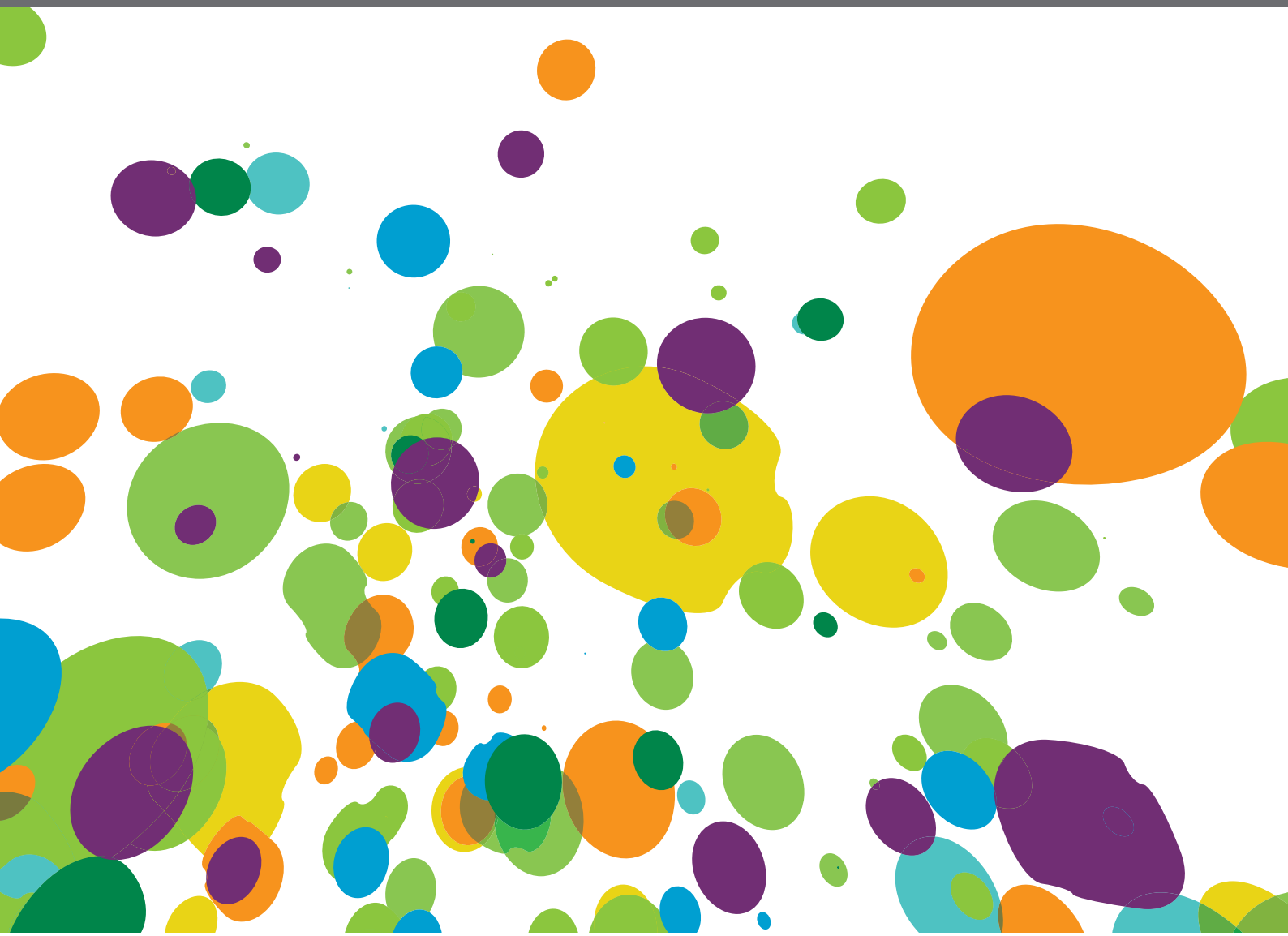

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THYROID HORMONES AND CARDIAC ARRHYTHMIA

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Editorial: Thyroid hormones and cardiac arrhythmia

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Editorial on the Research Topic:
Thyroid hormones and cardiac arrhythmia

The thyro-cardiac axis: Growing attention to a long-known connection

Among the premier effects of thyroid hormones in vertebrates are actions on the cardiovascular system (1–5). Cardiovascular complications rank among the key causes of death in thyroid emergencies (6).

While our knowledge of the link between thyroid disease and cardiac arrhythmia dates back more than two centuries, attention to this connection continues to rise. The number of publications meeting the search formula "thyroid AND heart" is approaching the mark of 10,000 results (Figure 1), and it is still exponentially growing. A considerable proportion of these publications covers cardiac arrhythmia.

Therapeutic algorithms protocolized by cardiovascular medicine benefitted the prognosis of patients with chronic heart disease, and preventive programs have reduced cardiovascular morbidity at the population level. However, a substantial residual hazard persists. Therefore, the rediscovery of thyroid function as a major determinant of cardiovascular health is timely to address this gap of fundamental significance.

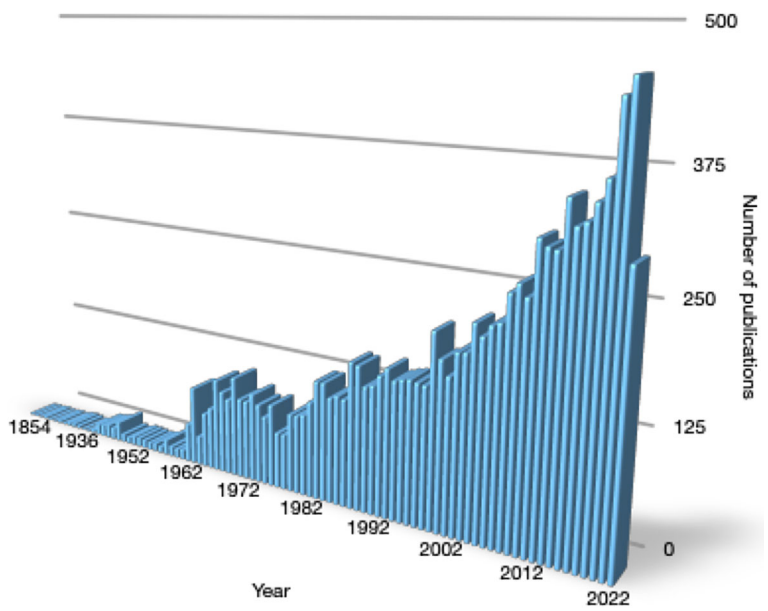

FIGURE 1
Yearly number of publications meeting the search term "thyroid AND heart" from 1854 to August 2022 in PubMed.

This Research Topic was initiated to provide a forum on recent developments in the thyro-cardiac nexus and to foster a deeper physiological understanding of this vitally important intersection. A series of articles summarising the state of current evidence deliver new perspectives on recent developments.

Thyroid dysfunction and supraventricular arrhythmia

The resting heart rate is strongly modulated by thyroid hormone. This is the reason, why it became integral to established scoring systems for the diagnosis of myxoedema coma and thyroid storm (7–10). Thyrotoxicosis may also potentiate ectopic beats and atrial fibrillation (AF) (11–14). In adults, AF is a common condition conveying significant health hazard. Current guidelines recommend assessing the thyroid status in subjects with AF and, vice versa, screening for AF in hyperthyroid patients (15).

Subclinical hyperthyroidism and even FT4 concentration in its highest quartile in persons with normal TSH are associated with increased incidence of AF (16). Gencer et al. review this observation and provide recommendations for the management of new-onset thyroid-related AF.

Unlike in adults, AF is exceedingly rare in children and adolescents. Subramonian et al. describe the case of a 15-year-old female with AF and thyrotoxic tachymyopathy due to Graves' disease, being reverted after successful treatment of the thyroid condition.

Subclinical hyperthyroidism is also associated with an increased risk for the recurrence of AF after catheter ablation, as demonstrated in the retrospective cohort study by Li et al.

Thyroid function and ventricular arrhythmic events

In the ventricles, thyrotoxicosis promotes triggered activity and the formation of re-entry circuits giving rise to ventricular tachycardia, flutter and fibrillation (17, 18). These forms of malignant arrhythmia contribute to the high fatality rate of untreated thyroid storm.

This is exemplified by the case of a young woman with Graves' disease and overt hyperthyroidism described by Fu et al. She suffered a cardiac arrest due to ventricular fibrillation but ultimately recovered following multimodal intensive care treatment including targeted temperature management with an intravascular cooling system.

Allostatic load – confounder or mediator of risk?

The hypothalamus-pituitary-thyroid axis can dynamically adapt to physiological requirements. In type 1 allostatic load (e.g.

in starvation or critical illness) the set point of the feedback loop is lowered, so that the concentrations of T3 (and occasionally TSH and T4) are down-regulated (19). A largely opposite endocrine pattern is observed in type 2 allostatic load (e. g. in psychosocial stress or certain psychiatric diseases) (19, 20).

Allostatic responses may raise considerable problems in the differential diagnosis of thyroid function. We (Dietrich et al.) demonstrated this for TSH, which correlates to a marker of type 2 allostatic load. Therefore, the prevalence of subclinical hypothyroidism may be overestimated in chronic psychosocial stress (21–24).

Low-T3 syndrome as the key component of thyroid allostasis in critical illness, tumours, uraemia and starvation (TACITUS) or non-thyroidal illness syndrome (NTIS) can be maladaptive and heralds a poor prognosis in severe illnesses. Two independent studies (Gao et al. and Abdu et al.) could demonstrate that this also applies to myocardial infarction with nonobstructive coronary arteries (MINOCA), a major subtype of type 2 myocardial infarction.

Clinical evidence from prospective studies

Overt thyroid dysfunction is an established risk factor for mortality and major adverse cardiovascular events (MACE) (25–29). For minor disorders of thyroid function (e.g. subclinical hypo- and hyperthyroidism and within-reference range variations of thyroid hormones), the evidence was less clear. A systematic review including 32 studies covering more than 1.3 million subjects and a subsequent meta-analysis (Müller et al.) found cardiovascular death (CVD) to be predicted by both subclinical hypo- and hyperthyroidism. Circulating FT4 concentration was positively associated with the hazard ratio for CVD and MACE. The results suggest a monotonic association of FT4 to cardiovascular risk, but a complex U-shaped pattern linking TSH to cardiovascular endpoints, supporting the assumption of heterogeneous patho physiological mechanisms.

Physiological evidence and molecular mechanisms

In the clinical setting, the risk for malignant arrhythmia can be estimated e.g. by measuring certain time intervals in the electrocardiogram (ECG). In addition to the QT interval, an established biomarker of thyroid function (30), we could show that the Tp-e and JT intervals, which are not affected by QRS duration, correlate to TSH, FT4 and FT3 concentration (Aweimer et al.).

The impact of thyroid hormones on cardiac electrophysiology is mediated by a plethora of mechanisms (31). This applies to normal automaticity, triggered activity, disorders of impulse conduction and re-entry mechanisms. At a molecular level, thyroid hormones act *via* four distinct signalling types involving different time scales ranging from minutes to hours, where the expression of multiple genes is profoundly modulated (Müller et al).

Aspects of therapy and prevention

Given the risk conferred by even slight deviations of thyroid hormones from an individual optimum, it is of paramount importance to restore euthyroidism as fast as possible in the case of thyroid emergencies (6). For thyroid storm, Lim et al. describe several options like pharmacotherapy and therapeutic plasma exchange, supported by adjuvant extra-corporal systems, including continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO). Irreversible brain damage in thyroid storm may be prevented by intravascular cooling devices, as demonstrated by Fu et al. For thyroid-related AF, Gencer et al. provide a comprehensive flow chart focussing on adjuvant non-endocrine treatment modalities.

Special caveats apply to substitution therapy with levothyroxine in hypothyroidism. In certain stages of thyroid cancer, TSH-suppressive therapy is recommended by current guidelines (32), but it may confer increased cardiovascular risk, as reviewed by Gluvic et al., thereby implying the need to evaluate its benefit:risk ratio and hence individualize the degree of TSH suppression that optimizes the health outcome.

Prospectus

This collection of articles provides a current overview of the interface between thyroid function and cardiac rhythmology from different perspectives. According to the available evidence, even slight deviations of thyroid hormones confer significant risks for MACE, including malignant arrhythmia. Advanced diagnostical strategies should address the whole feedback loop to avoid misinterpretation by allostatic load, hysteresis and other effects, and modern therapeutic measures should involve multimodal approaches (21–23, 33–37). This is of particular importance due to the biological potency and relatively long plasma half-life of thyroid hormones.

The findings presented in this Research Topic also affect the ongoing debate about cardiometabolic medicine (38–40), strongly supporting the integration of thyroidology and cardiovascular rhythmology in this emerging subspecialty.

Author contributions

JD, PM, and ML wrote some of the papers in this Research Topic and participated as guest editors for manuscripts, where they were not co-authors themselves. All authors listed have made a substantial, direct, and intellectual contribution to this editorial and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Corona G, Croce L, Sparano C, Petrone L, Sforza A, Maggi M, et al. Thyroid and heart, a clinically relevant relationship. *J Endocrinol Invest* (2021) 44(12):2535–44. doi: 10.1007/s40618-021-01590-9

2. Stojkovic M, Zarkovic M. Subclinical thyroid dysfunction and the risk of cardiovascular disease. *Curr Pharm Des* (2020) 26(43):5617–27. doi: 10.2174/1381612826666201118094747

3. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med* (2002) 137(11):904–14. doi: 10.7326/0003-4819-137-11-200212030-00011

4. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol* (2018) 71(16):1781–96. doi: 10.1016/j.jacc.2018.02.045

5. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* (2017) 14(1):39–55. doi: 10.1038/nrcardio.2016.174

6. Dietrich JW. Thyreotoxische krise und myxödemkoma. *Der Nuklearmediziner* (2016) 39(02):124–31. doi: 10.1055/s-0042-105786

7. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid* (2012) 22(7):661–79. doi: 10.1089/thy.2011.0334

8. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. *Thyroid storm Endocrinol Metab Clin North Am* (1993) 22(2):263–77. doi: 10.1016/S0889-8529(18)30165-8

9. Chiong YV, Bammerlin E, Mariash CN. Development of an objective tool for the diagnosis of myxedema coma. *Transl Res* (2015) 166(3):233–43. doi: 10.1016/j.trsl.2015.01.003

10. Popoveniuc G, Chandra T, Sud A, Sharma M, Blackman MR, Burman KD, et al. A diagnostic scoring system for myxedema coma. *Endocr Pract* (2014) 20(8):808–17. doi: 10.4158/EP13460.OR

11. Aguilar M, Rose RA, Takawale A, Nattel S, Reilly S. New aspects of endocrine control of atrial fibrillation and possibilities for clinical translation. *Cardiovasc Res* (2021) 117(7):1645–61. doi: 10.1093/cvr/cvab080

12. Komatsu R, Karimi N, Zimmerman NM, Sessler DI, Bashour CA, Soltesz EG, et al. Biochemically diagnosed hypothyroidism and postoperative complications after cardiac surgery: a retrospective cohort analysis. *J Anesth* (2018) 32(5):663–72. doi: 10.1007/s00540-018-2533-5

13. Meng X, Wang XL, Zhang ZY, Zhang K, Gao J, Zheng JL, et al. Association between thyroid dysfunction and incidence of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Front Endocrinol (Lausanne)* (2022) 13:875003. doi: 10.3389/fendo.2022.875003

14. Selmer C, Faber J. Mild thyroid dysfunction: A potential target in prevention of atrial fibrillation? *Circulation* (2017) 136(22):2117–8. doi: 10.1161/CIRCULATIONAHA.117.031283

15. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J* (2021) 42(5):373–498. doi: 10.1093/eurheartj/ehaa612

16. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation* (2017) 136(22):2100–16. doi: 10.1161/CIRCULATIONAHA.117.028753

17. Müller P, Dietrich JW, Lin T, Bejinariu A, Binnebössel S, Bergen F, et al. Usefulness of serum free thyroxine concentration to predict ventricular arrhythmia risk in euthyroid patients with structural heart disease. *Am J Cardiol* (2020) 125(8):1162–9. doi: 10.1016/j.amjcard.2020.01.019

18. Sharp NA, Neel DS, Parsons RL. Influence of thyroid hormone levels on the electrical and mechanical properties of rabbit papillary muscle. *J Mol Cell Cardiol* (1985) 17(2):119–32. doi: 10.1016/s0022-2828(85)80015-8

19. Chatzitomaris A, Hoermann R, Midgley JE, Hering S, Urban A, Dietrich B, et al. Thyroid allostasis-adaptive responses of thyrotropic feedback control to conditions of strain, stress, and developmental programming. *Front Endocrinol (Lausanne)* (2017) 8:163. doi: 10.3389/fendo.2017.00163

20. Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mugge A, Patsalis PC, et al. Abnormal thyroid function is common in takotsubo syndrome and depends on two distinct mechanisms: results of a multicentre observational study. *J Intern Med* (2021) 289(5):675–87. doi: 10.1111/joim.13189

21. Abbey EJ, McGready J, Ferrucci L, Simonsick EM, Mammen JSR. Thyroid hormone supplementation and all-cause mortality in community-dwelling older adults: Results from the Baltimore longitudinal study of aging. *J Am Geriatr Soc* (2021) 69(5):1283–90. doi: 10.1111/jgs.17015

22. Abbey EJ, McGready J, Sokoll LJ, Simonsick EM, Mammen JSR. Free thyroxine distinguishes subclinical hypothyroidism from other aging-related changes in those with isolated elevated thyrotropin. *Front Endocrinol (Lausanne)* (2022) 13:858332. doi: 10.3389/fendo.2022.858332

23. Alonso-Ventura V, Civeira F, Alvarado-Rosas A, Lou-Bonafonte M, Calmarza P, Moreno-Franco B, et al. A cross-sectional study examining the parametric thyroid feedback quantile index and its relationship with metabolic and cardiovascular diseases. *Thyroid* (2022). doi: 10.1089/thy.2022.0025

24. Mammen JS, McGready J, Ladenson PW, Simonsick EM. Unstable thyroid function in older adults is caused by alterations in both thyroid and pituitary physiology and is associated with increased mortality. *Thyroid* (2017) 27(11):1370–7. doi: 10.1089/thy.2017.0211

25. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jorgensen HL, Hegedus L. Duration of thyroid dysfunction correlates with all-cause mortality. *OPENTHYRO Register Cohort PloS One* (2014) 9(10):e110437. doi: 10.1371/journal.pone.0110437

26. Lillevang-Johansen M, Abrahamsen B, Jorgensen HL, Brix TH, Hegedus L. Over- and under-treatment of hypothyroidism is associated with excess mortality: A register-based cohort study. *Thyroid* (2018) 28(5):566–74. doi: 10.1089/thy.2017.0517

27. Liu X, Wong CKH, Chan WWL, Tang EHM, Woo YC, Liu SYW, et al. Attaining biochemical euthyroidism early after total thyroidectomy in graves'

disease may lower long-term morbidity risk. *BJS Open* (2022) 6(4). doi: 10.1093/bjsopen/zrac079

28. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE, et al. Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the health in men study. *Eur J Endocrinol* (2013) 169(4):401–8. doi: 10.1530/EJE-13-0306

29. Marrakchi S, Kanoun F, Idriss S, Kammoun I, Kachboura S. Arrhythmia and thyroid dysfunction. *Herz* (2015) 40 Suppl 2:101–9. doi: 10.1007/s00059-014-4123-0

30. Isaksen JL, Skov MW, Graff C, Ellervik C, Kanters JK. Electrocardiography in euthyroid individuals: a Danish general population study. *Minerva Endocrinol* (2022) 47(1):1119–30. doi: 10.23736/s2724-6507.20.03170-3

31. Lin H, Mitasikova M, Dlugosova K, Okruhlicova L, Imanaga I, Ogawa K, et al. Thyroid hormones suppress epsilon-PKC signalling, down-regulate connexin-43 and increase lethal arrhythmia susceptibility in non-diabetic and diabetic rat hearts. *J Physiol Pharmacol* (2008) 59(2):271–85.

32. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020

33. Fitzgerald SP, Falhammar H. Redefinition of successful treatment of patients with hypothyroidism. is TSH the best biomarker of euthyroidism? *Front Endocrinol (Lausanne)* (2022) 13:920854. doi: 10.3389/fendo.2022.920854

34. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Individualised requirements for optimum treatment of hypothyroidism: complex needs, limited options. *Drugs Context* (2019) 8:212597. doi: 10.7573/dic.212597

35. Leow MK. A review of the phenomenon of hysteresis in the hypothalamus-Pituitary-Thyroid axis. *Front Endocrinol (Lausanne)* (2016) 7:64. doi: 10.3389/fendo.2016.00064

36. Li E, Yen PM, Dietrich JW, Leow MK. Profiling retrospective thyroid function data in complete thyroidectomy patients to investigate the HPT axis set point (PREDICT-IT). *J Endocrinol Invest* (2021) 44(5):969–77. doi: 10.1007/s40618-020-01390-7

37. Jonklaas J, Razvi S. Reference intervals in the diagnosis of thyroid dysfunction: treating patients not numbers. *Lancet Diabetes Endocrinol* (2019) 7(6):473–83. doi: 10.1016/S2213-8587(18)30371-1

38. Eckel RH, Blaha MJ. Cardiometabolic medicine: A call for a new subspeciality training track in internal medicine. *Am J Med* (2019) 132(7):788–90. doi: 10.1016/j.amjmed.2019.02.027

39. Reiter-Brennan C, Cainzos-Achirica M, Soroosh G, Saxon DR, Blaha MJ, Eckel RH. Cardiometabolic medicine - the US perspective on a new subspecialty. *Cardiovasc Endocrinol Metab* (2020) 9(3):70–80. doi: 10.1097/XCE.0000000000000224

40. Soroosh GP, Dzaye O, Reiter-Brennan C, Blaha MJ. Cardiometabolic medicine: a review of the current proposed approaches to revamped training in the united states. *Cardiovasc Endocrinol Metab* (2021) 10(3):168–74. doi: 10.1097/XCE.0000000000000243

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The Two Faces of Janus: Why Thyrotropin as a Cardiovascular Risk Factor May Be an Ambiguous Target

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Elevated concentrations of free thyroid hormones are established cardiovascular risk factors, but the association of thyrotropin (TSH) levels to hard endpoints is less clear. This may, at least in part, ensue from the fact that TSH secretion depends not only on the supply with thyroid hormones but on multiple confounders including genetic traits, medication and allostatic load. Especially psychosocial stress is a still underappreciated factor that is able to adjust the set point of thyroid function. In order to improve our understanding of thyroid allostasis, we undertook a systematic meta-analysis of published studies on thyroid function in post-traumatic stress disorder (PTSD). Studies were identified *via* MEDLINE/PubMed search and available references, and eligible were reports that included TSH or free thyroid hormone measurements in subjects with and without PTSD. Additionally, we re-analyzed data from the NHANES 2007/2008 cohort for a potential correlation of allostatic load and thyroid homeostasis. The available evidence from 13 included studies and 3386 euthyroid subjects supports a strong association of both PTSD and allostatic load to markers of thyroid function. Therefore, psychosocial stress may contribute to cardiovascular risk *via* an increased set point of thyroid homeostasis, so that TSH concentrations may be increased for reasons other than subclinical hypothyroidism. This provides a strong perspective for a previously understudied psychoendocrine axis, and future studies should address this connection by incorporating indices of allostatic load, peripheral thyroid hormones and calculated parameters of thyroid homeostasis.

Keywords: allostatic load, subclinical hypothyroidism, thyroid homeostasis, thyrotropin, malignant arrhythmia, sudden cardiac death, post-traumatic stress disorder (PTSD)

INTRODUCTION

The prognostic and therapeutic implications of subclinical hypothyroidism remain to be debated (1–4). At least in elderly subjects, the benefits of levothyroxine substitution are questionable (5). While increased and high-normal free thyroxine (FT4) concentration is a well-established risk factor for malignant arrhythmia and sudden cardiac death (6, 7), the association between thyrotropin (TSH) concentration and cardiovascular mortality is less well understood (8–11). Studies reported either no relation at all (12, 13) or a rather complex U-shaped association (14, 15), as has been shown in a recent population study based on the large NHANES datasets (16). Likewise, a recent study observed elevated FT4 concentration in stress cardiomyopathy or Takotsubo syndrome (17). In the same cohort, the distribution of TSH levels was complex and ambiguous, however.

The conclusion by Inoue et al. that subclinical hypothyroidism is a risk factor for cardiovascular death (16) may be premature. High-normal or elevated TSH concentrations do not unequivocally indicate early thyroid failure but may also be reflective of an increased homeostatic set point of the hypothalamus-pituitary-thyroid axis (18). Apart from genetic traits manifestation of a high set point may ensue from chronic psychosocial stress. This is termed type 2 allostatic load and a well-recognized cardiovascular risk indicator (19–24). Set point alterations have been linked to acute and chronic stress situations including psychosis, alcohol withdrawal and post-traumatic stress disorder (PTSD), all of which are known risk factors for cardiovascular mortality (25–30). Here, we present a brief evaluation of the stress-thyroid axis and discuss an alternative explanation.

METHODS

Based on previous reports on a possible association of PTSD to thyroid function (19, 31–36) we performed a systematic meta-analysis summarizing the available evidence. Up to July 4th, 2020, a systematic search was executed of PubMed/MEDLINE by using the following search formula: "post-traumatic stress disorder AND (thyroid OR triiodothyronine OR thyrotropin OR TSH OR thyroxine)". Additionally, we screened the references of the retrieved publications for additional suitable publications. Studies were eligible if they compared TSH, FT4 or free T3 (FT3) concentration in subjects with and without PTSD, and if the definition of the disease was compatible with the criteria provided by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Summary measures were included in random effects meta-analysis. Between-study variance was assessed with the DerSimonian-Laird estimator, Cochran's Q and tau squared, and heterogeneity with Higgins' and Thompson's I squared. Small study effects were estimated with funnel plots and three tests statistics (Egger, Begg and Mazumdar, and Thompson and Sharp) with the null hypothesis of no bias in the meta-analysis. The quality of the studies was assessed with a Newcastle-Ottawa score. Calculations were supported by the packages meta and metaphor (37, 38) for the statistical environment R (39).

Additionally, we analyzed publicly available data from the NHANES 2007/2008 dataset (40) in order to re-assess the association between thyroid function and type 2 allostasis. A summative quantitative allostatic load score (SIQALS 2) was derived from the sum of sub-scores for pulse rate, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein (HDL), body mass index (BMI), HbA1c and c-reactive protein (CRP) concentration according to the procedure of the Scottish Health Survey (20). Each sub-score was graded as 1 if the results were in the upper quartile of the respective population distribution or 0 if they were in any of the lower quartiles, except for HDL, which was scaled in the opposite direction (20). Hence, the possible range for SIQALS is between 0 and 8, where a larger value indicates a higher amount of allostatic load. Analysis was restricted to euthyroid subjects (as defined by TSH and FT4 concentrations within their respective laboratory-defined reference ranges) without known thyroid disease, pregnancy or any major comorbidity potentially leading to non-thyroidal illness syndrome. We relied on Jostel's TSH index (JTI) as a marker for the location of the pituitary-thyroid set point (41). Additionally, estimates for thyroid's secretory capacity (SPINA-GT) and total deiodinase activity (SPINA-GD) were calculated in order to provide further insights into the physiological roots of potential variations in hormone levels (41).

We tested for associations between allostatic load and markers of thyroid function with unadjusted ordinary least squares (OLS) regression. In these univariate analyses, the multiple components contributing to type 2 allostatic load were expressed as an equally weighted summary score (SIQALS 2) in order to avoid potential issues with collinearity in multivariable analysis. To statistically account for direction of causality and derive more robust estimators in the possible presence of endogenous regressors and feedback (reversed causality), we relied on instrumental variables estimation (IV regression) (42), using the R package AER (43). We selected parameters from the somatic, psychological and social domain as candidates for instrumental variables. Eligible as instruments were parameters that correlated with both SIQALS 2 and JTI, and whose influence could be assumed to be mediated *via* allostatic load only (**Supplementary Tables 3** and **4**). The Durbin-Wu-Hausmann test was used to detect potential endogeneity and to decide if OLS and IV regressions are equally consistent or if IV are to be preferred over OLS models. The Sargan test was performed to test for over-identification, when multiple IVs were used. Additionally, a test for "weak instruments" was performed to decide about the validity of IVs.

RESULTS

We identified 16 studies investigating TSH and/or thyroid hormone concentrations in subjects with and without PTSD. Two older studies were excluded, since they reported a time

interval between trauma and evaluation of thyroid function of a month or less, rendering them incompatible with current definitions of PTSD, and one study was excluded, because only total thyroid hormones but neither TSH nor free thyroid hormones were determined. The remaining 13 studies could be included in the meta-analysis (**Supplementary Figure 1**) (25–27, 44–53).

With respect to TSH and FT3 concentrations the studies were highly heterogeneous, but the findings were unanimous for FT4 concentrations. Combining the results yields a positive association of PTSD with TSH levels in the random effects model, but unchanged FT4 concentrations (**Figure 1**). FT3 concentration tended to be higher in PTSD.

Meta-regression between concentration differences and time of the exposure to the triggering event revealed a significant correlation for TSH levels (**Supplementary Figure 2**). Accordingly, the observed pooled study effects were even more pronounced in a subset of results with chronic PTSD (24 months or more since the occurrence of the triggering event, **Supplementary Figure 3**). Total T3 concentrations were significantly higher in PTSD compared to controls (**Supplementary Figures 4** and **5**).

Funnel plots (**Supplementary Figure 6**) and tests for small study effects demonstrated that publication bias resulting from less frequent publication of non-significant results does not play a decisive role.

From the NHANES dataset records of 3386 euthyroid subjects (1579 female, mean ± SD of age 44.0 ± 14.0 years) were eligible. Median and interquartile range (IQR) of SIQALS 2 results were both 2 with a total range between 0 and 7. In the majority of subjects, Jostel's TSH index was in the reported

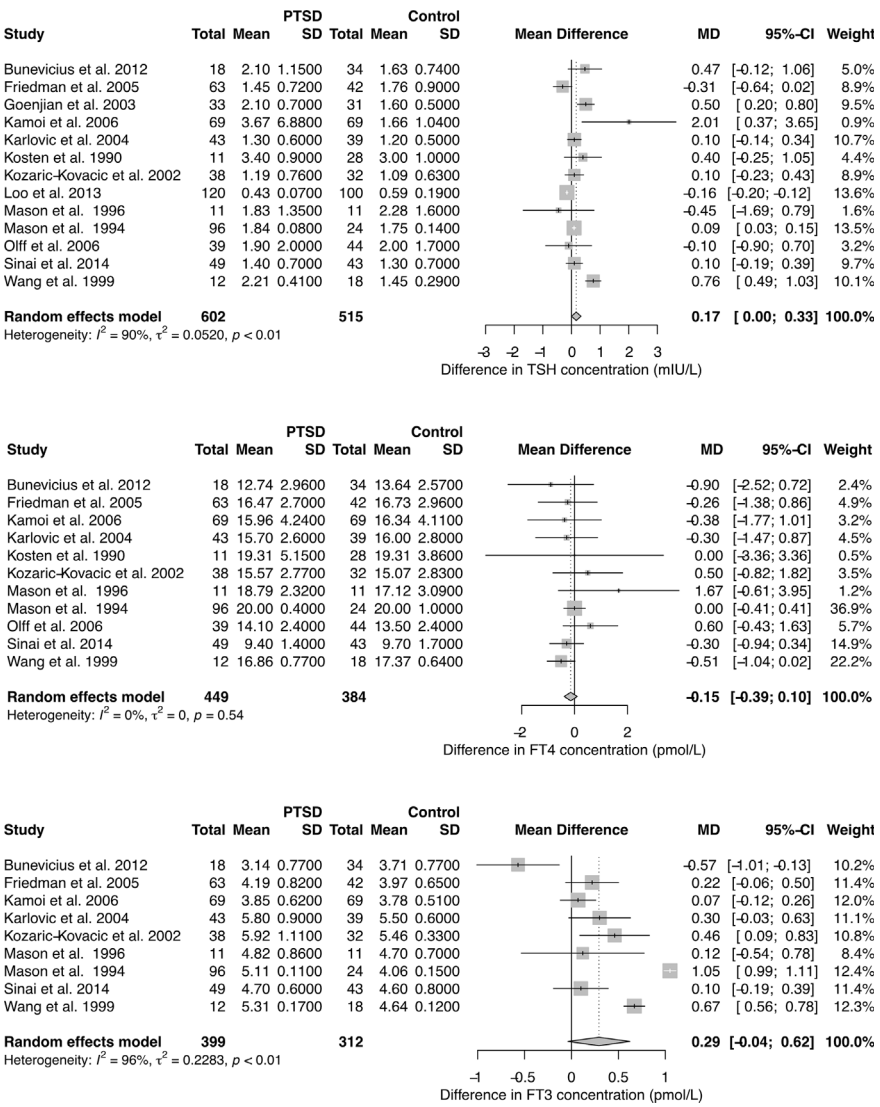

FIGURE 1 | Forest plots showing differences in TSH, FT4, and FT3 concentration between subjects with and without PTSD. See **Supplementary Figures 3–5** for results in chronic PTSD and for total T3 (TT3) and total T4 (TT4) concentration.

reference range (1.3 to 4.1) (41, 54) with a mean of 1.75 and SD of 0.57. Allostatic load was significantly positively associated with both TSH concentration and JTI, and negatively with SPINA-GT, as shown in **Figure 2** and **Supplementary Table 2**. JTI weakly, but significantly increased with age, beta coefficient per year ± SE = 3.8e–4 ± 5.9e–5, p < 1e–9. It was also slightly elevated in diabetes and prediabetes (mean ± SEM 1.85 ± 0.03 and 1.88 ± 0.06, resp., vs. 1.74 ± 0.01 and 1.73 ± 0.01, respective p < 0.001 and < 0.02).

Poor socio-economic status (assessed with the family monthly poverty level index) (40, 55), sleep disorder (snoring) and illicit drug usage (cannabis), as reported in the NHANES survey, met above eligibility criteria (**Supplementary Tables 3** and **4**) and were added as instrumental variables. Since in the multivariable model with 3 IVs the Durbin-Wu-Hausmann test did not reveal an advantage of IV over OLS models and the Sargan test suggested over-identification we simplified the model to two predictors (cannabis and snoring, **Supplementary Figure 7**). This model with two IVs confirmed the significant relationship between SIQALS 2 and JTI (beta ± SE = 0.09 ± 0.03, p < 0.01), TSH concentration (beta ± SE = 0.13 ± 0.05, p < 0.01) and SPINA-GT (beta ± SE = –0.16 ± 0.06, p < 0.01). No correlations were observed for FT4 or FT3 concentrations and deiodinase activity (SPINA-GD).

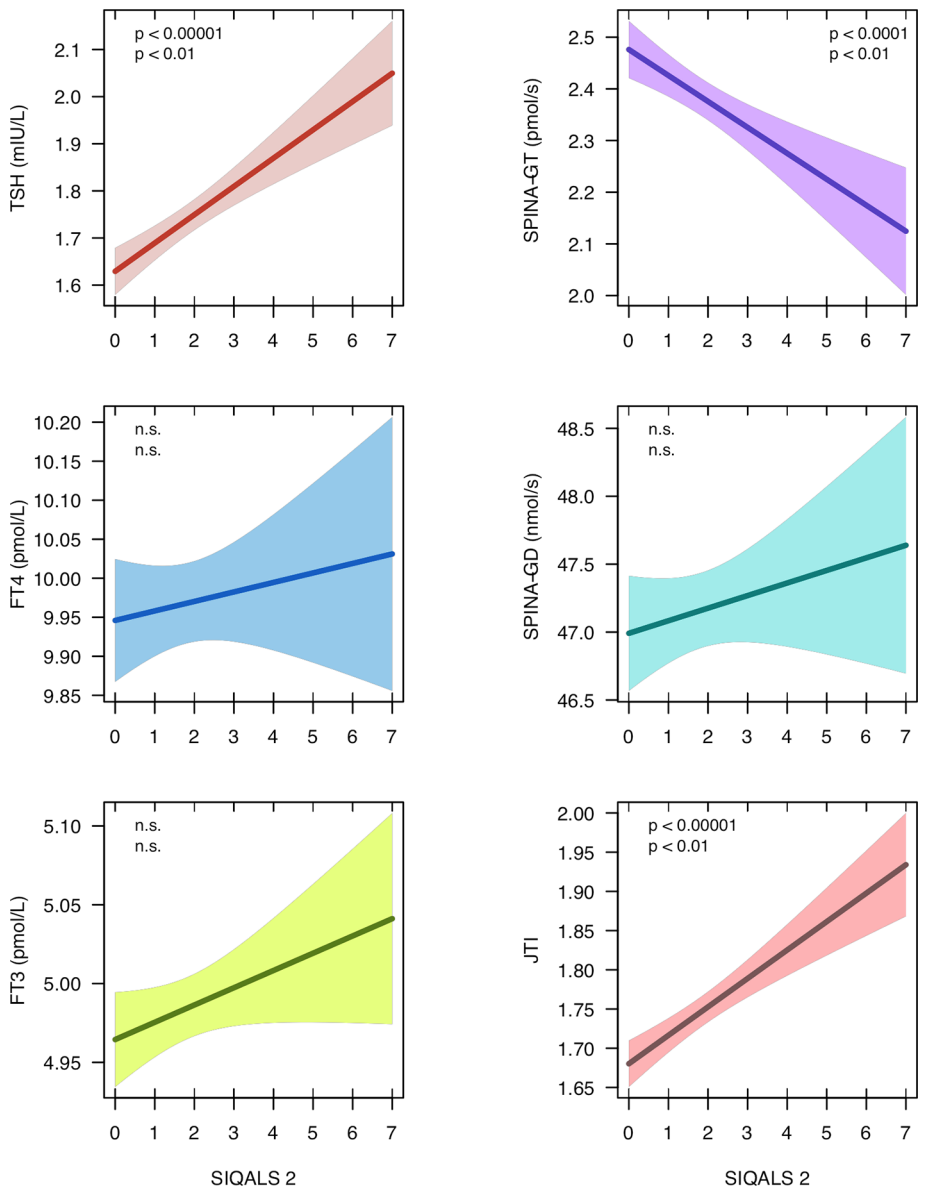

FIGURE 2 | Regression models between type 2 allostatic load (SIQALS 2) and parameters of thyroid homeostasis in 3386 euthyroid subjects. Data were obtained from the National Health and Nutrition Examination Survey (NHANES), 2007 to 2008 (40). Shown is the regression line with 95% confidence bands. In each panel, the first p value refers to unadjusted OLS regression and the second p value to estimates derived from instrumental variable (IV) regression. For regression details, see **Supplementary Tables 2** and **6**.

DISCUSSION

A high-normal or moderately elevated TSH concentration may arise from different causes including setpoint alterations of the homeostatic system in response to PTSD or other causes of allostatic load, as demonstrated here. High SIQALS 2 scores may raise the TSH concentration by 1.04 mIU/L and Jostel's TSH index by 0.72, compared to low allostatic load. Given the small dispersion of intra-individual variation in TSH concentration this influence is substantial (56). Therefore, the width of the observed broad interindividual reference ranges for TSH and thyroid hormones in population studies may at least partly result from inter-personal differences in allostatic load, age and other cardiovascular risk factors.

In this secondary analysis, we found allostatic load to be unrelated to FT4 or FT3 concentration, but to negatively correlate with maximum thyroid capacity (SPINA-GT). Likewise, PTSD was accompanied by increased TSH concentration, but did not show a clear association to FT4 levels. Interestingly, the association to TSH even grew stronger with a rising time interval since the traumatic event, possibly due to therapeutic interventions addressing a depression-related component of PTSD.

In summary, high-normal or slightly increased TSH concentration, as typically observed in patients with subclinical hypothyroidism, may ensue from two different etiologies, i.e. very early forms of primary hypothyroidism and set point elevation of the otherwise normal feedback control system. At the population level these two mechanisms may be conflated, so that mean concentrations of peripheral thyroid hormones may remain unaltered, although the underlying causal relationships differ.

Our analysis suggests a possible mechanism linking TSH to cardiovascular complications, which is a sensible alternative to the thyroid failure hypothesis by other authors (16). It also well accounts for the U-shaped relationship between TSH concentration and cardiovascular risk, as elsewhere described (14, 15). Hence, a dual etiology may explain the findings of previous studies. To resolve this ambiguity, measurements of peripheral thyroid hormones are required (11) and should be integrated into future studies—not only for the selection of subjects but also for functional assessment (10, 57, 58). Calculated parameters providing biomarkers for the set point of thyroid homeostasis and peripheral hormone metabolism may provide additional insights, especially in the setting of clinical trials (41). This should avoid ambiguities in the interpretation and provide further direction on potential therapeutic intervention (59).

In conclusion, the link between the central stress response and cardiovascular risk is empirically well established (24, 60, 61). Apparently, as demonstrated here, it also involves the central control of thyroid function. Since thyroid hormones have a profound effect on cardiovascular physiology (62–64), the set point of thyroid homeostasis appears to play a more important role than previously assumed.

DATA AVAILABILITY STATEMENT

The data used for secondary analysis was obtained from the National Health and Nutrition Examination Survey (NHANES) data set, period 2007 to 2008 (https://www.cdc.gov/nchs/nhanes/). The S scripts for generating the figures and meta-analysis, a graphical explanation of instrumental variable regression, supplementary figures and tables with additional results are available as online supplement to this article and from zenodo.org (DOI 10.5281/zenodo.3701232). The protocol for meta-analysis has been registered by PROSPERO with the ID CRD42020208436 and is available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020208436.

AUTHOR CONTRIBUTIONS

JD drafted a first version of the manuscript. RH, JM, FB, and PM edited the text and contributed additional ideas, material, and text passages. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.542710/full#supplementary-material

REFERENCES

1. Pasqualetti G, Tognini S, Polini A, Caraccio N, Monzani F. Is subclinical hypothyroidism a cardiovascular risk factor in the elderly? *J Clin Endocrinol Metab* (2013) 98(6):2256–66. doi: 10.1210/jc.2012-3818
2. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* (2015) 162(1):35–45. doi: 10.7326/M14-1456
3. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* (2010) 304(12):1365–74. doi: 10.1001/jama.2010.1361
4. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. *JAMA* (2019) 322(2):153–60. doi: 10.1001/jama.2019.9052
5. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *N Engl J Med* (2017) 376(26):2534–44. doi: 10.1056/NEJMoa1603825
6. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, et al. Thyroid Function and Sudden Cardiac Death: A Prospective Population-Based Cohort Study. *Circulation* (2016) 134(10):713–22. doi: 10.1161/CIRCULATIONAHA.115.020789
7. Müller P, Dietrich JW, Lin T, Bejinariu A, Binnebößel S, Bergen F, et al. Usefulness of Serum Free Thyroxine Concentration to Predict Ventricular

Arrhythmia Risk in Euthyroid Patients With Structural Heart Disease. *Am J Cardiol* (2020) 125(8):1162–9. doi: 10.1016/j.amjcard.2020.01.019
8. Li X, Yao Y, Chen Z, Fan S, Hua W, Zhang S, et al. Thyroid-stimulating hormone within the normal range and risk of major adverse cardiovascular events in nonischemic dilated cardiomyopathy patients with severe left ventricular dysfunction. *Clin Cardiol* (2019) 42(1):120–8. doi: 10.1002/clc.23117
9. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, et al. Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes. *Circ Heart Fail* (2018) 11(12):e005266. doi: 10.1161/CIRCHEARTFAILURE.118.005266
10. Dietrich JW, Makimoto H, Muller P. Letter by Dietrich, et al. Regarding Article, "Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes". *Circ Heart Fail* (2019) 12(4):e005854. doi: 10.1161/CIRCHEARTFAILURE.118.005854
11. Fitzgerald SP, Bean NG, Falhammar H, Tuke J. Clinical Parameters Are More Likely to Be Associated with Thyroid Hormone Levels than with Thyrotropin Levels: A Systematic Review and Meta-analysis. *Thyroid* (2020). doi: 10.1089/thy.2019.0535
12. Perez AC, Jhund PS, Stott DJ, Gullestad L, Cleland JG, van Veldhuisen DJ, et al. Thyroid-stimulating hormone and clinical outcomes: the CORONA trial (controlled rosuvastatin multinational study in heart failure). *JACC Heart Fail* (2014) 2(1):35–40. doi: 10.1016/j.jchf.2013.07.008
13. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* (2006) 295(9):1033–41. doi: 10.1001/jama.295.9.1033
14. Rhee CM, Ravel VA, Streja E, Mehrotra R, Kim S, Wang J, et al. Thyroid Functional Disease and Mortality in a National Peritoneal Dialysis Cohort. *J Clin Endocrinol Metab* (2016) 101(11):4054–61. doi: 10.1210/jc.2016-1691
15. Langen VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, et al. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf)* (2018) 88(1):105–13. doi: 10.1111/cen.13472
16. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of Subclinical Hypothyroidism and Cardiovascular Disease With Mortality. *JAMA Netw Open* (2020) 3(2):e1920745. doi: 10.1001/jamanetworkopen.2019.20745
17. Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mügge A, Pataslis PC, et al. Abnormal Thyroid Function is Common in Takotsubo Syndrome and Depends on two Distinct Mechanisms: Results of a Multicenter Observational Study. *J Internal Med* (2020). doi: 10.1111/joim.13189
18. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Homeostatic Control of the Thyroid-Pituitary Axis: Perspectives for Diagnosis and Treatment. *Front Endocrinol (Lausanne)* (2015) 6:177. doi: 10.3389/fendo.2015.00177
19. Chatzitomaris A, Hoermann R, Midgley JE, Hering S, Urban A, Dietrich B, et al. Thyroid Allostasis–Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming. *Front Endocrinol* (2017) 8:163. doi: 10.3389/fendo.2017.00163
20. Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: Evidence from the Scottish Health Survey. *PLoS One* (2017) 12(8):e0183297. doi: 10.1371/journal.pone.0183297
21. Fava GA, McEwen BS, Guidi J, Gostoli S, Offidani E, Sonino N. Clinical characterization of allostatic overload. *Psychoneuroendocrinology* (2019) 108:94–101. doi: 10.1016/j.psyneuen.2019.05.028
22. Gillespie SL, Anderson CM, Zhao S, Tan Y, Kline D, Brock G, et al. Allostatic load in the association of depressive symptoms with incident coronary heart disease: The Jackson Heart Study. *Psychoneuroendocrinology* (2019) 109:104369. doi: 10.1016/j.psyneuen.2019.06.020
23. Mazgelyte E, Karciauskaite D, Linkeviciute A, Mazeikiene A, Burokiene N, Matuzeviciene R, et al. Association of Hair Cortisol Concentration with Prevalence of Major Cardiovascular Risk Factors and Allostatic Load. *Med Sci Monit* (2019) 25:3573–82. doi: 10.12659/MSM.913532
24. McEwen BS, Akil H. Revisiting the Stress Concept: Implications for Affective Disorders. *J Neurosci* (2020) 40(1):12–21. doi: 10.1523/jneurosci.0733-19.2019
25. Friedman MJ, Wang S, Jalowiec JE, McHugo GJ, McDonagh-Coyle A. Thyroid hormone alterations among women with posttraumatic stress disorder due to childhood sexual abuse. *Biol Psychiatry* (2005) 57(10):1186–92. doi: 10.1016/j.biopsych.2005.01.019
26. Mason J, Weizman R, Laor N, Wang S, Schujovitsky A, Abramovitz-Schneider P, et al. Serum triiodothyronine elevation with posttraumatic stress disorder: a cross-cultural study. *Biol Psychiatry* (1996) 39(10):835–8. doi: 10.1016/0006-3223(95)00310-x
27. Wang S, Mason J. Elevations of serum T3 levels and their association with symptoms in World War II veterans with combat-related posttraumatic stress disorder: replication of findings in Vietnam combat veterans. *Psychosom Med* (1999) 61(2):131–8. doi: 10.1097/00006842-199903000-00001
28. Armario A, Garcia-Marquez C, Jolin T. The effects of chronic stress on corticosterone, GH and TSH response to morphine administration. *Brain Res* (1987) 401(1):200–3. doi: 10.1016/0006-8993(87)91184-x
29. Johansson G, Laakso ML, Karonen SL, Peder M. Examination stress affects plasma levels of TSH and thyroid hormones differently in females and males. *Psychosom Med* (1987) 49(4):390–6. doi: 10.1097/00006842-198707000-00008
30. Schedlowski M, Wiechert D, Wagner TO, Tewes U. Acute psychological stress increases plasma levels of cortisol, prolactin and TSH. *Life Sci* (1992) 50(17):1201–5. doi: 10.1016/0024-3205(92)90319-k
31. Yehuda R. Psychoneuroendocrinology of post-traumatic stress disorder. *Psychiatr Clin North Am* (1998) 21(2):359–79. doi: 10.1016/s0193-953x(05)70010-1
32. Newport DJ, Nemeroff CB. Neurobiology of posttraumatic stress disorder. *Curr Opin Neurobiol* (2000) 10(2):211–8. doi: 10.1016/s0959-4388(00)00080-5
33. Vermetten E, Bremner JD. Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. *Depress Anxiety* (2002) 16(1):14–38. doi: 10.1002/da.10017
34. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. *Ann N Y Acad Sci* (2004) 1032:141–53. doi: 10.1196/annals.1314.011
35. Wang S. Traumatic stress and thyroid function. *Child Abuse Negl* (2006) 30(6):585–8. doi: 10.1016/j.chiabu.2005.11.012
36. Daya SK, Paulus AO, Braxton EEJr., Vroman PJ, Mathis DA, Lin R, et al. Delayed Diagnosis of TSH-Secreting Adenoma Attributed to Worsening Post-Traumatic Stress Disorder Symptoms in a Military Veteran Because of Provider Anchoring Bias. *Mil Med* (2017) 182(3):e1849–e53. doi: 10.7205/MILMED-D-16-00241
37. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evidence-Based Ment Health* (2018) 22(4):153-60. doi: 10.1136/ebmental-2019-300117
38. Viechtauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* (2018) 36(3):1–48. doi: 10.18637/jss.v036.i03
39. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing (2018). RRID:SCR_001905.
40. National Center for Health Statistics. *National Health and Nutrition Examination Survey: Centers for Diesase Control and Prevention*. US Centers for Disease Control and Prevention (CDC) (2020). Available at: https://www.cdc.gov/nchs/nhanes/index.htm.
41. Dietrich JW, Landgrafe-Mende G, Wiora E, Chatzitomaris A, Klein HH, Midgley JE, et al. Calculated Parameters of Thyroid Homeostasis: Emerging Tools for Differential Diagnosis and Clinical Research. *Front Endocrinol (Lausanne)* (2016) 7:57. doi: 10.3389/fendo.2016.00057
42. Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. *Stat Med* (2014) 33(13):2297–340. doi: 10.1002/sim.6128
43. Kleiber C, Zeileis A. *Applied Econometrics with R*. New York: Springer-Verlag (2008).
44. Kosten TR, Wahby V, Giller EJr., Mason J. The dexamethasone suppression test and thyrotropin-releasing hormone stimulation test in posttraumatic stress disorder. *Biol Psychiatry* (1990) 28(8):657–64. doi: 10.1016/0006-3223(90)90452-8
45. Mason J, Southwick S, Yehuda R, Wang S, Riney S, Bremner D, et al. Elevation of serum free triiodothyronine, total triiodothyronine, thyroxine-binding globulin, and total thyroxine levels in combat-related posttraumatic stress disorder. *Arch Gen Psychiatry* (1994) 51(8):629–41. doi: 10.1001/archpsyc.1994.03950080041006
46. Kozaric-Kovacic D, Karlovic D, Kocijan-Hercigonja D. Elevation of serum total triiodothironine and free triiodothironine in Croatian veterans with combat-related post-traumatic stress disorder. *Mil Med* (2002) 167(10):846–9. doi: 10.1093/milmed/167.10.846
47. Goenjian AK, Pynoos RS, Steinberg AM, Endres D, Abraham K, Geffner ME, et al. Hypothalamic-pituitary-adrenal activity among Armenian adolescents with PTSD symptoms. *J Trauma Stress* (2003) 16(4):319–23. doi: 10.1023/A:1024453632458

48. Karlovic D, Marusic S, Martinac M. Increase of serum triiodothyronine concentration in soldiers with combat-related chronic post-traumatic stress disorder with or without alcohol dependence. *Wien Klin Wochenschr* (2004) 116(11-12):385–90. doi: 10.1007/BF03040918
49. Kamoi K, Tanaka M, Ikarashi T, Miyakoshi M. Effect of the 2004 mid niigata prefecture earthquake on patients with endocrine disorders. *Endocr J* (2006) 53(4):511–21. doi: 10.1507/endocrj.k06-022
50. Olff M, Guzelcan Y, de Vries GJ, Assies J, Gersons BP. HPA- and HPT-axis alterations in chronic posttraumatic stress disorder. *Psychoneuroendocrinology* (2006) 31(10):1220–30. doi: 10.1016/j.psyneuen.2006.09.003
51. Bunevicius A, Leserman J, Girdler SS. Hypothalamic-pituitary-thyroid axis function in women with a menstrually related mood disorder: association with histories of sexual abuse. *Psychosom Med* (2012) 74(8):810–6. doi: 10.1097/PSY.0b013e31826c3397
52. Loo WT, Liu Q, Yip MC, Wang M, Chow LW, Cheung MN, et al. Status of oral ulcerative mucositis and biomarkers to monitor posttraumatic stress disorder effects in breast cancer patients. *Int J Biol Markers* (2013) 28(2):168–73. doi: 10.5301/jbm.5000025
53. Sinai T, Hirvikoski T, Nordström A-L, Nordström P, Nilsonne Å, Wilczek A, et al. Hypothalamic pituitary thyroid axis and exposure to interpersonal violence in childhood among women with borderline personality disorder. *Eur J Psychotraumatol* (2014) 5(1):23911. doi: 10.3402/ejpt.v5.23911
54. Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. *Clin Endocrinol (Oxf)* (2009) 71(4):529–34. doi: 10.1111/j.1365-2265.2009.03534.x
55. ASPE. *The poverty guidelines updated periodically in the Federal Register by the U.S. Department of Health and Human Services under the authority of 42 U.S.C. 9902(2).* US Department of Health and Human Services (2007).
56. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Functional and Symptomatic Individuality in the Response to Levothyroxine Treatment. *Front Endocrinol (Lausanne)* (2019) 10:664. doi: 10.3389/fendo.2019.00664
57. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Recent Advances in Thyroid Hormone Regulation: Toward a New Paradigm for Optimal Diagnosis and Treatment. *Front Endocrinol (Lausanne)* (2017) 8:364. doi: 10.3389/fendo.2017.00364
58. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. The role of functional thyroid capacity in pituitary thyroid feedback regulation. *Eur J Clin Invest* (2018) 48(10):e13003. doi: 10.1111/eci.13003
59. Midgley JEM, Toft AD, Larisch R, Dietrich JW, Hoermann R. Time for a reassessment of the treatment of hypothyroidism. *BMC Endocr Disord* (2019) 19(1):37. doi: 10.1186/s12902-019-0365-4
60. Sterling P, Eyer J. Biological basis of stress-related mortality. *Soc Sci Med Part E: Med Psychol* (1981) 15(1):3–42. doi: 10.1016/0271-5384(81)90061-2
61. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* (2017) 389(10071):834–45. doi: 10.1016/S0140-6736(16)31714-7
62. Vargas-Uricoechea H, Sierra-Torres CH. Thyroid hormones and the heart. *Horm Mol Biol Clin Invest* (2014) 18(1):15–26. doi: 10.1515/hmbci-2013-0059
63. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* (2017) 14(1):39–55. doi: 10.1038/nrcardio.2016.174
64. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol* (2018) 71(16):1781–96. doi: 10.1016/j.jacc.2018.02.045

Conflict of Interest: JD received funding and personal fees by Sanofi-Henning, Hexal AG, Bristol-Myers Squibb, and Pfizer, and is co-owner of the intellectual property rights for the patent "System and Method for Deriving Parameters for Homeostatic Feedback Control of an Individual" (Singapore Institute for Clinical Sciences, Biomedical Sciences Institutes, Application Number 201208940-5, WIPO number WO/2014/088516). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. RH has been paid personal fees in the past for consultancy and code development in general research methods and data analysis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Low Free Triiodothyronine as a Predictor of Poor Prognosis in Patients With Myocardial Infarction With Non-Obstructive Coronary Arteries

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Background: Low free triiodothyronine (fT3) level is strongly associated with poor prognosis in various patient populations. However, the role of fT3 in the risk of clinical outcomes in myocardial infarction with non-obstructive coronary arteries (MINOCA) has not been studied. Our study aimed to evaluate the association between low fT3 levels and the clinical outcomes of MINOCA patients.

Methods: A total of 218 MINOCA patients without a history of thyroid disease were enrolled in the study. Demographic, baseline clinical data, thyroid hormones, and other biochemical parameters were assessed in all patients. According to the fT3 levels, the present study was classified into two groups: the low fT3 group (fT3<3.5 pmol/L) and the normal fT3 group (fT3 3.5-6.5 pmol/L). The endpoint of the study was major adverse cardiac events (MACE).

Results: Fifty-nine patients were in the low fT3 group and 159 patients were in the normal fT3 group. Over the two years of follow-up, 36 MACE have occurred. The occurrence of MACE was higher in the low fT3 group compared with normal fT3 group (25.4% vs 13.2%; P=0.031). Kaplan-Meier survival curves showed a significantly increased risk of MACE in patients with low fT3 (log-rank P=0.027). Multivariable logistic regression analysis stated that high fT3 was independently associated with lower risk of MACE after two years of follow up (OR, 0.623; 95% CI, 0.399- 0.972; P=0.037).

Conclusion: Low fT3 levels were significantly associated with increased risk of MACE in patients with MINOCA. This finding suggests that the fT3 levels may serve as a potential biomarker in risk stratification of MINOCA patients.

Keywords: MINOCA, thyroid, low free triiodothyronine level, prognosis, predictors

INTRODUCTION

With the continuous improvement in understanding of acute myocardial infarction (AMI), a group of AMI patients with no angiographic obstructive CAD (stenosis<50%) were gradually discovered, and the term myocardial infarction with non-obstructive coronary arteries (MINOCA) was given for this illness (1, 2). MINOCA represents a group of heterogeneous disorder with various pathological mechanisms (3, 4), and it is not a benign disease, the one-year mortality rate is 4.7% (5), however, the five-year mortality exceeds 10.9% (6), as well as a major adverse cardiac event (MACE) occurs in one in five patients with MINOCA over one year (7). Considering the heterogeneity and poor prognosis of MINOCA patients, it might be necessary to accurately use clinical predictors to stratify patients with varying risks of new cardiovascular events to help clinicians to develop adequate management strategies and to reduce the occurrence of MACE in such patient population.

There is a strong relation between thyroid hormones (THs) especially the active hormone triiodothyronine (T3) and cardiovascular system (8, 9). T3 plays a significant role in modulating cardiac contractility, increasing heart rate, and decreasing arterial resistance (9, 10). Low levels of free triiodothyronine (fT3) are correlated with worse prognosis in various patient populations such as cardiac patients (10), heart failure (11–13), AMI (14, 15), acute myocarditis (16), coronary artery bypass grafting (CABG) (17), acute ischaemic stroke (18), and in other groups of patients (19–24), however, the role of fT3 in the risk of clinical outcomes in MINOCA population and whether fT3 can improve risk prediction of MACE in such patients group has not been evaluated.

Therefore, the purpose of this study was to evaluate the association between low fT3 levels and the clinical outcomes of MINOCA patients.

METHODS

Study Population and Participants

This was an observational study of 218 consecutive patients from 2014 to 2018 diagnosed with MINOCA and undergoing coronary angiography (CAG) at the department of cardiology, Shanghai Tenth People's Hospital.

The inclusion criterion of the present study was (1): A diagnosis of MINOCA according to the ESC guidelines (2) and the fourth universal definition of myocardial infarction guidelines (1), which include: complies with the AMI's diagnostic criteria (1); CAG showed non-obstructive coronary disease (< 50% stenosis) in any infarct related coronary artery; there is no other obvious clinically evident explanation which may explain the acute presentation such as myocarditis or pulmonary embolism (2); Age >18 years old.

The exclusion criteria were (1) Patients with thrombolytic therapy given before CAG, patients with a history of MI or coronary intervention (2), Patients with severe liver, kidney disorders and had a malignant tumor (3), Patients with thyroid disorder history, such as hyperthyroidism, hypothyroidism, or thyroiditis (4), Patients who are receiving thyroid-related medications, or (5) Patients without THs baseline data.

Our study complied with the Helsinki Declaration and was approved by the hospital's ethical review board (Shanghai Tenth People's Hospital, Tongji University, Shanghai, China). Informed written consent was received from all patients participating in this study.

Data Collection

Demographic and baseline clinical information (such as age, sex, smoking history, hypertension, diabetes mellitus, body mass index, hyperlipidemia, heart failure, atrial fibrillation, heart rate, and blood pressure) were meticulously documented after admission. The electrocardiogram (ECG) and echocardiography (Echo) were performed in all the patients. All participants were undergoing the CAG procedure after admission.

Biochemical Assessment

Fasting blood was obtained within 24 hours of admission to analyze biochemical parameters. The serum levels of THs [including fT3, total triiodothyronine (TT3), free tetraiodothyronine (fT4), total tetraiodothyronine (TT4), and thyroid stimulating hormone (TSH)], and serum cardiac biomarkers [including troponin-T (cTnT), myoglobin, creatine kinase-MB (CK-MB), and N-terminal pro-brain natriuretic peptide (NT-proBNP)] were measured in all patients. As described previously (25), the serum levels of THs in our department were measured using chemiluminescence (Automatic Chemiluminescence Immune Assay System ACS 180 with related kits; Bayer, Berlin, Germany). The levels of NT-ProBNP were measured using the Eleusis electro-chemiluminescent immunoassay (Roche Diagnostics Ltd. Rotkreuz, Switzerland).

The normal ranges for fT3, TT3, fT4, TT4, and TSH uses in our department are 3.5-6.5 pmol/L, 1.2-3.4 nmol/L,10.2-31 pmol/L, 4-174 nmol/L, and 0.35-5.5 mIU/L, respectively (25).

According to fT3 level at admission, the present study was classified into two groups: low fT3 group (fT3 < 3.5 pmol/L) and normal fT3 group (fT3 3.5-6.5 pmol/L).

Follow-Up and Endpoints

Follow-up started from the day of admission and was performed at 3, 6, 12 months, and 2 years after discharge by interviewing the patients by trained cardiologists at the Shanghai Tenth People's Hospital. Follow-up information was carried out through

Abbreviations: AMI, acute myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; MACE, major adverse cardiac events; THs, thyroid hormones; T3, hormone triiodothyronine; fT3, free triiodothyronine; CAG, coronary angiography; TT3, total triiodothyronine; fT4, free tetraiodothyronine; TT4, total tetraiodothyronine; TSH, thyroid stimulating hormone; cTnT, cardiac troponin T; CK-MB, creatine kinase isoenzyme; NT-proBNP, N-terminal pro-brain natriuretic peptide; BMI, body mass index; LVEF, left ventricular ejection fraction; CI, confidence interval; OR, odds ratio; ROC, receiver operating characteristic.

outpatient visits, telephone calls, reviewing electronic medical records, and clinical notes.

The primary endpoint of our study was MACE, described as cardiovascular death, heart failure, nonfatal MI, stroke, and angina rehospitalization. The definitions of concepts in the primary endpoint have been described in our previous study (26). Death from ACS, severe cardiac arrhythmia, or refractory congestive heart failure was defined as cardiovascular death. The diagnosis of nonfatal MI was based on the established guidelines for myocardial infarction (1). Stroke was defined as an ischemic cerebral infarction caused by embolic or thrombotic occlusion of a major intracranial artery. Heart failure is a progressive disorder identified by severe forms, which might be followed by symptoms of structural and/or functional cardiac abnormality, culminating in decreased cardiac output and/or increased intracardiac pressure during rest or stress.

Statistical Analysis

The data in this study were analyzed using the Statistical Package for Social Sciences (SPSS) v.22. Figures were formed by using GraphPad softwarev.8.0.1. For numerical variables, the mean ± SE with a normal distribution was used, and percentages (%) were used for categorical variables. The chi-square test and Fisher's exact tests were used to compare categorical variables. An independent sample t-test was used to compare numerical variables between groups. Logistic regression analysis was used to determine the adjusted odds ratio (OR) for MACE to evaluate predictors of clinical endpoints. Sex, age, traditional cardiovascular risk factors (BMI, smoking history, diabetes, hypertension, hyperlipidaemia, atrial fibrillation, heart failure and alcohol), systolic and diastolic blood pressure, heart rate, left ventricular ejection fraction (LVEF), ECG findings, angiographic characteristics, and biochemical parameters (cTnT, CK-MB, myoglobin, NT-proBNP, and THs) were considered as covariates in the univariate models. For the multivariable models, clinical risk factors and biochemical parameters which were univariate predictors (at $P < 0.10$) were considered as covariates. Further subgroup analysis was performed to determine the interactions between fT3 levels and clinically associated variables using Cox proportional hazards analysis. The Kaplan-Meier analysis was used to evaluate MACE-free survival rates, and the differences between the two groups were determined using the log-rank test. The ability of fT3 to predict MACE in MINOCA patients was displayed using receiver operating characteristic (ROC) curves analysis. All analysis was conducted two-sided and identified statistically significant at P-value < 0.05.

RESULTS

Baseline Characteristics

A total of 218 patients who met the diagnostic criteria of MINOCA were enrolled in the present study. Among these, 59 (27.1%) were in the low fT3 group and 159 (72.9%) were in the normal fT3 group. Baseline characteristics, laboratory findings, and angiographic data of low and normal fT3 are summarized in **Tables 1**, **2**. Patients with low fT3 levels were older (70.18 ± 12.96 vs. 60.77 ± 13.01, $p < 0.001$), whereas systolic and diastolic blood pressure in normal fT3 was higher ($P < 0.05$). Echocardiography data showed that the LVEF in the normal fT3 group was higher than the low fT3 group (56.49% vs. 48.75%, $P < 0.001$). The serum levels of fT3, TT3, fT4, and TT4 in the low fT3 group were lower ($P < 0.05$); by comparison, the levels of cardiac cTnT, CK-MB, myoglobin, and NT-proBNP in the low fT3 group were significantly higher than normal fT3 group. According to CAG results, patients with 3 vessels disease were more common in the low fT3 group (16.9% vs. 3.8%, $P = 0.002$). There were no significant differences in sex, smoking history, diabetes, hypertension, hyperlipidemia, atrial fibrillation, previous heart failure, alcohol use, and body mass index between the two groups ($P > 0.05$).

TABLE 1 | Baseline characteristics of the study population.

	Low fT3 (*n* = 59)	Normal fT3 (*n* = 159)	*P* value
Age (years)	70.18 ± 12.96	60.77 ± 13.01	<0.001
Female, n (%)	34 (57.6)	74 (46.5)	0.146
BMI (kg/m2)	23.36 ± 4.59	24.37 ± 3.63	0.111
Smoking history, n (%)	21 (35.6)	62 (39.0)	0.646
Diabetes, n (%)	8 (13.6)	25 (15.7)	0.692
Hypertension, n (%)	32 (54.2)	75 (47.2)	0.354
Hyperlipidaemia, n (%)	7 (11.9)	31 (19.5)	0.187
Atrial fibrillation, n (%)	8 (13.6)	13 (8.2)	0.231
Previous heart failure, n (%)	2 (3.4)	4 (2.5)	0.726
Alcohol use	5 (8.5)	18 (11.3)	0.543
LVEF (%)	48.75 ± 13.69	56.49 ± 11.01	<0.001
STEMI, n (%)	25 (42.4)	57 (35.8)	0.377
NSTEMI, n (%)	34 (57.6)	102 (64.2)	0.377
Systolic blood pressure (mmHg)	135.31 ± 25.49	142.98 ± 23.25	0.036
Diastolic blood pressure (mmHg)	75.06 ± 13.22	82.13 ± 13.10	0.001
Heart rate, beats per minute	84.81 ± 23.38	80.22 ± 17.58	0.121

Values are expressed as mean ± SD or number (%); BMI, body mass index; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; fT3, free triiodothyronine.

TABLE 2 | Laboratory findings and angiographic data of the study population.

	Low fT3 (*n* = 59)	Normal fT3 (*n* = 159)	*P* value
laboratory findings			
fT3 (pmol/L)	2.95 ± 0.49	4.59 ± 1.67	<0.001
TT3 (nmol/L)	0.99 ± 0.28	1.52 ± 0.46	<0.001
fT4 (pmol/L)	14.58 ± 3.33	16.59 ± 5.08	0.005
TT4 (nmol/L)	86.79 ± 24.28	100.34 ± 30.14	0.002
TSH (mIU/L)	4.30 ± 19.36	1.97 ± 1.50	0.133
cTnT (ng/mL)	0.69 ± 1.64	0.38 ± 0.77	0.053
CK-MB (ng/mL)	30.82 ± 75.98	14.43 ± 27.39	0.020
Myoglobin (ng/ml)	285.63 ± 471.78	99.15 ± 164.94	<0.001
NT-proBNP (pg/mL)	4731.77 ± 6846.12	1209.66 ± 2681.39	<0.001
Angiographic data			
Normal coronary arteries (0% stenosis), n (%)	22 (37.3)	76 (47.8)	0.166
Vessel with any stenosis (> 0 to < 50% stenosis), n (%)			
1-vessel, n (%)	19 (32.2)	46 (28.9)	0.639
2-vessel, n (%)	8 (13.6)	31 (19.5)	0.310
3-vessel, n (%)	10 (16.9)	6 (3.8)	0.002

Values are expressed as mean ± SD or number (%); fT3, free triiodothyronine; TT3, total triiodothyronine; fT4, free tetraiodothyronine; TT4, total tetraiodothyronine; TSH, thyroid stimulating hormone; cTnT, cardiac troponin T; CK-MB, creatine kinase isoenzyme; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Association Between fT3 and the Primary Endpoints

No patients were excluded because of missing data. Over the two years of follow-up, a total of 36 MACE have occurred. MACE occurred in 15 patients (6 cardiovascular deaths, 1 heart failure, 1 stroke, and 7 angina rehospitalization) in the low fT3 group, and 21 patients (3 cardiovascular deaths, 2 nonfatal MI, 1 heart failure, 2 strokes, and 13 angina rehospitalization) in the normal fT3 group. The occurrence of MACE and cardiovascular deaths were substantially more frequent in the low fT3 group compared with the normal fT3 group (25.4% vs 13.2% and 10.2% vs. 1.9%, respectively; all P < 0.05) (**Figure 1**). Two years Kaplan-Meier survival curves for cardiovascular deaths and total MACE in patients with low and normal fT3 levels are displayed in **Figures 2**, **3**, which showed a significantly increased risk of cardiovascular deaths in patients with low fT3 (log-rank P = 0.007). Similarly, when total MACE was analyzed, the Kaplan-Meier analysis demonstrated a higher risk of total MACE in low fT3 (log-rank P = 0.027). The ROC curve of fT3 was shown in **Figure 4** for the prediction of clinical MACE, which showed that the fT3 has moderate significance in predicting MACE in MINOCA patients, with an AUC of 0.690 (95% CI, 0.583-0.798; P = 0.002).

Predictive Factors of MACE

The univariable and multivariable predictors of MACE are included in **Table 3**. Logistic regression analysis demonstrates that high fT3 in univariate analysis was independently associated with lower risk of MACE (OR, 0.647; 95% CI, 0.422- 0.991; P = 0.045). After excluding confounding factors, multivariable logistic regression analysis still stated that high fT3 was strongly associated with lower risk of MACE after two years of

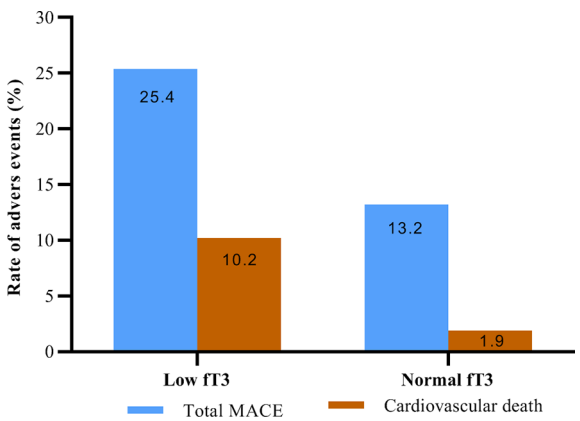

FIGURE 1 | Rate of adverse events in MINOCA patients with low fT3 versus normal fT3 levels. fT3, free triiodothyronine; MACE, major adverse cardiovascular events.

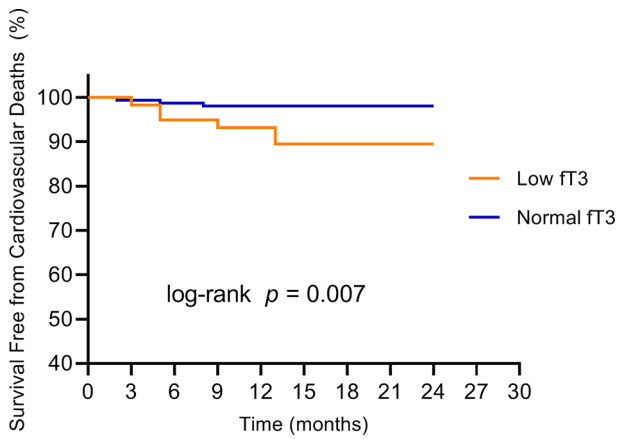

FIGURE 2 | Kaplan-Meier survival curves for cardiovascular deaths in MINOCA patients with low fT3 versus normal fT3 levels. fT3, free triiodothyronine.

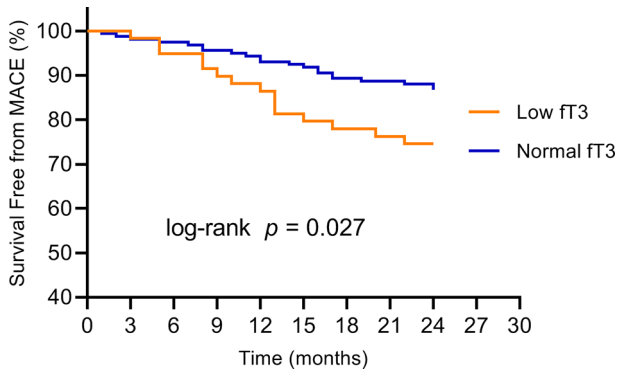

FIGURE 3 | Kaplan-Meier survival curves for MACE in MINOCA patients with low fT3 versus normal fT3 levels. fT3, free triiodothyronine; MACE, major adverse cardiovascular events.

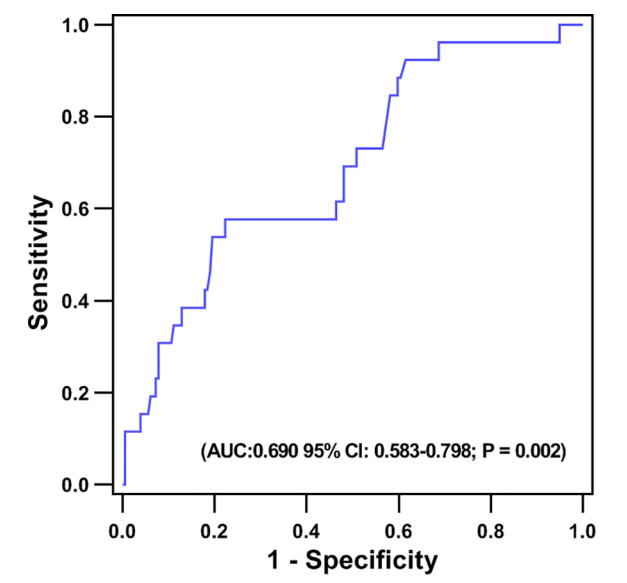

FIGURE 4 | Receiver operating characteristic (ROC) curve of the ability of fT3 to predict MACE in MINOCA patients.

follow up (OR, 0.623; 95% CI, 0.399- 0.972; P = 0.037), followed by LVEF (OR, 0.957; 95% CI, 0.928- 0.986; P = 0.004).

Subgroup Analysis

Further subgroup analyses for associations of fT3 levels with MACE stratified by age, sex, traditional cardiovascular risk factors, LVEF, cTnT, NT-proBNP levels, and the number of vessel diseases are shown in supplemental **Table 1**. Subgroup analysis showed that there was no significant interaction between fT3 levels and age (<65 years or ≥65 years), sex, traditional cardiovascular risk factors (hypertension, diabetes mellitus, smoking, BMI, and atrial fibrillation), LVEF, cTnT, NT-proBNP levels, and the number of vessel diseases (all P for interaction > 0.05).

DISCUSSIONS

The aim of this study was to evaluate the association between low fT3 levels and the clinical outcomes of MINOCA patients. The main findings of our study were (1); Low fT3 levels were frequently found in MINOCA patients (2), Low fT3 levels were strongly associated with increased risk of MACE in MINOCA patients. The findings of this study suggest that measuring fT3 levels may be a useful tool for clinicians to stratify patients at risk of poor outcomes following MINOCA.

The importance of MINOCA has attracted much attention and has been recently introduced in the European Society of Cardiology (ESC) (2) and the Fourth Universal Definition of Myocardial Infarction guidelines (1) as a special type of myocardial infarction (MI). Early large cohort studies indicated that the prognosis of MINOCA patients is not favorable. A large cohort study of 16849 MINOCA patients reported that one in every five MINOCA patients experienced a major adverse event over one year (7). Furthermore, Lindahl et al. concluded that 23.9% of MINOCA patients suffered MACE over a four-year follow-up period in a study of 9466 MINOCA patients (27). Consequently, MINOCA remains a particularly challenging illness due to numerous pathophysiological mechanisms with different causes and unclear management therapy. Thus, clinical predictors can be used to guide the medical triage process and to quantify the risk of major cardiovascular events in the MINOCA population, which may be beneficial to improve treatment options.

TABLE 3 | Univariate and Multivariable analysis of predictors of MACE within 2 years.

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*P* value	*OR* (95% CI)	*P* value
fT3	0.647 (0.422- 0.991)	0.045	0.623 (0.399- 0.972)	0.037
NT-proBNP	1.000 (1.000- 1.000)	0.053		
TT3	0.398 (0.148- 1.070)	0.068		
LVEF	0.950 (0.926- 0.976)	<0.001	0.957 (0.928- 0.986)	0.004
Age	1.031 (1.002- 1.061)	0.036		
Systolic blood pressure	1.017 (1.001- 1.032)	0.032		

fT3, free triiodothyronine; NT-proBNP, N-terminal pro-brain natriuretic peptide; TT3, total triiodothyronine; LVEF, left ventricular ejection fraction; CI, confidence interval; OR, odds ratio.

Low T3 levels are often seen in severe non-thyroidal diseases, such as cardiovascular disorders (10). According to a recent systemic review, the incidence of low T3 syndrome was 18.9%, 24.5%, and 17.1% in patients with MI, heart failure, and acute coronary syndrome (ACS), respectively (28). In the present study, the prevalence of low fT3 in MINOCA patients was 27.1%, which is relatively high. Interestingly, the level of myocardial injury markers (cTnT, CK-MB, and myoglobin) and NT-proBNP were higher in the low fT3 group. Moreover, LVEF in the low fT3 group was lower, besides, patients with the three-vessel disease were more common in the low fT3 group, suggesting that fT3 level is associated with the degree of myocardial injury and severity in MINOCA patients. Similar findings were observed in a study by Yuan et al, which indicates that a low level of fT3 was linked with an increased incidence of long-term cardiovascular mortality and composite MACE in euthyroid patients with the three-vessel disease (29). Thus, low fT3 could possibly relate to sicker patients and reflect non-thyroidal illness.

Previous studies have demonstrated that low fT3 levels were associated with a worse short and long-term prognosis in various patient groups. A study by Iervasi et al. showed that low fT3 is a strong predictor of mortality in 573 patients with different cardiac diseases (10). Accordingly, another study of 699 STEMI patients showed low fT3 levels were significantly associated with increased risks of mortality and MACE (14). Low fT3 was also found to be a significant predictor of poor prognosis in a recent Chinese study in adult patients with acute myocarditis (16). In 2459 AMI patients, Wen Su et al. also found a strong link between poor prognosis and low fT3 syndrome (15). Another study observed that low T3 is a powerful factor of mortality and low cardiac output in CABG patients (17). A recent Japanese study demonstrated low fT3 to be a predictor of MACE and all-cause mortality in hemodialysis patients (30). Multiple studies have reported low T3 levels to be a predictor of poor prognosis in acute and chronic heart failure (12, 13, 31, 32). In patients with acute ischaemic stroke, low T3 syndrome was associated with hemorrhagic transformation (18). Low T3 was found to be correlated with poor prognosis in some cancer diseases such as chronic lymphocytic leukemia (20), brain tumor (33), and diffuse large B cell lymphoma (21). Besides, Low T3 was also reported to be a useful predictor of poor clinical outcomes in patients with pyogenic liver abscess (19), chronic fatigue syndrome (22), community-acquired pneumonia (23), secondary hemophagocytic lymph histiocytosis (24), and respiratory failure (34). In a community dwelling elderly population, low fT3 was linked to low muscle mass and poor physical ability (35). In MINOCA patients, two recent case studies have shown that thyroid diseases such as thyrotoxicosis may be a potential cause for MINOCA, suggesting that thyroid hormones may play an important role in the pathogenesis of MINOCA and may have an impact on the prognosis of such patients group (36, 37). To the best of our knowledge, this is the first study to demonstrate a relationship between lower fT3 levels and increased risk of MACE and cardiovascular deaths in the MINOCA population. In the present study, the occurrence of MACE and cardiovascular deaths were more frequent in the low fT3 group compared to the normal fT3 group. The Kaplan-Meier analysis also showed a significantly increased risk of cardiovascular deaths and total MACE in MINOCA patients with low fT3. Furthermore, multivariable logistic regression analysis stated that fT3 was significantly associated with poor prognosis in the MINOCA population, this correlation was consistent throughout subgroups of the patient's population. In addition, the ROC curve analysis showed that the fT3 has moderate significance in predicting MACE in MINOCA patients. Considering the poor prognosis of MINOCA patients, it might be necessary to use clinical predictors to stratify patients with varying risks of new cardiovascular events to help clinicians develop adequate management strategy and to reduce the occurrence of MACE. Thus, the findings of the present study are of significant clinical interest, which suggests that determination of fT3 levels in the early stage could be a useful tool to identify the risk of poor clinical outcomes and improve the management strategy of high-risk MINOCA patients. The assessment of fT3 levels in cardiovascular risk scores of MINOCA patients may provide significant information on clinical implications, however, these findings require further verification by large scale prospective cohorts.

Some limitations were associated with our research study. First, this was an observational study with small sample size. Second, this study has only two years follow-up duration. Third, some confounders such as a family history of heart disease, etc., might have influenced our findings in few patients, therefore, the results of the present study may not be generalizable to populations of different ethnic backgrounds. Fourth, we do not have data on autoantibodies, and the frequency of autoimmune thyroid conditions in this study is unclear. In addition, since thyroid function was only assessed at baseline, we cannot conclude that the associations with MACE would be different if data were collected over the follow-up period. Furthermore, it is unclear if increasing the fT3 level into its normal range would benefit patients with low fT3 to improve their outcomes. Multi-center prospective analyses with long-term follow-up are needed to verify the findings of the present study.

CONCLUSION

The present study is the first to evaluate the association between low fT3 levels and the prognosis of MINOCA patients. Our study revealed that low fT3 levels are frequently found in MINOCA patients and were significantly associated with increased risk of MACE. This finding suggests that the fT3 levels may serve as a potential biomarker in the risk stratification of MINOCA patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the hospital's ethical review board (Shanghai Tenth People's Hospital, Tongji University, Shanghai, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FA, YX, and WC designed the study. A-QM, LL, WZ, and GY collected the data. BX and SX. were involved in data cleaning, follow-up, and verification. FA, YX, and WC drafted the manuscript and revised it critically for important intellectual content. YX and WC approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.681978/full#supplementary-material

REFERENCES

1. Thygesen K, Alpert J, Jaffe A, Chaitman B, Bax J, Morrow D, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* (2018) 72(18):2231–64. doi: 10.1016/j.jacc.2018.08.1038
2. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio ALP, et al. ESC Working Group Position Paper on Myocardial Infarction With non-Obstructive Coronary Arteries. *Eur Heart J* (2016) 38(3):143–53. doi: 10.1093/eurheartj/ehw149
3. Tamis-Holland J, Jneid H, Reynolds H, Agewall S, Brilakis E, Brown T, et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation* (2019) 139(18):e891–908. doi: 10.1161/cir.0000000000000670
4. Niccoli G, Scalone G, Crea F. Acute Myocardial Infarction With No Obstructive Coronary Atherosclerosis: Mechanisms and Management. *Eur Heart J* (2015) 36(8):475–81. doi: 10.1093/eurheartj/ehu469
5. Pasupathy S, Air T, Dreyer R, Tavella R, Beltrame J. Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries. *Circulation* (2015) 131(10):861–70. doi: 10.1161/circulationaha.114.011201
6. Bainey KR, Welsh RC, Alemayehu W, Westerhout CM, Traboulsi D, Anderson T, et al. Population-Level Incidence and Outcomes of Myocardial Infarction With non-Obstructive Coronary Arteries (MINOCA): Insights From the Alberta Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies (COAPT) Study. *Int J Cardiol* (2018) 264:12–7. doi: 10.1016/j.ijcard.2018.04.004
7. Dreyer R, Tavella R, Curtis J, Wang Y, Pauspathy S, Messenger J, et al. Myocardial Infarction With Non-Obstructive Coronary Arteries as Compared With Myocardial Infarction and Obstructive Coronary Disease: Outcomes in a Medicare Population. *Eur Heart J* (2020) 41(7):870–8. doi: 10.1093/eurheartj/ehz403
8. Klein I, Ojamaa K. Thyroid Hormone and the Cardiovascular System. *N Engl J Med* (2001) 344(7):501–9. doi: 10.1056/nejm200102153440707
9. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid Hormones and Cardiovascular Disease. *Nat Rev Cardiol* (2017) 14(1):39–55. doi: 10.1038/nrcardio.2016.174
10. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, et al. Low-T3 Syndrome: A Strong Prognostic Predictor of Death in Patients With Heart Disease. *Circulation* (2003) 107(5):708–13. doi: 10.1161/01.cir.0000048124.64204.3f
11. Passino C, Pingitore A, Landi P, Fontana M, Zyw L, Clerico A, et al. Prognostic Value of Combined Measurement of Brain Natriuretic Peptide and Triiodothyronine in Heart Failure. *J Card Fail* (2009) 15(1):35–40. doi: 10.1016/j.cardfail.2008.08.008
12. Rothberger GD, Gadhvi S, Michelakis N, Kumar A, Calixte R, Shapiro LE. Usefulness of Serum Triiodothyronine (T3) to Predict Outcomes in Patients Hospitalized With Acute Heart Failure. *Am J Cardiol* (2017) 119(4):599–603. doi: 10.1016/j.amjcard.2016.10.045
13. Sato Y, Yoshihisa A, Kimishima Y, Kiko T, Kanno Y, Yokokawa T, et al. Low T3 Syndrome Is Associated With High Mortality in Hospitalized Patients With Heart Failure. *J Card Fail* (2019) 25(3):195–203. doi: 10.1016/j.cardfail.2019.01.007
14. Song Y, Li J, Bian S, Qin Z, Song Y, Jin J, et al. Association Between Low Free Triiodothyronine Levels and Poor Prognosis in Patients With Acute St-Elevation Myocardial Infarction. *BioMed Res Int* (2018) 2018:9803851. doi: 10.1155/2018/9803851
15. Su W, Zhao XQ, Wang M, Chen H, Li HW. Low T3 Syndrome Improves Risk Prediction of In-Hospital Cardiovascular Death in Patients With Acute Myocardial Infarction. *J Cardiol* (2018) 72(3):215–9. doi: 10.1016/j.jjcc.2018.02.013
16. Zhao Y, Wang W, Zhang K, Tang Y-D. Association Between Low T3 Syndrome and Poor Prognosis in Adult Patients With Acute Myocarditis. *Front Endocrinol* (2021) 12:571765. doi: 10.3389/fendo.2021.571765
17. Cerillo AG, Storti S, Kallushi E, Haxhiademi D, Miceli A, Murzi M, et al. The Low Triiodothyronine Syndrome: A Strong Predictor of Low Cardiac Output and Death in Patients Undergoing Coronary Artery Bypass Grafting. *Ann Thorac Surg* (2014) 97(6):2089–95. doi: 10.1016/j.athoracsur.2014.01.049
18. Huang GQ, Zeng YY, Cheng QQ, Cheng HR, Ruan YT, Yuan CX, et al. Low Triiodothyronine Syndrome Is Associated With Hemorrhagic Transformation in Patients With Acute Ischaemic Stroke. *Aging* (2019) 11(16):6385–97. doi: 10.18632/aging.102195
19. Xu J, Wang L. Low T3 Syndrome as a Predictor of Poor Prognosis in Patients With Pyogenic Liver Abscess. *Front Endocrinol* (2019) 10:541. doi: 10.3389/fendo.2019.00541
20. Gao R, Chen RZ, Xia Y, Liang JH, Wang L, Zhu HY, et al. Low T3 Syndrome as a Predictor of Poor Prognosis in Chronic Lymphocytic Leukemia. *Int J Cancer* (2018) 143(3):466–77. doi: 10.1002/ijc.31327
21. Gao R, Liang JH, Wang L, Zhu HY, Wu W, Wu JZ, et al. Low T3 Syndrome Is a Strong Prognostic Predictor in Diffuse Large B Cell Lymphoma. *Br J Haematol* (2017) 177(1):95–105. doi: 10.1111/bjh.14528
22. Ruiz-Núñez B, Tarasse R, Vogelaar EF, Janneke Dijck-Brouwer DA, Muskiet FAJ. Higher Prevalence of "Low T3 Syndrome" in Patients With Chronic Fatigue Syndrome: A Case-Control Study. *Front Endocrinol* (2018) 9:97. doi: 10.3389/fendo.2018.00097
23. Liu J, Wu X, Lu F, Zhao L, Shi L, Xu F. Low T3 Syndrome Is a Strong Predictor of Poor Outcomes in Patients With Community-Acquired Pneumonia. *Sci Rep* (2016) 6:22271. doi: 10.1038/srep22271
24. Yin G, Huang J, Tian T, Duan L, Xu J, Qiu H. Low T3 Syndrome Is a Prognostic Marker of Poor Outcomes in Secondary Hemophagocytic

Lymphohistiocytosis. *Leuk Lymphoma* (2020) 61(12):2947–54. doi: 10.1080/10428194.2020.1789623
25. Zhang B, Peng W, Wang C, Li W, Xu Y. A Low fT3 Level as a Prognostic Marker in Patients With Acute Myocardial Infarctions. *Internal Med* (2012) 51(21):3009–15. doi: 10.2169/internalmedicine.51.7902
26. Abdu FA, Liu L, Mohammed AQ, Luo Y, Xu S, Auckle R, et al. Myocardial Infarction With non-Obstructive Coronary Arteries (MINOCA) in Chinese Patients: Clinical Features, Treatment and 1year Follow-Up. *Int J Cardiol* (2019) 287:27–31. doi: 10.1016/j.ijcard.2019.02.036
27. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A, et al. Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease. *Circulation* (2017) 135(16):1481–9. doi: 10.1161/CIRCULATIONAHA.116.026336
28. Wang B, Liu S, Li L, Yao Q, Song R, Shao X, et al. Non-Thyroidal Illness Syndrome in Patients With Cardiovascular Diseases: A Systematic Review and Meta-Analysis. *Int J Cardiol* (2017) 226:1–10. doi: 10.1016/j.ijcard.2016.10.039
29. Yuan D, Zhang C, Jia S, Liu Y, Jiang L, Xu L, et al. Predictive Value of Free Triiodothyronine (FT3) to Free Thyroxine (FT4) Ratio in Long-Term Outcomes of Euthyroid Patients With Three-Vessel Coronary Artery Disease. *Nutr Metab Cardiovasc Dis* (2021) 31(2):579–86. doi: 10.1016/j.numecd.2020.10.011
30. Yamazaki Y, Shoji T, Miyashima M, Nagata Y, Kakutani Y, Ochi A, et al. Low Free Triiodothyronine Level as a Predictor of Cardiovascular Events and All-Cause Mortality in Patients Undergoing Hemodialysis: The DREAM Cohort. *J Atheroscler Throm* (2020). doi: 10.5551/jat.60624
31. Mitchell J, Hellkamp A, Mark D, Anderson J, Johnson G, Poole J, et al. Thyroid Function in Heart Failure and Impact on Mortality. *JACC Heart failure* (2013) 1(1):48–55. doi: 10.1016/j.jchf.2012.10.004
32. Okayama D, Minami Y, Kataoka S, Shiga T, Hagiwara N. Thyroid Function on Admission and Outcome in Patients Hospitalized for Acute Decompensated Heart Failure. *J Cardiol* (2015) 66(3):205–11. doi: 10.1016/j.jjcc.2015.04.006
33. Bunevicius A, Deltuva V, Tamasauskas S, Tamasauskas A, Laws ERJr., Bunevicius R. Low Triiodothyronine Syndrome as a Predictor of Poor Outcomes in Patients Undergoing Brain Tumor Surgery: A Pilot Study: Clinical Article. *J Neurosurg* (2013) 118(6):1279–87. doi: 10.3171/2013.1.jns121696
34. Scoscia E, Baglioni S, Eslami A, Iervasi G, Monti S, Todisco T. Low Triiodothyronine (T3) State: A Predictor of Outcome in Respiratory Failure? Results of a Clinical Pilot Study. *Eur J Endocrinol* (2004) 151 (5):557–60. doi: 10.1530/eje.0.1510557
35. Kong S, Kim J, Park Y, Lee J, Hong A, Shin C, et al. Low Free T3 to Free T4 Ratio was Associated With Low Muscle Mass and Impaired Physical Performance in Community-Dwelling Aged Population. *Osteoporos Int* (2020) 31(3):525–31. doi: 10.1007/s00198-019-05137-w
36. Anderton TS, Saunderson CED, Jain M, Sengupta A, Bernstein BS, Halliday B, et al. A Case Report of Acute Myopericarditis Associated With Graves' Thyrotoxicosis. *Eur Heart J - Case Rep* (2020) 4(6):1–5. doi: 10.1093/ehjcr/ytaa465
37. Krishnan GD, Yahaya N, Yahaya M. Hyperthyroidism Presenting as ST Elevation Myocardial Infarction With Normal Coronaries – A Case Report. *J ASEAN Fed Endocrine Societies* (2019) 34(1):92–4. doi: 10.15605/jafes.034.01.14

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CASE REPORT
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Targeted Temperature Management for In-hospital Cardiac Arrest Caused by Thyroid Storm: A Case Report

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Background: Malignant ventricular arrhythmias caused by thyroid storm, such as ventricular tachycardia (VT) or ventricular fibrillation (VF), which are life-threatening, are rare. We report the case of a patient who suffered from cardiac arrest caused by thyroid storm and the rare VF; the patient showed a favorable neurologic outcome after receiving targeted temperature management (TTM) treatment by intravascular cooling measures.

Case presentation: A 24-year-old woman who had lost 20 kg in the preceding 2 months presented to the emergency department with diarrhea, vomiting, fever, and tachycardia. Thyroid function testing showed increased free triiodothyronine (FT3) and free thyroxine (FT4), decreased thyroid-stimulating hormone (TSH), and positive TSH-receptor antibody (TRAB). She was diagnosed with hyperthyroidism and had experienced sudden cardiac arrest (SCA) due to ventricular fibrillation (VF) caused by thyroid storm. The patient was performed with targeted temperature management (TTM) by intravascular cooling measures. Regular follow-up in the endocrinology department showed a good outcome.

Conclusions: Our case not only suggests a new method of cooling treatment for thyroid storm, but also provides evidence for the success of TTM on patients resuscitated from in-hospital cardiac arrest (IHCA) who remain comatose after return of spontaneous circulation (ROSC).

Keywords: thyroid storm, ventricular arrhythmia, cardiac arrest, cardiopulmonary resuscitation, targeted temperature management

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INTRODUCTION

Thyroid storm is an endocrine emergency that is characterized by multiple organ failure due to severe thyrotoxicosis. The most common arrhythmias caused by thyrotoxicosis are sinus tachycardia and atrial fibrillation (AF), which present in 28% of patients. Malignant ventricular arrhythmias, such as ventricular tachycardia (VT) or ventricular fibrillation (VF), which are life-threatening, are rare (1). We thus report a case of cardiac arrest induced by torsade de pointes (TdP) and VF due to thyroid storm, in which the patient was treated with intravascular cooling measures to protect neurological function. We investigate the mechanism of malignant ventricular arrhythmia caused by thyrotoxicosis and explore hypothermia therapy for patients who suffer from cardiac arrest caused by thyroid storm.

CASE PRESENTATION

A 24-year-old Asian woman presented to the emergency department, who had no previous medical history, psychosocial history and family history. She had lost 20 kg in the previous 2 months with no other symptoms, but 10 days before admission, the patient presented to emergency department because of diarrhea for unknown reasons, accompanied by vomiting and fever. Then physical examination revealed body temperature at 37.4°C, heart rate 160 bpm, and blood pressure 128/108 mmHg. The patient was successively treated with latamoxef, moxifloxacin for anti-infection treatment, and metoprolol for heart rate control. She had to present to emergency department again when her condition did not improve after 4 days of continuous treatment and her heart rate continued to fluctuate between 100 and 160 bpm. Then physical examination showed no other positive findings except grade II thyroid enlargement. Thyroid function testing showed increased free triiodothyronine (FT3) and free thyroxine (FT4), decreased thyroid-stimulating hormone (TSH), and positive TSH-receptor antibody (TRAB). Thyroid ultrasound revealed diffuse thyroid parenchyma lesions. Based on these findings, the patient was diagnosed with hyperthyroidism, and received treatment with metoprolol 25 mg b.i.d. as well as methimazole 30 mg q.d. orally for 4 days in emergency observation room.

No significant remission in her symptoms of vomiting and diarrhea during or following treatment had been observed. In the emergency observation room, the patient lost consciousness and the electrocardiogram (ECG) monitor showed VF; she was thus immediately transferred to the resuscitation room for cardiopulmonary resuscitation (CPR). After 16 min of CPR, return of spontaneous circulation (ROSC) was observed, with Glasgow coma scale (GCS) <8. Physical examination showed a heart rate of 166 bpm, blood pressure of 98/73 mmHg, and body temperature of 39.1°C. The patient was diagnosed with thyroid storm based on clinical presentation and her Burch-Wartofsky score of 50 when first presented to the emergency department. She was admitted to the emergency intensive care unit (EICU) for therapeutic hypothermia treatment.

Laboratory data, including complete blood cell counts, liver function, renal function, cardiac enzyme, and electrolyte levels were all within normal limits when the patient first presented to the emergency department. Four days after emergency treatment, a thyroid function test showed the following levels: FT3 > 20.00 (2.3–4.2) pg/ml, FT4 > 12.00 (0.89–1.80) ng/dl, TSH < 0.008 (0.55–4.78) uIU/ml; TRAb > 40 (<60) U/L; thyroglobulin antibodies (TGAb) 222.0 (<60) U/ml, and thyroid microsomal antibody (TMAb) 34.3 (<60) U/ml. Thyroid ultrasound revealed diffuse thyroid parenchyma lesions. Based on these findings, the patient presented with thyroid storm due to uncontrolled Graves' disease.

The patient's ECG before cardiac arrest revealed sinus tachycardia and a prolonged QTc. The measured QTc interval was 0.498 s at a heart rate of 105 bpm (**Figure 1**). We reviewed ECG monitor data after cardiac arrest (**Figure 2**) and found that transient ST-segment elevation induced TdP and VF after the R-on-T phenomenon, which suggested that the cause of cardiac arrest in the patient was malignant ventricular arrhythmia. The patient's echocardiogram before cardiac arrest showed left ventricular ejection fraction (LVEF) was 74% and decreased to 40% after ROSC.

On admission to EICU for thyroid storm, the patient was initiated on propylthiouracil 400 mg which could inhibit both thyroid hormone synthesis and peripheral conversion of T4–T3, and maintained on 200 mg t.i.d. The dose was then gradually reduced to 100 mg t.i.d. The patient was also treated with propranolol 40 mg t.i.d. to achieve adequate control of heart rate, which could also block the stimulating effects of thyroid hormones on the heart and inhibit the transformation of peripheral T4–T3. The patient was also started on hydrocortisone 100 mg q.8h. for 3 days, followed by 50 mg q.8h. for 2 days and then 50 mg q.12h. for 5 days, which could prevent adrenocortical dysfunction. The hydrocortisone was discontinued on day 10 after admission. The patient exhibited favorable outcome, and was discharged on a medication regimen including propylthiouracil 100 mg t.i.d. and propranolol 20 mg t.i.d.

After resuscitation, the patient had shown coma and high fever with a body temperature of 39.1°C; consequently, mild hypothermia therapy was started within the first 4 h after resuscitation and targeted temperature management (TTM) was performed by intravascular cooling measures to protect neurological function. CoolGard 3000 system and CoolLine catheter were used to provide stable TTM. The target temperature was set to 34°C. The patient's temperature dropped to 35.4°C 4 h later, and fluctuated around the target temperature at hour 12. During the following 24 h, the patient was maintained in a hypothermic state at 34°C followed by controlled rewarming (0.1°C/h). After a 72-h maintenance period, endotracheal intubation and the intravascular cooling catheter were removed. The patient recovered consciousness but had intermittent fever, and thus was treated with an ice blanket as well as an ice cap until her temperature returned to normal (**Figure 3**).

The patient's condition improved gradually, whereupon she was transferred from EICU on day 10 after admission. Cardiac MRI was performed before discharge, which showed LVEF was 72% and right ventricular ejection fraction (RVEF) was 66%. Regular follow-up in the endocrinology department showed a good outcome.

DISCUSSION

Thyroid storm is a life-threatening condition that has a mortality of 10–20%, which thus requires rapid diagnosis and emergent treatment (2, 3). In our case, the patient had a definite diagnosis of hyperthyroidism when she initially presented to

Abbreviations: AF, Atrial fibrillation; VT, Ventricular tachycardia; VF, Ventricular fibrillation; TdP, Torsade de pointes; FT3, Free triiodothyronine; FT4, Free thyroxine; TSH, Thyroid-stimulating hormone; TRAB, TSH-receptor antibody; ECG, Electrocardiogram; CPR, Cardiopulmonary resuscitation; ROSC, Return of spontaneous circulation; GCS, Glasgow coma scale; EICU, Emergency intensive care unit; TGAb, Thyroglobulin antibodies; TMAb, Thyroid microsomal antibody; TTM, Targeted temperature management; OHCA, Out-of-hospital cardiac arrest; IHCA, In-hospital cardiac arrest; JTA/JES, Japan Thyroid Association and the Japan Endocrine Society; CPC, Cerebral performance category; ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ICD, Implantable cardioverter defibrillator.

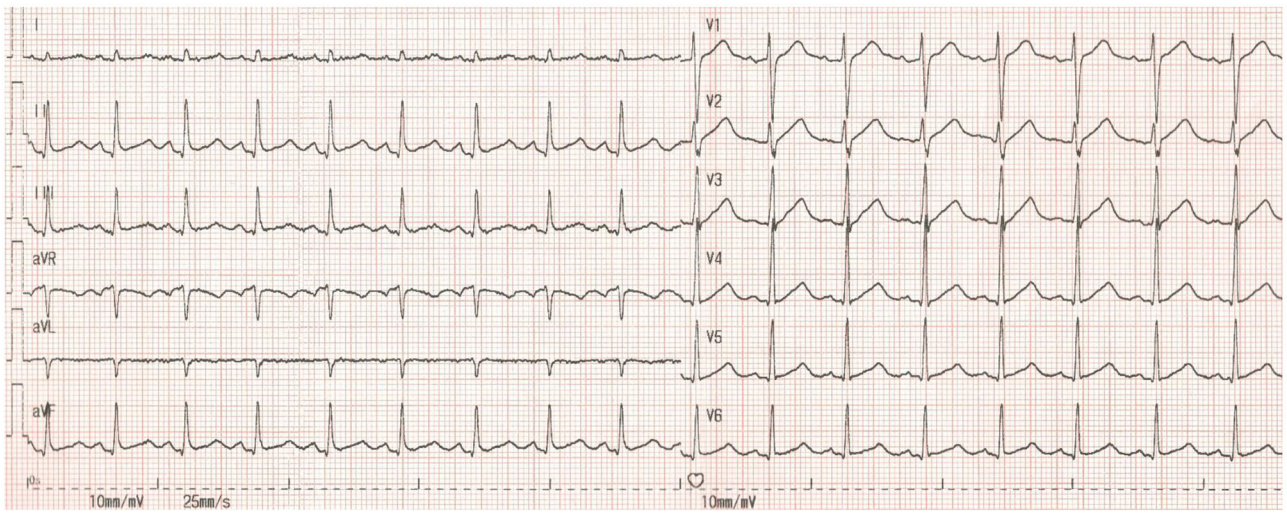

FIGURE 1 | The patient's ECG before cardiac arrest. HR = 105 bpm, RR = 0.568 s, QT = 0.375 s. QTc = 0.498 s, QTc = QT /(RR)1/2.

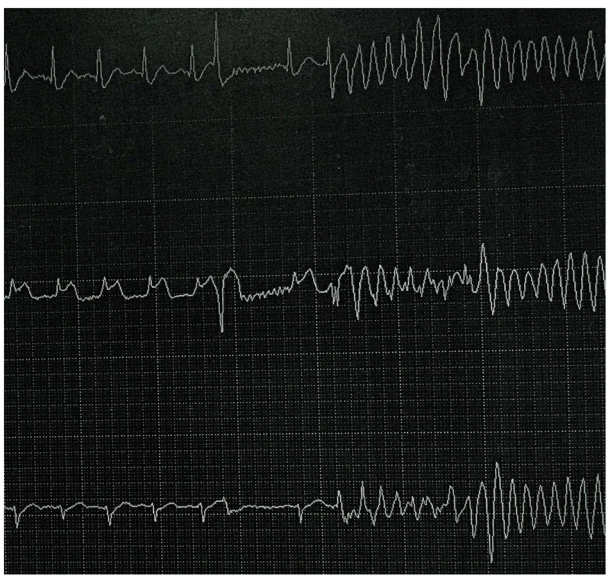

FIGURE 2 | ECG monitor data after cardiac arrest. ST-segment elevation induced TdP and VF after R-on-T phenomenon.

the emergency department. Indications that thyroid storm should be considered included her Burch-Wartofsky score of 50, fever (temperature 37.4°C), tachycardia (heart rate 160 bpm), moderate gastrointestinal-hepatic dysfunction (vomiting and diarrhea), and precipitating event (irregular antithyroid drugs). We reviewed her ECG monitor data after cardiac arrest and found TdP and VF, which suggested that the cause of cardiac arrest was malignant ventricular arrhythmia. Severe thyrotoxicosis has been shown to increase cardiac excitability and induce coronary vasospasm, which may lead to ventricular arrhythmias.

In general, the most common arrhythmia caused by thyrotoxicosis is supraventricular arrhythmia. Malignant ventricular arrhythmias, such as VT or VF, are rare, and usually occur in patients with underlying heart disease. The density of myocardial adrenergic binding sites has been shown to be enhanced by thyroid hormones. In addition, thyroid hormones induce a rate-dependent lengthening of the Purkinje fiber action potential while the ventricular action potential is shortened. These changes can consequently enhance dispersion of myocardial repolarization, facilitate reentry arrhythmia and induce VF. Thyrotoxicosis may also affect myocardial electrical stability: increased excitability related to triggered activity can result in premature ventricular beats that often induce malignant arrhythmias (1). In addition, severe hypokalemia, coronary vasospasm, and prolonged or shortened QT interval may also induce malignant ventricular arrhythmias.

Review of ECG monitor data showed transient ST-segment elevation, indicating that coronary vasospasm should be considered. The patient was a young woman who did not have any risk factors for coronary heart disease. The electrocardiogram showed transient ST-segment elevation without pathological Q wave and neither echocardiogram nor cardiac MRI showed signs of myocardial infarction. The patient's troponin level increased to 0.51 ng/ml after resuscitation, which was considered to be relevant to myocardial injury during cardiopulmonary resuscitation. Therefore, we believed that the ST segment elevation was secondary to coronary spasm and that's why a cardiac catheterization was not performed. Similar cases have been reported in past research (4). Coronary vasospasm associated with thyrotoxicosis must be considered in the patient without any cardiac risk factors. Coronary vasospasm in thyrotoxicosis might result from an amplified sensitivity to norepinephrine and/or a diminished response to nitric

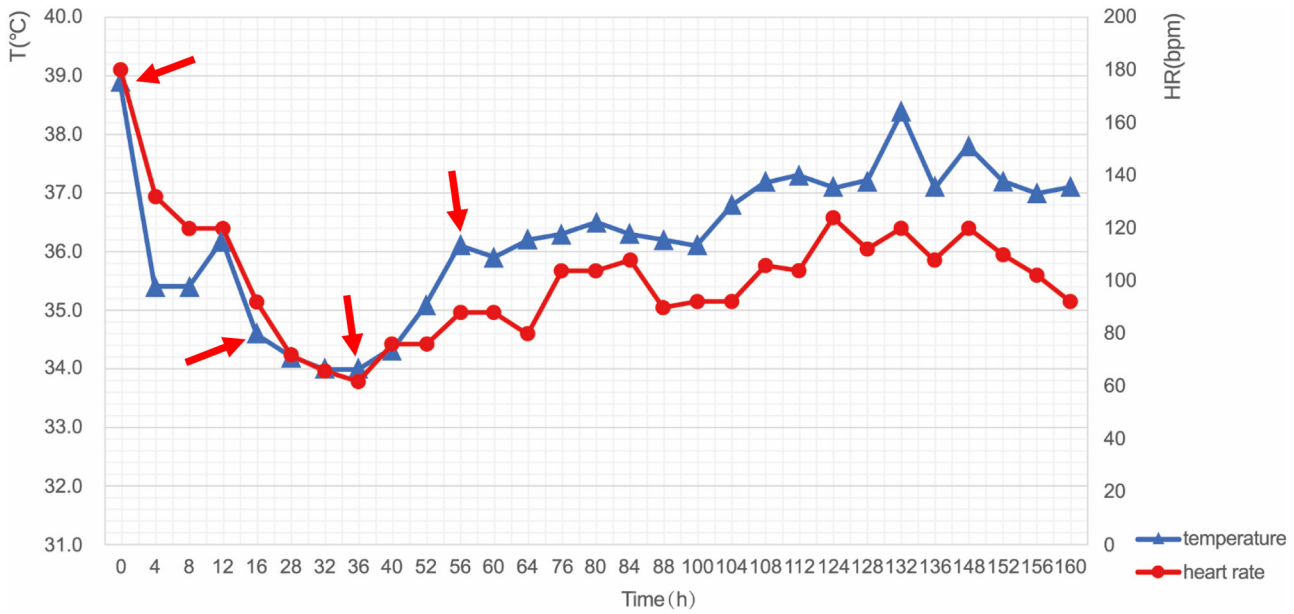

FIGURE 3 | Changes in body temperature and heart rate during TTM. The key moments included: start of cooling (Hour 0, 38.9°C), reaching the target temperature (Hour 12, 34.0°C), start of rewarming (Hour 36, 33.8°C), and end of rewarming (Hour 56, 36.5°C). T, temperature; HR, heart rate; TTM, targeted temperature management.

oxide-mediated vasodilatation in the coronary arteries (5). Hyperthyroidism enhances the sensitivity of the vascular contractile responses to catecholamines, which can induce coronary vasospasm.

On the other hand, the ECG before cardiac arrest showed a mild prolonged QTc interval, which may induce ventricular arrhythmias. In thyrotoxicosis, the activity of cardiac Na^+/K^+ ATPase is increased, resulting in increased intracellular potassium, membrane hyperpolarization, and prolonged repolarization, all of which cause QTc prolongation. However, this theory has not yet been confirmed (6, 7). The utilization of quinolones may also exacerbate the QTc prolongation.

The patient was diagnosed with thyroid storm complicated with coma and hyperpyrexia after resuscitation. Based on the necessity of cooling and protecting neurologic function, we adopted intravascular cooling measures for TTM. High fever often occurs in thyroid storm due to thermoregulatory dysfunction and conventional cooling measures are often ineffective. Fever can increase metabolic rate and adrenergic response, which thus exacerbate multiple organ failure. Since the control of fever may reduce adverse effects on the central nervous system and cardiovascular function, cooling measures must be needed for thyroid storm patients with high fever. The 2016 Japan Thyroid Association and the Japan Endocrine Society (JTA/JES) guidelines recommend aggressive cooling, including use of acetaminophen and surface cooling devices, for patients with thyroid storm, but do not mention invasive intravascular cooling (2).

The neuroprotective efects of TTM occur through the following mechanism (8): (1) reducing brain metabolism and lowering the intracranial pressure; (2) reducing the initiation of brain cell apoptosis and necrosis; (3) decreasing the local release of lactate and excitotoxic compounds; (4) reducing the inflammatory response of brain tissue and systemic inflammatory response; (5) reducing the production of oxygen free radicals; (6) decreasing cerebral capillary permeability. The 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend all comatose adult patients with ROSC after cardiac arrest should start TTM as soon as possible, with a target temperature between 32 and 36°C, then maintain constantly for at least 24 h (9). Recent studies have confirmed that TTM can improve neurological outcome in survivors resuscitated from out-of-hospital cardiac arrest (OHCA) and who remain comatose after ROSC (8, 10). However, whether therapeutic hypothermia has neuroprotective effects in in-hospital cardiac arrest (IHCA) patients is controversial (11). In our case, the patient was treated with advanced intravascular cooling devices in time. Her cerebral performance category (CPC) was one when she was discharged from hospital with good neurologic outcome.

The new intravascular cooling device has favorable effect during the induction phase and maintenance phase of TTM. Compared with conventional cooling methods, the advanced methods with servo-regulated cooling device can provide more rapid, more stable, more accurate therapeutic hypothermia and better control during rewarming to optimize TTM. This is the first time that intravascular cooling technique has been applied to both thyroid storm and cardiac arrest in China.

2017 AHA/ACC/HRS Guideline recommend implantable cardioverter defibrillator (ICD) therapy in patients with ischemic

heart disease, who either survive cardiac arrest due to VF or hemodynamically unstable sustained VT or stable sustained VT, after any reversible cause is excluded (12). Results from a multicenter observational study of patients who underwent ICD suggest that ICD therapy should be strongly recommended for patients with coronary spasm and fatal ventricular arrhythmia even if they had no obstructive coronary artery disease (13). However, the use of ICD in patients with fatal ventricular arrhythmias due to coronary spasm remains controversial because coronary spasm can be controlled by medication (14). Therefore, in the absence of structural heart disease, we consider ICD is not indicated for the patient with ventricular arrhythmias that are due to completely reversible primary disease, but rather that the hyperthyroidism should be controlled actively.

CONCLUSION

We report a case of IHCA caused by thyroid storm. Advanced cooling techniques were performed immediately for TTM. Eventually, the patient was discharged from hospital with good neurologic outcome and controlled hyperthyroidism. This case not only suggests a new method for cooling treatment of thyroid storm but also provides evidence for TTM in patients who were resuscitated from IHCA and remained comatose after ROSC. However, Further wider studies are needed to confirm the results achieved and to obtain a standardization of the treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YF wrote the initial draft for this case and this was corrected and reviewed by HG and QM. YZ, YL, BM, and WS participated in treatment and provided information about the patient. SL provided part of references. All authors have read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.634987/full#supplementary-material

REFERENCES

1. Marrakchi S, Kanoun F, Idriss S, Kammoun I, Kachboura S. Arrhythmia and thyroid dysfunction. *Herz.* (2015) 40:101–9. doi: 10.1007/s00059-014-4123-0
2. Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, et al. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition). *Endocr J.* (2016) 63:1025–64. doi: 10.1507/endocrj.EJ16-0336
3. Jochum S, Brockmann C, Lederle K, Schönberg SO, Diehl SJ. Scharf J. Thyreotoxische Krise - ein Update. *Dtsch Med Wochenschr.* (2008) 133:479–84. doi: 10.1055/s-2008-1046737
4. Menichetti F, Orsini E, Delle DM, Dini FL, Marzilli M. ST-segment elevation acute myocardial infarction associated with hyperthyroidism: beware of coronary spasm! *J Cardiovasc Med.* (2017) 18:798–9. doi: 10.2459/JCM.0b013e328365b8f5
5. Napoli R, Biondi B, Guardasole V, Matarazzo M, Pardo F, Angelini V, et al. Impact of hyperthyroidism and its correction on vascular reactivity in humans. *Circulation.* (2001) 104:3076–80. doi: 10.1161/hc5001.100621
6. Chieng D, Maggiore P, Keren A. Graves thyrotoxicosis and long QT in a young female with out of hospital cardiac arrest. *Heart Lung Circulation.* (2017)26:S117. doi: 10.1016/j.hlc.2017.06.170
7. Kulairi Z, Deol N, Tolly R, Manocha R, Naseer M. QT Prolongation due to Graves' disease. *Case Rep Cardiol.* (2017) 2017:1–3. doi: 10.1155/2017/7612748
8. Cariou A, Payen J, Asehnoune K, Audibert G, Botte A, Brissaud O, et al. Targeted temperature management in the ICU: guidelines from a French expert panel. *Ann Intensive Care.* (2017) 7:70. doi: 10.1186/s13613-017-0294-1
9. Berg KM, Cheng A, Panchal AR, Topjian AA, Aziz K, Bhanji F, et al. Part 7: systems of care: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* (2020) 142(16_suppl.2):S580–604. doi: 10.1161/CIR.0000000000000918
10. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* (2002) 346:549–56. doi: 10.1056/NEJMoa012689
11. Kory P, Fukunaga M, Mathew JP, Singh B, Szainwald L, Mosak J, et al. Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. *Neurocrit Care.* (2012) 16:406–12. doi: 10.1007/s12028-011-9664-y
12. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. *Circulation.* (2018) 138:e210–71. doi: 10.1161/CIR.0000000000000548
13. Matsue Y, Suzuki M, Nishizaki M, Hojo R, Hashimoto Y, Sakurada H, et al. Clinical implications of an implantable cardioverter-defibrillator in patients with vasospastic angina and lethal ventricular arrhythmia. *J Am Coll Cardiol.* (2012) 60:908–13. doi: 10.1016/j.jacc.2012.03.070
14. Morikawa Y, Mizuno Y, Yasue H. Letter by Morikawa et al. regarding article, "Coronary Artery Spasm: a 2009 update". *Circulation.* (2010) 121:e16. doi: 10.1161/CIR.0b013e3181ce1bcc

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Predictive Value of Free Triiodothyronine to Free Thyroxine Ratio in Euthyroid Patients With Myocardial Infarction With Nonobstructive Coronary Arteries

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Background: Thyroid function is closely involved in cardiovascular diseases. The free triiodothyronine (fT3) to free thyroxine (fT4) ratio has been reported as a risk factor for coronary artery disease, but its prognostic value in euthyroid patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) remains unclear.

Methods: A total of 1162 euthyroid patients with MINOCA were enrolled and divided according to decreased tertiles of fT3/fT4 ratio. The study endpoint was major adverse cardiovascular events (MACE), including all-cause death, nonfatal MI, nonfatal stroke, revascularization, and hospitalization for unstable angina or heart failure. Kaplan-Meier, Cox regression, and receiver-operating characteristic analyses were performed.

Results: Patients with lower fT3/fT4 tertile levels had a significantly higher incidence of MACE (10.0%, 13.9%, 18.2%; p=0.005) over the median follow-up of 41.7 months. The risk of MACE increased with the decreasing fT3/fT4 tertiles even after multivariate adjustment (tertile1 as reference, tertile2: HR 1.58, 95% CI: 1.05-2.39, p=0.030; tertile3: HR 2.06, 95% CI: 1.17-3.11, p=0.006). Lower level of fT3/fT4 ratio remained a robust predictor of MACE in overall (HR 1.64, 95% CI: 1.18-2.29, p=0.003) and in subgroups. When adding fT3/fT4 ratio [area under the curve (AUC) 0.61] into the thrombolysis in myocardial infarction (TIMI) risk score (AUC 0.69), the combined model (AUC 0.74) yielded a significant improvement in discrimination for MACE (ΔAUC 0.05, p=0.023).

Conclusions: Low level of fT3/fT4 ratio was strongly associated with a poor prognosis in euthyroid patients with MINOCA. Routine assessment of fT3/fT4 ratio may facilitate risk stratification in this specific population.

Keywords: thyroid function, FT3/FT4 ratio, myocardial infarction with nonobstructive coronary arteries (MINOCA), cardiovascular outcomes (CV outcomes), euthyroid

INTRODUCTION

Acute myocardial infarction (AMI) remains the leading cause of high morbidity and mortality of cardiovascular (CV) diseases worldwide (1). Recently, a distinct population with myocardial infarction with nonobstructive coronary arteries (MINOCA) has been increasingly recognized due to the widespread use of coronary angiography. MINOCA occurs in 5% to 10% of all AMIs and they are younger and more often women compared to those with AMI and obstructive coronary artery disease (CAD) (2–5). It has been found that the prognosis of MINOCA is not trivial and these patients are still at considerable risks for long-term adverse CV events despite optimal secondary prevention treatments (6–10). Thus, it is of necessity to find potential residual risk factors and improve prognosis for MINOCA population.

Thyroid hormones (TH) have been linked with a variety of CV processes. Subclinical or overt thyroid diseases such as hyperthyroidism and hypothyroidism are significantly associated with the development of atherosclerosis and subsequent worse CV outcomes, and the underlying mechanisms may include inflammation, endothelial injury, changes in blood pressure, dyslipidemia, atherogenesis, and cardiac dysfunction (11, 12). Even in euthyroid individuals, minor alterations in TH concentration may lead to increased CV morbidity and mortality (13, 14). Recently, the ratio of free triiodothyronine (fT3) to free thyroxine (fT4) has been suggested as an indirect index reflecting the conversion of T4 to T3 and the peripheral deiodinase activity (15, 16). As reported, the reduction of fT3/fT4 ratio is commonly seen in CV diseases, especially during acute illness (17–19). Meanwhile, lower fT3/fT4 ratio is closely related to unfavorable prognosis in different cohorts with CAD (20–22). However, the predictive value of fT3/fT4 ratio in euthyroid patients with MINOCA remains unclear. Here, we investigated the association between fT3/fT4 ratio and long-term outcomes after MINOCA and explored whether this ratio might provide significant prognostic information in this population.

METHODS

Study Population

This was a single-center, prospective and observational cohort study of patients with MINOCA. From January 2015 to December 2019, a total of 23460 unique AMI patients with coronary angiogram were consecutively hospitalized in Fuwai hospital, including non ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Patients were diagnosed with MINOCA if they met the 4th universal definition of AMI (23) and the coronary angiography did not show a stenosis of ≥50% in epicardial coronary arteries (2). Patients were excluded due to: (1) presence of obstructive CAD (n=21696); (2) prior revascularization (n=312); (3) thrombolytic therapy for STEMI since the coronary lesion may be affected by thrombolysis (n=126); (4) alternate explanations for elevated troponin rather than coronary-related causes (e.g., acute heart failure, myocarditis, pulmonary embolism, takotsubo syndrome, n=46); (5) concomitant with hyperthyroidism (n=7) or hypothyroidism (n=10); (6) lack of detailed baseline data (n=33); (7) lost at follow up (n=68). As a result, 1162 eligible MINOCA patients with euthyroid were enrolled in final analysis (**Figure 1**). Patients were prescribed the evidence-based secondary therapies, including dual anti-platelet therapy (DAPT), statins, β-blocker, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor antagonist (ARB) (24, 25). This study was approved by the Ethics Committee of Fuwai hospital and complied with the Declaration of Helsinki. All enrolled subjects provided the written informed consent.

Data Collection

Patients' demographics, medical history, laboratory test, echocardiographic data and medication were collected and verified from in-person interviews and medical records. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. The thyroid function profiles including fT3, fT4, and TSH were measured using a direct chemiluminescence method (ADVIA Centaur, Siemens, USA). The reference intervals were as follows: fT3, 2.36-4.21 pg/mL; fT4, 0.89-1.76 ng/dL; TSH, 0.55-4.78 μIU/mL. The concentrations of fasting blood glucose (FBG), low density lipoprotein cholesterol (LDL-C), creatinine, and high-sensitive C-reactive protein (hs-CRP) were tested using an automatic biochemistry analyzer. The N-terminal po-B-type natriuretic peptide (NT-proBNP) and

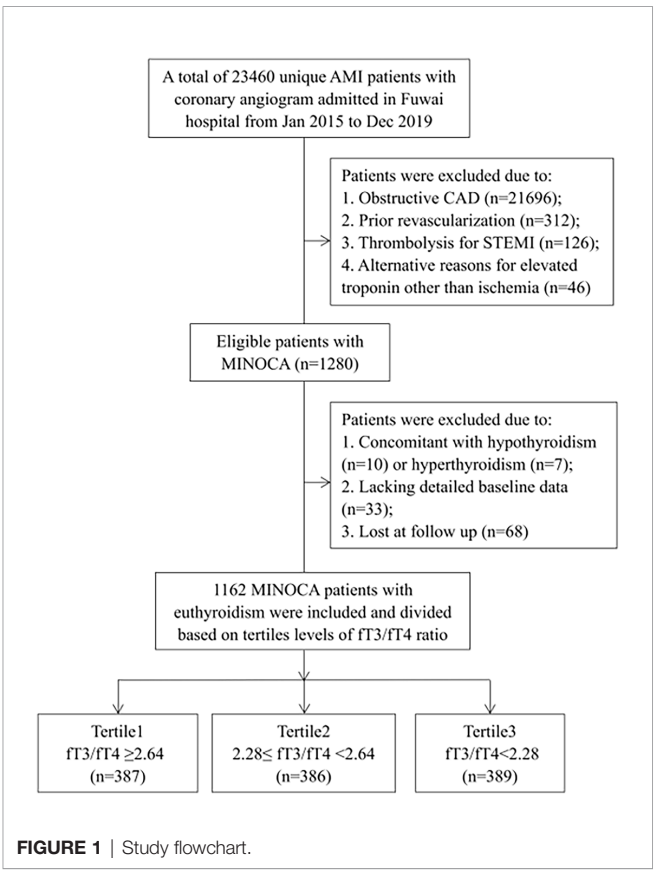

FIGURE 1 | Study flowchart.

cardiac troponin I (TnI) values at admission were recorded. The left ventricular ejection fraction (LVEF) was measured using echocardiography with the biplane Simpson method. The Thrombolysis in Myocardial Infarction (TIMI) risk score was calculated since admission as previously described (26, 27).

Definitions and Outcomes

In this study, euthyroidism was defined as having no history of hyperthyroidism or hypothyroidism and with normal levels of fT3, fT4, and TSH (11). Diabetes was defined with FBG ≥7.0 mmol/L, 2-h plasma glucose ≥11.1 mmol/L, or having a diabetic history (28). Hypertension was defined as repeated blood pressure ≥140/90 mmHg, use of anti-hypertensive drugs, or having a history of hypertension. Dyslipidemia was diagnosed by medical history or having LDL-C≥3.4 mmol/L, high density lipoprotein cholesterol <1.0 mmol/L, or triglyceride≥ 1.7mmol/L (29).

The primary study endpoint was a composite of major adverse cardiovascular events (MACE), including all-cause death, nonfatal MI, revascularization, nonfatal stroke, and hospitalization for unstable angina (UA) or heart failure (HF). The MACE was assessed as time to first event. The secondary endpoints included each component of MACE and the composite "hard" endpoint of death, nonfatal MI, revascularization, and nonfatal stroke. Reinfarction was diagnosed according to the 4th universal definition of MI (23). Revascularization was performed at the operator's discretion due to recurrent ischemia and progression of coronary lesion. Stroke was defined by the presence of neurological dysfunction and vascular brain injury caused by cerebral ischemia or hemorrhage (30). Hospitalization for UA or HF reflected the clinical status and quality of life after AMI. Patients were regularly followed up at clinics or *via* telephone by a team of independent researchers. The endpoints were confirmed by at least two professional cardiologists.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or median with interquartile range for continuous variables and numbers with percentages for categorical variables. Differences were evaluated using the analysis of variance or Kruskal-Wallis H test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Cumulative incidence of MACE among groups were showed by Kaplan-Meier analysis and compared using log-rank test. The univariable and multivariable Cox proportional regression analyses were used to identify association between levels of fT3/fT4 ratio and outcomes. The risk of MACE was adjusted by age and sex and further adjusted by multiple clinically relevant variables, including age, sex, MI classification (NSTEMI or STEMI), hypertension, diabetes and dyslipidemia. The hazard ratio (HR) with 95% confidence interval (CI) were calculated. Discrimination was defined with areas under the curve (AUC) using a receiver-operating characteristic curve (ROC) analysis. The AUC values were categorized as negligible (≤0.55), small (0.56-0.63), moderate (0.64-0.70) or strong (≥0.71) (31), and compared by Delong's test (32) with MedCalc version 11.4 (MedCalc Inc., Ostend, Belgium). A combined risk model incorporating fT3/fT4 ratio into the original TIMI risk score was generated using Cox regression. A two-tailed P<0.05 was considered statistically significant. Unless stated otherwise, most of the analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

Patients were divided according to decreasing tertile levels of fT3/fT4 ratio (tertile1: fT3/fT4 ≥2.64, n=387; tertile2: 2.28≤ fT3/fT4 <2.64, n=386; tertile3: fT3/fT4 <2.28, n=389) (**Figure 1**). As shown in **Table 1**, patients with lower fT3/fT4 tertiles were older and more often female. They had more presence of STEMI and higher prevalence of hypertension and diabetes. They also had higher Killip class, lower LVEF, higher TIMI score, and higher values of FBG, hs-CRP, NT-proBNP and peak TnI. There were no significant differences in BMI, dyslipidemia, prior MI, LDL-C, creatinine levels, and in-hospital medication among the 3 groups. In this regard, patients with lower levels of fT3/fT4 ratio had more baseline risk profiles.

Association Between fT3/fT4 Ratio and Outcomes

During the median follow-up of 41.7 months, 164 euthyroid patients with MINOCA developed MACE (16 died, 40 had recurrent MI, 46 had revascularization, 12 suffered stroke, 70 was hospitalized for UA and 46 hospitalized for HF) (**Table 2**). Patients with lower fT3/fT4 had a significantly higher incidence of MACE (10.0%, 13.9%, 18.2%; p=0.005). The rate of the composite endpoint of death, reinfarction, revascularization, or stroke also increased with decreasing fT3/fT4 tertiles (5.4%, 8.5%, 11.5%; p=0.035). In addition, the Kaplan-Meier analysis showed that the cumulative incidence of MACE was significantly higher in patients with lower fT3/fT4 (log rank p=0.011) (**Figure 2**).

At multivariate Cox analysis, patients with lower fT3/fT4 tertiles had an increased risk of MACE after adjustment for age and sex (tertile 1 as reference; tertile 2: HR 1.69, 95% CI: 1.11-2.56, p=0.014; tertile 3: HR 2.17 95% CI: 1.25-3.26, p=0.001) or after multivariate adjustment (tertile 1 as reference; tertile 2: HR 1.58, 95% CI: 1.05-2.39, p=0.030; tertile 3: HR 2.06, 95% CI: 1.17-3.11, p=0.006) (**Table 3**). Meanwhile, the fT3/fT4 level was significantly correlated with the adjusted risk of MACE (for per 1SD increase in fT3/fT4, HR 0.57, 95% CI: 0.38-0.84, p=0.005) (**Table 3**). At ROC analysis, the cutoff of fT3/fT4 that maximized sensitivity and specificity for MACE prediction in all patients was identified as 2.50. Totally, 535 patients (46.0%) had a ratio above the cutoff value. The incidence of MACE was 11.3% and 17.3% (p<0.001) in patients with fT3/fT4 above and below the cutoff, respectively (HR 1.64, 95% CI: 1.18-2.29, p=0.003) (**Figure 3**). At subgroup analysis, lower fT3/fT4 (<2.50) remained a robust risk factor in subsets of patients stratified by sex, age, BMI, MI classification, history of hypertension, diabetes, and dyslipidemia (all p<0.05) (**Figure 3**), suggesting that the

TABLE 1 | Baseline characteristics in MINOCA patients based on tertiles of fT3/fT4 ratio.

Variable	Tertile1 (n=387)	Tertile2 (n=386)	Tertile3 (n=389)	p value
Male, n(%)	300 (77.5%)	291 (75.3%)	265 (68.1%)	<0.001
Age, years	54.0±12.3	55.1±11.6	57.8±11.1	<0.001
BMI, kg/m^2	25.2±3.5	25.4±3.8	25.8±3.9	0.252
STEMI, n(%)	128 (33.0%)	155 (40.1%)	173 (44.4%)	0.022
Past history				
Hypertension	195 (50.3%)	204 (52.8%)	220 (56.5%)	0.035
Diabetes	51 (13.1%)	57 (14.7%)	75 (19.2%)	0.043
Dyslipidemia	231 (59.6%)	225 (58.2%)	217 (55.7%)	0.172
Previous MI	18 (4.6%)	20 (5.1%)	20 (5.1%)	0.931
Killip class≥2, n(%)	21 (5.4%)	29 (7.5%)	36 (9.2%)	0.036
LVEF, %	61.2±6.0	60.9±6.0	59.4±7.5	<0.001
TIMI risk score	3.2±1.1	3.4±1.2	3.7±1.5	0.002
Laboratory test				
fT3, pg/mL	3.03±0.36	2.87±0.31	2.56±0.39	<0.001
fT4, ng/dL	1.04±0.13	1.17±0.13	1.28±0.19	<0.001
fT3/fT4 ratio	2.93±0.27	2.46±0.10	2.01±0.21	<0.001
TSH, μIU/mL	2.13±1.51	2.14±1.59	2.08±1.33	0.162
FBG, mmol/L	5.53±1.55	5.60±1.51	5.95±1.92	0.001
LDL-C, mmol/L	2.28±0.78	2.30±0.73	2.29±0.76	0.901
Creatinine, μmol/L	78.9±14.5	79.9±15.2	81.4±18.7	0.566
hs-CRP, mg/L	1.98 (0.95, 4.40)	2.09 (1.07, 5.17)	2.86 (1.17, 8.40)	<0.001
NT-proBNP, pg/mL	302 (107, 653)	351 (118, 695)	403 (121, 786)	0.023
TnI, ng/mL	1.31 (0.32, 3.73)	1.52 (0.41, 4.85)	1.76 (0.72, 5.13)	0.011
In-hospital medication				
DAPT	353 (91.2%)	364 (94.3%)	361 (92.8%)	0.253
Statin	372 (96.1%)	368 (95.3%)	373 (95.8%)	0.856
ACEI or ARB	243 (62.7%)	238 (61.6%)	263 (67.6%)	0.186
Beta-blocker	269 (69.5%)	284 (73.5%)	295 (75.8%)	0.133

Patients were divided according to decreasing tertile levels of fT3/fT4 ratio (Tertile1: fT3/fT4≥2.64, Tertile2: 2.28≤ fT3/fT4 <2.64, Tertile3: fT3/fT4 <2.28). BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; TIMI, Thrombolysis in Myocardial Infarction; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TnI, Troponin I; DAPT, dual anti-platelet therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist.

TABLE 2 | Clinical outcomes in MINOCA patients based on tertiles of fT3/fT4 ratio.

CV outcomes	Tertile1 (n=387)	Tertile2 (n=386)	Tertile3 (n=389)	p value
MACE	39 (10.0%)	54 (13.9%)	71 (18.2%)	0.005
Death, nonfatal MI, stroke or revascularization	21 (5.4%)	33 (8.5%)	45 (11.5%)	0.035
All-cause death	3 (0.7%)	3 (0.7%)	10 (2.5%)	0.047
Nonfatal MI	9 (2.3%)	12 (3.1%)	19 (4.8%)	0.072
Revascularization	7 (1.8%)	18 (4.6%)	21 (5.3%)	0.031
Nonfatal stroke	4 (1.0%)	3 (0.7%)	5 (1.2%)	0.359
Hospitalization for UA	14 (3.6%)	24 (6.2%)	32 (8.2%)	0.018
Hospitalization for HF	12 (3.1%)	10 (2.6%)	24 (6.1%)	0.022

Tertile1: fT3/fT4≥2.64, Tertile2: 2.28≤ fT3/fT4 <2.64, Tertile3: fT3/fT4 <2.28. MACE, major adverse cardiovascular events; MI, myocardial infarction; UA, unstable angina; HF, heart failure.

prognostic effect of fT3/fT4 was not affected by clinically relevant demographic or traditional risk factors.

Predictive Value of fT3/fT4 Ratio for MACE

The ROC analysis confirmed the value of fT3/fT4 ratio for MACE prediction (AUC 0.61, 95% CI: 0.55-0.66, p<0.001) (**Figure 4**). Meanwhile, the TIMI risk score showed a moderate discrimination for MACE (AUC 0.69, 95% CI: 0.64-0.73, p<0.001). When adding fT3/fT4 ratio to the original TIMI risk score using Cox regression, the combined model yielded a significant improvement in risk prediction (AUC increased from 0.69 to 0.74, ΔAUC 0.05, p=0.023 by DeLong's test).

DISCUSSION

The present study, for the first time, verified the clinical significance of the fT3/fT4 ratio in euthyroid patients with MINOCA, and found that decreased fT3/fT4 ratio was independently associated with an increased risk of long-term MACE. Adding fT3/fT4 ratio to traditional risk score further improved the outcome prediction. Our data support the utility of fT3/fT4 ratio as a prognostic marker for risk stratification in contemporary real-world management of MINOCA.

MINOCA represents a distinct clinical entity with multiple underlying mechanisms, including plaque rupture or erosion,

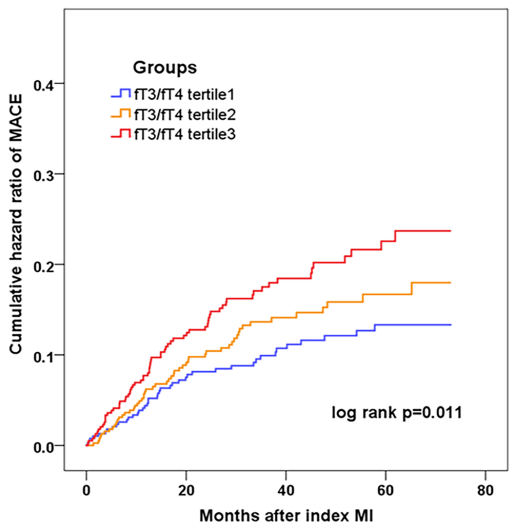

FIGURE 2 | Cumulative hazard ratio of MACE in MINOCA patients based on tertile levels of fT3/fT4 ratio.

thromboembolism, spasm, spontaneous dissection, microvascular dysfunction and supply/demand mismatch. Some non-ischemic diseases such as myocarditis may also mimic the presentation of MINOCA (5). More recently, however, it has been used to primarily describe patients with coronary-related ischemia. We adopted this criteria and established a long-term cohort with relatively large sample size. A systematic review estimated the prevalence of MINOCA to be 6% in all AMIs (4), which is close to the prevalence of 5.1% in our study. As reported, nearly one-third of MINOCA would present with STEMI. Patients with MINOCA were more likely to be younger, female, and had fewer comorbidities compared to patients with AMI and obstructive CAD (4). We described the clinical profiles of MINOCA across the fT3/fT4 ratio tertile levels. Meanwhile, we found that the course of MINOCA was not benign. Over the median follow-up of 3.5 years, about 1.4% of MINOCA patients died and 14.1% of them developed MACE. Similarly, previous studies showed that these patients were still at considerable risks for long-term mortality and CV events after MINOCA (4–10). Therefore, the prognosis of MINOCA should be more emphasized and it is necessary to find potential residual risk factors and further improve healthcare for this population.

Thyroid function has a complex relationship with CV physiology (11, 12). Overt thyroid disease or even subclinical thyroid dysfunction can result in alterations in cardiac output, heart rate, vascular resistance, and blood pressure (11). There are also significant changes in atherosclerotic risk factors, including dyslipidemia, hypertension, hypercoagulation, arterial stiffness, and LV dysfunction (12), which may markedly increase CV morbidity and mortality. In addition, euthyroid patients with CV disease may also have alterations in TH concentrations that are associated with worse outcomes (13, 14). TH mainly consist of iodinated T3 and T4 and the free forms of fT3 and fT4. Previous studies have verified the prognostic values of free TH in euthyroid patients with CAD. Lower level of fT3 is commonly seen in AMI, which is not only associated with the severity of myocardial injury and LV dysfunction, but also predicts poor prognosis after AMI (33–35). Meanwhile, high fT4 level is also a potential CV risk factor. Several population-based studies have confirmed that higher fT4 level is independently correlated with atherosclerosis (36) and increased risks of MACE even in euthyroid subjects (37–39). Recent evidence suggest that the combined evaluation of fT3 and fT4 (fT3/fT4 ratio) may serve as a reasonable index of metabolic variation of TH compared with fT3 or fT4 alone and may thus provide a more accurate outcome prediction in different clinical settings. A British cohort study found that lower fT3/fT4 ratio was associated with frailty and long-term mortality in hospitalized older patients (17). The fT3/fT4 ratio was still a robust risk factor for cardiac dysfunction and 1-year mortality in dilated cardiomyopathy (18). In terms of CAD, the fT3/fT4 ratio was reported to be inversely associated with an increased risk of death in euthyroid patients with ACS (19–21). This is not only the case in acute setting, but also in the longer term after recovery from ACS. Another study also indicated that low fT3/fT4 ratio was related to long-term MACE in euthyroid patients with three-vessel disease (22).

In line with previous results, we found that the incidence and adjusted risk of MACE significantly increased with the decreasing tertiles of fT3/fT4 ratio. The fT3/fT4 ratio was inversely correlated with risk of MACE. Meanwhile, lower fT3/fT4 ratio defined by the cut-off of 2.50 remained an independent

TABLE 3 | Association between tertile levels of fT3/fT4 ratio and the risk of MACE.

Group	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
fT3/fT4 ratio, per 1SD increase	0.49 (0.33-0.71)	<0.001	0.53 (0.36-0.77)	0.001	0.57 (0.38-0.84)	0.005
Tertile 1	1 (reference)	…	1 (reference)	…	1 (reference)	…
Tertile 2	1.71 (1.12-2.61)	0.013	1.69 (1.11-2.56)	0.014	1.58 (1.05-2.39)	0.030
Tertile 3	2.22 (1.28-3.33)	<0.001	2.17 (1.25-3.26)	0.001	2.06 (1.17-3.11)	0.006

Tertile1: fT3/fT4≥2.64, Tertile2: 2.28≤ fT3/fT4 <2.64, Tertile3: fT3/fT4 <2.28. Model 1 included age and sex. Model 2 included age, sex, MI classification (NSTEM or STEMI), hypertension, diabetes and dyslipidemia in the multivariate Cox analysis. fT3, free triiodothyronine; fT4, free thyroxine; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

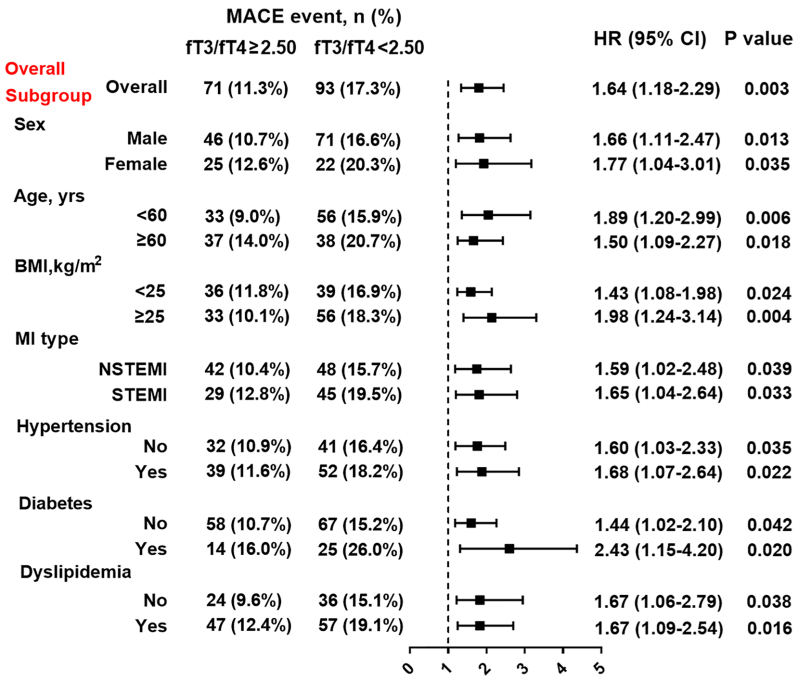

FIGURE 3 | Association between fT3/fT4 ratio and the risk of MACE in overall and subgroups. Subgroup analysis showing the incidence and risk of MACE in patients with fT3/fT4 ratio above and below the cut-off value of 2.50, which was identified with maximum Youden index in all MINOCA patients for MACE prediction. Hazard ratio (HR) was calculated by univariate Cox regression analysis. Vertical dotted line indicated the HR value of 1. BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; NSTEMI; non-ST-segment elevation myocardial infarction, CI, confidence interval.

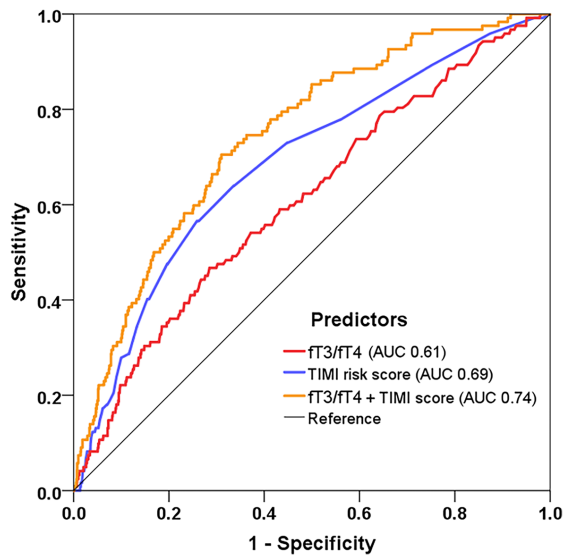

FIGURE 4 | Model improvement in predicting MACE. Receiver operating characteristic curves showing predictive value of the fT3/fT4 ratio, TIMI risk score, and the combined model incorporating fT3/fT4 and TIMI score using Cox regression. fT3, free triiodothyronine; fT4, free thyroxine; TIMI, Thrombolysis in Myocardial Infarction.

predictor of MACE in overall and in subgroups. Further, fT3/fT4 ratio provided an incremental predictive value of MACE when added to the TIMI risk score. These results extended the utility of fT3/fT4 ratio to euthyroid patients with MINOCA, suggesting that it might be reasonable to use the ratio as a prognostic marker in daily clinical practice for this specific population.

Actually, both T3 and T4 constitute the active forms of TH, but the majority of T3 is converted from T4 in the process of peripheral deiodination. Moreover, T3 has a higher affinity than T4 for TH receptors in myocardium and vascular tissue, and exerts various bioactive effects on CV system *via* nongenomic and genomic approaches (40). Thus, the conversion of T4 to T3 is critical for the production of circulating T3 and the TH actions on CV function. Decrease in fT3/fT4 ratio reflects the disturbance of T4 converting to T3, and is commonly seen in acute or chronic processes of myocardial injury as cardiac disease itself may lead to alterations in TH concentrations (17–19). Lower fT3/fT4 ratio, in turn, have deleterious effects on CV systems including reduced cardiac contractility and increased vascular resistance (12–14). Other mechanisms such as cardiac dysfunction, inflammation and oxidative stress have also been proposed (41, 42). Several studies, along with ours, have found that CAD patients with lower fT3/fT4 ratio tended to have more severe myocardial injury (e.g., higher TnI), more impaired LV mechanics (e.g., lower LVEF, higher NT-proBNP) and higher plasma inflammatory markers (e.g., higher hs-CRP) (20–22). All

these changes may finally contribute to the increased risks of CV events. However, the pathophysiological and therapeutic relevance of thyroid dysregulation in euthyroid patients after AMI are far from elucidated. Future studies are warranted to confirm our findings and to better understand the biological mechanisms underlying this prognostic association.

LIMITATION

Some limitations should be mentioned. First, the percentage of women was relatively low in our cohort, possibly due to the large proportion of men in all AMIs treated in our center and a lower rate for women to receive coronary angiography. Given the potential selection bias in single-center studies, future nationwide registry cohorts of MINOCA are warranted to validated our findings. Second, we did not capture and record the exact mechanism for every MINOCA patient. The association between etiology of MINOCA and outcomes should be further investigated. Third, despite multivariate adjustment and subgroup analyses were performed, there might be other unmeasured confounders that may affect the prognosis. Fourth, the fT3/fT4 ratio was only measured at baseline, and the follow-up levels of fT3/fT4 ratio may also be clinically significant.

CONCLUSION

Decreased fT3/fT4 ratio was an independent predictor of poor outcomes in euthyroid patients with MINOCA. Routine assessment of fT3/fT4 ratio might provide significant prognostic value and facilitate risk stratification and decision making in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Fuwai hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG conceived and designed the study. SG, WM, SH and XL performed data analysis and interpretation. SG drafted the manuscript. MY reviewed and gave final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol* (2017) 70(1):1–25. doi: 10.1016/j.jacc.2017.04.052
2. Beltrame JF. Assessing Patients With Myocardial Infarction and Nonobstructed Coronary Arteries (MINOCA). *J Intern Med* (2013) 273 (2):182–85. doi: 10.1111/j.1365-2796.2012.02591.x
3. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, et al. ESC Working Group Position Paper on Myocardial Infarction With Non-Obstructive Coronary Arteries. *Eur Heart J* (2017) 38(3):143–53. doi: 10.1093/eurheartj/ehw149
4. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries. *Circulation* (2015) 131(10):861–70. doi: 10.1161/CIRCULATIONAHA.114.011201
5. Niccoli G, Scalone G, Crea F. Acute Myocardial Infarction With No Obstructive Coronary Atherosclerosis: Mechanisms and Management. *Eur Heart J* (2015) 36(8):475–81. doi: 10.1093/eurheartj/ehu469
6. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, et al. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. *J Am Heart Assoc* (2018) 7(13):e009174. doi: 10.1161/JAHA.118.009174
7. Bainey KR, Welsh RC, Alemayehu W, Westerhout CM, Traboulsi D, Anderson T, et al. Population-Level Incidence and Outcomes of Myocardial Infarction With Non-Obstructive Coronary Arteries (MINOCA): Insights From the Alberta Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies (COAPT) Study. *Int J Cardiol* (2018) 264:12–7. doi: 10.1016/j.ijcard.2018.04.004
8. Andersson HB, Pedersen F, Engstrøm T, Helqvist S, Jensen MK, Jørgensen E, et al. Long-Term Survival and Causes of Death in Patients With ST-Elevation Acute Coronary Syndrome Without Obstructive Coronary Artery Disease. *Eur Heart J* (2018) 39(2):102–10. doi: 10.1093/eurheartj/ehx491
9. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, et al. Prognosis of Patients With Non-ST-Segment-Elevation Myocardial Infarction and Nonobstructive Coronary Artery Disease: Propensity-Matched Analysis From the Acute Catheterization and Urgent Intervention Triage Strategy Trial. *Circ Cardiovasc Interv* (2014) 7(3):285–93. doi: 10.1161/CIRCINTERVENTIONS.113.000606
10. Abdu FA, Liu L, Mohammed AQ, Luo Y, Xu S, Auckle R, et al. Myocardial Infarction With Non-Obstructive Coronary Arteries (MINOCA) in Chinese Patients: Clinical Features, Treatment and 1 Year Follow-Up. *Int J Cardiol* (2019) 287:27–31. doi: 10.1016/j.ijcard.2019.02.036
11. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol* (2018) 71:1781–96. doi: 10.1016/j.jacc.2018.02.045
12. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S, et al. Thyroid Hormones and Cardiovascular Disease. *Nat Rev Cardiol* (2017) 14:39–55. doi: 10.1038/nrcardio.2016.174

13. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid Function in Critically Ill Patients. *Lancet Diabetes Endocrinol* (2015) 3:816–25. doi: 10.1016/S2213-8587(15)00225-9
14. Pingitore A, Chen Y, Gerdes AM, Iervasi G. Acute Myocardial Infarction and Thyroid Function: New Pathophysiological and Therapeutic Perspectives. *Ann Med* (2012) 44(8):745–57. doi: 10.3109/07853890.2011.573501
15. Maia AL, Goemann IM, Meyer EL, Wajner SM. Deiodinases: The Balance of Thyroid Hormone: Type 1 Iodothyronine Deiodinase in Human Physiology and Disease. *J Endocrinol* (2011) 209(3):283–97. doi: 10.1530/JOE-10-0481
16. Bassols J, Prats-Puig A, Soriano-Rodríguez P, García-González MM, Reid J, Martínez-Pascual M, et al. Lower Free Thyroxin Associates With a Less Favorable Metabolic Phenotype in Healthy Pregnant Women. *J Clin Endocrinol Metab* (2011) 96(12):3717–23. doi: 10.1210/jc.2011-1784
17. Pasqualetti G, Calsolaro V, Bernardini S, Linsalata G, Bigazzi R, Caraccio N, et al. Degree of Peripheral Thyroxin Deiodination, Frailty, and Long-Term Survival in Hospitalized Older Patients. *J Clin Endocrinol Metab* (2018) 103 (5):1867–76. doi: 10.1210/jc.2017-02149
18. Kozdag G, Ural D, Vural A, Agacdiken A, Kahraman G, Sahin T, et al. Relation Between Free Triiodothyronine/Free Thyroxine Ratio, Echocardiographic Parameters and Mortality in Dilated Cardiomyopathy. *Eur J Heart Fail* (2005) 7(1):113–8. doi: 10.1016/j.ejheart.2004.04.016
19. Lamprou V, Varvarousis D, Polytarchou K, Varvarousi G, Xanthos T. The Role of Thyroid Hormones in Acute Coronary Syndromes: Prognostic Value of Alterations in Thyroid Hormones. *Clin Cardiol* (2017) 40(8):528–33. doi: 10.1002/clc.22689
20. Yu T, Tian C, Song J, He D, Wu J, Wen Z, et al. Value of the Ft3/Ft4 Ratio and its Combination With the GRACE Risk Score in Predicting the Prognosis in Euthyroid Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention: A Prospective Cohort Study. *BMC Cardiovasc Disord* (2018) 18(1):181. doi: 10.1186/s12872-018-0916-z
21. Brozaitiene J, Mickuviene N, Podlipskyte A, Burkauskas J, Bunevicius R. Relationship and Prognostic Importance of Thyroid Hormone and N-Terminal Pro-B-Type Natriuretic Peptide for Patients After Acute Coronary Syndromes: A Longitudinal Observational Study. *BMC Cardiovasc Disord* (2016) 16:45. doi: 10.1186/s12872-016-0226-2
22. Yuan D, Zhang C, Jia S, Liu Y, Jiang L, Xu L, et al. Predictive Value of Free Triiodothyronine (FT3) to Free Thyroxine (FT4) Ratio in Long-Term Outcomes of Euthyroid Patients With Three-Vessel Coronary Artery Disease. *Nutr Metab Cardiovasc Dis* (2021) 31(2):579–86. doi: 10.1016/j.numecd.2020.10.011
23. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* (2018) 72:2231–64. doi: 10.1016/j.jacc.2018.08.1038
24. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* (2016) 37:267–315. doi: 10.1093/eurheartj/ehv320
25. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393
26. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI Risk Score for Unstable Angina/non-ST Elevation MI: A Method for Prognostication and Therapeutic Decision Making. *JAMA* (2000) 284:835–42. doi: 10.1001/jama.284.7.835
27. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI Risk Score for ST-Elevation Myocardial Infarction: A Convenient, Bedside, Clinical Score for Risk Assessment at Presentation: An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial Substudy. *Circulation* (2000) 102:2031–7. doi: 10.1161/01.cir.102.17.2031
28. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* (2018) 41:S13–27. doi: 10.2337/dc18-S002
29. Rabar S, Harker M, O'Flynn N, Wierzbicki ASGuideline Development Group. Lipid Modification and Cardiovascular Risk Assessment for the Primary and Secondary Prevention of Cardiovascular Disease: Summary of Updated NICE Guidance. *BMJ* (2014) 349:g4356. doi: 10.1136/bmj.g4356
30. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *J Am Coll Cardiol* (2018) 71:1021–34. doi: 10.1016/j.jacc.2017.12.048
31. Ma H, Bandos AI, Rockette HE, Gur D. On Use of Partial Area Under the ROC Curve for Evaluation of Diagnostic Performance. *Stat Med* (2013) 32:3449–58. doi: 10.1002/sim.5777
32. Delong ER, Delong DM, ClarkePearson DL. Comparing the Areas Under Two or More Correlated Receiver Operating Characteristic Curves: A Non-Parametric Approach. *Biometrics* (1988) 44:837–45. doi: 10.2307/2531595
33. Wang WY, Tang YD, Yang M, Cui C, Mu M, Qian J, et al. Free Triiodothyronine Level Indicates the Degree of Myocardial Injury in Patients With Acute ST-Elevation Myocardial Infarction. *Chin Med J (Engl)* (2013) 126:3926–9. doi: 10.3760/cma.j.issn.0366-6999.20130087
34. Jankauskienė E, Orda P, Barauskienė G, Mickuvienė N, Brožaitienė J, Vaškelytė JJ, et al. Relationship Between Left Ventricular Mechanics and Low Free Triiodothyronine Levels After Myocardial Infarction: A Prospective Study. *Intern Emerg Med* (2016) 11:391–8. doi: 10.1007/s11739-015-1370-x
35. Wang B, Liu S, Li L, Yao Q, Song R, Shao X, et al. Non-Thyroidal Illness Syndrome in Patients With Cardiovascular Diseases: A Systematic Review and Meta-Analysis. *Int J Cardiol* (2017) 226:1–10. doi: 10.1016/j.ijcard.2016.10.039
36. Bano A, Chaker L, Mattace-Raso FUS, van der Lugt A, Ikram MA, Franco OH, et al. Thyroid Function and the Risk of Atherosclerotic Cardiovascular Morbidity and Mortality: The Rotterdam Study. *Circ Res* (2017) 121 (12):1392–400. doi: 10.1161/CIRCRESAHA.117.311603
37. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, et al. Thyroid Function and Sudden Cardiac Death: A Prospective Population-Based Cohort Study. *Circulation* (2016) 134(10):713–22. doi: 10.1161/CIRCULATIONAHA.115.020789
38. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE, et al. Higher Free Thyroxine Levels are Associated With All-Cause Mortality in Euthyroid Older Men: The Health In Men Study. *Eur J Endocrinol* (2013) 169 (4):401–8. doi: 10.1530/EJE-13-0306
39. Golledge J, Hankey GJ, Almeida OP, Flicker L, Norman PE, Yeap BB. Plasma Free Thyroxine in the Upper Quartile is Associated With an Increased Incidence of Major Cardiovascular Events in Older Men That Do Not Have Thyroid Dysfunction According to Conventional Criteria. *Int J Cardiol* (2018) 254:316–21. doi: 10.1016/j.ijcard.2017.10.100
40. Sandler B, Webb P, Apriletti JW, Huber BR, Togashi M, Cunha Lima ST, et al. Thyroxine-Thyroid Hormone Receptor Interactions. *J Biol Chem* (2004) 279 (53):55801–8. doi: 10.1074/jbc.M410124200
41. Mancini A, Di Segni C, Raimondo S, Olivieri G, Silvestrini A, Meucci E, et al. Thyroid Hormones, Oxidative Stress, and Inflammation. *Mediators Inflammation* (2016) 2016:6757154. doi: 10.1155/2016/6757154
42. Galli E, Pingitore A, Iervasi G. The Role of Thyroid Hormone in the Pathophysiology of Heart Failure: Clinical Evidence. *Heart Fail Rev* (2010) 15(2):155–69. doi: 10.1007/s10741-008-9126-6

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frontiers in Endocrinology

MINI REVIEW
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Crash Landing of Thyroid Storm: A Case Report and Review of the Role of Extra-Corporeal Systems

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Thyroid storm is a rare but life-threatening endocrinological emergency with significant mortality ranging from 10-30% with multi-organ involvement and failure. In view of the rarity of this condition and efficacy of established first line medical treatment, use of extra-corporeal treatments are uncommon, not well-studied, and its available evidence exists only from case reports and case series. We describe a 28-year-old man who presented with an out-of-hospital cardiac arrest secondary to thyroid storm. Despite conventional first-line pharmacotherapy, he developed cardiogenic shock and circulatory collapse with intravenous esmolol infusion, as well as multi-organ failure. He required therapeutic plasma exchange, concurrent renal replacement therapy, and veno-arterial extra-corporeal membrane oxygenation, one of the few reported cases in the literature. While there was clinical stabilization and improvement in tri-iodothyronine levels on three extra-corporeal systems, he suffered irreversible hypoxic-ischemic brain injury. We reviewed the use of early therapeutic plasma exchange and extra-corporeal membrane oxygenation, as well as the development of other novel extra-corporeal modalities when conventional pharmacotherapy is unsuccessful or contraindicated. This case also highlights the complexities in the management of thyroid storm, calling for caution with beta-blockade use in thyrocardiac disease, with close monitoring and prompt organ support.

Keywords: thyroid storm, multi-organ failure, extra-corporeal membrane oxygenation, therapeutic plasma exchange, continuous renal replacement therapy, out-of-hospital cardiac arrest

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INTRODUCTION

Thyroid storm (TS) is a life-threatening exacerbation of the hyperthyroid state characterized by multi-organ dysfunction of the cardiovascular, thermoregulatory, gastrointestinal-hepatic and central nervous systems. While the incidence among hospitalized patients is estimated to be low at 1-2% (1), the overall mortality is 10-30% (2), with a 12-fold increase in mortality compared to individuals with thyrotoxicosis (3). The diagnosis of TS is additionally challenging due to the absence of specific clinical or laboratory findings. Early recognition of this condition is key, as it

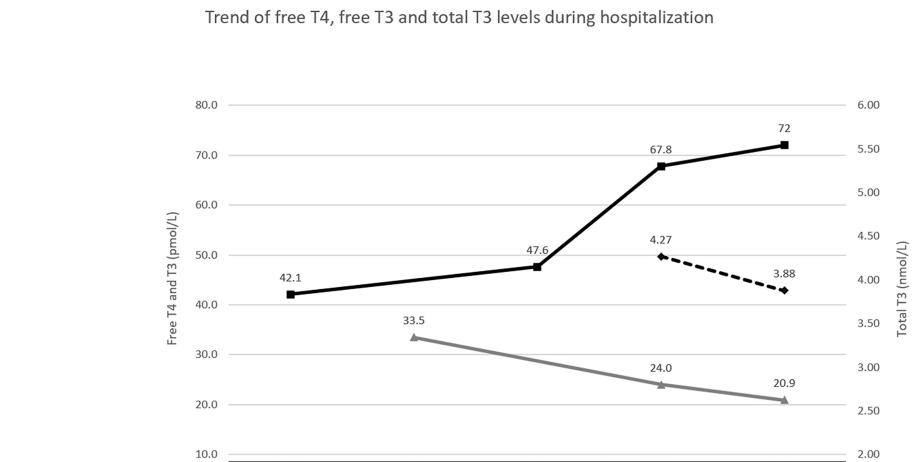
allows for prompt and specific treatment, as well as early identification of organ dysfunction with initiation of supportive measures in the intensive care setting if required.

We present a case of TS in a young patient with undiagnosed Graves' disease, presenting with an out-of-hospital cardiac arrest. Initially hemodynamically stable following return of spontaneous circulation, he developed circulatory collapse after intravenous esmolol infusion, initiated for control of tachycardia. There was consequent multi-organ failure which contraindicated the use of standard anti-thyroid drug therapy. He required three extra-corporeal systems of continuous renal replacement therapy (CRRT), veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) and therapeutic plasma exchange (TPE) for stabilization, one of the few reported cases in the literature.

CASE DESCRIPTION

A 28-year-old male presented with an out-of-hospital ventricular fibrillation (VF) arrest, preceded by an acute respiratory illness. There was return of spontaneous circulation after 60 minutes of resuscitation with bystander cardiopulmonary resuscitation and external defibrillation by paramedics. In the Emergency Department, he was febrile at 40.5 degrees Celsius, hypertensive with a blood pressure of 146/83mmHg and tachycardic with a heart rate of 155 beats per minute. Physical examination was unremarkable, except for a Glasgow Coma Scale of 3. No goiter was seen on examination. Corroborative history from his family confirmed symptoms of heat intolerance, loss of weight, hand tremors and palpitations in the preceding two months, as well as a maternal history of Graves' thyrotoxicosis.

Initial investigations showed elevated inflammatory markers, mixed respiratory and metabolic acidosis, raised troponin I, but with normal electrolyte levels. Electrocardiogram confirmed sinus tachycardia. Chest radiograph showed prominent pulmonary vasculature without evidence of pneumonia. Point-of-care echocardiogram showed impaired left ventricular systolic function without other obvious abnormalities; the marked sinus tachycardia precluded accurate estimation of the left ventricular ejection fraction (LVEF). Computed tomographic (CT) scan of the brain was normal, and urine drug screen was negative. A coronary angiogram performed was normal, and a provisional diagnosis of acute myocarditis was made. Thyroid function test, sent as part of investigations for myocarditis, showed thyrotoxicosis with an elevated serum free thyroxine (FT4) level of 42.1pmol/L (reference range: 8.0-16.0pmol/L) and a suppressed serum thyroid stimulating hormone (TSH) at <0.01mIU/L (reference range: 0.45-4.50mIU/L) (**Figure 1**) –



	30/11/2019 16:30	30/11/2019 19:47	01/12/2019 03:33	01/12/2019 09:36	02/12/2019 02:37
Free T4 (normal: 8.0-16.0pmol/L)	42.1		47.6	67.8	72
Free T3 (normal: 3.5-6.0pmol/L)		33.5		24.0	20.9
Total T3 (normal: 0.90-2.60nmol/L)				4.27	3.88
TSH (normal: 0.45-4.50mIU/L) (Not charted)	<0.01				
Pharmacotherapy for Thyroid Storm		NG PTU 200mg Q4H; IV NaI 1g Q12H; IV hydrocortisone 100mg Q6H; IV esmolol infusion started at 25mcg/kg/min		Stopped PTU, NaI Started NG cholestyramine 4g Q6H	Started NG MMZ 20mg OM Started NG Lugols Iodine 65mg TDS
Key Clinical Events	Resuscitation with intubation; coronary angiogram	Circulatory collapse; Started vasopressor; Started VA-ECMO;		Started CRRT ; Started TPE #1	Started TPE #2

FIGURE 1 | Timeline of key clinical events. T4, thyroxine; T3, tri-iodothyronine; TSH, thyroid-stimulating hormone; NG, nasogastric; IV, intravenous; PTU, propylthiouracil; NaI, sodium iodide; VA-ECMO, veno-arterial extra-corporeal membrane oxygenation; CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; MMZ, methimazole.

our patient had thyroid storm complicated by thyrocardiac disease, with a Burch-Wartofsky score of 105. His thyroid-stimulating hormone receptor antibody eventually returned elevated at >40IU/L (normal ≤2.0IU/L), confirming underlying Graves' disease.

Treatment was promptly initiated with nasogastric propylthiouracil, intravenous sodium iodide and hydrocortisone (**Figure 1**). Temperature was controlled with a cooling blanket. Judicious low dose esmolol infusion was commenced at 25mcg/kg/min to manage the tachycardia. This was followed shortly by a pulseless electrical activity arrest. Despite a short downtime of three minutes and prompt cessation of beta-blockade, he required high doses of noradrenaline and vasopressin thereafter. He remained persistently hypotensive with maximal dual vasopressor support, and was initiated on VA-ECMO support (**Figure 2**).

Further investigations revealed worsening transaminitis and anuric acute kidney injury, requiring CRRT. Transthoracic echocardiogram showed severe left ventricular systolic dysfunction with estimated LVEF of 10%. Pharmacological options were now limited to cholestyramine and hydrocortisone. We decided to institute TPE; with the first cycle performed on day 2 of admission, with 2.5L of albumin and 0.5L of saline (**Figure 1**). After the first cycle, his vasopressor support reduced significantly (only requiring low dose noradrenaline infusion) and his tri-iodothyronine (T3) levels improved (**Figure 1**). As his FT4 continued to worsen, nasogastric methimazole and Lugol's iodine were cautiously started, along with second TPE cycle, on the third day.

His pupils were noted to be fixed and dilated with the second cycle of TPE ongoing. Urgent CT scan of the brain revealed diffuse cerebral edema with severe mass effect and tonsillar herniation. A decision was made in conjunction with his family for withdrawal of care, given the grave prognosis.

DISCUSSION

Evidence of Use of Extra-Corporeal Systems in TS

Our patient is one of the few reported cases where multiple extra-corporeal systems were used (TPE, CRRT, and VA-ECMO) in TS management. On review of the medical literature of articles in English, there has only been four case reports describing the concurrent use of TPE and ECMO in patients with thyrotoxicosis with circulatory collapse (4–7), with one of them reporting the use of three extra-corporeal systems (4).

Characterized by extreme multi-systemic manifestations of thyrotoxicosis, TS is uncommon but potentially fatal, with a mortality rate of 10-30% (2). Standard first-line pharmacotherapy in TS aims to block production and release of thyroid hormones with propylthiouracil or methimazole, inhibit release of pre-formed thyroid hormones with iodine, decrease peripheral conversion of T4 to T3 with propylthiouracil and steroids, and treat adrenergic symptoms with beta-blockade, prior to definitive treatment in the form of surgery or radioactive iodine (RAI) ablation. These methods are efficacious and rapid acting. However, certain patients are not

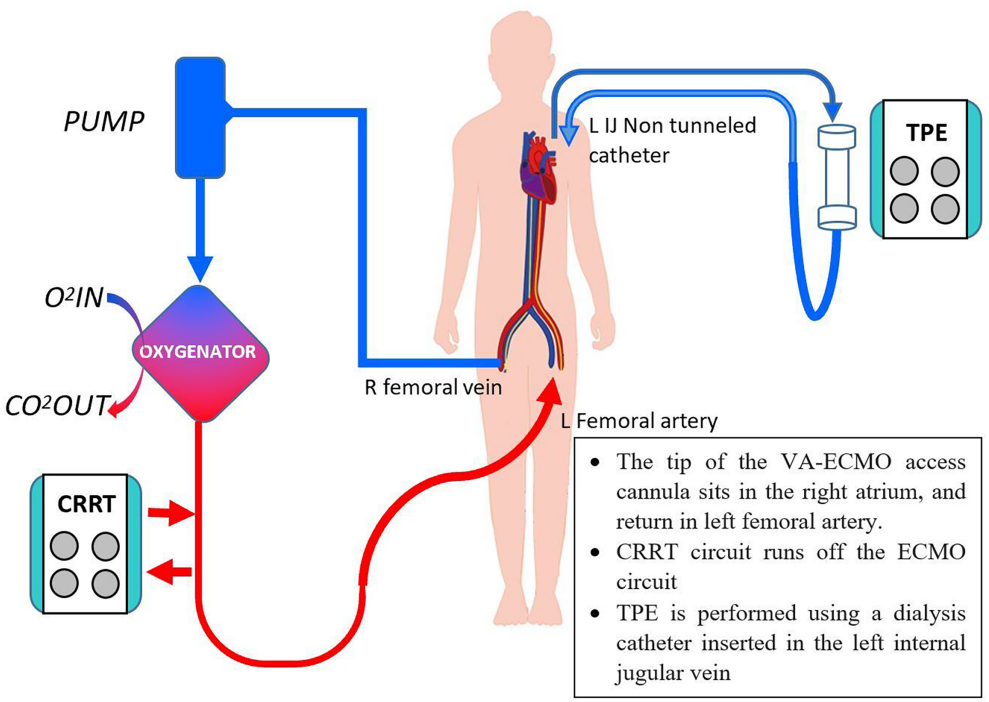


FIGURE 2 | Concurrent CRRT, VA-ECMO and TPE. O_2, oxygen, CO_2, carbon dioxide, others as per **Figure 1**.

able to tolerate, or fail pharmacotherapy, as seen in our patient with multi-organ failure precluding the use of conventional treatment. In such cases, alternative treatment including use of extra-corporeal systems must be considered, of which TPE is the most well established.

TPE is an extra-corporeal blood purification technique used for eliminating large molecular substances. Currently, TPE has a Class II indication for TS in the 2019 American Society for Apheresis (ASFA) guidelines, either as a standalone or adjunct therapy, although the grade 2C level of recommendation suggests the evidence arises mostly from case reports and case series, with an absence of prospective randomized controlled trials (8). TPE is postulated to work by several mechanisms including: 1) reducing protein-bound thyroid hormones of which 99.97% of total serum T4 and 99.7% of total serum T3 are bound to plasma proteins thyroxine binding globulin (TBG), transthyretin and albumin (9), 2) additionally reducing autoantibodies and cytokines of a predominantly Th1 pattern including interleukin-2, interferon-γ and tumor necrosis factor-α (10–12), and 3) removing 5'-monodeiodinase which converts T4 to T3 (12). TPE is shown to reduce all of free and total T4 and T3 (13), by an estimated 10-80% (12), and at a greater rate than standard medical therapy for patients with hyperthyroidism (14). However, these effects are transient and usually last for only 24-48 hours, with a potential risk for rebound thyrotoxicosis (12). This appears related to the fact that only thyroid hormones from the intravascular compartment is removed, with rapid re-equilibrium from the extravascular spaces. A study in 13 healthy individuals showed the intravascular component of thyroxine accounts for only 26% of the distribution (15), with the other sites of distribution found to be 14% in the liver, 34% in extrahepatic tissue and 26% in extracellular fluid pools. These transient effects suggest that multiple cycles of TPE may be required, and should be used only as a temporizing measure for definitive treatment (12). TPE can be performed with either plasma or albumin replacement, and the ASFA guideline does not preferentially recommend the use of plasma or albumin. It has been proposed that plasma has the theoretical advantage of containing binding proteins TBG and transthyretin, which has higher affinity to bind free T4 and T3, as well as avoid depleting coagulation factors thus avoiding complications of bleeding (13). However, there is similarly a theoretical risk of the presence of thyroid hormones from donor plasma, as well as higher risks of transfusions reactions and infections with use of plasma. Till date, there are no direct head-to-head trials between the use of plasma and albumin in TPE in patients with TS. TPE is generally well tolerated, with risks of minor side effects ranging from about 5% (9) to 36% (16), including nausea and vomiting, vagal or hypotensive response and transfusion reactions. The risk of death with TPE for any indication is exceedingly rare at 0.05% (17), and this is usually attributed to the severity of the underlying condition.

ECMO is an established life-saving treatment option for patients who develop acute cardiopulmonary failure (18), although its use in endocrinological emergencies is still under research (19). Use of ECMO in patients with thyrotoxicosis have largely been reported in the form of case reports or case series within the literature. In 2011, Hsu et al. (20) first reported a series with the use of supportive ECMO ranging from 19-114 hours in four cases of thyrotoxicosis-induced cardiovascular collapse. Three patients survived, with normalization of thyroid function and improved cardiovascular function. A subsequent review by White et al. (21) published in 2018 reported the successful use of ECMO with survival in 11 out of 14 patients (22–24) between 1970 to 2017 with thyrotoxicosis-induced cardiomyopathy, with near complete recovery of left ventricular function. A review of the cases with the use of ECMO and other extra-corporeal systems in patients with severe thyrotoxicosis or thyroid storm has been summarized in **Table 1**, including additional new cases reported from 2018 to 2021 (25–28) and conference poster reports (29–32). These 27 cases (inclusive of our case) showed survival in 85.2% (23 of the 27 cases), with survival in all four of the reported cases requiring additional extra-corporeal support of TPE or CRRT (4–7). ECMO was initiated for either cardiovascular collapse or circulatory shock, and lasted between 19 hours to 18 days. Within the reports of successful outcomes, all cases reported clinical and biochemical improvement in thyrotoxicosis, as well as improvement in cardiac function, although numerical data were not available in some of the reports. The details of these cases are reported in **Table 1**. The use of ECMO however, must be weighed against the contraindications and complications of ECMO use, including bleeding, thromboembolism, strokes and access injuries such as hemorrhage, arterial dissection, and distal limb ischemia (18).

Novel therapies are also increasingly considered for TS, using principles similar to TPE by removing protein bound thyroid hormones. Case reports with the use of dialysis has been proposed in management of thyroid storm, most notably with CRRT, which is preferred due to its better tolerability in hemodynamically unstable patients due to its slower rate of exchange of fluids and solutes. Parikh et al. (33) and Koball et al. (34) illustrated the sequential use of single pass continuous veno-venous albumin dialysis after limited response to TPE, demonstrating a more sustained improvement in thyroid hormones with less rebound thyrotoxicosis, as well as greater removal of thyroid hormones overall. Other studies have shown the additive effects of TPE and CRRT in removal of thyroid hormones (35), while another study reported a correlation of improvement of total T3 and free T4 levels of up to 80% with concomitant CRRT and standard medical therapy (without TPE), although the exact mechanisms are unclear (36). The Molecular Adsorption Recirculation Systems (MARS) has also been used, with one case report with TS and severe liver dysfunction showing rapid resolution of thyroid hormones and improvement of bilirubin (37). A retrospective case series also demonstrated significant improvement in thyroid hormone levels in patients with hyperthyroidism with severe liver dysfunction (although this study was primarily powered to show improvement and safety of use of RAI with combined with MARS in patients with severe hyperthyroidism and liver disease) (38). These reports provide early evidence of the utility

TABLE 1 | Summary of cases with use of ECMO and other extra-corporeal systems in patients with severe thyrotoxicosis or thyroid storm.

Study	Patient gender	Patient age	Indication for ECMO	Duration of ECMO	Pre-ECMO LVEF	Post-ECMO LVEF	Other extra-corporeal system used	Biochemical response after extra-corporeal treatment	Outcome
Koh et al. (4)	Male	44	PEA collapse with shock	~3 days	20-25%	–	TPE (4 cycles), CRRT	fT4 from 57 to 22pmol/L; fT3 from 12.4 to 6.0pmol/L	Survived. Underwent thyroidectomy.
Wong et al. (5)	Male	44	Recurrent PEA collapse	3 days	20%	35%	TPE (3 days)	fT4 from 61.3 to 22.0pmol/L; fT3 from 23.5 to 4.3pmol/L	Survived. Underwent thyroidectomy.
Eyadiel et al. (6)	Female	27	Cardiogenic shock	6 days	<10%	*Almost completely recovered**	TPE (3 cycles)	*Normalization of T3**	Survived.
Manuel et al. (7)	Male	26	PEA collapse with shock	24 hours	–	-	TPE (2 cycles) *via* ECMO circuit	*fT4 >100pmol/L at baseline, reportedly improved on discharge**	Survived. Underwent thyroidectomy.
Chao et al. (19)	Male	47	Refractory shock	19-115.6 hours (mean 82 hours)	20-40% (Mean 24%)	38-64% (mean 55%) on day 6	–	–	Expired, from multi-organ failure
	Male	43						–	Expired, from hepatic failure
	Female	37						*fT4 54.8-308.9pmol/L at baseline, reportedly improved on discharge**	Survived
	Male	42							Survived
	Female	33							Survived
Hsu et al. (20)	Male	47	Cardiogenic shock	19 hours	32%	–	–	–	Expired
	Male	43	PEA collapse	114 hours	20%	64%		fT4 31.1pmol/L at baseline; serum T3 3.64 improved to 1.69nmol/L	Survived
	Female	37	PEA collapse	94 hours	32%	60%		fT4 96.5 improved to 19.3pmol/L	Survived
	Male	42	Shock	102 hours	29%	58%		fT4 57.9 improved to 18.3pmol/L	Survived
White et al. (21)	Female	57	PEA collapse	10 days	<10%	20-30%	–	Clinical improvement. *Improvements in thyroid hormone not documented**	Survived
Pong et al. (22)	Male	33	Cardiogenic shock	4 days	10%	51%	–	fT4 55pmol/L, normalized after 1 week	Survived
	Female	35	Cardiogenic shock	4 days	17%	52%	–	fT4 44pmol/L, normalized after 4 days	Survived
Allencheril et al. (23)	Male	29	PEA collapse	7 days	<20%	45-49%	–	Clinical improvement. *Improvements in thyroid hormone not documented**	Survived
Kiriyama et al. (24)	Female	54	Cardiogenic shock	18 days	<20%	*Almost completely recovered**	–	*fT4 49.3pmol/L, fT3 7.04pmol/L at baseline, reportedly improved on discharge**	Survived
Kim et al. (25)	Male	52	Cardiogenic shock	6 days	<20%	40%	–	*fT4 100.0pmol/L, fT3 7.04pmol/L at baseline, reportedly improved on discharge**	Survived
Genev et al. (26)	Female	37	Cardiogenic shock	8 days	30%	35%	–	fT4 from 60.5 to 12.9pmol/L; fT3 from 13.6 to 2.5pmol/L	Survived
Voll et al. (27)	Female	35	Recurrent PEA collapse with shock	3 days	<20%	*Normalized**	–	*fT4 79pmol/L, fT3 47pmol/L, reportedly improved on discharge**	Survived. Underwent thyroidectomy.
Chao et al. (28)	Female	35	PEA collapse	65 hours	5%	65%	–	*fT4 100.8pmol/L, fT3 16.3pmol/L, reportedly improved on discharge**	Survived
Al-Saadi et al. (29)	Male	29	Cardiac arrest	6 days	<20%	–	–	*fT4 83.5pmol/L, fT3 7.04pmol/L at baseline, reportedly improved on discharge**	Survived

(Continued)

TABLE 1 | Continued

Study	Patient gender	Patient age	Indication for ECMO	Duration of ECMO	Pre-ECMO LVEF	Post-ECMO LVEF	Other extra-corporeal system used	Biochemical response after extra-corporeal treatment	Outcome
Kauth et al. (30)	Male	53	PEA collapse	12 days	–	*Normalized**	–	*fT4 66.2pmol/L, fT3 19.2pmol/L, normalized on discharge**	Survived
Karahalios et al. (31)	Female	29	PEA collapse	2 weeks	*Biventricular failure**	*Improved**	–	*fT4 79.8pmol/L at baseline*	Survived
Starobin et al. (32)	Male	33	Cardiogenic shock	–	10%	*Normalized**	–	–	Survived

"" denotes incomplete data from articles, while "-" denotes absence of reported data.*

of novel extra-corporeal systems in correcting thyroid hormone levels especially in patients with either kidney or liver dysfunction, although more research into the underlying mechanism and validation of results are required before recommendations can be made for its supportive use.

These cases provide some evidence of the use and benefits of extra-corporeal systems in the management of TS, after conventional pharmacotherapy is unsuccessful or contraindicated. Owing to the efficacy of pharmacotherapy and risks of extra-corporeal systems, conventional pharmacotherapy should be always be instituted as initial therapy. Comparison trials between pharmacotherapy and extra-corporeal systems or randomized controlled trials are unavailable due to the rarity of TS, and are unlikely to be performed now given the established efficacy of first line pharmacological agents. Retrospective analysis from the National Inpatient Database in Japan has shown that use of extra-corporeal systems is associated with higher mortality. It reported increased mortality in patients requiring hemodialysis and TPE with adjusted odds ratio for mortality at 4.81. The mortality was 61.9% in 13 out of 21 patients, compared to a mortality of 43.3% requiring either hemodialysis or TPE, and 7.8% requiring neither support. The use of ECMO had a trend towards increased mortality (2.86, CI 0.69-11.92), with a mortality of 72.2% among 13 of 18 patients, as compared to 9.3% in patients not requiring ECMO (39). These numbers, albeit small, suggest a significantly higher mortality in patients requiring use of extra-corporeal systems, and this differs from the established mortality rate of 10-30%, and vary significantly from the numbers in our review and White et al.'s review in patients requiring ECMO (21). Similarly Muller et al. (12) showed the use of TPE showed significant clinical and biochemical improvement. As patients requiring extra-corporeal systems are typically patients who are more critically ill and have multi-organ failure, as well as the possibility of publication bias, it is likely that the true survival rate of these patients in thyroid storm treated with extra-corporeal systems is likely lower than the published literature. Further research, possibly in the form of prospective multinational studies, may be required in view of the small numbers and limited data currently.

Beta-Blockade – A Double-Edged Sword in TS

While our patient received guideline-directed TS pharmacological therapy in a timely fashion, the development of circulatory collapse with consequent multi-organ failure following intravenous esmolol infusion, an ultra-short acting beta-blocker, deserves further discussion.

The cardiovascular effects in TS are driven largely by T3, leading to increased chronotropy and inotropy, improved diastolic relaxation and decreased peripheral resistance, eventually resulting in high cardiac output (CO) heart failure (HF), estimated to be seen in 6% of patients with thyrotoxicosis. This is thought to be reversible with treatment with thyrotoxicosis, with a small study showing improving in LVEF from 28% to 55% (40). Cardiomyopathy and LV dysfunction, on the other hand, are only seen in 1% (20, 41). HF with low CO has been reported with prolonged severe hyperthyroidism, consequent to persistent tachycardia, and pathologic increase in cardiac workload with demand-supply mismatch (42). Aside

from cardiomyopathy, there is an increased risk of arrhythmias with thyrotoxicosis, typically supraventricular, with rare reported cases of thyrotoxicosis-related VF related to congenital coronary anomalies, hypokalemia, coronary vasospasm and early repolarization (43), none of which were present in our patient. It is plausible that our patient had low CO thyrocardiac disease with an additional component of myocardial stunning post-cardiac arrest, but his stormy course precluded detailed cardiac imaging.

Tachycardia is almost always present in TS, and patients with tachycardia exceeding 150 beats per minute are associated with a higher mortality rate in a retrospective Japanese cohort (44). Accordingly, the Japanese Thyroid Association and Japanese Endocrine Society 2016 guidelines (45) recommend aggressive control of tachycardia including the use of ultra-short acting beta-blockers including esmolol or landiolol. New data are emerging which support the use of esmolol over propranolol, due to its shorter half-life elimination (nine minutes, *versus* 2.3 hours respectively) and duration of action, as well as its relatively higher beta 1-selectivity (46). The comparative use of esmolol and propranolol has been studied in other populations such as patients with supraventricular tachycardia, which showed similar response rate but more adverse effect of hypotension seen in the esmolol group (45%, as compared to 18%), although these were mostly asymptomatic and resolved quickly with no complications (47). Regardless of choice of beta-blockers, its use must be considered with caution in patients with decompensated HF or other features of low CO, where the thyroid-induced hyperadrenergic state plays an important compensatory role in maintaining CO. This is related to either direct catecholamine action or an interaction between the adrenergic system and excessive circulating thyroid hormone (48). The abolishment of that sympathetic drive through the use of beta-blockers is postulated to lead to the circulatory collapse, as seen in our case. Though initially hypertensive, the temporal association of esmolol infusion and PEA arrest led us to conclude it caused or at least triggered the hemodynamic decompensation in our patient. Abubaker et al. (49) reviewed a total of 11 cases of circulatory collapse with the use of beta-blockade, mostly with long acting agents including bisoprolol, metoprolol, propranolol, with all but one patient showing evidence of underlying heart failure or cardiomyopathy. The author also highlighted the challenges in managing uncontrolled tachycardia in these patients, with two cases eventually requiring esmolol and landiolol use. To date, there has been no head-to-head trials between the longer acting propranolol as compared to the ultra-short acting esmolol or landiolol. There has no reports of circulatory collapse with use of intravenous esmolol, and only one case report with landiolol (50). Despite the use of ultra-short acting esmolol, circulatory collapse in our case underscores its class effect, and is strongly associated with fatal outcomes in TS. Close cardiac monitoring and prompt institution of VA ECMO support, as what was done in this case, are recommended. Other forms of supportive therapy including CRRT may be considered until effective and definitive therapies can be instituted to treat TS.

CONCLUSION

We highlight a case of TS presenting with out-of-hospital cardiac arrest, with further hemodynamic decompensation following beta-blockade and multi-organ failure which limited therapeutic options. Despite prompt initiation of CRRT, VA-ECMO and TPE, he sustained hypoxic-ischemic brain injury. Underscoring the complexities in TS, this case calls for caution with beta-blockade in thyrocardiac disease, close monitoring and prompt organ support, and consideration of early TPE when conventional options fail. A review of the use of TPE and other extra-corporeal systems shows that TPE may be an underutilized rescue treatment for severe thyroid storm not amenable to conventional pharmacotherapy or contraindicated due to side effects or multi-organ involvement. Further study of novel extra-corporeal therapies for TS is needed to uncover its therapeutic potential, especially in the Intensive Care setting.

AUTHOR CONTRIBUTIONS

All authors were involved in the management of the patient. SL, KW, and SY wrote the first draft of the manuscript. PL and KR reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Klubo-Gwiezdzinska J, Wartofsky L. Thyroid Emergencies. *Med Clin North Am* (2012) 96(2):385–403. doi: 10.1016/j.mcna.2012.01.015
2. Chiha M, Samarasinghe S, Kabaker AS. Thyroid Storm: An Updated Review. *J Intensive Care Med* (2015) 30(3):131–40. doi: 10.1177/0885066613498053
3. Galindo RJ, Hurtado CR, Pasquel FJ, Tome RG, Peng L, Umpierrez GE. National Trends in Incidence, Mortality, and Clinical Outcomes of Patients Hospitalized for Thyrotoxicosis With and Without Thyroid Storm in the United States, 2004-2013. *Thyroid* (2019) 29(1):36–43. doi: 10.1089/thy.2018.0275
4. Koh H, Kaushik M, Loh JK, Chng CL. Plasma Exchange and Early Thyroidectomy in Thyroid Storm Requiring Extracorporeal Membrane Oxygenation. *Endocrinol Diabetes Metab Case Rep* (2019) 1):1–6. doi: 10.1530/EDM-19-0051
5. Wong IMJ, Lim JY, Goh JTK, Tan QL, Tay CK. Thyroid Storm Rescued by Extracorporeal Membrane Oxygenation Support, Plasmapheresis and Thyroidectomy: A Case Report. *J Emerg Crit Care Med* (2021) 5:19. doi: 10.21037/jeccm-20-147
6. Eyadiel L, Amjad A, Pisani B, Miller P, Jain R. Use of Therapeutic Plasma Exchange and ECMO Support With Impella for LV Vent as Treatment for Cardiogenic Shock in Acute Thyrotoxicosis/Thyroid Storm. *J Card Fail* (2018) 24:S84–5. doi: 10.1016/j.cardfail.2018.07.337
7. Manuel L, Fong LS, Lahanas A, Grant P. How to do it: Plasmapheresis via Venoarterial Extracorporeal Membrane Oxygenation Circuit for Thyroid Storm. *Ann Med Surg (Lond)* (2021) 67:102485. doi: 10.1016/j.amsu.2021.102485
8. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice –

Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. *J Clin Apher* (2019) 34 (3):171–354. doi: 10.1002/jca.21705
9. Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ. *Williams Textbook of Endocrinology. 14th Edition*. Philadelphia, PA: Elsevier (2020).
10. Ganesh BB, Bhattacharya P, Gopisetty A, Prabhakar BS. Role of Cytokines in the Pathogenesis and Suppression of Thyroid Autoimmunity. *J Interferon Cytokine Res* (2011) 31(10):721–31. doi: 10.1089/jir.2011.0049
11. Tan AWK, Lim BSP, Hoe JKM, Hoi WH, Leow MKS. Therapeutic Plasma Exchange for Control of Thyroid Storm. *J Clin Apher* (2021) 36:189–95. doi: 10.1002/jca.21832
12. Muller C, Perrin P, Faller B, Richter S, Chantrel F. Role of Plasma Exchange in the Thyroid Storm. *Ther Apher Dial* (2011) 15(6):522–31. doi: 10.1111/j.1744-9987.2011.01003.x
13. Garla V, Kovvuru K, Ahuja S, Palabindala V, Malhotra B, Salim SA. Severe Hyperthyroidism Complicated by Agranulocytosis Treated With Therapeutic Plasma Exchange: A Case Report and Review of the Literature. *Case Rep Endocrinol* (2008) 4135940. doi: 10.1155/2018/4135940
14. Binimelis J, Bassas L, Marruecos L, Rodriguez J, Domingo ML, Madoz P, et al. Massive Thyroxine Intoxication: Evaluation of Plasma Extraction. *Intensive Care Med* (1987) 13(1):33–8. doi: 10.1007/BF00263555
15. Nicoloff JT, Dowling JT. Estimation of Thyroxine Distribution in Man. *J Clin Invest* (1986) 47(1):26–37. doi: 10.1172/JCI105712
16. Shemin D, Briggs D, Greenan M. Complications of Therapeutic Plasma Exchange: A Prospective Study of 1,727 Procedures. *J Clin Apher* (2007) 22 (5):270–6. doi: 10.1002/jca.20143
17. McLeod BC, Sniecinski I, Ciavarella D, Owen H, Price TH, Randels MJ, et al. Frequency of Immediate Adverse Effects Associated With Therapeutic Apheresis. *Transfusion* (1999) 39(3):282–8. doi: 10.1046/j.1537-2995.1999.39399219285.x
18. Ventetuolo CE, Muratore CS. Extracorporeal Life Support in Critically Ill Adults. *Am J Respir Crit Care Med* (2014) 190(5):497–508. doi: 10.1164/rccm.201404-0736CI
19. Chao A, Wang CH, You HC, Chou NK, Yu HY, Chi NH, et al. Highlighting Indication of Extracorporeal Membrane Oxygenation in Endocrine Emergencies. *Sci Rep* (2015) 5:13361. doi: 10.1038/srep13361
20. Hsu LM, Ko WJ, Wang CH. Extracorporeal Membrane Oxygenation Rescues Thyrotoxicosis-Related Circulatory Collapse. *Thyroid* (2011) 21(4):439–41. doi: 10.1089/thy.2010.0230
21. White A, Bozso SJ, Moon MC. Thyrotoxicosis Induced Cardiomyopathy Requiring Support With Extracorporeal Membrane Oxygenation. *J Crit Care* (2018) 45:140–3. doi: 10.1016/j.jcrc.2018.01.026
22. Pong V, Yeung C, Ko RL, Tse H, Siu C. Extracorporeal Membrane Oxygenation in Hyperthyroidism-Related Cardiomyopathy: Two Case Reports. *J Endocrinol Metab* (2013) 3(1-2):24–8. doi: 10.4021/jem144w
23. Allencherril J, Birnbaum I. Heart Failure in Thyrotoxic Cardiomopathy: Extracorporeal Membrane Oxygenation Treatment for Graves' Disease. *J Extra Corpor Technol* (2015) 47(4):231–2.
24. Kiriyama H, Amiya E, Hatano M, Hosoya Y, Maki H, Nitta D, et al. Rapid Improvement of Thyroid Storm-Related Hemodynamic Collapse by Aggressive Anti-T Hyroid Therapy Including Steroid Pulse: A Case Report. *Med (Baltimore)* (2017) 96(22):e7053. doi: 10.1097/MD.0000000000007053
25. Kim S, Seol SH, Kim YS, Kim DK, Kim KH, Kim DI. Thyrotoxicosis Induced Cardiogenic Shock Rescued by Extracorporeal Membrane Oxygenation. *J Geriatr Cardiol* (2018) 15:203–4. doi: 10.11909/j.issn.1671-5411.2018.02.003
26. Genev I, Lundholm MD, Emanuele MA, McGee E, Mathew V. Thyrotoxicosis-Induced Cardiomyopathy Treated With Venoarterial Extracorporeal Membrane Oxygenation. *Heart Lung* (2020) 49:165–6. doi: 10.1016/j.hrtlng.2019.06.006
27. Voll M, Øystese KA, Høiskar E, Johansen O, Nyvold C, Norheim I, et al. Case Report: A Patient With Thyroid Storm, Refractory Cardiogenic Shock, and Cardiac Arrest Treated With Lugol's Iodine Solution and Veno-Arterial Extra Corporal Membrane Oxygenation Support. *Eur Heart J - Case Rep* (2021) 5 (2):ytab017. doi: 10.1093/ehjcr/ytab017
28. Chao J, Cook R, Dhingra V. Escaping a Storm Alive: A Case Report of a Young Woman's Acute Presentation of Thyroid Storm Leading to Cardiac Arrest Salvaged by VA-ECMO. *J Clin Anesth Intensive Care* (2021) 2(1):26–30.
29. Al-Saadi M, Sista R, Lan C. Veno-Arterial Extracorporeal Membrane Oxygenation Saved A Young Patient In Refractory Cardiogenic Shock Precipitated By Thyroid Storm. *Am J Respir Crit Care Med* (2016) 193:A6918.
30. Kauth M, Sheikh A, Hinkle L. In the "I" of the Storm: Thyroid Storm Induced by Iodine Contrast in Thyrotoxicosis. *Am J Respir Crit Care Med* (2019) 199:A1713. doi: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A1713
31. Karahalios BA, Singh R, Boyd K, Ogbonna M. A Perfect Storm: A Case Of Managing Cardiogenic Shock Due To Thyrotoxic Cardiomyopathy With Extracorporeal Membrane Oxygenation. *J Hosp Med* (2020).
32. Starobin B, Afari M. Through The Storm: Veno-Arterial Extracorporeal Membranous Oxygenation Therapy For Treatment Of Thyroid Storm Induced Cardiogenic Shock. *J Am Coll Cardiol* (2021) 77(18_Supplement_1):215.
33. Parikh T, Sharma M, Hegde A. SUN-559 Refractory Thyroid Storm: Role of Single Pass Albumin Dialysis (SPAD). *J Endocr Soc* (2019) 3(Suppl 1):SUN–559. doi: 10.1210/js.2019-SUN-559
34. Koball S, Hickstein H, Gloger M, Hinz M, Henschel J, Stange J, et al. Treatment of Thyrotoxic Crisis With Plasmapheresis and Single Pass Albumin Dialysis: A Case Report. *Artif Organs* (2010) 34(2):E55–58. doi: 10.1111/j.1525-1594.2009.00924.x
35. Haley PA, Zabaneh I, Bandak DN, Iskapalli MD. The Resolution of Thyroid Storm Using Plasma Exchange and Continuous Renal Replacement Therapy. *J Adv Biol Biotechnol* (2019) 20(1):1–4. doi: 10.9734/JABB/2018/45719
36. Park HS, Kwon SK, Kim YN. Successful Treatment of Thyroid Storm Presenting as Recurrent Cardiac Arrest and Subsequent Multiorgan Failure by Continuous Renal Replacement Therapy. *Endocrinol Diabetes Metab Case Rep* (2017) 1:16–0115. doi: 10.1530/EDM-16-0115
37. Tan YW, Sun L, Zhang K, Zhu L. Therapeutic Plasma Exchange and a Double Plasma Molecular Absorption System in the Treatment of Thyroid Storm With Severe Liver Injury: A Case Report. *World J Clin Cases* (2019) 7 (10):1184–90. doi: 10.12998/wjcc.v7.i10.1184
38. Zhang Q, Guan Y, Xiang T, Liu S, Chen Q, Zhang Q. Combination of Molecular Adsorbent Recirculating System and Radioiodine for the Treatment of Concurrent Hyperthyroiditism and Severe Liver Dysfunction: A Retrospective Cohort Study. *Endocr Pract* (2017) 23(2):141–8. doi: 10.4158/EP161417.OR
39. Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Factors Associated With Mortality of Thyroid Storm: Analysis Using a National Inpatient Database in Japan. *Med (Baltimore)* (2016) 95(7):e2848. doi: 10.1097/MD.0000000000002848
40. Umpierrez GE, Challapalli S, Patterson C. Congestive Heart Failure Due to Reversible Cardiomyopathy in Patients With Hyperthyroidism. *J Med Sci* (1995) 310(3):99–102. doi: 10.1097/00000441-199531030-00003
41. Dahl P, Danzi S, Klein I. Thyrotoxic Cardiac Disease. *Curr Heart Fail Rep* (2008) 5(3):170–6. doi: 10.1007/s11897-008-0026-9
42. Klein I, Danzi S. Thyroid Disease and the Heart. *Circulation* (2007) 116 (15):1725–35. doi: 10.1161/CIRCULATIONAHA.106.678326
43. Nakashima Y, Kenzaka T, Okayama M, Kajii E. A Case of Thyroid Storm With Cardiac Arrest. *Int Med Case Rep J* (2014) 7:89–92. doi: 10.2147/IMCRJ.S63475
44. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, et al. Diagnostic Criteria, Clinical Features, and Incidence of Thyroid Storm Based on Nationwide Surveys. *Thyroid* (2012) 22:661–79. doi: 10.1089/thy.2011.0334
45. Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, et al. 2016 Guidelines for the Management of Thyroid Storm From The Japan Thyroid Association and Japan Endocrine Society (First Edition). *Endocr J* (2016) 63 (12):1025–64. doi: 10.1507/endocrj.EJ16-0336
46. Brunette DD, Rothong C. Emergency Department Management of Thyrotoxic Crisis With Esmolol. *Am J Emerg Med* (1991) 9:232–4. doi: 10.1016/0735-6757(91)90083-V
47. Morganroth J, Horowitz LN, Anderson J, Turlapaty P. Comparative Efficacy and Tolerance of Esmolol to Propranolol for Control of Supraventricular Tachyarrhythmia. *Am J Cardiol* (1985) 56(11):33F–9F. doi: 10.1016/0002-9149(85)90914-2
48. Landsberg L. Catecholamines and Hyperthyroidism. *Clin Endocrinol Metab* (1977) 6:697–718. doi: 10.1016/S0300-595X(77)80076-5

49. Abubakar H, Singh V, Arora A, Alsunaid S. Propranolol-Induced Circulatory Collapse in a Patient With Thyroid Crisis and Underlying Thyrocardiac Disease: A Word of Caution. *J Investig Med High Impact Case Rep* (2017) 5(4):2324709617747903. doi: 10.1177/2324709617747903
50. Misumi K, Kodera S, Nagura F, Kushida S, Shiojiri T, Kanda J. Cardiac Arrest Caused by Landiolol in a Patient in Thyroid Crisis. *J Cardiol Cases* (2016) 14 (2):62–4. doi: 10.1016/j.jccase.2016.04.002

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Hyperthyroidism With Atrial Fibrillation in Children: A Case Report and Review of the Literature

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Atrial fibrillation is exceedingly rare in children with structurally and functionally normal hearts. We present a novel case of a 15-year-old female with known hyperthyroidism who subsequently developed atrial fibrillation. She had been suffering from fatigue, heat intolerance and myalgias for 6 months. Her initial TSH was 0.01mU/L, and free T4 was 75.4 pmol/L, with a free T3 of >30.8 pmol/L. An electrocardiogram showed atrial fibrillation with a ventricular rate of 141 beats per minute. An echocardiogram demonstrated an enlarged left atrium and ventricle, with mild mitral regurgitation. She was treated with methimazole and underwent synchronized cardioversion. She subsequently returned to a euthyroid state and remained in normal sinus rhythm. In this case, we discuss the physiologic and arrhythmogenic properties of thyroid hormone, with a summary of the existing literature on atrial fibrillation in hyperthyroidism in children. Current guidelines for treatment of atrial fibrillation are also outlined.

Keywords: atrial fibrillation, hyperthyroidism, heart, thyroid hormones, arrhythmia, cardioversion

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INTRODUCTION

Atrial fibrillation (AF) occurs commonly in hyperthyroidism in the adult population. However, it is a rare occurrence in children (1). To date, there have been three reported cases of hyperthyroidism accompanied by AF in children (2–4), and one reported case of atrial flutter associated with hyperthyroidism (5). We report a rare case of a 15-year-old female with hyperthyroidism complicated by AF. The important link between endocrine disorders and the heart is discussed, along with the physiologic and arrhythmogenic properties of thyroid hormone. A summary of current guidelines for the treatment of AF in hyperthyroidism in children is also provided.

Case Report

A 15-year-old female was referred to the cardiology clinic with tachycardia, murmur and known hyperthyroidism. She had been suffering from fatigue, heat intolerance and nonspecific myalgias for six months, and subsequently developed shortness of breath on exertion. Her past medical history was unremarkable and there was no known family history of AF.

Abbreviations: AF, Atrial fibrillation; ECG, electrocardiogram; FT4, free thyroxine; FT3, free triiodothyronine; LV, left ventricle; TSH, Thyroid stimulating hormone; T4, Thyroxine; T3, Triiodothyronine; TIA, Transient ischaemic attack.

On initial visit, her weight was 53.9 kg (57.6th percentile, +0.19 SDs) and height was 158.8 cm (31.9th percentile, -0.47 SDs). Heart rate was 148 beats per minute and irregular, with a blood pressure of 138/72 mmHg. The precordium was hyperdynamic with normal first and second heart sounds, and a gallop rhythm. There was a grade II/VI systolic regurgitant murmur audible at the left lower sternal border and over the apex. Her thyroid was moderately enlarged with no palpable nodules. There was no peripheral edema or hepatosplenomegaly.

Investigations

An electrocardiogram (ECG) showed AF with an average ventricular rate of 141 beats per minute, with irregular conduction and left ventricular hypertrophy (**Figure 1**). Laboratory studies revealed a TSH of 0.01mU/L, free T4 of 75.4 pmol/L, free T3 of >30.8 pmol/L, thyroperoxidase antibodies of 114 IU/mL, and TSH receptor antibody of 25 U/L. She had a normal complete blood count, electrolytes and renal function (**Table 1**). An echocardiogram revealed an enlarged left atrium, left ventricle (>6cm), moderate mitral regurgitation and mild mitral valve prolapse with low normal cardiac function (**Table 2**).

Treatment and Follow Up

The patient had a transesophageal echocardiogram that demonstrated no thrombus in the left atrium. She underwent synchronized cardioversion as daycare procedure, and successfully reverted to normal sinus rhythm at a rate of 90 beats per minute (**Figure 2**). Warfarin was started post cardioversion and anticoagulation was discontinued after evidence of persistent sinus rhythm. Low dose aspirin was added as part of our institutional practice to use aspirin for patients with AF at low risk of an embolic event. Her medical management included methimazole at a dose of 0.5 mg/kg/day and bisoprolol 2.5mg once daily. A euthyroid state was achieved, and AF did not recur. She was seen in follow-up clinic in a week, a month, 6 months and 1 year period. She continued to be in sinus rhythm. Bisoprolol was discontinued 4 months after her initial presentation.

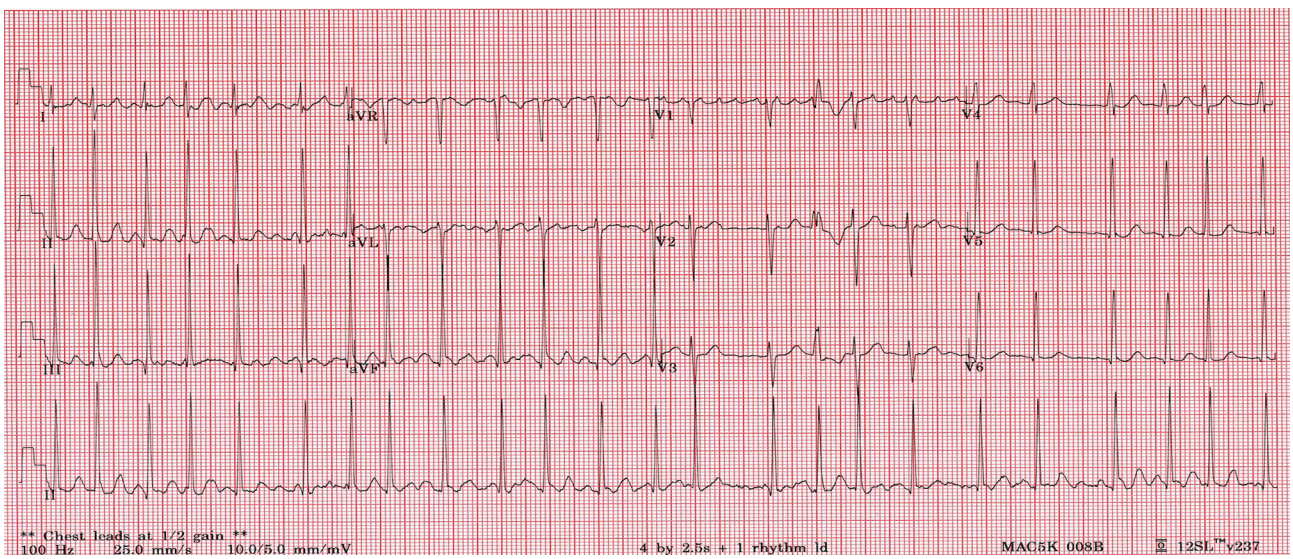

FIGURE 1 | 12 lead ECG demonstrating AF with variable conduction and left ventricular hypertrophy.

TABLE 1 | Lab values.

Lab values	Pre-treatment	5months post-treatment	Reference range
Free T4 (pmol/L)	75.4	16.7	10.5 - 20
Free T3 (pmol/L)	>30.8	6.7	3.5 - 6.5
TSH (mU/L)	0.01	<0.06	0.3 - 6.0
Thyroperoxidase antibody (IU/ml)	114		0 - 9
TSH receptor antibody(U/L)	25		< 1.8
Hematocrit	0.391		0.350 - 0.440
Sodium (mmol/L)	143		135 - 145
Potassium (mmol/L)	4.1		3.5 - 5.0
Creatinine (umol/L)	38		39 - 97

T4, Thyroxine; T3, Triiodothyronine; TSH, Thyroid stimulating hormone.
Thyroid function was tested frequently after initiation of methimazole until stabilization. This thyroid panel represents 5 months after presentation when thyroid function stabilized.

TABLE 2 | Key Echocardiogram parameters.

Parameters	Value	Z score
LV end-diastolic dimension	6.1 cm	3.18
LV end-systolic dimension	4.2 cm	3.25
Interventricular septum thickness in diastole	1.0 cm	1.37
LV posterior wall thickness in systole	1.2 cm	0.31
LV posterior wall thickness in diastole	0.6 cm	0.49
LV ejection fraction	59%	
LV fractional shortening	31.9%	
LV wall stress	128.3 g/cm^2	
LV Cardiac Index	2.73 l/min/m^2	
Left atrial diameter	4.9 cm	
Mitral Valve E/A	1.0	
Mitral Valve E Velocity	1.3 m/s	

LV, Left Ventricle; E/A, Ratio of E (early diastolic wave)/A (late diastolic wave); E Velocity, early diastolic velocity.

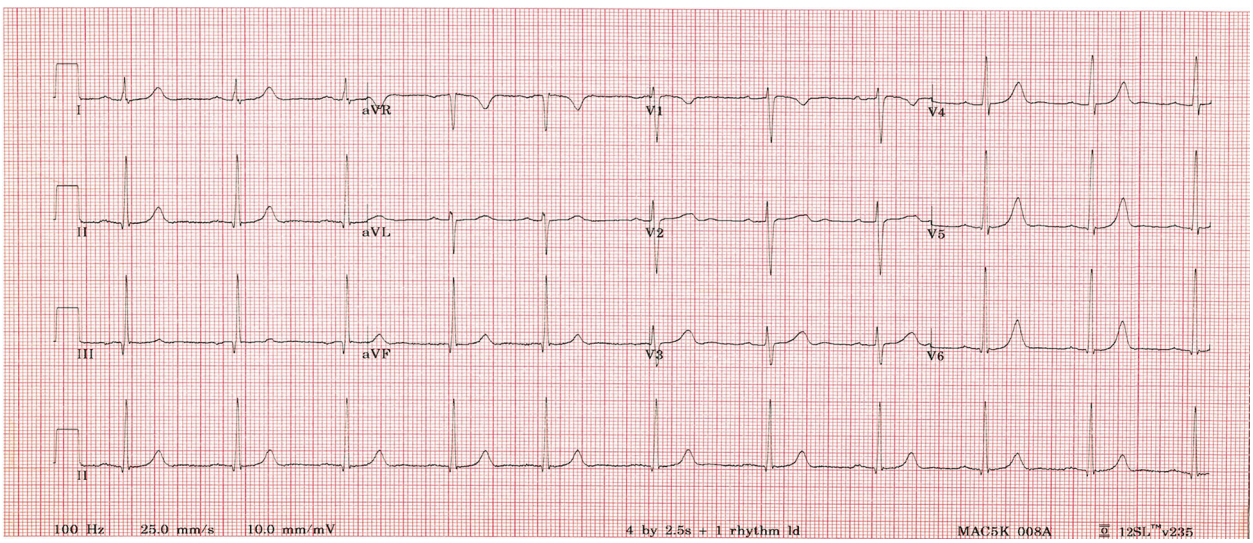

FIGURE 2 | 12 lead ECG demonstrating sinus rhythm.

DISCUSSION

The incidence of AF is rare in childhood, and the recognized association of adult thyroid disease and atrial fibrillation does not occur in pediatrics (1). In hyperthyroidism, the incidence of AF was found to be high in those with male sex, advancing age, coronary heart disease, congestive heart failure and valvular heart disease. Even subclinical hyperthyroidism is associated with a threefold increase in the risk of atrial fibrillation in older persons (6). Hyperthyroid patients may experience more significant clinical symptoms such as palpitations, fatigue, dizziness, reduced exercise capacity or mild dyspnea when accompanied by AF. We present a rare case of AF in a 15-year-old female with known hyperthyroidism. It is important to note the link between endocrine disorders and the heart. Thyroid hormones have several effects on the cardiovascular system (7–9).

The thyroid secretes two hormones, thyroxine (T4), a prohormone, and triiodothyronine (T3), the active hormone (7). Thyroid hormone has both physiologic and arrhythmogenic properties (8, 10). In hyperthyroidism there is excessive production of T3 as a result of hypersecretion by the thyroid gland, and an increase in the peripheral monodeiodination of T4. This leads to marked changes in the cardiovascular system through both nuclear and nonnuclear actions at the cellular level (8, 11). T3 increases myocardial contractility, resting heart rate, systolic and mean pulmonary artery pressure, myocardial oxygen consumption and reduces afterload by acting on vascular smooth muscle and reducing systemic vascular resistance (8, 12, 13). Most of the measures of cardiac function, including left ventricular (LV) ejection fraction, the rate of ventricular pressure development, diastolic relaxation, and cardiac output, are increased (14). These functional changes are most likely the result of an increase in expression of myocardial sarcoplasmic reticulum calcium-dependent adenosine triphosphatase, a decrease in the expression of its inhibitor, phospholamban, and reduction in systemic vascular resistance (12, 13).

On the other hand, thyroid hormone has arrhythmogenic properties affecting both atria and ventricles (10). Elevated thyroid hormone (T3) results in increased sympathetic function, tachycardia and decreased atrial refractory period which are mediated by alteration in the sensitivity of β1-adrenergic and M2-muscarinic receptors of the heart, vagolytic effects and alteration of ionic channel activity by T3 respectively. Thyroid hormone decreases L-type calcium channel mRNA expression and increases expression of Kv 1.5 mRNA which causes increase in the rate of K efflux and in turn shortening of atrial refractory period (6). The effective refractory period shortening of atrial myocytes increases the susceptibility of cardiomyocytes to reactivation from electrical impulses, which in turn can lead to reentry atrial circuits and AF (10, 15, 16). Thyroid hormone also increases the automaticity of pulmonary vein cardiomyocytes (17). Pulmonary veins have been demonstrated to be important origins of ectopic beats in the initiation of AF (17, 18).

The physiology behind the initiation and maintenance of paroxysmal AF is multi-factorial. Dominant theories of the pathogenesis of AF highlight electrical remodeling, structural remodeling and inflammation (19). Hyperthyroidism is primarily known to affect electrical remodeling through shortening of the effective refractory period of atrial myocytes and in increasing the arrhythmogenicity of pulmonary vein myocytes.

Hyperthyroid patients with undetectable structural heart disease have more premature supraventricular depolarizations, and non-sustained supraventricular tachycardias, as well as premature atrial complex and reduced heart rate variability (20). The latter is primarily the result of decreased parasympathetic tone. These electrical triggers may contribute to paroxysmal atrial tachycardia, AF, and atrial flutter. Among these arrhythmias, AF is the most common (21). Mendelian randomization studies (22, 23) have provided evidence that the relationship between thyroid function and AF is causal.

Lone AF occurring in younger patients without underlying cardiovascular disease or comorbidities represents less than 5% of all types of AF (24, 25). The majority of documented AF in children has been associated with cardiomyopathy and congenital heart disease, such as transposition of great vessels (25). It has also been documented in children after undergoing cardiac surgery, namely the Fontan or Mustard procedures (25–27). There was an increased rate of AF in pediatric patients with unrepaired cardiac lesions resulting in significant left sided hemodynamic effects and in those who had never undergone cardiac surgery (26). The workup for AF should evaluate the presence of triggers, predisposing factors (family history, obesity, excessive participation in endurance sports, hyperthyroidism, smoking, alcohol use, drugs or stimulants use) and inherited channelopathies (28). Lone AF can occur with rare channelopathies in children like Brugada syndrome (BrS), Long QT syndrome (LQTS) and Short QT syndrome (SQTS). The prevalence of AF is 10-20%, 2-30% and upto 30% in patients with BrS, LQTS and SQTS respectively (28–30). Lone AF does carry substantial symptomatic burden and has a high recurrence rate (31). Identification of associated diseases considerably alters prognosis and therapy. However, we demonstrate a case of AF in a child with undetected structural heart disease, secondary to hyperthyroidism.

The specific management strategies for pediatric AF in general have not been well defined, but there is a need for an organized and consistent approach. Current guidelines for treatment of AF with hyperthyroidism recommend achieving a clinically euthyroid state, and most patients will spontaneously revert to sinus rhythm. Beta blockers are recommended to control the ventricular rate (32, 33). If there is persistent AF after return to euthyroid state, cardioversion is recommended (32–34). Adult studies have shown that a fraction of patients will remain in AF despite restoration of euthyroid state and may require catheter ablation (35). Recent adult studies also propose patients with hyperthyroidism may have an increased prevalence of pulmonary venous and non-pulmonary venous ectopic foci and are susceptible to an increased risk of recurrence of AF after a single ablation procedure (35).

Complications of AF in patients with hyperthyroidism include heart failure and thromboembolism, although it remains controversial whether AF in hyperthyroidism is associated with a higher thromboembolic risk than AF in other settings (13, 14, 36). Approximately 10 to 15 percent of adult patients with overt hyperthyroidism who have AF have an arterial embolic event (37, 38). The literature to date does not provide consistent recommendations on the need for anticoagulation in hyperthyroid patients with AF, with no published studies focusing on anticoagulants in childhood. The CHADS2 [Congestive Heart failure, Hypertension, Age ≥ 75, Diabetes, and prior Stroke or TIA (double)] or CHA2DS2- VASc [Congestive Heart failure, Hypertension, Age ≥ 75 (double), Diabetes, and prior Stroke or TIA (double), Vascular disease, Age 65–74, and Sex (female)] risk score is recommended to guide long-term anticoagulation decisions in adult patients (39, 40). While no such score has been validated in children, and subclinical stroke can occur early in the clinical course (41), even with a CHADS2 score of 0-1, the benefits of anticoagulant therapy have yet to be assessed. Like in adults, the CHA2DS2-VASc could be used to assess the stroke risk and in the absence of any risk factor (i.e., hypertension, diabetes, stroke, or TIA or vascular disease) oral anticoagulation is not recommended for young patients with lone AF. If duration of AF is more than 48 h or unknown, transoesophageal echocardiography or 4-weeks of anticoagulation therapy is recommended prior to cardioversion with anticoagulation continuing for 4 weeks following the cardioversion (39). Anticoagulation treatment should be continued for 4 weeks following the cardioversion regardless of the risk of thromboembolism (39). The anticoagulant therapy can be discontinued after successful treatment of the disorder along with periodic assessment for any recurrence of AF and guided by patient's underlying risk for stroke (42). The absence of signs and symptoms of AF and 24 hr monitoring showing no AF can be considered adequate to stop anticoagulants.

The studies to date on AF in the young have required multicenter collaborations to gather reasonable numbers of patients (31, 43). It is not likely feasible to have large

populations with AF and thyroid disease in the young, thus the novelty of this case. There are other methods to advance our knowledge. Since the last decade, preclinical studies involving human induced pluripotent stem cells derived cardiomyocytes have shown promising role in modelling various cardiac diseases including AF and as a potential platform for drug development (44, 45). In Hyperthyroidism with AF in children, given the paucity of studies and patient population, future research with human induced pluripotent stem cells-derived cardiomyocytes or tissue engineering are plausible tools to provide important insight into the mechanism of AF in hyperthyroidism and to develop specific management strategies.

This particular case is demonstrative of a rare and serious complication of hyperthyroidism in a child, and we have reviewed the physiology underlying the propensity toward AF in hyperthyroidism. The general principles in the treatment of AF secondary to hyperthyroidism have also been outlined. In the adult population, it is common for clinicians to investigate for thyroid disease in patients with AF. Thus, for the general pediatric clinician, it is important to have AF and atrial arrhythmias on the differential diagnosis of complications for the hyperthyroid patient.

Learning Points:

- There is an important link between endocrine disorders and the cardiovascular system.
- Thyroid hormone has both physiologic and arrhythmogenic properties.
- Patients with clinical hyperthyroidism have an increased risk of AF.
- Although rare, pediatricians should be aware of AF as a complication of hyperthyroidism in children with structurally and functionally normal hearts.

AUTHOR CONTRIBUTIONS

DS and YW prepared the body of the manuscript. SS and SA critically reviewed the publication. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Radford DJ, Izukawa T. Atrial Fibrillation in Children. *Pediatrics* (1977) 59 (2):250–6.
2. Perry LW, Hung W. Atrial Fibrillation and Hyperthyroidism in a 14-Year-Old Boy. *J Pediatr* (1971) 79(4):668–71. doi: 10.1016/s0022-3476(71)80319-0
3. Takasugi H, Ao K, Sato T, Maeda A, Okada T, Wakiguchi H. Atrial Fibrillation With Hyperthyroidism in a 14-Year-Old Male. *Pediatr Cardiol* (2006) 27(6):772–4. doi: 10.1007/s00246-006-1409-x
4. Williams-Phillips S. Atrial Fibrillation in Childhood With Familial Hyperthyroidism in Afro-Caribbeans. *EMJ Cardiol* (2013) 1:82–5.
5. Suarez WA, Van Hare GF, Wexler ID, Arnold JE. Atrial Flutter: An Uncommon Pediatric Manifestation of Hyperthyroidism. *Pediatrics* (1997) 100(2):E11. doi: 10.1542/peds.100.2.e11
6. Reddy V, Tahab W, Kundumadam S, Khan M. Atrial Fibrillation and Hyperthyroidism: A Literature Review. *Indian Heart J* (2017) 69:545–50. doi: 10.1016/j.ihj.2017.07.004
7. Fadel BM, Ellahham S, Ringel MD, Lindsay J, Wartofsky L, Burman KD. Hyperthyroid Heart Disease. *Clin Cardiol* (2000) 23(6):402–8. doi: 10.1002/clc.4960230605
8. Toft AD, Boon NA. Thyroid Disease and the Heart. *Heart* (2000) 84(4):455–60. doi: 10.1136/heart.84.4.455
9. Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mügge A, Patsalis PC, et al. Abnormal Thyroid Function Is Common in Takotsubo Syndrome and Depends on Two Distinct Mechanisms: Results of a Multicentre Observational Study. *J Intern Med* (2021) 289(5):675–87. doi: 10.1111/joim.13189
10. Marrakchi S, Kanoun F, Idriss S, Kammoun I, Kachboura S. Arrhythmia and Thyroid Dysfunction. *Herz* (2015) 40(Suppl 2):101–9. doi: 10.1007/s00059-014-4123-0
11. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of Thyroid Hormone on the Cardiovascular System. *Recent Prog Horm Res* (2004) 59:31–50. doi: 10.1210/rp.59.1.31
12. Kiss E, Jakab G, Kranias EG, Edes I. Thyroid Hormone-Induced Alterations In Phospholamban Protein Expression: Regulatory Effects on Sarcoplasmic Reticulum Ca2+ Transport and Myocardial Relaxation. *Circ Res* (1994) 75:245–51. doi: 10.1161/01.res.75.2.245
13. Klein I, Danzi S. Thyroid Disease and the Heart. *Circulation* (2007) 116 (15):1725. doi: 10.1161/CIRCULATIONAHA.106.678326
14. Klein I, Ojamaa K. Thyroid Hormone and the Cardiovascular System. *N Engl J Med* (2001) 344:501–9. doi: 10.1056/NEJM200102153440707
15. Freedberg AS, Papp JG, Williams EM. The Effect of Altered Thyroid State on Atrial Intracellular Potentials. *J Physiol* (1970) 207(2):357–69. doi: 10.1113/jphysiol.1970.sp009066
16. Komiya N, Isomoto S, Nakao K, Hayano M, Yano K. Electrophysiological Abnormalities of the Atrial Muscle in Patients With Paroxysmal Atrial Fibrillation Associated With Hyperthyroidism. *Clin Endocrinol (Oxf)* (2002) 56(1):39–44. doi: 10.1046/j.0300-0664.2001.01459.x
17. Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, Lin CI. Effects of Thyroid Hormone on the Arrhythmogenic Activity of Pulmonary Vein Cardiomyocytes. *J Am Coll Cardiol* (2002) 39(2):366–72. doi: 10.1016/s0735-1097(01)01731-4
18. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *N Engl J Med* (1998) 339(10):659–66. doi: 10.1056/NEJM199809033391003
19. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current Concepts in the Pathogenesis of Atrial Fibrillation. *Am Heart J* (2009) 157 (2):243–52. doi: 10.1016/j.ahj.2008.10.009
20. Wustmann K, Kucera JP, Zanchi A, Burow A, Stuber T, Chappuis B, et al. Activation of Electrical Triggers of Atrial Fibrillation in Hyperthyroidism. *J Clin Endocrinol Metab* (2008) 93(6):2104–8. doi: 10.1210/jc.2008-0092
21. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and Risk of Atrial Fibrillation or Flutter: A Population-Based Study. *Arch Intern Med* (2004) 164 (15):1675. doi: 10.1001/archinte.164.15.1675
22. Ellervik C, Roselli C, Christophersen IE, Alonso A, Pietzner M, Sitlani CM, et al. Assessment of the Relationship Between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study. *JAMA Cardiol* (2019) 4(2):144–52. doi: 10.1001/jamacardio.2018.4635
23. Larsson SC, Allara E, Mason AM, Michaëlsson K, Burgess S. Thyroid Function and Dysfunction in Relation to 16 Cardiovascular Diseases: A Mendelian Randomisation Study. *Circ Genom Precis Med* (2019) 12(3): e002468. doi: 10.1161/CIRCGEN.118.002468
24. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes Jr DR, Ilstrup DM, et al. The Natural History of Lone Atrial Fibrillation. A Population-Based Study Over Three Decades. *N Engl J Med* (1987) 10(317):669–74. doi: 10.1056/NEJM198709103171104
25. Ceresnak SR, Liberman L, Silver ES, Fishberger SB, Gates GJ, Nappo L, et al. Lone Atrial Fibrillation in the Young - Perhaps Not So "Lone"? *J Pediatr* (2013) 162(4):827–31. doi: 10.1016/j.jpeds.2012.09.016
26. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and Risk Factors for Atrial Fibrillation and Intra-Atrial Reentrant Tachycardia Among Patients With

Congenital Heart Disease. *Am J Cardiol* (2002) 90(3):338–40. doi: 10.1016/s0002-9149(02)02480-3
27. Gelatt M, Hamilton RM, McCrindle BW, Gow RM, Williams WG, Trusler GA, et al. Risk Factors for Atrial Tachyarrhythmias After the Fontan Operation. *J Am Coll Cardiol* (1994) 24(7):1735–41. doi: 10.1016/0735-1097(94)90181-3
28. Gourraud JB, Khairy P, Abadir S, Tadros R, Cadrin-Tourigny J, Macle L, et al. Atrial Fibrillation in Young Patients. *Expert Rev Cardiovasc Ther* (2018) 16:489–500. doi: 10.1080/14779072.2018.1490644
29. El-Battrawy I, Besler J, Liebe V, Schimpf R, Tülümen E, Rudic B, et al. Long-Term Follow-Up of Patients With Short QT Syndrome: Clinical Profile and Outcome. *J Am Heart Assoc* (2018) 7(23):e010073. doi: 10.1161/JAHA.118.010073
30. ElBattrawy I, Roterberg G, Schlentrich K, Liebe V, Lang S, Rudic B, et al. Clinical Profile And Long–Term Follow–Up Of Children With Brugada Syndrome. *Pediatr Cardiol* (2020) 41(2):290–6. doi: 10.1007/s00246-019-02254-5
31. Mills LC, Gow RM, Myers K, Kantoch MJ, Gross GJ, Fournier A, et al. Lone Atrial Fibrillation in the Pediatric Population. *Can J Cardiol* (2013) 29:1227–33. doi: 10.1016/j.cjca.2013.06.014
32. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland J, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* (2014) 64(21):e1–76. doi: 10.1016/j.jacc.2014.03.022
33. Shimizu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the Management of Atrial Fibrillation. *Thyroid* (2002) 12(6):489–93. doi: 10.1089/105072502760143863
34. Ari H, Gurdogan M, Erdogan E, Ari S, Ata Y, Tiryakioglu SK, et al. Short-Term Outcome of Early Electrical Cardioversion for Atrial Fibrillation in Hyperthyroid Versus Euthyroid Patients. *Cardiol J* (2012) 19(1):53–60. doi: 10.5603/CJ.2011.0022
35. Wongcharoen W, Lin YJ, Chang SL, Lo LW, Hu YF, Chung FP, et al. History of Hyperthyroidism and Long-Term Outcome of Catheter Ablation of Drug-Refractory Atrial Fibrillation. *Heart Rhythm* (2015) 12(9):1956–62. doi: 10.1016/j.hrthm.2015.06.004
36. Petersen P. Thromboembolic Complications in Atrial Fibrillation. *Stroke* (1990) 21(1):4. doi: 10.1161/01.str.21.1.4
37. Staffurth JS, Gibberd MC, Ng Tang Fui S. Arterial Embolism in Thyrotoxicosis With Atrial Fibrillation. *BMJ* (1977) 2:688–90. doi: 10.1136/bmj.2.6088.688
38. Presti CF, Hart RG. Thyrotoxicosis, Atrial Fibrillation, and Embolism, Revisited. *Am Heart J* (1989) 117:976–7. doi: 10.1016/0002-8703(89)90642-x
39. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Eur Heart J* (2016) 37:2893–962. doi: 10.1093/eurheartj/ehw210
40. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: The Euro Heart Survey on Atrial Fibrillation. *Chest* (2010) 137:26. doi: 10.1378/chest.09-1584
41. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, et al. Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function. *J Am Coll Cardiol* (2013) 62:1990–7. doi: 10.1016/j.jacc.2013.05.074
42. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* (2012) 141:e531S–75S. doi: 10.1378/chest.11-2304
43. Furst ML, Saarel EV, Hussein AA, Wazni OM, Tchou P, Kanj M, et al. Medical and Interventional Outcomes in Pediatric Lone Atrial Fibrillation. *JACC Clin Electrophysiol* (2018) 4(5):638–48. doi: 10.1016/j.jacep.2018.02.014
44. Barichello S, Roberts JD, Backx P, Boyle PM, Laksman Z. Personalizing Therapy for Atrial Fibrillation: The Role of Stem Cell And in Silico Disease Models. *Cardiovasc Res* (2018) 114:931–43. doi: 10.1093/cvr/cvy090
45. van Gorp PRR, Trines SA, Pijnappels DA, de Vries AAF. Multicellular *In Vitro* Models of Cardiac Arrhythmias: Focus on Atrial Fibrillation. *Front Cardiovasc Med* (2020) 7:43. doi: 10.3389/fcvm.2020.00043

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REVIEW
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Levothyroxine Treatment and the Risk of Cardiac Arrhythmias – Focus on the Patient Submitted to Thyroid Surgery

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Levothyroxine (LT4) is used to treat frequently encountered endocrinopathies such as thyroid diseases. It is regularly used in clinical (overt) hypothyroidism cases and subclinical (latent) hypothyroidism cases in the last decade. Suppressive LT4 therapy is also part of the medical regimen used to manage thyroid malignancies after a thyroidectomy. LT4 treatment possesses dual effects: substituting new-onset thyroid hormone deficiency and suppressing the local and distant malignancy spreading in cancer. It is the practice to administer LT4 in less-than-high suppressive doses for growth control of thyroid nodules and goiter, even in patients with preserved thyroid function. Despite its approved safety for clinical use, LT4 can sometimes induce side-effects, more often recorded with patients under treatment with LT4 suppressive doses than in unintentionally LT4-overdosed patients. Cardiac arrhythmias and the deterioration of osteoporosis are the most frequently documented side-effects of LT4 therapy. It also lowers the threshold for the onset or aggravation of cardiac arrhythmias for patients with pre-existing heart diseases. To improve the quality of life in LT4-substituted patients, clinicians often prescribe higher doses of LT4 to reach low normal TSH levels to achieve cellular euthyroidism. In such circumstances, the risk of cardiac arrhythmias, particularly atrial fibrillation, increases, and the combined use of LT4 and triiodothyronine further complicates such risk. This review summarizes the relevant available data related to LT4 suppressive treatment and the associated risk of cardiac arrhythmia.

Keywords: levothyroxine, thyroid, hypothyroidism, cardiac arrhythmias, osteoporosis, replacement therapy

1 INTRODUCTION

Thyroidectomy is a surgical procedure, performed either as a standard open surgery or as an alternative approach surgery, such as minimally invasive video-assisted thyroidectomy (MIVAT) or robot-assisted transaxillary thyroidectomy, aiming to remove all or part of the thyroid gland (1). The procedure is commonly used to treat a range of thyroid-related disorders, including thyroid cancer, hyperthyroidism goiters, and thyroid nodules that can be obstructive and cause swallowing or breathing difficulties (2). The introduction of MIVAT improved the treatment options for some thyroid conditions. Despite superiority regarding patients' satisfaction with faster recovery and decreased complications associated with standard open thyroidectomy (neck pain, voice problems, anxiety), it is confirmed as a reliable procedure in only strictly indicated cases (1). It is not suitable for patients with thyroiditis, large multinodular goiters, locally invasive thyroid carcinoma, or the presence of lateral neck compartment malignant lymph nodes. It evolves as standard procedure in the carefully selected cases with low- and intermediate-risk differentiated thyroid carcinoma (3, 4).

The thyroid gland produces the iodine-containing thyroid hormones, triiodothyronine (T3) and thyroxine (T4) in response to thyroid stimulation hormone (TSH) and the peptide hormone calcitonin, which is primarily regulated by serum calcium levels (5, 6). Together, these hormones regulate a wide range of metabolic and cardiovascular processes, including basal metabolic rate, appetite, gut motility, nutrient absorption, rate and strength of heart contractions, breathing, and oxygen consumption (7). Thyroid hormones also play a developmental role; they are essential for cell growth, while cells of the developing brain are a major target for T3 and T4 (8).

When the whole thyroid is extirpated, such gland surgery is referred to as total thyroidectomy. Knowing that thyroid hormones are essential for life, it is necessary to permanently replace the resultant deficiency with thyroxine after total thyroidectomy. Without replacement, a patient will develop signs and symptoms of hypothyroidism. Standard treatment in such instances is the long-term prescription of the synthetic thyroid hormone levothyroxine (LT4, a manufactured form of T4). In cancer cases, LT4 treatment after thyroidectomy can have the added advantage of suppressing local and distant malignancies from spreading. However, the LT4 dose must be carefully optimized to avoid potential adverse effects such as weight loss, sweating, anxiety, insomnia, osteoporosis (increased bone fracture risk), and an increased heart rate. Thus, LT4 treatment in individuals that have suffered a recent heart attack is cautiously recommended (9). It is not surprising that some individuals experience cardiovascular complications following LT4 treatment as thyroid hormones regulate cardiac functioning. Indeed, increased thyroid hormone levels are associated with an increased risk of developing heart arrhythmias (10). Here we examine the relevant literature related to LT4 treatment after thyroidectomy and the associated risk of cardiac arrhythmias in such patients.

2 LEVOTHYROXINE (LT4): STRUCTURE, BRIEF HISTORY, PHARMACOKINETICS, PHARMACODYNAMICS, DOSING REGIMENS

Levothyroxine is a synthetic version of the secreted thyroid hormone thyroxine (T4) that completely mimics all physiologic effects of T4 (**Figure 1**). LT4 is used as replacement therapy in

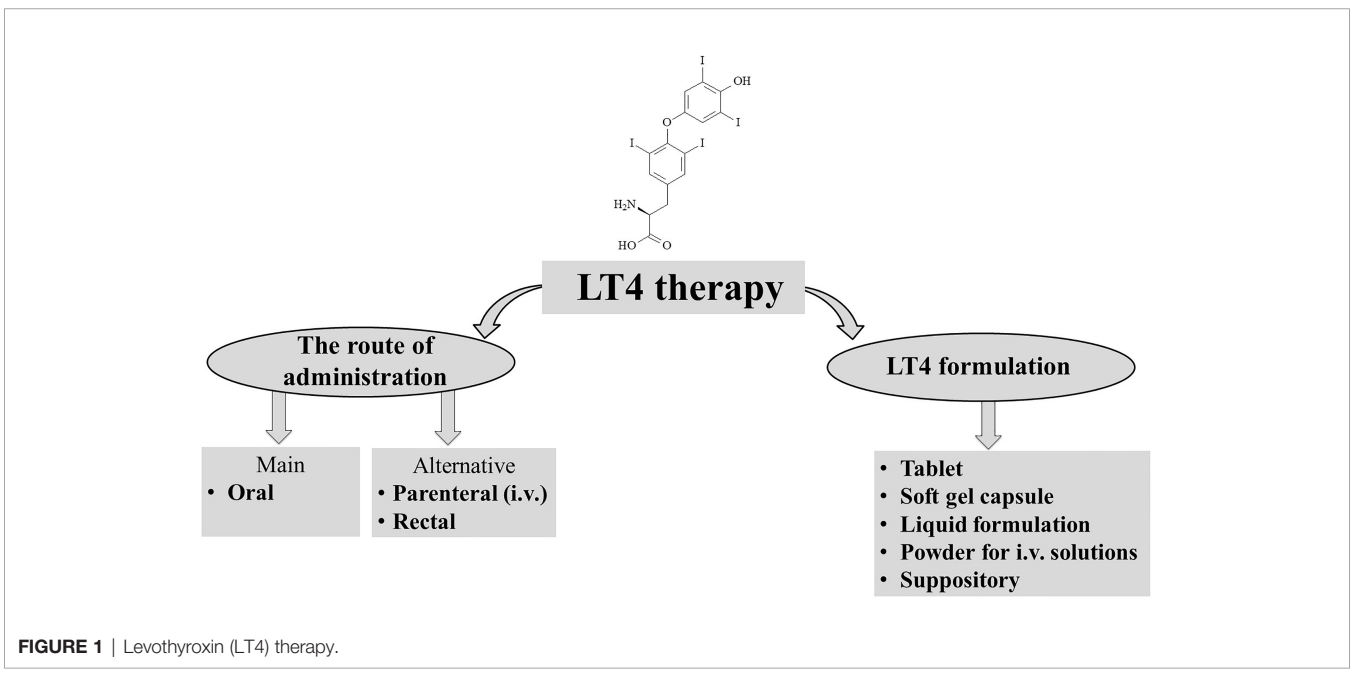

FIGURE 1 | Levothyroxin (LT4) therapy.

primary-thyroidal, secondary-pituitary, and tertiary-hypothalamic hypothyroidism (11, 12). Despite T4 being naturally present as a racemic mixture of the levo and dextro forms, LT4 is produced as a levo-isomer due to its greater physiological activity than the dextro form (13, 14).

The use of LT4 as a standard monotherapy came to the fore in the 1970s with evidence that T3 is predominantly produced by peripheral deiodination of T4. In patients treated with LT4 alone, thyroid function becomes normalized (15–17). Before that, combination therapy of synthetic LT4 and LT3 was the standard hormone replacement therapy in hypothyroid patients (18). Hypothyroidism treatment dates from the 6th century and Chinese medicine, where animal thyroid was used for therapy (17, 19). The same approach was applied in Europe but later in the 19th century (17, 19). In the 20th century, the discovery of thyroid hormones accelerated progress towards developing the current therapies (13, 17).

Adults with newly diagnosed hypothyroidism and without other complications receive an initial dose of 1.6 μg/kg/day for a few months. After dose modification, it is recommended to check the TSH level every 6-8 weeks (11, 12). In adult hypothyroid patients, hypothyroid patients with pre-existing heart diseases or >65 years old, an initial dose of 25 μg/day of LT4 is given, followed by an adjusted dose of 12.5 to 25 mcg every 4-6 weeks (11, 12). In patients with severe hypothyroidism or myxedema coma, the initial dose may be 200 to 400 μg administered *via* nasogastric tube or intravenously, followed by a daily dose of 1.2 μg/kg/day. Older patients or patients with heart disease are recommended to use lower doses (11, 12). It is recommended to decrease the LT4 dose for elderly patients. Regarding suppressive treatment for the control of thyroid nodule growth, the LT4 dose is individually tailored to maintain TSH levels as low-normal or at a partial suppressive level. In the high-risk patients following thyroidectomy for well-differentiated thyroid cancer, the estimated LT4 full suppressive dose is ≥2 μg/kg body weight (11, 12, 20–23).

The level of thyroid-stimulating hormone (TSH) in serum is used as an indicator of monitoring and adjusting the dose of LT4 therapy in hypothyroid patients, except in patients with secondary or tertiary hypothyroidism, where the level of free or total T4 is used as a marker for the success of the therapy (11, 12, 24). The standard monitoring procedure requires determining TSH levels 6-8 weeks after the initial treatment with LT4 (11, 12). After achieving the correct dose of LT4, the level of TSH is monitored firstly at 4-6 months, and after that, every 12 months (11, 12).

LT4 toxicity is rare, but adverse effects due to inappropriate dosage (over-or under-dose) can occur, especially in patients with pre-existing comorbidities such as cardiovascular disease, uncorrected adrenal insufficiency, and elderly patients (25).

Absorption of orally administered LT4 from the gastrointestinal tract mainly occurs in the small intestine rather than the stomach (26, 27). The absorbed LT4 varies from 60% to 80%, with the maximum concentration in circulation achieved 3 hours after administration in hypothyroid subjects and slightly faster in euthyroid subjects, approximately 2 hours (28–30). Several factors influence LT4 absorption, including deranged small intestine physiology (e.g. bowel resection reduced absorption), fasting increased absorption, while different foods, drugs, and supplements can also disturb LT4 absorption (30, 31). All these factors indicate the need for permanent monitoring in individual approaches in LT4 replacement (32). The half-life for T_4 is ~7.5 days in patients with primary hypothyroidism, with a daily turnover rate of ~10% for T_4 and 50–70% for T_3 (33). Contrary, in euthyroid subjects, the half-life for T4 is 6.2 days, and a little faster turnover rate (34–36). In addition, the estimated T_3 half-life is 1.4 days in hypothyroid patients and 1.0 days for euthyroid individuals (34–36). The values reported for T4 clearance are very close in hypothyroid subjects (approx. 0.04-0.06 l/h) and normal control individuals (0.05-0.06 l/h) (33, 37).

The liver is the primary site of LT4 degradation (38, 39). Although T_4 is catabolized *via* several routes, the major pathway of T_4 catabolism is sequential deiodination in the presence of deiodinase enzymes (38–40). The removal of iodine from carbon 5 of the outer ring of T4 converts it to T3, while removing iodine from the inner ring of T4 leads to the formation of inactive reverse T3 (rT3) (41, 42). T3 and rT3 originate from T4 at an ~1:1 ratio, and about 80% of T3 in circulation stems from peripheral T4 (43, 44). Subsequently, T3 can be converted to both diiodothyronine (T2) and iodothyronine (T1), and rT3 to both rT2 and rT1 (45, 46).

3 THYROID DISEASES AND CONDITIONS ASSOCIATED WITH LT4 USE

Long-term use of levothyroxine (LT4) has been demonstrated to be effective and safe. Initially, LT4 was used only in thyroxin (T4) deficiency cases, but LT4 usage has evolved and includes substitution and suppressive therapy (17). The aim of LT4 treatment differs according to the indication of use. In hypothyroid subjects, the goal of LT4 substitution is to establish a euthyroid rank of TSH while improving quality of life. The goal of LT4 treatment in controlling nodule growth is a low normal TSH level but avoiding LT4 overdose (47). After surgical management of malignant disease, treatment goals are to obtain suppressed levels of both TSH and thyroglobulin (48). Lower doses of LT4 are necessary to achieve substitution goals in elderly patients, while higher LT4 doses are required in patients undergoing total thyroidectomy (49). Long-term use of LT4 substitution reduces the risk of bradycardia, which is often associated with hypothyroidism (50). In patients with low-normal or suppressed TSH levels, an increased risk of cardiac arrhythmias, primarily atrial fibrillation (AF), is observed (10, 51, 52), as is an increased risk of osteoporosis (53, 54) and overall mortality (55). However, Flynn et al. (52) showed that patients with TSH levels between 0.04 to 0.4 mIU/ml did not experience an increased risk of cardiovascular disease, arrhythmias, or osteoporotic fractures (56).

The management with LT4 after MIVAT, either substitutive or suppressive modality, depends on the pathology of the partially or entirely extirpated thyroid gland. Each LT4

management modality must be individually tailored to the patient. MIVAT treated benign diseases require standard LT4 substitution therapy, while malignant disease (i.e. differentiated thyroid cancer) requires partial or complete TSH suppression depending on assigned risk. In high-risk patients, a complete suppressive LT4 regimen (TSH <0.1 mIU/ml) is recommended opposite to a partial LT4 suppressive regimen in lower-risk patients (TSH 0.1-0.4 mIU/ml) (48, 57).

In addition to hypothyroidism classification according to clinical presentation (subclinical or latent and clinical or overt), there is another classification based on the level of lesion-induced thyroid dysfunction. Primary hypothyroidism is the most frequently encountered in clinical practice (49). Secondary (at pituitary level) hypothyroidism, tertiary (at hypothalamus level) hypothyroidism, and thyroid hormone resistance account for less than 1% of overall hypothyroidism. They are mostly presented with symptoms and signs of mild hypothyroidism and sometimes with local effects (i.e., symptoms and signs of increased intracranial pressure). Besides the clinical presentation of hypothyroidism, thyroid hormone resistance syndromes can also present as mental health problems (49, 58, 59). LT4-dose tapering is more complex in patients with secondary and tertiary hypothyroidism as the fT4 levels, which is the basis of how the quality of LT4 dosing is assessed, are less flexible (49, 60). Whether iatrogenic or disease-induced, all forms of hypothyroidism (subclinical or clinical) unequivocally accelerate atherosclerosis processes, which can contribute to increased cardiovascular morbidity and mortality (61–66).

The prevalence of overt hypothyroidism in the general population is 0.3–3.7% in the USA (67) and 0.2–5.3% in Europe (68) depending on the definition of hypothyroidism. Hypothyroidism is more common in people over 65 years, women, and Caucasians. Among these, the most common cause of primary hypothyroidism in iodine-sufficient areas is chronic autoimmune thyroiditis. Although thyroid anti-peroxidase antibodies are of diagnostic significance, they also present in about 11% of people with no thyroid disease (49, 69).

4 LT4 REPLACEMENT THERAPY IN CARDIOVASCULAR PATIENTS

LT4 replacement therapy compensates for endogenous thyroxine deficiency, whether the disease's latent (subclinical) or manifested (clinical) form or post-procedural hypothyroidism. Excessive LT4 substitution in cardiovascular patients can have serious side effects, such as AF and osteoporosis, especially in postmenopausal women and elderly patients (49, 52). These complications are frequently observed in Hashimoto's thyroiditis patients due to LT4 over-supplementation (54). In cases of long-term TSH suppression, an increase in left ventricular mass and consequent diastolic dysfunction may occur, which further contributes to cardiovascular morbidity, especially in those patients with already diagnosed cardiovascular disease (70). A study by Petersen et al. (71), suggested that the prevalence of ischemic heart disease in people over 65 years of age with suppressed TSH levels on LT4 substitution was increased relative to the general population. Other studies suggest that atherosclerosis acceleration can occur during subclinical hypothyroidism development (72, 73).

It is known that thyroid hormones, when present in excess, affect the cardiovascular (CV) system by increasing heart rate, myocardial contractility, left ventricular mass, and the predisposition to supraventricular arrhythmias (74). Lipophilic T3 binds to the thyroid hormone receptor (TR) upon entry into the cardiomyocyte nucleus. Activation of TR results in stimulating gene transcription of the heavy alpha chain of myosin, calcium ATPase, Na/K-ATPase, beta 1 adrenergic receptor, and atrial natriuretic peptide (75–77). Genomic and non-genomic effects of thyroid hormones on cardiomyocytes lead to increased myocardial contractility, which, among other hemodynamic effects, results in increased heart rate, increased circulating volume, left ventricular volume, ejection fraction, and cardiac output (74).

Subclinical thyroidopathies can harm the cardiovascular system and manifest as an increase in CV morbidity and mortality by 20-80% (78, 79). Regardless of whether it is of endogenous or exogenous origin, in subclinical hyperthyroidism type 2 (TSH <0.1mIU/ml), the risk of AF presence is higher (HR 2.54 *vs.* 1.63) than in type 1 (TSH 0.1-0.4mIU/ml) (80, 81). Subclinical hyperthyroidism is associated with an increased left ventricular mass that increases ejection fraction (EF) and diastolic dysfunction (80, 82, 83). Clinical hyperthyroidism is associated with a 16% increased risk of major CV events commonly manifested as worsening heart failure, including high-output heart failure (84). It is noteworthy that an increased supraventricular ectopic activity often accompanies hyperthyroidism (85).

5 PATHOPHYSIOLOGY OF CARDIAC RHYTHM DISORDERS

Abnormal Ca^{2+} handling within cardiomyocytes is central to many types of arrhythmias. Arrhythmia-related contractions begin with external Ca^{2+} entering the cell's cytosol through the L-type calcium channels to signal the sarcoplasmic reticulum to release more Ca^{2+} *via* ryanodine receptor channels (RyRs) - specifically the RyR2 isoform (86, 87). RyRs facilitate downstream calcium-dependent processes throughout the cell, e.g., actin-myosin contraction (88, 89). Inositol 1,4,5-trisphosphate receptor (IP3R) also responds to cellular cues to release Ca^{2+} from the SR (90). Ca^{2+} release from the SR initiates contraction in cardiac myocytes, but removing Ca^{2+} from the cytosol following systole is equally vital. In diastole, sarco/endoplasmic reticulum calcium ATPase translocates cytosolic Ca^{2+} back into the SR. Diastole is a sensitive time window for Ca^{2+} clearance, and improper Ca^{2+} clearance can have significant arrhythmogenic consequences (87). Mutations or covalent modifications of RyR channels can cause Ca^{2+} leakage across the SR membrane during diastole, promoting arrhythmias (91, 92). Our recent work shows that Zn^{2+} regulates the open probability of

RyR2 in a manner that regulates beat-to-beat contractions in cardiomyocytes (93). This finding suggests that aberrant intracellular zinc homeostasis could contribute to arrhythmogenic events. Premature Ca^{2+} flux from the SR results in untimely depolarization events known as early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) (87). Ventricular arrhythmias can be caused by abnormal Ca^{2+} handling, electrolyte imbalance, and/or myocardial scarring (94). Physical barriers can also promote arrhythmia (e.g., fibrotic tissue) developing from ischemia and subsequent scarring (95, 96). Although myocardial scarring is the common feature in fatal ventricular arrhythmias, metabolic abnormalities may also play a significant role.

5.1 Cardiac Arrhythmias Associated With Thyroid Hormones

Cardiac arrhythmias are defined as irregular heartbeats and range in severity. They are generally defined by the affected region of the heart and the type of defect: supraventricular arrhythmias (brady- and tachyarrhythmias including atrial premature complexes) and ventricular arrhythmias. AF is one of the most common types of chronic arrhythmia, recognized in an electrocardiogram as an irregular P–R interval and a missing P wave. AF occurs more frequently in obese people and is the most common arrhythmia associated with abnormal thyroid hormone levels (97). It is a highly prevalent arrhythmia promoting heart failure, embolic stroke, and death (98). Even short, subclinical episodes of AF are associated with an increased risk of stroke (99). Paroxysmal and sustained or permanent forms of AF confer a significant clinical burden and worsens the patient's quality of life. AF is the most common cardiac complication of hyperthyroidism and LT4-induced thyrotoxicosis (97, 100) (**Figure 2**). Sinus tachycardia and atrial flutter are also commonly associated with hyperthyroidism (101). AF in thyrotoxicosis is associated with significant mortality and morbidity resulting from embolic events (97). The risk factors for AF in patients with hyperthyroidism are similar to those in the general population. They include age, male sex, and a history of ischemic, congestive, or valvular heart diseases (102).

AF occurs in up to 15% of patients with hyperthyroidism (103), compared with 4% in the general population (104). AF is more common in men and patients with T3 toxicosis (97). Also, subclinical hyperthyroidism is associated with an almost 3-fold increase in the risk of developing AF (103). Once initiated, AF alters the electrical and structural properties of the atria in a manner that affects its maintenance, increasing the risk of recurrence and can alter the response to antiarrhythmic drugs (97, 105). In addition, AF increases the risk of cerebrovascular stroke, peripheral embolization, and overall mortality (106–108). About 13-15% of individuals with newly developed AF have biochemical hyperthyroidism (103). The risk factors of developing AF in hyperthyroid individuals are age, pre-existing ischemic or valvular heart disease, or heart failure (85). Analysis of Framingham study results, related to the frequency of AF

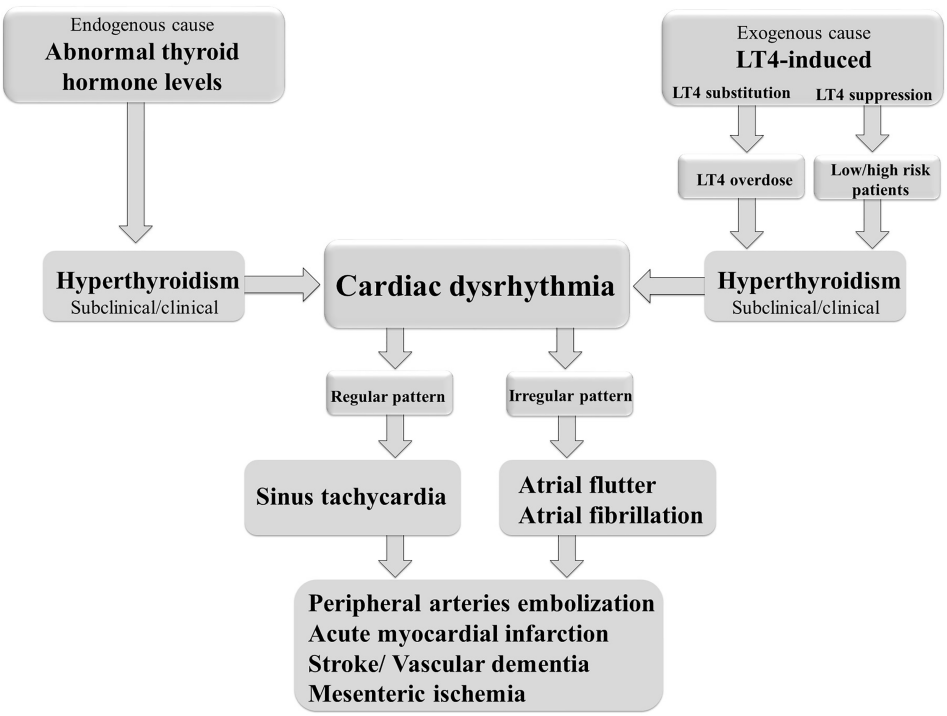

FIGURE 2 | Thyroid dysfunction and the risk of cardiac arrhythmias.

during a ten-year follow-up of patients >60 years, showed that AF occurred in 28% of those with subclinical hyperthyroidism, as opposed to 11% euthyroid patients. Furthermore, decreased TSH values, even with normal serum thyroid hormone values, were associated with a 3-fold increase in the frequency of AF (103). Heering et al. (Rotterdam study) showed a higher incidence of AF and sudden cardiac death in people >55 years with low normal TSH values and high normal FT4 levels (109). Studies using Mendeleev's randomization to demonstrate an association between thyroid dysfunction and cardiovascular disease also reported an association between hyperthyroidism and AF (110, 111).

5.1.1 LT4 Therapy and Cardiac Arrhythmias

Effects of T3 such as acceleration of cardiac depolarization and repolarization, the shortening of the action potential duration, and the refractory period of the atrial myocardium and AV node are not observed in mono-LT4 therapy. Namely, the production of T3 in patients on LT4 substitution, primarily after thyroidectomy, is related to the peripheral deiodination of T4. Antithyroid therapy and beta-blockers affect heart rate control, even conversion to normal sinus rhythm in about 60% of patients (85, 112, 113). The most important factor influencing the conversion of AF to sinus rhythm in hyperthyroidism is the duration of AF (114). In cases where AF lasts for more than a year in the elderly and is resistant to antithyroid and beta-blocker therapy, AF is often associated with ischemic heart disease (115). In the cases where LT4 use (exogenous hyperthyroidism) induces TSH suppression, incidences of CV and arrhythmic events are increased compared to the general population (52). AF, provoked either by endogenous or exogenous hyperthyroidism, results in a significant increase in overall morbidity and mortality, mainly caused by the consequences of systemic embolism (97). Compared to euthyroid subjects, patients with suppressed TSH have increased sympathetic autonomic activity and decreased parasympathetic tone, resulting in increased heart rate variability and prolonged QT interval (116). The mentioned changes in the CV system in patients with subclinical or clinical hyperthyroidism may result in an increased frequency of cardiac arrhythmias, primarily AF (106), and a higher frequency of systolic and diastolic left ventricular dysfunction (74, 117).

In addition to AF, in patients on LT4 suppressive therapy, sinus tachycardia and shortening of the PR interval are often detected electrocardiographically as manifestations of accelerated atrioventricular conduction (118–120). The prolonged P wave is most often seen as a manifestation of impaired interatrial conduction, while a delay in intraventricular conduction often results in a right bundle branch block (121). Ventricular arrhythmias in patients on LT4 suppressive therapy are rare, and their presence should always arouse suspicion of pre-existing heart disease. It should be noted that the incidence of ventricular fibrillation (VF) attributed solely to the thyroid status imbalance is less frequent in humans compared to experimental animals, which are prone to both AF and VF in response to an excess of thyroid hormones (TH) (101, 122, 123).

Epidemiological studies have shown higher cardiovascular and all-cause mortality in patients with endogenous and exogenous hyperthyroidism than in the general population (55, 124, 125). Also, a study by Klein-Hesselink et al. reports 3.3 times higher mortality due to CV in patients with differentiated thyroid cancer (DTC). In comparison, mortality from all causes was 4.4 times higher than in the general population, regardless of age, gender, and cardiovascular risk factors. Furthermore, each 10-fold decrease in TSH levels increased the risk of cardiovascular death by 3-fold (126). A study by Suha et al. showed similar results, demonstrating a higher incidence of coronary heart disease (CVD) and cerebrovascular insult (CVI) in patients diagnosed with DTC, with the risk of CVD and CVI being directly proportional to the dose of LT4 administered (127).

Although the use of suppressive doses of LT4 can lead to a significant reduction in TN volume and diffuse atoxic goiter, the potential side effects of this therapy on the CV system and bone metabolism, especially in people over 60 years and postmenopausal women, are limiting factors for the routine use of this therapeutic approach (48). However, using supraphysiological LT4 doses in younger patients to suppress TSH levels reduces TN volume in one out of six patients without significant comorbidity (128).

5.1.2 LT4 Combined With T3 Therapy and Cardiac Arrhythmias

The combined use of LT4 and LT3 has multiplied over the last decade. The impression is that such increases in use are rarely observed in the group of patients that strictly require combination therapy, but mainly result from patients wishing to have experience with its use or pharmaceutical companies' pressure that favors its use in patients unsatisfied with LT4 treatment alone. The rationale for using T4 and T3 combination therapy is that defects in deiodinase enzymes that convert thyroxine to triiodothyronine could lead to persistent symptoms in patients despite being biochemically well-regulated on LT4 monotherapy (129). A lack of more extensive studies pointed out LT3+LT4 positive effects on patients' wellbeing and the increase in the previously insufficient functional capacity of peripheral tissues. The real benefit of the LT3+LT4 combination could be expected in a relatively small number of hypothyroid patients. ETA suggests the LT3+LT4 combination as an experimental 3-month trial observed by an experienced endocrinologist in LT4 well-compliant patients persistently presented with hypothyroidism-associated complaints, despite normal TSH levels. If there is no improvement in LT3+LT4 treated patients after 3 months of use, it should be discontinued (130). LT3+LT4 combination is not recommended in patients with cardiac arrhythmias, as increased free T3 could act pro-arrythmically in prone patients (130, 131).

Additionally, Regalbuto et al. did not show any advantage of combined LT3+LT4 over LT4 monotherapy suppression in totally thyroidectomized patients for thyroid cancer regarding improved wellbeing and peripheral tissue response. Even though thyroid function tests suggested subclinical hyperthyroidism, the clinical syndrome of LT3 and LT4 excess

was not registered (132). Similarly, Tariq et al. did not find any additional risk for atrial fibrillation and cardiovascular disease in patients on combined LT3+LT4 therapy (133).

6 CARDIAC ELECTRICAL REMODELING ASSOCIATED WITH HYPERTHYROIDISM AND LT4 TREATMENT

Electrophysiological studies reveal that TH modifies f-channel conductance in sinoatrial cells, which changes the diastolic depolarization rate (134–136). This finding suggests a direct effect on myocardial membrane-related electrogenesis. Moreover, it provides the potential mechanism behind bradycardia and sinus tachycardia's association with hyperthyroidism.

Cardiac arrhythmia classification assumes disturbance of rhythm results from abnormal 1) impulse initiation and/or 2) intercellular impulse propagation (137). The abnormal impulse initiation is associated with abnormal automaticity and/or a triggered activity (induced by EAD or DAD). On the other hand, abnormal intercellular impulse propagation refers to a block of conduction and re-entry. Re-entry occurs when the propagating impulse persists due to continuous activity, after normal activation of the heart, instead of dying out, that re-excites the heart after the refractory period has ended (138).

TH effects on the development of AF and VF are more complex than chronotropic effects. There are several potential mechanisms by which TH can trigger arrhythmicity in the heart. Such effects are likely exerted through the same mechanisms as hyperthyroidism. One such mechanism is its direct involvement in controlling the transcription of genes encoding ion channels and other proteins involved in signal transduction. For example, TH regulates mRNA transcription of voltage-activated K^+ channel genes, including those encoding Kv4.3, Kv.4.2 (which contribute to the transient outward potassium current) and Kv1.4, Kv1.5, and Kv1.2 (which contribute to the ultra-rapid delayed rectifier potassium current) (139–143), and about nine ion channel α- and β-subunits (144). Hyperthyroidism was found to up-regulate the expression of Kv1.5 mRNA, particularly in the atrium of the heart (145). Sunagawa et al. demonstrated decreased L-type Ca^{2+} channel expression in the atria and Kv1.2 and Kv1.4 in both atrial and ventricular tissue in LT4-treated rats (136). Interestingly, despite this decrease in L-type Ca^{2+} channel expression, the L-type Ca^{2+} current increased (146–148), most likely due to the TH-induced transcriptional regulation of myocardial Ca^{2+} cycling proteins.

TH has the potential to influence Ca^{2+} levels in cardiomyocytes through multiple mechanisms, including regulating the expression of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2) and RyR2 [Ca^{2+} cycling proteins; (149)], and down-regulating Na^+/Ca^{2+} exchanger and phospholamban (150–153). Increased Ca^{2+} influx and efflux rates also characterize hyperthyroidism in ventricular cells (154) most likely due to altered activation of sarcolemmal Ca^{2+} channels and SERCA2 activity (148, 155). There are also rapid non-genomic TH responses that modulate the activity of Ca^{2+} cycling proteins and have consequent effects on intracellular Ca^{2+} currents (147, 148, 150, 156). It is expected that LT4 therapy can induce aberrant Ca^{2+} homeostasis through altered Ca^{2+} handling similar to hyperthyroidism/TH activity.

Another mechanism by which clinical use of LT4 may trigger arrhythmia is the modulation of cardiac connexins. Connexin-43 (Cx43) is expressed in the ventricles and atria of the heart and is responsible for gap junction formation and thus the transmission of electrical signals between cells. TH receptors bind to the Cx43 promoter, indicating that TH can modify the expression of Cx43 mRNA synthesis (157). For example, it has been shown that Cx43 protein levels increase in TH-treated neonatal cultured cardiomyocytes (158). Also, in the atria and ventricles of hyperthyroid rats, phosphorylation of Cx43 isoforms is reduced, compared to untreated controls (159, 160). This is interesting as VF (159) and AF (101) susceptibility increases in T3-treated rats when myocardial Cx43 phosphorylation decreases. Also, TH-treated rat liver epithelial cells stimulate gap junctional communication and Cx43 mRNA expression (161).

7 CONCLUSIONS

Patients who have undergone thyroidectomy exhibit compromised production of thyroid hormones, which warrant hormone replacement therapy to avoid developing hypothyroidism. To date, the standard treatment in such instances is a long-term LT4 treatment regimen. LT4 treatment after thyroidectomy to treat cancer has the added advantage of suppressing the local and distant malignancy from spreading. However, each patient's LT4 dose must be optimized to avoid potential side effects such as weight loss, sweating, anxiety, insomnia, osteoporosis (increased bone fracture risk), and an increased heart rate. Thus, LT4 treatment is not recommended in recent heart attack patients.

Nonetheless, patients with no known CV issues can experience CV complications following LT4 treatment, which is not surprising given the role of TH in regulating cardiac functioning. It is associated with an increased risk of developing heart arrhythmias, primarily AF, as well as osteoporosis. Although, studies do show that LT4 treated patients with TSH levels from 0.04 to 0.4 mIU/ml had not experienced an increased risk of cardiovascular disease, arrhythmias, or osteoporotic fracture. Also, LT4 doses in younger patients to suppress TSH levels reduce TN volume in one out of six patients without significant comorbidities. Nevertheless, suppressive LT4 doses can lead to potential side effects of this therapy on the CV system and bone metabolism, especially in people over 60 years and postmenopausal women. Thus, there are limiting factors for the routine use of this therapeutic approach, but improving the approach to individualized medicine in the at-risk population (implementing less excessive LT4 treatment regimens and monitoring more LT4 arrhythmia triggers) may reduce cardiac arrhythmia risk and mortality.

AUTHOR CONTRIBUTIONS

ZG, MO, and EI designed, wrote and supervised the manuscript. AJS, ME, SJP, VS, and SS wrote the manuscript. AJS and TG critically revised the manuscript. All authors contributed to manuscript revision, and approved the submitted version.

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REFERENCES

1. Rossi L, Materazzi G, Bakkar S, Miccoli P. Recent Trends in Surgical Approach to Thyroid Cancer. *Front Endocrinol (Lausanne)* (2021) 12:699805. doi: 10.3389/fendo.2021.699805
2. Dotter K. Obstructive Dysphagia and Positional Dyspnea: Can You Identify the Cause? *J Adv Practitioner Oncol* (2018) 9:441–4. doi: 10.6004/jadpro.2018.9.4.8
3. Kania R, Kania R, Hammami H, Vérillaud B, Blancal JP, Sauvaget E, et al. Minimally Invasive Video-Assisted Thyroidectomy: Tips and Pearls for the Surgical Technique. *Ann Otol Rhinol Laryngol* (2014) 123:409–14. doi: 10.1177/0003489414526845
4. Miccoli P, Fregoli L, Rossi L, Papini P, Ambrosini CE, Bakkar S, et al. Minimally Invasive Video-Assisted Thyroidectomy (MIVAT). *Gland Surg* (2020) 9:S1–5. doi: 10.21037/gs.2019.12.05
5. Colledge NR, Walker BR, Ralston S, Davidson S. *Davidson's Principles and Practice of Medicine*. Edinburgh: Churchill Livingstone/Elsevier (2010).
6. Xie J, Guo J, Kanwal Z, Wu M, Lv X, Ibrahim NA, et al. Calcitonin and Bone Physiology: *In Vitro*, *In Vivo*, and Clinical Investigations. *Int J Endocrinol* (2020) 2020:3236828. doi: 10.1155/2020/3236828
7. Hall JE, Guyton AC. *Guyton and Hall Textbook of Medical Physiology* (2011). Available at: http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090602506.
8. Rovet JF. The Role of Thyroid Hormones for Brain Development and Cognitive Function. *Endocr Dev* (2014) 26:26–43. doi: 10.1159/0003
9. Eghtedari B, Correa R. Levothyroxine. [Updated 2020 Oct 12]. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing (2021). Available at: https://www.ncbi.nlm.nih.gov/books/NBK539808/.
10. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. *Circulation* (2017) 136:2100–16. doi: 10.1161/CIRCULATIONAHA.117.028753
11. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* (2012) 18:988–1028. doi: 10.4158/EP12280.GL
12. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid* (2014) 24:1670–751. doi: 10.1089/thy.2014.0028
13. Harington CR, Barger G. Chemistry of Thyroxine: Constitution and Synthesis of Thyroxine. *Biochem J* (1927) 21:169–83. doi: 10.1042/bj0210169
14. Benvenga S, Carlé A. Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution. *Adv Ther* (2019) 36:59–71. doi: 10.1007/s12325-019-01079-1
15. Surks MI, Schadlow AR, Oppenheimer JH. A New Radioimmunoassay for Plasma L-Triiodothyronine: Measurements in Thyroid Disease and in Patients Maintained on Hormonal Replacement. *J Clin Invest* (1972) 51:3104–13. doi: 10.1172/JCI107137
16. Surks MI, Schadlow AR, Stock JM, Oppenheimer JH. Determination of Iodothyronine Absorption and Conversion of L-Thyroxine (T 4) to L-Triiodothyronine (T 3) Using Turnover Rate Techniques. *J Clin Invest* (1973) 52:805–11. doi: 10.1172/JCI107244
17. Mateo RCI, Hennessey JV. Thyroxine and Treatment of Hypothyroidism: Seven Decades of Experience. *Endocrine* (2019) 66:10–7. doi: 10.1007/s12020-019-02006-8
18. Taylor S, Kapur M, Adie R. Combined Thyroxine and Triiodothyronine for Thyroid Replacement Therapy. *Br Med J* (1970) 2:270–1. doi: 10.1136/bmj.2.5704.270
19. Slater S. The Discovery of Thyroid Replacement Therapy. Part 3: A Complete Transformation. *J R Soc Med* (2011) 104:100–6. doi: 10.1258/jrsm.2010.10k052
20. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J* (2013) 2:215–28. doi: 10.1159/000356507
21. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M, et al. Management of Primary Hypothyroidism: Statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)* (2016) 84:799–808. doi: 10.1111/cen.12824
22. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid Hormones Treatment for Subclinical Hypothyroidism: A Clinical Practice Guideline. *Bmj* (2019) 365:l2006. doi: 10.1136/bmj.l2006
23. NICE. Thyroid Disease: Assessment and Management, in: *NICE Guideline [NG145]* (2019). Available at: https://www.nice.org.uk/guidance/ng145/chapter/Recommendations (Accessed Jul 2020).
24. Duntas LH, Jonklaas J. Levothyroxine Dose Adjustment to Optimise Therapy Throughout a Patient's Lifetime. *Adv Ther* (2019) 36:30–46. doi: 10.1007/s12325-019-01078-2
25. Bartalena L, Bogazzi F, Martino E. Adverse Effects of Thyroid Hormone Preparations and Antithyroid Drugs. *Drug Safety* (1996) 15:53–63. doi: 10.2165/00002018-199615010-00004
26. Hays MT. Thyroid Hormone and the Gut. *Endocr Res* (1988) 14:203–24. doi: 10.3109/07435808809032986
27. Hays MT. Localization of Human Thyroxine Absorption. *Thyroid* (1991) 1:241–8. doi: 10.1089/thy.1991.1.241
28. Read DG, Hays MT, Hershman JM. Absorption of Oral Thyroxine in Hypothyroid and Normal Man. *J Clin Endocrinol Metab* (1970) 30:798–9. doi: 10.1210/jcem-30-6-798
29. Hasselström K, Siersbaek-Nielsen K, Lumholtz IB, Faber J, Kirkegaard C, Friis T. The Bioavailability of Thyroxine and 3,5,3'-Triiodothyronine in Normal Subjects and in Hyper- and Hypothyroid Patients. *Acta Endocrinol (Copenh)* (1985) 110:483–6. doi: 10.1530/acta.0.1100483
30. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed Intestinal Absorption of Levothyroxine. *Thyroid* (1995) 5:249–53. doi: 10.1089/thy.1995.5.249

31. Stone E, Leiter LA, Lambert JR, Silverberg JD, Jeejeebhoy KN, Burrow GN. L-Thyroxine Absorption in Patients With Short Bowel. *J Clin Endocrinol Metab* (1984) 59:139–41. doi: 10.1210/jcem-59-1-139
32. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Individualised Requirements for Optimum Treatment of Hypothyroidism: Complex Needs, Limited Options. *Drugs Context* (2019) 8:212597–7. doi: 10.7573/dic.212597
33. Nicoloff JT, Low JC, Dussault JH, Fisher DA. Simultaneous Measurement of Thyroxine and Triiodothyronine Peripheral Turnover Kinetics in Man. *J Clin Invest* (1972) 51:473–83. doi: 10.1172/JCI106835
34. Braverman LE, Vagenakis A, Downs P, Foster AE, Sterling K, Ingbar SH. Effects of Replacement Doses of Sodium L-Thyroxine on the Peripheral Metabolism of Thyroxine and Triiodothyronine in Man. *J Clin Invest* (1973) 52:1010–7. doi: 10.1172/JCI107265
35. Colucci P, Yue CS, Ducharme M, Benvenga S. A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism. *Eur Endocrinol* (2013) 9:40–7. doi: 10.17925/EE.2013.09.01.40
36. Dayan C, Panicker V. Management of Hypothyroidism With Combination Thyroxine (T4) and Triiodothyronine (T3) Hormone Replacement in Clinical Practice: A Review of Suggested Guidance. *Thyroid Res* (2018) 11:1. doi: 10.1186/s13044-018-0045-x
37. Pittman CS, Shimizu T, Burger A, Chambers JBJr. The Nondeiodinative Pathways of Thyroxine Metabolism: 3,5,3',5-Tetraiodothyroacetic Acid Turnover in Normal and Fasting Human Subjects. *J Clin Endocrinol Metab* (1980) 50:712–6. doi: 10.1210/jcem-50-4-712
38. Mol JA, Visser TJ. Rapid and Selective Inner Ring Deiodination of Thyroxine Sulfate by Rat Liver Deiodinase. *Endocrinology* (1985) 117:8–12. doi: 10.1210/endo-117-1-8
39. Rutgers M, Heusdens FA, Visser TJ. Deiodination of Iodothyronine Sulfamates by Type I Iodothyronine Deiodinase of Rat Liver. *Endocrinology* (1991) 129:1375–81. doi: 10.1210/endo-129-3-1375
40. Galton VA, Larsen PR, Berry MJ. The Deiodinases: Their Identification and Cloning of Their Genes. *Endocrinology* (2021) 162:1–9. doi: 10.1210/endocr/bqab005
41. Braverman LE, Ingbar SH, Sterling K. Conversion of Thyroxine (T4) to Triiodothyronine (T3) in Athyreotic Human Subjects. *J Clin Invest* (1970) 49:855–64. doi: 10.1172/JCI106304
42. Sterling K, Brenner MA, Newman ES. Conversion of Thyroxine to Triiodothyronine in Normal Human Subjects. *Science* (1970) 169:1099–100. doi: 10.1126/science.169.3950.1099
43. Pittman CS, Chambers JBJr., Read VH. The Extrathyroidal Conversion Rate of Thyroxine to Triiodothyronine in Normal Man. *J Clin Invest* (1971) 50:1187–96. doi: 10.1172/JCI106596
44. Inada M, Kasagi K, Kurata S, Kazama Y, Takayama H, Torizuka K, et al. Estimation of Thyroxine and Triiodothyronine Distribution and of the Conversion Rate of Thyroxine to Triiodothyronine in Man. *J Clin Invest* (1975) 55:1337–48. doi: 10.1172/JCI108053
45. Engler D, Merkelbach U, Steiger G, Burger AG. The Monodeiodination of Triiodothyronine and Reverse Triiodothyronine in Man: A Quantitative Evaluation of the Pathway by the Use of Turnover Rate Techniques. *J Clin Endocrinol Metab* (1984) 58:49–61. doi: 10.1210/jcem-58-1-49
46. Burger AG, O'Connell M, Scheidegger K, Woo R, Danforth EJr. Monodeiodination of Triiodothyronine and Reverse Triiodothyronine During Low and High Calorie Diets. *J Clin Endocrinol Metab* (1987) 65:829–35. doi: 10.1210/jcem-65-5-829
47. Biondi B, Cooper DS. Thyroid Hormone Suppression Therapy. *Endocrinol Metab Clin North Am* (2019) 48:227–37. doi: 10.1016/j.ecl.2018.10.008
48. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients With Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
49. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet* (2017) 390:1550–62. doi: 10.1016/S0140-6736(17)30703-1
50. Hylander B, Kennebäck G, Rosenqvist U, Edhag O. Long-Term ECG Recordings in Thyroxine-Substituted Hypothyroid Subjects. *Acta Med Scand* (1987) 222:429–32. doi: 10.1111/j.0954-6820.1987.tb10960.x
51. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults. *Jama* (2006) 295:1033–41. doi: 10.1001/jama.295.9.1033
52. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum Thyroid-Stimulating Hormone Concentration and Morbidity From Cardiovascular Disease and Fractures in Patients on Long-Term Thyroxine Therapy. *J Clin Endocrinol Metab* (2010) 95:186–93. doi: 10.1210/jc.2009-1625
53. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on Bone Mass of Long Term Treatment With Thyroid Hormones: A Meta-Analysis. *J Clin Endocrinol Metab* (1996) 81:4278–89. doi: 10.1210/jcem.81.12.8954028
54. Mincer DL, Jialal I. Hashimoto Thyroiditis. In: *StatPearls*. Treasure Island (FL: StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC (2021).
55. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of All-Cause and Cardiovascular Mortality in Elderly People From One Low Serum Thyrotropin Result: A 10-Year Cohort Study. *Lancet* (2001) 358:861–5. doi: 10.1016/S0140-6736(01)06067-6
56. Toft AD, Beckett GJ. Thyroid Function Tests and Hypothyroidism. *Bmj* (2003) 326:295–6. doi: 10.1136/bmj.326.7384.295
57. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the Management of Thyroid Cancer. *Clin Endocrinol (Oxf)* (2014) 81 Suppl 1:1–122. doi: 10.1111/cen.12515
58. Barbesino G, Sluss PM, Caturegli P. Central Hypothyroidism in a Patient With Pituitary Autoimmunity: Evidence for TSH-Independent Thyroid Hormone Synthesis. *J Clin Endocrinol Metab* (2012) 97:345–50. doi: 10.1210/jc.2011-1591
59. Pappa T, Refetoff S. Resistance to Thyroid Hormone Beta: A Focused Review. *Front Endocrinol (Lausanne)* (2021) 12:656551. doi: 10.3389/fendo.2021.656551
60. Persani L. Clinical Review: Central Hypothyroidism: Pathogenic, Diagnostic, and Therapeutic Challenges. *J Clin Endocrinol Metab* (2012) 97:3068–78. doi: 10.1210/jc.2012-1616
61. Kharbanda RK, Walton B, Allen M, Klein N, Hingorani AD, MacAllister RJ, et al. Prevention of Inflammation-Induced Endothelial Dysfunction: A Novel Vasculo-Protective Action of Aspirin. *Circulation* (2002) 105:2600–4. doi: 10.1161/01.CIR.0000017863.52347.6C
62. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, et al. Impaired Endothelium-Dependent Vasodilatation in Subclinical Hypothyroidism: Beneficial Effect of Levothyroxine Therapy. *J Clin Endocrinol Metab* (2003) 88:3731–7. doi: 10.1210/jc.2003-030039
63. Schuett H, Luchtefeld M, Grothusen C, Grote K, Schieffer B. How Much Is Too Much? Interleukin-6 and Its Signalling in Atherosclerosis. *Thromb Haemost* (2009) 102:215–22. doi: 10.1160/TH09-05-0297
64. Türemen EE, Çetinarslan B, Şahin T, Cantürk Z, Tarkun İ. Endothelial Dysfunction and Low Grade Chronic Inflammation in Subclinical Hypothyroidism Due to Autoimmune Thyroiditis. *Endocr J* (2011) 58:349–54. doi: 10.1507/endocrj.K10E-333
65. Obradovic M, Gluvic Z, Sudar-Milovanovic E, Panic A, Trebaljevac J, Bajic V, et al. Nitric Oxide as a Marker for Levo-Thyroxine Therapy in Subclinical Hypothyroid Patients. *Curr Vasc Pharmacol* (2016) 14:266–70. doi: 10.2174/1570161114666160208143537
66. Gluvic ZM, Obradovic MM, Sudar-Milovanovic EM, Zafirovic SS, Radak DJ, Essack MM, et al. Regulation of Nitric Oxide Production in Hypothyroidism. *BioMed Pharmacother* (2020) 124:109881. doi: 10.1016/j.biopha.2020.109881
67. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med* (2000) 160:526–34. doi: 10.1001/archinte.160.4.526
68. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis. *J Clin Endocrinol Metab* (2014) 99:923–31. doi: 10.1210/jc.2013-2409
69. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. T(4), and Thyroid Antibodies in the United States Population 1998 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* (2002) 87:489–99. doi: 10.1210/jcem.87.2.8182

70. Fazio S, Biondi B, Carella C, Sabatini D, Cittadini A, Panza N, et al. Diastolic Dysfunction in Patients on Thyroid-Stimulating Hormone Suppressive Therapy With Levothyroxine: Beneficial Effect of Beta-Blockade. *J Clin Endocrinol Metab* (1995) 80:2222–6. doi: 10.1210/jcem.80.7.7608283
71. Petersen K, Bengtsson C, Lapidus L, Lindstedt G, Nyström E. Morbidity, Mortality, and Quality of Life for Patients Treated With Levothyroxine. *Arch Intern Med* (1990) 150:2077–81. doi: 10.1001/archinte.1990.00390210063015
72. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The Beneficial Effect of L-Thyroxine on Cardiovascular Risk Factors, Endothelial Function, and Quality of Life in Subclinical Hypothyroidism: Randomized, Crossover Trial. *J Clin Endocrinol Metab* (2007) 92:1715–23. doi: 10.1210/jc.2006-1869
73. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol* (2018) 71:1781–96. doi: 10.1016/j.jacc.2018.02.045
74. Klein I, Danzi S. Thyroid Disease and the Heart. *Circulation* (2007) 116:1725–35. doi: 10.1161/CIRCULATIONAHA.106.678326
75. Izumo S, Nadal-Ginard B, Mahdavi V. All Members of the MHC Multigene Family Respond to Thyroid Hormone in a Highly Tissue-Specific Manner. *Science* (1986) 231:597–600. doi: 10.1126/science.3945800
76. Morkin E. Regulation of Myosin Heavy Chain Genes in the Heart. *Circulation* (1993) 87:1451–60. doi: 10.1161/01.CIR.87.5.1451
77. Zarain-Herzberg A, Marques J, Sukovich D, Periasamy M. Thyroid Hormone Receptor Modulates the Expression of the Rabbit Cardiac Sarco (Endo) Plasmic Reticulum Ca(2+)-ATPase Gene. *J Biol Chem* (1994) 269:1460–7. doi: 10.1016/S0021-9258(17)42279-4
78. Larsen PR. Thyroid-Pituitary Interaction: Feedback Regulation of Thyrotropin Secretion by Thyroid Hormones. *N Engl J Med* (1982) 306:23–32. doi: 10.1056/NEJM198201073060107
79. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid Hormones and Cardiovascular Disease. *Nat Rev Cardiol* (2017) 14:39–55. doi: 10.1038/nrcardio.2016.174
80. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of Thyroid Hormone on Cardiac Function: The Relative Importance of Heart Rate, Loading Conditions, and Myocardial Contractility in the Regulation of Cardiac Performance in Human Hyperthyroidism. *J Clin Endocrinol Metab* (2002) 87:968–74. doi: 10.1210/jcem.87.3.8302
81. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, et al. Subclinical Hyperthyroidism and the Risk of Coronary Heart Disease and Mortality. *Arch Intern Med* (2012) 172:799–809. doi: 10.1001/archinternmed.2012.402
82. Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, et al. Minimal Cardiac Effects in Asymptomatic Athyreotic Patients Chronically Treated With Thyrotropin-Suppressive Doses of L-Thyroxine. *J Clin Endocrinol Metab* (1997) 82:2592–5. doi: 10.1210/jc.82.8.2592
83. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left Ventricular Diastolic Dysfunction in Patients With Subclinical Hypothyroidism. *J Clin Endocrinol Metab* (1999) 84:2064–7. doi: 10.1210/jcem.84.6.5733
84. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, et al. Subclinical and Overt Thyroid Dysfunction and Risk of All-Cause Mortality and Cardiovascular Events: A Large Population Study. *J Clin Endocrinol Metab* (2014) 99:2372–82. doi: 10.1210/jc.2013-4184
85. Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M. The Mechanisms of Atrial Fibrillation in Hyperthyroidism. *Thyroid Res* (2009) 2:4. doi: 10.1186/1756-6614-2-4
86. Lanner JT, Georgiou DK, Joshi AD, Hamilton SL. Ryanodine Receptors: Structure, Expression, Molecular Details, and Function in Calcium Release. *Cold Spring Harb Perspect Biol* (2010) 2:a003996. doi: 10.1101/cshperspect.a003996
87. Wakili R, Voigt N, Kääb S, Dobrev D, Nattel S. Recent Advances in the Molecular Pathophysiology of Atrial Fibrillation. *J Clin Invest* (2011) 121:2955–68. doi: 10.1172/JCI46315
88. Peng W, Shen H, Wu J, Guo W, Pan X, Wang R, et al. Structural Basis for the Gating Mechanism of the Type 2 Ryanodine Receptor Ryr2. *Science* (2016) 354:aah5324. doi: 10.1126/science.aah5324
89. Santulli G, Lewis D, des Georges A, Marks AR, Frank J. Ryanodine Receptor Structure and Function in Health and Disease. *Subcell Biochem* (2018) 87:329–52. doi: 10.1007/978-981-10-7757-9_11
90. Ai X, Curran JW, Shannon TR, Bers DM, Pogwizd SM. Ca2+/calmodulin-Dependent Protein Kinase Modulates Cardiac Ryanodine Receptor Phosphorylation and Sarcoplasmic Reticulum Ca2+ Leak in Heart Failure. *Circ Res* (2005) 97:1314–22. doi: 10.1161/01.RES.0000194329.41863.89
91. Shan J, Xie W, Betzenhauser M, Reiken S, Chen BX, Wronska A, et al. Calcium Leak Through Ryanodine Receptors Leads to Atrial Fibrillation in 3 Mouse Models of Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Res* (2012) 111:708–17. doi: 10.1161/CIRCRESAHA.112.273342
92. Uehara A, Murayama T, Yasukochi M, Fill M, Horie M, Okamoto T, et al. Extensive Ca2+ Leak Through K4750Q Cardiac Ryanodine Receptors Caused by Cytosolic and Luminal Ca2+ Hypersensitivity. *J Gen Physiol* (2017) 149:199–218. doi: 10.1085/jgp.201611624
93. Woodier J, Rainbow RD, Stewart AJ, Pitt SJ. Intracellular Zinc Modulates Cardiac Ryanodine Receptor-Mediated Calcium Release. *J Biol Chem* (2015) 290:17599–610. doi: 10.1074/jbc.M115.661280
94. Skogestad J, Aronsen JM. Hypokalemia-Induced Arrhythmias and Heart Failure: New Insights and Implications for Therapy. *Front Physiol* (2018) 9:1500–0. doi: 10.3389/fphys.2018.01500
95. Homan EA, Reyes MV, Hickey KT, Morrow JP. Clinical Overview of Obesity and Diabetes Mellitus as Risk Factors for Atrial Fibrillation and Sudden Cardiac Death. *Front Physiol* (2018) 9:1847. doi: 10.3389/fphys.2018.01847
96. Gowen BH, Reyes MV, Joseph LC, Morrow JP. Mechanisms of Chronic Metabolic Stress in Arrhythmias. *Antioxid (Basel Switzerland)* (2020) 9:1012. doi: 10.3390/antiox9101012
97. Staffurth JS, Gibberd MC, Fui SN. Arterial Embolism in Thyrotoxicosis With Atrial Fibrillation. *Br Med J* (1977) 2:688–90. doi: 10.1136/bmj.2.6088.688
98. Packer M. Effect of Catheter Ablation on Pre-Existing Abnormalities of Left Atrial Systolic, Diastolic, and Neurohormonal Functions in Patients With Chronic Heart Failure and Atrial Fibrillation. *Eur Heart J* (2019) 40:1873–9. doi: 10.1093/eurheartj/ehz284
99. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, et al. Subclinical Device-Detected Atrial Fibrillation and Stroke Risk: A Systematic Review and Meta-Analysis. *Eur Heart J* (2018) 39:1407–15. doi: 10.1093/eurheartj/ehx731
100. Gong IY, Atzema CL, Lega IC, Austin PC, Na Y, Rochon PA, et al. Levothyroxine Dose and Risk of Atrial Fibrillation: A Nested Case-Control Study. *Am Heart J* (2021) 232:47–56. doi: 10.1016/j.ahj.2020.09.016
101. Tribulova N, Knezl V, Shainberg A, Seki S, Soukup T. Thyroid Hormones and Cardiac Arrhythmias. *Vasc Pharmacol* (2010) 52:102–12. doi: 10.1016/j.vph.2009.10.001
102. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and Risk of Atrial Fibrillation or Flutter: A Population-Based Study. *Arch Intern Med* (2004) 164:1675–8. doi: 10.1001/archinte.164.15.1675
103. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low Serum Thyrotropin Concentrations as a Risk Factor for Atrial Fibrillation in Older Persons. *New Engl J Med* (1994) 331:1249–52. doi: 10.1056/NEJM199411103311901
104. Forfar JC, Miller HC, Toft AD. Occult Thyrotoxicosis: A Correctable Cause of "Idiopathic" Atrial Fibrillation. *Am J Cardiol* (1979) 44:9–12. doi: 10.1016/0002-9149(79)90243-1
105. Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, et al. Atrial Fibrillation After Isolated Coronary Surgery Affects Late Survival. *Circulation* (2008) 118:1612–8. doi: 10.1161/CIRCULATIONAHA.108.777789
106. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study. *Stroke* (1991) 22:983–8. doi: 10.1161/01.STR.22.8.983
107. Frost L, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident Thromboembolism in the Aorta and the Renal, Mesenteric, Pelvic, and Extremity Arteries After Discharge From the Hospital With a Diagnosis of Atrial Fibrillation. *Arch Intern Med* (2001) 161:272–6. doi: 10.1001/archinte.161.2.272
108. Wong CL, Tam HV, Fok CV, Lam PE, Fung LM. Thyrotoxic Atrial Fibrillation: Factors Associated With Persistence and Risk of Ischemic Stroke. *J Thyroid Res* (2017) 2017:4259183. doi: 10.1155/2017/4259183
109. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, Incidence and Lifetime Risk of Atrial Fibrillation: The Rotterdam Study. *Eur Heart J* (2006) 27:949–53. doi: 10.1093/eurheartj/ehi825

110. Ellervik C, Roselli C, Christophersen IE, Alonso A, Pietzner M, Sitlani CM, et al. Assessment of the Relationship Between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study. *JAMA Cardiol* (2019) 4:144–52. doi: 10.1001/jamacardio.2018.4635
111. Larsson SC, Allara E, Mason AM, Michaëlsson K, Burgess S. Thyroid Function and Dysfunction in Relation to 16 Cardiovascular Diseases. *Circ Genom Precis Med* (2019) 12:e002468. doi: 10.1161/CIRCGEN.118.002468
112. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of Atrial Fibrillation in the Post-Thyrotoxic State. *Am J Med* (1982) 72:903–6. doi: 10.1016/0002-9343(82)90850-6
113. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. *Eur Thyroid J* (2015) 4:149–63. doi: 10.1159/000438750
114. Banach M, Mariscalco G, Ugurlucan M, Mikhailidis DP, Barylski M, Rysz J. The Significance of Preoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery: Preoperative Atrial Fibrillation–Still Underestimated Opponent. *Europace* (2008) 10:1266–70. doi: 10.1093/europace/eun273
115. Shimizu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the Management of Atrial Fibrillation. *Thyroid* (2002) 12:489–93. doi: 10.1089/105072502760143863
116. Liu C, Lv H, Li Q, Fu S, Tan J, Wang C, et al. Effect of Thyrotropin Suppressive Therapy on Heart Rate Variability and QT Dispersion in Patients With Differentiated Thyroid Cancer. *Med (Baltimore)* (2020) 99: e21190. doi: 10.1097/MD.0000000000021190
117. Ikram H. The Nature and Prognosis of Thyrotoxic Heart Disease. *Q J Med* (1985) 54:19–28. doi: 10.1093/oxfordjournals.qjmed.a067825
118. Iskandar SB, Jordan RM, Peiris AN. Electrocardiographic Abnormalities and Endocrine Diseases–Part a: Hyperthyroidism. *Tenn Med* (2007) 100, 47:50.
119. Zhang Y, Post WS, Cheng A, Blasco-Colmenares E, Tomaselli GF, Guallar E. Thyroid Hormones and Electrocardiographic Parameters: Findings From the Third National Health and Nutrition Examination Survey. *PloS One* (2013) 8:e59489. doi: 10.1371/journal.pone.0059489
120. Baladi IH, Rai AA, Ahmed SM. ECG Changes in Patients With Primary Hyperthyroidism. *Pan Afr Med J* (2018) 30:246. doi: 10.11604/pamj.2018.30.246.12244
121. von Olshausen K, Bischoff S, Kahaly G, Mohr-Kahaly S, Erbel R, Beyer J, et al. Cardiac Arrhythmias and Heart Rate in Hyperthyroidism. *Am J Cardiol* (1989) 63:930–3. doi: 10.1016/0002-9149(89)90142-2
122. Szeiffová Bačová B, Egan Beňová T, Viczenczová C, Soukup T, Rauchová H, Pavelka S, et al. Cardiac Connexin-43 and PKC Signaling in Rats With Altered Thyroid Status Without and With Omega-3 Fatty Acids Intake. *Physiol Res* (2016) 65 Suppl 1:S77–90. doi: 10.33549/physiolres.933413
123. Bačová BS, Vinczenzová C, Žurmanová J, Kašparová D, Knezl V, Beňová TE, et al. Altered Thyroid Status Affects Myocardial Expression of Connexin-43 and Susceptibility of Rat Heart to Malignant Arrhythmias That Can be Partially Normalized by Red Palm Oil Intake. *Histochem Cell Biol* (2017) 147:63–73. doi: 10.1007/s00418-016-1488-6
124. Osman F, Franklyn JA, Holder RL, Sheppard MC, Gammage MD. Cardiovascular Manifestations of Hyperthyroidism Before and After Antithyroid Therapy: A Matched Case-Control Study. *J Am Coll Cardiol* (2007) 49:71–81. doi: 10.1016/j.jacc.2006.08.042
125. Brandt F, Green A, Hegedüs L, Brix TH. A Critical Review and Meta-Analysis of the Association Between Overt Hyperthyroidism and Mortality. *Eur J Endocrinol* (2011) 165:491–7. doi: 10.1530/EJE-11-0299
126. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredeveld EJ, et al. Long-Term Cardiovascular Mortality in Patients With Differentiated Thyroid Carcinoma: An Observational Study. *J Clin Oncol* (2013) 31:4046–53. doi: 10.1200/JCO.2013.49.1043
127. Suh B, Shin DW, Park Y, Lim H, Yun JM, Song SO, et al. Increased Cardiovascular Risk in Thyroid Cancer Patients Taking Levothyroxine: A Nationwide Cohort Study in Korea. *Eur J Endocrinol* (2019) 180:11–20. doi: 10.1530/EJE-18-0551
128. Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of Simple Nodular Goiter: Current Status and Future Perspectives. *Endocr Rev* (2003) 24:102–32. doi: 10.1210/er.2002-0016
129. Michaelsson LF, Medici BB, la Cour JL, Selmer C, Røder M, Perrild H, et al. Treating Hypothyroidism With Thyroxine/Triiodothyronine Combination Therapy in Denmark: Following Guidelines or Following Trends? *Eur Thyroid J* (2015) 4:174–80. doi: 10.1159/000437262
130. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. *Eur Thyroid J* (2012) 1:55–71. doi: 10.1159/000339444
131. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* (2011) 21:593–646. doi: 10.1089/thy.2010.0417
132. Regalbuto C, Maiorana R, Alagona C, Paola RD, Cianci M, Alagona G, et al. Effects of Either LT4 Monotherapy or LT4/LT3 Combined Therapy in Patients Totally Thyroidectomized for Thyroid Cancer. *Thyroid* (2007) 17:323–31. doi: 10.1089/thy.2006.0084
133. Tariq A, Wert Y, Cheriyath P, Joshi R. Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life. *South Med J* (2018) 111:363–9. doi: 10.14423/SMJ.0000000000000823
134. Renaudon B, Lenfant J, Decressac S, Bois P. Thyroid Hormone Increases the Conductance Density of F-Channels in Rabbit Sino-Atrial Node Cells. *Recept Channels* (2000) 7:1–8.
135. Sun Z-Q, Ojamaa K, Nakamura TY, Artman M, Klein I, Coetzee WA. Thyroid Hormone Increases Pacemaker Activity in Rat Neonatal Atrial Myocytes. *J Mol Cell Cardiol* (2001) 33:811–24. doi: 10.1006/jmcc.2001.1353
136. Sunagawa M, Yamakawa M, Shimabukuro M, Higa N, Takasu N, Kosugi T. Electrophysiologic Characteristics of Atrial Myocytes in Levo-Thyroxine-Treated Rats. *Thyroid* (2005) 15:3–11. doi: 10.1089/thy.2005.15.3
137. Hoffman BF, Rosen MR. Cellular Mechanisms for Cardiac Arrhythmias. *Circ Res* (1981) 49:1–15. doi: 10.1161/01.RES.49.1.1
138. Tribulova N, Kurahara LH, Hlivak P, Hirano K, Szeiffova Bacova B. Pro-Arrhythmic Signaling of Thyroid Hormones and Its Relevance in Subclinical Hyperthyroidism. *Int J Mol Sci* (2020) 21:2844. doi: 10.3390/ijms21082844
139. Shimoni Y, Severson D, Giles W. Thyroid Status and Diabetes Modulate Regional Differences in Potassium Currents in Rat Ventricle. *J Physiol* (1995) 488(Pt 3):673–88. doi: 10.1113/jphysiol.1995.sp020999
140. Shimoni Y, Fiset C, Clark RB, Dixon JE, McKinnon D, Giles WR. Thyroid Hormone Regulates Postnatal Expression of Transient K+ Channel Isoforms in Rat Ventricle. *J Physiol* (1997) 500(Pt 1):65–73. doi: 10.1113/jphysiol.1997.sp021999
141. Wickenden AD, Kaprielian R, Parker TG, Jones OT, Backx PH. Effects of Development and Thyroid Hormone on K+ Currents and K+ Channel Gene Expression in Rat Ventricle. *J Physiol* (1997) 504(Pt 2):271–86. doi: 10.1111/j.1469-7793.1997.271be.x
142. Ojamaa K, Sabet A, Kenessey A, Shenoy R, Klein I. Regulation of Rat Cardiac Kv1.5 Gene Expression by Thyroid Hormone Is Rapid and Chamber Specific. *Endocrinology* (1999) 140:3170–6. doi: 10.1210/endo.140.7.6776
143. Ma ML, Watanabe K, Watanabe H, Hosaka Y, Komura S, Aizawa Y, et al. Different Gene Expression of Potassium Channels by Thyroid Hormone and an Antithyroid Drug Between the Atrium and Ventricle of Rats. *Jpn Heart J* (2003) 44:101–10. doi: 10.1536/jhj.44.101
144. Le Bouter S, Demolombe S, Chambellan A, Bellocq C, Aimond F, Toumaniantz G, et al. Microarray Analysis Reveals Complex Remodeling of Cardiac Ion Channel Expression With Altered Thyroid Status: Relation to Cellular and Integrated Electrophysiology. *Circ Res* (2003) 92:234–42. doi: 10.1161/01.RES.0000053185.75505.8E
145. Watanabe H, Ma M, Washizuka T, Komura S, Yoshida T, Hosaka Y, et al. Thyroid Hormone Regulates mRNA Expression and Currents of Ion Channels in Rat Atrium. *Biochem Biophys Res Commun* (2003) 308:439–44. doi: 10.1016/S0006-291X(03)01420-7
146. Mager S, Palti Y, Binah O. Mechanism of Hyperthyroidism-Induced Modulation of the L-Type Ca2+ Current in Guinea Pig Ventricular Myocytes. *Pflugers Arch* (1992) 421:425–30. doi: 10.1007/BF00370252
147. Gøtzsche LB. L-Triiodothyronine Acutely Increases Ca2+ Uptake in the Isolated, Perfused Rat Heart. Changes in L-Type Ca2+ Channels and Beta-Receptors During Short- and Long-Term Hyper- and Hypothyroidism. *Eur J Endocrinol* (1994) 130:171–9. doi: 10.1530/eje.0.1300171
148. Watanabe H, Washizuka T, Komura S, Yoshida T, Hosaka Y, Hatada K, et al. Genomic and Non-Genomic Regulation of L-Type Calcium Channels in Rat Ventricle by Thyroid Hormone. *Endocr Res* (2005) 31:59–70. doi: 10.1080/07435800500229227

149. Campanha F, Perone D, de Campos D, Luvizotto R, de Síbio M, de Oliveira M, et al. Thyroxine Increases Serca2 and Ryr2 Gene Expression in Heart Failure Rats With Euthyroid Sick Syndrome. *Arch Endocrinol Metab* (2013) 60:582–6. doi: 10.1590/2359-3997000000208
150. Connelly TJ, el-Hayek R, Sukhareva M, Coronado R. L-Thyroxine Activates the Intracellular Ca2+ Release Channel of Skeletal Muscle Sarcoplasmic Reticulum. *Biochem Mol Biol Int* (1994) 32:441–8.
151. Kiss E, Jakab G, Kranias EG, Edes I. Thyroid Hormone-Induced Alterations in Phospholamban Protein Expression. Regulatory Effects on Sarcoplasmic Reticulum Ca2+ Transport and Myocardial Relaxation. *Circ Res* (1994) 75:245–51. doi: 10.1161/01.RES.75.2.245
152. Cernohorský J, Kolár F, Pelouch V, Korecky B, Vetter R. Thyroid Control of Sarcolemmal Na+/Ca2+ Exchanger and SR Ca2+-ATPase in Developing Rat Heart. *Am J Physiol* (1998) 275:H264–73. doi: 10.1152/ajpheart.1998.275.1.H264
153. Shenoy R, Klein I, Ojamaa K. Differential Regulation of SR Calcium Transporters by Thyroid Hormone in Rat Atria and Ventricles. *Am J Physiol Heart Circ Physiol* (2001) 281:H1690–6. doi: 10.1152/ajpheart.2001.281.4.H1690
154. Kim D, Smith TW. Effects of Thyroid Hormone on Calcium Handling in Cultured Chick Ventricular Cells. *J Physiol* (1985) 364:131–49. doi: 10.1113/jphysiol.1985.sp015735
155. Mylotte KM, Cody V, Davis PJ, Davis FB, Blas SD, Schoenl M. Milrinone and Thyroid Hormone Stimulate Myocardial Membrane Ca2+-ATPase Activity and Share Structural Homologies. *Proc Natl Acad Sci USA* (1985) 82:7974–8. doi: 10.1073/pnas.82.23.7974
156. Segal J, Masalha S, Schwalb H, Merin G, Borman JB, Uretzky G. Acute Effect of Thyroid Hormone in the Rat Heart: Role of Calcium. *J Endocrinol* (1996) 149:73–80. doi: 10.1677/joe.0.1490073
157. Stock A, Sies H. Thyroid Hormone Receptors Bind to an Element in the Connexin43 Promoter. *Biol Chem* (2000) 381:973–9. doi: 10.1515/BC.2000.120
158. Tribulova N, Shneyvays V, Mamedova LK, Moshel S, Zinman T, Shainberg A, et al. Enhanced Connexin-43 and Alpha-Sarcomeric Actin Expression in Cultured Heart Myocytes Exposed to Triiodo-L-Thyronine. *J Mol Histol* (2004) 35:463–70. doi: 10.1023/B:HIJO.0000045945.16046.b5
159. Lin H, Mitasikova M, Dlugosova K, Okruhlicova L, Imanaga I, Ogawa K, et al. Thyroid Hormones Suppress Epsilon-PKC Signalling, Down-Regulate Connexin-43 and Increase Lethal Arrhythmia Susceptibility in Non-Diabetic and Diabetic Rat Hearts. *J Physiol Pharmacol* (2008) 59:271–85.
160. Mitašíková M, Lin H, Soukup T, Imanaga I, Tribulová N. Diabetes and Thyroid Hormones Affect Connexin-43 and PKC-Epsilon Expression in Rat Heart Atria. *Physiol Res* (2009) 58:211–7. doi: 10.33549/physiolres.931425
161. Stock A, Sies H, Stahl W. Enhancement of Gap Junctional Communication and Connexin43 Expression by Thyroid Hormones. *Biochem Pharmacol* (1998) 55:475–9. doi: 10.1016/S0006-2952(97)00473-5

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Abnormal Cardiac Repolarization in Thyroid Diseases: Results of an Observational Study

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Background: The relationship between thyroid function and cardiac disease is complex. Both hypothyroidism and thyrotoxicosis can predispose to ventricular arrhythmia and other major adverse cardiovascular events (MACE), so that a U-shaped relationship between thyroid signaling and the incidence of MACE has been postulated. Moreover, recently published data suggest an association between thyroid hormone concentration and the risk of sudden cardiac death (SCD) even in euthyroid populations with high-normal FT4 levels. In this study, we investigated markers of repolarization in ECGs, as predictors of cardiovascular events, in patients with a spectrum of subclinical and overt thyroid dysfunction.

Methods: Resting ECGs of 100 subjects, 90 patients (LV-EF > 45%) with thyroid disease (60 overt hyperthyroid, 11 overt hypothyroid and 19 L-T4-treated and biochemically euthyroid patients after thyroidectomy or with autoimmune thyroiditis) and 10 healthy volunteers were analyzed for Tp-e interval. The Tp-e interval was measured manually and was correlated to serum concentrations of thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and thyroxine (FT4).

Results: The Tp-e interval significantly correlated to log-transformed concentrations of TSH (Spearman's rho = 0.30, $p < 0.01$), FT4 (rho = −0.26, $p < 0.05$), and FT3 (rho = −0.23, $p < 0.05$) as well as log-transformed thyroid's secretory capacity (SPINA-GT, rho = −0.33, $p < 0.01$). Spearman's rho of correlations of JT interval to log-transformed TSH, FT4, FT3, and SPINA-GT were 0.51 ($p < 1e{-}7$), −0.45 ($p < 1e{-}5$), −0.55 ($p < 1e{-}8$), and −0.43 ($p < 1e{-}4$), respectively. In minimal multivariable regression models, markers of thyroid homeostasis correlated to heart rate, QT, Tp-e, and JT intervals. Group-wise evaluation in hypothyroid, euthyroid and hyperthyroid subjects revealed similar correlations in all three groups.

Conclusion: We observed significant inverse correlations of Tp-e and JT intervals with FT4 and FT3 over the whole spectrum of thyroid function. Our data suggest a possible mechanism of SCD in hypothyroid state by prolongation of repolarization. We do not observe a U-shaped relationship, so that the mechanism of SCD in patients with high FT4 or hyperthyroidism seems not to be driven by abnormalities in repolarization.

Keywords: repolarization, T-peak-to-end interval, JT interval, thyroid hormones, thyroid disorder and heart

INTRODUCTION

The relationship of thyroid disorders and cardiovascular diseases raises growing interest (1–3). Both, hypothyroid or hyperthyroid conditions may lead to increased cardiovascular morbidity and mortality (4). This well-accepted U-shaped relationship between thyroid function and cardiac disease is, however, still not fully clarified (5). As far as we know today, the mechanisms of hypo- or hyperthyroidism leading to cardiac diseases are diverse with effects on cardiac contractility, vasculature and cardiac electrophysiology (6, 7).

In a general population study an association between thyroid hormone levels, even within the respective normal range, and ECG changes has been described (8). Published data suggest an association between thyroid hormone concentrations and the risk of sudden cardiac death (SCD) even in euthyroid populations with high-normal FT4 concentration (9). Recently, similar relations between thyroid function and the incidence of other endpoints, including malignant arrhythmia and stress cardiomyopathy (Takotsubo syndrome), have been described (10, 11). However, the electrophysiological mechanisms underlying these observations are poorly understood up to now.

Repolarization abnormalities, especially prolonged repolarization, are assumed to be among the major risk factors for SCD (12, 13). Contradicting observations have been published concerning the effect of thyroid hormone levels especially on the QTc interval (14–18). Whereas, the effect of thyroid hormone disorders on the QTc interval has been extensively studied, very little is known on ventricular repolarization as measured by more specific repolarization markers including Tpeak-to T-end interval (Tp-e) or JT interval. The Tp-e interval has been established and recognized as a correlate of dispersion of ventricular repolarization (19). A prolonged Tp-e interval, and therefore a longer dispersion of ventricular repolarization, may be associated with ventricular tachyarrhythmias (20); similar findings were reported regarding the JT interval (13).

Interestingly, a prolonged Tp-e interval seems independently associated with SCD, even if the QTc is normal (21). Recently, one study showed a prolongation of Tp-e interval in patients with subclinical hypothyroidism (22). However, data on patients with overt thyroid disorders and hyperthyroidism have not been published up to now.

In this study, we investigated the Tp-e and JT intervals in ECGs of patients with a spectrum of subclinical and overt thyroid dysfunction and a euthyroid control group to assess pathological repolarization as a potential indicator of SCD.

METHODS

Study Design and Population

This study included 90 patients of the NOMOTHETICOS cohort (23) with untreated and treated primary thyroid dysfunction and for comparison 10 healthy volunteers. In all subjects a full thyroid hormone profile and 12-lead ECG measurements were performed.

None of the subjects had a severely impaired left ventricular ejection fraction (LV-EF $< 45\%$) or a left bundle branch block.

Additional inclusion criteria for patients with thyroid disease were

- Disconnected feedback control due to the following conditions at the time of recruitment:
  - Overt primary hypothyroidism with TSH level being higher than 10 mIU/l and FT4 concentration below 7 pmol/l (5.4 ng/l) (group 1)
  - Overt primary hyperthyroidism with TSH level below 0.1 mIU/l and FT4 concentration higher than 18 pmol/l (14 ng/l) (group 3)
  - All other constellations, if the patient receives substitution therapy with more than 1.75 μg Levothyroxin per kg of body mass (group 2).
- System in equilibrium (requiring no or unchanged substitution dose over the previous 6 weeks before investigation).

Inclusion criterion for healthy volunteers (group 0) were normal thyroid function with ruled out thyroid disease via ultrasound and normal concentrations of antibodies to thyroid peroxidase (TPOAb), thyroglobulin (TgAb), and TSH receptors (TRAb).

Exclusion criteria for all subjects were pituitary or hypothalamic disease, resistance to thyroid hormone, Allan-Herndon-Dudley syndrome, severe illness possibly associated with non-thyroidal illness syndrome (TACITUS), medication influencing pituitary function and pregnancy.

All subjects delivered written informed consent. The study design was approved by the local institutional ethics committee of the Medical Faculty at the Ruhr University of Bochum under the file number 3718-10. The protocol of the NOMOTHETICOS study (UTN U1111-1122-3273) has been

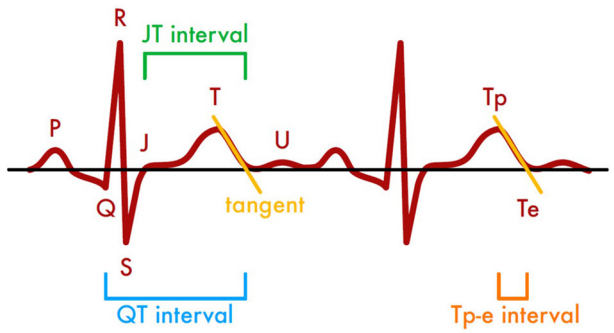

FIGURE 1 | Methods of assessing time intervals in ECG recordings based on the tangent method.

registered at ClinicalTrials.gov (ID NCT01145040) and in the German Clinical Trials Register (ID DRKS00003153).

ECG Measurements

All anonymized ECG recordings were distributed to three independent cardiologists blinded for laboratory results. The QT interval, defined as beginning of Q wave to the end of T wave, the JT interval, defined as the period from the J point (junction between the termination of the QRS complex and the beginning of the ST segment) to the end of the T wave, and Tp-e interval, defined as the distance of T wave peak to the end of T wave, were measured (**Figure 1**). The end of the T wave was determined by the tangent method (24). All measurements were performed manually and preferentially in lead V5. If a measurement in V5 was not possible the investigators were instructed to select alternatively lead V2–V4 or lead II (25).

Laboratory Measurements

Serum concentrations of TSH, FT4, and FT3 were determined with a fully automated chemiluminescence-based system (DxI800, Beckman-Coulter, Krefeld, NRW, Germany). The intra-assay and inter-assay CVs for these analyses vary with concentrations but are <10% for the range of measurement. Thyroid tissue antibodies (TPOAb, TgAb, and TRAb) were measured with quantitative radioimmunoassays (anti-TPOn, anti-Tgn and TRAKhuman, ThermoFisher, BRAHMS division, Henningsdorf, BB, Germany).

To assess the relative contributions of the pituitary and thyroid gland to the variations in hormone concentrations, Jostel's TSH index (JTI), thyroid's secretory capacity (SPINA-GT), and the sum activity of peripheral deiodinases (SPINA-GD) were calculated from steady-state concentrations of TSH and FT4 and constants for plasma protein binding and kinetics, as recently recommended for thyroid trial design (23, 26).

Statistical Analysis

Statistical analyses were performed with custom S scripts written for the environment R 3.6.3 on macOS. Depending on the class of analyzed data and possible direction of causality, distributions were compared with multivariable regression, 2-sample Student's *t*-test (Gaussian distributed variables), Wilcoxon's rank sum test (non-Gaussian variables) or chi-square test (counts). All four groups were compared with one-way ANOVA and *post-hoc* pairwise *t*-test. Alpha error correction for multiple testing was performed with the Benjamini-Hochberg procedure. Continuous variables were tested for normality with quantile-quantile (Q-Q) plots of z-transformed values.

To identify parameters that independently correlate to electrophysiological markers we conducted step-wise multivariable regression analysis based on variables that had a significant association to ECG markers in a univariable investigation. For this purpose, an initial maximal model including all possible predictors as suggested by univariable analysis was successively simplified by eliminating non-significant parameters to deliver a final minimal model containing significant predictors only. Thyroid volume and calculated parameters of thyroid homeostasis were not included in multivariable models in order to avoid multicollinearity. Before inclusion in a multivariable model TSH and thyroid hormone concentrations were logarithmically transformed to meet criteria of a normal distribution.

Where not otherwise specified, data are presented as mean value ± standard error of the mean (SEM) for normally distributed continuous data, as median (interquartile range) for non-normally distributed data or as absolute numbers (percentages) for count data. A p-value < 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

One hundred subjects were included in the analysis, 90 patients with thyroid disease (60 overt hyperthyroid, 11 overt hypothyroid and 19 L-T4-treated and biochemically euthyroid patients after thyroidectomy or with autoimmune thyroiditis) and 10 healthy volunteers for comparison purposes (**Table 1**). The mean age of the subjects was 52.8 ± 1.60 years, and 69 patients were women.

Phenotype of Thyroid Homeostasis

As shown in **Table 2**, TSH and thyroid hormones of subjects in group 0 were in the respective reference ranges. This also applies to calculated parameters for thyroid output (SPINA-GT), total deiodinase activity (SPINA-GD) and Jostel's TSH index and, with the exception of a slightly higher mean TSH concentration, to all markers in group 2. Deiodinase activity was elevated in group 1, representing an activated TSH-T3 feedforward control in the setting of elevated TSH concentrations (**Table 2**).

In univariable regression analysis, the correlation of heart rate to clinical and endocrine parameters demonstrated an inverse pattern to that of repolarization markers (**Figure 2**). In detail, the Tp-e interval significantly correlated to log-transformed concentrations of TSH (Spearman's rho = 0.30, $p < 0.01$), FT4 (rho = −0.26, $p < 0.05$), and FT3 (rho = −0.23, $p < 0.05$) as well as log-transformed thyroid's secretory capacity (SPINA-GT, rho = −0.33, $p < 0.01$). Spearman's rho of correlations of JT interval to log-transformed TSH, FT4, FT3, and SPINA-GT were 0.51 ($p < 1e{-}7$), −0.45 ($p < 1e{-}5$),

TABLE 1 | Basic characteristics of study population.

	Group 0 (normal subjects)	Group 1 (hypothyroidism)	Group 2 (full-dose L-T4 substitution therapy)	Group 3 (thyrotoxicosis)
N	10	11	19	60
Age (years)	56.3 ± 4.9	56.7 ± 4.6	45.1 ± 3.0	54.0 ± 2.1
Female (%)	6 (60%)	6 (54%)	17 (89%)	40 (67%)
BMI (kg/m^2)	27.5 ± 1.0	32.7 ± 3.4††	25.1 ± 1.7**	25.0 ± 0.7**
Atrial fibrillation (%)	0 (0%)	1 (9%)	0 (0%)	10 (17%)
Thyroid disease				
Acute or subacute thyroiditis	0	0	0	8
Amiodarone-induced thyroid disease	0	1	0	7
Toxic adenoma	0	0	1	5
Hashimoto's disease	0	0	1	1
Ord's disease	0	5	0	0
Graves' disease	0	2	2	16
Graves' disease with Hashimoto component	0	1	3	20
Schmidt-Carpenter's syndrome	0	0	1	0
Marine-Lenhart syndrome	0	0	0	3
Post-surgical or radiogenic hypothyroidism	0	2	11	0
Sodium (135–145 mmol/L)	138.8 ± 0.6	139.9 ± 1.0	139.6 ± 0.9	138.8 ± 0.4
Potassium (3.5–5 mmol/L)	4.1 ± 0.2	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.1
Calcium (2.2–2.6 mmol/L)	2.3 ± 0.0	2.2 ± 0.1	2.2 ± 0.1†	2.4 ± 0.0
Creatinine (71–124 μmol/L)	75.1 (35.4)†	97.2 (35.4)†††	61.9 (8.8)*	61.9 (26.5)***
HbA1c (4–6%)	5.8 ± 0.3	6.4 ± 0.5	5.6 ± 0.3	5.6 ± 0.1
Beta1-selective beta-blocker use	3 (30%)	4 (36%)	5 (26%)	27 (45%)
Unselective beta-blocker use	0 (0%)†††	0 (0%)†††	0 (0%)†††	21 (35%)***‡‡‡
Cardiac glycoside use	0 (0%)	1 (9%)	0 (0%)	2 (3%)
Amiodarone use	0 (0%)	1 (9%)	0 (0%)	7 (12%)
Carbamazepine use	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Methylphenidate use	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Antipsychotic drug use	0 (0%)	1 (9%)	1 (5%)	2 (3%)
Selective serotonin reuptake inhibitor use	0 (0%)	0 (0%)	1 (5%)	2 (3%)
Tricyclic antidepressant used	2 (20%)	0 (0%)	1 (5%)	2 (3%)
Antihistamine use	0 (0%)	1 (9%)	0 (0%)	1 (2%)
Thyroid volume (mL)	11.0 ± 0.6	12.3 ± 3.4††	8.4 ± 3.2†††	27.9 ± 2.1**
Levothyroxine dosage (μg/day)	0 ± 0	52.3 ± 23.0	88.2 ± 22.7†††‡‡‡	8.3 ± 5.3

*Corrected $p < 0.05$ (*), < 0.01 (**), < 0.001 (***) compared to group 1 (hypothyroidism). Corrected $p < 0.05$ (†), < 0.01 (††), < 0.001 (†††) compared to group 3. Corrected $p < 0.001$ (‡‡‡) compared to group 0. See **Supplementary Tables 1–20** for detailed p-values.*

-0.55 ($p < 1e{-}8$), and -0.43 ($p < 1e{-}4$), respectively (**Figure 3**). Group-wise evaluation in hypothyroid, euthyroid and hyperthyroid subjects revealed similar correlations in all three groups.

Consistently with the results of group-wise hormone statistics (**Table 2**) and regression analysis the heart rate and markers of repolarization were significantly different between the four groups (**Table 3**). The P wave duration did not differ among the groups. In minimal models of multivariable analysis markers of thyroid homeostasis remained predictors of electrophysiological parameters after adjustment for medication, and they were the only predictors of Tp-e and JT intervals after step-wise reduction (**Table 4**).

DISCUSSION

In this study we investigated a potential relationship between thyroid function and several markers of cardiac repolarization. The data reveal a robust association of heart rate and several time constants in the resting ECG, especially of the JT interval, to thyroid function. This connection is stronger than that to other physiological predictors of heart rhythm including BMI, renal function and serum electrolytes. With respect to heart rate and QT interval, biomarkers of thyroid homeostasis remained significant predictors of cardiac electrophysiology in minimal multivariable regression models adjusting for antiarrhythmic medication including selective betablockers and amiodarone. Step-wise model simplification arrived at the elimination of all

TABLE 2 | Measured and calculated parameters of thyroid homeostasis in the four groups.

Parameter (reference range)	Group 0 (normal subjects)	Group 1 (hypothyroidism)	Group 2 (full-dose L-T4 substitution therapy)	Group 3 (thyrotoxicosis)
TSH (0.35–3.5 mIU/L)	1.47 (0.91)***††††	76.33 (92.48)††††‡‡‡	1.41 (3.33)****††††	0.03 (0.04)****‡‡‡‡
FT4 (8–18 pmol/L)	12.2 (3.2)***††††	3.9 (2.3)****††††‡‡‡	12.9 (3.9)****††††	45.0 (22.5)****‡‡‡‡
FT3 (3.5–6.3 pmol/l)	4.9 (0.6)***††††	3.0 (0.8)††††‡‡‡	4.7 (1.0)****††††	16.1 (13.6)****‡‡‡‡
SPINA-GT (1.4–8.7 pmol/s)	2.74 (1.24)***††††	0.31 (0.18)††††‡‡‡	N/A	307.27 (940.48)****‡‡‡‡
SPINA-GD (20–60 nmol/s)	34.7 (7.1)****	62.9 (50.6)††††‡‡‡	35.4 (15.9)****††††	30.2 (16.2)****
JTI (1.3–4.1)	2.0 ± 0.2*	4.9 ± 0.2†	1.6 ± 0.5**	2.7 ± 0.4*

Corrected $p < 0.05$ (*), < 0.01 (**), < 0.001 (***), $< 1e{-}4$ (****) compared to group 1. Corrected $p < 0.05$ (†), < 0.01 (††), < 0.001 (†††), $< 1e{-}4$ (††††) compared to group 3. Corrected $p < 0.001$ (‡‡‡), $< 1e{-}4$ (‡‡‡‡) compared to group 0.

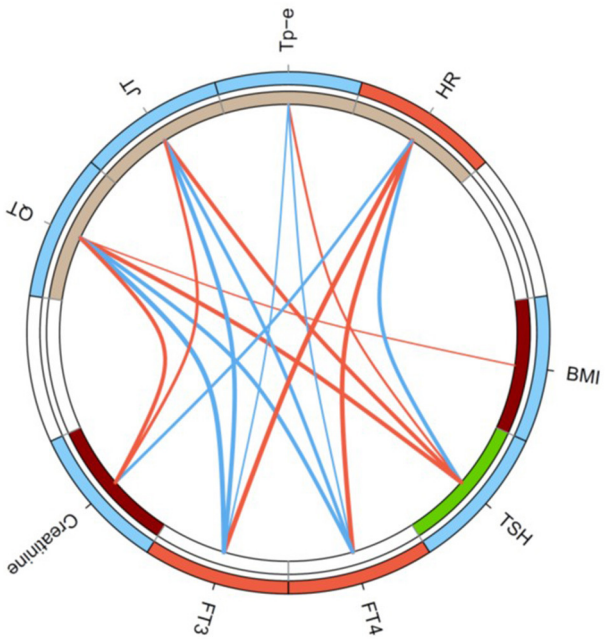

FIGURE 2 | Circular map of the univariable correlation network of ECG markers to clinical and endocrine parameters. Shown are significant correlations ($p < 0.05$) only, and line thickness indicates the strength of negative (blue) or positive (red) correlation. Colors of circle segments indicate increased (red) or decreased values (blue), respectively, in thyrotoxicosis compared to hypothyroidism (outer ring) and higher (dark red) or lower values (green) in atrial fibrillation (inner ring).

predictors except TSH and/or FT3 for Tp-e and JT intervals, so that these ECG constants are explained by thyroid function only.

Subjects in group 2 were slightly younger than in the other groups. The difference wasn't significant, however, nor did the age correlate to TSH concentration, thyroid hormone concentration, heart rate, TPE interval or JT interval. We therefore don't expect the results to be distorted by age.

Unlike previous studies our observations extend to overt thyroid abnormalities, too. Our findings indicate a positive correlation of Tp-e and JT intervals to TSH concentration and an inverse correlation to FT4 and FT3 serum concentrations as well as to thyroid's secretory capacity (SPINA-GT).

The correlations on the level of current hormone concentrations are also reflected by consistent associations to diagnostic groups. The Tp-e and JT intervals were elevated in the hypothyroid and reduced in the thyrotoxic group. This also applied to the QT interval, whereas the heart rate showed an inverse association to the functional categories. Heart rate and time intervals were identical in euthyroid subjects (group 0) and patients receiving full-dose substitution therapy with levothyroxine (group 2), rendering them biochemically euthyroid. This observation indicates that the observed effects on ECG parameters are causally mediated by thyroid hormone concentration and not by accompanying effects of thyroid function, including nerval damage or impaired calcium homeostasis in the postoperative state, or autoimmunity.

An overt hypothyroid status results in a prolongation of cardiac repolarization. Overt hypothyroidism is accompanied by an excess of mortality of up to 34% in 5 years as long as the underlying thyroid hormone disorder is untreated or undertreated (27). Whereas, the reason for increased mortality in affected patients was discussed to be caused by comorbidities and frailty (27, 28) a large register-based study observed the mortality to be increased in subjects without comorbidities, too (29). The well-documented effects of thyroid hormones on myocardial physiology may explain the close association of cardiovascular morbidity to hypothyroidism. Overt hypothyroidism is able to induce heart failure via many effects including bradycardia, impaired systolic function, impaired left ventricular diastolic filling or diastolic hypertension (6). Although thyroid hormones have a strong impact on cardiac electrophysiology, the specific effects of overt hypothyroidism on novel repolarization markers have not been extensively studied up to now. Our observations demonstrate that the hypothyroid group, in addition to a decreased heart rate as expected, is hallmarked by significantly prolonged Tp-e and JT intervals, which are established markers for increased mortality risk. Therefore, major adverse cardiovascular endpoints in patients with overt hypothyroidism might as well result from arrhythmic events driven by repolarization abnormalities.

Previous studies arrived at conflicting results regarding the association of cardiac repolarization with thyroid function in the range of high T3 or T4 concentrations. Some reports described prolonged time constants of repolarization in thyrotoxicosis (14, 16, 30), whereas others reported an inverse association

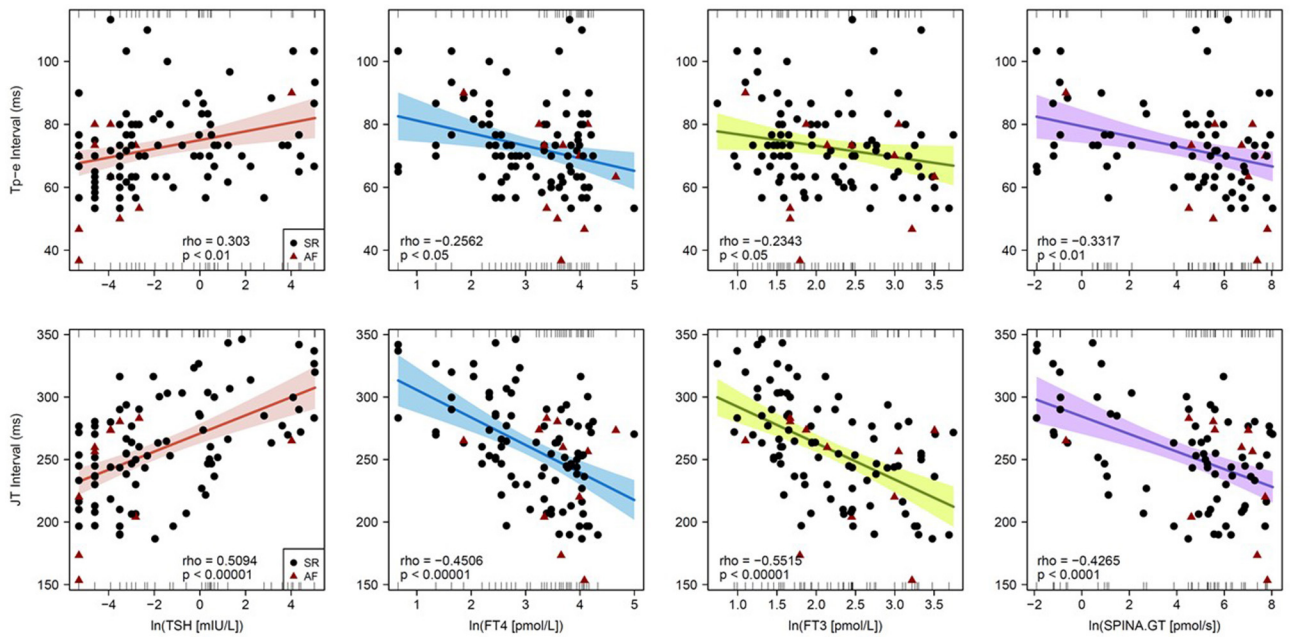

FIGURE 3 | Correlations of Tp-e interval **(top)** and JT interval **(bottom)** with endocrine parameters of thyroid homeostasis. Shown are single data points, linear models from Pearson regression with 95% confidence intervals and models of Spearman correlation (in the bottom of each panel).

TABLE 3 | Heart rhythm characteristics in the four groups.

	Group 0 (normal subjects)	Group 1 (hypothyroidism)	Group 2 (full-dose L-T4 substitution therapy)	Group 3 (thyrotoxicosis)
Heart rate (min^{-1})	75 ± 5†††	71 ± 6††††	77 ± 3††††	100 ± 3****
QT interval (ms)	362 ± 12*†	399 ± 9††††	368 ± 8*††	330 ± 5****
Tp-e interval (ms)	73 ± 3	83 ± 4†	73 ± 3	70 ± 2*
JT interval (ms)	280 ± 13††	297 ± 9††††	278 ± 8†††	241 ± 5****
P wave duration (ms)	94 ± 4	96 ± 4	92 ± 3	93 ± 2

Corrected $p < 0.05$ (*), $< 1e4$ (****) compared to group 1. Corrected $p < 0.05$ (†), < 0.01 (††), < 0.001 (†††), $< 1e{-}4$ (††††) compared to group 3.

TABLE 4 | Minimal models of multivariable regression.

	B	SE	Wald	d.f.	*p*	OR (95% CI)	VIF
Heart rate (min^{-1})							
FT4 (pmol/L)*	12.92	2.06	39.2	1	1.1e−8	4.1e5 (7143–2.3e7)	1.02
Selective beta-blocker	8.25	3.91	4.4	1	0.04	3832.8 (1.8–8.2e6)	1.02
QT interval (ms)							
TSH (mIU/L)*	4.96	1.82	7.5	1	0.008	142.5 (4.1–5004.9)	2.42
FT3 (pmol/L)*	−18.97	7.29	6.8	1	0.01	5.8e−9 (3.6e−15–9.3e−3)	2.41
Amiodarone	34.88	13.16	7.0	1	0.009	1.4e15 (8900.1–2.2e26)	1.03
Tp-e interval (ms)							
TSH (mIU/L)*	1.39	0.43	10.2	1	0.002	4.0 (1.7–9.4)	N/A
JT interval (ms)							
TSH (mIU/L)*	4.18	1.73	5.8	1	0.02	65.4 (2.2–1953)	2.36
FT3 (pmol/L)*	−16.32	6.98	5.1	1	0.02	8.1e−8 (9.4e−14–0.07)	2.36

*Variables were chosen by a priori selection and step-wise model simplification as described in the Methods section. Initial maximal models included BMI, medication (selective and unselective beta blockers, amiodarone, antihistamines) and serum concentrations of TSH, FT4, FT3, calcium, and creatinine. B, Beta coefficient; SE, standard error; Wald, Chi-squared from Wald's test; d.f., degrees of freedom; OR, odds ratio; VIF, variance inflation factor. *Logarithmically transformed to account for asymmetrical distribution.*

of repolarization intervals with thyroid hormones (15, 17). Our results, based on the whole range of thyroid function, including hypothyroid, euthyroid and hyperthyroid subjects, suggest a uniform inverse correlation of repolarization constants, especially the Tp-e and JT intervals, to thyroid hormones.

Cardiac repolarization or ventricular dispersion results from an interplay of ionic potassium currents, which are influenced by beta-adrenergic stimulation, depending particularly on the expression of beta-adrenoreceptors (31, 32). Kang et al. demonstrated potassium channels in human left ventricular tissue to be modulated by beta-adrenoceptors. Beta-adrenergic stimulation led to increased transmural dispersion of repolarization, resulting in elevated

arrhythmogenic risk (31). Likewise, imbalances of sympathetic and vagal tone in hyperthyroidism and TSH-suppressive therapy were promotive for increased QT dispersion (33). Interestingly, increased dispersion of the QT interval was also observed in hypothyroidism (34), Akin et al. suggesting a U-shaped relationship between thyroid hormones and certain markers of cardiac electrophysiology.

Of note, thyroid hormones are able to modulate the susceptibility of the heart for catecholamines by stimulating the expression of beta-adrenoceptors in cardiomyocytes, with subsequent positive inotropic and chronotropic effects (35–38). Conversely, intracellular cAMP formed by activated beta-adrenoceptors is able to stimulate the expression of a number of genes including that of type 2 deiodinase (DIO2), which converts T4–T3 and 3,5-T2, i.e., to more active thyroid hormones (39). The resulting latch-like behavior of cardiomyocytes leads to bifurcation, i.e., a radically different response to catecholamines in situations of even slightly elevated thyroid hormone concentration.

Bosch et al. previously described a delay of repolarization in hypothyroidism to be mediated by decreasing potassium channel currents in the ventricular tissue of guinea pig hearts (40). Conversely, thyrotoxicosis is expected to trigger shortened cardiac repolarization. This would be in accordance with our results and prior studies (15, 17, 22).

In addition to the well-recognized thyroid hormones FT4 or FT3 even TSH can affect cardiac repolarization via TSH-receptors (TSHR) on cardiomyocytes by modulating potassium and calcium channel currents (41). Additionally, cAMP formed by TSHR activation may contribute to local hyperdeiodination and activation of the above-mentioned latch-like response.

Therefore, the distinct effects of thyrotropin and thyroid hormones on ventricular dispersion and its interaction with ionic currents via modulation of beta-adrenoceptors seem to be part of a complex scenario. Since both elevated iodothyronine and TSH concentrations are able to contribute to bifurcation, one might assume a U-shaped relationship between thyroid function and certain electrophysiological constants (5, 8). In our observations covering the whole range of thyroid function we didn't obtain, however, any hint for a U-shaped relationship. The increased risk of SCD in patients with high-normal FT4 concentration or thyrotoxicosis seems to be driven by mechanisms different from abnormalities in repolarization. This conclusion is also underscored by the fact that we saw in the thyrotoxic group only a moderate correlation of FT3 concentration to heart rate and the QT interval, but no correlations to other repolarization markers nor any correlations for other functional thyroid parameters (**Supplementary Table 21**).

Limitations of our approach are in the comparably small sample size and in the fact that subjects were recruited based on routine investigations, so that we were unable to determine non-classical thyroid hormones including 3,5-diiodothyronine (3,5-T2), thyronamines and iodothyroacetates, which may have a strong impact on cardiovascular physiology (42–44). Furthermore, our ECGs were not obtained digitally so that automatic measurements with a higher accuracy than the manual method could not be performed.

Strengths include multivariable modeling including medication, calcium and creatinine concentration, the evaluation of previously under-recognized biomarkers of cardiac electrophysiology and of calculated structure parameters of thyroid homeostasis, the determination of biologically more active free thyroid hormones and the inclusion of subjects from a broad range of thyroid function.

Motivated by previously observed but still poorly understood associations of SCD to within-reference range variations of thyroid hormone concentrations (3, 9–11), our research aimed at unveiling possible relationships between cardiac repolarization and derailed thyroid function. Our observations suggest that pathological repolarization might contribute to increased mortality in hypothyroidism. In thyrotoxicosis, however, the pathophysiology of major adverse cardiovascular end points seems to be mediated by mechanisms beyond repolarization.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local Institutional Ethics Committee of the Medical Faculty at the Ruhr University of Bochum under the file number 3718-10.

AUTHOR CONTRIBUTIONS

AA, JD, AM, IA, and IE-B made substantial contributions to the study conception and design and to the drafting and critical revision of the manuscript for important intellectual content. AA and JD performed the statistical analysis. FS, PP, DS, GL-M, HB, and MG organized the database. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.738517/full#supplementary-material

REFERENCES

1. Doshi R, Dhawan T, Rendon C, Rodriguez MA, Nutakki K, Gianopulos J, et al. New-onset arrhythmia associated with patients hospitalized for thyroid dysfunction. *Heart Lung.* (2020) 49:758–62. doi: 10.1016/j.hrtlng.2020.08.023
2. Fitzgerald SP, Bean NG, Falhammar H, Tuke J. Clinical parameters are more likely to be associated with thyroid hormone levels than with thyrotropin levels: a systematic review and meta-analysis. *Thyroid.* (2020) 30:1695–709. doi: 10.1089/thy.2019.0535
3. Tribulova N, Kurahara LH, Hlivak P, Hirano K, Szeiffova Bacova B. Pro-arrhythmic signaling of thyroid hormones and its relevance in subclinical hyperthyroidism. *Int J Mol Sci.* (2020) 21:2844. doi: 10.3390/ijms21082844
4. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation.* (2012) 126:1040–9. doi: 10.1161/CIRCULATIONAHA.112.096024
5. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, et al. Thyroid dysfunction in heart failure and cardiovascular outcomes. *Circ Heart Fail.* (2018) 11:e005266. doi: 10.1161/CIRCHEARTFAILURE.118.005266
6. Biondi B. Mechanisms in endocrinology: heart failure and thyroid dysfunction. *Eur J Endocrinol.* (2012) 167:609–18. doi: 10.1530/EJE-12-0627
7. Klein I, Danzi S. Thyroid disease and the heart. *Circulation.* (2007) 116:1725–35. doi: 10.1161/CIRCULATIONAHA.106.678326
8. Zhang Y, Post WS, Cheng A, Blasco-Colmenares E, Tomaselli GF, Guallar E. Thyroid hormones and electrocardiographic parameters: findings from the third national health and nutrition examination survey. *PLoS ONE.* (2013) 8:e59489. doi: 10.1371/journal.pone.0059489
9. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, et al. Thyroid function and sudden cardiac death: a prospective population-based cohort study. *Circulation.* (2016) 134:713–22. doi: 10.1161/CIRCULATIONAHA.115.020789
10. Müller P, Dietrich JW, Lin T, Bejinariu A, Binnebößel S, Bergen F, et al. Usefulness of serum free thyroxine concentration to predict ventricular arrhythmia risk in euthyroid patients with structural heart disease. *Am J Cardiol.* (2020) 125:1162–9. doi: 10.1016/j.amjcard.2020.01.019
11. Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mügge A, Patsalis PC, et al. Abnormal thyroid function is common in takotsubo syndrome and depends on two distinct mechanisms: results of a multicentre observational study. *J Intern Med.* (2021) 289:675–87. doi: 10.1111/joim.13189
12. Wellens HJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J.* (2014) 35:1642–51. doi: 10.1093/eurheartj/ehu176
13. Narayanan K, Chugh SS. The 12-lead electrocardiogram and risk of sudden death: current utility and future prospects. *Europace.* (2015) 17(Suppl. 2):ii7–13. doi: 10.1093/europace/euv121
14. Colzani RM, Emdin M, Conforti F, Passino C, Scarlattini M, Iervasi G. Hyperthyroidism is associated with lengthening of ventricular repolarization. *Clin Endocrinol (Oxf).* (2001) 55:27–32. doi: 10.1046/j.1365-2265.2001.01295.x
15. Dörr M, Ruppert J, Robinson DM, Kors JA, Felix SB, Völzke H. The relation of thyroid function and ventricular repolarization: decreased serum thyrotropin levels are associated with short rate-adjusted QT intervals. *J Clin Endocrinol Metab.* (2006) 91:4938–42. doi: 10.1210/jc.2006-1017
16. Owecki M, Michalak A, Nikisch E, Sowiński J. Prolonged ventricular repolarization measured by corrected QT interval (QTc) in subclinical hyperthyroidism. *Horm Metab Res.* (2006) 38:44–7. doi: 10.1055/s-2006-924977
17. Galetta F, Franzoni F, Fallahi P, Tocchini L, Braccini L, Santoro G, Antonelli A. Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. *Eur J Endocrinol.* (2008) 158:85–90. doi: 10.1530/EJE-07-0357
18. Madhukar R, Jagadeesh AT, Moey MYY, Vaglio M, Badilini F, Leban M, et al. Association of thyroid-stimulating hormone with corrected QT interval variation: a prospective cohort study among patients with type 2 diabetes. *Arch Cardiovasc Dis.* (2021). doi: 10.1016/j.acvd.2021.06.008. [Epub ahead of print].
19. Kors JA. Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol.* (2008) 41:575–80. doi: 10.1016/j.jelectrocard.2008.07.030
20. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol.* (2004) 37:191–200. doi: 10.1016/j.jelectrocard.2004.02.002
21. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak-to-Tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol.* (2011) 4:441–7. doi: 10.1161/CIRCEP.110.960658
22. Gürdal A, Eroglu H, Helvaci F, Sümerkan MÇ, Kasali K, Çetin S, et al. Evaluation of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with subclinical hypothyroidism. *Ther Adv Endocrinol Metab.* (2017) 8:25–32. doi: 10.1177/2042018816684423
23. Dietrich JW, Landgrafe-Mende G, Wiora E, Chatzitomaris A, Klein HH, Midgley JE, et al. Calculated parameters of thyroid homeostasis: emerging tools for differential diagnosis and clinical research. *Front Endocrinol (Lausanne).* (2016) 7:57. doi: 10.3389/fendo.2016.00057
24. Rosenthal TM, Masvidal D, Abi Samra FM, Bernard ML, Khatib S, Polin GM, et al. Optimal method of measuring the T-peak to T-end interval for risk stratification in primary prevention. *Europace.* (2017) 20:698–705. doi: 10.1093/europace/euw430
25. Postema PG, Wilde AA. The measurement of the QT interval. *Curr Cardiol Rev.* (2014) 10:287–94 doi: 10.2174/1573403X10666140514103612
26. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? *J Thyroid Res.* (2018) 2018:3239197. doi: 10.1155/2018/3239197
27. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jørgensen HL, Hegedüs L. Duration of thyroid dysfunction correlates with all-cause mortality. The OPENTHYRO Register Cohort. *PLoS ONE.* (2014) 9:e110437. doi: 10.1371/journal.pone.0110437
28. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. *Thyroid.* (2018) 28:566–74. doi: 10.1089/thy.2017.0517
29. Thvilum M, Brandt F, Almind D, Christensen K, Hegedüs L, Brix TH. Excess mortality in patients diagnosed with hypothyroidism: a nationwide cohort study of singletons and twins. *J Clin Endocrinol Metab.* (2013) 98:1069–75. doi: 10.1210/jc.2012-3375
30. Lee YS, Choi JW, Bae EJ, Park WI, Lee HJ, Oh PS. The corrected QT (QTc) prolongation in hyperthyroidism and the association of thyroid hormone with the QTc interval. *Korean J Pediatr.* (2015) 58:263–6. doi: 10.3345/kjp.2015.58.7.263
31. Banyasz T, Jian Z, Horvath B, Khabbaz S, Izu LT, Chen-Izu Y. Beta-adrenergic stimulation reverses the I Kr-I Ks dominant pattern during cardiac action potential. *Pflugers Arch.* (2014) 466:2067–76. doi: 10.1007/s00424-014-1465-7
32. Kang C, Badiceanu A, Brennan JA, Gloschat C, Qiao Y, Trayanova NA, et al. β-adrenergic stimulation augments transmural dispersion of repolarization via modulation of delayed rectifier currents IKs and IKr in the human ventricle. *Sci Rep.* (2017) 7:15922. doi: 10.1038/s41598-017-16218-3
33. Liu C, Lv H, Li Q, Fu S, Tan J, Wang C, et al. Effect of thyrotropin suppressive therapy on heart rate variability and QT dispersion in patients with differentiated thyroid cancer. *Medicine (Baltimore).* (2020) 99:e21190. doi: 10.1097/MD.0000000000021190
34. Akin A, Unal E, Yildirim R, Ture M, Balik H, Haspolat YK. Evaluation of QT dispersion and Tp-e interval in children with subclinical hypothyroidism. *Pacing Clin Electrophysiol.* (2018) 41:372–5. doi: 10.1111/pace.13286
35. Bahouth SW. Thyroid hormones transcriptionally regulate the beta1-adrenergic receptor gene in cultured ventricular myocytes. *J Biol Chem.* (1991) 266:15863–9. doi: 10.1016/S0021-9258(18)98488-7
36. Vassy R, Yin YL, Perret GY. Acute effect of T3 on beta-Adrenoceptors of CulturedChick Cardiac Myocytes. In: Braverman LE, Eber O, Langsteger W, editors. *Heart and Thyroid*. Wien: Blackwell-MZV (1994). p. 165–8.
37. Vassy R, Nicolas P, Yin YL, Perret GY. Nongenomic effect of triiodothyronine on cell surface beta-adrenoceptors in cultured embryonic cardiac myocytes. *Proc Soc Exp Biol Med.* (1997) 214:352–8. doi: 10.3181/00379727-214-44103

38. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The colorado thyroid disease prevalence study. *Arch Intern Med.* (2000) 160:526–34. doi: 10.1001/archinte.160.4.526
39. Bianco AC, Maia AL, da Silva WS, Christoffolete MA. Adaptive activation of thyroid hormone and energy expenditure. *Biosci Rep.* (2005) 25:191–208. doi: 10.1007/s10540-005-2885-6
40. Bosch RF, Wang Z, Li GR, Nattel S. Electrophysiological mechanisms by which hypothyroidism delays repolarization in guinea pig hearts. *Am J Physiol.* (1999) 277:H211–20. doi: 10.1152/ajpheart.1999.277.1.H211
41. Alonso H, Fernández-Ruocco J, Gallego M, Malagueta-Vieira LL, Rodríguez-de-Yurre A, Medei E, et al. Thyroid stimulating hormone directly modulates cardiac electrical activity. *J Mol Cell Cardiol.* (2015) 89:280–6. doi: 10.1016/j.yjmcc.2015.10.019
42. Dietrich JW, Müller P, Schiedat F, Schlömicher M, Strauch J, Chatzitomaris A, et al. Nonthyroidal illness syndrome in cardiac illness involves elevated concentrations of 3,5-diiodothyronine and correlates with atrial remodeling. *Eur Thyroid J.* (2015) 4:129–37. doi: 10.1159/000381543
43. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Homeostatic control of the thyroid-pituitary axis: perspectives for diagnosis and treatment. *Front Endocrinol (Lausanne).* (2015) 6:177. doi: 10.3389/fendo.2015.00177
44. Homuth G, Lietzow J, Schanze N, Golchert J, Köhrle J. Endocrine, Metabolic and Pharmacological Effects of Thyronamines (TAM), Thyroacetic Acids (TA) and Thyroid Hormone Metabolites (THM)–evidence from *in vitro*, cellular, experimental animal and human studies. *Exp Clin Endocrinol Diabetes.* (2020) 128:401–13. doi: 10.1055/a-1139-9200

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REVIEW
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Challenges in the Management of Atrial Fibrillation With Subclinical Hyperthyroidism

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Subclinical thyroid disorders have a high prevalence among older individuals and women. Subclinical hypothyroidism is diagnosed by elevated serum levels of thyroid-stimulating hormone (TSH) with thyroxine levels within the reference range, and subclinical hyperthyroidism is diagnosed by low TSH in conjunction with thyroxine and triiodothyronine levels within reference ranges. Atrial fibrillation is the most commonly diagnosed cardiac arrhythmia and has been associated with an increased risk of mortality, heart failure, stroke, and depression. Mechanistic data from animal and human physiology studies as well as observational data in humans support an association of subclinical hyperthyroidism with atrial fibrillation. Guidelines recommend the measurement of TSH in the evaluation of new-onset atrial fibrillation. All patients with overt hyperthyroidism should be treated, and treatment of subclinical hyperthyroidism should be considered in patients older than 65 years with TSH < 0.4 mIU/L, or in younger patients with TSH < 0.1 mIU/L. Guidelines also recommend screening for AF in patients with known hyperthyroidism. Wearable devices that measure the heart electrical activity continuously may be a novel strategy to detect atrial fibrillation in patients at risk. In this review, we explore the interplay between thyroid hormones and atrial fibrillation, management controversies in subclinical hyperthyroidism, and potential strategies to improve the management of atrial fibrillation in patients with subclinical hyperthyroidism.

Keywords: atrial fibrillation, subclinical hyperthyroidism, rate control, rhythm control, amiodarone

1 INTRODUCTION

Subclinical thyroid dysfunction (SCTD) is a common condition in the general population, especially in older individuals and women, with a prevalence of 10-15% in some cohort studies (1–3). The prevalence of asymptomatic patients with SCTD is estimated to be 10-15% depending on the cohort (2, 3), while symptoms were more often reported by patients with hypothyroidism than those in euthyroidism

although no specific symptom was sensitive enough for diagnosis (2). SCTD comprises both subclinical hypothyroidism and subclinical hyperthyroidism, which are diagnosed using serum blood tests. Subclinical hypothyroidism is diagnosed by elevated serum levels of thyroid-stimulating hormone (TSH) with free thyroxine (T4) levels within the reference range, and subclinical hyperthyroidism is diagnosed by low TSH in conjunction with free T4 and triiodothyronine (T3) levels within reference ranges (4–6).

Most patients with SCTD are asymptomatic or have non-specific symptoms (e.g., fatigue, weight loss/gain, heat/cold intolerance, poor concentration reported as 'brain fog'). In subclinical hypothyroidism, bradycardia and diastolic hypertension may be found, whereas subclinical hyperthyroidism may be associated with tachycardia and dyspnea on exertion. In addition to increased risk of coronary heart disease in subclinical hypothyroidism (7) and subclinical hyperthyroidism (8), there is an increased risk for arrhythmia in SCTD due to the effects of circulating thyroid hormones on cardiac function. In particular, the risk of atrial fibrillation (AF) ranged from a hazard ratio (HR) of 1.68 (95% confidence interval [CI], 1.16-2.43) (8) to a relative risk (RR) of 3.1 (95% CI 1.7-5.5) (9), depending on the studied population as detailed in section *Association Between Thyroid Function and Atrial Fibrillation*.

In this narrative review, we focus on the latest scientific knowledge on the association between subclinical hyperthyroidism and atrial fibrillation (AF), the most common arrhythmia (10). We also discuss potential strategies to improve the management of AF in patients diagnosed with these two conditions.

2 EPIDEMIOLOGY OF ATRIAL FIBRILLATION AND RISK FACTORS

AF is a common medical condition that increases with age (10). The definition includes paroxysmal, persisting, long-standing and permanent AF based upon the duration of the arrhythmia, and the strategy chosen for cardioversion (11). The lifetime risk for AF is 30-40%, i.e. approximately 1 in 3 individuals will develop this arrhythmia, with an estimated peak of 15 million cases in Europe in 2050 (12). The risk factors contributing to incident AF are usually multifactorial and include heart failure, valvular disease, coronary artery disease, vascular disease, established or borderline hypertension, diabetes, chronic kidney disease, physical inactivity, alcohol consumption, smoking, obesity, inflammatory disease, chronic obstructive pulmonary disease, obstructive sleep apnea, acute illness, surgery, and hyperthyroidism (11). It is recommended to diagnose and treat these risk factors to reduce the burden of AF and its complications. Hyperthyroidism or subclinical hyperthyroidism with low TSH (<0.45 mIU/L) is a reversible, treatable but also an uncommon contributing factor to AF. In any case, guidelines recommend the screening of thyroid disorder in patients with AF.

In addition to these modifiable risk factors, non-modifiable risk factors contributing to the development of AF include ageing, genetics, ethnicity and male sex (13).

AF varies widely in presentation, from asymptomatic or silent AF, to symptomatic AF with palpitations, dyspnea, or fatigue, or, rarely, hemodynamic instability (e.g., syncope, lightheadedness, pulmonary edema, myocardial ischemia, or cardiogenic shock) (11). A diagnosis of AF is associated with a 2-3 fold higher risk of death, as well as stroke, left ventricular dysfunction or heart failure, cognitive decline or vascular dementia, depression, impaired quality of life, and hospitalizations (11).

Integrating the multiple contributing comorbidities is important when managing patients with both AF and SCTD. Indeed, the risk of AF associated with subclinical hyperthyroidism is not a homogenous entity and depends on the co-existence of other risk factors. In a large registry of 40,628 patients with subclinical hyperthyroidism, the male sex, age, coronary heart disease, heart failure and valve disease were all independent predictors of AF (14). All those factors need to be considered in the management of AF. For instance, the reparation of a severe mitral regurgitation is recommended in patients with a dilated left atrium to correct a structural substrate of the arrhythmia (15). Coronary revascularization could also be required in case of acute coronary syndrome or a significant cardiac ischemia.

3 EFFECTS OF THYROID HORMONES ON HEART RHYTHM AND FUNCTION

Thyroid hormones have direct actions on the cardiac and vascular function. In animal models, elevated thyroid hormones act on the β1-adrenergic and muscarinic receptors of the heart resulting in an increased sympathetic function and decreased atrial refractory period. The thyroid hormones also act on the gene expression of major ionic channels with decreased L-type calcium channel, and increased expression of Kv1.5 resulting in shorter action potential duration in left atrium (16, 17). Another animal study reported an increased triggered activity and automaticity located in the pulmonary vein cardiomyocytes with thyroid hormones (18) explaining the potential arrhythmogenic effect of hyperthyroidism in AF *via* decreased action potential duration, increased spontaneous activity in pulmonary veins, increased delayed after-depolarizations in pulmonary veins and increased after-depolarizations.

Thyroid hormones accelerate myocardial inotropy and heart rate, and consequently the cardiac output through two mechanistic pathways: nuclear thyroid receptors and the adrenergic system. The binding of thyroid hormones to nuclear receptors enhances the gene expression of the cardiac myocyte proteins and upregulates sarcoplasmic calcium ATPase, myosin heavy chain alpha, voltage gated K+ channels, Na+ channels and beta1-adrenergic receptors. The mechanisms explaining the increased risks of AF with subclinical hyperthyroidism are not entirely clear, but some possible pathways involve T3: (1) T3 reduces heart rate variability due to the inhibition of the vagal system and results in arrhythmogenic effect; (2) T3 binds to nuclear receptors and increases specific cardiac gene expression; and (3) T3 causes peripheral vasodilatation and interfere with cardiac preload and contractility (9, 19). In addition, metabolites of thyroid hormones, such as diiodothyronine (T2), have been implicated in the process of

AF (20). Animal studies have shown the effects of thyroid hormones on conduction in atrial cardiomyocytes, with increased spontaneous activity in the pulmonary veins, shorter duration of action potentials, faster beating rates and higher incidence of delays after depolarization (18).

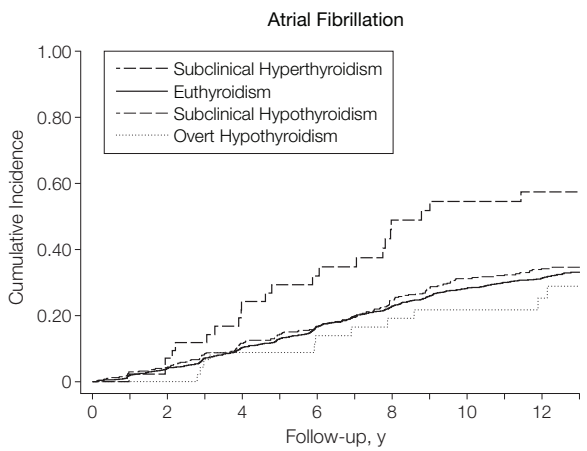
4 ASSOCIATION BETWEEN THYROID FUNCTION AND ATRIAL FIBRILLATION

The increased automaticity and enhanced triggered activity could explain the increased risk of AF observed with subclinical hyperthyroidism (see section *Epidemiology of Atrial Fibrillation and Risk Factors*). Observational studies suggest up to a 2.8-fold increased risk of AF among patients with subclinical hyperthyroidism compared to patients with euthyroidism (8, 9, 21). In a cross-sectional study of 132,707 patients, hyperthyroidism was significantly associated with higher heart rate and prolonged QTc interval (22). Therefore, clinical guidelines recommend testing thyroid hormones in the diagnostic work-up and follow-up of all patients with AF.

Besides subclinical hyperthyroidism, some data investigated the association between free T3 levels and the recurrence of AF after catheter ablation (23). In a cohort of 1115 patients who underwent catheter ablation, those in the lowest quintile (HR 1.60, 95% CI 1.26-2.03), as well as those in the highest quintile of free T3 (HR 1.47, 95%CI 1.16-1.87) had increased risks of AF over a median follow-up of 2 years compared to those in the median quintiles. This U-shaped found with free T3 was not observed with TSH or free T4 and needs to be confirmed in other studies.

The management of SCTD has been debated for many years. All human studies have been observational studies, or small and physiological studies, thus large enough randomized controlled trials are needed (24). Of note, the randomized controlled trial on the incidence of AF after radioiodine treatment of subclinical hyperthyroidism vs. active medical surveillance conducted in France could not recruit enough participants (ClinicalTrials.gov registration noNCT00213720).

The advent of the second-generation TSH assay in the 1980s allowed for improved precision of measurement of TSH in the lower ranges. In people aged 60 years and older enrolled in the Framingham Heart Study, Sawin et al. reported an incidence of AF at 28 per 1000 person-years in individuals with TSH ≤ 0.1 mIU/L compared to 16 per 1000 person-years with TSH 0.1 to 0.4 mIU/L, and 11 per 1000 person-years with TSH 0.4 to 5.0 mIU/L (9). The RR of AF in hyperthyroidism was 3.8 (95% 1.7–8.3, P < 0.001) for those with TSH ≤ 0.1 mIU/L and 1.6 (95%CI 1.0–2.5, P = 0.05) for those with TSH 0.1–0.4 mIU/L compared to the euthyroid state. In a subgroup analysis excluding those with thyroid hormone replacement, the RR was slightly more elevated suggesting a higher risk of AF with endogenous hyperthyroidism compared to thyroid overreplacement. In a cross-sectional study from Tenerz et al., AF was present in 28% of patients (mean age 65) with subclinical hyperthyroidism compared to 10% of those who were euthyroid (25). In the Cardiovascular Health Study, Cappola et al. found a greater incidence of AF in subclinical hyperthyroidism than in the euthyroid state over 13 years of follow-up: 67 vs. 31 events per 1000 person-years, respectively (P < 0.001), and a hazard ratio of 2.18 (95%CI 1.42–3.33) (**Figure 1**) (26). Compared to the euthyroid state, those with subclinical



No. at Risk							
Subclinical Hyperthyroidism	47	41	31	27	19	17	14
Euthyroidism	2502	2336	2093	1823	1576	1342	1150
Subclinical Hypothyroidism	472	440	393	348	293	243	208
Overt Hypothyroidism	49	47	40	35	32	29	22

FIGURE 1 | Cumulative incidence of atrial fibrillation according to the thyroid function tests, defined as: subclinical hyperthyroidism TSH 0.10 to 0.44 mIU/L and normal free T4; euthyroidism TSH 0.45 to 4.50 mIU/L; subclinical hypothyroidism TSH > 4.50 and < 20.0 mIU/L, and normal free T4. The 2 individuals with TSH < 0.10 mIU/L were not represented due to the small group size, adapted from Cappola et al. (26) (*with permission to reproduce*).

hyperthyroidism and TSH 0.1 to 0.44 mIU/L had an incidence rate of 59 events per 1000 person-years (P = 0.007) and a hazard ratio of 1.85 (95%CI 1.14–3.00).

Recently studies have revisited the role of TSH as a marker of disease compared to thyroid hormones: TSH is a pituitary regulatory hormone, while the effectors on the target tissues are the circulating thyroid hormones, namely T4 and especially the active T3 (section *Effects of Thyroid Hormones on Heart Rhythm and Function*). In a systematic review, Fitzgerald et al. showed that thyroid hormones were better predictors than TSH, but this was limited to observational data and no effect size was reported (27). Gammage et al. also found a cross-sectional association of AF with higher free T4 levels in participants with TSH levels within the reference range (28). A difference in free T4 of 1 pmol/L (0.08 ng/dL) was associated with an odds ratio of 1.08 (95%CI 1.03-1.14) for AF.

Based on ICD-10 codes at hospital admissions in a Danish population registry over 13 years of follow-up, Selmer et al. found that atrial flutter and AF could be predictive of subsequent subclinical hyperthyroidism (21). Among those who had a new-onset AF (mean age 66, 55% men), 3% developed subclinical hyperthyroidism after the hospitalization compared to 1% in the general population. This increased incidence was particularly seen in the first few years after the AF onset, more often with age and in women. However, these findings are most likely due to the surveillance bias because patients with atrial arrhythmia are more likely to have regular thyroid function tests. In addition, in a registry-based study, all uses of amiodarone may not have been accounted for. Finally, there is not a clear mechanistic explanation how the incidence of AF could cause subclinical hyperthyroidism.

In the context of AF, physicians and patients must take into account the association of subclinical hyperthyroidism with CHD, stroke and mortality (8), as well as the complications of AF itself (29). Since heart failure is commonly associated with AF, it is important to mention that in large observational studies, both subclinical hypothyroidism and hyperthyroidism were associated with heart failure events (30). The effect of thyroid hormones on cardiac function in patients with subclinical hypothyroidism was investigated in a nested study of the TRUST trial (185 individuals, mean age 74 years) (31). TSH decreased from a mean of 6.35 mIU/L to 3.55 mIU/L with thyroid hormone replacement while the TSH remained stable in the placebo arm (mean 5.29 mIU/L). There was no significant difference between both arms for the systolic function (LVEF: 62.7% vs. 62.5%, P = 0.72) and the diastolic function (E/e' ratio: 10.6 vs. 10.1, P = 0.47). The cardiac function of older adults with subclinical hypothyroidism was not impacted with thyroid hormone replacement and the hypothesis that the U-shaped relationship (30) could be attenuated with therapy remains unresolved. However, this trial included a limited number of adults with TSH ≥ 10 mU/L and none with subclinical hyperthyroidism, and the association between free T4 and AF was not assessed.

4.1 Findings From the Thyroid Studies Collaboration

Subclinical hyperthyroidism has a prevalence of 1-2%, which limits the statistical power to examine incident events in a single cohort. To overcome this limitation, the Thyroid Studies Collaboration (TSC) sought to assess the risk of cardiovascular outcomes in SCTD by combining data from multiple cohorts. Using a common methodology, the TSC obtained data from original cohort studies and performed an individual data analysis that standardized the baseline data, the potential predictors, and the outcomes of interest. This approach was used to recalculate the risk of cardiovascular outcomes using a uniform definition of subclinical thyroid disorders and the outcomes of interest (7) (https://www.thyroid-studies.org).

Within the TSC, the risk of AF in subclinical hyperthyroidism was analyzed using participant-level data from 5 cohort studies (8). Collet et al. showed an age- and sex-adjusted HR of 1.68 (95%CI 1.16–2.43) for incident AF in subclinical hyperthyroidism. Stratified analyses showed that a lower TSH level < 0.10 mIU/L was associated with AF compared to the euthyroid reference group (HR 2.54, 95% CI 1.08-5.99). A TSH between 0.10 and 0.44 mIU/L was also associated with AF compared with the euthyroid group (HR 1.63, 95%CI 1.10-2.41). However, this analysis was limited to 5 cohort studies and the definition of AF differed among the cohorts. In a follow-up TSC analysis of 11 cohorts with 30,085 participants who were either euthyroid or had subclinical hypothyroidism (6.5%), Baumgartner et al. found no association between TSH levels in the reference range and AF, but the risk of AF increased with low-normal TSH levels in an analysis of continuous levels of TSH (32). In the analysis of free T4 in relation with AF, a higher free T4 level at baseline, even within the euthyroid range of TSH, was associated with incident AF: age- and sex-adjusted HR 1.45 (95%CI 1.26–1.66) for the highest quartile vs. the lowest quartile of free T4 (**Figure 2**).

5 NEW TOOLS TO DETECT ATRIAL FIBRILLATION IN THYROID DISORDERS

New data have emerged regarding the options to diagnose AF (11). An electrocardiogram (ECG) is required to formally establish the diagnosis of AF. A standard 12-lead ECG or a single-lead ECG tracing of ≥ 30 seconds showing no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is the diagnostic criterion of clinical AF.

The traditional tools to detect AF are multiple and include oscillometric blood pressure cuff, pulse palpation, auscultation, wearable belts for continuous recordings, long-term Holter and implantable cardiac monitors. However new devices have been developed for the screening of AF (33). Some are controlled by users, where the patient (or medical professional) initiates the measurements, such as intermittent ECG rhythm strip using a smartphone or dedicated connected device, or patient initiated photoplethysmogram on a smartphone (34). As an alternative to user-initiated recording devices, other methods use a smartwatch or wearable device: the ECG is initiated by semi-continuous photoplethysmogram and the device notifies the user in case of irregular rhythm or symptoms (35, 36). The smartphone apps have 92-98% sensitivity to detect AF with a specificity of 91%-100% compared to the 12-lead ECG (11).

The pragmatic cluster-randomized trial VITAL-AF investigated whether a one-lead wearable ECG applied in primary care can detect more AF cases compared with a traditional approach in patients older than 65 (ClinicalTrials.gov registration no

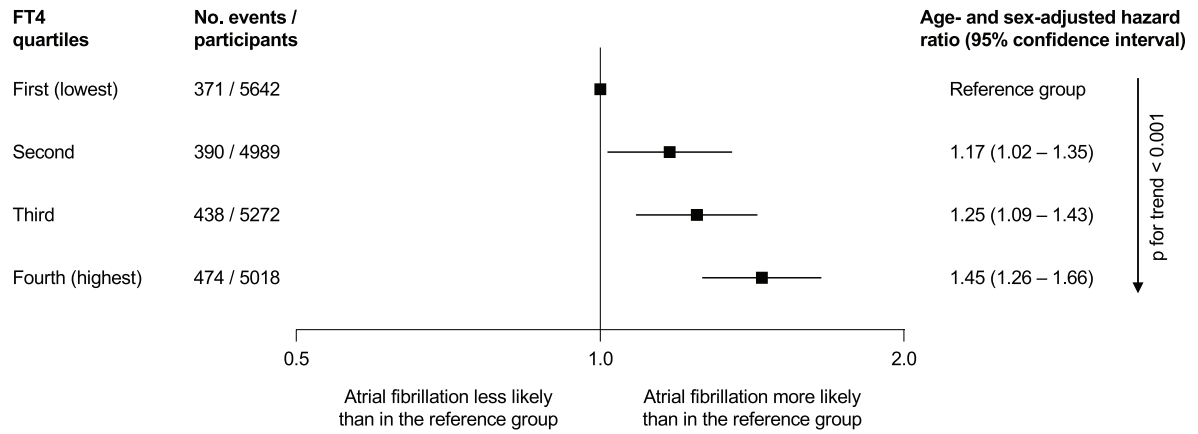


FIGURE 2 | Association of free thyroxine (FT4) quartiles and the incidence of atrial fibrillation in the Thyroid Studies Collaboration, when thyroid-stimulating hormone was within the reference range (0.45 to 4.49 mIU/L) [*figure based on data by Baumgartner et al.* (24)].

NCT03515057) (37). Across 16 primary care centers in the US, 30,722 patients with no AF history were randomized to ECG screening vs. standard care. The results of this trial presented at the AHA 2020 meeting showed that the screening with the single-lead ECG was feasible but did not increase the rate of AF diagnosis compared with standard care. At 12 months, the rates of new-onset AF were 1.74% in the screening group vs. 1.60% in the control group (P = 0.33). A subgroup analysis of patients 85 and older found an absolute risk difference of 1.88% and a number needed to screen of 53. Regarding the initiation of anticoagulation, the proportion was similar in both arms (70%, P = 0.61). The authors concluded that screening for AF using a wearable ECG was feasible in primary care, but with neutral results in term of AF detection. However, this approach could potentially be more efficient in a high-risk subgroup such as older adults.

In the setting of subclinical hyperthyroidism, no study has tested whether an aggressive strategy with a regular one-lead ECG can be an approach to detect subclinical AF, especially if TSH abnormalities persist with treatment. It is also unclear how the detection of subclinical AF would finally translate into a reduction of hard clinical endpoints, such as stroke or heart failure.

6 MANAGEMENT OF SUBCLINICAL THYROID DISORDERS AND GAPS OF KNOWLEDGE

In the management of AF, clinical guidelines recommend the measurement of TSH in the diagnostic work-up and treatment based on the degree of thyroid abnormality (**Figure 3**). This simple screening recommendation allows clinicians to detect undiagnosed hyperthyroidism that could affect the management of AF (see section *Management of Atrial Fibrillation With Thyroid Disorder*). However, there is no data on whether treatment should be initiated in the case of newly diagnosed subclinical hyperthyroidism in a patient with preexisting AF.

Conversely, guidelines also propose to screen actively for AF in patients with known hyperthyroidism. In the case of overt hyperthyroidism, treatment is advised to avoid the symptoms and complications of hyperthyroidism (such as debilitating fatigue, anxiety, heat intolerance, arrhythmia, bone mass reduction, weight loss, thyroid storm, myxedematous coma) (38).

However, clinical recommendations differ between professional societies in the situation of subclinical hyperthyroidism. For the *European Thyroid Association* (ETA) (39), an electrocardiogram (ECG) ± 24h continuous ambulatory ECG (Holter) are recommended to assess the cardiac rhythm, and a cardiac echocardiography to assess cardiovascular morphology and function in subclinical hyperthyroidism with TSH levels < 0.1 mIU/L. Treatment could be considered in patients older than 65 years with TSH levels 0.1–0.39 mIU/L, because of their increased risk of AF, and might also be reasonable in younger (< 65 years) patients with TSH levels < 0.1 mIU/L, because of the risk of progression, especially in the presence of symptoms and/or underlying risk factors or co-morbidity. The *American Thyroid Association* (40) states that "data provide a strong argument for the treatment of subclinical hyperthyroidism in older subjects to avoid dysrhythmias and possible subsequent stroke. Whether younger patients should be treated for the same preventive indications is less clear". The recent *French Endocrine Society* consensus statement on the management of thyroid disorders in the elderly (41) reviews the different definite therapeutic options to control hyperthyroidism based on the etiology and comorbid conditions, i.e. by surgery or radioiodine, while keeping long-course anti-thyroid medication only when these latter options are not available or not feasible. However, the authors highlight the lack of clear evidence in the case of subclinical hyperthyroidism.

Large randomized clinical trials of treatment of subclinical hyperthyroidism are needed. Of note, the randomized controlled trial on the incidence of AF after radioiodine treatment of subclinical hyperthyroidism vs. active medical surveillance conducted in France had to be terminated due to low recruitment (ClinicalTrials.gov registration no NCT00213720).

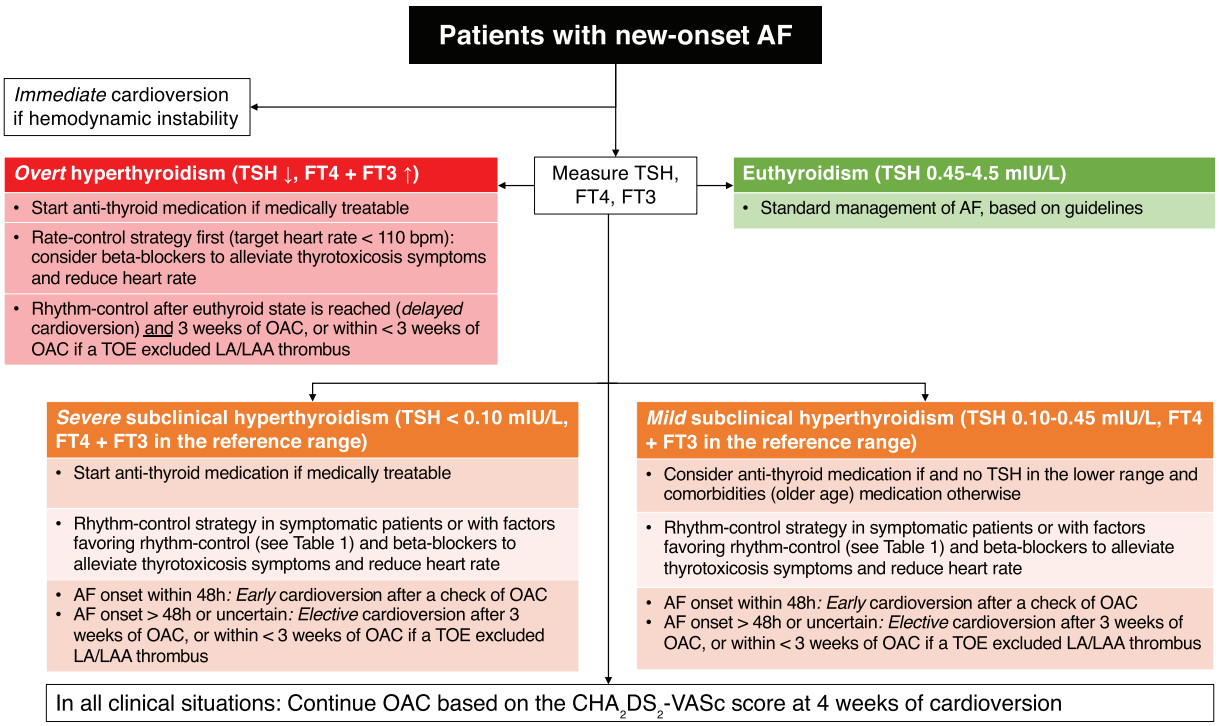


FIGURE 3 | Flowchart of clinical decision making for patients with new-onset atrial fibrillation and subclinical hyperthyroidism. AF, atrial fibrillation; FT3, free triiodothyronine; FT4, free thyroxine; LA, left atrium; LAA, left atrial appendage; OAC, oral anticoagulation; TOE, trans-esophageal echocardiography; TSH, thyroid-stimulating hormone.

Following the TSH cut-off values of the ETA, we suggest that treatment of subclinical hyperthyroidism should be considered in patients older than 65 years with TSH < 0.4 mU/L, or in younger patients with TSH < 0.1 mU/L, due to the increased risk of AF and its complications, albeit this is still debated. The detection of AF tends to lower the threshold for initiating anti-thyroid medication. However, the decision should be balanced with the comorbidities and quality of life of the patient. In addition, the treatment of subclinical or overt hyperthyroidism should also address the cause of hyperthyroidism and not focus only on a range of laboratory values. For instance, the remission of hyperthyroidism is unlikely if it is due to a toxic adenoma. In such a case, clinical intervention with an anti-thyroid treatment (minimal invasive interventions, radioiodine or medication) would normalize TSH and thus treat the causal factor of AF.

7 MANAGEMENT OF ATRIAL FIBRILLATION WITH THYROID DISORDER

Recommendations for AF management with SCTD are general and not always based on strong evidence. The management of patients with AF and subclinical hyperthyroidism should follow the same goals as in other patients with AF: (1) long-term prevention of AF-complications such as stroke or heart failure (2) and alleviate symptoms burden with optimal rate-control strategy or rhythm-control strategy (11). Since subclinical hyperthyroidism is a correctable cause of AF, the management should target an euthyroid state (TSH 0.45-4.49 mIU/L) to maintain cardioversion or catheter ablation and prevent recurrence of subsequent AF events. If the euthyroid state cannot be achieved for any reason, then the decision for anticoagulation should be based on available risk scores (CHA_2DS_2-VASc and HAS-BLED). In case of a high-risk score (CHA_2DS_2-VASc score ≥ 2), anticoagulation is recommended. In case of a low risk (CHA_2DS_2-VASc score 0-1), the persistence of subclinical hyperthyroidism and AF would be an argument for the use of anticoagulation given the possible hypercoagulable stable. The indication for the cardioversion of AF in case of persisting subclinical hyperthyroidism should be evaluated case by case. In case of invalidating symptoms, a rhythm-control strategy with an attempt of cardioversion could be indicated even in a hyperthyroid state. A regular Holter monitoring thereafter would be useful to evaluate recurrent episodes of AF.

The management of AF is based on the assessment of the 4S (Stroke risk, Symptom severity, Severity of AF burden, and Substrate Severity) (11). Hyperthyroidism could be considered

as a substrate aggravating or predisposing for AF. The goal for patients with AF and subclinical hyperthyroidism is to reach the euthyroid state, although the quality of data is limited (**Figure 3**). A retrospective observational study of 163 patients with thyrotoxic AF and a mean follow-up of 34 months showed that 101 patients had spontaneous reversion and 62 patients had persisting AF (42). Those with longer duration of AF prior to thyroid function normalization were more likely to have persisting AF. In the absence of spontaneous cardioversion, pharmacological or electrical methods were described to be successful to maintain sinus rhythm (43). Beta-blockers could be used to control heart rate and heart failure, as well as in the management of thyrotoxic symptoms. In a small sample of 11 patients with hyperthyroidism, the addition of a beta-blocker improved cardiac function parameters, the control of adrenergic symptoms and quality of life (44).

Beta-blockers are indicated in the rate-control strategy of AF. Guidelines recommend the use of metoprolol, bisoprolol, carvedilol or nebivolol in patients with heart failure and reduced left ventricular ejection fraction (HFrEF) or after a myocardial infarction or as an antianginal treatment (45). When patients present both AF and HF, they can also benefit from beta-blockers (45). Propranolol is an old and nonselective beta-blocker, which is typically considered for thyrotoxicosis symptoms, including tachycardia. Compared to other beta-blockers, propranolol has a shorter elimination half-life and can be taken several times a day based on the clinical response. However, propranolol has not been trialed in patients with HFrEF or after myocardial infarction. Therefore, the use of propranolol would be indicated only in case of thyroid induced tachycardia or palpitations but without cardiac comorbidities.

The decision between the rate control and rhythm control strategies depends on the hemodynamic instability, time of onset and degree of symptoms (11). **Table 1** summarizes the criteria favoring a rhythm control strategy. In any case, hemodynamically unstable AF needs urgent cardioversion, whereas as stable AF can benefit from a cardioversion after a careful assessment of symptom onset (**Figure 3**). Those with an AF onset < 48 hours might benefit from cardioversion without starting anticoagulation, whereas for patients with an uncertain onset of symptoms, a period of 3 weeks of anticoagulation is required or alternatively a transesophageal echocardiography can be indicated to exclude the presence of thrombus in the left atrium. The correction of subclinical hyperthyroidism is indicated in AF patients with TSH < 0.10 mlU/L to eliminate a secondary cause of AF and prevent AF recurrence after cardioversion. The decision to postpone the cardioversion after reaching the euthyroid state is acceptable since the anti-thyroid medication can usually normalize T4 and T3 within their normal range in approximately 3 weeks (42).

Another clinically relevant intersection between thyroid dysfunction and AF is amiodarone-induced thyrotoxicosis (AIT) (46, 47). Amiodarone is one of the recommended drugs for the cardioversion of AF and the maintenance of sinus rhythm, especially in case of structural heart disease and left ventricular systolic dysfunction. However, amiodarone presents several safety concerns for the long-term use, including thyroid dysfunction. Each molecule of amiodarone contains two iodine atoms, thus an estimated 3 mg of iodine is released by the liver after metabolizing 100 mg of amiodarone (46). In addition, amiodarone is lipophilic and tends to concentrate in adipose-rich tissues with a long elimination from the body (estimated half-life of 2 to 3 months (48)) and sometimes toxicity, even weeks or months after amiodarone has been discontinued, resulting in amiodarone-induced thyrotoxicosis [AIT]).

The clinical effects of amiodarone depends on the thyroid function and dietary iodine status of each individual (47). It is therefore very important to measure the thyroid function before starting the drug (46). Most patients remain euthyroid (>70%), while about 5-22% present with hypothyroidism and 2-9.6% hyperthyroidism (49). The management of AIT will depend on the thyroid function, the presence of clinical features and consist of amiodarone withdrawal, the introduction of anti-thyroid therapies and/or corticosteroids. Specialized endocrine care in case of AIT is strongly recommended due to the difficult differential diagnosis (46). In short, type I AIT leads to an increased synthesis of T4 and T3 from the excess iodine of amiodarone, whereas type II AIT is a destructive process resulting in excess release of T4 and T3 without actual synthesis. These two entities require specific management strategies and specialized endocrine care.

The choice of alternative treatments to amiodarone depends on whether a rate vs. rhythm control strategy is chosen. The classical options for rate control are beta-blockers, calcium-channel blockers and in case of left ventricular dysfunction digoxin, although this last option is not the first choice given the risk of intoxication. For rhythm control strategy, flecainide is an effective option, but needs to be used with a beta-blocker to prevent a 1:1 conduction of atrial flutter and remains contra-indicated in case of a cardiac structural disease. Other options include propafenone, vernakalant and ibutilide, but the availability of those drugs depends on the country. Of note, clinical trials testing those trials have in general excluded AF secondary to thyrotoxicosis.

SCTD are associated with increased risk of stroke, both in subclinical hypothyroidism (50) and in subclinical hyperthyroidism (51). The risk of stroke in case of hyperthyroidism-related AF does not seem to be increased compared to strokes in case of AF with euthyroidism, but there is no clear evidence to definitively conclude whether the indication for anticoagulation should differ between hyperthyroid vs. euthyroid patients (52). In 2006, the American College of Cardiology (ACC) considered hyperthyroidism as a high-risk state and recommended anticoagulation for patients in a hyperthyroid state, regardless of the CHA_2DS_2-VASc score (53). In contrast, the 2020 European Society of Cardiology (ESC) guidelines

TABLE 1 | Factors favoring the rhythm control strategy, adapted from the 2020 European society of cardiology guidelines for the diagnosis and management of atrial fibrillation (AF) (11).

- Younger age
- First AF episode or short history of AF onset
- Rate control target unachievable
- Tachycardia-mediated cardiomyopathy
- No or few comorbidities/heart disease
- AF precipitated by acute illness or reversible events
- AF-related symptoms
- Patient's choice

for the diagnosis and management of AF did not specify whether the coexistence of subclinical hyperthyroidism should change the threshold for initiating oral anticoagulation (11). Of note, the 2019 ACC guidelines did not mention hyperthyroidism either (54).

Patients with subclinical hyperthyroidism might have a hypercoagulable state due to higher concentrations of several coagulation factors in comparison to patients with euthyroidism. It is however unclear whether those biochemical abnormalities translate to a higher risk of thrombo-embolic event (55–57). Guidelines do not clearly state hyperthyroidism as a risk factor of stroke or systemic embolism in patients with AF. The use of clinical score such as CHA_2DS_2-VASc and HAS-BLED can help stratify the risk of thrombo-embolic vs. bleeding events in AF patients, and to guide the decision to continue anticoagulation after an episode of AF associated with hyperthyroidism. Patients with a high CHA_2DS_2-VASc score (≥ 2 points) or with structural abnormalities detected on the echocardiography, such as left atrium dilation or reduced ejection fraction, are factors contributing to a higher risk of complications related to AF and would probably need long-term anticoagulation even after achieving euthyroidism. In contrast, younger patients with a low CHA_2DS_2-VASc score (0-1 point) and normal echocardiography could discontinue anticoagulation after cardioversion and reaching euthyroid state. In any case, a follow-up monitoring with ECG or Holter cam confirm the absence of AF in the euthyroid state.

Regarding the choice of anticoagulants, vitamin K antagonists can be monitored and adapted with INR measurements in the presence of possible hypercoagulable state. The trials testing novel oral anticoagulation (NOAC) have in general excluded transient AF secondary to reversible disorder (e.g. thyrotoxicosis), and subgroups analyses according to thyroid disorder or use of thyroid medications are lacking. However, the use NOAC is recommended as first choice and no data so far reported safety concerns of NOAC in patients with thyroid disorder.

However, the distinction between subclinical and overt hyperthyroidism is not systematically well-defined in the management of AF and no range for TSH is clearly provided as a treatment target in this setting, except for the achievement of euthyroidism. The correction of FT4 and FT3 is in general detected faster in the blood while the normalization of TSH follows 6-8 weeks after treatment initiation or modification.

Since both conditions tend to occur in patients with age-related comorbidities, the CHA_2DS_2-VASc score should correctly predict the risk of stroke based on those comorbidities regardless of thyroid function. Of note, the initiation of oral anticoagulation is indicated in all patients three weeks prior undertaking cardioversion and needs to be pursued at least four weeks after cardioversion (11).

8 CONCLUSION

Subclinical hyperthyroidism and AF are interconnected conditions in an ageing population. The threshold for AF screening should be lower in patients with subclinical hyperthyroidism, conversely for the threshold for testing thyroid function in patients with AF. In practice, this would imply to assess regularly cardiac symptoms, undertake routine 12-lead ECG, and in case of doubt consider Holter, or wearable device monitoring. Although the evidence is limited, the same proactive approach should be considered when initiating anti-thyroid medication in patients with AF especially in case of low TSH levels (< 0.10 mlU/L). The prevention of stroke and heart failure events with oral anticoagulation remains the priority in those patients, as well as the maintenance of quality of life.

AUTHOR CONTRIBUTIONS

Conceptualization: BG and T-HC. Writing—original draft: BG and T-HC. Writing—review and editing: all authors. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The Incidence of Thyroid Disorders in the Community: A Twenty-Year Follow-Up of the Whickham Survey. *Clin Endocrinol (Oxf)* (1995) 43:55–68. doi: 10.1111/j.1365-2265.1995.tb01894.x
2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. *JAMA Intern Med* (2000) 160:526–34. doi: 10.1001/archinte.160.4.526
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* (2002) 87:489–99. doi: 10.1210/jcem.87.2.8182
4. Surks MI, Hollowell JG. Age-Specific Distribution of Serum Thyrotropin and Antithyroid Antibodies in the US Population: Implications for the Prevalence of Subclinical Hypothyroidism. *J Clin Endocrinol Metab* (2007) 92:4575–82. doi: 10.1210/jc.2007-1499

5. Biondi B, Cooper DS. The Clinical Significance of Subclinical Thyroid Dysfunction. *Endocr Rev* (2008) 29:76–131. doi: 10.1210/er.2006-0043
6. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. *JAMA* (2019) 322:153–60. doi: 10.1001/jama.2019.9052
7. Rodondi N, den Elzen WPJ, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality. *JAMA* (2010) 304:1365–74. doi: 10.1001/jama.2010.1361
8. Collet T-H, Gussekloo J, Bauer DC, den Elzen WPJ, Cappola AR, Balmer P, et al. Subclinical Hyperthyroidism and the Risk of Coronary Heart Disease and Mortality. *JAMA Intern Med* (2012) 172:799–809. doi: 10.1001/archinternmed.2012.402
9. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low Serum Thyrotropin Concentrations as a Risk Factor for Atrial Fibrillation in Older Persons. *N Engl J Med* (1994) 331:1249–52. doi: 10.1056/NEJM199411103311901
10. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circ Res* (2017) 120:1501–17. doi: 10.1161/CIRCRESAHA.117.309732
11. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed With the Special Contribution of the European Heart Rhythm Association (EHRA) of. *Eur Heart J* (2021) 42:373–498. doi: 10.1093/eurheartj/ehaa612
12. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the Number of Individuals With Atrial Fibrillation in the European Union, From 2000 to 2060. *Eur Heart J* (2013) 34:2746–51. doi: 10.1093/eurheartj/eht280
13. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, et al. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the Biomarcare Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* (2017) 136:1588–97. doi: 10.1161/CIRCULATIONAHA.117.028981
14. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and Risk of Atrial Fibrillation or Flutter: A Population-Based Study. *JAMA Intern Med* (2004) 164:1675–8. doi: 10.1001/archinte.164.15.1675
15. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. *Eur Heart J* (2021), ehab395. doi: 10.1093/eurheartj/ehab395
16. Watanabe H, Ma M, Washizuka T, Komura S, Yoshida T, Hosaka Y, et al. Thyroid Hormone Regulates mRNA Expression and Currents of Ion Channels in Rat Atrium. *Biochem Biophys Res Commun* (2003) 308:439–44. doi: 10.1016/s0006-291x(03)01420-7
17. Hu Y, Jones SVP, Dillmann WH. Effects of Hyperthyroidism on Delayed Rectifier K+ Currents in Left and Right Murine Atria. *Am J Physiol Heart Circ Physiol* (2005) 289:H1448–1455. doi: 10.1152/ajpheart.00828.2004
18. Chen Y-C, Chen S-A, Chen Y-J, Chang M-S, Chan P, Lin C-I. Effects of Thyroid Hormone on the Arrhythmogenic Activity of Pulmonary Vein Cardiomyocytes. *J Am Coll Cardiol* (2002) 39:366–72. doi: 10.1016/s0735-1097(01)01731-4
19. Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WCJ, et al. High-Normal Thyroid Function and Risk of Atrial Fibrillation: The Rotterdam Study. *JAMA Intern Med* (2008) 168:2219–24. doi: 10.1001/archinte.168.20.2219
20. Dietrich JW, Müller P, Schiedat F, Schlömicher M, Strauch J, Chatzitomaris A, et al. Nonthyroidal Illness Syndrome in Cardiac Illness Involves Elevated Concentrations of 3,5-Diiodothyronine and Correlates With Atrial Remodeling. *Eur Thyroid J* (2015) 4:129–37. doi: 10.1159/000381543
21. Selmer C, Hansen ML, Olesen JB, Mérie C, Lindhardsen J, Olsen A-MS, et al. New-Onset Atrial Fibrillation Is a Predictor of Subsequent Hyperthyroidism: A Nationwide Cohort Study. *PloS One* (2013) 8:e57893. doi: 10.1371/journal.pone.0057893
22. Tayal B, Graff C, Selmer C, Kragholm KH, Kihlstrom M, Nielsen JB, et al. Thyroid Dysfunction and Electrocardiographic Changes in Subjects Without Arrhythmias: A Cross-Sectional Study of Primary Healthcare Subjects From Copenhagen. *BMJ Open* (2019) 9:e023854. doi: 10.1136/bmjopen-2018-023854
23. Wei S-B, Wang W, Liu N, Chen J, Guo X-Y, Tang R-B, et al. U-Shaped Association Between Serum Free Triiodothyronine and Recurrence of Atrial Fibrillation After Catheter Ablation. *J Interv Card Electrophysiol* (2018) 51:263–70. doi: 10.1007/s10840-018-0337-z
24. Goichot B, Pearce SHS. Subclinical Thyroid Disease: Time to Enter the Age of Evidence-Based Medicine. *Thyroid* (2012) 22:765–8. doi: 10.1089/thy.2012.2208.com
25. Tenerz A, Forberg R, Jansson R. Is a More Active Attitude Warranted in Patients With Subclinical Thyrotoxicosis? *J Intern Med* (1990) 228:229–33. doi: 10.1111/j.1365-2796.1990.tb00223.x
26. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults. *JAMA* (2006) 295:1033–41. doi: 10.1001/jama.295.9.1033
27. Fitzgerald SP, Bean NG, Falhammar H, Tuke J. Clinical Parameters are More Likely to be Associated With Thyroid Hormone Levels Than With Thyrotropin Levels: A Systematic Review and Meta-Analysis. *Thyroid* (2020) 30:1695–709. doi: 10.1089/thy.2019.0535
28. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FDR, Wilson S, et al. Association Between Serum Free Thyroxine Concentration and Atrial Fibrillation. *JAMA Intern Med* (2007) 167:928–34. doi: 10.1001/archinte.167.9.928
29. Biondi B. How Could We Improve the Increased Cardiovascular Mortality in Patients With Overt and Subclinical Hyperthyroidism? *Eur J Endocrinol* (2012) 167:295–9. doi: 10.1530/EJE-12-0585
30. Gencer B, Collet T-H, Virgini VS, Bauer DC, Gussekloo J, Cappola AR, et al. Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events: An Individual Participant Data Analysis From 6 Prospective Cohorts. *Circulation* (2012) 126:1040–9. doi: 10.1161/CIRCULATIONAHA.112.096024
31. Gencer B, Moutzouri E, Blum MR, Feller M, Collet T-H, Delgiovane C, et al. The Impact of Levothyroxine on Cardiac Function in Older Adults With Mild Subclinical Hypothyroidism: A Randomized Clinical Trial. *Am J Med* (2020) 133:848–856.e5. doi: 10.1016/j.amjmed.2020.01.018
32. Baumgartner C, da Costa BR, Collet T-H, Feller M, Floriani C, Bauer DC, et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. *Circulation* (2017) 136:2100–16. doi: 10.1161/CIRCULATIONAHA.117.028753
33. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation* (2017) 135:1851–67. doi: 10.1161/CIRCULATIONAHA.116.026693
34. Brasier N, Raichle CJ, Dörr M, Becke A, Nohturfft V, Weber S, et al. Detection of Atrial Fibrillation With a Smartphone Camera: First Prospective, International, Two-Centre, Clinical Validation Study (DETECT AF PRO). *Europace* (2019) 21:41–7. doi: 10.1093/europace/euy176
35. Tison GH, Sanchez JM, Ballinger B, Singh A, Olgin JE, Pletcher MJ, et al. Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch. *JAMA Cardiol* (2018) 3:409. doi: 10.1001/jamacardio.2018.0136
36. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* (2019) 381:1909–17. doi: 10.1056/NEJMoa1901183
37. Ashburner JM, Atlas SJ, McManus DD, Chang Y, Trisini Lipsanopoulos AT, Borowsky LH, et al. Design and Rationale of a Pragmatic Trial Integrating Routine Screening for Atrial Fibrillation at Primary Care Visits: The VITAL-AF Trial. *Am Heart J* (2019) 215:147–56. doi: 10.1016/j.ahj.2019.06.011
38. Nordyke RA, Gilbert FI, Harada AS. Graves' Disease. Influence of Age on Clinical Findings. *JAMA Intern Med* (1988) 148:626–31. doi: 10.1001/archinte.148.3.626
39. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. *Eur Thyroid J* (2015) 4:149–63. doi: 10.1159/000438750
40. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid* (2016) 26:1343–421. doi: 10.1089/thy.2016.0229
41. Goichot B, Raverot V, Klein M, Vija Racaru L, Abeillon–Du Payrat J, Lairez O, et al. Management of Thyroid Dysfunctions in the Elderly. French Endocrine Society Consensus Statement 2019. Long Version. *Ann Endocrinol (Paris)* (2020) 81:89–100. doi: 10.1016/j.ando.2020.04.010

42. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of Atrial Fibrillation in the Post-Thyrotoxic State. *Am J Med* (1982) 72:903–6. doi: 10.1016/0002-9343(82)90850-6
43. Nakazawa HK, Handa S, Nakamura Y, Oyanagi H, Hasegawa M, Ishikawa N, et al. High Maintenance Rate of Sinus Rhythm After Cardioversion in Post-Thyrotoxic Chronic Atrial Fibrillation. *Int J Cardiol* (1987) 16:47–55. doi: 10.1016/0167-5273(87)90269-5
44. Biondi B, Fazio S, Carella C, Sabatini D, Amato G, Cittadini A, et al. Control of Adrenergic Overactivity by Beta-Blockade Improves the Quality of Life in Patients Receiving Long Term Suppressive Therapy With Levothyroxine. *J Clin Endocrinol Metab* (1994) 78:1028–33. doi: 10.1210/jcem.78.5.8175955
45. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393
46. Basaria S, Cooper DS. Amiodarone and the Thyroid. *Am J Med* (2005) 118:706–14. doi: 10.1016/j.amjmed.2004.11.028
47. Narayana SK, Woods DR, Boos CJ. Management of Amiodarone-Related Thyroid Problems. *Ther Adv Endocrinol Metab* (2011) 2:115–26. doi: 10.1177/2042018811398516
48. Latini R, Tognoni G, Kates RE. Clinical Pharmacokinetics of Amiodarone. *Clin Pharmacokinet* (1984) 9:136–56. doi: 10.2165/00003088-198409020-00002
49. Batcher EL, Tang XC, Singh BN, Singh SN, Reda DJ, Hershman JM. SAFE-T Investigators. Thyroid Function Abnormalities During Amiodarone Therapy for Persistent Atrial Fibrillation. *Am J Med* (2007) 120:880–5. doi: 10.1016/j.amjmed.2007.04.022
50. Chaker L, Baumgartner C, den Elzen WPJ, Ikram MA, Blum MR, Collet T-H, et al. Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis. *J Clin Endocrinol Metab* (2015) 100:2181–91. doi: 10.1210/jc.2015-1438
51. Chaker L, Korevaar TIM, Rizopoulos D, Collet T-H, Völzke H, Hofman A, et al. Defining Optimal Health Range for Thyroid Function Based on the Risk of Cardiovascular Disease. *J Clin Endocrinol Metab* (2017) 102:2853–61. doi: 10.1210/jc.2017-00410
52. Traube E, Coplan NL. Embolic Risk in Atrial Fibrillation That Arises From Hyperthyroidism: Review of the Medical Literature. *Tex Heart Inst J* (2011) 38:225–8.
53. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation–Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* (2006) 48:854–906. doi: 10.1016/j.jacc.2006.07.009
54. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* (2019) 74:104–32. doi: 10.1016/j.jacc.2019.01.011
55. Erem C. Blood Coagulation, Fibrinolytic Activity and Lipid Profile in Subclinical Thyroid Disease: Subclinical Hyperthyroidism Increases Plasma Factor X Activity. *Clin Endocrinol (Oxf)* (2006) 64:323–9. doi: 10.1111/j.1365-2265.2006.02464.x
56. Homoncik M, Gessl A, Ferlitsch A, Jilma B, Vierhapper H. Altered Platelet Plug Formation in Hyperthyroidism and Hypothyroidism. *J Clin Endocrinol Metab* (2007) 92:3006–12. doi: 10.1210/jc.2006-2644
57. Ordookhani A, Burman KD. Hemostasis in Overt and Subclinical Hyperthyroidism. *Int J Endocrinol Metab* (2017) 15:e44157. doi: 10.5812/ijem.44157

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The Association Between Subclinical Thyroid Dysfunction and Recurrence of Atrial Fibrillation After Catheter Ablation

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Objective: The aim of this study was to evaluate the association between subclinical thyroid dysfunction and the recurrence of atrial fibrillation (AF) after radiofrequency catheter ablation (RFCA).

Methods: We examined the association between subclinical thyroid dysfunction and the recurrence of AF at a large university-affiliated cardiac arrhythmia center in China. Data were collected from consecutive patients who underwent RFCA for AF, excluding those with a history of hypothyroidism, hyperthyroidism, or ongoing medical treatment for hypothyroidism or hyperthyroidism, biochemically defined overt thyroid disease, and long-term use of amiodarone before admission. The primary end point was the recurrence of AF in a time-to-event analysis. We compared outcomes in patients who had subclinical hyperthyroidism or hypothyroidism with those who had euthyroid state, using a multivariable Cox model with inverse probability weighting and propensity score matching.

Results: In all, 93 patients were excluded from 435 consecutive patients who underwent RFCA for AF. Of the remaining 342 patients for the analysis, the prevalence of subclinical hyperthyroidism and subclinical hypothyroidism were 26 (7.6%) and 41 (12.0%), respectively; during a median follow-up of 489 days, 91 patients (26.6%) developed a primary end point event. In the main analysis of the multivariable Cox model, only subclinical hyperthyroidism [hazard ratio: 3.07, 95% confidence interval (CI): 1.54–6.14] was associated with an increased risk of end point event after adjusting for potential confounders. However, the association between subclinical hypothyroidism and the end point event was not significant (hazard ratio: 0.66, 95% CI: 0.31–1.43). Results were consistent either in multiple sensitivity analyses or across all subgroups of analysis. Compared with individuals with free triiodothyronine (fT3) in the lowest quintile, those with fT3 in the highest quintile had an HR of 2.23 (95% CI: 1.16–4.28) for recurrence of AF. With the increase of thyroid-stimulating hormone (TSH), a reduction in the risk of recurrence of AF was detected in the adjusted model, and the hazard ratio (HR) per standard deviation (SD) increase was 0.82 (95% CI: 0.68–0.98).

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Conclusion: In this retrospective cohort study involving patients who underwent RFCA for AF, patients with subclinical hyperthyroidism were associated with a markedly higher prevalence of recurrence of AF, whereas patients with subclinical hypothyroidism had a similar recurrence rate of AF compared to those with the euthyroid state.

Keywords: atrial fibrillation, radiofrequency catheter ablation, recurrence, subclinical thyroid dysfunction, subclinical hyperthyroidism, subclinical hypothyroidism

INTRODUCTION

Atrial fibrillation (AF) is known as the most common cardiac arrhythmia in adults worldwide. Approximately 1 in 3 individuals will develop this arrhythmia in a lifetime. In addition, AF leads to significant disability and mortality, which in consequence portends a heavy burden on patients and social health (1).

Rhythm control therapies for AF include antiarrhythmic drugs (AADs) that are often ineffective in preventing recurrence. Catheter ablation, which has been the first-line treatment for symptomatic AF (1), could not prevent the recurrence of AF either (2), probably because of the persistence of the modifiable risk factors (1) and arrhythmogenic substrate (3). Furthermore, early intervention of modifiable risk factors has been recommended to improve catheter ablation in AF (1).

Subclinical thyroid dysfunction, which includes subclinical hyperthyroidism and hypothyroidism [defined as decreased or elevated thyroid-stimulating hormone (TSH), respectively, with free triiodothyronine (fT3) and free thyroxine (fT4) in the normal range] (4), is prevalent, with 1–10% of the adults being affected by subclinical hyperthyroidism (5–7) and up to 20% by subclinical hypothyroidism (4, 8). Additionally, subclinical thyroid dysfunction is also a common condition among patients with AF (9). The association between subclinical hyperthyroidism and the incidence of AF has been well established (10–14). Many studies have also found an association between subclinical hypothyroidism and increased insulin resistance, dyslipidemia, hypertension (4), left ventricular dysfunction (15), increased prevalence of aortic atherosclerosis, and myocardial infarction (16), all of which predispose to AF.

Given the association between subclinical thyroid dysfunction and AF occurrence and the high prevalence of subclinical thyroid dysfunction among patients with AF, subclinical thyroid dysfunction may be associated with the outcome of catheter ablation for AF too. However, very little evidence in this regard has been established. Therefore, we conducted this retrospective cohort study to elucidate the association between subclinical thyroid dysfunction and the recurrence of AF after RFCA, considering the euthyroid state as a reference.

Abbreviations: AF, atrial fibrillation; AADs, antiarrhythmic drugs; AFL, atrial flutter; AT, atrial tachycardia; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blocker; AIC, Akaike Information Criterion; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; EP, electrophysiological; fT4, free thyroxine; fT3, free triiodothyronine; HF, heart failure; HR, hazard ratio; HGB, hemoglobin; IPTW, inverse probability treatment weighting; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; PV, pulmonary vein; PSM, propensity score matching; RFCA, radiofrequency catheter ablation; SMD, standardized mean difference; TSH, thyroid-stimulating hormone; TC, total cholesterol; SD, standard deviation.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at the Second Hospital of Hebei Medical University, a large university-affiliated cardiac arrhythmia center in China. The study was approved by the Research Ethics Committee of the Second Hospital of Hebei Medical University. All patients gave written informed consent before the AF ablation procedure.

Data Source

The data was obtained from an electronic data warehouse (http://hbeyxn.edc-china.com.cn/login.jsp) of AF undergoing RFCA in our hospital. This disease-specific warehouse was established on 1 January 2017, and information from all consecutive patients with AF undergoing RFCA in our department was included in this database.

In the database, clinical and demographic characteristics of all patients were recorded, including sex, age, height, weight, smoking and drinking status, medical history, patient symptoms, laboratory tests, medication use, and the operation information. AADs were used for 3 months after AF ablation if there were no contraindications, and AADs were discontinued after 3 months if there was no recurrence of atrial tachyarrhythmia. Follow-up appointments in our outpatient electrophysiological (EP) clinic were scheduled at 3, 6, and 12 months for the first year and 6 months thereafter; unscheduled visits could be performed at any time if necessary. At each visit, a detailed medical and physical examination, 12-lead electrocardiogram, 24-h Holter, and cardiac ultrasound were performed. All baseline and subsequent follow-up visit measurements were entered into the AF database by an experienced investigator.

Study Population

Consecutive patients who received an initial RFCA for drug-refractory paroxysmal or persistent AF between 1 January 2017 and 1 June 2021 at our department were included. Follow-up continued through 1 December 2021, by which time all the participants had completed at least 6 months of follow-up. The diagnosis of AF was based on an established practice guideline (1). Exclusion criteria were known thyroid disease, which was defined as a previous history of hypothyroidism, hyperthyroidism, or ongoing medical treatment for hypothyroidism or hyperthyroidism, biochemically defined

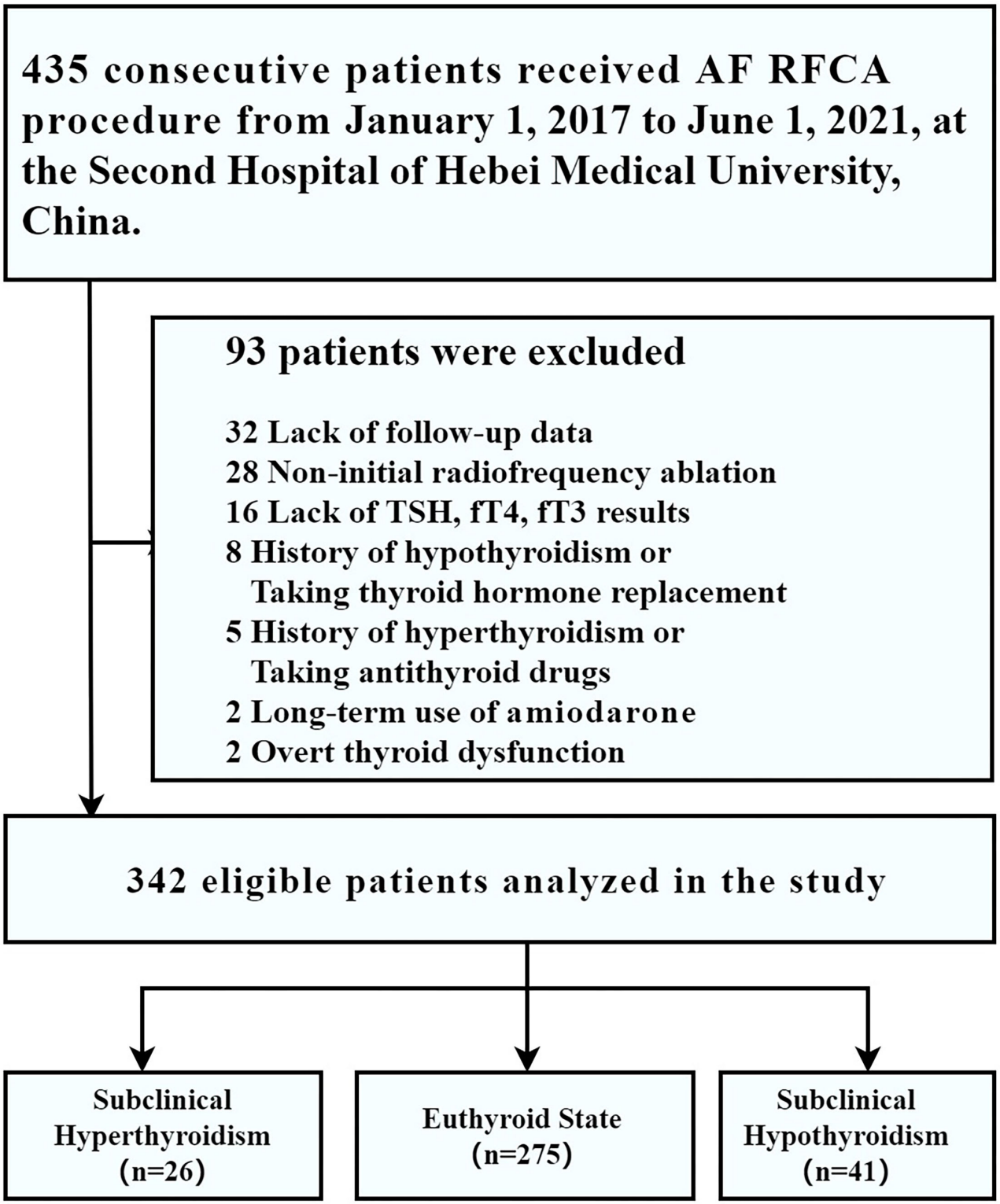

FIGURE 1 | Study cohort.

TABLE 1 | Baseline characteristics of included participants stratified by thyroid function.

Characteristic	Overall ($n = 342$)	Subclinical hyperthyroidism ($n = 26$)	Euthyroid state ($n = 275$)	Subclinical hypothyroidism ($n = 41$)
Demographic data				
Age (year)	63.00 (56.00, 69.00)	65.50 (55.50, 71.25)	63.00 (56.00, 69.00)	63.00 (57.00, 68.00)
Gender (Female)	141 (41.2)	8 (30.8)	114 (41.5)	19 (46.3)
BMI (kg/m2)	24.49 (23.15, 27.06)	23.94 (23.00, 25.30)	24.80 (23.42, 27.05)	24.44 (22.72, 27.68)
Current smoking	53 (15.5)	3 (11.5)	46 (16.7)	4 (9.8)
Current drinking	46 (13.5)	3 (11.5)	39 (14.2)	4 (9.8)
Paroxysmal AF	223 (65.2)	14 (53.8)	181 (65.8)	28 (68.3)
CHA2DS2-VASc score	2.00 (1.00, 3.00)	1.50 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)
AF duration (months)	12.37 (1.03, 39.57)	24.33 (1.02, 62.72)	12.63 (1.20, 40.07)	6.07 (0.95, 24.35)
Echocardiogram				
LAD* (mm)	37.14 (5.86)	37.93 (7.19)	37.13 (5.69)	36.60 (6.29)
LVEF (%)	65.40 (60.35, 68.65)	60.40 (56.70, 67.20)	65.90 (60.75, 69.20)	64.65 (60.92, 66.70)
Initial laboratory tests				
HGB(g/L)	140.00 (130.00, 149.00)	140.00 (127.75, 149.00)	140.00 (131.00, 149.00)	137.50 (129.75, 148.00)
Fasting glucose (mmol/L)	5.18 (4.76, 5.78)	5.12 (4.51, 6.24)	5.20 (4.79, 5.74)	4.92 (4.48, 5.56)
Creatinine (umol/L)	72.00 (61.00, 82.85)	80.00 (75.25, 85.25)	71.00 (61.00, 83.00)	72.00 (60.75, 80.50)
Total cholesterol (mmol/L)	3.99 (3.42, 4.59)	3.74 (3.03, 4.34)	4.09 (3.55, 4.60)	3.80 (3.22, 4.24)
Past diagnoses				
CAD	59 (17.3)	4 (15.4)	46 (16.7)	9 (22.0)
Hypertension	186 (54.4)	14 (53.8)	154 (56.0)	18 (43.9)
Diabetes	40 (11.7)	4 (15.4)	30 (10.9)	6 (14.6)
Stroke	39 (11.4)	6 (23.1)	29 (10.5)	4 (9.8)
HF	36 (10.5)	4 (15.4)	27 (9.8)	5 (12.2)
Medications at baseline				
Diuretics	74 (21.6)	7 (26.9)	61 (22.2)	6 (14.6)
Statin	117 (34.2)	9 (34.6)	89 (32.4)	19 (46.3)
ACEI/ARB	78 (22.8)	4 (15.4)	64 (23.3)	10 (24.4)
β-blockers	127 (37.1)	11 (42.3)	99 (36.0)	17 (41.5)
CCB	50 (14.6)	1 (3.8)	43 (15.6)	6 (14.6)
Procedure parameters				
Procedure time (min)	120.00 (100.00, 130.00)	120.00 (120.00, 130.00)	120.00 (100.00, 130.00)	120.00 (90.00, 132.00)
RF power (W)	35.00 (30.00, 40.00)	35.00 (33.75, 40.00)	40.00 (30.00, 40.00)	35.00 (30.00, 40.00)
Duration of hospital stay (Days)	7.00 (6.00, 9.00)	7.00 (6.00, 8.00)	7.00 (6.00, 9.00)	8.00 (6.00, 10.00)
Ablation strategy (PVI Plus)	39 (11.4)	3 (11.5)	27 (9.8)	9 (22.0)
Thyroid condition				
fT3 (pmol/L)	4.86 (4.43, 5.44)	5.62 (4.64, 6.45)	4.86 (4.46, 5.32)	4.60 (4.21, 5.51)
fT4 (pmol/L)	15.66 (14.21, 17.40)	17.90 (14.63, 22.52)	15.62 (14.26, 17.30)	15.37 (14.00, 16.70)
TSH (mIU/L)	1.93 (1.15, 3.00)	0.07 (0.02, 0.39)	1.85 (1.22, 2.58)	6.04 (5.30, 8.13)

*AF, atrial fibrillation; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; BMI, body mass index; HGB, hemoglobin; CAD, coronary artery disease; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CCB, calcium channel blockers; PVI Plus, cavotricuspid isthmus, superior vena cava, arrhythmogenic substrate modification or LA linear ablation beyond pulmonary vein isolation; RF power, radiofrequency power; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine. *Data is given as mean (SD); the other data are given as medians (interquartile range) or frequencies (percentages). Data on the LAD and LVEF level are missing for 87 patients, RF power for 71, on the CHA2DS2-VASc score level for 62, on the AF duration level for 35, on the fasting glucose for 28, on the total cholesterol for 16, on the procedure time for 14, creatinine for 8, HGB for 6, and BMI for 5.*

overt thyroid disease and long-term use of amiodarone for more than 3 months before admission.

AF Ablation Procedures

Treatment decisions (medical therapy or RFCA) were mainly based on practice guidelines at that time. RFCA was performed by two specialized physicians, including Ji-dong Zhang and Rui-bin Li, with more than 1,000 and 500 cases of experience in AF RFCA, respectively. The procedure was performed under local anesthesia and mild conscious sedation. The CARTO3 system (Biosense Webster, Diamond Bar, CA, USA) was used for three-dimensional electroanatomic left atrium (LA) reconstruction; ablation was performed with a 3.5-mm-tip irrigated catheter (TheromoCool SmartTouchTM, Biosense Webster, Diamond Bar, CA, USA). All patients achieved pulmonary vein isolation (PVI), and we checked the completeness of the two circular lesions in all patients with a decapolar circular catheter (LassoTM) or a multipolar mapping catheter with a 2-6-2 interelectrode spacing catheter (PentaRay, Biosense Webster, Diamond Bar, CA, USA). Decisions on whether to perform additional ablations (cavotricuspid isthmus, superior vena cava, arrhythmogenic substrate modification, or LA linear ablation) were left to the discretion of the operator. In patients who needed linear atrial lesions, the bidirectional conduction block across the lesions would be assessed by differential pacing maneuvers.

TABLE 2 | Associations between subclinical thyroid dysfunction and the recurrence after radiofrequency catheter ablation for atrial fibrillation in the crude, multivariate, and PS analyses.

Analyses	Recurrence
No. of events / No. at risk (%)	
Subclinical hyperthyroidism	13/26 (50.0)
Euthyroid state	69/275 (25.1)
Subclinical hypothyroidism	9/41 (22.0)
Crude analyses— HR (95% CI)	
Ref = Euthyroid state	
Subclinical hyperthyroidism	1.98 (1.10–3.59)
Subclinical hypothyroidism	0.81 (0.40-1.61)
Multivariable analyses— HR (95% CI)	
Ref = Euthyroid State*	
Model1	
Subclinical hyperthyroidism	2.12 (1.17, 3.86)
Subclinical hypothyroidism	0.80 (0.40, 1.60)
Model2	
Subclinical hyperthyroidism	2.93 (1.56, 5.53)
Subclinical hypothyroidism	0.71 (0.34, 1.46)
Model3	
Subclinical hyperthyroidism	3.07 (1.54, 6.14)
Subclinical hypothyroidism	0.66 (0.31, 1.43)
PS analyses— HR (95% CI)	
Ref= Euthyroid State	
With IPTW†	
Subclinical hyperthyroidism	2.97 (1.44, 6.13)
Subclinical hypothyroidism	0.52 (0.23, 1.19)
With PSM‡	
Subclinical hyperthyroidism	2.92 (1.25, 6.85)
Subclinical hypothyroidism	0.60 (0.28, 1.28)
Adjusted for PS§	
Subclinical hyperthyroidism	3.40 (1.65, 6.97)
Subclinical hypothyroidism	0.62 (0.28, 1.35)

**Model1 with additional adjustment for age and gender. Model2 with additional adjustment for age, current smoking status, duration of hospital stay, LAD, HGB, hypertension, stroke, HF, diuretics, ACEI/ARB, procedure time, and RF power using Akaike information criterion (AIC) for model selection. Model3 with additional adjustment for age, BMI, gender, current smoking and drinking status, AF pattern, CHA2DS2-VASc score, AF duration, echocardiogram information, past diagnoses, current medications, laboratory tests, and procedure parameters. The analysis includes all 342 patients. † Adjust for the same covariates in model3 with IPTW according to the PS. The analysis includes all 342 patients. ‡Without additional adjustment because of the well balance of the covariates after PSM. The analysis includes 78 patients (26 in subclinical hyperthyroidism state and 52 in the euthyroid state) and 123 patients (41 in subclinical hypothyroidism state and 82 in the euthyroid state), respectively. §Adjust for the same covariates in model3, with additional adjustment for the PS. The analysis includes all 342 patients. HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; PS, propensity score; IPTW, inverse probability treatment weighting.*

Exposure Measurement

All blood samples were drawn in the morning in the fasting state after hospitalization. Electrochemiluminescence immunoassays for TSH, fT4, and fT3 were performed using the Elecsys detection method (Cobas Elecsys, Roche Diagnostics GmbH). The thyroid function can be classified as the euthyroid state (0.45 mIU/L $\leq$ TSH $\leq$ 4.5 mIU/L), subclinical hyperthyroidism (TSH $<$ 0.45 mIU/L with fT4 and fT3 within the reference range), and subclinical hypothyroidism (TSH 4.51–19.99 mIU/L with fT4 level within the reference range) (17, 18). All measurements were performed by laboratory staff unaware of the patients' clinical characteristics.

Outcome

The end point event was a recurrence of AF after RFCA. Recurrence was defined as documented AF, atrial flutter (AFL), or atrial tachycardia (AT) lasting for more than 30 s after the 3-month blanking period.

Covariates Assessed

We obtained the following covariates, which were associated with AF for each patient from the clinical electronic data warehouse: age, sex, body mass index (BMI), patient-reported smoking status and alcohol use, AF pattern (paroxysmal AF and persistent AF) and AF duration (since the earliest evidence of AF), CHA2DS2-VASc score, duration of hospital stay, the first recorded inpatient laboratory tests (hemoglobin, fasting glucose, creatinine, and total cholesterol), echocardiogram results (left atrial diameter and left ventricular ejection fraction), past diagnoses (coronary artery disease, hypertension, diabetes, stroke, and heart failure), medication administration at baseline (diuretics, statin, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, and β-blocker, calcium channel blockers), and procedure parameters (procedure time, radiofrequency power, and ablation strategy).

The BMI was defined as the weight in kilograms divided by the square of the height in meters. All blood samples were drawn in the morning in the fasting state. Past diagnoses were defined based on the clinical history or specific treatments. Medication information was obtained from preadmission medication lists or

treatment plans that were followed from the day of admission. In the AF pattern, persistent and long-standing persistent AFs were collectively classified as persistent AF. The ablation strategy included PVI and PVI Plus (cavotricuspid isthmus, superior vena cava, arrhythmogenic substrate modification, or LA linear ablation beyond PVI).

Statistical Analysis

Data were given as means with standard deviation (SD) for normally distributed variables, as medians and interquartile range (IQR) for skewed data, and as frequencies (percentage) for categorical variables. Normality of continuous variables was tested by the Shapiro-Wilk test; variance homogeneity was verified by the Bartlett test. Differences between groups were assessed using the chi-squared test or Fisher's exact test for categorical variables, and the Student's *t*-test or the Mann–Whitney U test for continuous variables.

Multivariate survival analyses were performed using the Cox proportional hazards model to estimate the association between subclinical thyroid dysfunction and the end point of recurrence of AF. Proportional hazard assumptions were checked using Schoenfeld residuals, and no violations were found. According to the recommendation of the STROBE statement (19), we simultaneously showed the results of unadjusted and adjusted analyses. All the analyses were first adjusted for age and sex (model 1) and subsequently using the lowest Akaike Information Criterion (AIC) for stepwise backward/forward model selection (model 2) (20). Furthermore, a fully adjusted multivariate Cox regression model with the euthyroid state as reference included demographic factors, clinical information, laboratory and echocardiogram results, medications, and procedure parameters (model 3). The survival and recurrence curves were estimated using the Kaplan–Meier method and compared using the Log-rank test.

To help account for the non-randomized distribution of the covariates, we conducted a second analysis using three propensity score (PS) methods. In the PS analysis, the euthyroid state was taken as the control group; PS was calculated in patients with subclinical hyperthyroidism and subclinical hypothyroidism, respectively. Inverse probability treatment weighting (IPTW) by PS was applied first. We fitted a logistic regression model of subclinical hyperthyroidism that regressed the same covariates as the Cox regression model and obtained the predicted probability of subclinical hyperthyroidism compared to euthyroid. We used the predicted probabilities to calculate the stabilized IPW weight. And then, we did the same calculation for

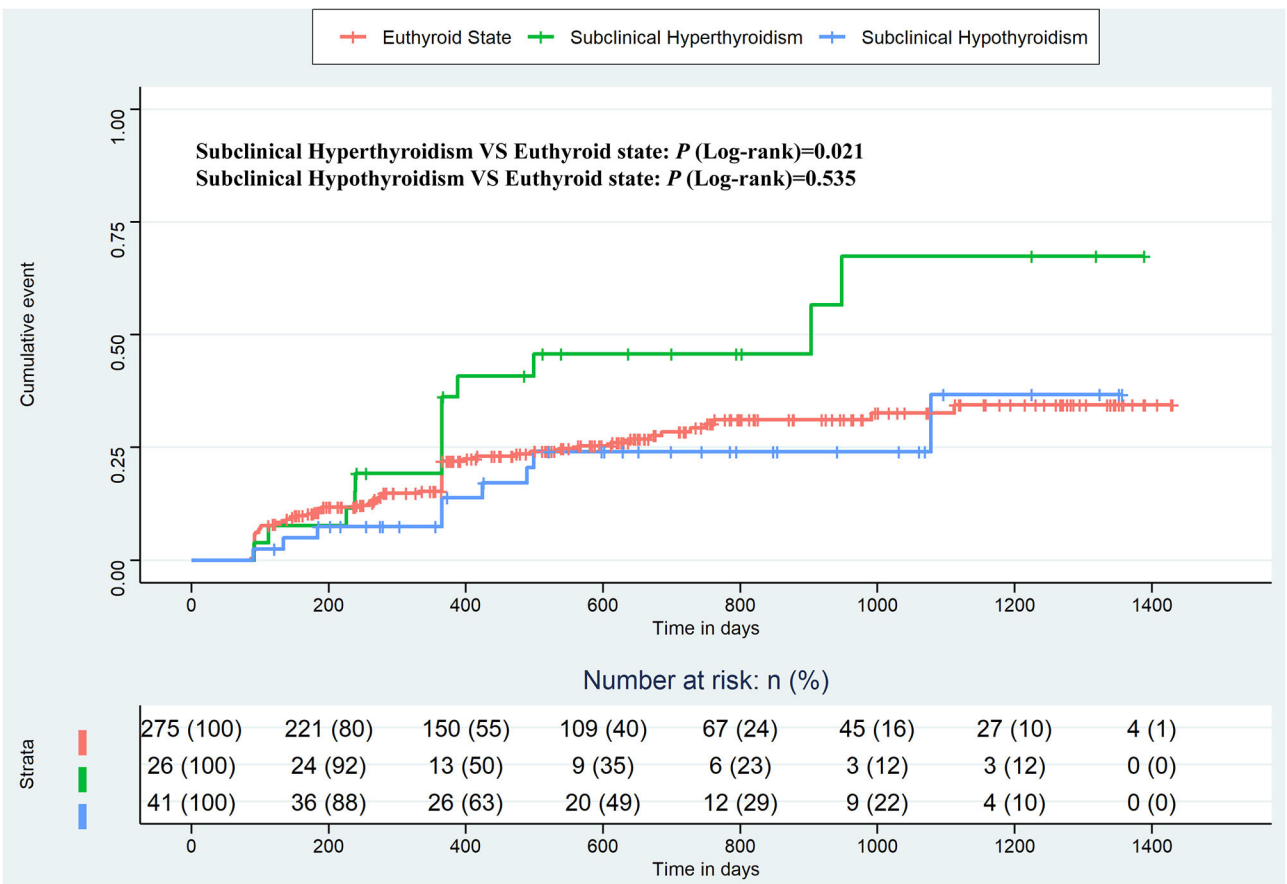

FIGURE 2 | Kaplan–Meier plot estimates of the rate of recurrence of atrial fibrillation according to thyroid function, considering the euthyroid state as a reference.

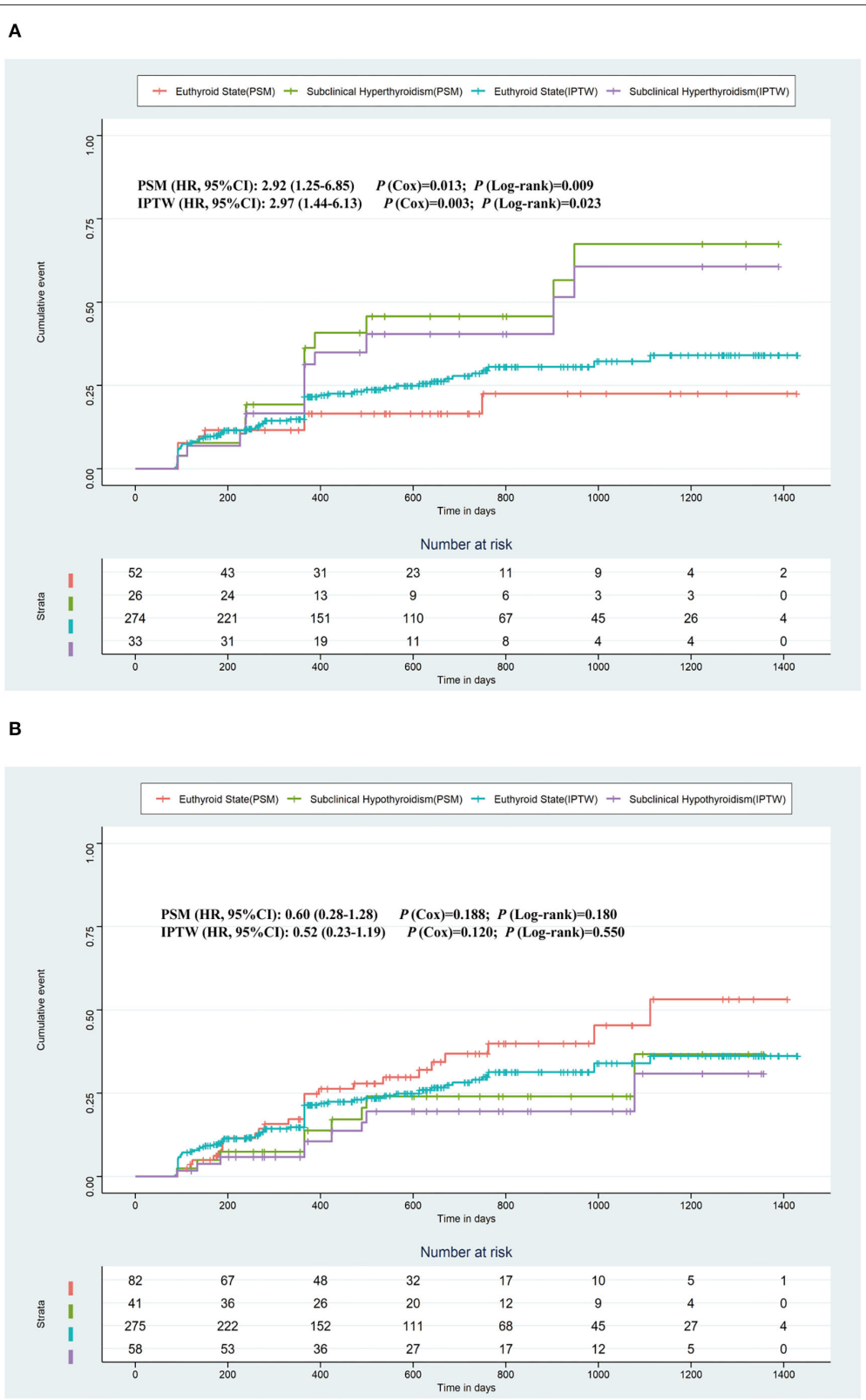

FIGURE 3 | Kaplan–Meier plot estimates of the rate of recurrence of atrial fibrillation based on PSM and IPTW. **(A)** Kaplan–Meier plot estimates of the rate of recurrence of atrial fibrillation in the populations who were with subclinical hyperthyroidism or the euthyroid state. **(B)** Kaplan–Meier plot estimates of the rate of recurrence of atrial fibrillation in the populations who were with subclinical hypothyroidism or the euthyroid state. PSM, propensity score matching; IPTW, inverse probability treatment weighting.

subclinical hypothyroidism. **Supplementary Materials** provided more detailed methods for the propensity score model and IPTW. Propensity score matching (PSM) was then conducted by nearest-neighbor matching without replacement with an algorithm of 1:2 matching. PSM was conducted separately in patients with subclinical hyperthyroidism and subclinical hypothyroidism like IPTW. A standardized mean difference (SMD) was assessed to evaluate the balancing of covariates between matching groups (21). The results of the balancing test are shown in the **Supplementary Materials**. Finally, PS was further adjusted as an additional covariate. The Cox models and Kaplan–Meier curves based on IPTW and PSM were reported.

Stratified analyses were performed to estimate the associations of subclinical thyroid dysfunction and the end point event according to gender (male and female) and age (<65 and ≥65 years) because TSH distribution differed significantly by age and sex (18). The cutoff for age was determined to avoid inappropriately small participant numbers within individual subgroups. And we further conducted subgroup analyses on different AF patterns (paroxysmal AF and persistent AF). The likelihood ratio test was used to calculate *P*-values to test for interaction in the subgroup analyses.

Missing values were interpolated by multivariate imputation by chained equations based on random forests (22). Using multiple imputations, we generated five complete datasets, results based on the first imputed dataset were presented, and the other results were similar, as shown in the **Supplementary Materials**.

Multivariate Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of recurrence of AF for TSH, fT4, and fT3 concentrations, and similar analyses were conducted for TSH, fT4, and fT3 quintiles. Both the unadjusted and the fully adjusted models were reported. Due to the skewness of the distribution, TSH, fT4, and fT3 were modeled with Log transformation, and SD units centered on the mean were reported to make TSH, fT3, and fT4 values comparable and interpretable across studies. At the same time, the untransformed outcomes are presented in the **Supplementary Materials**. We used restricted cubic spline curves based on Cox proportional hazards models with 3 knots at the 10th, 50th, and 90th percentiles of TSH, fT4, and fT3 to flexibly model the association of TSH, fT4, and fT3 with the recurrence of AF. Spline regression analyses were adjusted for potential confounders. In the spline models, the potential non-linearity was evaluated using the likelihood ratio test comparing the models, namely, linear and non-linear (23).

The statistical analyses were performed using the R software, version 4.1.2 (R Project for Statistical Computing). *P*-values < 0.05 were considered to indicate a significant difference.

RESULTS

Characteristics of the Cohort

From 1 January 2017 to 1 June 2021, 435 consecutive patients who underwent RFCA for drug-refractory symptomatic AF were enrolled in our disease-specific database. Among them, 32 patients were excluded owing to lack of follow-up data; 28 patients were excluded because of non-initial radiofrequency ablation; 16 were excluded for lack of TSH, fT4, and fT3 results; 15 patients were excluded because of a history of hypothyroidism ($n = 8$) or a history of hyperthyroidism ($n = 5$), current overt thyroid dysfunction ($n = 2$); 2 patients were excluded for the long-term use of amiodarone, thus leaving 342 patients for the analysis (subclinical hyperthyroidism, $n = 26$; euthyroid state, $n = 275$; subclinical hypothyroidism, $n = 41$) (**Figure 1**).

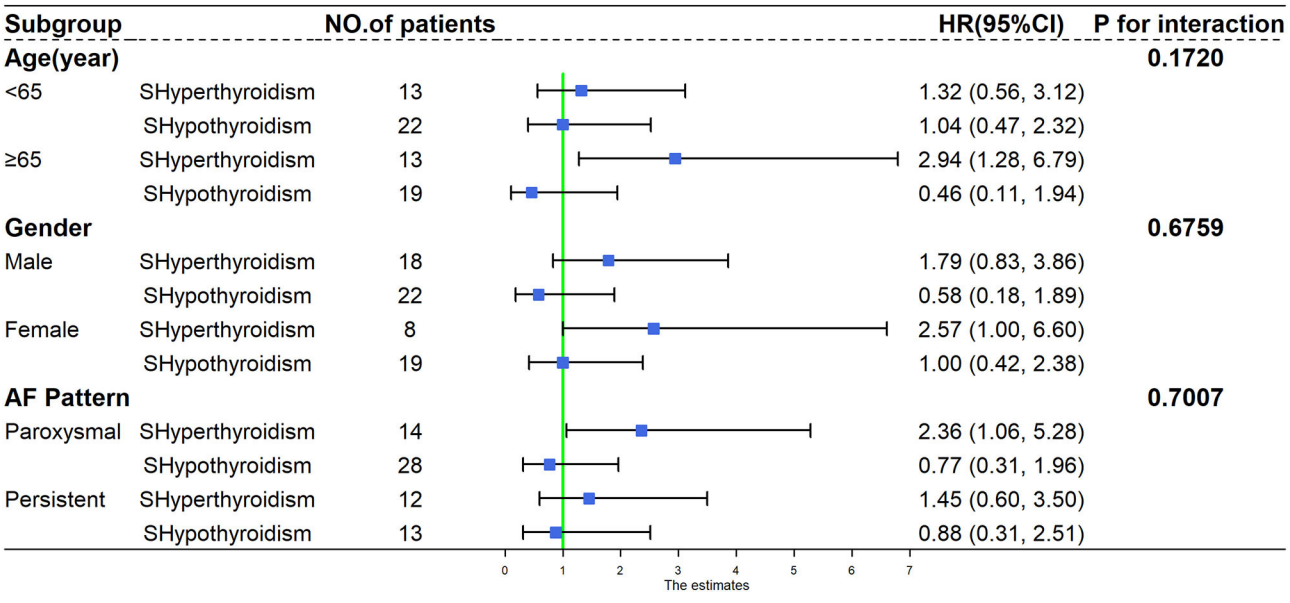

FIGURE 4 | Subgroup analysis of recurrence of atrial fibrillation according to different age, gender, and atrial fibrillation pattern. HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; SHyperthyroidism, subclinical hyperthyroidism; SHypothyroidism, subclinical hypothyroidism.

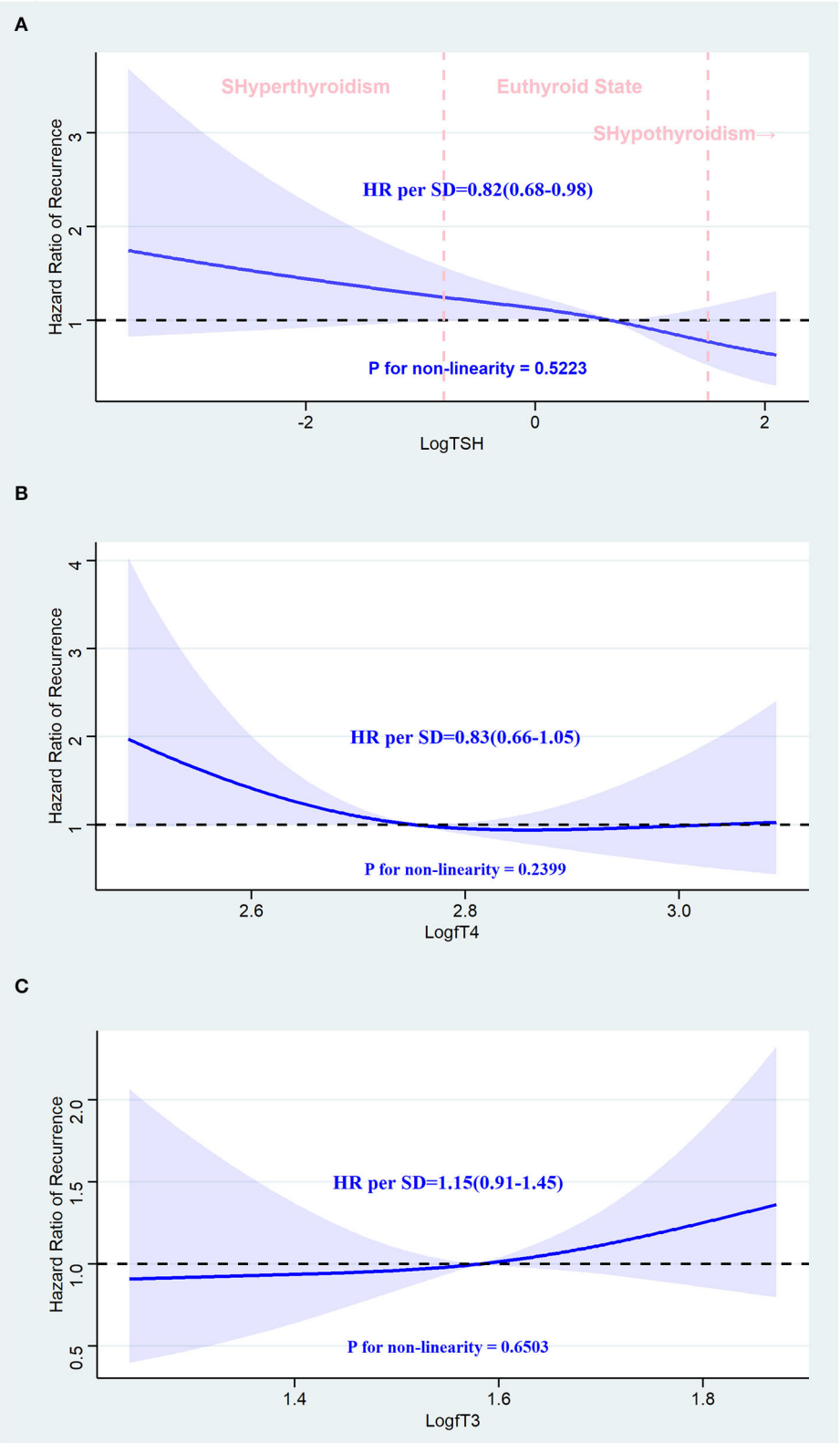

FIGURE 5 | Association between thyroid hormone and recurrence of atrial fibrillation after radiofrequency catheter ablation using a restricted cubic spline regression model. **(A)** TSH and recurrence of AF after RFCA. **(B)** fT4 and recurrence of AF after RFCA. **(C)** fT3 and recurrence of AF after RFCA. Results are adjusted for age, BMI, gender, current smoking and drinking status, AF pattern, CHA2DS2-VASc score, AF duration, echocardiogram information, past diagnoses, current medications,

(Continued)

FIGURE 5 | laboratory tests, and procedure parameters. The restricted cubic spline regression model is conducted with three knots at the 10th, 50th, and 90th percentiles of TSH, fT4, and fT3, and they are modeled with Log transformation. The blue ribbon represents the 95% CI for the spline model. Reference lines for no association are indicated by the dashed black lines at an HR of 1.0. HR, hazard ratio; CI, confidence interval; SD, standard deviation; SHyperthyroidism, subclinical hyperthyroidism; SHypothyroidism, subclinical hypothyroidism; AF, atrial fibrillation; RFCA, radiofrequency catheter ablation.

The prevalence of subclinical hyperthyroidism and hypothyroidism in our study were 26 (7.6%) and 41 (12.0%), respectively. The median age was 63 years at inclusion, 41.2% were women, the median AF duration was 12.37 months, 65.2% were paroxysmal AF, the median procedure time was 120 min, and 11.4% of patients underwent additional ablation beyond PVI. More detailed characteristics of the study population are shown in **Table 1**.

The odds ratios (with 95% CI) of all the variables included in the logistic PS models are shown in **Supplementary Table 1**. The C-statistics for the PS models were 0.792 and 0.790, respectively (**Supplementary Figure 1**). Compared to the euthyroid state, the distribution of the PS for subclinical hyperthyroidism and subclinical hypothyroidism before and after PSM is shown in **Supplementary Figure 2**.

In the subclinical hyperthyroidism and euthyroid matched analytic samples, 52 euthyroid patients and 26 subclinical hyperthyroidism patients were matched. The differences between variables were attenuated in the matched samples vs. unmatched samples (**Supplementary Table 2**; **Supplementary Figure 3**). The subclinical hypothyroidism and euthyroid-matched samples showed similar results (**Supplementary Table 2**; **Supplementary Figure 3**). Based on the PS models, stabilized IPTW was applied, and the summaries of the data after IPTW are shown in **Supplementary Table 3** and **Supplementary Figure 4**.

Study End Point

Over a median of 489 days (maximum 1,430 days) of follow-up of the 342 patients in the cohort, the end point event of recurrence of AF developed in 91 patients (26.6%) (subclinical hyperthyroidism, 13/26, 50.0%; euthyroid state, 69/275, 25.1%; subclinical hypothyroidism, 9/41, 22.0%).

Figure 2 shows the Kaplan–Meier estimates of the recurrence rate of AF during follow-up, differentiating between patients with subclinical hyperthyroidism and hypothyroidism, compared to patients with a euthyroid state. The cumulative event was higher in patients with subclinical hyperthyroidism than in patients with the euthyroid states (Log-rank test, $p = 0.021$), but there was no significant difference in patients with subclinical hypothyroidism compared to patients with normal thyroid function (Log-rank test, $p = 0.535$). The Kaplan–Meier estimates based on PSM and IPTW are shown in **Figure 3**, all of which revealed that subclinical hyperthyroidism rather than subclinical hypothyroidism was associated with a significantly higher recurrence rate of AF.

To further determine the impact of subclinical thyroid dysfunction on the recurrence of AF, a stepwise Cox regression analysis adjusted for potential confounding factors was performed. In the crude analysis, patients who had subclinical hyperthyroidism were more likely to have an end point event than patients with the euthyroid state (HR: 1.98; 95% CI: 1.10–3.59), while patients with subclinical hypothyroidism were not (HR: 0.81; 95% CI: 0.40–1.61). In the primary multivariable analysis, only subclinical hyperthyroidism (HR: 2.12; 95% CI: 1.17–3.86) was associated with an increased risk of end point event compared with euthyroidism after adjusting for age and sex. The association between subclinical thyroid dysfunction and the recurrence of AF demonstrated similar results in models of different adjustment strategies and additional PS analyses (**Table 2**).

We observed a similar trend of association between subclinical thyroid dysfunction and the recurrence of AF across all subgroups of analysis, and no significant interaction was found when analyses were stratified by age (<65 and ≥ 65 years), gender (male and female), and AF pattern (paroxysmal AF and persistent AF) (*P*-values for interaction were 0.1720, 0.6759, and 0.7007, respectively). The results of the stratified analysis are presented in **Figure 4**.

Relationship Between TSH, fT3, fT4, and AF Recurrence

In **Figure 5**, we used restricted cubic splines to visualize the relationship between TSH, fT4, and fT3 and the recurrence of AF, and no statistically significant departure from linearity was detected (*p*-values for non-linearity were 0.5223, 0.2399, and 0.6503, respectively). Regarding the linear relationship between TSH and recurrence of AF, the plot showed a significant reduction in the risk of recurrence of AF with the increase in TSH, and the HR per SD increase was 0.82 (95% CI: 0.68–0.98) in the adjusted model. We also examined differences in recurrence rates across quintiles. Compared with individuals in the lowest quintile, the risk of AF recurrence slightly decreased with the second to fifth TSH quintiles, and the HRs were 1.06, 0.88, 0.94, and 0.70, respectively, but the trend was not significant (*p*-value for the trend is 0.291). Although TSH was negatively associated with the recurrence of AF in the crude model, this trend was not statistically significant (HR: 0.86; 95% CI: 0.72–1.01). When modeled as continuous measures, we detected associations between fT4 and fT3 and the recurrence of AF, and fT4 and fT3 were not associated with AF recurrence [fT4: crude model, HR: 0.84 (0.68, 1.04); adjusted model, HR: 0.83 (0.66, 1.05). fT3: crude model, HR: 1.15 (0.95, 1.40); adjusted model, HR: 1.15 (0.91, 1.45)]. When modeled as quintile categorical measures, compared with individuals with fT3 in the lowest quintile, those with fT3 in the highest quintiles had an HR of 2.23 (95% CI: 1.16–4.28) for recurrence of AF, while the HR was similar (HR: 2.13; 95% CI: 1.04–4.37) after adjusting for the potential confounders. Regarding the fT4 level, all of the models revealed that fT4 was not related to the recurrence of AF (**Table 3**).

TABLE 3 | Recurrence of atrial fibrillation by fT3, fT4, and TSH as quintiles and fT3, fT4, and TSH as a continuous exposure at baseline.

Variable		fT3			fT4			TSH	
	Events/N	Crude model (HR, 95%CI)	Adjusted model (HR, 95%CI)	Events/N	Crude model (HR, 95%CI)	Adjusted model (HR, 95%CI)	Events/N	Crude model (HR, 95%CI)	Adjusted model (HR, 95%CI)
Per SD increase	91/342	1.15 (0.95, 1.40)	1.15 (0.91, 1.45)	91/342	0.84 (0.68, 1.04)	0.83 (0.66, 1.05)	91/342	0.86 (0.72, 1.01)	0.82 (0.68, 0.98)
Quintiles									
Q1	14/69	Ref	Ref	24/69	Ref	Ref	20/69	Ref	Ref
Q2	19/69	1.44 (0.72, 2.87)	1.80 (0.84, 3.85)	18/68	0.75 (0.41, 1.39)	0.57 (0.29, 1.12)	19/69	1.00 (0.53, 1.87)	1.06 (0.54, 2.11)
Q3	14/68	1.04 (0.49, 2.18)	0.85 (0.38, 1.88)	13/68	0.55 (0.28, 1.08)	0.58 (0.28, 1.18)	18/67	0.97 (0.51, 1.83)	0.88 (0.44, 1.76)
Q4	18/67	1.43(0.71, 2.88)	1.91(0.90, 4.05)	20/68	0.90(0.50, 1.63)	0.90(0.47, 1.76)	19/68	1.08(0.58, 2.03)	0.94(0.47, 1.89)
Q5	26/69	2.23 (1.16, 4.28)	2.13 (1.04, 4.37)	16/69	0.66 (0.35, 1.25)	0.62 (0.32, 1.22)	15/69	0.73 (0.37, 1.43)	0.70 (0.34, 1.41)
P for trend	–	0.024	0.055	–	0.342	0.463	–	0.485	0.291

TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; SD, standard deviation. Adjusted model: adjust for age, BMI, gender, current smoking and drinking status, AF pattern, CHA2DS2-VASc score, AF duration, echocardiogram information, past diagnoses, current medications, laboratory tests, and procedure parameters. TSH, fT4, and fT3 are modeled with Log transformation.

DISCUSSION

To our knowledge, this is the first study focused on the association between the whole spectrum of subclinical thyroid dysfunction and the subsequent risk of recurrence of AF after RFCA. The major findings of our investigation are as follows: (1) patients with subclinical hyperthyroidism have a markedly higher prevalence of recurrence of AF after ablation procedures than those with euthyroid state, whereas the patients with subclinical hypothyroidism have the recurrence rate similar to those with euthyroid state and (2) high-normal fT3 level is associated with a significantly higher prevalence of recurrence of AF in the patients with all levels of subclinical thyroid dysfunction.

Many clinical studies have investigated the relationship between subclinical thyroid dysfunction and the new-onset of AF. The current evidence suggests an association between subclinical hyperthyroidism and AF. A population-based study of 5,860 people found that AF occurred in 9.5% of people with subclinical hyperthyroidism, compared with 4.7% in euthyroid individuals (10). In addition, in three prospective studies, a similar association between subclinical hyperthyroidism and AF was noted (11, 12, 14). In a retrospective cross-sectional study including 23,000 individuals with cardiovascular disease, the incidence of AF was similar in patients with subclinical hyperthyroidism (13%) and overt hyperthyroidism (14%), compared with 2% in patients with the euthyroid state (13). However, the role of subclinical hypothyroidism in atrial arrhythmogenesis has not been fully investigated, and a clear association has not been shown. A retrospective study of 586,460 participants found a protective effect of subclinical hypothyroidism on AF. On the contrary, subclinical hyperthyroidism was associated with the new onset of AF (24). In addition, no significant association between subclinical hypothyroidism and a 10-year risk of incident AF was detected in a community-based study (25). In two cohort studies of patients undergoing cardiac surgery, subclinical hypothyroidism was not associated with an increased risk of AF either (26, 27).

Until now, the evidence of the association between subclinical thyroid dysfunction and the recurrence of AF after RFCA has been sparse. Based on the evidence of subclinical thyroid dysfunction and the new onset of AF, it was reasonable to hypothesize that patients with subclinical hyperthyroidism rather than subclinical hypothyroidism were associated with the increased risk of recurrence of AF after RFCA. In accordance with that, we found an increased risk of recurrence of AF in patients with subclinical hyperthyroidism, while no significant association was detected between subclinical hypothyroidism and the recurrence of AF in this study.

Several studies have assessed the effects of thyroid hormone in the normal range on the recurrence of AF after RFCA. In 2010, it was first reported that a high-normal fT4 was related to the recurrence of AF after RFCA of paroxysmal AF (28). Subsequently, a large-scale study confirmed this association (29). Unfortunately, these studies did not include measurements of fT3. Wei reported that the association between the fT3 levels and the recurrence of AF followed a U-shape (30), which slightly differed from our findings. In a recent Chinese study,

high-normal fT3 and fT4 levels were associated with a recurrence of AF after catheter ablation (31). Recently, a cohort study involving patients with overt hypothyroidism and subclinical hypothyroidism revealed that a high-normal TSH level might be an independent predictor of atrial tachyarrhythmia recurrence after catheter ablation of AF (32).

In this study, we focused on patients with subclinical thyroid dysfunction, defined as abnormal TSH with fT3 and fT4 in the normal range, in which the association between thyroid hormone and recurrence of AF after RFCA was little investigated. In our study, we detected an association between high-normal fT3 level and a higher risk for recurrence of AF, whereas fT4 was not. Furthermore, a lower concentration of TSH was negatively related to the recurrence of AF in our adjusted result; however, this result must be interpreted with caution because of the non-significant trend in the unadjusted model. And the difference in study population from the studies mentioned above might be the reason for the inconsistent results. Another difference from the previously published studies was that the participants in our study were defined based on comprehensive consideration of TSH, fT3, and fT4, which was in accordance with clinical practice for subclinical thyroid disease (4, 18). On the contrary, all of the aforementioned studies tried to discuss the relationship between thyroid hormones like TSH, fT3, and fT4 and the recurrence of AF separately. To our knowledge, we were the first to demonstrate an association between subclinical hyperthyroidism and a recurrence of AF after ablation procedures. None of the studies mentioned above were able to show such a relationship.

Due to the log-linear relationship between TSH and fT4, minor alterations in fT4 induced disproportionately larger changes in TSH (33). In addition, T3 has generally been considered to be the only biologically active form of thyroid hormone (34) and has had multiple effects on the cardiovascular system (35–37). As a result, TSH and T3 might play a more sensitive role in predicting arrhythmia recurrence after RFCA, which was supported by our findings and previous observational studies (12, 13, 24, 38–42). Higher thyroid hormone could shorten the action potential duration, decrease the speed of repolarization in pulmonary vein (PV) cardiomyocytes (43), and increase the frequency of atrial premature beats (44) and was correlated with more severe cardiac fibrosis, which facilitates the maintenance of multiple reentrant circuits in the heart (24, 45). These effects might explain the observation of an increased risk of recurrence of AF in patients with subclinical hyperthyroidism.

Regarding the strengths of our study, this is the first cohort investigating the whole spectrum of subclinical thyroid disease and the subsequent risk of recurrence of AF after RFCA. Our study has an adequate number of patients and a detailed evaluation of each participant. Moreover, we define subclinical thyroid dysfunction based on serum TSH, fT4, and fT3, which had not been implemented in previous studies. With the analytic approaches, we tried to minimize possible confounding factors in a variety of ways. We performed a series of analyses using several PS approaches and multivariate Cox regression analysis with different adjustment strategies. The findings are similar in the multiple analyses and different subgroups, and the consistency of the outcomes of these analyses is reassuring. The association between high level of fT3 and a higher risk of recurrence of AF further confirms our findings.

Our findings have great clinical implications. Subclinical hyperthyroidism behaves as an independent risk factor for the development of postoperative AF in patients undergoing RFCA, and maintenance of sinus rhythm may be improved by the treatment of modifiable risk factors (1). It has been reported that the prolonged atrial conduction time could be reversed by treatment of subclinical hyperthyroidism to restore biochemical euthyroidism (46). Furthermore, antithyroid therapy in patients with subclinical hyperthyroidism could reduce heart rate and improve supraventricular arrhythmias (47, 48). Our findings underline the importance of early detection and comprehensive management of thyroid function in patients who undergo RFCA for AF. However, future studies are needed to investigate whether antithyroid therapy and more aggressive postoperative adjuvant treatment in patients with subclinical hyperthyroidism could really provide a clinical benefit.

Our research has some limitations too. There are missing data for some variables. On the contrary, we used the multiple imputation method to account for missing data and minimize bias. The single-center design might hamper the generalization of our conclusions. We did not construct thyroid measurements as time-dependent covariates, so it was not possible to identify any changes in thyroid function over time. Finally, the recurrence of AF could have been asymptomatic, and monitoring using an implantable recorder could have revealed a higher recurrence rate.

CONCLUSION

In this retrospective cohort study involving patients who underwent RFCA for AF, patients with subclinical hyperthyroidism had a significantly higher prevalence of recurrence of AF, whereas patients with subclinical hypothyroidism had a similar recurrence risk of AF compared to those in the euthyroid state.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of The Second Hospital of Hebei Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

R-bL performed the statistical analyses, interpreted data, and drafted and revised the manuscript. X-hY, DW, LB, LZ, J-dZ, and X-rC acquired data. WC interpreted data, designed the study, revised the manuscript for important intellectual content, and approved the final version. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.902411/full#supplementary-material

REFERENCES

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 Esc guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (Eacts): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (Esc) developed with the special contribution of the European heart rhythm association (Ehra) of the Esc. *Eur Heart J*. (2021) 42:373–498. doi: 10.1093/eurheartj/ehab648
2. Natale A, Reddy Vy, Monir G, Wilber Dj, Lindsay Bd, Mcelderry Ht, et al. Paroxysmal af catheter ablation with a contact force sensing catheter: results of the prospective, multicenter smart-Af trial. *J Am Coll Cardiol.* (2014) 64:647–56. doi: 10.1016/j.jacc.2014.04.072
3. Packer M. Effect of catheter ablation on pre-existing abnormalities of left atrial systolic, diastolic, and neurohormonal functions in patients with chronic heart failure and atrial fibrillation. *Eur Heart J*. (2019) 40:1873–9. doi: 10.1093/eurheartj/ehz284
4. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. (2012) 379:1142–54. doi: 10.1016/S0140-6736(11)60276-6
5. Laurberg P, Pedersen Km, Hreidarsson A, Sigfusson N, Iversen E, Knudsen Pr. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in iceland and in Jutland, Denmark. *J Clin Endocrinol Metab.* (1998) 83:765–9. doi: 10.1210/jcem.83.3.4624
6. Carlé A, Andersen Sl, Boelaert K, Laurberg P. Management of endocrine disease: subclinical thyrotoxicosis: prevalence, causes and choice of therapy. *Eur J Endocrinol*. (2017) 176:R325–325r337. doi: 10.1530/EJE-16-0276
7. Wollenweber FA, Zietemann V, Gschwendtner A, Opherk C, Dichgans M. Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke. *Stroke*. (2013) 44:1446–8. doi: 10.1161/STROKEAHA.113.000833
8. Sairaku A, Nakano Y, Uchimura Y, Tokuyama T, Kawazoe H, Watanabe Y, et al. Increased left atrial pressure in non-heart failure patients with subclinical hypothyroidism and atrial fibrillation. *Endocr Connect.* (2016) 5:101–6. doi: 10.1530/EC-16-0012
9. Vergara P, Picardi G, Nigro G, Scafuro F, De Chiara A, Calabrò R, et al. Evaluation of thyroid dysfunction in patients with paroxysmal atrial fibrillation. *Anadolu Kardiyol Derg.* (2007) 7:104–6. doi: 10.1016/j.jelectrocard.2007.03.168
10. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, et al. Association between serum free thyroxine concentration and atrial fibrillation. *Arch Intern Med*. (2007) 167:928–34. doi: 10.1001/archinte.167.9.928
11. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. (2006) 295:1033–41. doi: 10.1001/jama.295.9.1033
12. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. (1994) 331:1249–52. doi: 10.1056/NEJM199411103311901
13. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J.* (2001) 142:838–42. doi: 10.1067/mhj.2001.119370
14. Collet TH, Gussekloo J, Bauer DC, Den Elzen WP, Cappola AR, Balmer P, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. (2012) 172:799–809. doi: 10.1001/archinternmed.2012.402
15. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med.* (2002) 137:904–14. doi: 10.7326/0003-4819-137-11-200212030-00011
16. Rodondi N, Den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. (2010) 304:1365–74. doi: 10.1001/jama.2010.1361
17. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, Da Costa BR, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA*. (2015) 313:2055–65. doi: 10.1001/jama.2015.5161
18. Evron JM, Papaleontiou M. Decision making in subclinical thyroid disease. *Med Clin North Am*. (2021) 105:1033–45. doi: 10.1016/j.mcna.2021.05.014
19. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (Strobe): explanation and elaboration. *PLoS Med*. (2007) 4:E297. doi: 10.1371/journal.pmed.0040297
20. Ho AS, Luu M, Barrios L, Chen I, Melany M, Ali N, et al. Incidence and mortality risk spectrum across aggressive variants of papillary thyroid carcinoma. *JAMA Oncol*. (2020) 6:706–13. doi: 10.1001/jamaoncol.2019.6851
21. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol*. (2001) 54:387–98. doi: 10.1016/S0895-4356(00)00321-8
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. (2011) 30:377–99. doi: 10.1002/sim.4067
23. Keum N, Bao Y, Smith-Warner SA, Orav J, Wu K, Fuchs Cs, et al. Association of physical activity by type and intensity with digestive system cancer risk. *JAMA Oncol.* (2016) 2:1146–53. doi: 10.1001/jamaoncol.2016.0740
24. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ.* (2012) 345:E7895. doi: 10.1136/bmj.e7895
25. Kim EJ, Lyass A, Wang N, Massaro JM, Fox CS, Benjamin EJ, et al. Relation of hypothyroidism and incident atrial fibrillation (from the framingham heart study). *Am Heart J*. (2014) 167:123–6. doi: 10.1016/j.ahj.2013.10.012
26. Zhao D, Xu F, Yuan X, Feng W. Impact of subclinical hypothyroidism on outcomes of coronary bypass surgery. *J Card Surg.* (2021) 36:1431–8. doi: 10.1111/jocs.15395
27. Komatsu R, Karimi N, Zimmerman NM, Sessler DI, Bashour CA, Soltesz EG, et al. Biochemically diagnosed hypothyroidism and postoperative complications after cardiac surgery: a retrospective cohort analysis. *J Anesth.* (2018) 32:663–72. doi: 10.1007/s00540-018-2533-5
28. Tang RB, Liu DL, Dong JZ, Liu XP, Long DY, Yu RH, et al. High-normal thyroid function and risk of recurrence of atrial fibrillation after catheter ablation. *Circ J*. (2010) 74:1316–21. doi: 10.1253/circj.CJ-09-0708
29. Sousa PA, Providência R, Albenque JP, Khoueiry Z, Combes N, Combes S, et al. Impact of free thyroxine on the outcomes of left atrial ablation procedures. *Am J Cardiol*. (2015) 116:1863–8. doi: 10.1016/j.amjcard.2015.09.028

30. Wei SB, Wang W, Liu N, Chen J, Guo XY, Tang RB, et al. U-Shaped association between serum free triiodothyronine and recurrence of atrial fibrillation after catheter ablation. *J Interv Card Electrophysiol*. (2018) 51:263–70. doi: 10.1007/s10840-018-0337-z
31. Shu Z, Chen M, Wang Q, Lai J, Zhao J, Zhuo C, et al. High-normal thyroid function and recurrence of atrial fibrillation after catheter ablation: a prospective observational study. *Cardiology*. (2021) 146:607–15. doi: 10.1159/000517092
32. Morishima I, Okumura K, Morita Y, Kanzaki Y, Takagi K, Yoshida R, et al. High-normal thyroid-stimulating hormone shows a potential causal association with arrhythmia recurrence after catheter ablation of atrial fibrillation. *J Am Heart Assoc*. (2018) 7:e009158. doi: 10.1161/JAHA.118.009158
33. Snyder PJ, Utiger RD. Inhibition of thyrotropin response to thyrotropin-releasing hormone by small quantities of thyroid hormones. *J Clin Invest*. (1972) 51:2077–84. doi: 10.1172/JCI107014
34. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol*. (2017) 14:39–55. doi: 10.1038/nrcardio.2016.174
35. Wang W, Guan H, Fang W, Zhang K, Gerdes Am, Iervasi G, et al. Free triiodothyronine level correlates with myocardial injury and prognosis in idiopathic dilated cardiomyopathy: evidence from cardiac Mri and Spect/Pet imaging. *Sci Rep*. (2016) 6:39811. doi: 10.1038/srep39811
36. Watanabe H, Ma M, Washizuka T, Komura S, Yoshida T, Hosaka Y, et al. Thyroid hormone regulates mrna expression and currents of ion channels in rat atrium. *Biochem Biophys Res Commun*. (2003) 308:439–44. doi: 10.1016/S0006-291X(03)01420-7
37. Chen WJ, Yeh YH, Lin KH, Chang GJ, Kuo CT. Molecular characterization of thyroid hormone-inhibited atrial L-type calcium channel expression: implication for atrial fibrillation in hyperthyroidism. *Basic Res Cardiol*. (2011) 106:163-74. doi: 10.1007/s00395-010-0149-5
38. Larsson SC, Allara E, Mason AM, Michaëlsson K, Burgess S. Thyroid function and dysfunction in relation to 16 cardiovascular diseases. *Circ Genom Precis Med*. (2019) 12:E002468. doi: 10.1161/CIRCGEN.118.002468
39. Ellervik C, Roselli C, Christophersen IE, Alonso A, Pietzner M, Sitlani CM, et al. Assessment of the relationship between genetic determinants of thyroid function and atrial fibrillation: a mendelian randomization study. *JAMA Cardiol*. (2019) 4:144–52. doi: 10.1001/jamacardio.2018.4635
40. Salem JE, Shoemaker MB, Bastarache L, Shaffer Cm, Glazer AM, Kroncke B, et al. Association of thyroid function genetic predictors with atrial fibrillation: a phenome-wide association study and inverse-variance weighted average meta-analysis. *JAMA Cardiol*. (2019) 4:136–43. doi: 10.1001/jamacardio.2018.4615
41. Heeringa J, Hoogendoorn EH, Van Der Deure WM, Hofman A, Peeters RP, Hop WC, et al. High-normal thyroid function and risk of atrial fibrillation: the rotterdam study. *Arch Intern Med*. (2008) 168:2219–24. doi: 10.1001/archinte.168.20.2219
42. Cappola AR, Desai AS, Medici M, Cooper LS, Egan D, Sopko G, et al. Thyroid and cardiovascular disease research agenda for enhancing knowledge, prevention, and treatment. *Thyroid*. (2019) 29:760–77. doi: 10.1089/thy.2018.0416
43. Davis Pj, Leonard JL, Davis FB. Mechanisms of nongenomic actions of thyroid hormone. *Front Neuroendocrinol*. (2008) 29:211–8. doi: 10.1016/j.yfrne.2007.09.003
44. Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Saccà L, et al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J Clin Endocrinol Metab*. (2000) 85:4701–5. doi: 10.1210/jcem.85.12.7085
45. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement mri and atrial fibrillation catheter ablation: the decaaf study. *JAMA*. (2014) 311:498–506. doi: 10.1001/jama.2014.3
46. Nacar AB, Acar G, Yorgun H, Akçay A, Özkaya M, Canpolat U, et al. The effect of antithyroid treatment on atrial conduction times in patients with subclinical hyperthyroidism. *Echocardiography*. (2012) 29:950–5. doi: 10.1111/j.1540-8175.2012.01718.x
47. Kaminski G, Michalkiewicz D, Makowski K, Podgajny Z, Szalus N, Ruchala M, et al. Prospective echocardiographic evaluation of patients with endogenous subclinical hyperthyroidism and after restoring euthyroidism. *Clin Endocrinol (Oxf)*. (2011) 74:501–7. doi: 10.1111/j.1365-2265.2010.03957.x
48. Wiersinga WM. Should we treat mild subclinical/mild hyperthyroidism? yes. *Eur J Intern Med*. (2011) 22:324–9. doi: 10.1016/j.ejim.2011.03.008

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Minor perturbations of thyroid homeostasis and major cardiovascular endpoints—Physiological mechanisms and clinical evidence

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It is well established that thyroid dysfunction is linked to an increased risk of cardiovascular morbidity and mortality. The pleiotropic action of thyroid hormones strongly impacts the cardiovascular system and affects both the generation of the normal heart rhythm and arrhythmia. A meta-analysis of published evidence suggests a positive association of FT4 concentration with major adverse cardiovascular end points (MACE), but this association only partially extends to TSH. The risk for cardiovascular death is increased in both subclinical hypothyroidism and subclinical thyrotoxicosis. Several published studies found associations of TSH and FT4 concentrations, respectively, with major cardiovascular endpoints. Both reduced and elevated TSH concentrations predict the cardiovascular risk, and this association extends to TSH gradients within the reference range. Likewise, increased FT4 concentrations, but high-normal FT4 within its reference range as well, herald a poor outcome. These observations translate to a monotonic and sensitive effect of FT4 and a U-shaped relationship between TSH and cardiovascular risk. Up to now, the pathophysiological mechanism of this complex pattern of association is poorly understood. Integrating the available evidence suggests a dual etiology of elevated FT4 concentration, comprising both ensuing primary hypothyroidism and a raised set point of thyroid function, e. g. in the context of psychiatric disease, chronic stress and type 2 allostatic load. Addressing the association between thyroid homeostasis and cardiovascular diseases from a systems perspective could pave the way to new directions of

research and a more personalized approach to the treatment of patients with cardiovascular risk.

KEYWORDS

thyroid function, sudden cardiac death, ventricular arrhythmia, cardiac electrophysiology, MACE, hypothyroidism, thyrotoxicosis, type 2 allostatic load

Introduction

Sudden cardiac death (SCD) is a global health issue that causes more than 600,000 fatalities per annum in the United States and Europe alone (1–3) being responsible for 15–20% of total mortality in industrialized societies (4–7). Therefore, the prevention of SCD continues to be a major task of cardiovascular medicine (8). Several conditions are known to be associated with increased risk of SCD including higher age, male sex, coronary artery disease (previous myocardial infarction), cardiomyopathies, primary electrical disorders, aortopathies or aortic dissection, and decreased left ventricular systolic function (7, 9). The main underlying pathologic substrate that conveys the development of ventricular tachyarrhythmias responsible for SCD involves channelopathies and/or the presence of myocardial fibrosis.

With the advent of implantable cardioverter-defibrillators (ICDs), accurate assessment of risk for SCD becomes crucial in clinical practice, the more as the majority of all first clinical events is fatal (10). Current guidelines on primary prevention for SCD recommend risk stratification solely on heart failure symptoms and reduced left ventricular ejection fraction (LVEF) (11–14). Several studies confirmed LVEF as a strong predictor of arrhythmic death (15, 16). For example, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study revealed that LVEF $< 35\%$ was associated with a relative risk for cardiac mortality of 7.3 in short-term survivors of myocardial infarction (17, 18). Moreover, randomized controlled ICD trials for primary prevention in patients with reduced LVEF demonstrated improved survival within the ICD arms (19). However, using LVEF as a sole risk stratifier for SCD has several limitations. First, a relevant number of SCD continues to occur in subjects with LVEF $> 40\%$. The Maastricht Circulatory Arrest Registry reported that more than 50% of victims of sudden circulatory arrest had LVEF $> 40\%$ (20, 21). Therefore, a significant proportion of those at risk for SCD live unnoticed when stratified by LVEF alone. Second, even in patients with LVEF $< 35\%$ only a small proportion will benefit from ICD. Recent data of the DANISH trial revealed a low incidence of appropriate ICD shocks (11.5%) in patients with non-ischemic cardiomyopathy after a median follow-up of 67.6 months, whereas on the other hand the incidence of device infection (4.9%) and inappropriate shocks (5.9%) was considerable (22). Third, further developments of heart failure medications such as the angiotensin-neprilysin inhibitor combination LCZ696 (sacubitril/valsartan) may improve LVEF and minimize the risk for SCD (23–25).

Therefore, it is highly needed to identify additional markers potentially predicting a higher relative risk for SCD (26). This form of biomarkers would also open avenues to a better understanding, which are the patients that mainly benefit from ICD treatment (27).

Among prevalent, but previously underrecognized conditions, hyperthyroidism and thyrotoxicosis are known to significantly increase the risk for cardiac morbidity and mortality (28–33). Elevated concentration of free thyroxine (FT4) in overt thyrotoxicosis is an established risk factor for major cardiovascular endpoints (including cardiovascular death, hospital admission, ventricular arrhythmia and ICD therapy) (28, 30, 31). Subclinical thyroid disorders and "euthyroid" variations of FT4 within their respective reference range have been linked to cardiovascular outcome measures as well, but their mechanisms are less well understood (34, 35). Likewise, the implications of altered thyrotropin (TSH) concentration continue to be unclear (36–39). Although major cardiovascular endpoints define an important health issue, the available evidence from the literature is ambiguous, leaving important questions unsolved (29, 37).

Despite the established pro-arrhythmic role of thyroid hormones, treatment with levothyroxine may have favorable effects in heart failure (40), and both subclinical and overt hypothyroidism are established risk factors for coronary heart disease and mortality (41). The line between beneficial and harmful effects of substitution therapy, is small, however, since thyrotoxicosis and even subclinical hyperthyroidism may be independent triggers for heart failure and cardiovascular mortality (42–44). In two large population-based studies even the use of antithyroid drugs was found to be a risk factor for SCD (45), but causality remains unclear.

Until recently, the question could not be resolved if screening of subclinical and undiagnosed overt thyroid dysfunction and treatment of subclinical hypothyroidism is beneficial in adults without goiter or thyroid nodules (46). Potential reasons for this persisting vagueness include the complexity of thyroid hormone action in the cardiovascular system, age dependence of the involved effects

and misconceptions about the role of thyrotropin in thyroid homeostasis, as well as insufficient sample size and heterogeneity of study designs (37, 38, 47–52).

Our systematic analysis was motivated by the hypothesis that both TSH and T4 concentrations are associated to important end points of cardiac arrhythmia, but that the specific relationships are different from a qualitative perspective. The underlying differences might arise from the dual role of both TSH and thyroid hormones, acting as controlling as well as controlled elements, from the inverse relationship between T4 and TSH in primary thyroid dysfunction and from the fact that TSH (and TRH) secretion is controlled by multiple central afferences reflecting the role of the TRH neuron as an integrator of stress signaling and energy homeostasis (53–59).

This review article is organized in four parts. In the next section we summarize known fundamental concepts including historical notes and insights from basic research. The subsequent section covers the methodology and results of a systematic search and meta-analysis of the association of mild disorders of thyroid homeostasis with major adverse cardiovascular endpoints (MACE). Toward the end of the article, we discuss the implications of the findings and try to integrate the available evidence in a comprehensive model that provides a possible explanation of all observations including previously poorly understood phenomena as well.

Fundamental physiological evidence

Thyroid hormones are key regulators of growth, differentiation and integrative energy homeostasis. They orchestrate the trade-off between–often conflicting–demands of supply with energy and substrates, ontogeny, thermoregulation and fight-and-flight reactions (56). As slow mediators of allostatic load, they represent the fourth level of the stress response after the sensorimotor and autonomic nervous system, the release of catecholamines and the secretion of glucocorticoids (56). It is therefore not surprising that their role as a switch between anabolic and catabolic functions includes the cardiovascular system as well. Cardiac complications of thyrotoxicosis were probably first observed as early as 1,785 by Caleb Hillier Parry, who portrayed a series of cases with exophthalmic goiter that was associated with palpitations and tachycardia (60), shortly later followed by similar observations made in other countries (61–63).

Today it is well recognized that a broad spectrum of heart diseases may ensue from disorders of thyroid homeostasis (31, 32, 64). Established scoring systems for the diagnosis of myxoedema coma and thyroid storm, two life-threatening thyroid conditions, comprise cardiac manifestations including brady- and tachycardia, congestive heart failure and atrial fibrillation (30).

On a molecular and cellular level pleiotropic effects of iodothyronines on gene expression, metabolism and electrophysiological mechanisms have been described (64). The effects of thyroid hormones are mediated by four different signaling types (Figure 1) (48). Type 1 of thyroid hormone action represents classical, genomic effects. Here, iodothyronines dock to thyroid hormone receptors (THR) bound to DNA as monomer, homodimer or heterodimer and modify the expression of regulated genes. THRs may also bind to RNA *via* a specific binding site, such that their binding and recruitment of RNA can accentuate its transcriptional activity of thyroid hormone responsive genes (70). Five types of THRs are able to both bind thyroid hormones and form active dimers, THRα1, which is the main receptor in myocardial tissue and bone, THRβ1, THRβ2 and THRβ3, which play an important role in extracardiac tissue (e.g., pituitary, liver and adipose tissue) (65) and the mitochondrial p43 receptor (71). In type 2 signaling, hormone-receptor complexes are indirectly bound to DNA *via* adaptor proteins. In type 3 action, iodothyronines are bound to (cytoplasmic) thyroid hormone receptors, and their effects are mediated *via* intracellular transmitters (second messengers), e. g. the MAPK and PI3K/AKT/mTOR pathways. The term Type 4 signaling refers to responses mediated *via* integrin receptors on the cell membrane (48). Of note, genomic effects (type 1 and 2 signaling) occur on a much slower time scale (hours) than non-genomic effects (type 3 and 4 signaling, minutes) (66, 72). The signaling types 1 to 3 require two iodine atoms at the inner ring of the hormone molecule, but a maximum of one iodine atom bound to the outer ring. Therefore, triiodothyronine (T3), triiodothyroacetic acid (TRIAC) and 3,5-diiodothyronine (3,5-T2) exert strong and direct genomic and non-genomic effects, whereas thyroxine (T4) and tetraiodothyroacetic acid (TETRAC) act directly *via* non-genomic signaling only, and only indirectly (after deiodination to T3, 3,5-T2 or TRIAC) *via* genomic signaling (67, 73, 74). It could be recently demonstrated that the effects of thyroid hormones on the heart rate involve type 3 signaling in a complex interaction with the autonomic nervous system (66).

The transcription of multiple genes is stimulated by classical thyroid hormone signaling. They include alpha-myosin heavy chain, atrial natriuretic hormone, beta1- and beta-2-adrenergic receptors, sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), Na^{+}/K^{+}-ATPase, and voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3). Negatively regulated genes include adenylyl cyclase catalytic subunits, beta-myosin heavy chain, phospholamban, THRα1 and the Na^{+}/Ca^{2+} exchanger. Animal experiments revealed complex remodeling of cardiac ion channel expression depending on thyroid status (75). Fast responses of ion channels result from

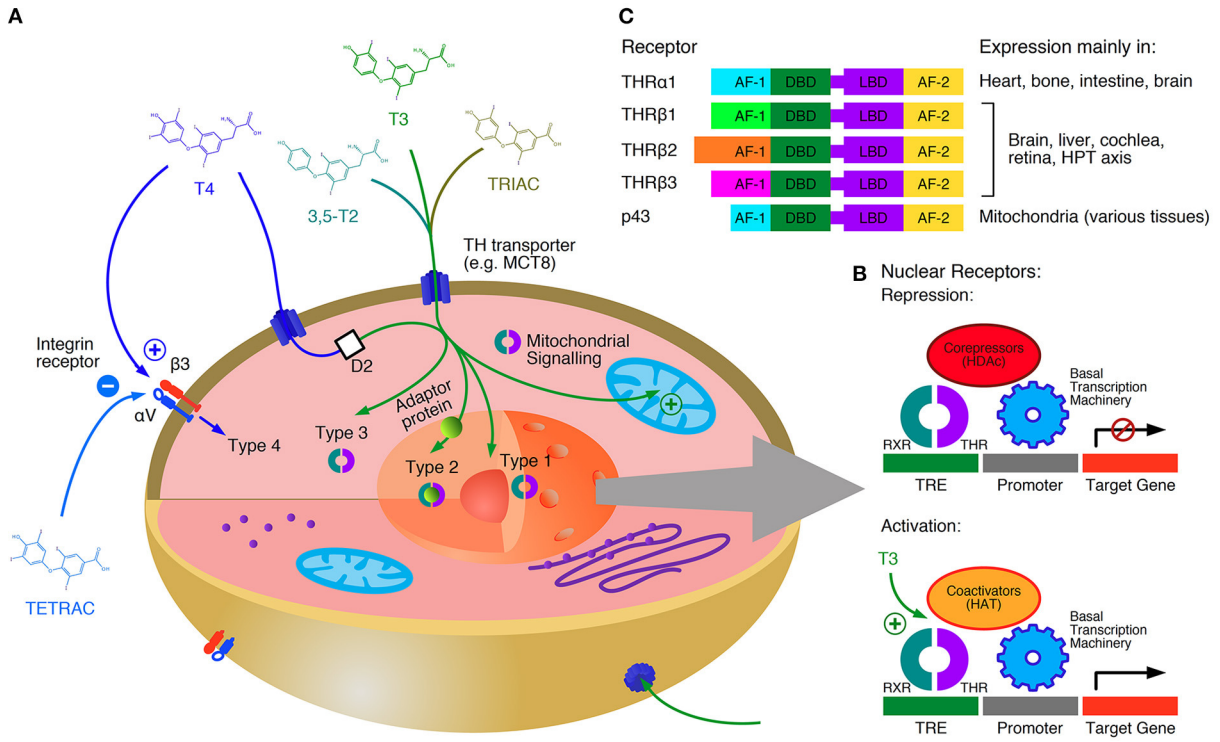

FIGURE 1
Types and mechanisms of thyroid hormone signaling. T4 is a prohormone with respect to genomic signaling, but a true fast-acting hormone regarding type 4 action (which is inhibited by the iodothyroacetate TETRAC). Genomic action (type 1, type 2 and mitochondrial signaling) occurs on a slow time scale, whereas non-genomic effects (type 3 and type 4 signaling) represent a fast response **(A)**. Thyroid hormone receptors (THR) usually act as heterodimers. Without thyroid hormone bound they block the transcription together with corepressors. Iodothyronines displace the corepressors and stimulate gene expression together with coactivators **(B)**. Tissue specific distributions of THRs further contribute to the diversity of signaling patterns in the organism **(C)** (48, 65–69). AF-1, activation function 1; AF-2, activation function 2; D2, type 2 deiodinase; DBD, DNA-binding domain; HAT, histone acetyl-transferase; HDAc, histone deacetylase; LBD, ligand-binding domain; RXR, retinoid X receptor; TRE, thyroid-hormone response element.

direct modulation *via* non-genomic type 4 signaling (31, 64, 76).

Additional effects on cardiovascular physiology may result from extracardiac mechanisms in the cardiovascular system, e. g., increased pulmonary arterial pressure, stimulation of tissue thermogenesis and a decline of both systemic vascular resistance and diastolic blood pressure, resulting in reduced afterload (31, 49, 64, 76–79).

Links between thyroid hormone action and arrhythmogenesis

The mechanisms underlying arrhythmogenesis can be divided into disorders of impulse formation, disorders of impulse conduction or a combination of both (80). All of these scenarios can be critically modulated by thyroid hormones (Table 1).

Effects of thyroid hormones on normal automaticity

Within the framework of their normal physiological function thyroid hormones have strong effects on the heart rate. Sinus bradycardia and sinus tachycardia are typical sequelae of hypothyroidism and thyrotoxicosis, respectively.

This association is well explained by modulation of the impulse formation in pacemaker cells of the sinoatrial node and (in pathological conditions) other cell types. The normal automaticity in pacemaker cells is ensured by two redundant, but intertwined loops, as suggested by Maltsev et al. (85) (Figure 2). Both an external membrane loop and an internal calcium loop, buffered by calcium storage in the sarcoplasmic reticulum, are independently able to maintain the generation of a depolarisation rhythm. They are coupled *via* late diastolic depolarisation and a slow L-type calcium current, thereby providing a better failure tolerance in impulse generation. Thyroid hormones can modulate both to generate a higher frequency of action potentials. The involved mechanisms include an acceleration of diastolic depolarisation (86–88),

activation of potassium currents (81, 89) and synchronized loading of the sarcoplasmic reticulum with calcium *via* SERCA (75, 90, 91).

In addition to thyroid hormones, thyroid-stimulating hormone (TSH) is able to modulate the function of the sinoatrial node as well. Among its extrathyroidal actions are myocardial effects that are mediated *via* G protein-coupled TSH receptors (TSHR), which are expressed in various tissues. The resulting impact of TSH on the physiological rhythm generator is mainly of decelerating nature by inhibiting several ion currents (Figure 2) (92). Since the effects of TSH action are largely antagonistic to those of beta-adrenergic stimulation they are probably mediated by pathways other than the cAMP signaling, e.g., *via* inositol trisphosphate (IP3) (93, 94).

Although we write about the "normal heart rhythm" and "physiological function" here, the mentioned mechanisms may lead to substantial pathology, e. g., in cases of severe bradycardia or tachycardia in thyroid dysfunction or activation of ectopic rhythm generators. "Normality" refers to the fact that it is physiological mechanisms that are controlled by thyroid hormone signaling. This is different in the situations mentioned in the subsequent section, which ensue from a qualitative difference and represent pathological processes *per se*.

Mechanisms linking thyroid dysfunction to cardiac arrhythmia

In addition to the modulation of physiological mechanisms, high concentrations of thyroid hormones can ignite triggers for additional scenarios of arrhythmogenesis.

Afterdepolarisations, i.e., depolarising oscillations of membrane potential after one or more preceding action potentials, are able to initiate myocardial activity. Both early (occurring before full repolarisation) and delayed afterdepolarisations (arising after completion of repolarisation) can be mediated by elevated concentrations of thyroid hormones, giving rise to triggered activity (81).

Additionally, iodothyronines shorten the effective refractory period (ERP) of cardiomyocytes in a concentration-dependent manner (95–97), and they reduce the conduction velocity (θ), e.g. by downregulating the expression of connexin 43, a key component of gap junctions (Figure 3) (75, 96–98). As a result, the wavelength of excitation (λ), which is defined by the product of *ERP* and θ, is considerably diminished, so that it may become shorter than the dimensions of potential re-entry circuits, e.g., in the vicinity of scars (99) (Figure 4). Consequently, an electrical impulse traversing a cardiac fiber bundle is slowed down and may, provided electrical irregularities are present in the tissue, meet excitable fibers after the refractory period has passed. Therefore, the combination of both mechanisms permits the evolution of re-entry or spiral wave processes (100).

The probability for successful action potential propagation depends on the safety factor for conduction, i.e., the ratio of the energy for normal conduction to the minimum propagating energy (80). Impaired function of gap junctions may lead to decremental conduction, where an impulse with a low safety factor loses activation effectiveness along with its propagation. This mechanism may cause rare paradoxical bradycardia or heart blocks in thyrotoxicosis (82, 83).

TABLE 1 Mechanisms of arrhythmia in different thyroid conditions (76, 81–84).

Disorder	Hypothyroidism	Thyrotoxicosis
Disorders of impulse formation		
Automaticity		
Normal automaticity	Sinus bradycardia	Sinus tachycardia
Triggered activity		
Early afterdepolarisations		Ventricular tachyarrhythmia
Delayed afterdepolarisations		Atrial and ventricular sustained triggered arrhythmia
Disorders of impulse conduction		
Block and re-entry		
Uni- or bidirectional block without re-entry	SA block AV block	Decremental conduction with paradox bradycardia or heart block
Unidirectional block with re-entry		Atrial fibrillation Ventricular flutter Ventricular fibrillation Ventricular tachycardia

Controversial topics and open questions

The term of "subclinical" thyroid diseases continues to be debated. It is unclear if this class of diseases is a proper representation of physiological processes (101–104), and the implications with respect to meaningful endpoints are unclear (105, 106). Therefore, useful cut-off values serving as a threshold for initiating therapy, could not be established (35). Recently, a more detailed grading system has been suggested, including FT3 and different zones of TSH concentration (107). It may be beneficial for a better classification of primary thyroid dysfunction.

This new classification cannot, however, address the dual role of TSH as both a regulator and indicator of thyroid function (53, 102, 103, 108, 109). Deviations of thyrotropin concentration may indicate ensuing or manifest primary thyroid disorders, but pituitary disease and variations in the central hypothalamic

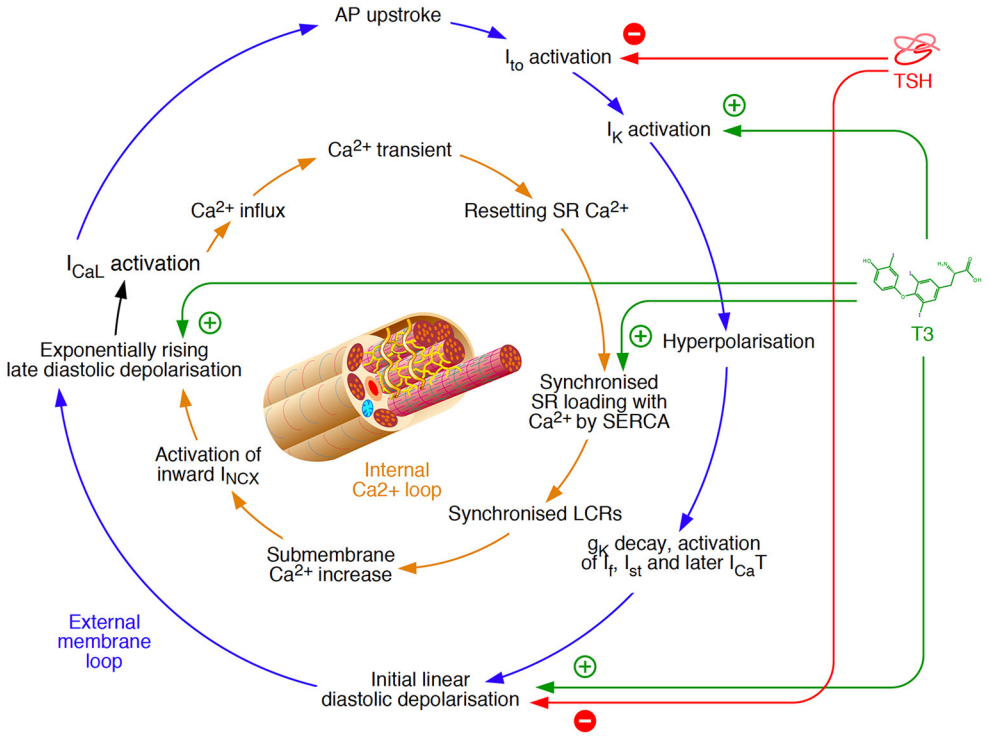

FIGURE 2
Mechanisms of rhythm generation in cardiomyocytes based on a model by Maltsev et al. (85). Two loops, an external membrane loop and an internal calcium loop independently ensure the generation of impulses. Therefore, they provide some redundancy, but they are also intertwined at the stage of slow L-type Ca^{2+} current (I_{CaL}) activation. Thyroid hormone signaling is able to modulate both loops simultaneously *via* interfaces at several sites (75, 81, 86–91), and direct myocardial effects of TSH are largely opposing (92). g_K, ionic conductance for K^+; INCX, Na^+/Ca^{2+} exchange current; I_{CaT}, T-type Ca2+ current; I_f, hyperpolarisation-activated "funny" current; I_K, voltage-gated K^+ current; I_{st}, sustained non-selective current; I_{to}, transient outward potassium current; LCR, local Ca^{2+} release; SERCA, sarcoendoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum.

set point as well (37, 47). This physiological heterogeneity may explain why thyroid hormones are better predictors of clinical outcome measures than TSH concentration (38).

Furthermore, universal reference ranges for thyrotropin and thyroid hormones have recently been more and more questioned, since the intraindividual variation of TSH and thyroid hormone concentration is smaller than the interindividual variation (110, 111). This non-ergodicity of laboratory results reflects an individual set point of the homeostatic systems, and deviations from this setpoint may from a personalized perspective be of higher importance than the position of laboratory results with respect to population-derived reference ranges (37, 112–116).

Clinical evidence

Review criteria

To compile the most comprehensive list of pertinent publications electronic literature searches in English, German and Mandarin were performed in the PubMed and Web of Science databases for relevant publications up to December 2021, evaluating a potential connection between minimal disorders of thyroid function and sudden cardiac death or malignant arrhythmia. The following query formula was used: "[(thyroid function) OR (free t4)] AND [(sudden cardiac death) OR (ventricular fibrillation) OR (ventricular tachycardia)]". Our search was limited to studies that were performed in humans and investigated the thyroid function in relation to sudden cardiac death, a combination of major endpoints including cardiovascular death (CVD) or the result of continuous recording *via* an implanted device (pacemaker, ICD or event recorder).

Among the larger set of identified studies, the meta-analysis subproject was restricted to longitudinal investigations that reported quantitative information on thyroid homeostasis and a hazard or odds ratio for one of the mentioned cardiovascular endpoints. If adjusted and unadjusted analyses with the same outcome measures and thyroid-related predictors were reported in one paper a fully adjusted multivariable analysis was selected for further evaluation.

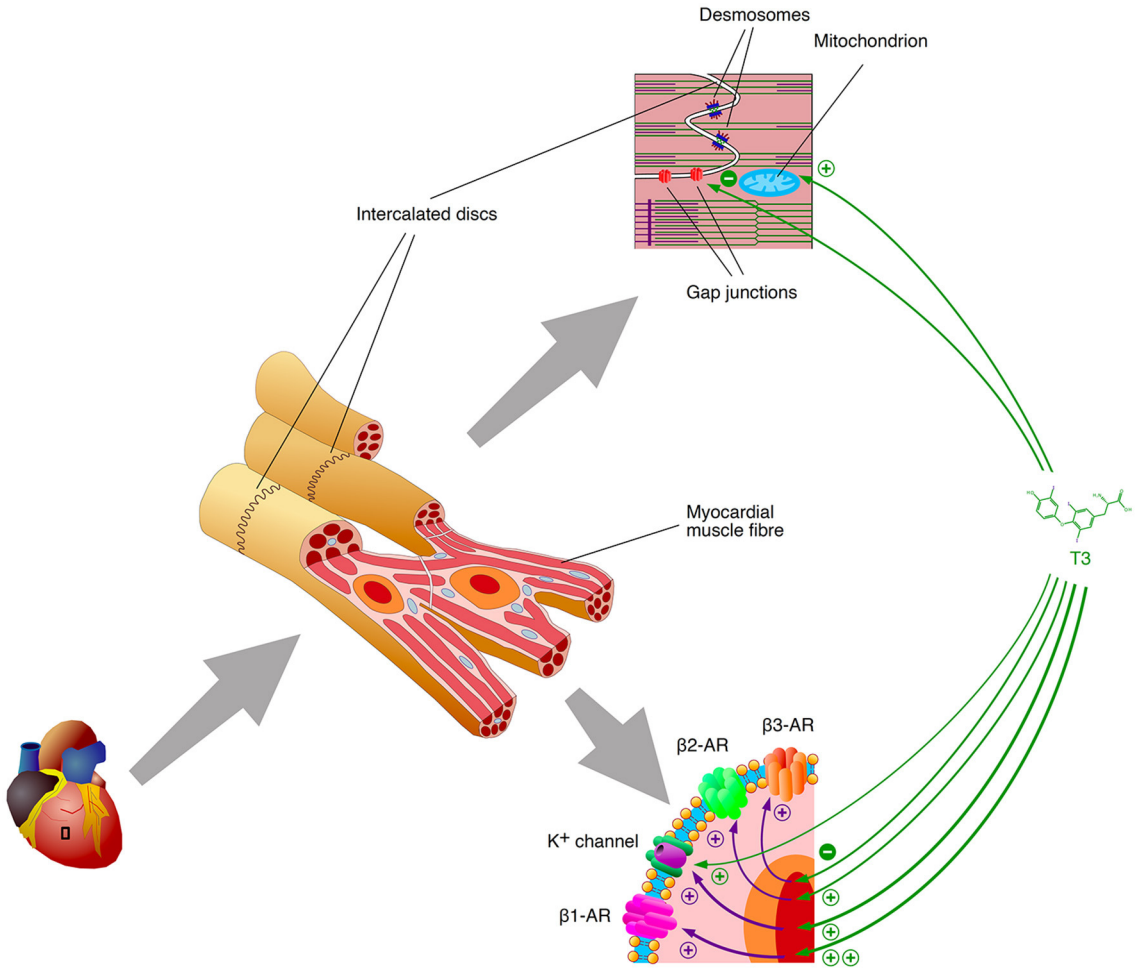

FIGURE 3
Selected mechanisms of arrhythmogenesis by thyroid hormones. T3 (and other active thyroid hormones) upregulate the gene expression of beta1 and beta2 adrenoceptors *via* classical genomic signaling, but downregulate protective beta3 adrenoceptor expression. The transcription of critical genes for the formation of gap junctions is downregulated as well. Potassium channels are regulated *via* classical type 1 signaling and *via* non-genomic effects (type 4 action) as well. Purple arrows indicate the effects of gene expression (transcription, translation and associated processing steps), green arrows visualize the impact of T3-agonistic thyroid hormones.

Exclusion criteria were case reports, animal or cell culture experiments, therapeutic trials, studies on non-thyroidal illness (TACITUS) syndrome, studies on amiodarone effects, surveys, review articles or correspondence without original data. After removing duplicates, three authors (P.M, M.K.L and J.W.D.) screened all found studies for eligibility by abstract screening and full-text reviewing. From the included publications quantitative data, including sample size, mean and standard error (or 95% confidence interval) of hormone concentrations, hazard ratio or odds ratio for cardiovascular endpoints and type of study (prospective or retrospective) were extracted.

In order to address a potentially low number of studies and to reduce the effects of bias arising from heterogeneities in MACE definitions (117–119), we used a hierarchical approach, where we analyzed the association of thyroid function separately with SCD, CVD, study-specific MACE (as defined by the authors of included publications) and inclusive MACE (the union set of MACE and cardiovascular death).

For studies reporting FT4 concentration in other units of measurement than pmol/L, HRs were converted with

$$HR_C = 1 + (HR - 1) \cdot conversion\ factor.$$

Likewise, if TSH concentration was reported in logarithmic presentation, the HR was adjusted with

$$HR_C = 1 + \frac{HR - 1}{e^1}$$

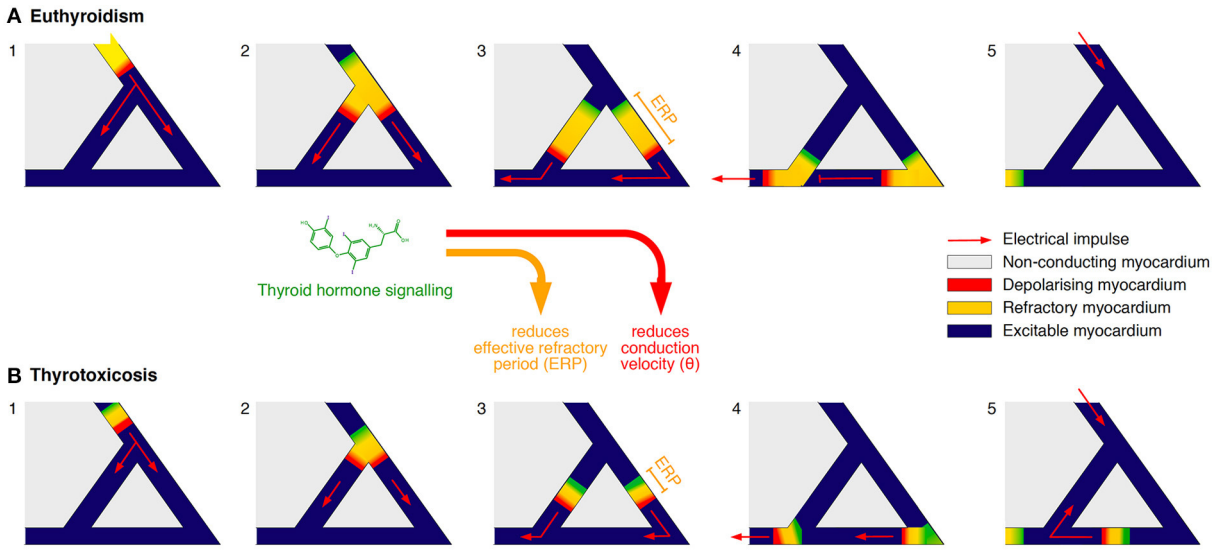

FIGURE 4
(A,B) Simplified model of the effects of thyroid hormone signaling facilitating disorders of impulse conduction. Iodothyronine action reduces both the effective refractory period (*ERP*) and the conduction velocity (θ). As a consequence, the wavelength of excitation $\lambda = ERP \times \theta$ may get shorter than the dimensions of a potential re-entry circuit, thus giving rise to re-entrant tachycardia (99).

In studies that reported HRs for increases of TSH and FT4 in standard deviations adjustments were performed with

$$HR_C = 1 + \frac{HR - 1}{SD}$$

The quality of included studies was assessed with the Newcastle-Ottawa score (NOS). In order to control for small-study effects leading to potential bias, funnel plots were drawn for analyses with five or more studies. Quantitative papers were pooled and summary measures were included in random-effects meta-analysis. The between-study variance was assessed with the DerSimonian-Laird estimator, Cochran's Q and tau squared, and heterogeneity with Higgins' and Thompson's I^2. Calculations were performed with custom S scripts for the statistical environment R (version 4.1.1 for macOS) and supported by the R packages meta and metaphor.

The protocol for the meta-analysis has been registered in the PROSPERO International prospective register of systematic reviews with the ID CRD42022311340 and is available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022311340.

Results of longitudinal studies

Via the described search strategy and other sources, we identified 32 eligible publications that were included in the systematic review (Figure 5). From these, 18 studies reported an association of thyroid homeostasis to the hazard ratio of SCD, CVD, ICD therapy or major cardiovascular events comprising one of these outcome measures. These studies could be included in the meta-analysis. See Supplementary figure 1 for the numbers of included studies with respect to different outcome measures.

Seven studies, including more than 1.2 million subjects, observed an association of reduced TSH concentration with major cardiovascular endpoints (Table 2). A very large register-based study including more than half a million citizens of Copenhagen found reduced TSH concentration to be associated with MACE, heart failure and all-cause mortality (42). In another large cohort study with elderly community-dwelling individuals diminished TSH levels were associated with a higher incidence of all-cause death (121). In a similar study with subjects aged 85 years or older reduced TSH concentration predicted both all-cause and cardiovascular mortality (120). A prospective multicentre cohort study observed a suppressed TSH concentration to be associated with higher cardiovascular mortality and risk of stroke. However, after multivariable association it was associated with stroke only (123). Another multicentre cohort study observed increased all-cause mortality in subjects with systolic heart failure and reduced TSH concentration, but the association vanished in an adjusted model (124). A study with 1 000 diabetic patients on haemodialysis found a reduced TSH level to be associated with a doubled risk of SCD, and this effect was preserved in an adjusted model (126).

Elevated TSH levels were identified in seven studies as risk factors for MACE as well. In sum, these studies comprised about 720 000 subjects. In the community-based Wickham survey elevated TSH concentration predicted a higher mortality of

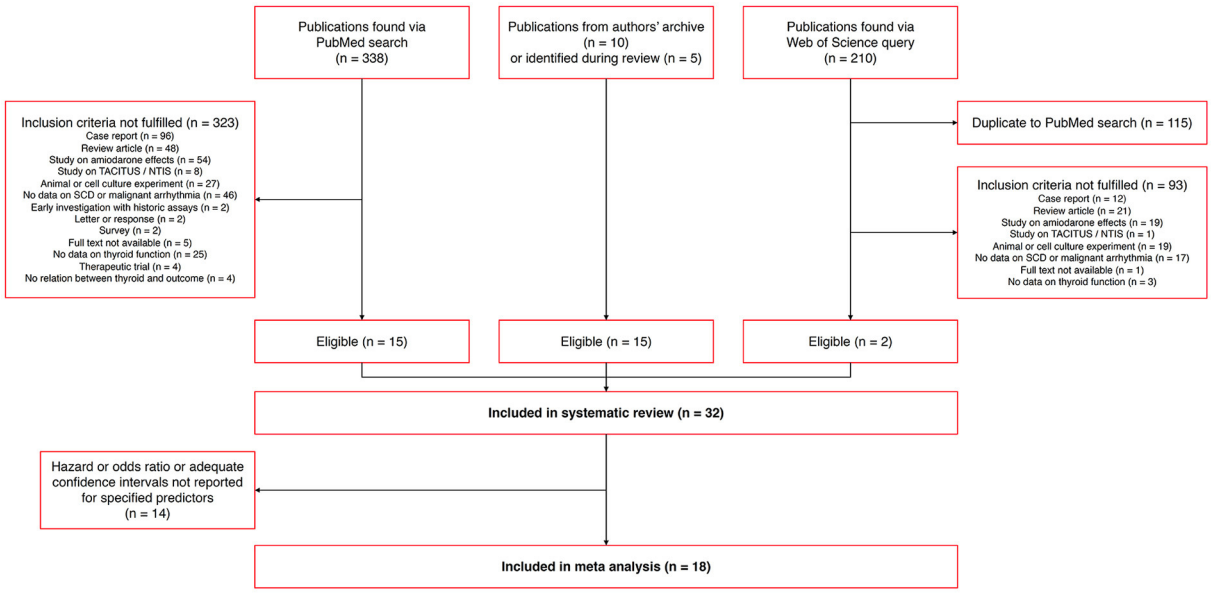

FIGURE 5
Flowchart of identified, eligible and included publications.

ischaemic heart disease and an elevated rate of fatal and nonfatal events (122). A study including subjects with systolic heart failure found TSH elevations to be associated with increased all-cause and cardiovascular mortality, but this association was lost after adjustment (127). Similar associations were observed in subjects with myocardial infarction and community-dwelling adults aged 30 years and older (130, 134). In subjects with heart failure elevated TSH concentration was associated with increased hazard ratio for a composite end point (131). Patients undergoing cardiac surgery with ischaemic heart disease demonstrated elevated TSH concentration to be associated with higher all-cause and cardiovascular mortality (136).

A small study in subjects with cardiomyopathy found TSH concentration within its reference range to be positively associated with risk for ventricular arrhythmia events in both adjusted and unadjusted models (133). The cardiovascular mortality was also associated to within-reference TSH in the PREVEND study covering community dwelling subjects younger than 72 years (39).

Additionally, several studies did not identify a relation between TSH concentration and major cardiovascular end points. These studies included in sum about 15 000 subjects. In the large community-based Rotterdam study, the TSH concentration did not predict the risk for SCD (36). Likewise, the Health in Men Study did not observe an association of TSH concentration or its quartiles to a composite end point in more than 3 000 elderly men (132). TSH concentration was not associated with all-cause or cardiovascular mortality in the Newcastle 85+ study as well. This study included more than 600 elderly subjects (129). Two studies including subjects undergoing device implantation did not find an association of TSH levels with all-cause mortality (137, 138), but one of these studies observed elevated TSH to predict appropriate ICD therapy (138).

In a meta-analysis of studies reporting hazard ratios (36, 39, 120, 129, 131), we observed no association of TSH concentration to MACE in random effect models, but a significant negative association in both fixed and random effects models with CVD as end point (Figure 6). However, the number of eligible studies was small for CVD and the unexplained heterogeneity was substantial for MACE, as demonstrated by an I^2 value of 75%.

U-shaped relationships between TSH and end points were described in 5 studies covering more than 720 000 subjects. In patients with heart failure both reduced and elevated TSH predicted increased mortality (125). Another study with patients receiving peritoneal dialysis observed both reduced and elevated TSH to be associated with increased mortality (128). This applied to unadjusted and adjusted models. After spline transformation, a study with community-dwelling individuals found a U-shaped association of TSH to total mortality (130). Similar observations were made in another population-based study that found low-normal, high-normal and elevated TSH to be associated with higher all-cause mortality than middle-normal TSH (135). This effect was partly mediated by cardiovascular disease. In the large population-based study by Selmer et al. both reduced and elevated TSH concentration was associated to cardiovascular endpoints (42). However, high TSH concentration predicted myocardial infarction only, whereas

TABLE 2 Association between TSH concentration and major cardiovascular outcome measures.

Study	Study population	Number of included subjects	Study design	Evaluation period	Outcome	Main results
Gussekloo et al. (120)	Population-based sample of elderly subjects aged 85 years or older	599	Population-based prospective cohort study	Mean 3.7 years	All-cause mortality, disability, depressive symptoms, cognitive function	Reduced TSH concentration was associated with higher all-cause and cardiovascular mortality rate.
Cappola et al. (121)	Community-dwelling individuals aged 65 years or older	3,233	Population-based prospective cohort study	Mean 12.5 years	All-cause mortality, coronary heart disease, cerebrovascular disease, atrial fibrillation	Reduced TSH was associated with higher incidence of all-cause death and atrial fibrillation.
Razvi et al. (122)	Community-dwelling subjects from the Wickham survey	2,376	Population-based prospective cohort study	Up to 20 years	Incidence and mortality of ischaemic heart disease (IHD)	Elevated TSH concentration in subclinical hypothyroidism associated with higher rate of fatal and nonfatal events and mortality of IHD.
Schultz et al. (123)	Random sample from general practitioners aged 50–91 years with normal LVEF	605	Prospective multicentre cohort study	Median 5 years	All-cause and cardiovascular mortality, stroke	Reduced TSH was associated with higher cardiovascular mortality and risk of stroke (after multivariable adjustment associated with stroke only)
Frey et al. (124)	Subjects with systolic heart failure	758	Prospective multicentre cohort study	3 years	All-cause mortality	Reduced TSH was associated with increased mortality in unadjusted model. No association in adjusted model.
Mitchell et al. (125)	Subjects with heart failure	2,225	Prospective multicentre cohort study	Median 3.8 years	All-cause mortality	Both reduced and elevated TSH was associated with increased mortality.
Drechsler et al. (126)	Diabetic haemodialysis patients	1,000	Prospective multicentre cohort study	4 years	All-cause mortality, sudden cardiac death, stroke, combined CV events (sudden death, MI or stroke)	Reduced TSH was associated with doubled risk of sudden cardiac death (in adjusted and unadjusted models). Elevated TSH was not associated with outcome measures.
Perez et al. (127)	Patients with systolic heart failure	4,987	Prospective multicentre cohort study	Median 2.7 years	Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	Elevated TSH was associated with increased all-cause and cardiac mortality in unadjusted model. No association after adjustment.
Selmer et al. (42)	Citizens of Copenhagen without previous thyroid dysfunction undergoing thyroid function testing	563,700	Population-based prospective cohort study	Median 5.5 years	Myocardial infarction (MI), heart failure, stroke, composite MACE (CVD, nonfatal MI or nonfatal stroke) and all-cause mortality	Reduced TSH concentration was associated with MACE, heart failure and all-cause mortality. Elevated TSH was associated with MI.

(Continued)

TABLE 2 Continued

Study	Study population	Number of included subjects	Study design	Evaluation period	Outcome	Main results
Chaker et al. (36)	Community-dwelling individuals included in the Rotterdam study	10,318	Population-based prospective cohort study	Median 9.1 years	Sudden cardiac death	TSH concentration was not associated with risk for sudden cardiac death
Rhee et al. (128)	Patients receiving peritoneal dialysis	1,484	Prospective multicentre cohort study	Median 1.0 years	All-cause mortality.	Both reduced and elevated TSH was associated with increased mortality (unadjusted and adjusted models).
Pearce et al. (129)	Members of the Newcastle 85+ study, recruited from general (family) practices	643	Prospective cohort study	Up to 9 years	All-cause and cardiovascular mortality	TSH concentration was not associated with all-cause or cardiovascular mortality after adjustment.
Langén et al. (130)	Community-dwelling individuals aged ≥ 30 years	5,211	Population-based prospective cohort study	Median 13.2 years	All-cause mortality, sudden cardiac death, CHD events, CVD, stroke, MACE (CVD or heart failure), AF	Elevated TSH was associated with increased all-cause mortality and SCD, no association to other outcomes. U-shaped association of TSH to total mortality after spline transformation.
Kannan et al. (131)	Patients with heart failure enrolled in the Penn Heart Failure Study	1,365	Prospective multicentre cohort study	Median 4.2 years	Composite end point of all-cause mortality, cardiac transplant or VAD placement.	Elevated TSH was associated with increased hazard for composite end point.
Golledge et al. (132)	Community-recruited elderly men without known thyroid disease	3,712	Population-based prospective cohort study	Mean 9.5 years	Composite end point of cardiovascular death, myocardial infarction or stroke	TSH concentration or its quartiles were not associated to the composite end point.
Li et al. (133)	Euthyroid patients with nonischemic dilated cardiomyopathy	184	Prospective unicentre cohort study	Median 4.6 years	All-cause and cardiac mortality, events of ventricular arrhythmia, exacerbation of heart failure, heart transplant	TSH concentration within its reference range was positively associated with risk for VA events (unadjusted and adjusted models). No association to other outcome measures.
Seo et al. (134)	Patients with acute myocardial infarction	1,977	Prospective multicentre cohort study	Median 3.5 years	All-cause and cardiac mortality	Elevated TSH was associated with higher all-cause and cardiac mortality.
Groothof et al. (39)	Community-dwelling euthyroid individuals aged 28–75 years	6,054	Population-based prospective cohort study	Mean 7.9 years	All-cause and cardiovascular mortality	In subjects younger than 72 years TSH concentration within reference range was positively associated with cardiovascular mortality in adjusted model.

(Continued)

TABLE 2 Continued

Study	Study population	Number of included subjects	Study design	Evaluation period	Outcome	Main results
Inoue et al. (135)	Community-dwelling individuals included in the NHANES study	9,020	Population-based prospective cohort study	Median 7.3 years	All-cause mortality	Low-normal, high-normal and elevated TSH was associated with higher all-cause mortality than middle-normal TSH, partly mediated by cardiovascular disease.
Kim et al. (136)	Patients undergoing cardiac surgery	565	Retrospective unicentre case-control study	Mean 7.6 years	All-cause and cardiovascular mortality, stroke, hospitalization for heart failure, coronary revascularisation and MACE (CVD, non-fatal MI, non-fatal stroke or hospitalization for heart failure)	Elevated TSH was associated with higher all-cause and cardiovascular mortality in subgroup with ischaemic heart disease (n=461, adjusted and unadjusted models), but not in group with valvular heart disease (n=104).
Müller et al. (137)	Euthyroid patients undergoing implantation of an ICD device	115	Prospective unicentre cohort study	Mean 3.3 years	Cardiovascular mortality, appropriate ICD therapy	TSH within its reference range was not associated with mortality or ICD therapy.
Yang et al. (138)	Patients receiving cardiac resynchronization therapy	1,316	Retrospective unicentre cohort study	Median 3.6 years	All-cause mortality, appropriate ICD therapy	Elevated TSH was not associated with all-cause mortality, but with increased risk for appropriate ICD therapy.
Evron et al. (139)	US veterans receiving thyroid hormone replacement therapy	705,307	Retrospective cohort study based on a data warehouse system	Median 4 years	Cardiovascular mortality	Risk for CVD was elevated in both cohorts with TSH < 0.1 mIU/L and > 5.5 mIU/L. Dose-dependent increase toward the more extreme phenotypes of dysregulation.

low TSH concentration was associated to MACE (CVD, non-fatal MI and non-fatal stroke), heart failure and all-cause mortality. An even larger data warehouse-based study by Evron et al. found a strong association of both reduced and elevated TSH concentration with cardiovascular mortality (139) in adults receiving thyroid hormone replacement therapy. In this study the increase in the adjusted hazard ratio was concentration-dependent, with a positive gradient toward both lower and higher TSH concentrations.

Elevated FT4 concentrations were associated with major endpoints in seven studies comprising in sum more than 720 000 subjects (Table 3). A positive association to the risk of SCD was observed in large community-based studies (36, 39, 120, 132). Two of these studies also observed FT4 concentration to be related to all-cause mortality (39, 120). The FT4 concentration predicted the hazard for a composite endpoint in subjects with heart failure (131). In a small study the FT4 concentration predicted the risk for appropriate ICD therapy and the hazard for ICD therapy-free survival (137). Two of the described studies also saw a positive association of within-reference FT4 concentration to major endpoints (36, 137). In a large data warehouse-based study including US veterans aged 18 or older on levothyroxine replacement therapy, both reduced and elevated FT4 concentrations were associated with the risk of cardiovascular mortality (139).

After adjustment, the Newcastle 85+ study did not find an association of FT4 concentration with all-cause or

TABLE 3 Association between FT4 concentration and major cardiovascular outcome measures.

Study	Study population	Number of included subjects	Study design	Evaluation period	Outcome	Main results
Gussekloo et al. (120)	Population-based sample of elderly subjects aged 85 years or older	599	Population-based prospective cohort study	Mean 3.7 years	All-cause mortality, disability, depressive symptoms, cognitive function	Elevated FT4 concentration was associated with higher all-cause and cardiovascular mortality rate.
Chaker et al. (36)	Community-dwelling individuals included in the Rotterdam study	10,318	Population-based prospective cohort study	Median 9.1 years	Sudden cardiac death	FT4 concentration, even within its reference ranges was positively associated with hazard for sudden cardiac death. Risk for SCD was increased if FT4 was in the 3rd tertile of the reference range unadjusted and adjusted models).
Pearce et al. (129)	Members of the Newcastle 85+ study, recruited from general (family) practices	643	Prospective cohort study	Up to 9 years	All-cause and cardiovascular mortality	FT4 concentration was not associated with all-cause or cardiovascular mortality after adjustment.
Kannan et al. (131)	Patients with heart failure enrolled in the Penn Heart Failure Study	1,365	Prospective multicentre cohort study	Median 4.2 years	Composite end point of all-cause mortality, cardiac transplant or VAD placement.	FT4 concentration was positively associated with hazard for composite end point.
Golledge et al. (132)	Community-recruited elderly men without known thyroid disease	3,712	Population-based prospective cohort study	Mean 9.5 years	Composite end point of cardiovascular death, myocardial infarction or stroke	Increased risk for the MACE and myocardial infarction in the highest quartile for FT4 concentration.
Groothof et al. (39)	community-dwelling individuals aged 28–75 years	6,054	Prospective cohort study	Mean 7.9 years	All-cause and cardiovascular mortality	FT4 concentration was positively associated with both all-cause and cardiovascular mortality (unadjusted and adjusted models).
Müller et al. (137)	Euthyroid patients undergoing implantation of an ICD device	115	Prospective unicentre cohort study	Mean 3.3 years	Cardiovascular mortality, appropriate ICD therapy	FT4 in the 2nd and 3rd tertiles of the reference range was positively associated with increased risk for appropriate ICD therapy. FT4 concentration associated to hazard for ICD therapy-free survival (unadjusted and adjusted models).
Evron et al. (139)	US veterans receiving thyroid hormone replacement therapy	705,307	Retrospective cohort study based on a data warehouse system	Median 4 years	Cardiovascular mortality	Risk for CVD was elevated in both cohorts with FT4 $<$ 9.0 pmol/L and $>$ 24.5 pmol/L.

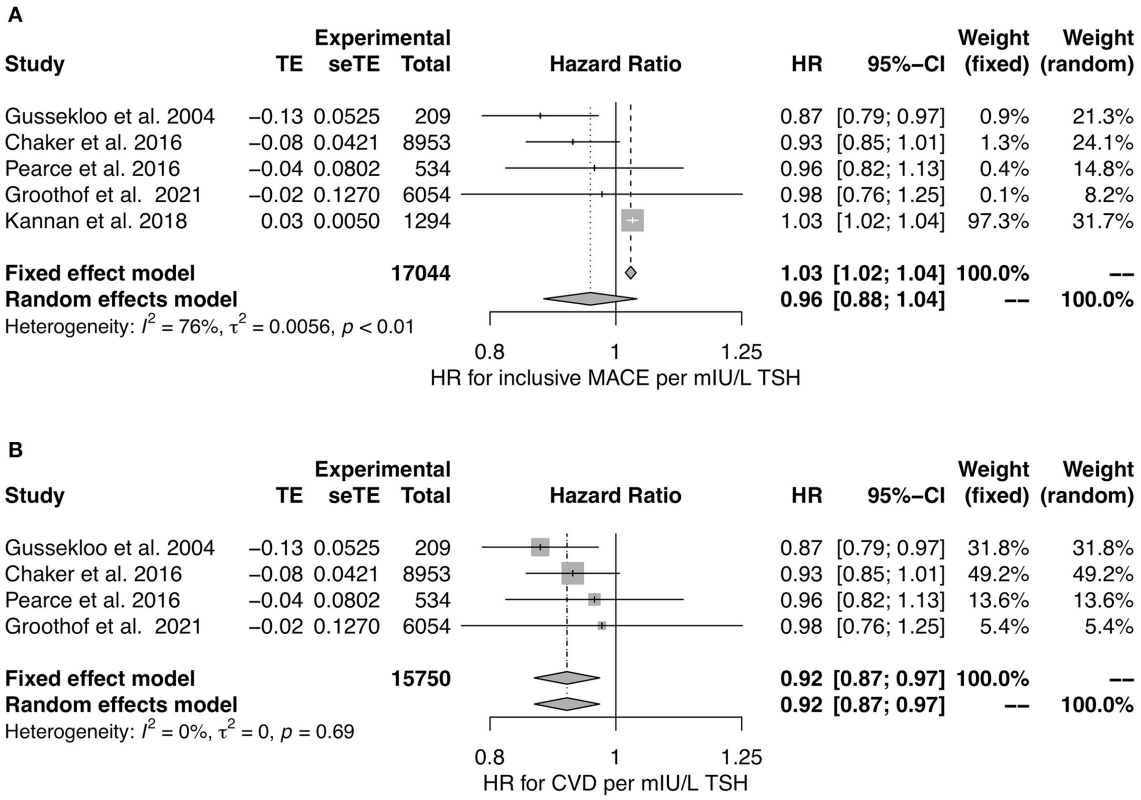

FIGURE 6
Hazard ratio for major cardiovascular events **(A)** and cardiovascular death **(B)** in relation to TSH concentration (36, 39, 120, 129, 131).

cardiovascular mortality. This study had a comparably small sample size of 643 elderly subjects (129).

Including studies reporting hazard ratios in a meta-analysis (36, 39, 120, 129, 131), we observed a significant association of FT4 concentration to MACE and a potential association to CVD (Figure 7). The heterogeneity between studies was moderate for both MACE and CVD with I^2 values being 53 and 57%, respectively. Therefore, random effects models may be preferable over fixed-effects models to draw conclusions.

The heterogeneity between studies was moderate to substantial in the meta-analysis for subclinical hypothyroidism (42, 121, 123, 126, 130, 131, 136, 140–143). Random effects models reveal an association to inclusive MACE, but not to study-specific MACE (Figures 8A,B). Both fixed effects and random effects models confirm subclinical hypothyroidism to predict CVD (Figure 8C).

In the meta-analyses for subclinical hyperthyroidism the heterogeneity was very low (study-specific MACE) or moderate (MACE and CVD) (42, 121, 123, 126, 140, 142–144). The fixed effects model suggests a small effect with a hazard ratio of 1.10 with respect to both inclusive MACE and study-specific MACE (Figures 9A,B). An association to CVD was confirmed by both fixed effects and random effects models (Figure 9C).

The studies included in meta-analyses had a mean Newcastle-Ottawa score of 7.7, suggesting a sufficient quality of the available evidence. Funnel plots did not signify considerable bias, but support the assumption of heterogeneity among included studies. Detailed information is provided in the Supplementary material.

Discussion

Both the generation of normal cardiac automaticity and the pathogenesis of arrhythmia are critically dependent on thyroid hormone signaling. Basic research identified multiple mechanisms linking thyroid hormone action to the formation of the normal and pathological heart rhythm. On a molecular level, classical thyroid hormone signaling (type 1 action) modulates the expression of multiple genes involved in the generation and conduction of excitation. On the level of electrophysiological processes, critical components of the rhythm-generating loops are sensitive to active iodothyronines. Interestingly, TSH has

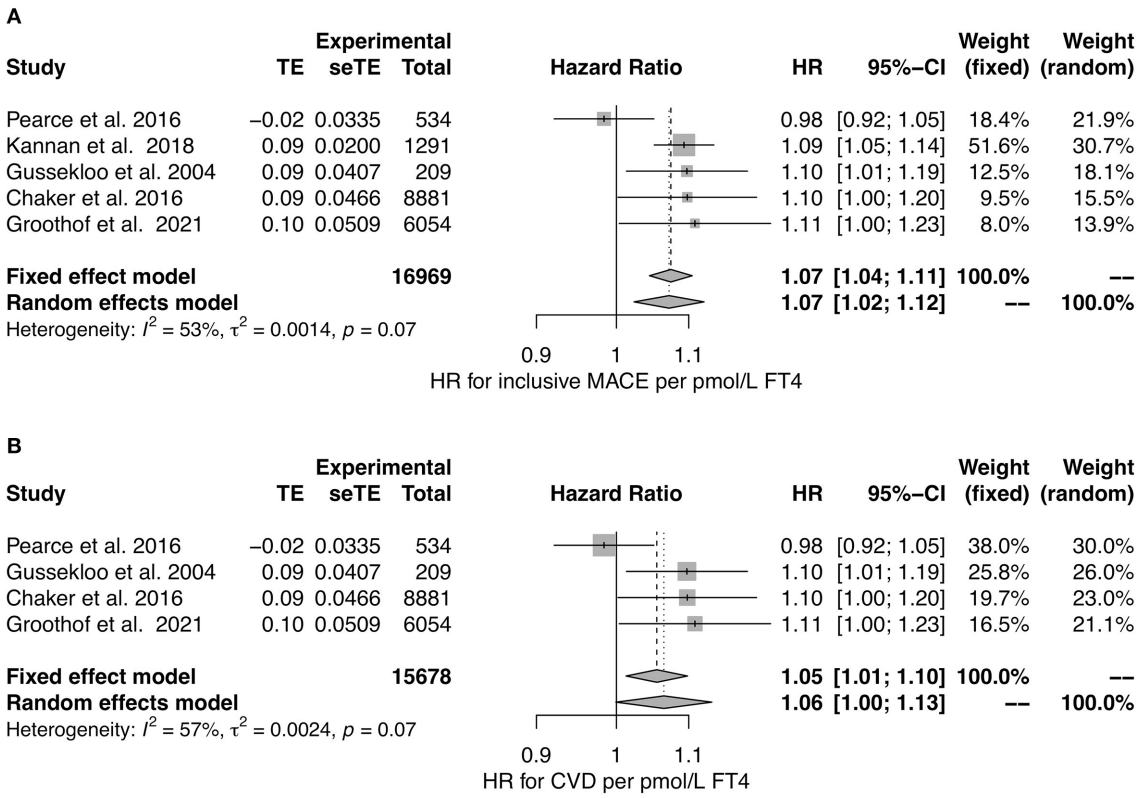

FIGURE 7
HR for MACE **(A)** and CVD **(B)** in relation to FT4 concentration (36, 39, 120, 129, 131).

fundamentally opposing effects on generator loops, probably mediated *via* IP3 signaling.

Non-canonical thyroid hormone signaling has been linked to heart rate as well. The detailed mechanisms are not well understood up to now.

Although thyroid hormones increase the heart rate, they slow down the velocity of impulse conduction (θ), mainly due to down-regulation of critical components of gap junctions. Together with a shortened effective refractory period (ERP), this may lead to re-entrant tachycardia, if the wavelength of excitation

$$\lambda = ERP \cdot \theta$$

gets shorter than the length of potential anatomical re-entry circles. Necessary for this mechanism to come into effect is some heterogeneity in the myocardial tissue, e.g., due to the existence of scars forming the center of latent re-entry circles and to some electrophysiological variety of conducting tissue. This may explain why the probability of thyrogenic arrhythmia increases with age and in subjects with pre-existing cardiac disease.

From a clinical perspective, a relation of thyroid function to mortality is well established. Both the described physiological mechanisms and several prospective studies suggest this association to be mediated by arrhythmia.

With our search strategy we identified 32 publications investigating a potential relation between minimal deviations of thyroid function and major cardiovascular end points. Several studies with large sample sizes found reduced and/or elevated TSH concentration to predict cardiovascular or all-cause mortality, or composite MACE endpoints. Two studies described even a positive correlation of the TSH concentration within its reference range with cardiovascular events. However, several studies, even with large sample size, did not find an association of TSH concentration to major outcome measures. Our meta-analyses identified a negative relation of TSH to hazard ratios of CVD, but no clear association to MACE.

The situation was clearer for FT4 concentration. Six studies with a large cumulative sample size found a significant positive association between FT4 and cardiovascular events, including composite endpoints, mortality and appropriate ICD therapy. In two studies this association was also present if FT4 concentration was restricted to its reference interval. Only one study described both reduced and elevated FT4 concentrations to be associated to CVD (139), but this study included subjects on levothyroxine replacement therapy and may, therefore, represent slightly

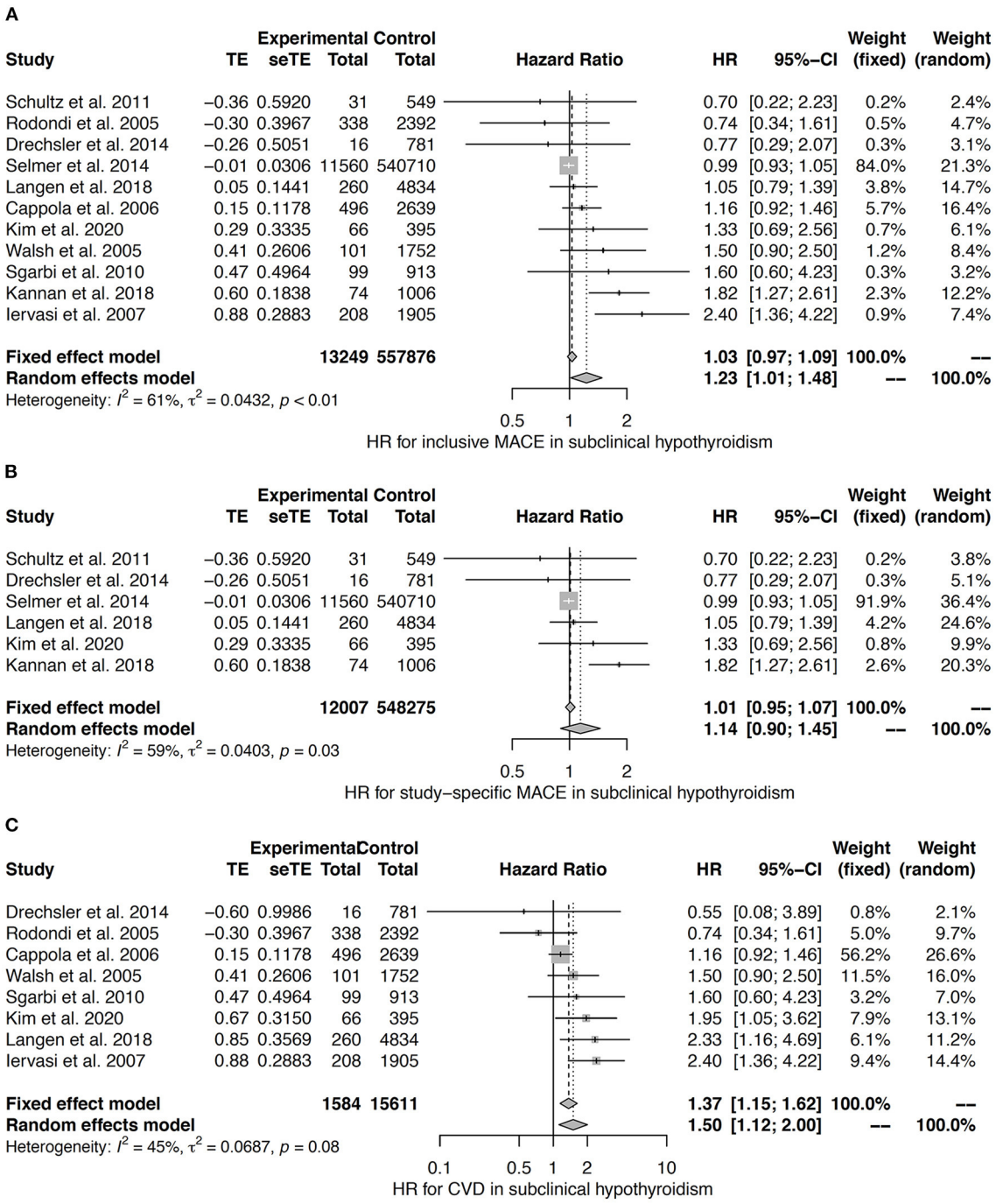

FIGURE 8
HR for inclusive MACE **(A)**, study-specific MACE **(B)**, and CVD **(C)** in subclinical hypothyroidism (42, 121, 123, 126, 130, 131, 136, 140–143).

different pathophysiological mechanisms. *Via* meta-analysis we found a positive association of FT4 to MACE and a tendency for CVD.

The dissimilarity between these results, with a strong monotone prediction model for FT4, but a much less clear association of TSH to major endpoints, may be traced back to several causes. One may be the considerable heterogeneity of the results in the included studies, so that less powerful random effects models had to be preferred to fixed effects models, especially for the association of TSH concentration to MACE.

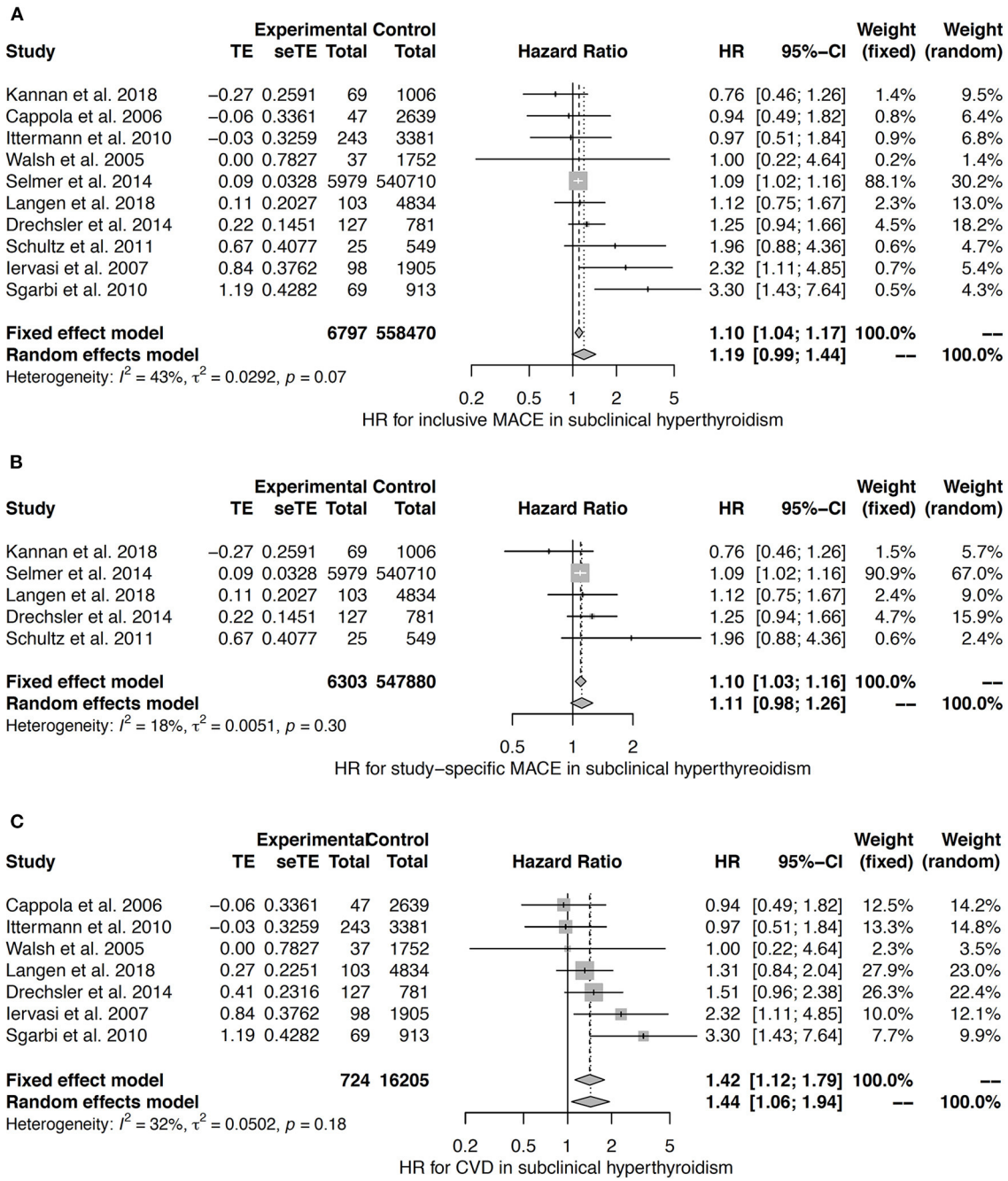

FIGURE 9
HR for MACE **(A,B)** and CVD **(C)** in subclinical hyperthyroidism (42, 121, 123, 126, 140, 142–144).

Another explanation may be a U-shaped relation between TSH concentration and the risk for cardiovascular events (145). This form of nonlinear interaction was revealed by four studies that found both reduced and elevated TSH to predict mortality. Studies with negative results may have missed this complex association due to the use of over-simplified statistical models. It is corroborated, however, by our meta-analyses revealing both subclinical hypothyroidism and hyperthyroidism to predict cardiovascular mortality (Figures 8C, 9C).

Our results are consistent with the outcomes of previous studies and meta-analyses (146). However, a U-shaped link between TSH and cardiovascular risk is not straightforward to be explained from a physiological perspective. A recent study described very similar results for the link between thyroid

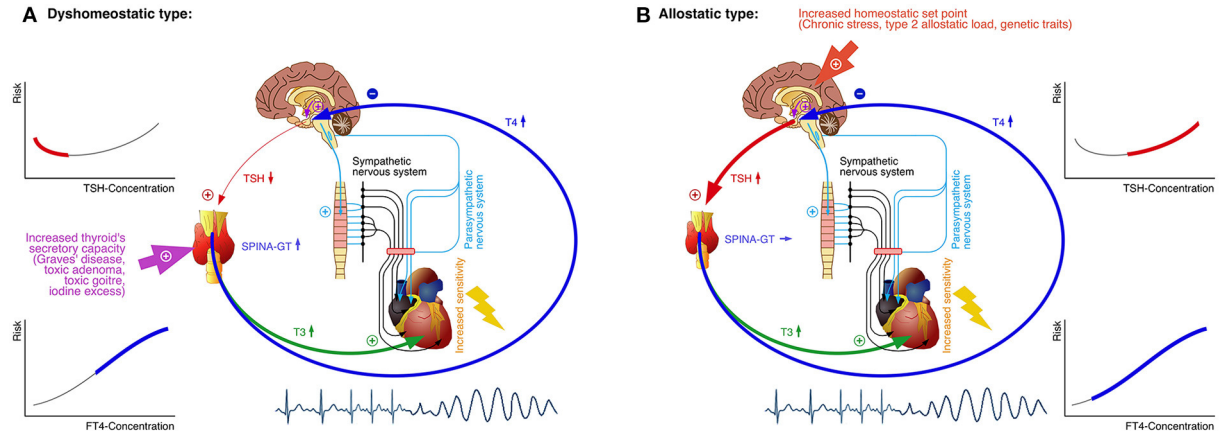

FIGURE 10
An integrated model for the association between thyroid homeostasis and major cardiovascular events. In the dyshomeostatic type of thyrogenic arrhythmia elevated FT4 concentration, caused by primary thyrotoxicosis, increases the risk for severe arrhythmia as a major cause for cardiovascular mortality. The TSH concentration is reduced in this case, represented by the left, declining, branch of the U-shaped relation between TSH level and risk **(A)**. In the allostatic type, mainly caused by type 2 allostatic load and genetic traits, the set point of thyroid homeostasis is raised, resulting in increased TSH and FT4 concentration and subsequently elevated risk for arrhythmia. This situation is mirrored in the right, rising, branch of the relation between TSH concentration and cardiovascular risk **(B)**. In any case, elevated concentrations of T3, T4 and other T3-agonistic thyroid hormones increase the sensitivity to catecholamines and sympathetic signaling (*via* upregulated expression of beta1 and beta2 adrenoceptors), thereby contributing to reduced stress tolerance. SPINA-GT, "gain of thyroid," i.e., thyroid's secretory capacity (150).

function to Takotsubo syndrome, and the pathogenesis was explained by nosological heterogeneity, where two different scenarios overlapped (147). These considerations may be extended to cardiovascular endpoints in general (Figure 10). A dyshomeostatic type of thyrogenic arrhythmia may result from primary hyperthyroidism and other forms of non-central thyrotoxicosis. Here, the TSH secretion responds inversely to rising FT4 concentrations, so that FT4 is positively, but TSH negatively associated to the event rate (53, 148, 149). In an allostatic type of thyro-cardiac linkage, however, TSH concentrations rise with acute stress levels and long-term type 2 allostatic load, with consecutive, centrally-mediated, increasing T4 secretion (47, 56, 147). This case reflects a raised set-point of thyroid homeostasis. Therefore, both TSH and FT4 are positively associated to mortality and other major endpoints. Taken together, the blending of both types in population-based studies yields a U-shaped association between TSH concentration and the hazard of cardiovascular events, but a simpler monotonic prediction model for FT4 (Figure 10).

Multiple studies, reviews and meta-analyses described reduced T3 concentrations and other phenotypes of non-thyroidal illness syndrome (representing a type 1 allostatic response being also known as euthyroid sick syndrome or TACITUS—thyroid allostasis in critical illness, tumors, uraemia and starvation) to be linked to cardiovascular and general mortality and arrhythmia as well (56, 78, 151–153). Up to now, it is still not established whether low-T3 syndrome represents an adaptive response, a maladaptive mechanism or a combination of both (79). We did not address this topic in detail here and even excluded studies on TACITUS from the systematic review part, since this association may reflect common causes of mortality rather than a direct effect of low-T3 syndrome on cardiac electrophysiology. However, some non-classical thyroid hormones, especially 3,5-T2, which is thyromimetic and upregulated in critical illness, may increase both heart rate and risk for arrhythmia (152, 154).

Type 1 allostatic response in heart failure may to a certain extent limit our conclusions since FT4 concentrations could rise if the pathway *via* deiodinases to T3 formation is down-regulated (56). Decreased deiodinase activity may result from critical illness, but also from therapy with certain drugs, including amiodarone, beta-blockers and glucocorticoids (155). Additionally, the free fraction of thyroid hormones may increase due to drug interference with plasma protein binding, which may originate, e.g., from the use of furosemide, aspirin, heparin or other substances (156–158). Therefore, elevated FT4 concentration might as well partly reflect therapeutic decisions in subjects with cardiac failure. It is, however, unlikely that major bias arises from this fact since most of the described effects are rapidly settled by the hypothalamus-pituitary-thyroid feedback loop and, therefore, of temporary nature, whereas the follow-up time in most of the included studies extended to several years (55, 159).

The selection criteria for the systematic review may have led to the under-representation of studies reporting the risk in alternative form, e.g., in form of quantiles. This

potential bias may have been mitigated by the fact that we included publications from other sources, e. g., own archives. Unfortunately, it was impossible to sensibly combine quantile-based studies in a meta-analysis, since the numbers of quantiles (tertiles, quartiles and quintiles were used) differed among the publications. Qualitative analysis suggests, however, an association of FT4 in the highest tertiles or quartiles to cardiovascular risk.

In summary, basic research and physiological studies suggest a strong link of thyroid hormones to cardiac rhythm generation and the pathogenesis of arrhythmia. The clinical evidence suggests a monotonic and unambiguous relation of FT4 concentration to arrhythmia, which seems to be one of the most important mediators of major cardiovascular endpoints. The relationship of TSH levels to arrhythmia, mortality and other outcome measures is less clear and best explained by a U-shaped link, which may reflect the overlap of two different scenarios, a dyshomeostatic type of thyrogenic arrhythmia resulting from ensuing primary thyrotoxicosis, and an allostatic response with an increased set point of the feedback loop. This hypothesis may serve as a starting point for future targeted research projects.

Conclusions and outlook

Variations of thyroid function, even the slightest forms within the respective reference ranges of TSH and thyroid hormones, are strong predictors of major cardiovascular endpoints. However, the nature of this relation is more complex than previously assumed.

In addition to the well-established effects of primary thyrotoxicosis, central mechanisms of the hypothalamus-pituitary-thyroid (HPT) axis may play an important, but previously under recognized, role as well. This class of diseases includes secondary and tertiary hyperthyroidism in pituitary-related and hypothalamic disorders and in central resistance to thyroid hormone (RTH). These conditions are rare diseases, however, with respective prevalence of about 1 in 100 000 subjects. Much more common are adaptive responses representing type 2 allostatic load (160). Examples include post-traumatic stress disorder (PTSD), certain psychiatric diseases and long-term effects of social disparity. It could be demonstrated that conditions associated to type 2 allostatic load involve an elevated set point of the HPT axis and that they convey an increased risk for major cardiovascular events (5, 47, 56, 147, 161–163). The heterogeneity of pathophysiological mechanisms provides a plausible explanation for the U-shaped relation between TSH concentration and cardiovascular risk.

The new understanding of the dual etiology of the thyro-cardiac link has important therapeutic implications. First of all, the threshold for the treatment of thyrotoxicosis may be in future adjusted to include subclinical hyperthyroidism (SH) as well. This decision may be supported by results of a meta-analysis revealing a 24% increased risk of overall mortality in SH (164). However, the potentially beneficial effects of a more intensive correction of low-grade thyrotoxicosis have to be balanced against the risks resulting from treatment with thyrostatic agents and from definitive therapy (surgery or radioiodine treatment). The European Thyroid Association recommended treatment of SH in subjects of 65 years or older and in younger persons with concomitant cardiovascular disease (165).

The situation is more straightforward regarding the treatment of hypothyroidism. Here, it may prove advantageous if dosage titration algorithms for levothyroxine approach the target from below and prevent the free T4 concentration from entering the zone of the highest quartile of its reference range (166). This consideration also applies to the secondary prophylaxis of differentiated thyroid cancer (DTC). Accordingly, recent guidelines have also addressed cardiovascular concerns when overturning the previous recommendation of universal TSH suppression in low- and intermediate-risk DTC (167).

Treatment of type 2 allostatic load with a subsequently elevated set point of the HPT axis should address its origins. Sensible starting points include psychosocial support and lifestyle interventions (168–172). Early addressing of socioeconomic disparity and environmental factors may provide the basis for primary prevention of cardiovascular mortality (173, 174), and this may in part be due to a readjustment of thyroid homeostasis toward a healthier phenotype.

Where possible, future studies on the association of thyroid function with major cardiovascular endpoints should be based on validated criteria, including standardized MACE sets and uniform quantile definitions, in order to support replication, comparison and aggregation of results (118).

Author contributions

PM, JD, and ML defined the selection criteria and screened all found studies for eligibility by abstract screening and full-text reviewing. JD maintained the study table and performed the meta-analyses. JD and PM drafted a first version of the manuscript. ML edited the text and contributed additional ideas, material, and text passages. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.942971/full#supplementary-material

References

1. Jean-Philippe E, Lerner I, Valentin E, Folke F, Bottiger B, Gislason G, et al. Incidence of sudden cardiac death in the European Union. *J Am Coll Cardiol.* (2022) 79:1818–27. doi: 10.1016/j.jacc.2022.02.041

2. Kumar A, Avishay DM, Jones CR, Shaikh JD, Kaur R, Aljadah M, et al. Sudden cardiac death: epidemiology, pathogenesis and management. *Rev Cardiovasc Med.* (2021) 22:147–58. doi: 10.31083/j.rcm.2021.01.207

3. Rogers AJ, Selvalingam A, Alhusseini MI, Krummen DE, Corrado C, Abuzaid F, et al. Machine learned cellular phenotypes in cardiomyopathy predict sudden death. *Circ Res.* (2021) 128:172–84. doi: 10.1161/CIRCRESAHA.120.317345

4. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. *Circulation.* (2003) 107:2096–101. doi: 10.1161/01.CIR.0000065223.21530.11

5. Batelaan NM, Seldenrijk A, van den Heuvel OA, van Balkom A, Kaiser A, Reneman L, et al. Anxiety, mental stress, and sudden cardiac arrest: epidemiology, possible mechanisms and future research. *Front Psychiatry.* (2021) 12:813518. doi: 10.3389/fpsyt.2021.813518

6. Gräsner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation.* (2016) 105:188–95. doi: 10.1016/j.resuscitation.2016.10.001

7. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res.* (2015) 116:1887–906. doi: 10.1161/CIRCRESAHA.116.304521

8. Trayanova NA. Learning for prevention of sudden cardiac death. *Circ Res.* (2021) 128:185–7. doi: 10.1161/CIRCRESAHA.120.318576

9. Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, et al. Epidemiology of sudden cardiac death: global and regional perspectives. *Heart Lung Circ.* (2019) 28:6–14. doi: 10.1016/j.hlc.2018.08.026

10. Breitenstein A, Steffel J. Devices in heart failure patients-who benefits from ICD and CRT? *Front Cardiovasc Med.* (2019) 6:111. doi: 10.3389/fcvm.2019.00111

11. Kusumoto FM, Calkins H, Boehmer J, Buxton AE, Chung MK, Gold MR, et al. HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *Circulation.* (2014) 130:94–125. doi: 10.1161/CIR.0000000000000056

12. NICE. *Technology appraisal guidance: Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.* London: National Institute for Health and Care Excellence (2014).

13. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* (2015) 36:2793–867. doi: 10.1093/eurheartj/ehv316

14. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* (2013) 128:e240–327. doi: 10.1161/CIR.0b013e3182742cf6

15. Huikuri HV, Makikallio TH, Raatikainen MJ, Perkiomaki J, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation.* (2003) 108:110–5. doi: 10.1161/01.CIR.0000077519.18416.43

16. Lopera G, Curtis AB. Risk stratification for sudden cardiac death: current approaches and predictive value. *Curr Cardiol Rev.* (2009) 5:56–64. doi: 10.2174/157340309787048130

17. La Rovere MT, Bigger JT. Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet.* (1998) 351:478–84. doi: 10.1016/S0140-6736(97)11144-8

18. La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation.* (2001) 103:2072–7. doi: 10.1161/01.CIR.103.16.2072

19. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* (2002) 346:877–83. doi: 10.1056/NEJMoa013474

20. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJ, Houben LG, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol.* (1997) 30:1500–5. doi: 10.1016/S0735-1097(97)00355-0

21. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest–the relevance of heart failure. The Maastricht Circulatory arrest registry. *Eur Heart J.* (2003) 24:1204–9. doi: 10.1016/S0195-668X(03)00191-X

22. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med.* (2016) 375:1221–30. doi: 10.1056/NEJMoa1608029

23. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J.* (2015) 36:1990–7. doi: 10.1093/eurheartj/ehv186

24. Suematsu Y, Miura S, Goto M, Matsuo Y, Arimura T, Kuwano T, et al. LCZ696, an angiotensin receptor-neprilysin inhibitor, improves cardiac function

with the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. *Eur J Heart Fail.* (2016) 18:386–93. doi: 10.1002/ejhf.474

25. von Lueder TG, Wang BH, Kompa AR, Huang L, Webb R, Jordaan P, et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. *Circ Heart Fail.* (2015) 8:71–8. doi: 10.1161/CIRCHEARTFAILURE.114.001785

26. Wu KC, Calkins H. Powerlessness of a number: why left ventricular ejection fraction matters less for sudden cardiac death risk assessment. *Circ Cardiovasc Imaging.* (2016) 9:e005519. doi: 10.1161/CIRCIMAGING.116.005519

27. Zaman S, Goldberger JJ, Kovoor P. Sudden Death Risk-Stratification in 2018-2019: the old and the new. *Heart Lung Circ.* (2019) 28:57–64. doi: 10.1016/j.hlc.2018.08.027

28. Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. *Curr Heart Fail Rep.* (2008) 5:170–6. doi: 10.1007/s11897-008-0026-9

29. Dalan R, Leow MK. Cardiovascular collapse associated with beta blockade in thyroid storm. *Exp Clin Endocrinol Diabetes.* (2007) 115:392–6. doi: 10.1055/s-2007-971065

30. Dietrich JW. Thyroid storm. *Med Klin Intensivmed Notfmed.* (2012) 107:448–53. doi: 10.1007/s00063-012-0113-2

31. Klein I, Danzi S. Thyroid disease and the heart. *Circulation.* (2007) 116:1725–35. doi: 10.1161/CIRCULATIONAHA.106.678326

32. Fadel BM, Ellahham S, Ringel MD, Lindsay J. Jr., Wartofsky L, Burman KD. Hyperthyroid heart disease. *Clin Cardiol.* (2000) 23:402–8. doi: 10.1002/clc.4960230605

33. Yamakawa H, Kato TS, Noh JY, Yuasa S, Kawamura A, Fukuda K, et al. Thyroid hormone plays an important role in cardiac function: from bench to bedside. *Front Physiol.* (2021) 12:606931. doi: 10.3389/fphys.2021.606931

34. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med.* (2002) 137:904–14. doi: 10.7326/0003-4819-137-11-200212030-00011

35. Floriani C, Gencer B, Collet TH, Rodondi N. Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. *Eur Heart J.* (2018) 39:503–7. doi: 10.1093/eurheartj/ehx050

36. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, et al. Thyroid function and sudden cardiac death: a prospective population-based cohort study. *Circulation.* (2016) 134:713–22. doi: 10.1161/CIRCULATIONAHA.115.020789

37. Dietrich JW, Makimoto H, Muller P. Letter by dietrich et al. regarding article, "thyroid dysfunction in heart failure and cardiovascular outcomes". *Circ Heart Fail.* (2019) 12:e005854. doi: 10.1161/CIRCHEARTFAILURE.118.005854

38. Fitzgerald SP, Bean NG, Falhammar H, Tuke J. Clinical parameters are more likely to be associated with thyroid hormone levels than with thyrotropin levels: a systematic review and meta-analysis. *Thyroid.* (2020) 30:1695–709. doi: 10.1089/thy.2019.0535

39. Groothof D, Flores-Guerrero JL, Nolte IM, Bouma HR, Gruppen EG, Bano A, et al. Thyroid function and risk of all-cause and cardiovascular mortality: a prospective population-based cohort study. *Endocrine.* (2021) 71:385–96. doi: 10.1007/s12020-020-02397-z

40. Abdel-Moneim A, Gaber AM, Gouda S, Osama A, Othman SI, Allam G. Relationship of thyroid dysfunction with cardiovascular diseases: updated review on heart failure progression. *Hormones (Athens).* (2020) 19:301–9. doi: 10.1007/s42000-020-00208-8

41. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA.* (2010) 304:1365–74. doi: 10.1001/jama.2010.1786

42. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. *J Clin Endocrinol Metab.* (2014) 99:2372–82. doi: 10.1210/jc.2013-4184

43. Sohn SY, Lee E, Lee MK, Lee JH. The association of overt and subclinical hyperthyroidism with the risk of cardiovascular events and cardiovascular mortality: meta-analysis and systematic review of cohort studies. *Endocrinol Metab (Seoul).* (2020) 35:786–800. doi: 10.3803/EnM.2020.728

44. Faber J, Selmer C. Cardiovascular disease and thyroid function. *Front Horm Res.* (2014) 43:45–56. doi: 10.1159/000360558

45. van Noord C, Sturkenboom MC, Straus SM, Hofman A, Witteman JC, Stricker BH. Population-based studies of antithyroid drugs and sudden cardiac death. *Br J Clin Pharmacol.* (2009) 68:447–54. doi: 10.1111/j.1365-2125.2009.03474.x

46. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force. *Ann Intern Med.* (2015) 162:35–45. doi: 10.7326/M14-1456

47. Dietrich JW, Hoermann R, Midgley JEM, Bergen F, Muller P. The two faces of janus: why thyrotropin as a cardiovascular risk factor may be an ambiguous target. *Front Endocrinol (Lausanne).* (2020) 11:542710. doi: 10.3389/fendo.2020.542710

48. Flamant F, Cheng SY, Hollenberg AN, Moeller LC, Samarut J, Wondisford FE, et al. Thyroid hormone signaling pathways: time for a more precise nomenclature. *Endocrinology.* (2017) 158:2052–7. doi: 10.1210/en.2017-00250

49. Stamatouli A, Bedoya P, Yavuz S. Hypothyroidism: cardiovascular endpoints of thyroid hormone replacement. *Front Endocrinol (Lausanne).* (2019) 10:888. doi: 10.3389/fendo.2019.00888

50. Recker S, Voigtlander R, Viehmann A, Dunschen K, Kerp H, Frank-Raue K, et al. Thyroid related quality of life in elderly with subclinical hypothyroidism and improvement on levothyroxine is distinct from that in young patients (TSAGE). *Horm Metab Res.* (2019) 51:568–74. doi: 10.1055/a-0897-8785

51. Dietrich JW, Midgley JEM, Hoermann R. Editorial: "homeostasis and allostasis of thyroid function". *Front Endocrinol (Lausanne).* (2018) 9:287. doi: 10.3389/fendo.2018.00287

52. Midgley JE, Larisch R, Dietrich JW. Hoermann R. Letter to the editor: comment on "Reconciling the Log-Linear and Non-Linear Aspects of the TSH-Free T4 Relationship: Intra-Individual Analysis of a Large Population" by Rothacker KM, et al. *J Clin Endocrinol Metab.* (2016) 101:L40–1. doi: 10.1210/jc.2016-1115

53. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Homeostatic control of the thyroid-pituitary axis: perspectives for diagnosis and treatment. *Front Endocrinol (Lausanne).* (2015) 6:177. doi: 10.3389/fendo.2015.00177

54. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Relational stability in the expression of normality, variation, and control of thyroid function. *Front Endocrinol (Lausanne).* (2016) 7:142. doi: 10.3389/fendo.2016.00142

55. Hoermann R, Pekker MJ, Midgley JE, Larisch R, Dietrich JW. Principles of endocrine regulation: reconciling tensions between robustness in performance and adaptation to change. *Front Endocrinol. (Lausanne).* (2022) 13:825107. doi: 10.3389/fendo.2022.825107

56. Chatzitomaris A, Hoermann R, Midgley JE, Hering S, Urban A, Dietrich B, et al. Thyroid allostasis-adaptive responses of thyrotropic feedback control to conditions of strain, stress, and developmental programming. *Front Endocrinol (Lausanne).* (2017) 8:163. doi: 10.3389/fendo.2017.00163

57. Joseph-Bravo P. Hypophysiotropic thyrotropin-releasing hormone neurons as transducers of energy homeostasis. *Endocrinology.* (2004) 145:4813–5. doi: 10.1210/en.2004-0979

58. Joseph-Bravo P, Jaimes-Hoy L, Charli JL. Advances in TRH signaling. *Rev Endocr Metab Disord.* (2016) 17:545–58. doi: 10.1007/s11154-016-9375-y

59. Lechan RM, Fekete C. The TRH neuron: a hypothalamic integrator of energy metabolism. *Prog Brain Res.* (2006) 153:209–35. doi: 10.1016/S0079-6123(06)53012-2

60. Parry CH. Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart. *Collections from the unpublished medical writings of the late Caleb Hillier Parry.* London: Underwoods. (1825). p. 111–25.

61. Flajani G. *Collezione d'osservazioni e riflessioni di chirurgia.* Roma: stamp. di S. Michele a Ripa (1802).

62. Graves RJ. Newly observed affection of the thyroid gland in females. *London Med Surg J.* (1835) 7:516–7.

63. von Basedow K. Exophtalmos durch Hypertrophie des Zellgewebes in der Augenhöhle. *Wschr ges Heilk.* (1840) 13:197–228.

64. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev.* (2005) 26:704–28. doi: 10.1210/er.2003-0033

65. Ortiga-Carvalho TM, Sidhaye AR, Wondisford FE. Thyroid hormone receptors and resistance to thyroid hormone disorders. *Nat Rev Endocrinol.* (2014) 10:582–91. doi: 10.1038/nrendo.2014.143

66. Hönes GS, Rakov H, Logan J, Liao XH, Werbenko E, Pollard AS, et al. Noncanonical thyroid hormone signaling mediates cardiometabolic effects in vivo. *Proc Natl Acad Sci U S A.* (2017) 114:E11323–E32. doi: 10.1073/pnas.1706801115

67. Saponaro F, Sestito S, Runfola M, Rapposelli S, Chiellini G. Selective thyroid hormone receptor-beta (TRbeta) agonists: new perspectives for the treatment of metabolic and neurodegenerative disorders. *Front Med (Lausanne).* (2020) 7:331. doi: 10.3389/fmed.2020.00331

68. Davis PJ, Davis FB, Lin HY, Mousa SA, Zhou M, Luidens MK. Translational implications of nongenomic actions of thyroid hormone initiated at its integrin receptor. *Am J Physiol Endocrinol Metab.* (2009) 297:E1238–46. doi: 10.1152/ajpendo.00480.2009

69. Köhrle J. The colorful diversity of thyroid hormone metabolites. *Eur Thyroid J.* (2019) 8:115–29. doi: 10.1159/000497141

70. Xu B, Koenig RJ. An RNA-binding domain in the thyroid hormone receptor enhances transcriptional activation. *J Biol Chem.* (2004) 279:33051–6. doi: 10.1074/jbc.M404930200

71. Lanni A, Moreno M, Goglia F. Mitochondrial actions of thyroid hormone. *Compr Physiol.* (2016) 6:1591–607. doi: 10.1002/cphy.c150019

72. Milo R, Phillips R. *Cell Biology by the Numbers*. New York, Abingdon: Garland Science. (2016). doi: 10.1201/9780429258770

73. Giammanco M, Liegro CMD, Schiera G, Liegro ID. Genomic and non-genomic mechanisms of action of thyroid hormones and their catabolite 3,5-Diiodo-L-thyronine in mammals. *Int J Mol Sci.* (2020) 21:4140. doi: 10.3390/ijms21114140

74. Köhrle J. Thyroid hormones and derivatives: endogenous thyroid hormones and their targets. *Methods Mol Biol.* (2018) 1801:85–104. doi: 10.1007/978-1-4939-7902-8_9

75. Le Bouter S, Demolombe S, Chambellan A, Bellocq C, Aimond F, Toumaniantz G, et al. Microarray analysis reveals complex remodeling of cardiac ion channel expression with altered thyroid status: relation to cellular and integrated electrophysiology. *Circ Res.* (2003) 92:234–42. doi: 10.1161/01.RES.0000053185.75505.8E

76. Chatzitomaris A, Scheeler M, Gotzmann M, Koditz R, Schildroth J, Knyhala KM, et al. Second degree AV block and severely impaired contractility in cardiac myxedema: a case report. *Thyroid Res.* (2015) 8:6. doi: 10.1186/s13044-015-0018-2

77. Panagoulis C, Halapas A, Chariatis E, Driva P, Matsakas E. Hyperthyroidism and the heart. *Hellenic J Cardiol.* (2008) 49:169–75.

78. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol.* (2018) 71:1781–96. doi: 10.1016/j.jacc.2018.02.045

79. Galli E, Pingitore A, Iervasi G. The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. *Heart Fail Rev.* (2010) 15:155–69. doi: 10.1007/s10741-008-9126-6

80. Nattel S, Tomaselli GF. Mechanisms of Cardiac Arrhythmia. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D, Solomon SD, et al., editors. *Braunwald's Heart Disease*. 2. Philadelphia, PA: Elsevier (2021). p. 1163-90.

81. Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, Lin CI. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. *J Am Coll Cardiol.* (2002) 39:366–72. doi: 10.1016/S0735-1097(01)01731-4

82. Kausel A, Korniyenko A, Sandhu G. Bradyarrhythmia as a presenting feature of subclinical hyperthyroidism. *QJM.* (2012) 105:461–2. doi: 10.1093/qjmed/hcr049

83. Krishnamoorthy S, Narain R, Creamer J. Unusual presentation of thyrotoxicosis as complete heart block and renal failure: a case report. *J Med Case Rep.* (2009) 3:9303. doi: 10.1186/1752-1947-3-9303

84. Gavrilescu S, Luca C, Streian C, Lungu G, Deutsch G. Monophasic action potentials of right atrium and electrophysiological properties of AV conducting system in patients with hypothyroidism. *Br Heart J.* (1976) 38:1350–4. doi: 10.1136/hrt.38.12.1350

85. Maltsev VA, Vinogradova TM, Lakatta EG. The emergence of a general theory of the initiation and strength of the heartbeat. *J Pharmacol Sci.* (2006) 100:338–69. doi: 10.1254/jphs.CR0060018

86. Freedberg AS, Papp JG, Williams EM. The effect of altered thyroid state on atrial intracellular potentials. *J Physiol.* (1970) 207:357–69. doi: 10.1113/jphysiol.1970.sp009066

87. Johnson PN, Freedberg AS, Marshall JM. Action of thyroid hormone on the transmembrane potentials from sinoatrial node cells and atrial muscle cells in isolated atria of rabbits. *Cardiology.* (1973) 58:273–89. doi: 10.1159/000169643

88. Sun ZQ, Ojamaa K, Nakamura TY, Artman M, Klein I, Coetzee WA. Thyroid hormone increases pacemaker activity in rat neonatal atrial myocytes. *J Mol Cell Cardiol.* (2001) 33:811–24. doi: 10.1006/jmcc.2001.1353

89. Sun ZQ, Ojamaa K, Coetzee WA, Artman M, Klein I. Effects of thyroid hormone on action potential and repolarizing currents in rat ventricular myocytes. *Am J Physiol Endocrinol Metab.* (2000) 278:E302–7. doi: 10.1152/ajpendo.2000.278.2.E302

90. Chang KC, Figueredo VM, Schreur JH, Kariya K, Weiner MW, Simpson PC, et al. Thyroid hormone improves function and Ca2+ handling in pressure overload hypertrophy. Association with increased sarcoplasmic reticulum Ca2+-ATPase and alpha-myosin heavy chain in rat hearts. *J Clin Invest.* (1997) 100:1742–9. doi: 10.1172/JCI119699

91. Kaasik A, Minajeva A, Paju K, Eimre M, Seppet EK. Thyroid hormones differentially affect sarcoplasmic reticulum function in rat atria and ventricles. *Mol Cell Biochem.* (1997) 176:119–26. doi: 10.1023/A:1006887231150

92. Alonso H, Fernandez-Ruocco J, Gallego M, Malagueta-Vieira LL, Rodriguez-de-Yurre A, Medei E, et al. Thyroid stimulating hormone directly modulates cardiac electrical activity. *J Mol Cell Cardiol.* (2015) 89:280–6. doi: 10.1016/j.yjmcc.2015.10.019

93. Thyroid stimulating hormone (TSH) signaling pathway (Homo sapiens) [Internet]. *WikiPathways.* (2011-2022). Available online at: https://www.wikipathways.org/instance/WP2032_r122770.

94. Holzapfel HP, Bergner B, Wonerow P, Paschke R. Expression of G(alpha)(s) proteins and TSH receptor signalling in hyperfunctioning thyroid nodules with TSH receptor mutations. *Eur J Endocrinol.* (2002) 147:109–16. doi: 10.1530/eje.0.1470109

95. Bosch RF, Wang Z, Li GR, Nattel S. Electrophysiological mechanisms by which hypothyroidism delays repolarization in guinea pig hearts. *Am J Physiol.* (1999) 277:H211–20. doi: 10.1152/ajpheart.1999.277.1.H211

96. Goel BG, Hanson CS, Han J, A-V. conduction in hyper- and hypothyroid dogs. *Am Heart J.* (1972) 83:504–11. doi: 10.1016/0002-8703(72)90041-5

97. Zhang Y, Dedkov EI, Teplitsky D, Weltman NY, Pol CJ, Rajagopalan V, et al. Both hypothyroidism and hyperthyroidism increase atrial fibrillation inducibility in rats. *Circ Arrhythm Electrophysiol.* (2013) 6:952–9. doi: 10.1161/CIRCEP.113.000502

98. Tribulova N, Kurahara LH, Hlivak P, Hirano K, Szeiffova Bacova B. Pro-arrhythmic signaling of thyroid hormones and its relevance in subclinical hyperthyroidism. *Int J Mol Sci.* (2020) 21:2844. doi: 10.3390/ijms21082844

99. King JH, Huang CL, Fraser JA. Determinants of myocardial conduction velocity: implications for arrhythmogenesis. *Front Physiol.* (2013) 4:154. doi: 10.3389/fphys.2013.00154

100. Richter Y, Lind PG, Seemann G, Maass P. Anatomical and spiral wave reentry in a simplified model for atrial electrophysiology. *J Theor Biol.* (2017) 419:100–7. doi: 10.1016/j.jtbi.2017.02.008

101. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Is pituitary TSH an adequate measure of thyroid hormone-controlled homoeostasis during thyroxine treatment? *Eur J Endocrinol.* (2013) 168:271–80. doi: 10.1530/EJE-12-0819

102. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Heterogenous biochemical expression of hormone activity in subclinical/overt hyperthyroidism and exogenous thyrotoxicosis. *J Clin Transl Endocrinol.* (2020) 19:100219. doi: 10.1016/j.jcte.2020.100219

103. Midgley JE, Hoermann R, Larisch R, Dietrich JW. Physiological states and functional relation between thyrotropin and free thyroxine in thyroid health and disease: in vivo and in silico data suggest a hierarchical model. *J Clin Pathol.* (2013) 66:335–42. doi: 10.1136/jclinpath-2012-201213

104. Midgley JEM, Toft AD, Larisch R, Dietrich JW, Hoermann R. Time for a reassessment of the treatment of hypothyroidism. *BMC Endocr Disord.* (2019) 19:37. doi: 10.1186/s12902-019-0365-4

105. Pasqualetti G, Tognini S, Polini A, Caraccio N, Monzani F. Is subclinical hypothyroidism a cardiovascular risk factor in the elderly? *J Clin Endocrinol Metab.* (2013) 98:2256–66. doi: 10.1210/jc.2012-3818

106. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? *J Thyroid Res.* (2018) 2018:3239197. doi: 10.1155/2018/3239197

107. Wiersinga WM. Guidance in subclinical hyperthyroidism and subclinical hypothyroidism: are we making progress? *Eur Thyroid J.* (2015) 4:143–8. doi: 10.1159/000438909

108. Hoermann R, Midgley JEM, Dietrich JW, Larisch R. Dual control of pituitary thyroid stimulating hormone secretion by thyroxine and triiodothyronine in athyreotic patients. *Ther Adv Endocrinol Metab.* (2017) 8:83–95. doi: 10.1177/2042018817716401

109. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. The role of functional thyroid capacity in pituitary thyroid feedback regulation. *Eur J Clin Invest.* (2018) 48:e13003. doi: 10.1111/eci.13003

110. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab.* (2002) 87:1068–72. doi: 10.1210/jcem.87.3.8165

111. Larisch R, Giacobino A, Eckl W, Wahl HG, Midgley JE, Hoermann R. Reference range for thyrotropin. Post hoc assessment. *Nuklearmedizin.* (2015) 54:112–7. doi: 10.3413/Nukmed-0671-14-06

112. Goede SL, Latham KR, Leow MK, Jonklaas J. High resolution free triiodothyronine-thyrotropin (FT3-TSH) responses to a single oral dose of liothyronine in humans: evidence of distinct inter-individual differences unraveled using an electrical network model. *J Biol Syst.* (2017) 25:119–43. doi: 10.1142/S0218339017500073

113. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Functional and symptomatic individuality in the response to levothyroxine treatment. *Front Endocrinol (Lausanne).* (2019) 10:664. doi: 10.3389/fendo.2019.00664

114. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Individualised requirements for optimum treatment of hypothyroidism: complex needs, limited options. *Drugs Context.* (2019) 8:212597. doi: 10.7573/dic.212597

115. Leow MK, Goede SL. The homeostatic set point of the hypothalamus-pituitary-thyroid axis–maximum curvature theory for personalized euthyroid targets. *Theor Biol Med Model.* (2014) 11:35. doi: 10.1186/1742-4682-11-35

116. Meng F, Li E, Yen PM, Leow MKS. Hyperthyroidism in the personalized medicine era: the rise of mathematical optimization. *J R Soc Interface.* (2019) 16:20190083. doi: 10.1098/rsif.2019.0083

117. Bonsu JM, Guha A, Charles L, Yildiz VO, Wei L, Baker B, et al. Reporting of cardiovascular events in clinical trials supporting FDA approval of contemporary cancer therapies. *J Am Coll Cardiol.* (2020) 75:620–8. doi: 10.1016/j.jacc.2019.11.059

118. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. *BMC Med Res Methodol.* (2021) 21:241. doi: 10.1186/s12874-021-01440-5

119. Poudel I, Tejpal C, Rashid H, Jahan N. Major Adverse Cardiovascular Events: An Inevitable Outcome of ST-elevation myocardial infarction? A Literature Review. *Cureus.* (2019) 11:e5280. doi: 10.7759/cureus.5280

120. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA.* (2004) 292:2591–9. doi: 10.1001/jama.292.21.2591

121. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA.* (2006) 295:1033–41. doi: 10.1001/jama.295.9.1033

122. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. *J Clin Endocrinol Metab.* (2010) 95:1734–40. doi: 10.1210/jc.2009-1749

123. Schultz M, Kistorp C, Raymond I, Dimsits J, Tuxen C, Hildebrandt P, et al. Cardiovascular events in thyroid disease: a population based, prospective study. *Horm Metab Res.* (2011) 43:653–9. doi: 10.1055/s-0031-1283162

124. Frey A, Kroiss M, Berliner D, Seifert M, Allolio B, Guder G, et al. Prognostic impact of subclinical thyroid dysfunction in heart failure. *Int J Cardiol.* (2013) 168:300–5. doi: 10.1016/j.ijcard.2012.09.064

125. Mitchell JE, Hellkamp AS, Mark DB, Anderson J, Johnson GW, Poole JE, et al. Thyroid function in heart failure and impact on mortality. *JACC Heart Fail.* (2013) 1:48–55. doi: 10.1016/j.jchf.2012.10.004

126. Drechsler C, Schneider A, Gutjahr-Lengsfeld L, Kroiss M, Carrero JJ, Krane V, et al. Thyroid function, cardiovascular events, and mortality in diabetic hemodialysis patients. *Am J Kidney Dis.* (2014) 63:988–96. doi: 10.1053/j.ajkd.2013.10.009

127. Perez AC, Jhund PS, Stott DJ, Gullestad L, Cleland JG, van Veldhuisen DJ, et al. Thyroid-stimulating hormone and clinical outcomes: the CORONA trial (controlled rosuvastatin multinational study in heart failure). *JACC Heart Fail.* (2014) 2:35–40. doi: 10.1016/j.jchf.2013.07.008

128. Rhee CM, Ravel VA, Streja E, Mehrotra R, Kim S, Wang J, et al. Thyroid functional disease and mortality in a national peritoneal dialysis cohort. *J Clin Endocrinol Metab.* (2016) 101:4054–61. doi: 10.1210/jc.2016-1691

129. Pearce SH, Razvi S, Yadegarfar ME, Martin-Ruiz C, Kingston A, Collerton J, et al. Serum thyroid function, mortality and disability in advanced old age: the newcastle 85+ study. *J Clin Endocrinol Metab.* (2016) 101:4385–94. doi: 10.1210/jc.2016-1935

130. Langen VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, et al. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf).* (2018) 88:105–13. doi: 10.1111/cen.13472

131. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, et al. Thyroid dysfunction in heart failure and cardiovascular outcomes. *Circ Heart Fail.* (2018) 11:e005266. doi: 10.1161/CIRCHEARTFAILURE.118.005266

132. Golledge J, Hankey GJ, Almeida OP, Flicker L, Norman PE, Yeap BB. Plasma free thyroxine in the upper quartile is associated with an increased incidence of major cardiovascular events in older men that do not have thyroid dysfunction according to conventional criteria. *Int J Cardiol.* (2018) 254:316–21. doi: 10.1016/j.ijcard.2017.10.100

133. Li X, Yao Y, Chen Z, Fan S, Hua W, Zhang S, et al. Thyroid-stimulating hormone within the normal range and risk of major adverse cardiovascular events in nonischemic dilated cardiomyopathy patients with severe left ventricular dysfunction. *Clin Cardiol.* (2019) 42:120–8. doi: 10.1002/clc.23117

134. Seo SM, Koh YS, Park HJ, Kim DB, Her SH, Lee JM, et al. Thyroid stimulating hormone elevation as a predictor of long-term mortality in patients with acute myocardial infarction. *Clin Cardiol.* (2018) 41:1367–73. doi: 10.1002/clc.23062

135. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of subclinical hypothyroidism and cardiovascular disease with mortality. *JAMA Netw Open.* (2020) 3:e1920745. doi: 10.1001/jamanetworkopen.2019.20745

136. Kim H, Kong SH, Moon JH, Kim SY, Park KH, Kim JS, et al. Subclinical hypothyroidism affects the long-term outcomes of patients who undergo coronary artery bypass grafting surgery but not heart valve surgery. *Endocrinol Metab (Seoul).* (2020) 35:308–18. doi: 10.3803/EnM.2020.35.2.308

137. Müller P, Dietrich JW, Lin T, Bejinariu A, Binnebössel S, Bergen F, et al. Usefulness of serum free thyroxine concentration to predict ventricular arrhythmia risk in euthyroid patients with structural heart disease. *Am J Cardiol.* (2020) 125:1162–9. doi: 10.1016/j.amjcard.2020.01.019

138. Yang M, Li X, Morris JC. 3rd, Liang J, Deshmukh AJ, Hodge D, et al. Outcomes of cardiac resynchronization therapy in patients with hypothyroidism and heart failure. *BMC Cardiovasc Disord.* (2020) 20:424. doi: 10.1186/s12872-020-01693-w

139. Evron JM, Hummel SL, Reyes-Gastelum D, Haymart MR, Banerjee M, Papaleontiou M. Association of thyroid hormone treatment intensity with cardiovascular mortality among US veterans. *JAMA Netw Open.* (2022) 5:e2211863. doi: 10.1001/jamanetworkopen.2022.11863

140. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med.* (2007) 167:1526–32. doi: 10.1001/archinte.167.14.1526

141. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med.* (2005) 165:2460–6. doi: 10.1001/archinte.165.21.2460

142. Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 75-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol.* (2010) 162:569–77. doi: 10.1530/EJE-09-0845

143. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med.* (2005) 165:2467–72. doi: 10.1001/archinte.165.21.2467

144. Ittermann T, Haring R, Sauer S, Wallaschofski H, Dorr M, Nauck M, et al. Decreased serum TSH levels are not associated with mortality in the adult northeast German population. *Eur J Endocrinol.* (2010) 162:579–85. doi: 10.1530/EJE-09-0566

145. Osman F, Gammage MD, Sheppard MC, Franklyn JA. Clinical review 142: cardiac dysrhythmias and thyroid dysfunction: the hidden menace? *J Clin Endocrinol Metab.* (2002) 87:963–7. doi: 10.1210/jcem.87.3.8217

146. Sun J, Yao L, Fang Y, Yang R, Chen Y, Yang K, et al. Relationship between subclinical thyroid dysfunction and the risk of cardiovascular outcomes: a systematic review and meta-analysis of prospective cohort studies. *Int J Endocrinol.* (2017) 2017:8130796. doi: 10.1155/2017/8130796

147. Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mugge A, Patsalis PC, et al. Abnormal thyroid function is common in takotsubo syndrome and depends on two distinct mechanisms: results of a multicentre observational study. *J Intern Med.* (2021) 289:675–87. doi: 10.1111/joim.13189

148. Goede SL, Leow MK, Smit JW, Dietrich JW, A. novel minimal mathematical model of the hypothalamus-pituitary-thyroid axis validated for individualized clinical applications. *Math Biosci.* (2014) 249:1–7. doi: 10.1016/j.mbs.2014.01.001

149. Goede SL, Leow MK, Smit JW, Klein HH, Dietrich JW. Hypothalamus-pituitary-thyroid feedback control: implications of mathematical modeling and consequences for thyrotropin (TSH) and free thyroxine (FT4) reference ranges. *Bull Math Biol.* (2014) 76:1270–87. doi: 10.1007/s11538-014-9955-5

150. Dietrich JW, Landgrafe-Mende G, Wiora E, Chatzitomaris A, Klein HH, Midgley JE, et al. Calculated parameters of thyroid homeostasis: emerging tools for differential diagnosis and clinical research. *Front Endocrinol (Lausanne).* (2016) 7:57. doi: 10.3389/fendo.2016.00057

151. Chang CY, Chien YJ, Lin PC, Chen CS, Wu MY. Nonthyroidal illness syndrome and hypothyroidism in ischemic heart disease population: a

systematic review and meta-analysis. *J Clin Endocrinol Metab.* (2020) 105:e3414–e3425. doi: 10.1210/clinem/dgaa310

152. Dietrich JW, Muller P, Schiedat F, Schlomicher M, Strauch J, Chatzitomaris A, et al. Nonthyroidal illness syndrome in cardiac illness involves elevated concentrations of 3,5-diiodothyronine and correlates with atrial remodeling. *Eur Thyroid J.* (2015) 4:129–37. doi: 10.1159/000381543

153. Özturk S, Kayacioglu I, Sensoz Y, Ozdemir K, Özturk I. Efficiency of Thyroid Function Test in the Prediction of Atrial Fibrillation Following Open Heart Surgery. *J Coll Physicians Surg Pak.* (2020) 30:740–4. doi: 10.29271/jcpsp.2020.07.740

154. Langouche L, Lehmphul I, Perre SV, Kohrle J, Van den Berghe G. Circulating 3-T1AM and 3,5-T2 in critically ill patients: a cross-sectional observational study. *Thyroid.* (2016) 26:1674–80. doi: 10.1089/thy.2016.0214

155. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med.* (1995) 333:1688–94. doi: 10.1056/NEJM199512213332507

156. Carvalho GA, Perez CL, Ward LS. The clinical use of thyroid function tests. *Arq Bras Endocrinol Metabol.* (2013) 57:193–204. doi: 10.1590/S0004-27302013000300005

157. Dietrich JW, Ackermann A, Kasippillai A, Kanthasamy Y, Tharmalingam T, Urban A, et al. Adaptive Veränderungen des Schilddrüsenstoffwechsels als Risikoindikatoren bei Traumata. *Trauma und Berufskrankheit.* (2019) 21:260–7. doi: 10.1007/s10039-019-00438-z

158. Stockigt JR, Lim CF. Medications that distort in vitro tests of thyroid function, with particular reference to estimates of serum free thyroxine. *Best Pract Res Clin Endocrinol Metab.* (2009) 23:753–67. doi: 10.1016/j.beem.2009.06.004

159. Dietrich JW, Landgrafe G, Fotiadou EH. TSH and thyrotropic agonists: key actors in thyroid homeostasis. *J Thyroid Res.* (2012) 2012:351864. doi: 10.1155/2012/351864

160. Peters A, McEwen BS. Stress habituation, body shape and cardiovascular mortality. *Neurosci Biobehav Rev.* (2015) 56:139–50. doi: 10.1016/j.neubiorev.2015.07.001

161. Guidi J, Lucente M, Sonino N, Fava GA. Allostatic load and its impact on health: a systematic review. *Psychother Psychosom.* (2021) 90:11–27. doi: 10.1159/000510696

162. Steptoe A, Hackett RA, Lazzarino AI, Bostock S, La Marca R, Carvalho LA, et al. Disruption of multisystem responses to stress in type 2 diabetes: investigating the dynamics of allostatic load. *Proc Natl Acad Sci U S A.* (2014) 111:15693–8. doi: 10.1073/pnas.1410401111

163. Logan JG, Barksdale DJ. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. *J Clin Nurs.* (2008) 17:201–8. doi: 10.1111/j.1365-2702.2008.02347.x

164. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med.* (2012) 172:799–809. doi: 10.1001/archinternmed.2012.402

165. Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. *Eur Thyroid J.* (2015) 4:149–63. doi: 10.1159/000438750

166. Wolff TM, Dietrich JW, Müller MA. Optimal hormone replacement therapy in hypothyroidism - a model predictive control approach. *Front Endocrinol.* (2022) 13:884018. doi: 10.3389/fendo.2022.884018

167. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* (2016) 26:1–133. doi: 10.1089/thy.2015.0020

168. D'Alessio L, Korman GP, Sarudiansky M, Guelman LR, Scevola L, Pastore A, et al. Reducing allostatic load in depression and anxiety disorders: physical activity and yoga practice as add-on therapies. *Front Psychiatry.* (2020) 11:501. doi: 10.3389/fpsyt.2020.00501

169. Ferrara I, Egan CG, Foletti A. Pilot study on the effect of biophysical therapy on salivary alpha-amylase as a surrogate measure of anxiety/stress: in search of a novel noninvasive molecular approach for the management of stress. *Int J Mol Sci.* (2020) 21:415. doi: 10.3390/ijms21020415

170. Macit MS, Acar-Tek N. Current perspectives for diabetes and allostatic load: the role of nutrition. *Curr Nutr Food Sci.* (2018) 14:1–7. doi: 10.2174/1573401314666180620164859

171. Tan M, Mamun A, Kitzman H, Dodgen L. Longitudinal changes in allostatic load during a randomized church-based, lifestyle intervention in African American women. *Ethn Dis.* (2019) 29:297–308. doi: 10.18865/ed.29.2.297

172. Lipowicz A, Szklarska A, Malina RM. Allostatic load and socioeconomic status in Polish adult men. *J Biosoc Sci.* (2014) 46:155–67. doi: 10.1017/S0021932013000345

173. Christodoulou I. Reversing the allostatic load. *J Sport Health Sci.* (2010) 3:331−2.

174. Nauck MA, Dietrich JW. Understanding the restrictions in the prescription and use of potentially beneficial diabetes medications associated with low socio-economic status. *Lancet Reg Health Eur.* (2022) 14:100318. doi: 10.1016/j.lanepe.2022.100318

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