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Women in drugs outcomes research and policies 2023

Edited by
Suzete Costa, Victoria Garcia-Cardenas, Ceu Mateus, Clara L. Rodríguez-Bernal, Michela Tinelli and Ana Paula Beck Da Silva Etges

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Women in drugs outcomes research and policies: 2023

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Ana Paula Beck Da Silva Etges — PEV Healthcare Consulting, Brazil

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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Viktorija Erdeljic Turk,
University Hospital Centre Zagreb, Croatia

*CORRESPONDENCE
Rachele M. Hendricks-Sturrup,
rachele.hendricks.sturrup@duke.edu

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Leveraging stories of cardiac amyloidosis patients of African ancestry or descent to support patient-derived data elements for efficient diagnosis and treatment

Rachele M. Hendricks-Sturrup[1,2,3]*, Lauren M. Edgar[4] and Christine Y. Lu[2,5,6]

[1]National Alliance Against Disparities in Patient Health, Woodbridge, VA, United States, [2]Department of Population Medicine, Harvard Pilgrim Healthcare Institute and Harvard Medical School, Boston, MA, United States, [3]Duke-Margolis Center for Health Policy, Washington, DC, United States, [4]Southern Nevada Black Nurses Association, Las Vegas, NV, United States, [5]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [6]Kolling Institute, Faculty of Medicine and Health, The University of Sydney and the Northern Sydney Local Health District, Sydney, NSW, Australia

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Introduction

Storytelling is a powerful tool that continuously drives knowledge development and sharing about the patient experience with managing hereditary diseases and comorbidities, including patient values and preferences, and medication adherence and persistence. Patient stories are often key to developing patient-reported outcomes (PROs) data that are specific to or reflective of a patient's lived experience, most bothersome or frequent symptoms, and socioeconomic circumstances (Kwan et al., 2016; Boyd et al., 2023; Boyd et al., 2023). Thus, there is power in the potential to leverage patient stories to inform the development of new or refinement of existing PRO collection tools for more accurate and timely diagnosis and optimizing the management and treatment of rare diseases, which are often challenging to diagnose particularly among minority populations (e.g., Patient Reported Outcomes Measurement Information System [PROMIS®], United States [US] National Cancer Institute's PRO-CTCAE, Transthyretin Amyloidosis—Quality of Life Questionnaire [ATTR-QOL], interviews, and focus groups; D'Souza et al., 2023; O'Connor, 2023). Below we discuss the potential benefits of incorporating patient stories into PRO instruments to screen and manage African, African American, and/or Afro-Caribbean (A/AA/AC) patients with suspected amyloidosis, a rare disease that occurs when a protein called amyloid builds up in organs (heart, kidneys, liver, spleen, digestive tract, and nervous system).

There are 18 different types of systemic forms of amyloidosis, as well as 22 localized forms. Two major forms of amyloidosis include but are not limited to immunoglobulin light chain (AL) and transthyretin amyloidosis (ATTR; Benson et al., 2020). Additional forms of amyloidosis beyond these two types are secondary, dialysis-related, hereditary (hATTR), organ-specific, insulin-related, or associated with a myriad of pathologies (Gorevic, 2023). Based on stories shared broadly to date, A/AA/AC patients with amyloidosis often experience a lengthy diagnostic odyssey following initial presence of clinical symptoms. Confusion among themselves, their families, and their healthcare providers often cause delays in diagnosis, misdiagnosis, and/or treatment. Such delays directly contribute to often-

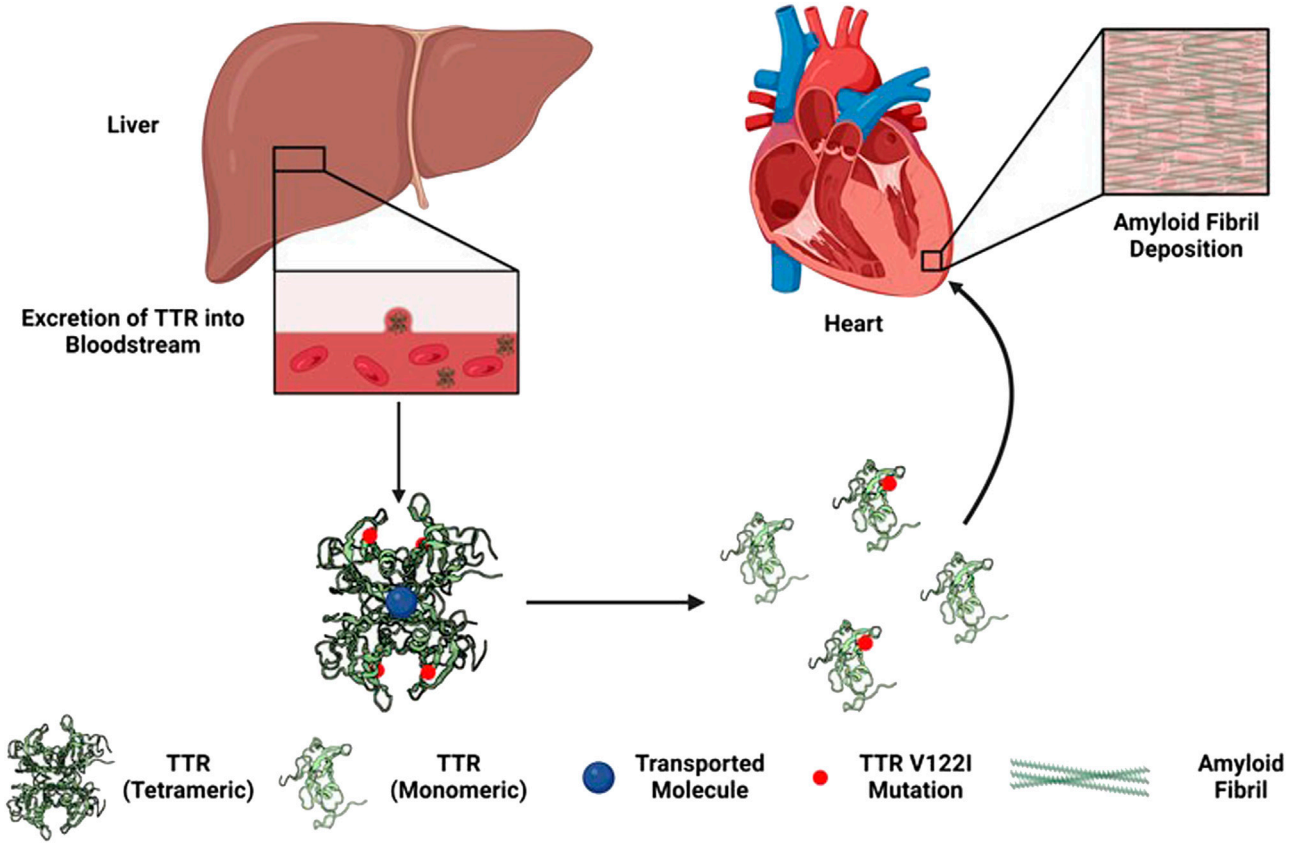

FIGURE 1
Development of hereditary transthyretin cardiac amyloidosis via *TTR* V122I (pV142I) allele mutation (Williams et al., 2022).

fatal outcomes observed. Therefore, all of these factors considered, the true prevalence of AL and ATTR amyloidosis, among other forms, across A/AA/AC populations is neither well-understood nor well-documented in the literature.

To help address this issue and better serve these populations and health systems they encounter, we highlight and discuss patient stories from A/AA/AC patients living with AL and ATTR amyloidosis. We also, 1) summarize the underlying disease etiology; 2) share A/AA/AC amyloidosis patient stories to inform or enrich PRO themes that may convey the important spectrum of the patient experience, from symptom onset, to diagnosis, to treatment and/or management; and 3) inform efforts toward the development of data elements, fields, and features within electronic health record systems that may better align with these patient experiences and stories.

Signs and symptoms of amyloidosis in A/AA/AC patients

Cardiac amyloidosis is caused by abnormal amyloid protein aggregate deposits that form insoluble plaques in the myocardium, leading to a progressive disorder that often results in restrictive cardiomyopathy (see Figure 1; Ruberg et al., 2019; Williams et al., 2022). Tetrameric thyroxine transport protein transthyretin (*TTR*) is a homotetrameric protein complex that is synthesized in and secreted by the human liver for retinol and vitamin A transfer within the circulatory system (Saelices and Cascio, 2015; Saelices and Johnson, 2015). The most common mutation associated with hATTR is the V122I (pV142I) allele, whereas a valine-to-isoleucine substitution at position 122 (*TTR* V122I; pV142I) in *TTR*-derived fibrils (Buxbaum and Ruberg, 2017). Thus, suspected cases of transthyretin amyloid cardiomyopathy (ATTR-CM) and hATTR among individuals of A/AA/AC descent must often include, in addition to the gold standard cardiac biopsy, molecular testing to confirm the presence or absence of a *TTR* mutation (Dungu, 2015).

hATTR is a hereditary form of cardiac amyloidosis, versus the non-hereditary or wild-type form, that can be fatal, as ATTR accompanied by cardiomyopathy (i.e., ATTR-CM) and heart failure (i.e., fatal arrhythmias or complete heart blockage) are common (Jain and Zahra, 2023). hATTR diagnosis is often delayed, with a late diagnosis often translating into two to 3 years of remaining life expectancy (Jain and Zahra, 2023). Liver or consolidated heart and liver transplantation have been the main treatment for patients with changes caused by ATTR, including those with cardiovascular signs and symptoms. In addition, tafamidis treatment, among others (i.e., patisiran, vutrisiran, and inotersen), may increase the life expectancy of ATTR-CM patients by 4.19 years (Tran et al., 2020). Tafamidis (i.e., Vyndaqel) is presently regulated by the US Food and Drug Administration with clinical pharmacology and clinical study labeling sections, corresponding to *TTR* as its corresponding pharmacogenomic biomarker (Center for Drug Evaluation and Research, 2023).

ATTR-CM is an under-recognized cause of cardiac/heart weakness and failure among middle aged and geriatric adults. Moreover, ATTR-CM disproportionately affects individuals of A/AA/AC descent; in ~3.4% of populations with ancestral origins from coastal west Africa and clinical signs of hATTR, a high frequency of the *TTR* V122I (pV142I) allele can be observed (Jacobson et al., 2016).

AL amyloidosis is the most common form of amyloidosis, whereas the immune system produces "light chains" or abnormal antibodies/immunoglobulins. In AL amyloidosis, light chains are deposited in major organs, such as the heart and nerves, thereby compromising their optimal function. AL amyloidosis is also associated multiple myeloma, a form of cancer that disproportionately affects A/AA/AC populations, lending AL amyloidosis symptoms as often treated in cancer centers (Kumar et al., 2017; Lee et al., 2021; Gorevic, 2023; *AL (Primary) Amyloidosis*, n.d.). However, the incidence of AL amyloidosis related multiple myeloma in A/AA/AC populations in the US remains unclear.

Because amyloidosis does not present as a single condition when phenotypes are observed among A/AA/AC patients, clinicians may erroneously steer towards clinical reasoning that supports diagnosis and treatment of a neurological disorder or cardiac and musculoskeletal manifestations/disorders (Nativi-Nicolau et al., 2022). In other instances, clinicians may rule signs and symptoms as idiopathic or of unknown cause (Nativi-Nicolau et al., 2022). Therefore, when seeking solutions to diagnose A/AA/AC patients more efficiently and effectively, it is necessary to acknowledge overall that 1) diagnosis can be difficult due to heterogeneity in phenotypes; and 2) clinical signs and clues of AL and ATTR amyloidosis among suspected A/AA/AC patients may differ from more generalized cases, warranting clinical suspicion and/or equipoise (*Geographic Origins, Diagnosis and Treatment of Hereditary Amyloidosis - African Americans*, 2023).

Leveraging A/AA/AC amyloidosis patient stories for better care

Prior work and A/AA/AC amyloidosis patient stories have highlighted important themes on which to build and that likely capture the range of lived experiences among populations managing genetic diseases and their comorbidities (National Black Nurses Association [NBNA], 2019; Hendricks-Sturrup, 2021; Brown, 2022; *Genetic Origins, Diagnosis and Treatment of Hereditary Amyloidosis on African Americans*, 2022; Baxton II, n.d.; Beckwith, n.d.; Foster, n.d.; Jackson-Webb, n.d.; Strickland, n.d.). These themes are as follows:

- Access to clinical, molecular diagnostic testing for *TTR* mutations, as lack of access to testing may hinder prior/initial authorization for pharmacogenomic treatment for health-compromised patients with hATTR (Blue Cross Blue Shield, 2019; Cigna, 2023; UnitedHealthcare, 2023).
- Diagnosed populations may lose life insurance coverage, especially if molecularly diagnosed (i.e., genetic testing) during late disease stages.
- Access to follow-up testing and/or care (i.e., tissue biopsy, echocardiogram, cardiac magnetic resonance imaging, radionuclide imaging, technetium pyrophosphate scan, etc.) (Blue Cross Blue Shield, 2019; Cigna, 2023; UnitedHealthcare, 2023).
- Lack of personal and family understanding of amyloidosis.
- Struggle to maintain and active lifestyle in later life.
- Clinical signs tend to include a mixture of carpal tunnel syndrome, arrhythmia, gastrointestinal issues, and common signs of heart failure.
- Underdiagnosis of the disease in African American populations results in late-stage diagnosis, contributing to poor outcomes and prognosis due to poor stabilization that is needed to seek and engage in preventive care.
- Chronic, acute, and prolonged stress, including general malaise, affects day-to-day life functioning and increases risk of mental illness (e.g., depression, anxiety, etc.).
- Fragmented, under-resourced, under-educated, and underprepared health systems and healthcare providers contribute to delayed diagnosis.

A/AA/AC nursing professionals, who often spend time at the bedside learning patients' stories and experiences to document such information within electronic health records, and other health system stakeholders consider patient community stories as powerful resources to directly address health disparities through intentional data collection, use, and reporting (Hendricks-Sturrup, 2021; Hendricks-Sturrup et al., 2021; Evidation, n.d.). Moreover, A/AA/AC nursing professionals, in addition to caregivers of A/AA/AC patients with AL and ATTR amyloidosis, are well-positioned to inform the development of both objective and subjective PROs (i.e., PROMIS®, PRO-CTCAE, ATTR-QOL, interviews and focus groups) intended to capture the AL and ATTR A/AA/AC patient experience within the electronic health record. For example, PROMIS®, PRO-CTCAE, and ATTR-QOL do not currently contain domains focused on access to molecular testing, access to non-health insurance following testing, follow-up testing and/or care, concern about late-stage diagnosis and poor symptom stabilization, and experiences navigating complex health systems that contribute to delayed diagnosis. Therefore, it is imperative that such stakeholders learn from and disseminate these themes to encourage and support their integration into electronic PROs. Supplementary Table S1 provides two examples reported in recent literature of how PROs are currently used and embedded into electronic health records along with reported evidence of patient management and treatment outcomes.

Discussion

Consideration these themes across A/AA/AC amyloidosis patient stories is necessary to augment PRO instruments and collection processes that are typically used to understand quality of life, address diagnosis and treatment disparities, and reduce the likelihood of diagnostic odyssey among A/AA/AC patients with amyloidosis. Given that A/AA/AC patients with suspected amyloidosis may lack access to amyloidosis centers of excellence, the present themes herein should inform attempts to identify and

properly resource and educate healthcare providers located outside of such institutions where A/AA/AC patient populations are prevalent (Nativi-Nicolau et al., 2021).

The themes above may also inform novel approaches intended to address diagnosis and treatment disparities among A/AA/AC patients with amyloidosis (Alexander et al., 2018; Obi et al., 2022). For instance, A/AA/AC amyloidosis patient stories collected and assessed using advanced computing technologies, such as artificial intelligence (i.e., natural language processing of unstructured patient story data and clinical notes, etc.), coupled with systematically documenting genetic and social determinant of health International Classification of Diseases (ICD)-10 Z codes, could be a promising strategy to address amyloidosis diagnosis and treatment disparities among A/AA/AC patients (Center for Medicare and Medicaid, 2023; Centers for Medicare and Medicaid, 2023). Specifically, leveraging artificial intelligence for the purpose of effectively and efficiently identifying and diagnosing A/AA/AC patients with suspected amyloidosis, based on distinct clinical and diagnostic clues, could be key to addressing health disparities more rapidly and efficiently (*Geographic Origins, Diagnosis and Treatment of Hereditary Amyloidosis - African Americans*, 2023).

A/AA/AC patients with suspected amyloidosis and their families, as well as healthcare providers, health researchers, and policymakers must learn from diagnosed A/AA/AC amyloidosis patient stories to facilitate more informed decision-making. As cardiovascular disease continues to be a leading cause of death overall and among A/AA/AC populations in the United States, targeted and sustained research funding and support to empower racial/ethnic minority patient stories across the data lifecycle should be a national priority to address health disparities (Data Across Sectors for Health [DASH], All In and National Alliance Against Disparities in Patient Health [NADPH], 2022; FastStats, 2023). Similar approaches to improve diagnostic efficiency and accuracy in A/AA/AC amyloidosis patients could be applied to shorten or minimize diagnostic odyssey among patients of other genetically-derived rare diseases, lending to stronger opportunities to provide timely and targeted treatment and monitor treatment outcomes.

Author contributions

RH-S: Conceptualization, Formal Analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing, Resources. LE: Conceptualization, Formal Analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing. CL: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Writing–review and editing.

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Conflict of interest

CL reports receiving institutional funding to Harvard Pilgrim Healthcare Institute from Illumina Inc., for an unrelated research study and travel sponsorship from Illumina Inc., for a recent scientific meeting.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1276396/full#supplementary-material

SUPPLEMENTARY TABLE S1
Reported studies on how PROs can become embedded into electronic health records to generate evidence on patient outcomes.

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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Amelia Smith,
Trinity College Dublin, Ireland
Erick Lisboa,
Federal University of Bahia (UFBA), Brazil

*CORRESPONDENCE
Marcela Amaral Pontes,
apmarcela@gmail.com

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Comparative price analysis of biological medicines: disparities generated by different pricing policies

Marcela Amaral Pontes[1]*, Alane Andrelino Ribeiro[1], Flávia Caixeta Albuquerque[2] and Silvana Nair Leite Cotenzini[1]

[1]Pharmacy Department, University of Brasilia, Brasilia, Brazil, [2]Molecular Biology Department, University Catholic of Brasilia, Brasilia, Brazil

Introduction: Biological medicines have been assuming an important role among the therapeutic options for several diseases, however, due to their complex production process, the products obtained from this technology have a high added value and do not reach the purchasing power of most patients, which overwhelms the budget of health systems. With the development of biosimilars, which have reduced production costs, it is expected that access to biological medicines will become broader. However, in Brazil, the criteria for determining the price of biosimilars, unlike the generic policy in the country, do not foresee a price reduction due to the reduction of development costs.

Objective: To understand the impact of the current model of economic regulation on the availability and access of these products in the country, based on a comparative analysis in selected countries, and identify trends that can help to expand the availability and access to biological medicines.

Method: Quantitative and qualitative study, to identify the variation between the entry prices of biological medicines in Brazil and in selected countries, as well as the differences in the economic regulation policies established in these countries.

Results: The results demonstrate that the current pricing model in Brazil has generated distortions in the prices of biosimilars in the market, which, consequently, makes it difficult for the population to access this category of products, in addition to allowing unsustainable market practices for the systems of public and private health in Brazil. It was also found that most of the analyzed countries, unlike Brazil, seek to harmonize the prices of different brands of the same molecule marketed in the country and with the international market, in addition to establishing incentive policies for indication and replacement by biosimilars, which expands the participation of biosimilars in the market significantly.

Conclusion: Based on the data presented, it is concluded that it is essential to build a broader political and regulatory debate on the market for biologicals and biosimilars in the country to guarantee the access of the Brazilian population to more cost-effective technologies, generate a more competitive market and consequently contribute to the financial sustainability of health systems.

KEYWORDS

biological medicines, biosimilars, drug price, regulation, access to health technologies

Introduction

The growing number of biological medicines approved by regulatory agencies has generated the need for better understanding of the access to these technologies. However, the complex process of obtaining these products, the high investment in research and development, in addition to the market strategies, results in drugs with high added value, which do not reach the purchasing power of most patients and overload the budget of health systems (Bhatt, 2018; Sariahmed et al., 2022).

In Brazil, the National Health Surveillance Agency (Anvisa)–an agency linked to the Ministry of Health–is responsible for promoting the protection of the population's health by overseeing the sanitary control of the production, commercialization, and use of products and services subject to sanitary regulations. The registration of biologic drugs began in 2002, based on specific rules that have undergone constant updates to align with international standards for the registration of pharmaceutical products. The first biosimilar registered in the country–infliximab–occurred in 2015. Currently, Brazil has around 500 registered biologics, including vaccines, blood-derived products, monoclonal antibodies, and advanced therapies (Brasil, 2010).

However, the diffusion of biological medicines is still comparatively lower than that of synthetic medicines due to factors such as high prices, limited number of diseases treated and the need for a developed health system to oversee treatments with this type of medicine. (Brasil, 2016; Brasil, 2018b; Brasil, 2023).

Treatments with biological agents are already quite significant for some therapeutic areas, especially in high-income countries. It is estimated that 19% of patients with rheumatoid arthritis in Europe had access to biologics in 2010. In 2014, 3.1 million patients in the US were treated with one of the seven best-selling and available biologics in the country (Sengupta, 2018).

The World Health Organization (WHO) has been including new biological medicines in each edition of the list of essential medicines. In 2015, trastuzumab and rituximab were included, and in 2019, adalimumab and nivolumab. Previous lists had already included bevacizumab, pegylated interferon alpha and filgrastim (WHO, 2021b).

According to data released by the Chamber of Regulation of the Pharmaceutical Market (CMED), the sales of biologic medicines in Brazil in 2022 represented 26% of the total revenue of pharmaceutical companies and only 1.6% of units sold. Among the top 10 therapeutic classes by revenue, four are related to biologic products: coronavirus vaccines, anti-TNF (tumor necrosis factor) products, monoclonal antibodies for oncology (PD-1/PD-L1), and HER-2. According to Mega (2019), 40% of the federal public budget for pharmaceutical assistance is used to acquire biologic medicines, which serve around 2% of the total patients treated in the Brazilian Unified Health System (SUS).

The Organization for Economic Cooperation and Development (OECD) and the WHO have warned of the increased availability of high-priced medicines and questioned the current pricing models for these products in the world, since it is clear that high prices can make these medicines inaccessible, compromising equitable access and threatening the financial sustainability of health systems (WHO, 2011; OECD, 2018).

The development of biosimilars, defined as biological medicines that have a high similarity in quality, efficacy, and safety with the approved originating biological medicine, was carried out with the aim of reducing the production costs of biologicals with an expired patent. According to data from IQVIA (2020), the costs of biosimilars in Europe are about one-third of the originator biologicals. List prices are highly variable and depend on the health system and product model. It is also noted that, in addition to the reduced cost, the confidential discounts applied in the price negotiation process vary between 10% and 90%.

For biosimilar medicines to become the ideal way to expand access to biotechnological treatments in Brazil, there is a need for public and private investment in innovation, research, and development of biopharmaceuticals, with the objectives of increased competition in the Brazilian market and lower import dependency. It is also necessary that the sanitary and economic regulations of the pharmaceutical market understand the differences involved in the production process of this category of products and establish rules that help in the access to effective and safe products, with prices that reflect the reduction of research, development, and production costs, foreseen in production processes of similar products with expired patent.

The CMED, the body responsible for establishing criteria for setting and adjusting drug prices, published Communication No. 9 in 2016, containing rules for pricing "non-new biologics." This regulation foresees the use of methodologies such as external or internal referencing to determine the price of biologic medicines. The term "non-new biologics" began to be used by CMED to classify biologic products developed through individual development or comparability pathways, also known as "biosimilars" in various countries.

The pricing methodologies practiced by CMED are widely used in countries with price regulation policies. However, when it comes to setting prices for biosimilar drugs, it is observed that many European countries use the price link methodology, which involves fixing a percentage discount on the price of the reference or originator drug to determine the price of a generic or biosimilar medicine (Vogler et al., 2021). This discount on the price of the originator biologic medicine ranges from 15% to 30%, depending on the country (Vogler et al., 2021). In Pakistan, it was identified that the price of the first biosimilar can be reduced by up to 30% compared to the reference medicine (Babar, 2022).

Based on the highlighted points, this study intends to analyze the evolution of the entry price of biological and biosimilar medicines in Brazil over the years and establish a parallel with the pricing policies of this class of medicines in the countries used as an external price reference by Brazil, with a view to identify how the current pricing model behaves in the Brazilian market and what is its impact on access and availability of these products in the country.

Methodology

Based on data from the "Statistical Yearbook of the Pharmaceutical Market", 2019/20 edition (Brasil, 2021a), seven biological medicines were selected among the 20 substances with the highest revenues in the country in 2019. For each active ingredient selected, concentrations and pharmaceutical forms

TABLE 1 Price research websites by selected country.

Country	Price research website
Brazil	www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos
Australia	www.pbs.gov.au/pbs/industry/pricing/ex-manufacturer-price
New Zealand	www.schedule.pharmac.govt.nz/ScheduleReporting.php
Canada	www.idbl.ab.bluecross.ca/idbl/load.do
	www.ramq.gouv.qc.ca/en/about-us/list-medications
United States	www.department.va.gov/administrations-and-offices/acquisition-logistics-and-construction/freedom-of-information-act-requests/
Spain	www.sanidad.gob.es/profesionales/farmacia/financiacion/home.htm
France	www.codage.ext.cnamts.fr/
Greece	www.moh.gov.gr/articles/times-farmakwn/deltia-timwn
Italy	www.aifa.gov.it/web/guest/liste-farmaci-ah
Portugal	www.infarmed.pt/web/infarmed/servicos-on-line/pesquisa-do-medicamento

available in the Brazilian market and in the countries defined in CMED Resolution 2/2004 (Brasil, 2004) as an external reference price (ERP) were identified, which generated a list of 11 different presentations.

After defining the presentations, the Ex-Factory Prices (FP) were collected, that is, without taxes, in all price lists published and available on the official websites of the selected countries, as presented in Table 1. This search generated data from 2003 to 2022, depending on the country and medicine. Data collection took place between August 2021 and January 2023.

The database built in Microsoft Excel includes the active principle, concentration, pharmaceutical form, regulatory category (originating biological or biosimilar), brand name, quantity of pharmacotechnical unit per packaging, year, and FP for each year.

With the database built, the prices of drugs that have a patent in force and drugs that already have biosimilars on the market were compared, separately, in order to understand the different methodologies applied by the selected countries in the definition of the entry price of the different regulatory categories of biopharmaceuticals (biologics and biosimilars). For comparison purposes, drug prices were calculated per presentation and converted according to each country's purchasing power parity (PPP). PPP is an alternative method to the exchange rate, widely used for international comparisons and measures how much a particular currency could buy if it were not influenced by the market or economic policy reasons that determine the exchange rate. The calculation of the PPP is carried out and released by the World Bank and is based on the US dollar. For conversion purposes, the 2022 PPP was used in this study (OECD, 2023).

The prices collected were not adjusted for inflation since the prices displayed in the public lists, per year, are adjusted according to inflation or other adjustment methodologies, according to the country's economic regulation rules.

In addition, a documentary survey of normative acts and legislation in force was carried out to identify historical and conceptual elements related to the regulation of prices of biological medicines in the selected countries. The documentary research took place on the websites of organizations and government entities, such as health regulatory agencies, health technology assessment agencies and ministries of health.

Results

The seven biological medicines objects of this analysis, their respective presentations, and brands, as well as the prices registered in the selected countries in 2022, adjusted by the 2022 PPP and exempt from taxation, are presented in Table 2, where it is possible to identify that the prices of the biological medicines in Brazil are among the highest compared to the selected countries. It is noted that there is a considerably large difference in price variations between Brazil and selected countries for originator biological medicines that have biosimilars in the market and for biological medicines with a valid patent. Remicade FP in Brazil in 2022 was 1,054% higher than in France. The variation in prices of medicines with a valid patent is much smaller, for example, FP of Perjeta in Brazil is 159% higher than in Italy. In the comparative analysis of prices adjusted by the 2022 PPP, exempt from taxes and fees, it is reaffirmed that the entry price in Brazil, after years of commercialization, is the highest among the referenced countries, approaching only the United States. The cells without data in Table 2 may be related to the non-commercialization of the product in the market or the absence of a price in the official lists of the countries surveyed.

Table 3 details the pricing and price review rules in the selected countries and demonstrates that European countries and Australia have policies for reviewing and/or reducing the prices of biological medicines with or without a valid patent. These countries tend to harmonize the prices of different brands of the same molecule marketed in the country with the international market, based on the price link methodology, defined as the establishment of a percentage discount on the price of the reference or originator medicine to determine the price of a generic or biosimilar medicine (Vogler et al., 2019). In Greece, prices are revised annually based on the average of the 2 lowest prices in the European Union and cannot

TABLE 2 Comparison of FP in PPP dollar in selected countries in 2022.

Medicine (mg)	Brand	BRA (US$ PPP)	AUS (US$ PPP)	NZL (US$ PPP)	CAN (US$ PPP)	US (US$)	ESP (US$ PPP)	FRA (US$ PPP)	GRE (US$ PPP)	ITA (US$ PPP)	POR (US$ PPP)	Variation (%) between BRA price and lowest price
Bevacizumab 100	Avastim	675.37				765.78	**105.42**	107.73	179.22			541
	Mvasi		84.37			687.22	163.48	103.58	143.38			
	Zirabev				108.85	526.29	114.43	90.93	143.38			
	Alymsys					707.77		103.58	143.38			
	Oyavas							103.87	143.38			
	Aybintio								143.38			
Bevacizumab 400	Avastim	2,614.96				3,063.12	**421.10**		717.77			521
	Mvasi		337.48			2,748.81			574.21			
	Zirabev				435.41	2,105.17	421.10		574.21			
	Alymsys					2,831.07			574.21			
	Oyavas								574.21			
	Aybintio								574.21			
Infliximab 100	Remicade	1,613.89	221.79	749.60	**139.85**	610.41	140.94			558.95	253.79	1.05
	Remsima	919.40			**139.85**				238.33		215.89	557
	Biomanguinhos	1,589.32										
	Renflexis	610.36	**221.79**	393.14		504.58						175
	Inflectra		221.79				91.61		238.33			
	Flixabi								238.33			
	Xylfia	1,565.06		418.66							**200.30**	274
	Avsola			393.14								
	Zessly								238.33			
Nivolumab 100	Opdivo	3,242.15	1,364.39				**701.70**		829.25	1,823.83		362
Nivolumab 40	Opdivo	1,296.86	545.76		339.72		**280.68**		331.95	729.53		362
Pembrolizumab 100	Keytruda	5,835.88	2,644.36		2,125.34		**1,796.67**		2,115.08	3,245.49		225
Trastuzumab 150	Herceptin	1,665.15			237.48		**169.54**		356.61	936.20		882
	Ogivri		163.91				169.54					
	Trasimera	739.45	**163.91**				169.54					351
	Kanjinti	739.45	**163.91**				169.54		285.28			351
	Herzuma	877.96	**163.91**		237.48		169.54		285.28			436
	Ontruzant	847.16	**163.91**				169.54		285.28			417
Trastuzumab 440	Herceptin	4,151.32					**474.72**		1,019.89	2,687.24		774
	Ogivri						474.72		798.79			
	Zedora	4,884.16							**798.79**			511
	Trasimera	2,169.05					**474.72**		798.79			357
	Herzuma	2,575.34	**480.82**						798.79			436

(Continued on following page)

TABLE 2 (*Continued*) Comparison of FP in PPP dollar in selected countries in 2022.

Medicine (mg)	Brand	BRA (US$ PPP)	AUS (US$ PPP)	NZL (US$ PPP)	CAN (US$ PPP)	US (US$)	ESP (US$ PPP)	FRA (US$ PPP)	GRE (US$ PPP)	ITA (US$ PPP)	POR (US$ PPP)	Variation (%) between BRA price and lowest price
	An intruder	2,485.01					**474.72**		798.79			423
	Kanjinti	2,114.43	**458.96**				474.72		798.79			361
Rituximab 100	Mabthera	1,322.29								**745.84**		77
	Rixymio	1,322.29	234.99							**190.94**		593
	Tricks	1,322.29					**97.85**					1.25
Rituximab 500	Tricks	3,300.73	**234.99**				489.24					557
Pertuzumab 420	Life	4,381.05	2,018.50				1,784.53		**1,691.59**	2,723.30		159

The highest and lowest prices of the brands available in Brazil and other countries are highlighted in bold.

TABLE 3 Biosimilars pricing policy and biologicals and biosimilars pricing review.

	Pricing methodology	Price review
BR	External price referencing (REP) for biosimilars that demonstrate clinical benefit.	There is no price revision rule
	Internal price referencing (RIP) for biosimilars already on the market.	
AU	The reduction of the new brands will be based on previous price reductions. For example, if the first brand has reduced by 35% or less in 2016, the price of the new brand should not exceed the PF of the existing brand reduced by 25%.	5% reduction after 5 and 10 years on PBS. 26.1% or 30% after 15 years.
NZ	There is no specific rule set	There is no price revision rule
CA	There is no specific rule set	The revision of patent medicines prices considers an adjustment factor based on inflation and should not exceed the highest price among the comparison countries.
US	Does not have a drug price regulation policy	Does not have a drug price regulation policy
ES	Price link: −30% from originator	Annual review according to the sales and commercialization of new drugs of the same therapeutic class.
FR	Price link: −40% from originator and reduces originator 20%. After 18 and 24 months, further reductions (5%–15%) occur according to market share. Hospital: −30% biosimilar and originator	Review after 5 years of marketing for drugs with ASMR I to III and for other cases after 3 years. After 1 year of commercialization of the biosimilar, the price of the originator medicine can be revised to harmonize prices.
GR	Expired patent: −20%	Annual review and follows the same entry price definition rule (average of the 2 lowest prices in the EU).
	Biosimilar medicines: average of the 2 lowest prices in the EU.	
IT	Price link: −20% from the originator	Review from 36 months for innovative drugs and 18 months for drugs with potential innovation. May occur due to new therapeutic indication, dosage, or scientific evidence.
PT	Reimbursed medications: −20% or −30% for BP with a market share greater than 5%.	Annual review based on the REP or extraordinary according to the justification presented to INFARMED.

1CMED Communiqué 9, of 10 August 2016; 2National Health Act 1953; 3Clarivate Analytics. Cortellis for Regulatory Intelligence. Regulatory Summary Expert–Pricing and Reimbursement (New Zealand). 2021; 4Compendium of Policies, Guidelines and Procedures 2022; 5Vogler et al, 2021; 6Royal Legislative Decree 1/2015, of July 24; 7Accord-cadre du 03/05/2021; 8PPRI, Pharma Brief: Greece 2007; 9PPRI, Pharma Brief: Italy 2021; 10 Decree-Law 97, of 1 June 2015. AMSR: Amélioration du service médical rendu (improvement in medical benefit). INFARMED: national authority for medicines and health products.

be reduced by more than 7% of the current list price. In France, prices are revised after 3 or 5 years, according to the evaluation of the therapeutic progress of the medicine, and with the entry of biosimilars into the market, so that the prices of the active ingredient under analysis are harmonized, regardless of whether it is the originator biologic or biosimilar. New Zealand, due to the pricing model, which is linked to the process of purchasing medicines for the public health system, does not revise prices periodically. Brazil and the United States also do not have established criteria for price revision.

In the analysis of the historical prices of biologicals with a valid patent, it is observed that nivolumab, after 5 years of commercialization in Brazil, had its price adjusted by 30%. Pertuzumab, with 8 years on the market, increased the FP by

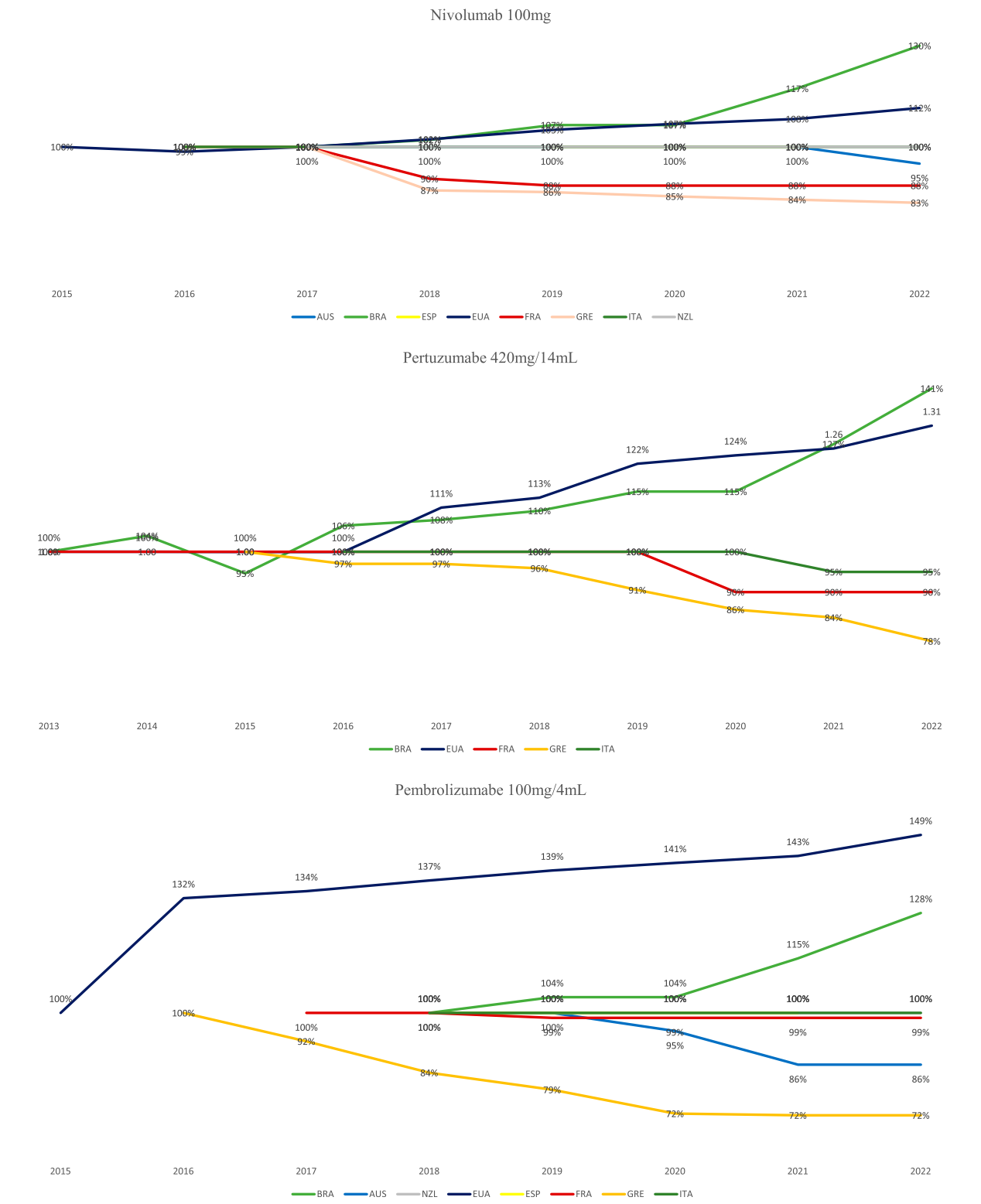
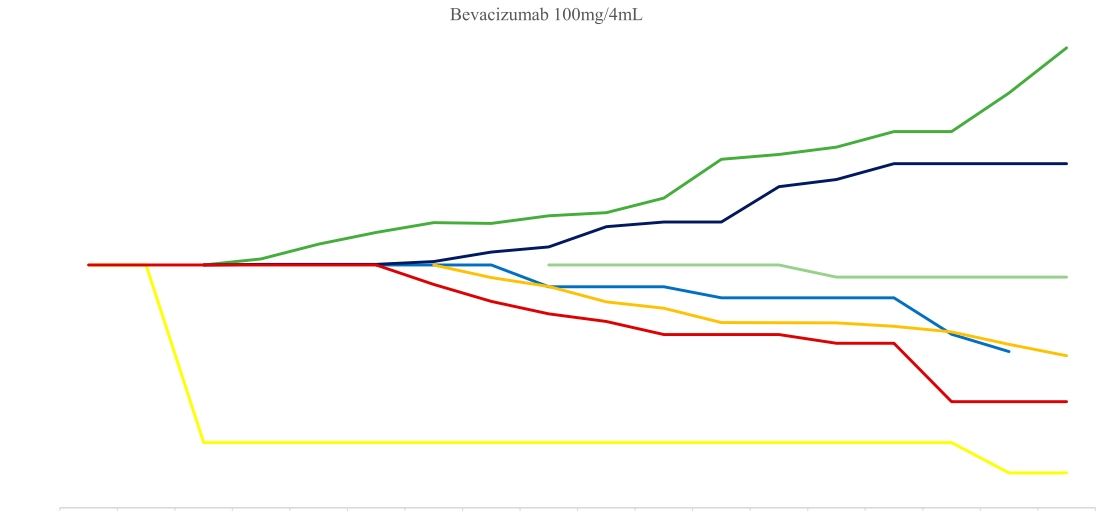


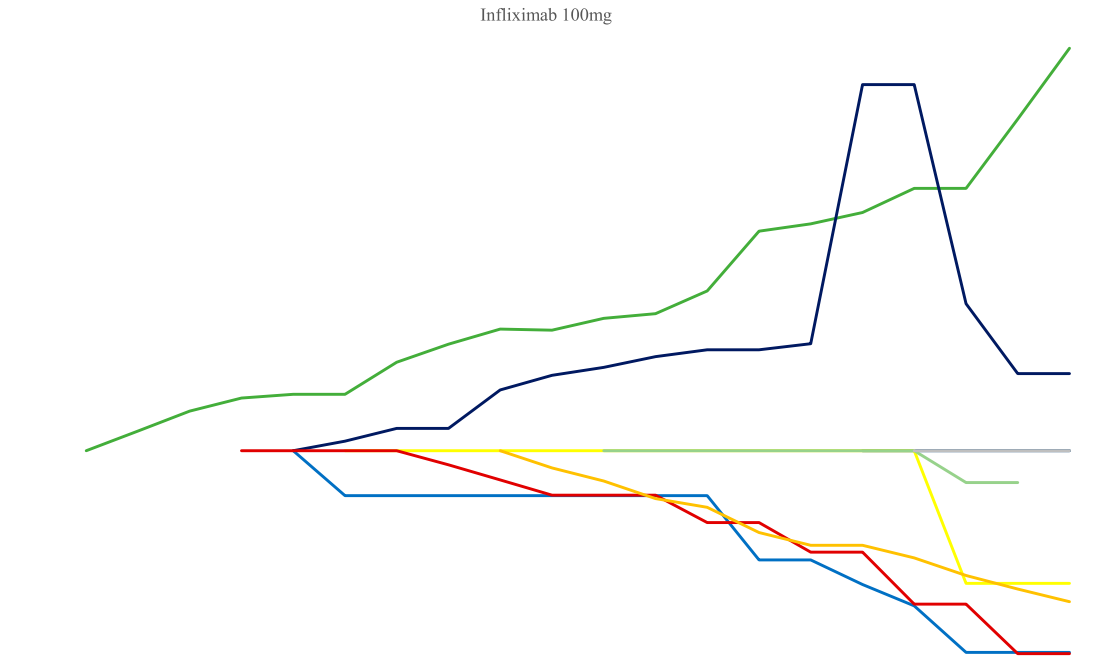
FIGURE 1
Prices course of biological medicines with a valid patent in selected countries, from 2013 to 2022.

35%, and pembrolizumab, in 4 years, had an increase of 28% over the FP. This percentage increase is even higher than in the United States, a country known for charging the highest prices for most medicines in the world (Daalen et al., 2021).

European countries and Australia register the biggest discounts in the entry prices of medicines with valid patent. Greece, through its annual review policy, has the greatest reduction in prices, for example, the price of nivolumab, after



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
AUS						100%	100%	100%	91%	91%	91%	86%	86%	86%	86%	71%	64%	
BRA			100%	103%	109%	113%	117%	117%	120%	122%	128%	144%	145%	149%	155%	155%	171%	189%
ESP	100%	100%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	14%	14%
EUA			100%	100%	100%	100%	101%	105%	107%	116%	118%	118%	132%	135%	142%	142%	142%	142%
FRA	100%	100%	100%	100%	100%	100%	92%	85%	80%	77%	71%	71%	71%	68%	68%	44%	44%	44%
GRE							100%	95%	91%	85%	82%	76%	76%	76%	75%	72%	67%	63%
ITA									100%	100%	100%	100%	100%	95%	95%	95%	95%	95%



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
AUS					100%	86%	86%	86%	86%	86%	86%	86%	86%	66%	66%	58%	51%	37%	37%	37%
BRA	100%	106%	112%	117%	118%	118%	128%	133%	138%	138%	142%	143%	150%	169%	171%	175%	182%	182%	204%	226%
CAN																100%	100%	100%	100%	100%
ESP						100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	58%	58%	58%
EUA					100%	103%	107%	107%	119%	124%	126%	130%	132%	132%	134%	215%	215%	146%	124%	124%
FRA				100%	100%	100%	100%	96%	91%	86%	86%	86%	77%	77%	68%	68%	52%	52%	36%	36%
GRE									100%	95%	90%	85%	82%	74%	70%	70%	66%	61%	57%	53%
ITA											100%	100%	100%	100%	100%	100%	100%	90%	90%	
NZL																	100%	100%	100%	100%

FIGURE 2
Price behaviour of biological medicines with expired patent in selected countries, from 2013 to 2022.

5 years on the market, has reduced by 17%. Pertuzumab reduced by 22% after 7 years in the market and pembrolizumab had its price reduced by 72% after 6 years of introduction into the country (Figure 1).

Figure 2 shows the price course of medicines with expired patents, that also have biosimilars on the market. Australia and European countries drastically reduce prices with the entry of biosimilars. As shown in Table 2, countries such as Australia,

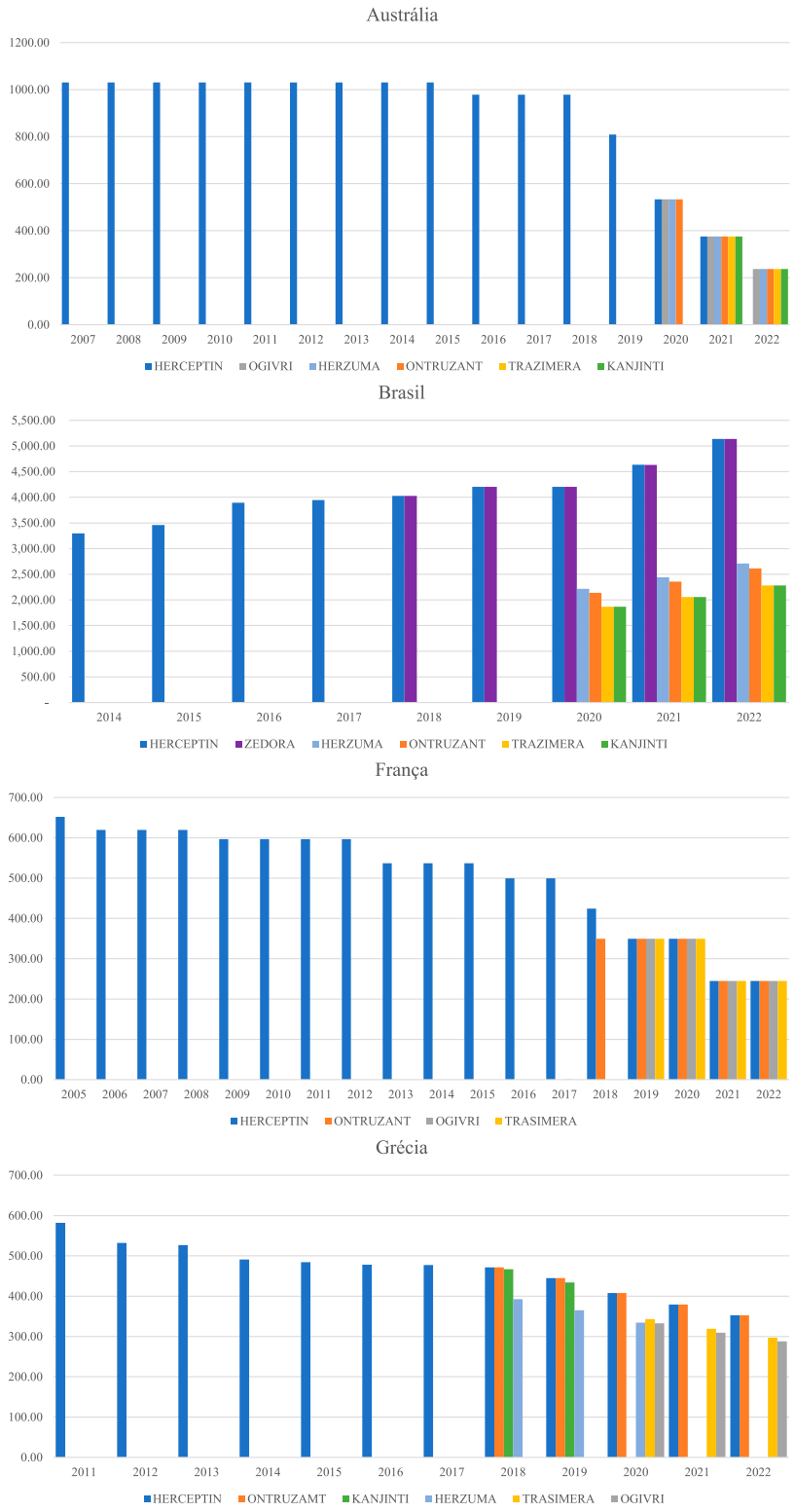


FIGURE 3
Trastuzumab 150 mg originator biological drug price history and biosimilars.

Spain, France, and Portugal use the price link methodology, while Greece and France also apply a reduction rate in the originator biological price to harmonize the prices of different brands of the same molecule. In Brazil, even with the entry of biosimilars into the market, the price of the originator biologic has been constantly growing.

Figures 3, 4 detail by country how the list prices of the originator biologics and biosimilars behave with the entry of new brands into

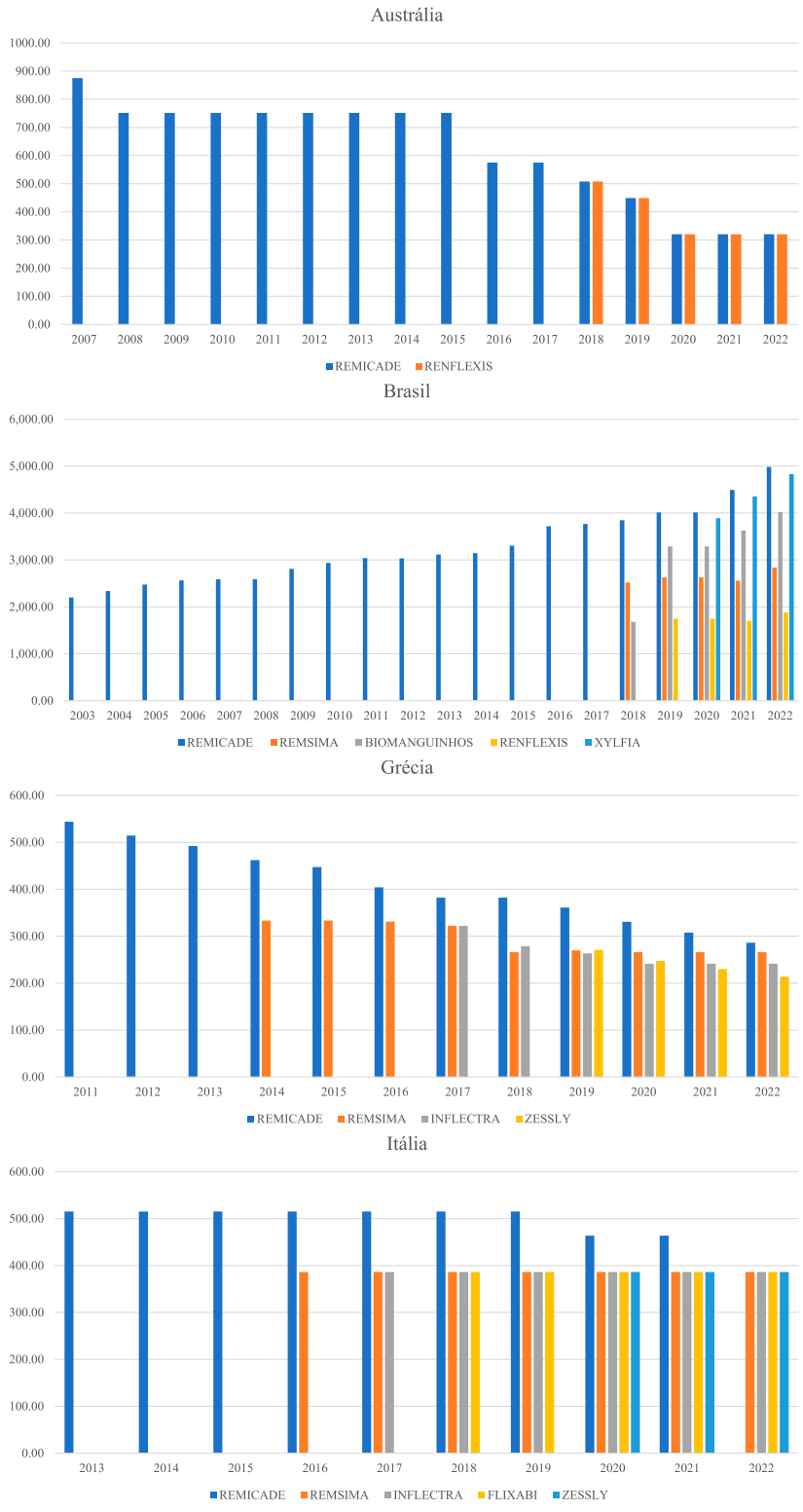


FIGURE 4
Price history of the originating biological medicine and biosimilars of Infliximab 100 mg.

the market. The values in the Figures are presented in the currency of the country analyzed. Infliximab 100 mg and Trastuzumab 150 mg were used as examples because they have a greater number of biosimilars on the market in the countries studied.

Hen observing the evolution of the prices of biological originators of trastuzumab 150 mg (Herceptin) and infliximab 100 mg (Remicade), it is noticed that Brazil generates great distortion in the prices of similar presentations. FP of

Trastuzumab in 2022 ranged from BRL 2,281.46 to BRL 5,137.60, which is equivalent of a difference of 125% between the lowest and the highest price. The FP of infliximab had a variation of 164%. Greece, due to the annual price review, manages to generate a much lower variation between the prices of biologicals with a similar molecule than in Brazil, that is, the prices of trastuzumab available in the Greek market varied 23% in 2022, and the prices of infliximab, 34%.

Australia, France, and Italy define rules for economic regulation that establish a percentage for reducing the price of biosimilars and, by establishing periodic price reviews, guarantee the same FP for different brands of the same molecule, which generates better competition with the potential to expand access to medicines. The entry price of the infliximab biosimilar in the Australian market was 42% lower than the originator entry price. In France, the trastuzumab biosimilar had its entry price recorded at 54% of the originator's value.

Discussion

This study presents the evidence for biological medicines price variation in Brazil and compares it with the prices in the countries used as an ERP for defining the entry price. The study identifies that the Brazilian population has access to biological medicines with some of the highest prices among the countries compared. This study corroborates the findings of Analytics (2021) and Moye Holz and Vogler, (2022), who identified that high prices are one of the causes of lower access to biological medicines for Latin American citizens.

The current methodology used in Brazil for pricing originator biologicals and biosimilars is based on ERP or IRP, by calculating the cost of treatment with therapeutically comparable drugs. These rules, according to data presented, have generated significant distortions in prices and do not help in the development of a market with perfect competition.

According to Holtorf et al. (2019), several authors have already concluded that ERP causes some reduction in drug prices, but there is little evidence on the concrete impact of this methodology on price, access, availability, quality, and the health system in the long term. This study demonstrated that the ERP has been described as an inefficient approach to reducing prices when used in isolation from other methodologies and, therefore, more value is seen when there are combinations of pricing policies. Another questioning that has been carried out in several discussion spaces about the use of the ERP is related to the selection of reference countries, which should consider nations with similar geographical proximity, income, availability of medicines, and market size, to guarantee that the definition of the price is adequate to the socioeconomic condition of the country (WHO, 2021a).

One of the objectives of using the ERP is to try to ensure that the price paid for a pharmaceutical product in Brazil does not excessively exceed the price paid in the countries it is compared to. However, other characteristics of the Brazilian model distance and distort these prices in the market. The high tax burden, the US dollar exchange variation, inflation and the lack of periodic monitoring and revision of prices make the availability of products in the market and access to medicines in Brazil increasingly difficult. In 2012, the report on judgment 3016 of the Federal Court of Auditors had already recommended that the Ministry of Health review and correct the regulatory model provided for in Law 10,742/2003, to detach inflation adjustments, as they found that 86% of drugs from a sample of drugs with the highest revenues were priced above the international average, with 46% having the highest price in Brazil (Brasil, 2012; Brasil, 2003a; Brasil, 2003b; Dias et al., 2019).

The Federal Court of Auditors also highlights the need to adapt the current economic regulation policy to make it more flexible and establish rules for reviewing prices in the country. In this context, WHO recommends providing information on rebates, discounts or other transactions between sellers, sponsors, and payers/buyers (WHO, 2019). The opacity of this information is an important component in the financial unsustainability of access to medicines by citizens and other payers, and transparency and information sharing has the potential to provide evidence for decision makers, to guide more accessible prices (Ribeiro et al., 2023a; Ribeiro et al., 2023b).

Price link methodology for defining biosimilar prices can be an alternative to generate a market in which competitors operate under similar conditions. In most of the analyzed European countries, it was observed that this has been a more efficient policy to align the prices of products with the same or similar therapeutic effects and to reduce price variability between comparable products.

In Brazil, the price link methodology is only used to define the prices of generic drugs, which must have their prices published with up to 35% discount on the price of the reference drug. For biosimilars, in addition to the need to improve the pricing policy, there is a lack of definition of the concept of this type of medication and the creation of a policy to encourage the use and replacement of these products, as occurred with generics with the publication of the Generic Law in 1999 (Brasil, 2019). These flaws in the execution of public policy generate price distortions in the market, do not stimulate the prescription and use of biosimilar products and create more barriers for a more competitive market. Countries in Europe that have incentives aimed at prescribers for the indication and replacement of biosimilars generated, for example, a market share of more than 95% for the biosimilar Infliximab and the increase to more than 82% of market share for the biosimilar Etanercept (Moorkens et al., 2021; Vogler et al., 2021).

In Ireland, due to low uptake of the use of biosimilars and the increasing availability of these products in the market, led the Health Service Medicines Management Executive Programme (HSE-MMP) to publish a guide to the prescription of value-based biologics in December 2018. This guide defines criteria for choosing biosimilars that will be used in the health system, based on the cost of acquiring the drug, therapeutic indications, range of products available, product stability, delivery devices, clinical guidelines, capacity to supply the Irish market and the potential savings. By applying the criteria set out in the guide, savings of €22.7 million were estimated by June 2020 (Duggan et al., 2021).

Kim et al. (2020), based on the sales values of biologicals in the United Kingdom, France, Japan, and South Korea, showed that the entry of the biosimilar infliximab decreased the market share of the originator in the United Kingdom, France, and Japan, in addition to confirming the price reduction of biosimilars in relation to the originator. One of the causes for this result is due to government

actions aimed to increase the penetration of biosimilars in the market, as is the case in the United Kingdom and France, a country that has a defined interchangeability policy. In South Korea, the entry of biosimilars generated a phenomenon contrary to the other countries analyzed, that is, there was an increase in the use of the originator and the biosimilar, and the author attributes this situation to the deficiency of specific policies for the use of these products in the country.

Carl et al. (2022) compared prices of biosimilars in the US, Germany, and Switzerland over the period 2011 to 2020 and found that prices of biosimilars and originator biologics were substantially higher in the United States compared to Germany and Switzerland. A possible reason for the limited availability of biosimilars in the United States could be an ongoing patent litigation or agreements to defer entry as a result of patent dispute resolution. He also highlighted that the limited availability of biosimilars in the United States may be a result of scepticism among prescribers and patients regarding the efficacy and safety of biosimilars. Biosimilar prices compared to originators ranged more widely in the United States (between 55% and 90%) and Germany (between 65% and 103%) compared to Switzerland (between 70% and 80%). The results for Switzerland can be explained with the price link policy. On the other hand, Germany does not consider the prices of the originator biologicals when negotiating the prices of biosimilars, which can lead to prices of biosimilars being higher than those of originators.

In 2018, Brazil created a working group to discuss and formulate the National Policy on Biological Medicines in the Unified Health System (SUS). Among the guidelines elaborated, the priority is the development of normative acts related to the interchangeability of biological medicines, based on the best available scientific evidence, to prevail the user safety, the public interest, and the expansion of access (Brasil, 2018a). The group held several discussions and propositions that so far have not been put into practice. However, biological products represent about 60% of public spending on medicines in Brazil, despite involving only 12% of the quantity of medicines, indicating urgent intervention to regulate this market (Brasil, 2018b).

The importance of including biosimilars in public health is strongly related to the costs of biological originators and the demographic and epidemiological profile of the population, therefore, the adoption of policies to encourage the use of these products can lead to considerable cost savings for the population and for systems health, in addition to expanding access to new technologies (Mosegui et al., 2021).

In addition, Brazil annually performs a positive price adjustment according to inflation and sector costs, without establishing any realignment of entry prices. According to the price cap model of economic regulation, the regulator must define the maximum amount to be charged for products/services and assumes periodic realignment of prices to market values, in accordance with efficiency gains and changes in the regulatory scenario. The usual review period is between 3 and 5 years, and, annually, the values can be readjusted by some inflation index (Brasil, 2012).

The Administrative Council for Economic Defense points to the use of inappropriate practices in the acquisition of biologicals in the private market due to the current distortion in the entry prices of biologicals. The CMED list is used by health insurance companies as a reference value for reimbursing hospitals, which results in choosing to buy the most expensive biologics and rely on their negotiating power to guarantee significant price discounts and generate a greater reimbursement margin for hospitals (Brasil, 2021b).

Another ineffective practice that stands out in the market for biologics, and for high-cost drugs, is the negotiation of prices during the process of incorporating technologies into the SUS. The National Commission for the Incorporation of Technologies in the SUS (Conitec) uses, as a basis for price negotiation, entry prices published monthly by CMED, and public purchases made available in the Health Price Database (BPS). However, at the time of acquisition, the recommended prices for incorporation into the SUS are not necessarily used as a basis for purchase by subnational public institutions.

Among the drugs analyzed in this study, it was observed that the initial price proposal by the pharmaceutical company for the incorporation of Pertuzumab, and purchase by SUS in 2018, was R$ 4,199.34 (FP0%), that is, a 50% discount on the price of the CMED list. However, in 2022, according to data published in the BPS, state purchases were made with a Maximum Sale Price to the Government (PMVG 18%) of R$ 10,479.08, (Brasil, 2019). Assuming that the price suggested by the pharmaceutical company in 2018 was adjusted in 2022, according to the cumulative adjustment for the period from 2018 to 2022, that is, 30.20%, it can be seen that the prices of state purchases occurred with prices much higher than those initially suggested for incorporation into the SUS. However, this price is within the PMVG published in the 2022 CMED list, that is, R$ 10,606.89.

When it comes to centralized purchasing by the federal government, Mega (2019) observed that unit prices between 2012 and 2017 reduced, on average, by 28% for 10 biologics analyzed. However, some products showed drops of more than 40%, such as Abatacept 250 mg (49%), Tocilizumab 20 mg (46%) and Golimumab 50 mg (40%) and Abatacept 125 mg (155%). In the same period, the CMED allowed a cumulative annul adjustment of the FP by 23.91%. Mosegui et al. (2021) identified that federal purchases of oncological biologics, carried out between 2015 and 2019, did not generate savings in resources when opting for the purchase of biosimilars. The influence of biosimilars on the prices of reference biologics was not evident.

These data point to some reasons that lead to price variation in public procurement, such as the presence or absence of competition in the market, the negotiation capacity and purchasing power of the federative entity, or even the availability of the product from national production, and the lack of a well-established policy to encourage biosimilars. The above-mentioned results also demonstrate that the negotiations carried out during the process of incorporation into the SUS and the process of public procurement do not guarantee that the health system will be able to acquire medicines with significant discounts on the FP, since the current legislation determines that any acquisition must consider the list price of the CMED as the maximum price, which has been shown to be much higher than the actual prices.

With the evidence presented here, the need for a broader political and regulatory debate on the biologics and biosimilars market in the country is reinforced, to guarantee the access of the Brazilian population to more cost-effective technologies, generate a more competitive market and consequently contribute for the financial sustainability of health systems.

This study has some limitations, such as a small sample of biologicals that does not allow extrapolating the results to the entire market. It is not possible to conclude that the price reductions of

biologics and biosimilars in the countries analyzed are the real prices practiced, because some countries use a regulatory methodology complementary to the REP and the price link–price negotiation–which is confidential and, therefore, it may be that the prices of biologics have different percentage variations from those presented. In addition, the countries analyzed have different health systems with different economic regulation policies.

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.

Author contributions

MP: Writing–original draft, Writing–review and editing. AR: Writing–review and editing. FA: Writing–review and editing. SL: Supervision, Writing–review and editing.

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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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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Bhuvan K. C.,
Queensland University of Technology, Australia
Nejc Horvat,
University of Ljubljana, Slovenia

*CORRESPONDENCE
Noelia Amador-Fernández,
noelia.amador-fernandez@unisante.ch

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Clinical relevance and implementation into daily practice of pharmacist-prescribed medication for the management of minor ailments

Noelia Amador-Fernández [1,2,3,4,5]*, Irina Botnaru[1], Samuel Sebastian Allemann [6], Véronique Kälin[1] and Jérôme Berger [1,2,3,4]

[1]Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland, [2]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [3]School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland, [4]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Lausanne, Switzerland, [5]Graduate School of Health, University of Technology Sydney, Sydney, Australia, [6]Pharmaceutical Care Research Group, University of Basel, Basel, Switzerland

Background: Autonomous pharmacist prescribing was legally introduced in Switzerland in 2019 with the reclassification from prescription medication to pharmacist prescribing of 105 medications for sixteen indications. Its aim was to limit medical consultations and healthcare costs.

Objectives: To evaluate the clinical relevance of the pharmacy prescribing medications compared to the over-the-counter medications (OTCs) and to evaluate its implementation into daily practice.

Methods: A comparison was undertaken by clinical pharmacists to evaluate chemical and galenical equivalences between pharmacy prescribing medications and OTCs using compendium. ch and pharmavista. ch. Then, a scoping review was carried out in October 2021 to determine clinical relevance according to clinical guidelines' recommendations. Clinical relevance was completed by determining if pharmacy prescribing medications were part of a homogeneous therapeutic class (no differences in efficacy and safety considered in clinical guidelines, but rather inter-molecular differences) that included an OTC medication. To identify the most clinically relevant pharmacy prescribing medications, first-line treatments were considered. The implementation into daily practice in Swiss community pharmacies was evaluated through an online questionnaire distributed via e-mail from the national pharmacists' association and LinkedIn®. It included 15 questions divided in: pharmacy demographics, experience on pharmacy prescribing, use of prescribing medications and opinion about the them.

Results: Of the 105 pharmacy prescribing medications, 20 (19.0%) were first-line treatments without OTC equivalences. Six of them were OTCs reclassified for safety reasons. Ten medications (9.5%) showed a negative clinical relevance (they were not first-line therapeutic options to support pharmacist when managing patients or considered as to be avoided) compared to the OTCs available. For the questionnaire,

283 pharmacists from the German (40.3%), French (37.1%) and Italian-speaking regions (16.9%) answered. In the previous 6 months, 41.7% pharmacies had delivered 10–50 medications and 30.0% between 1 and 10 medications. In situations where patients could be equally treated with a pharmacy prescribing medication or OTC (with an identical OTC, similar OTC or an OTC for the same therapeutic group): 75.6%, 74.9% and 84.8% of pharmacists, respectively, would have chosen OTCs because it required less documentation and it did not require patients' payment for the service. In addition, pharmacists' lack of training was also mentioned as barrier for providing the service.

Conclusion: Most pharmacist prescribing medications do not present clinical advantages compared to OTCs. In addition, other barriers for implementation were also pharmacists' training and patient medications costs.

KEYWORDS

community pharmacies, community pharmacy services, triage, autonomous pharmacist prescribing, implementation science

Introduction

Minor ailments are defined as "common or self-limiting or uncomplicated conditions which may be diagnosed and managed without medical intervention" (Jones et al., 2010). Examples of these conditions are allergic rhinitis or heartburn. In Switzerland, such conditions can be managed in community pharmacy with "over-the-counter (OTC)" products and medications autonomously prescribed by a pharmacist. Similarly, in countries such as United Kingdom or Canada pharmacist are allowed to act as supplementary or independent prescribers for certain health problems including minor ailments (Aly et al., 2018). These services have proven good clinical (Paudyal et al., 2013; Watson et al., 2015; Dineen-Griffin et al., 2020a) and economic outcomes (Rafferty et al., 2017; Dineen-Griffin et al., 2020b; Amador-et al., 2021).

Autonomous prescribing is defined as the act that occurs when "a prescriber undertakes prescribing within their scope of practice without the approval or supervision of another health professional" (Ahpra, 2019; Ogundipe et al., 2023). In Switzerland, autonomous pharmacist prescribing (PP) is allowed in some specific clinical situations, e.g., in order to avoid a direct risk for the patient. Federal laws were revised to broaden PP in order to address the lack of general medical practitioners (GPs), the need to facilitate access to primary care in case of minor ailment (Pharmasuisse, 2021) and to increase patients' self-care (FGSC, 2022). The Therapeutic Products Act (TPA) was revised in January 2019. Through this revision, a reclassification of medications was introduced stating that pharmacists could dispense, without a medical prescription, medications intended to be delivered under medical prescription. To do so, pharmacists must have direct contact with the patient and they must document the medication dispensed when the medication its indication had been designated by the Federal Council (FOPH, 2019). These medications and indications were defined by a group of experts, consisting of community pharmacists and GPs, and were named as the "list of indications and medicinal products under medical prescription which may be directly supplied by pharmacists" (further called "PP list" in this article).

The PP list has two different medication subcategories: those that were previously under prescription that could now be prescribed by pharmacists (e.g., sildenafil or topical ivermectin) and those that were non-prescription medication and were reclassified for safety reasons as prescription medication that could also be prescribed by pharmacists (e.g., domperidone or doxylamine) (FOPH, 2019). Community pharmacists can dispense medication included in the PP list for sixteen minor ailments (October 2021): seasonal allergic rhinitis, eye diseases, acute diseases of the respiratory system, diseases of the digestive tract, dermatitis, urogenital tract diseases, acute pain, migraine crisis, vitamin and mineral deficiencies, caries prophylaxis, difficulty falling asleep, low blood pressure, travel sickness and vertigo, emergency contraception, opioid overdose and smoking cessation. These are further divided into 43 indications (e.g., rhinitis, bronchospasms or cough for acute diseases of the respiratory system) and 41 therapeutic classes. A medication can have more than one indication (e.g., bilastine for seasonal allergic rhinitis and urticaria) and one indication can be treated by more than one therapeutic class (e.g., seasonal allergic rhinitis can be treated with antihistamines or corticoids).

Regarding the cost that might influence patients when choosing the setting for treating one of the sixteen health problems mentioned, it depends on the provider (Table 1) and on the patient's co-payment with the Swiss mandatory health insurance:

- Those patients with a lower monthly health insurance bill (around CHF 400, USD 433) are generally people in good health. However, they can pay the maximum yearly co-payment when they are sick (it can go up to CHF 2500, USD 2708) as they need to pay for their medical consultations and medications.
- Even when those patients are paying the maximum amount for the medication and the PP service, their payment is lower compared to the price when consulting a GP. This is a way of switching consultations from GPs to community pharmacists, at least for people in good health, to address the lack of GPs in the health system.

By establishing the PP list, the Swiss government have moved forward to PP. Nevertheless, the clinical relevance of the current list of medications compared to existing OTCs for such activity should be evaluated to determine whether this legal changes support pharmacists with new therapeutic options. In addition, the use of these medications by Swiss community pharmacists, notably compared to OTCs, needs to be explored. This study aims to evaluate both objectives, the clinical

TABLE 1 Prices and reimbursement for the consultation and medications of each one of the sixteen minor ailments included in the PP list.

Provider	Pricing			Reimbursement
	Consultation to get the prescription	Medication	Validation of the prescription by the pharmacist	
General practitioner	Fixed price (CHF 60/20 min) (USD 67/20 min)	Fixed price depending on the medication	Fixed prices for validations: prescription (CHF 4.30) (USD 4.80) and medication (CHF 3.60) (USD 3.99)	Yes, depending on the yearly patient's co-payment
Community pharmacist	Price freely determined by each pharmacy (usually a flat rate of CHF 20–30) (USD 22.30–33.50)		No charge	No

relevance of the medications included in PP list compared to OTC medications and to analyze how the use of medications from the PP list have been implemented in daily practices in community pharmacy since the law changed in 2019. This study is of interest beyond Swiss practice, as many countries are aiming to support the management of minor ailments in community pharmacies by developing PP and going beyond the delivery of OTCs.

Materials and methods

Objective 1. to evaluate the clinical relevance of the medication included in the PP list compared to OTC medications

A scoping review was carried out by clinical pharmacists in October 2021 to summarize the current evidence of each medication included in the PP list and to determine their clinical relevance, based on guidelines ratio and on comparison with medication already available in OTC. Off-market medications (those removed from the market) were first excluded.

Identification of identical or similar medications compared to OTC

A comparison between all medications included in the PP list and those available as OTC in October 2021 was undertaken to evaluate chemical and galenical equivalences. To compare them, usual medication databases in Switzerland were consulted: compendium.ch (HCI Solutions, 2022a) and pharmavista.ch (HCI Solutions, 2022b). The active ingredients were searched by their international non-proprietary names (INN; salts were considered, as these are taken into count in the PP list). Medication from the PP list with identical OTC medications (same active ingredient, dosage and dose form) or similar OTC medications (same active ingredient but different dosage and/or dose form) were considered as having no clinical relevance compared to OTC medications.

Evaluation of clinical relevance compared to OTC

The following sources were screened for evidence for each of the indications included in the PP list: National Institute for Health and Care Excellence (NICE), UpToDate, Cochrane Database, Prescrire.org (independent French organization composed by GPs, pharmacists, nurses and dentists), *Revue Medicale Suisse* (independent Swiss organization that is a reference in medical information) and Swiss Medical Society. The search was carried out using each of the indications included in the PP list as keywords. All identified guidelines in English and French were screened. Information about first-line treatments, recommended medication and medication related risks were extracted.

The current medication classification (e.g., prescription or OTC) is made by Swissmedic (Swiss agency for therapeutic products) based on benefit/risk ratio. Therefore, we further evaluated clinical relevance (positive for first-line treatments without an OTC equivalent or in the same therapeutic group or negative for non-first-line treatments or medications to be avoided) based on the utility as new therapeutic options for pharmacists compared to the OTCs already available. Clinical relevance was completed by determining if medications from the PP list were part of a homogeneous therapeutic class, and whether this class included an OTC medication. A therapeutic class was considered homogeneous in case of no differences in efficacy and safety considered in clinical guidelines, but rather inter-molecular differences (e.g., pharmacokinetics). A homogeneous therapeutic class that included an OTC medication determined a lack of clinical relevance for all medications from the PP list.

Finally, to identify the most clinically relevant medications from the PP list, the active ingredients were evaluated to determine if they were considered first-line treatment for the health problems for which they had the indication. When necessary, because of diverging clinical recommendations, consensus was reached by two different community pharmacists from the Centre for Primary Care and Public Health, University of Lausanne, (Switzerland) and a third one in case of disagreement. Not being first-line treatment was also considered a criterion for determining lack of clinical relevance.

Objective 2. to evaluate the implementation of the PP list for patient's daily care in community pharmacy

A cross-sectional electronic survey was developed and distributed to community pharmacists for 1 month between 16 September 2021 and 17 October 2021. It was distributed via e-mail from pharmaSuisse (national pharmacists' association) that counts with 83.3% of all pharmacies in Switzerland as members (Pharmasuisse, 2021) and through LinkedIn®. The study did not fulfill the criteria of the Federal Act on Research involving Human

Beings (Fedlex, 2022) by the Ethics Committee of Vaud and did therefore not need a formal approval by an Ethics committee given that data was collected anonymously and did not require personal health-related information.

The survey was developed by academic community pharmacists, experts in the field. It consisted of 15 categorical questions that were divided in four different parts: community pharmacy demographics; experience on autonomous prescribing activity; implementation of the medications from the PP list to manage patient's health problems, and opinion about the current list. The community pharmacy demographics included questions to determine the location and type of community pharmacy (3 questions). The questions on the experience of prescribing were related to the sources and tools to guide and document the service (8 questions). The implementation of the PP list was evaluated through clinical situations that could be managed in the pharmacy by using medication from the PP list or as OTC with similar clinical relevance (2 questions) (Paudyal et al., 2013). Personal opinion on the importance of the PP list and possible additions to the list were asked (2 questions).

The survey was completed in the REDcap® (Research Electronic Data capture) software (version 10.3.3) (Vanderbilt, 2023) which is a web based interface with a secure data collection that meets the HIPAA (Health Insurance Portability and Accountability Act) compliance standards (CDC, 2022). The survey was translated into the three of the official languages in Switzerland by native pharmacists in each of the languages working in Swiss community pharmacy (to improve contextualization for the different Swiss territories): German, French and Italian (Supplementary Appendix S1). Prior to its distribution, the French version of the survey was piloted by seven community pharmacists. Participation in the survey was voluntary and responses were anonymous. In case of several working places, the respondent pharmacist had to take into consideration the community pharmacy where his/her occupational rate was highest at the moment of completion.

Data analysis

The questionnaires completed on the REDCap® were exported and analyzed using Microsoft Excel® v2016. Descriptive analyses were carried out, data was presented as relative (%) and absolute (n) frequency for categorical variables.

Results

Objective 1. to evaluate the clinical relevance of the medications included in the PP list compared to OTC medications

As shown in Figure 1, from the 105 medications included in the PP list, 4 medications were excluded (flumetasone 0.2 mg/g ointment, prednisolone 2.5 mg/g ointment, desonide 1 mg/g cream and loratadine 10 mg 28/42tabs), as these were no longer marketed. Some of the medications (n = 13, 12.4%) were considered identical to OTC medications and other

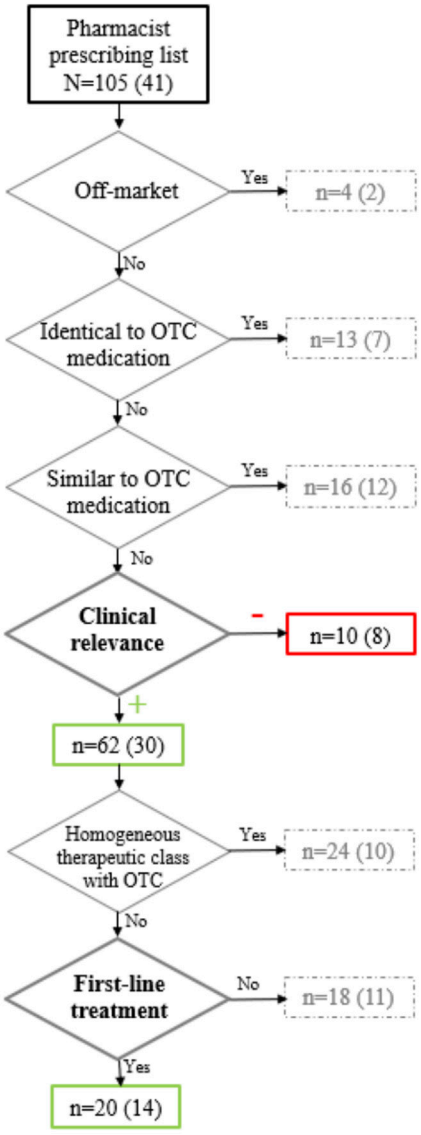

FIGURE 1
Clinical relevance of the active ingredients included in the pharmacist prescribing list.

medications (n = 16, 15.2%) had similar OTC medications. Ten medications (9.5%) from 8 different therapeutic classes were considered to have a negative clinical relevance. Out of the total medications studied, 62 (59.0%) from 30 therapeutic classes had positive clinical relevance. Among them, 24 medications (22.9%) were considered as part of a therapeutic class that already contain at least one OTC medication. Some of these were: proton pump inhibitors, non-steroidal anti-inflammatory drugs, anti-histaminic, corticoids, antifungals (Supplementary Appendix S2).

Finally, 20 active ingredients (19.0%) and 14 therapeutic classes for 14 indications were determined to be first-line treatments that were clinically relevant, e.g., that provided additional benefits to patients compared to those available in OTC (Figure 1).

TABLE 2 Medications included in the pharmacist prescribing list with no OTC equivalent and a positive clinical relevance.

Medication (INN)	Indication (according to pharmacist prescribing list)	Therapeutic class
Adapalene (topical)	Acne	Antiacne preparation for topical use
Isotretinoin (topical)		
Tretinoin (topical)		
Ivermectin (topical)	Acne rosacea	Other dermatological preparation
Hexamidine diisétionate (topical)[a]	Bacterial conjunctivitis	Antiseptic and disinfectant
Salbutamol (inhalation)	Bronchospasms	Short-acting beta-agonists (SABA)
Terbutaline (inhalation)		
Doxylamine[a]	Difficulty falling asleep	Antihistamine
Levonorgestrel[a]	Emergency contraception	Hormonal contraceptive for systemic use
Naloxone[a]	Emergency treatment of an opioid overdose	Peripheral opioid receptor antagonist
Sildenafil	Erectile dysfunction	Urological
Mebeverine hydrochloride	Functional disorders of the gastrointestinal tract	Drug for functional gastrointestinal disorders
Lidocaine + Prilocaine (topical)	Local anesthesia	Anesthetic local
Naratriptan	Migraine	Antimigraine preparation
Sumatriptan		
Permethrin (topical)	Parasitosis scabies	Ectorapasiticides, incl. scabicides, insecticides and repellents
Cinnarizine[a]	Travel sickness and dizziness	Antivertigo
Clobetasone 17-buthyrate (topical)	Uninfected dermatitis and eczema	Corticoid
Hydrocortisone 17-buthyrate (topical)		
Triamcinolone acetonide + Salicylic acid (topical)[a]		

[a]Non-prescription medication reclassified for safety reasons as prescription medication that could also be prescribed by pharmacists.

Detailed description about all medications analyzed are included in Supplementary Appendix S2.

The 20 medications without an OTC equivalent (e.g., identical, similar or part of a homogeneous therapeutic class including an OTC) found to have a positive clinical relevance that were first choice drug are included in Table 2. These represent 14 indications, as several medications are part of a homogenous therapeutic class that does not include an OTC: 3 topical medications against acne, 3 topical medications against uninfected dermatitis and eczema and 2 medications against migraine. Among these 20 medications, 6 were non-prescription medications that were reclassified for safety reasons as prescription medication that could also be prescribed by pharmacists.

Objective 2. to evaluate the implementation of the medications included in the PP list into patient's daily care in community pharmacy

A total of 283 pharmacists completed the survey, out of 5,769 pharmacists who worked in a community pharmacy in Switzerland (4.9% pharmacists in the whole country). Most respondents (40.3%, n = 114) were from the German part of Switzerland, 37.1% (n = 105) from the French speaking regions and 16.9% (n = 48) from the Italian speaking part (missing data for 16 respondents). The type of pharmacies were independent community pharmacies for 42.7% (n = 121) of the pharmacists, 36.4% (n = 103) were part of a group, 19.8% (n = 56) were chain pharmacies and 1.1% (n = 3) were under franchise.

Sources used to get information about the medications available in the PP list are presented in Table 3, with most pharmacists obtaining information from their pharmacy software (55.7%, n = 156). Regarding the support for implementation of medications included in the PP list, over a third of the pharmacists (38.5%, n = 109) answered that they would need additional help to integrate the PP list in their practice. Among these pharmacists, 78 specified the kind of help needed: algorithms (46.1%, n = 36), additional education (21.8%, n = 17), additional documentation (16.7%, n = 13) or a form included in the pharmacy IT system (15.4%, n = 12).

Figure 2 shows the medications dispensed in the pharmacies in the 6 months before the survey, with most pharmacists dispensing between 1 and 10 medications of the PP list (30.0%, n = 85) and between 10 and 50 medications (41.7%, n = 118). Most of the pharmacists who answered (89.8%, n = 254) prescribed these medications themselves.

TABLE 3 Sources of information and support for implementation in daily practice of medications included in the pharmacist prescribing list.

Source of information	Pharmacist; n (%) (N = 280)
Pharmacy IT system	156 (55.7)
Data sheets from Swiss Community Pharmacy Association	43 (15.4)
Articles provided by a training organization	36 (12.9)
Federal Office of Public Health (FOPH) website	25 (8.9)
Other[a]	12 (4.3)
None	7 (2.5)
Don't know/Don't want to answer	1 (0.3)

[a]Other sources reported: the lecture of internal documents (n = 2), by making documents available (n = 2) netCare (n = 1), other studies (n = 1).

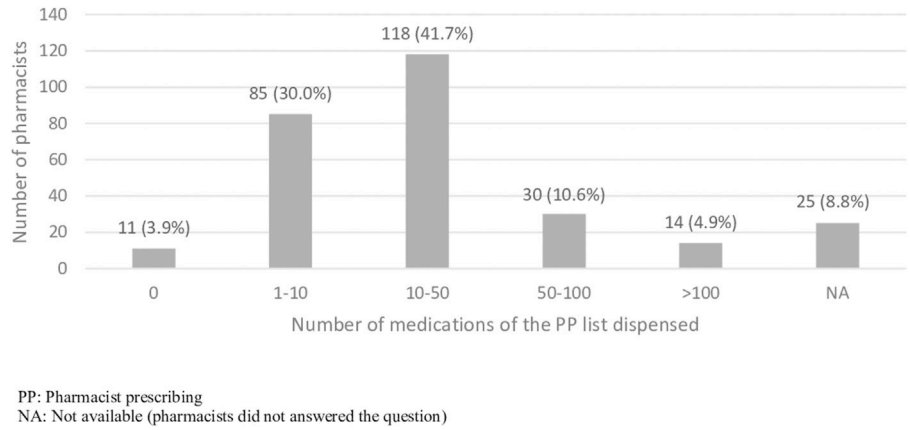

FIGURE 2
Pharmacies dispensing medications of the PP list 6 months before the survey.

Most pharmacies that prescribed a medication used an IT platform to document the service (71.1%, n = 180), some documented the process on paper (23.3%, n = 59) and a minority of pharmacies did not record the service (2.8%, n = 7) or used a different method (2.4%, n = 6).

The third area of assessment included in the survey was related to implemented strategies to recommend the medications included in the PP list. Most respondents (66.8%, n = 189) reported that no strategy related to the PP list was implemented in their pharmacy or did not want to answer (7.5%, n = 21). Out of those 73 who confirmed an implemented strategy (52.0%, n = 38 at a pharmacy level and 48.0%, n = 35 at a chain or group level) stated that the service was marketed in their pharmacy (42.5%, n = 31), communication techniques with patients were used such as websites or magazines (31.5%, n = 23), goals were set in terms of numbers of patients (31.5%, n = 23) or communication techniques with other health professionals were used (13.7%, n = 10) (multiple choice was available).

The last part of the survey concerning personal opinion of the pharmacists included their perception of the most important health problems included in the list for their practice (multiple choice). The following health problems were cited in descending order: emergency contraception (72.5%, n = 203), seasonal allergic rhinitis (69.6%, n = 195), eye disorders (62.9%, n = 176), dermatoses (56.8%, n = 159), urogenital diseases (43.9%, n = 123), acute diseases of the respiratory system (38.6%, n = 108) and diseases related to the digestive system (38.6%, n = 108).

In similar clinical situations, when the pharmacist could choose to prescribe identical medications either in PP list or in OTC (e.g., cetirizine or omeprazole), the majority would choose a medication in OTC (75.6%, n = 211). In the occasions where there were similar OTC medications or medication with the same indication as OTC presentation, pharmacists responded likewise: in case of acute pain (74.9%, n = 209) chose a similar OTC medication; or in case of functional disorder of the gastrointestinal tract (84.8%, n = 235) chose an OTC medication with a same indication. The reasons for this choice are included in Table 4.

The opinion of respondent pharmacists about the characteristics and importance of the PP list is included in Figure 3. Most pharmacists (86.4%, n = 242) considered that the PP list could limit unnecessary medical consultations, 78.9% (n = 221) that it could help limit healthcare costs, 76.1% (n = 210) believed it provides a real clinical benefit in patients' care, and 86% (n = 239) that it could help promoting pharmacists. Most pharmacists consider that the medications included in the list should be

TABLE 4 Reasons for prescribing a medication included in the pharmacist prescribing (PP) list or in OTC in case of similar clinical situations.

Reason to prescribe	In case of identical OTC medication (e.g., cetirizine 10 mg tabs)	In case of similar OTC medication (e.g., acute pain: acetaminophen 1 g VS 500 mg)	In case of OTC medication in the same therapeutic class (e.g., disorder of GIT: mebeverine VS Iberogast®)
	OTC: N = 211 (75.6%)	OTC: N = 209(74.9%)	OTC: N = 235 (84.8%)
	PP list: N = 68 (24.4%)	PP list: N = 70 (25.1%)	PP list: N = 42 (15.2%)
It allows to deliver an equally effective medication			
OTC medication	124 (58.8%)	115 (55.0%)	121 (51.9%)
PP list	42 (61.8%)	50 (71.4%)	27 (64.3%)
It is easier			
OTC medication	119 (56.4%)	99 (47.4%)	106 (45.5%)
PP list	45 (66.2%)	35 (50.0%)	24 (57.1%)
It does not require the payment of the service			
OTC medication	114 (54.0%)	93 (44.5%)	94 (40.3%)
PP list	23 (33.8%)	26 (37.1%)	19 (45.2%)
It is faster			
OTC medication	105 (49.8%)	90 (43.1%)	98 (42.1%)
PP list	12 (17.6%)	5 (7.1%)	6 (14.3%)
Other			
OTC medication	12 (5.7%)	35 (16.7%)	38 (16.3%)
PP list	4 (5.9%)	2 (2.9%)	2 (4.8%)

Multiple answers allowed.
*GIT: gastrointestinal tract.

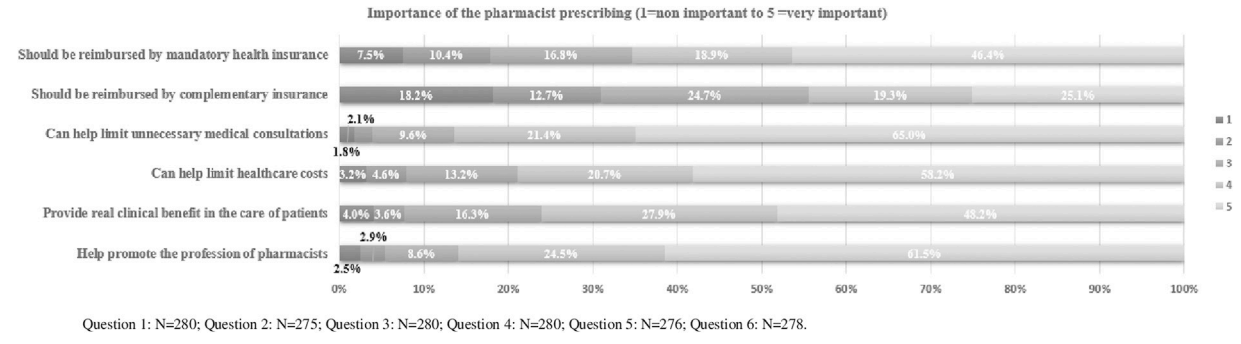

FIGURE 3
Characteristics and importance of the pharmacist prescribing list perceived by respondent pharmacists.

compensated either by the mandatory (65.3%, n = 183) or complementary healthcare insurance (44.4%, n = 122).

Most pharmacist did not respond when their opinion on additional medications to be included in the PP list was asked (66.9%, n = 184). Some pharmacists (12.7%, n = 35) thought that no medications should be added. Among the 56 (20.4%) who specified additional medications should be include: antibiotics (17.8%, n = 10), oral contraception (10.7%, n = 6), all the medications under medical prescription (8.9%, n = 5), oral corticosteroids (7.1%, n = 4), antimalarial (3.6%, n = 2), myorelaxants (3.6%, n = 2), antidiabetics (3.6%, n = 2) and vaccines (1.8%, n = 1).

Discussion

Objective 1. to evaluate the clinical relevance of the medications included in the PP list compared to OTC medications

To our knowledge, this is the first study to analyze the clinical relevance of a PP list. To increase the contribution of community pharmacists in Primary Care and to broad their scope of practice, it was important to understand the added value of the PP list for treating patients in community pharmacies compared to the medications that were already available. We believe that the method presented in this study could be replicated in other contexts to identify which medicines are clinically relevant to the management of patients through autonomous pharmacists prescribing. After the analysis of the list relevance, only 19.0% (20 medications with 14 different drug indications) of the products included in the list were considered to provide a real benefit to patients' care compared to medications already available in OTC. Reasons for limited clinical relevance could be that several medications are identical or similar to options already approved and available in pharmacies as OTCs or are part of homogenous therapeutic classes that already include OTC medications, such as proton pump inhibitors for gastro-esophageal reflux (e.g., omeprazole, pantoprazole) or antihistamines for seasonal allergic rhinitis or urticaria (e.g., cetirizine, fexofenadine). This is a low percentage to achieve the desired goal of the medication reclassification, such as limiting medical consultations or health costs. Also, six medications were already available as non-prescription medication but were reclassified for safety reasons as prescription medication that could also be prescribed by pharmacists. In addition, several of the 14 drug indications treated by one of the 20 medications considered first-line treatment are rare (e.g., scabies or emergency treatment of an opioid overdose–to be noted that this latter has been withdraw from the PP list in June 2023) which limits the use of those medications. Furthermore, the active ingredient mebeverine was considered as having a positive clinical relevance because it offers a new option of treatment for pharmacists compared to OTC medications, nevertheless, its efficacy is not well established. Since medications with a negative clinical relevance represented 9.5% of the total, the inclusion of these products in the PP list should be revised.

Objective 2. to evaluate the implementation of the medications included in the PP list into patient's daily care in community pharmacy

The second objective of the study was analyzing the use of the medications from the PP list in community pharmacies and the pharmacists' opinion. The number of respondents in each region could be explained by the total number pharmacies in each area (OFS, 2021). A research from the University of Basel (Giuranno et al., 2021) consisted in a questionnaire for community pharmacists took place on the same year in the German speaking regions on this topic and could explain why a part of responders chose not to answer the questionnaire. Both studies allow to complete the view on the use of PP list, as our study mostly include answers from French and Italian speaking pharmacists that were not included in this previous research from Basel.

Almost half of the pharmacies reported to have prescribed between 10 and 50 medications from the PP list in the last 6 months and 30% of the total respondents prescribed under 10 medications. This is lower, also when a sub analysis of the respondents from the German region was carried out, compared to the results obtained in the study from Basel (Giuranno et al., 2021) where it was reported that 35% of the pharmacies (n = 217) used to deliver medications from PP list several times per week and a further 35% reported to deliver these several times per month. This result illustrates the lower implementation of the medications included in the PP list in patients' care in the French and Italian speaking part of Switzerland which may be related to the differences in dispensing between the German speaking part (where medical practitioners are allowed to dispense medication in most of the regions) and the French and Italian speaking part (where only community pharmacists can dispense medication). Indeed, in regions where medical practitioners cannot dispense medication, community pharmacists are concerned about the opinions of GPs in relation to the autonomous pharmacists prescribing (Matthey de l'Endroit, 2022).

The most important drug indication according to pharmacists was emergency contraception, which is one of the medications with positive clinical relevance since levonorgestrel is the first choice for treatment. The second most important drug indication was bacterial conjunctivitis (eye disease) treated by hexamidine that also had a positive clinical relevance. These results could be related to patients' demands, because patients were still familiar to both medications that were non-prescription medication reclassified for safety reasons as prescription medication that could also be prescribed by pharmacists.

Pharmacists believed that certain treatments should be added to the list, most of them named the antibiotics for systemic use. Pharmacist diagnosing and managing acute common infections (e.g., cystitis) could limit the number of medical consultations and ultimately health costs. Such competencies for community pharmacists are now included in countries such as Australia since 2022 (The Guild of Australia, 2022). The second therapeutic class of medications demanded by pharmacists to be included in the PP list was oral hormonal contraception, as found in other studies (Yous et al., 2020; Eckhaus et al., 2021). This is in line with practice observed in other countries such as United States (Grossman and Fuentes, 2013) or Canada (Navarrete et al., 2022) where the service has shown users' acceptability and reach (Navarrete et al., 2021). Nevertheless, when GPs were asked through a study carried out in Switzerland, concerns about patients' safety aroused although combined access model (initial prescription from GPs and follow-up prescriptions by pharmacists) found acceptance (Yous et al., 2021).

In Switzerland, community pharmacists are already authorized to deliver treatments such as oral antibiotics or oral hormonal contraception in some specific conditions, for example, if delivery is intended to: avoid a direct danger, relieve acute symptoms that require immediate intervention or allow the continuation of a prescribed treatment that should not be interrupted (Hersberger and Beutler, 2010). The request by pharmacists to add such

medications to the list can be interpreted as a way of clarifying their role and responsibilities under these conditions and facilitating a practice that already exists.

In general, when PP has been studied from patients or any other stakeholders, common results have been found such as ease of patient access to healthcare, improved patient outcomes, better use of pharmacists' skills or reduced physician workload. But also, negative aspects have been highlighted such as the lack of access to patient clinical records or limited pharmacist diagnosis skills (Famiyeh and McCarthy, 2017; Jebara et al., 2018; Yous et al., 2021).

From the pharmacists' perspective, the PP list should ameliorate patients' care and pharmacists' practice and limit unnecessary medical consultations and healthcare costs. Nevertheless, in real practice the service was considered to confront numerous barriers (e.g., service not reimbursed by the mandatory health insurance or not sufficient external support to integrate the PP list in daily practice). In clinical situations where the patient could equally be managed with medications from the PP list or OTC, respondent pharmacists chose OTC on most occasions. The low clinical relevance of the medications in the pharmacist prescribing list could partially explain this situation. In addition, pharmacists are used to deliver OTC medications and the service is, at least partly, financed by the margin on the medication. For PP list, pharmacists need to charge a separate fee that might need to be explained to the patient. Hence, they continue to use OTC medications in patients' care. Also related to costs, most pharmacists considered that the medications included in the list should be compensated either by the mandatory (65.3%) or complementary healthcare insurance (44.4%). Similarly to the results found in the work carried out by the University of Basel (Giuranno et al., 2021). This could help to set a pricing of this service (nowadays the price for the service is freely determined by each pharmacy and usually it is a flat rate of CHF 20–30) and to legitimate it towards the patients. However, as the service is mainly intended to people in good health who do not have a GP and who generally choose a high yearly co-payment according to the Swiss health insurance system, this would probably have little influence on reimbursement to patients (as patients with high co-payment would have to pay out of pocket for the service).

Regarding to the implementation of the service, 39.8% of respondent would need more help through additional training or algorithms. The same results were obtained in the study from University of Basel on the use of the PP list (Giuranno et al., 2021). Nevertheless, from 2022 those requirements were offered for some medications and minor ailments through pharmaSuisse (Pharmasuisse, 2022).

Study limitations

It is important to notice that the study may have methodological limitations such as the absence of a systematic review for the evaluation of the clinical relevance of the PP list or few evidence-based data available for some medications treating minor ailments. Nevertheless, the most relevant sources and guidelines in Swiss community pharmacy for the consulted health problems were studied and, except for mebeverine, medications had a well-defined clinical relevance in the different guidelines. As these guidelines refer to international clinical studies or are edited by international medical societies, results are not only limited to the Swiss practice. In a conservative approach, medications in the PP list with similar OTC (same active ingredient but different dosage and/or dose form) were not considered in this study as clinically relevant. However, the difference will often be in the dosage, duration of treatment, and/or minimum age for treatment which could also be considered as new therapeutic options for the community pharmacists.

For the second objective of the study, a higher number of answers were obtained by pharmacists from the French and Italian part of Switzerland. Therefore, the study might not represent the whole population of Swiss pharmacists. However, a previous study carried out in the German regions showed similar results.

Conclusion

The Swiss PP list seems limited to achieve its goals of reducing medical consultations and healthcare costs. Most first-line treatments available in the PP list are already available as OTCs. However, this illustrates that pharmacists are trusted to correctly assess the clinical relevance even when first-line treatments are not an option. Pharmacists highlight the importance of prescribing medications from this list to achieve this goal; however, its use was not implemented after 3 years.

To better integrate medications from the PP list in patients' daily care, a revision to enhance its clinical relevance would be recommended. Other barriers found to the PP list implementation such as pharmacists' training or medications costs for patients could also be considered by policymakers.

Data availability statement

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

Author contributions

NA-F: Validation, Visualization, Writing–original draft, Writing–review and editing. IB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing–review and editing. SA: Validation, Writing–review and editing. VK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–review and editing. JB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1256172/full#supplementary-material

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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Huasheng Xiang,
Lancaster University, United Kingdom
Joana Gomes Da Costa,
University of Porto, Portugal

*CORRESPONDENCE
Jing Tang,
1817@fckyy.org.cn
JiaLei Zhu,
zhujialei7582@fckyy.org.cn
Jiaqian Pan,
panjiaqian7583@fckyy.org.cn

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Real world drug treatment models for pregnancy complicated with urinary tract infection in China from 2018 to 2022: a cross-section analysis

Jing Jin, Changyan Li, Yuqing He, Jiaqian Pan*, JiaLei Zhu* and Jing Tang*

Department of Pharmacy, The Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

Objective: Urinary tract infection (UTI) is common in pregnant women. The selection of anti-infection plans during pregnancy must take into account the dual factors of patient pregnancy status and urinary tract infection anti-infection treatment, as well as the efficacy, cost, risk, and potential adverse reactions associated with each method applied to individual patients. Consequently, there are numerous drugs from which to choose; presently, there is no unified conclusion regarding the choice of drug therapy, and there is a lack of long-term drug treatment for UTI during pregnancy. Our objective is to investigate the actual drug treatment patterns of UTI patients during pregnancy in China over the past 5 years, with a particular emphasis on the trend and rationality of antibiotic use in these patients over the past 5 years.

Method: We conducted a cross-sectional analysis of data from a China Medical Association-supervised hospital prescription analysis cooperation initiative. From January 2018 to December 2022, the information is extracted from prescriptions/medical orders of patients with UTI during pregnancy. Using a primary anatomical therapeutic chemistry (ATC) classification code and the US Food and Drug Administration (FDA) classification, we quantified the frequency of drug use and drug types. We also calculated the prevalence of the most frequently prescribed antibacterial medications and assessed the efficacy of anti-infection plans based on drug labels and guidelines.

Results: Among the 563 patients included in this research, Chengdu (36.59%), Guangzhou (27.72%), and Shanghai (8.70%) were the top three cities. Over the course of 5 years, the average age was 29.60% ± 6.59 years, with approximately 60.21% of women between the ages of 25 and 34. Each patient's primary anti-infection medications were statistically analyzed. Cephalosporins (403, 71.58%), enzyme inhibitors (66, 11.72%), and penicillins (34, 6.04%) were the first few categories, followed by the most commonly used cephalosporins. Cefuroxime, ceftriaxone, and cefdinib, rounded out the top five. Cefoxitin and cefaclor. According to the 5-year change in dosage, cephalosporins have always ranked first. Three of the top five most expensive drugs are cephalosporins, carbapenems, and enzyme inhibitors. Teicoplanin, tigecycline, nifurtel, linezolid, and quinolones ranked among the top five in terms of per-patient drug costs for patients receiving comprehensive treatment drugs.

Conclusion: In the 5 years of research, the average age of patients who visit a doctor has not increased substantially, but the opportunity cost of female fertility has increased, which has severely impeded the fulfillment of fertility desires. The selection of medications is generally reasonable, and the dosage of the first-line cephalosporins recommended by the guidelines is relatively high in this study. The dosage of furantoin and fosfomycin, which are more prevalent in urinary tract infections, is however relatively low. In addition, some expensive pharmaceuticals may increase patients' financial burden. On the premise of meeting clinical needs, future research will focus on how to further improve the level of rational drug use in outpatient clinics, attain economical, safe, and effective drug use, and thus reduce the economic burden on patients.

KEYWORDS

China, cross-sectional analysis, urinary tract infections during pregnancy, drug treatment models, real world

1 Background

Urinary tract infections (UTIs) are common in expectant women, and even asymptomatic infections can cause severe complications for the mother and fetus, including low birth weight, premature birth, stillbirth, preeclampsia, maternal anemia, sepsis, and amnionitis (Bigna et al., 2018; Tchatchouang et al., 2019; Ali et al., 2022). Increased likelihood of developing a UTI during pregnancy is attributable to alterations in expectant women's physiology and lowered immunity (Delzell and LeFevre, 2000; Hill et al., 2005; Haider et al., 2010; Kalinderi et al., 2018; Storme et al., 2019; Getaneh et al., 2021).

Current research is more concerned with the etiology, bacterial spectrum, and drug sensitivity of urinary tract infections in expectant women (Belete, 2020; Belete and Saravanan, 2020; Getaneh et al., 2021; Ali et al., 2022). The guidelines for drug treatment regimens and follow-up after mode treatment for UTI in pregnancy are consistent, but there are still inconsistencies, such as prenatal screening for bacteriuria and the use of fluoroquinolones in lower or upper urinary tract infections (Corrales et al., 2022). A study of 1,140 pregnant women with ASB revealed that it is impossible to determine which drug is the most effective or safe for treating UTIs during pregnancy (Guinto et al., 2010). One study demonstrated the efficacy of long-term treatment with furantoin, while another suggested that ampicillin is better tolerated. There is no evidence to suggest the benefits or drawbacks of various dosing regimens, which should be thoroughly considered. This gives us ideas for future investigation. There are still substantial disparities in the specific drug selection practices of various countries around the world, particularly in China, where there is no current consensus and authoritative literature reports. The Consensus of Chinese Women's Urinary Tract Infection Diagnosis and Treatment Experts points out that there is no unified opinion on the selection and treatment course of antibiotics for gestational urinary tract infections. Drugs should be selected based on urine bacterial culture and sensitivity, while considering the safety and effectiveness of medication for both the mother and fetus. The recommended drugs mainly include penicillin, cephalosporins, etc (China Medical Women's Association, 2017). In clinical practice, obstetricians must increasingly consider how to use anti-infective medications rationally and safely with expectant patients. By analyzing actual data from 2018 to 2022, we hope to close this knowledge gap. Our objective is to investigate the actual drug treatment patterns of UTI patients during pregnancy in China over the past 5 years, with a particular emphasis on the trend and rationality of antibiotic use in these patients over the past 5 years.

2 Methods

The data comes from the China Medical Association's Hospital Prescription Analysis Cooperation Project, which collects prescription/order data from nearly 120 hospitals in Beijing, Chengdu, Guangzhou, Harbin, Hangzhou, Shanghai, Shenyang, Tianjin, and Zhengzhou from 2018 to 2022 on a quarterly basis. This project provides the following data: time, city, hospital code, medication route, dosage, unit cost, medication frequency, single dose, quantity, age, and initial diagnosis.

This study collected outpatient and inpatient prescription/medical advice data for "pregnancy", "pregnancy", and "urinary tract infection" from 1 January 2018 to 31 December 2022. Other diagnoses, such as "ectopic pregnancy", "adverse pregnancy history", "infertility", and patients with urinary tract infections unrelated to pregnancy were excluded. This project only counts western antibiotics; traditional Chinese patent medicines and simple preparations, herbal medicine, and other drugs extraneous to urinary tract infection treatment are excluded.

For further analysis, we divided patients into various age groups and geographic regions, screened the most important treatment medications, and conducted additional analysis based on drug selection, administration route, drug dosage, *etc.* According to the pharmacological classification of therapeutic drugs, calculate the sales revenue of drug consumption in the past 5 years and calculate the proportion of sales revenue to total sales. Concurrently, we adhere to the World Health Organization (WHO) and Defined Daily Dose (DDD) system. The DDD value is determined using the "Clinical Medication Guidelines" (2010 edition) and "New Pharmacology" (17th edition) (National Pharmacopoeia Commission, 2010), in conjunction with the clinical medication situation and drug instructions. To conduct a rationality analysis, we evaluated the complete frequency and single dose information of

TABLE 1 Demographic characteristics of the patients (n = 563).

Year	2018	2019	2020	2021	2022	Total
Region, n (%)						
Beijing	6 (1.07%)	8 (1.42%)	8 (1.42%)	10 (1.78%)	3 (0.53%)	35 (6.22%)
Chengdu	33 (5.86%)	58 (10.30%)	36 (6.39%)	37 (6.57%)	42 (7.46%)	206 (36.59%)
Guangzhou	30 (5.33%)	40 (7.10%)	25 (4.44%)	34 (6.04%)	27 (4.80%)	156 (27.72%)
Haerbin	3 (0.53%)	3 (0.53%)	0 (0.00%)	5 (0.89%)	4 (0.71%)	15 (2.66%)
Hangzhou	4 (0.71%)	4 (0.71%)	9 (1.60%)	7 (1.24%)	13 (2.31%)	37 (6.57%)
Shanghai	7 (1.24%)	9 (1.60%)	9 (1.60%)	15 (2.66%)	9 (1.60%)	49 (8.70%)
Shenyang	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (0.89%)	0 (0.00%)	5 (0.89%)
Tianjin	5 (0.89%)	4 (0.71%)	5 (0.89%)	2 (0.36%)	0 (0.00%)	16 (2.84%)
Zhengzhou	6 (1.07%)	4 (0.71%)	7 (1.24%)	9 (1.60%)	18 (3.20%)	44 (7.82%)
Tatol	94 (16.70%)	130 (23.09%)	99 (17.58%)	124 (22.02%)	116 (20.60%)	563 (100%)
Drug costs	13,342.24 (16.08%)	18,420.57 (22.20%)	11,125.53 (13.41%)	20,861.09 (25.14%)	19,234.43 (23.18%)	82,983.86 (100%)
Cost per patient	141.94	141.70	112.38	168.23	165.81	147.40
Age, n (%)						
18-24	19 (3.37%)	21 (3.73%)	14 (2.49%)	33 (5.86%)	22 (3.91%)	109 (19.36%)
25-34	61 (10.83%)	82 (14.56%)	63 (11.19%)	60 (10.66%)	73 (12.97%)	339 (60.21%)
35-44	14 (2.49%)	26 (4.62%)	21 (3.73%)	29 (5.15%)	17 (3.02%)	107 (19.01%)
45-50	0 (0.00%)	1 (0.18%)	1 (0.18%)	2 (0.36%)	4 (0.71%)	8 (1.42%)
Average	29.02 ± 4.74	29.67 ± 6.04	30.26 ± 5.91	29.10 ± 8.72	29.98 ± 6.40	29.60 ± 6.59

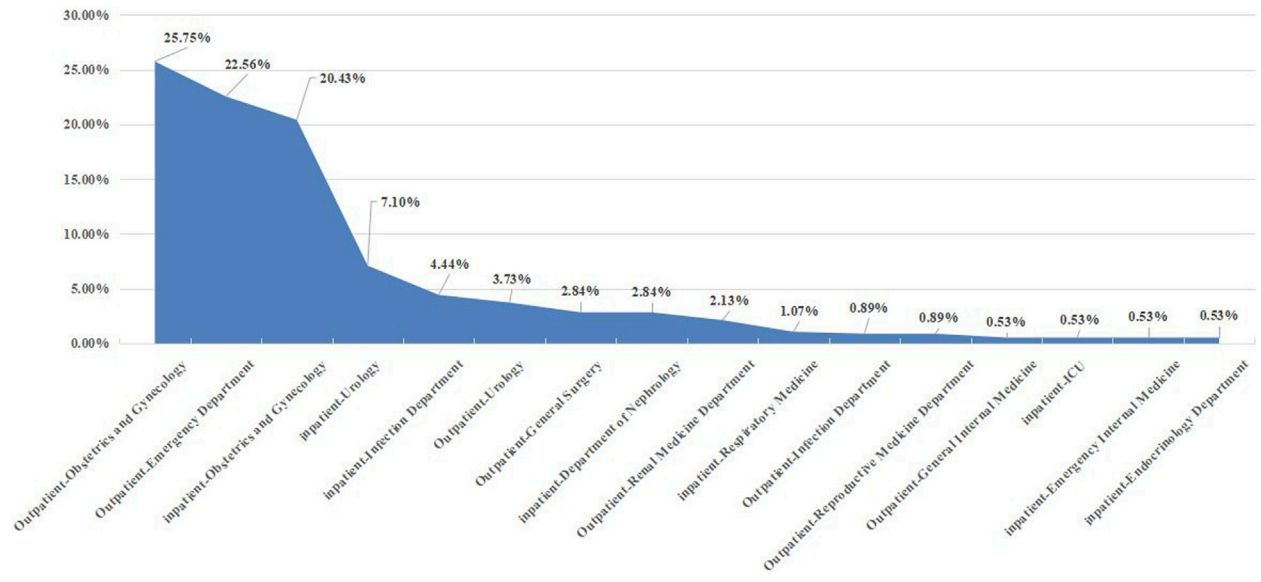

FIGURE 1
Proportion of outpatient/inpatient departments.

hormone prescriptions in accordance with the recommended drug labeling protocol and the most recent Chinese guidelines.

Statistical analysis was conducted using Excel 2013 and SPSS software (version 25; SPSSInc., Chicago, IL, United States). Continuous variables are shown as mean ± standard deviation. Categorical variables are presented as numbers and percentages. Demographic and prescription information was grouped into counts.

3 Results

3.1 Patients' demographic characteristics

We included 342 outpatient and 221 inpatient patients among 563 patients in this experiment based on the inclusion criteria, including prescription data such as region, reimbursement method, and expenses. Chengdu (36.59%), Guangzhou (27.72%), and

TABLE 2 Main therapeutic drugs of the patients (n = 563).

Drug classification	2018 (%)	2019 (%)	2020 (%)	2021 (%)	2022 (%)	Average (%)
Cephalosporins	8.67	14.67	16.67	14.00	13.17	13.43
Enzyme inhibitors	0.01	0.02	0.03	0.02	0.02	2.20
penicillins	1.83	0.83	0.67	0.67	1.67	1.13
Macrolides	0.83	1.33	0.67	0.17	0.17	0.63
Carbapenems	0.17	1.00	0.33	0.33	0.83	0.53
Nifurtyl	0.33	0.50	0.33	1.17	0.17	0.50
Clindamycins	0.33	0.50	0.00	0.50	0.67	0.50
Nitroimidazoles	0.33	0.50	0.50	0.67	0.00	0.50
Quinolones	0.33	0.50	0.50	0.33	0.33	0.50
Amtreonam	0.00	0.00	0.00	0.17	0.17	0.17
Furantoin	0.00	0.00	0.00	0.17	0.17	0.17
Linazolamide	0.00	0.17	0.00	0.00	0.17	0.17
Tegacyclin	0.00	0.17	0.00	0.00	0.00	0.17
Fosfomycin	0.00	0.00	0.00	0.17	0.00	0.17
Teicoplanin	0.00	0.00	0.00	0.17	0.00	0.17
vancomycin	0.17	0.00	0.00	0.00	0.00	0.17

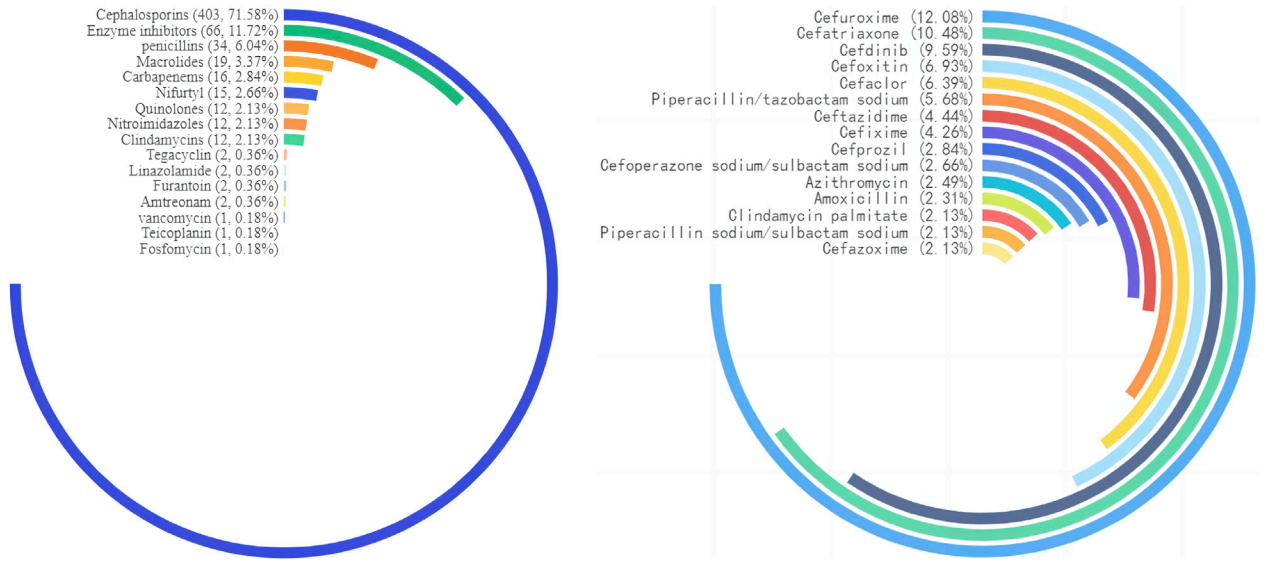

FIGURE 2
Circular bar chart map of drug type distribution.

Shanghai (8.70%) are the top three cities. Over a 5-year period, the average age was 29.60 6.59 years, with roughly 60.21% of women aged 25–34 years. Table 1 shows the demographic features of the patients. The main outpatient departments are Obstetrics and Gynecology (25.75%), Emergency (22.56%), and Urology (3.73%), whereas the main inpatient departments are Obstetrics and Gynecology (20.43%), Urology (7.10%), and Infection (4.44%). Figure 1 shows the departments that have three or more patients.

3.2 Drug classes used by patients

We counted the number of anti-infective medications used by each patient, and 37 of them used two types of antibiotics, including cephalosporins (403, 71.58%), enzyme inhibitors (66, 11.72%), and penicillin (34, 6.04%). The top five antibiotics were cefuroxime (68, 12.08%), ceftriaxone (59, 10.48%), and cefdinib (54, 9.59%), followed by cefoxitin (39, 6.93%) and cefaclor (36, 6.39%), as

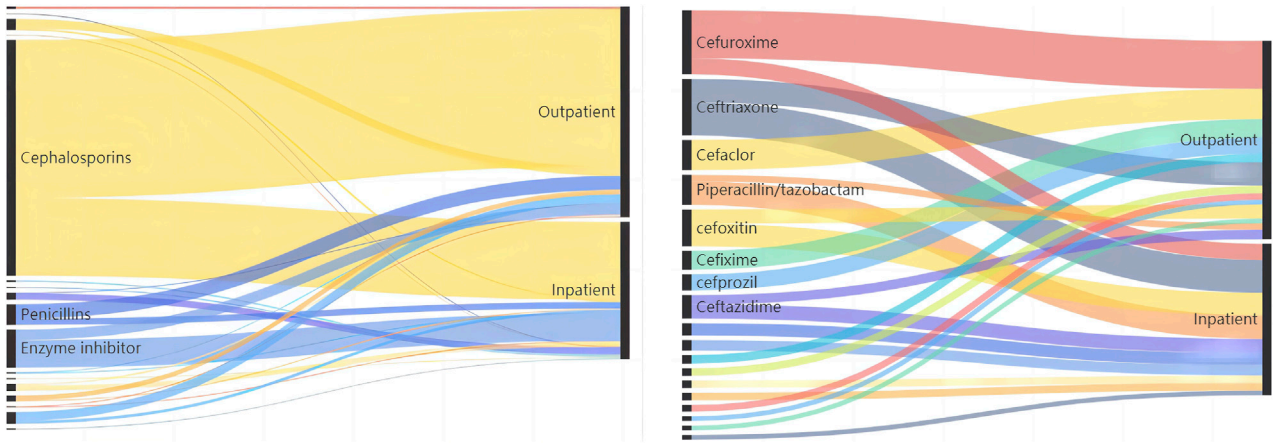

FIGURE 3
Top three anti-infective drug type/top ten anti-infective drug detected in the outpatient/inpatient patients.

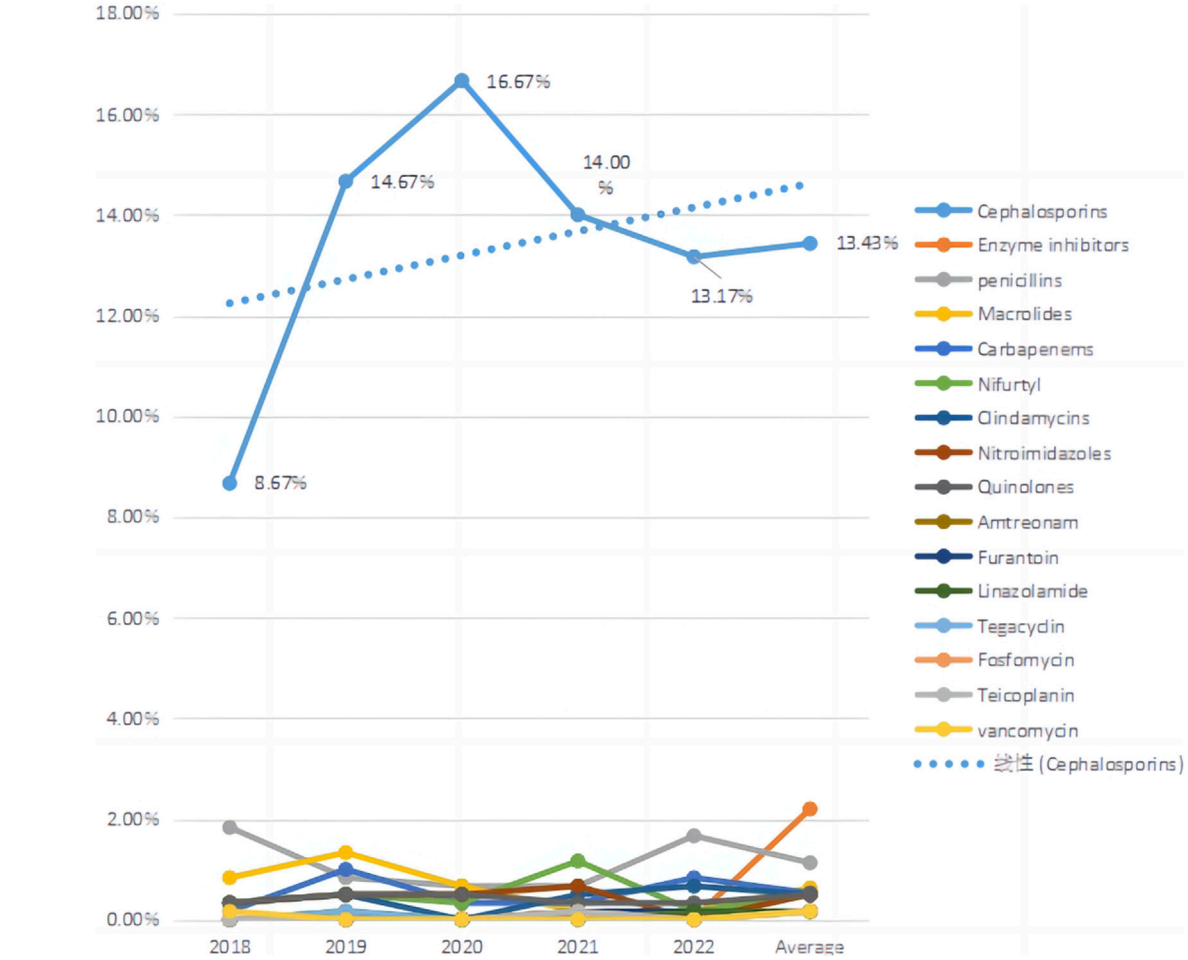

FIGURE 4
Trends in main therapeutic drugs use.

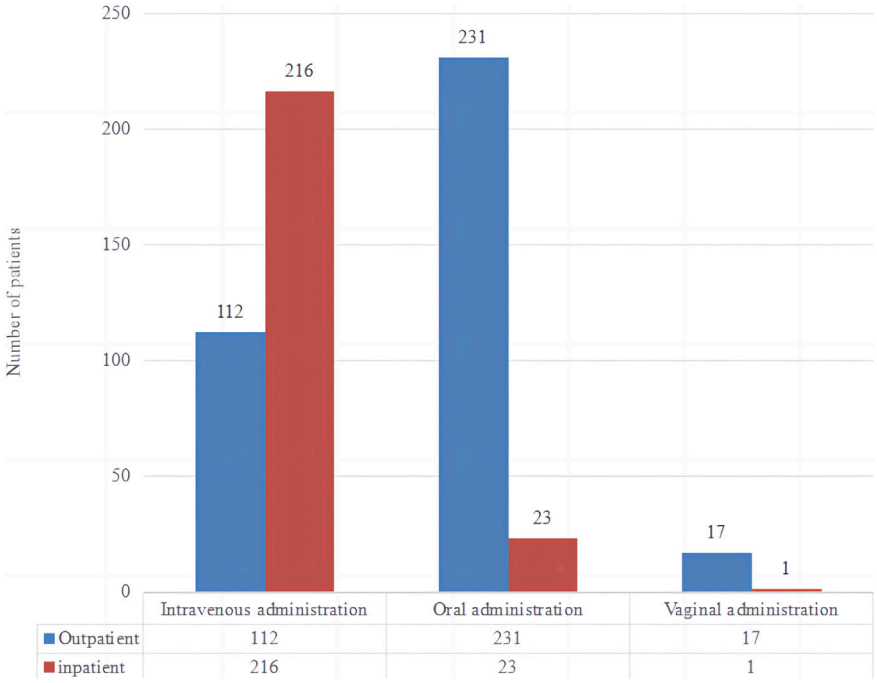

FIGURE 5
Amount of patient administration route.

shown in Table 2. Figure 2 depicts the distribution of all categories, whereas Figure 3 depicts the matching outpatient/inpatient services. During the 5-year period, there was no substantial change in the type and dosage of antibacterial medications. Cephalosporins were the most commonly used antibiotics overall, as illustrated by the trend chart in Figure 4.

3.3 Analysis of drug usage and dosage

When we analyzed the data, we discovered that there were primarily three types of medication based on the mode of administration: intravenous (328, 54.67%), oral (254, 42.33%), and vaginal (18, 3.00%). Please see Figure 5 for further information. According to the summary data, the dosage supplied was essentially reasonable. For a total of 20 patients, the combined usage and dosage were not given. The therapy period consists primarily of 1 day (234, 39.00%), 3 days (65, 10.83%), 5 days (21, 3.50%), and 7 days (24, 4.00%). Please see Figure 6 for further information.

3.4 Costs

We computed the total cost and cost *per capita* for patients utilizing various therapeutic medications. In terms of total cost, the top five medications were cephalosporins, carbapenems, enzyme inhibitors, quinolones, nifurtel, and the number of patients receiving comprehensive treatment drugs. The five most expensive medications *per capita* were cefuroxime, ceftriaxone, cefdinir, cefoxitin, and cefaclor. See Table 3 for details. Analyzing the data, it was found that the proportion of funds used for injection administration was 78.66%, the proportion for oral administration was 20.03%, and the proportion for vaginal administration was 1.32%.

4 Discussion

4.1 Demography characteristics

In the past 5 years, the majority of patients were between the ages of 25 and 34, with an average age of 29.60 6.60 years, according to statistical data. The age of treatment did not increase significantly, and there was no statistically significant change in age ($p > 0.01$). 50%–60% of pregnancies are diagnosed with a urinary tract infection, making it one of the most prevalent infections during pregnancy (Baraka et al., 2021). It can be separated into lower urinary tract infections, such as asymptomatic bacteriuria (ASB) or acute cystitis (AC), and upper urinary tract infections, such as acute pyelonephritis (APN) (Glaser and Schaeffer, 2015). Estimates place the incidence of ASB in expectant women between 2% and 10% (Bonkat et al., 2018). The exported data on pregnancy combined with UTI is relatively small compared to literature reports, which may be attributable to different diagnostic writing habits in different hospitals or to the large number of ASB patients who did not seek medical attention in a timely manner; simultaneously, there are significant differences in the proportion of patients in different regions due to a variety of factors. This may be the result of various diagnostic criteria, inconsistent calculation criteria, or regional variations in prevalence rates. This study will not draw any premature conclusions.

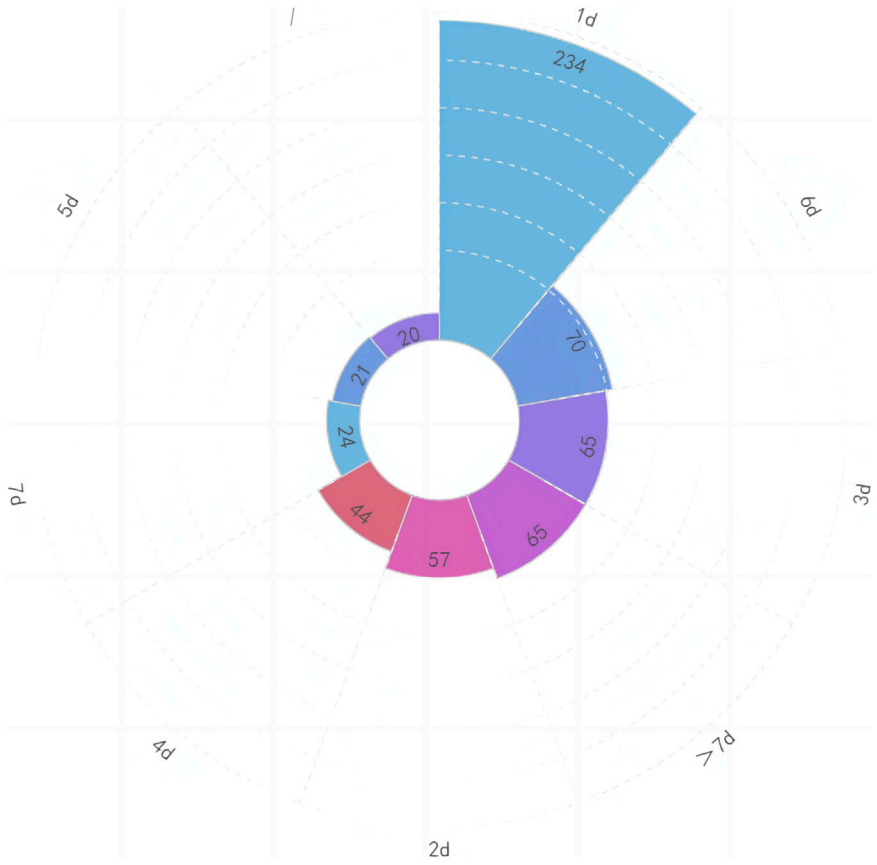

FIGURE 6
Amount of patient course of treatment.

The age of patients seeking medical treatment has not risen in the last 5 years, showing that patients' fertility demands are primarily centered around the age of 30. To some extent, the adjustment of childbearing time conventions indicates that as society develops, the number of people suffering from environmental pollution, increased work pressure, and delayed marriage and childbirth does not gradually increase, and people's ideological concepts are constantly improving and updating (Hu et al., 2004; Liang et al., 2021). Many women believe that age is a significant component in their childbirth decision-making and that they should complete the duty of delivering at a specific age. If they stray from this age convention and have difficulties giving birth, this becomes a major issue. The rising opportunity cost of women's fertility has made it difficult for them to achieve their fertility goals.

4.2 Types of drugs

According to data on antibiotic use by patients in major cities around the country, we discovered that outpatient and inpatient patients have the greatest variety and proportion of cephalosporins. When selecting antibiotics during pregnancy, consider the mother's and fetus's safety. According to the US Food and Drug Administration (FDA), the majority of the antibacterial medications indicated in International Guidelines are Class B, which indicates no adverse responses have been observed in well-controlled human pregnancy trials. There are limited guidelines that specify treatment for ASB and cystitis (Bonkat et al., 2018; Kranz et al., 2017; Betschart et al., 2020; de Cueto et al., 2017; Caron et al., 2018; Institute of Obstetricians and Gynaecologists, 2018; NICE NG109, 2022; NICE NG111, 2022). This could be due to shifting patterns of worldwide antimicrobial resistance, which means that therapy should be based on urine culture and sensitivity recommendations in laboratory reports, while also taking into account the authorized use of antibiotics during pregnancy.

The guidelines propose using furantoin, fosfomycin, and amoxicillin as the first line of treatment, followed by cephalosporin and amoxicillin (NICE NG109, 2022; Martinez et al., 2014). Distinct countries have distinct antibiotic preferences. A study of doctors in Denmark, Finland, Norway, and Sweden found that β-Lactam antibiotics (particularly pimecillin) and nitrofurantoin are their first-line treatments. In the United States, amoxicillin is commonly used, although trimethoprim and furantoin are favoured in Canada. Penicillin and cephalosporins are recommended in the United Kingdom (Christensen, 2000). This study's statistical material differs from earlier research in some ways. According to our findings, cephalosporins, penicillin, and enzyme inhibitors continue to have a significant advantage in the anti-infection therapy of pregnant women with UTI in China. This could be because

TABLE 3 Cost of therapeutic drugs use per person each year from 2018 to 2022.

Main therapeutic drugs	2018	2019	2020	2021	2022	Amount (RMB)	Frequency	Per capita (RMB)
Cephalosporins	6,548.17	9,136.52	8,170.11	8,881.42	4,813.26	37,549.48	403	93.17
Enzyme inhibitors	4,698.28	1,090.82	1829.78	4,183.2	0	11,802.08	66	178.82
penicillins	609.24	146.04	27.96	8.91	434.65	1,226.8	34	36.08
Macrolides	350.58	304.6	338.73	92.4	0	1,086.31	19	57.17
Quinolones	343.83	405.07	94.46	223	5,902.96	6,969.32	12	580.78
vancomycin	312.24	0	0	0	0	312.24	1	312.24
Carbapenems	259.2	4,033.14	311.98	503.68	7,527.48	12,635.48	16	789.72
Nifurtyl	164	174.86	131.72	2,346.51	41.4	2,858.49	15	190.57
Clindamycins	38.34	83.82	0	425.62	429.12	976.9	12	81.41
Nitroimidazoles	18.36	145.8	23.5	0	0	187.66	12	15.64
Tegacyclin	0	1800	0	0	0	1800	2	900.00
Linazolamide	0	1,420.56	0	0	0	1,420.56	2	710.28
Amtreonam	0	0	45.2	34.14	0	79.34	2	39.67
Furantoin	0	0	3.57	0.84	0	4.41	2	2.21
Teicoplanin	0	0	0	2015.55	0	2015.55	1	2015.55
Fosfomycin	0	0	0	48.56	0	48.56	1	48.56
Total	13,342.24	18,741.23	10,977.01	18,763.83	19,148.87	80,973.18	600	134.96

cephalosporins have good safety data (China Medical Women's Association, 2017), However, drugs such as furantoin, fosfomycin, and others with higher recommended usage levels in other countries are relatively lower in China (Gupta et al., 2011). Doctors may prescribe enzyme inhibitors to individuals who are suffering from severe symptoms.

The selection of medications for the treatment of UTIs during pregnancy must take the safety of the mother and fetus into account (Bookstaver PB et al., 2015). The majority of antibiotics can cross the placenta, and it is crucial to determine whether they will have negative effects on the fetus. However, there is limited research on the effects of medications on the fetus during pregnancy. The majority of information on drug safety comes from animal studies and observational studies. The FDA's classification of pregnancy lacks high-quality data. Despite the dearth of evidence, numerous antibacterial drugs, such as penicillin, cephalosporin, clindamycin, etc., have been used for several years during pregnancy without adverse maternal or fetal effects. Meta-analysis did not prove which antibacterial drug is best for ASB and symptomatic UTIs; therefore, empirical treatment is determined based on antibacterial spectrum, antibacterial activity, and pathogen culture results, as well as the cost (Gupta et al., 2011; Widmer et al., 2015). Few drugs have been definitively demonstrated safe. Therefore, care should be taken to minimize the number of drugs used, only when the benefits outweigh the risks, selecting drugs with the best safety profile, and employing the lowest effective dose and shortest treatment course.

Penicillin has been widely used and its safety has been confirmed in many studies (China Medical Women's Association, 2017), including penicillin G, ampicillin, and amoxicillin. Although bacterial resistance is common, it is still the most frontline treatment drug. Cephalosporins are also a class of antibiotics with high safety, and third-generation cephalosporins are commonly used in empirical treatment. Furantoin is very effective in treating lower UTI, and its safety is controversial. The US neonatal defect prevention study suggests that furantoin is associated with congenital malformations such as eye deformities, atrial septal defects, and cleft lip and palate. Looking at it correctly, only 35% of patients can recall the name of the medication used. ACOG believes that it should be used reasonably in the early stages of pregnancy, and can be used as a first-line treatment plan in the middle and late stages of pregnancy. Between 1999 and 2009, a total of 105,492 pregnant women were included, and a total of 6,561 fetuses and newborns were diagnosed with congenital malformations. The incidence of malformations was 5.7% (76 of 1,329) in the exposed group and 6.2% (6,485 of 104,163) in the unexposed group, with no statistically significant differences. Exposure to furantoin in early pregnancy did not increase the incidence of fetal malformations (Goldberg et al., 2013). Phosphomycin is a broad-spectrum antibacterial drug that plays an increasingly significant role in lower urinary tract infections. Trimethoprim sulfamethoxazole is not recommended as a first-line solution. The US neonatal defect prevention study suggests that SMZ is more teratogenic than other drugs, but other studies do not recognize it. ACOG believes that if there are no other drugs available in early pregnancy, this product can be chosen. In addition to teratogenesis, hyperbilirubinemia and nuclear jaundice may occur in late pregnancy.

A systematic evaluation in the Cochrane Database analyzed the most effective treatment methods for symptomatic UTI (cystitis and pyelonephritis) during pregnancy by analyzing the cure rate, recurrence rate, incidence of premature birth, and necessity for antibiotic replacement. The results showed that all the antibiotics studied were effective and had few complications. There is not enough evidence to recommend a specific treatment plan. This study shows that China places more emphasis on effectiveness and safety in the treatment process, with less use of drugs such as furantoin and fosfomycin. Further consideration may be needed on issues such as bacterial resistance (Keating, 2013).

4.3 Usage and dosage

In this study, cephalosporins and penicillin are first-line medications for the treatment of UTI during pregnancy in both outpatient and inpatient patients. A total of 20 patients' usage and dosage were not specified. Physiological changes in the mother can affect pharmacokinetics and decrease serum drug concentration, increase intravascular and extravascular fluid volume, increase renal blood flow velocity, GFR, and increase fetal drug distribution. In our study, however, we discovered that the dosage provided to pregnant patients stayed at adult levels with no significant modifications. More research is needed to understand whether the dosage of UTI should be increased during pregnancy or adjusted dependent on body weight.

There appears to be no difference in treatment outcomes between 3-day short courses and 7-day long courses, and short courses can reduce costs and side effects, have higher compliance, and reduce fetal drug exposure (Gupta et al., 2011). In our study, the majority of patients were treated for a single day. This may be because the majority of patients had ASB or lower UTI, which did not progress to upper UTI. It may also be due to patients' concerns regarding the influence of excessive antibiotic use on pregnancy outcomes.

4.4 Drug amount

Cephalosporins, carbapenems and enzyme inhibitors account for the highest amount of money used by patients with anti infective drugs. Teicoplanin, tigecycline and carbapenems rank first in terms of *per capita* cost. New anti infective drugs account for the highest *per capita* cost. The drugs with the top sales amount are commonly used drugs, including cephalosporin antibiotics. With the promotion of national volume procurement, many cephalosporin antibiotics have been included in the volume variety, which is relatively cheap compared to other types of drugs, but the frequency of use is also high. The *per capita* medication amount is significantly out of sync with DDDs, because these types of drugs are new types of antibiotics and special grade antibiotics, with relatively high prices. There is a certain trend in drug use in research data from different years. The changes in amount in different years and drug consumption structure show consistency in drug use in hospitals in different regions. It can be seen that everyone has a general consensus on the choice of main treatment drugs. The statistical results show that patients who receive intravenous medication have the highest proportion of medication costs, as compared to those who take oral medication, patients who use intravenous medication have a more severe condition, a larger dosage, and a longer course of treatment, all of which can lead to an increase in drug costs.

5 Conclusion

Our study counted the prescriptions/medical orders of patients with pregnancy complicated with UTI from 2018 to 2022. The average age of patients to see a doctor did not increase significantly from the 5 years of statistics. The opportunity cost of female fertility increased, which seriously hindered the realization of fertility desire. The overall medication selection is relatively reasonable, and the first-line cephalosporin antibiotics recommended by the guidelines are also used in relatively high amounts in this study. However, it should be noted that drugs recommended or used in other countries such as fosfomycin and furantoin are extremely low in China. However, our statistical data shows that some expensive drugs can increase the economic burden on patients. On the premise of meeting clinical needs, how to further improve the level of rational use of drugs in outpatient clinics, achieve economic, safe and effective use of drugs, and thus reduce the economic burden on patients will be the focus of future work.

For the treatment of UTIs during pregnancy, it is not possible to draw the conclusion of which drug is the most effective or safe. Empirical treatment is based on antibacterial spectrum, antibacterial activity, pathogenic results, and cost. In addition to well-established penicillin and cephalosporins, there is increasing evidence that furantoin, fosfomycin, and sulfonamide drugs can be applied to UTIs.

The follow-up after ASB treatment includes close supervision and prophylactic treatment with antibiotics, and there is currently no evidence to recommend which regimen is the optimal for preventing recurrence of UTI during pregnancy.

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 authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants and legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JJ: Funding acquisition, Writing–original draft. CL: Writing–review and editing. YH: Software, Writing–review and

editing. JP: Formal Analysis, Writing–review and editing. JZ: Funding acquisition, Writing–review and editing.

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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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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Teodora Alexa-Stratulat,
Grigore T. Popa University of Medicine and Pharmacy, Romania
Sirajudheen Anwar,
University of Hail, Saudi Arabia

*CORRESPONDENCE
Zhenwei Yu,
yzw_srrsh@zju.edu.cn
Minxian Li,
liminxian1985@126.com

†These authors have contributed equally to this work

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Prevalence of inappropriateness of elemene injection for hospitalized cancer patients: a multicenter retrospective study

Mingzheng Cen[1†], Guojun Jiang[2†], Yuhua Zhao[2], Zhenwei Yu[3*] and Minxian Li[2*]

[1]The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China, [2]Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou, China, [3]Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Background: Elemene injection could provide clinical benefit for the treatment of various cancers, but the clinical evidence is weak. Thus, its wide use in China has raised concerns about the appropriateness of its use.

Methods: This was a multicenter retrospective study to evaluate the prevalence of inappropriateness of elemene injection for hospitalized cancer patients. Patients who met the inclusion criteria were retrospectively included, and demographic characteristics were extracted from the hospital information systems. The inappropriateness of elemene injection use was assessed using the preset criteria, and the prevalence was calculated. Multivariate logistic analysis was applied to identify any factors associated with inappropriate use.

Results: A total of 275 patients were included in the analysis. The median age was 62 years, and 30.9% were females. The most common cancer was lung cancer (24.0%), and 68.2% of the patients were receiving chemotherapy. The overall prevalence of inappropriateness was 61.8%. The most common reason for inappropriateness was inappropriate indications, and the second was inappropriate doses. Age and oncological department were significant risk factors associated with inappropriate use, while lung cancer, liver cancer and admission to cardiothoracic surgery were associated with a low risk of inappropriate use.

Conclusion: The prevalence of inappropriateness among hospitalized elemene injection users was high. More efforts, especially those to improve the appropriateness of indications, should be made to improve the rational use of elemene, as well as other complementary medicines. Physicians should take caution to avoid inappropriate use when prescribing drugs with limited clinical evidence.

KEYWORDS

appropriateness, elemene injection, cancer, chemotherapy, rational

Introduction

Despite promising advances in cancer treatment in recent years, many challenges remain, such as drug resistance, metastasis, and severe adverse events associated with anticancer drugs (Ramos-Casals et al., 2020; Bagchi et al., 2021). People have tried to find new strategies to treat ethnodrugs, especially traditional Chinese medicines (Su et al., 2020). Elemene is the major active ingredient extracted from the rhizome of *Curcuma wenyujin* (Zhai et al., 2019). Its formulations, including oral emulsion and injection, were approved by the CFDA for the treatment of various cancers approximately 20 years ago (Bai et al., 2021). Elemene injection yields three isomers (δ, α, β), and β-elemene (1-methyl-1-vinyl-2,4-diisopropenyl-cyclohexane) is the predominant component. It has shown various antitumor effects in preclinical studies. Elemene can directly inhibit the proliferation and growth of various tumor cells; for example, it inhibits human cervical cancer cells in a concentration- and time-dependent manner, and the mechanism may be associated with the upregulation of P15 expression and the downregulation of cyclin D1 expression (Wang et al., 2018). A previous study also confirmed that elemene could induce apoptosis and exhibit antitumor effects (Liu et al., 2017). Other effects involved in the antitumor effect of elemene include the inhibition of tumor cell invasion and metastasis, reversal of multidrug resistance, enhancement of chemoradiotherapy sensitization, activation of protective autophagy, and regulation of the immune system (Xu et al., 2018; Qureshi et al., 2019; Tong et al., 2020; Bai et al., 2021; Tan et al., 2021). Many meta-analyses have also confirmed the benefit of elemene as a combined therapy or adjuvant therapy for the treatment of cancers (Wang et al., 2019; Liu et al., 2020). However, most of the included clinical studies were of low quality, and a recent umbrella review concluded that the benefits of elemene injection need to be proven by additional convincing trials. Moreover, no other regulatory agencies, such as the FDA or EMA, have approved the clinical use of elemene. Thus, we believe that the clinical evidence for elemene injection is weak, the benefits are uncertain, and elemene injection should be administered only to specific patients.

The use of complementary medicine, including elemene injection, is common in cancer patients and results in a substantial economic burden (Nie et al., 2023). This has raised concerns about the appropriateness of elemene use. Inappropriate use of drugs occasionally leads to the absence of clinical effects, but in most circumstances, adverse effects can occur, causing aggravation of the illness, additional diagnostic testing, and increased costs for the patient and health welfare system (Galimberti et al., 2022). Potential inappropriate drug use was significantly associated with a range of health-related and system-related outcomes (Mekonnen et al., 2021). The appropriateness of antibiotics, proton pump inhibitors, and some other drugs was assessed from different perspectives, and the results were unsatisfactory to various degrees (Khatter et al., 2021; Ardoino et al., 2022; Butler et al., 2022). Currently, there are few data regarding the appropriateness of elemene injection. These data are important for the improved application and management of elemene injection. We subsequently carried out this multicenter retrospective study to determine the prevalence of inappropriateness of elemene injection use in hospitalized patients with cancer.

Materials and methods

Study design and ethical approval

This was a multicenter retrospective study in which the prevalence of inappropriateness of elemene injection was evaluated in hospitalized cancer patients. The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, with reference number 2023-0293. Informed consent was waived as part of the approval due to the retrospective nature of the study.

Patient inclusion criteria

Patients were retrospectively searched in the hospital information system according to the following criteria: 1) had a diagnosis of cancer; 2) were admitted to Affiliated Xiaoshan Hospital, Hangzhou Normal University or Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; 3) were hospitalized from January 2021 to December 2021; and 4) received elemene injection treatment. The researchers reviewed the medical history, checked the eligibility of the patients and included eligible patients.

Data collection

The following data were extracted from the hospital information system and medical history: age, sex, diagnosis, admission department, days of hospital stay, dose regimen of elemene injection, and combined therapy.

Assessment of inappropriateness

The criteria for the inappropriateness of elemene injection use were set according to the drug label and clinical evidence. The detailed criteria were as follows: 1) Indication. The indications for elemene injection were limited to lung cancer, liver cancer, esophageal cancer, nasopharyngeal carcinoma, brain cancer, metastatic tumors of bone, gastric cancer, malignant pleural effusion and ascites. It would be inappropriate to use elemene for the treatment of other types of cancer. 2) Dosage and administration. Elemene injection should be administered intravenously at a dose of 352–528 mg every day. A dose that is not in the range is treated as inappropriate. For the treatment of malignant pleural effusion and ascites, these agents should be injected locally. The treatment duration should be no more than 21 days. 3) Contradiction. Patients with high fever or uncontrolled infection should not receive elemene. It is inappropriate to prescribe elemene injection to these patients. 4) Special patients. Patients who are pregnant or breastfeeding should be carefully evaluated for the risk and benefit of elemene use. 5) Caution. Patients with thrombocytopenia or bleeding risk should be carefully evaluated for the benefit and risk of elemene use. If no information about the evaluation was found in the patient's medical history, it was considered inappropriate. The inappropriateness of each patient

TABLE 1 Demographic characteristics of the included patients.

Characteristic	Total
Age (years)	62 (55–67)
Sex	
Female	85 (30.9%)
Male	190 (69.1%)
Diagnosis	
Lung cancer	66 (24.0%)
Colorectal cancer	35 (12.7%)
Gastric cancer	30 (10.9%)
Liver cancer	28 (10.2%)
Pancreatic cancer	26 (9.45%)
Throat cancer	23 (8.36%)
Esophageal cancer	22 (8.00%)
Biliary tract cancer	16 (5.82%)
Genital tract tumors	10 (3.64%)
Other cancer	19 (6.90%)
Department	
General surgery	97 (35.3%)
Radiosurgery department	83 (30.2%)
Oncology department	58 (21.1%)
Cardiothoracic surgery	37 (13.5%)
Length of hospital stay (days)	7 (4–17)
Dosing regimen of Elemene	
Dose (mg)	440 (264–528)
Duration of therapy (days)	3 (2–5)
Combined treatment	
Chemotherapy	199 (68.2%)
Radiotherapy	28 (9.58%))
Surgery	21 (6.84%)
Immunotherapy	15 (5.45%)
No treatment	45 (15.4%)

was assessed according to the inappropriateness criteria and personal medical history. If any criteria were met, it would be concluded that the elemene use in that patient was inappropriate.

Statistical analysis

The overall prevalence of inappropriateness was calculated as the percentage of patients who did not fully meet the appropriate criteria for elemene injection. The patients were subsequently divided into two groups according to the appropriateness of the treatment. Univariate logistic analysis was performed first to test the difference in patient characteristics between groups, and any variables with a p-value less than 0.05 were subjected to stepwise multivariate logistic analysis, which eliminated any variables with a p-value larger than 0.05 step by step. The remaining variables in the multivariate logistic analysis were found to be independent factors associated with the appropriate use of elemene. The statistical analysis was performed using SPSS software.

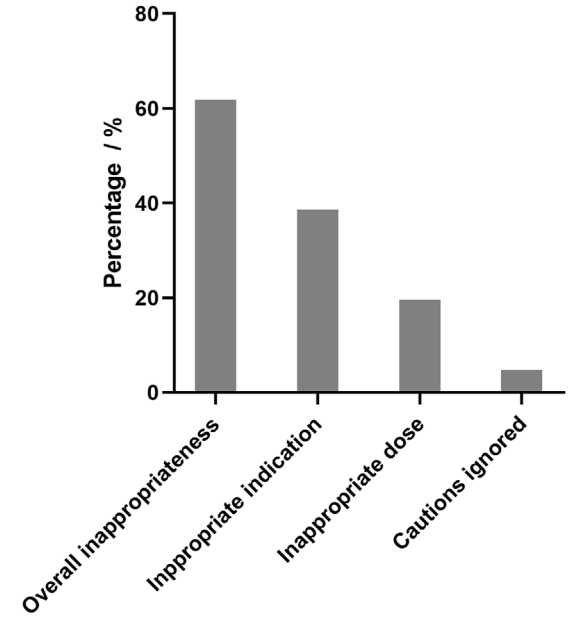

FIGURE 1
Overall prevalence of inappropriateness of elemene injection use in hospitalized patients with cancer. Appropriate indication means elemene injection can only be used for approved types of cancers, which are limited to lung cancer, liver cancer, esophageal cancer, nasopharyngeal carcinoma, brain cancer, metastatic tumors of bone, gastric cancer, malignant pleural effusion and ascites. Appropriate dose means elemene injection is administered intravenously at a dose of 352–528 mg every day. Caution ignored means elemene injection were used to patient with risk without evaluation. Patients with thrombocytopenia or bleeding risk should be carefully evaluated for the benefit and risk of elemene use.

Results

Patient inclusion

A total of 275 patients met the inclusion criteria and were included in the analysis. The patient demographic characteristics are shown in Table 1. Most of the patients were old. Various cancers were included, while most common was lung cancer. Elemene injection was combined with chemotherapy in the majority of patients. Notably, the median treatment length was 3 days.

Prevalence of inappropriateness of elemene injection use

As shown in Figure 1, the overall prevalence of inappropriate elemene injection use was 61.8%. The most

TABLE 2 Demographics of the patients in each group and logistic regression analysis.

Variable	Appropriate (n = 105)	Inappropriate (n = 170)	*p*-Value†	*p*-Value‡	OR‡
Age (years)	58 (51–65)	63 (56–67)	0.001	0.028	0.96 (0.93–1)
Sex					
Female	23 (21.9)	62 (36.47)	0.011	0.224	
Male	82 (78.1)	108 (63.53)	-		
Diagnosis*					
Lung cancer	44 (41.9)	22 (12.94)	<0.001	0.001	4.71 (1.91–11.58)
Gastric cancer	12 (11.43)	18 (10.59)	0.828		
Liver caner	22 (20.95)	6 (3.53)	<0.001	<0.001	12.02 (4.31–33.55)
Throat cancer	13 (12.38)	10 (5.88)	0.064		
Esophageal cancer	12 (11.43)	10 (5.88)	0.105		
Colorectal cancer	0	35 (20.6)	-		
Pancreatic cancer	0	26 (15.3)	-		
Biliary tract cancer	0	16 (9.41)	-		
Genital tract cancer	0	10 (5.88)	-		
Other	2 (1.90)	17 (10.0)	-		
Department					
General surgery	33 (31.43)	64 (37.65)	0.295		
Radiosurgery department	34 (32.38)	49 (28.82)	0.533		
Oncology department	3 (2.86)	55 (32.35)	<0.001	0.001	0.12 (0.03–0.43)
Cardiothoracic surgery	35 (33.33)	2 (1.18)	<0.001	<0.001	29.37 (6.24–138.18)
Length of stay (days)	6 (4–10)	10 (4–24)	<0.001	0.188	
Duration of therapy (days)	3 (2–4)	3 (2–6)	0.055		
Combined treatment					
Chemotherapy	85 (80.95)	114 (67.06)	0.017	0.976	
Radiotherapy	6 (5.71)	22 (12.94)	0.061		
Surgery	9 (8.57)	12 (7.06)	0.647		
Immunotherapy	12 (11.43)	3 (1.76)	0.008	0.004	6.94 (1.67–28.84)
No combined treatment	10 (9.52)	35 (20.59)	0.019	0.879	

†*p*-value of univariate logistic analysis; ‡*p*-value and odds ratio of multivariate logistic analysis.
*Statistical analysis was not carried out for unapproved indications of elemene injection.

common cause of inappropriate use is inappropriate indications. Many types of cancer, such as colorectal cancer and pancreatic cancer, have not been approved for treatment, and it is inappropriate to use elemene in these patients. The personal characteristics of appropriate use and inappropriate use are shown in Table 2. According to the results of the multivariate analysis, age and oncological department status were significant risk factors associated with inappropriate use, while lung cancer, liver cancer and admission to a cardiothoracic surgery were associated with a low risk of inappropriate use.

Discussion

To the best of our knowledge, this is the first study to evaluate the prevalence of inappropriateness of elemene injection in hospitalized cancer patients. Surprisingly, the

overall inappropriateness rate was high. Only 38.2% of the patients received elemene injection appropriately, and the main reason for inappropriate use was inappropriate indications. Our results highlight the need to pay attention to the rational use of elemene injection, and efforts should be made to reduce inappropriate use.

The prevalence of inappropriateness was higher than expected. This raised concerns about its rational use, as well as other complementary medicines. Although the outcome of inappropriate use of elemene injection was not evaluated in this study, previous studies had proved that inappropriate medicine use in cancer patients always associated with high risk of adverse effects and unfavorite outcome of therapy (Krečak et al., 2023; Mohamed et al., 2023). The reason for the prevalent inappropriate use of elemene injection might be as follows. First, physicians do not always care about the indications for complementary medicine, including elemene injection. Although elemene has various antitumor effects, its approved indications are limited. Physicians should be informed that elemene is not suitable for all types of cancer. Second, similar to other medicines, marketing efforts can increase the unnecessary use of elemene injection and increase the overall prevalence of inappropriateness (Yu et al., 2020). The healthcare system should also be aware of this effect. Finally, patients in East Asia have expectations for complementary medicine and would like to receive these medicines voluntarily (Sun et al., 2018).

The main cause of inappropriateness was inappropriate indication, and colorectal cancer was the most common nonindication use of elemene. The effect of elemene on colorectal cancer has been supported by preclinical studies, but clinical evidence for this cancer is rare (Chen et al., 2020; Wang et al., 2022). It is unclear whether patients with colorectal cancer could benefit from elemene treatment. Other nonindication uses of elemene, such as in pancreatic carcinoma and biliary tract cancer, have only been investigated in in vitro studies (Long et al., 2019; Wu et al., 2022). These findings indicated that efforts to reduce elemene use in patients without suitable indications should be made preferentially. Other reasons for inappropriateness were the inappropriate dose and administration to cautious patients without evaluation. Patients sometimes receive elemene at a dose lower than suggested, and this should be avoided because no evidence is available. Despite the good safety of elemene in the treatment of cancers, it can also cause severe adverse effects (Gao et al., 2018). Adverse effects more easily occur in patients under physio-pathological conditions. Patients with thrombocytopenia should be carefully evaluated when dosing elemene. Unfortunately, it is overlooked in clinical practice according to the results of our study.

The appropriateness of these treatments is significantly greater in patients with lung cancer and liver cancer. This may be associated with additional experience using elemene injection for treating these cancers. As mentioned above, lung cancer and liver cancer are approved indications of elemene injection. Numerous clinical studies have been carried out to assess the efficacy of elemene in treating lung cancer and liver cancer in combination with chemotherapy or radiotherapy (Jiang et al., 2017; Yao et al., 2019; Yang et al., 2022). The appropriateness of elemene use differed greatly among departments. Interestingly, admission to the oncological department was associated with a high risk of inappropriate use, but admission to the cardiothoracic surgery department was associated with a low risk of inappropriate use. Physicians in the oncology department specialize in cancer treatment, but they fail to appropriately use elemene injection. The reason for better appropriateness of surgery in the cardiothoracic surgery department is that lung cancer, the most common indication for elemene injection, is the main cancer type in this department.

Notably, older age is an independent risk factor for inappropriate use of elemene injection. Thus, more attention should be given to these patients, as older patients more easily develop adverse drug events, especially when inappropriate drugs are used (Yao et al., 2019).

This study has several limitations. The included centers were limited. The effect of the appropriateness of elemene use on clinical outcome was not investigated in the present study. Moreover, bias may exist due to the retrospective nature of the study.

Conclusion

This study assessed the prevalence of inappropriateness of elemene injection use in hospitalized patients with cancer. The results indicated that the overall prevalence of inappropriateness was as high as 61.8%. The main reason for inappropriateness was inappropriate indications. Moreover, several independent factors associated with inappropriate use were identified. This study raised the concern of the inappropriateness of elemene injection, as well as other complementary medicines. More efforts should be made to understand the status and improve the appropriate use of elemene injection. Physicians should make carefully evaluation and follow the guidance of inserts when prescribing drugs with limited clinical evidence, such as elemene injection, to avoid inappropriate use.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MC: Data curation, Formal Analysis, Investigation, Resources, Visualization, Writing–original draft. GJ: Formal analysis, Investigation, Writing–review and editing. YZ: Data curation, Formal Analysis, Investigation, Resources, Visualization, Writing–original draft. ZY: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Writing–original draft, Writing–review and editing. ML: Conceptualization, Methodology, Resources, Supervision, Validation, Writing–original draft.

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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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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Rafal Bobinski,
University of Bielsko-Biała, Poland
Aikaterini Andreadi,
University of Rome Tor Vergata, Italy

*CORRESPONDENCE
Guohua Cheng,
cgh1203@jnu.edu.cn

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Sotagliflozin versus dapagliflozin to improve outcome of patients with diabetes and worsening heart failure: a cost per outcome analysis

Weichen Zhang, Meichen Yu and Guohua Cheng*

Department of Pharmacy, Jinan University, Guangzhou, China

Background and aim: Dapagliflozin inhibits the sodium-glucose cotransporter protein 2 (SGLT-2), while sotagliflozin, belonging to a new class of dual-acting SGLT-1/SGLT-2 inhibitors, has garnered considerable attention due to its efficacy and safety. Both Dapagliflozin and sotagliflozin play a significant role in treating worsening heart failure in diabetes/nondiabetes patients with heart failure. Therefore, this article was to analyze and compare the cost per outcome of both drugs in preventing one event in patients diagnosed with diabetes-related heart failure.

Method: The Cost Needed to Treat (CNT) was employed to calculate the cost of preventing one event, and the Number Needed to Treat (NNT) represents the anticipated number of patients requiring the intervention treatment to prevent a single adverse event, or the anticipated number of patients needing multiple treatments to achieve a beneficial outcome. The efficacy and safety data were obtained from the results of two published clinical trials, DAPA-HF and SOLOIST-WHF. Due to the temporal difference in the drugs' releases, we temporarily analyzed the price of dapagliflozin to calculate the price of sotagliflozin within the same timeframe. The secondary analyses aimed to assess the stability of the CNT study and minimize differences between the results of the RCT control and trial groups, employing one-way sensitivity analyses.

Result: The final results revealed an annualized Number Needed to Treat (aNNT) of 4 (95% CI 3-7) for preventing one event with sotagliflozin, as opposed to 23 (95% CI 16-55) for dapagliflozin. We calculated dapagliflozin's cost per prevented event (CNT) to be $109,043 (95% CI $75,856-$260,755). The price of sotagliflozin was set below $27,260, providing a favorable advantage. Sensitivity analysis suggests that sotagliflozin may hold a cost advantage.

Conclusion: In this study, sotagliflozin was observed to exhibit a price advantage over dapagliflozin in preventing one events, cardiovascular mortality, or all-cause mortality in patients with diabetes.

KEYWORDS

sotagliflozin, dapagliflozin, heart failure, outcome analysis, diabetes

1 Introduction

Heart failure (HF) is a complex clinical syndrome characterized by symptoms and/or signs resulting from structural and/or functional abnormalities of the heart. In most cases, it refers to a condition where the myocardial contractile function is diminished, leading to an inability to achieve the metabolic needs of the body. (Owan et al., 2006; Fonarow et al., 2007; Pitt et al., 2014). According to data from the American Heart Association (AHA) between 2017 and 2020, the total number of individuals aged 20 and above with heart failure was 6.7 million. It is projected that from 2012 to 2030, the incidence of heart failure (HF) will grow by 46%, with the overall proportion of heart failure patients rising from 2.4% to 3.0% over the course of a decade. This is expected to affect over 8 million adult patients. (Tsao et al., 2023). Diabetes stands as a significant risk element in the terms of heart failure, with approximately 30% of patients diagnosed with heart failure also having type 2 diabetes (T2DM). (Thrainsdottir et al., 2005; Lehrke and Marx, 2017). The data in a study from the National Hospital Quality Monitoring System (HQMS) revealed a rapid increase in the proportion of patients experiencing heart failure syndrome among those with both type 1 diabetes (T1DM) and T2DM in tertiary hospitals from 2013 to 2017. (Li et al., 2022).

Dapagliflozin falls within the category of medications known as sodium-dependent glucose transporters 2 (SGLT2) inhibitors. By the functions of SGLT2, the reabsorption of glucose was reduced in the renal tubules, resulting in a significant excretion of glucose in the urine and consequently reducing the levels of blood glucose. Additionally, the DAPA-HF study has established its efficacy in patients diagnosed with heart failure and reduced ejection fraction (McMurray et al., 2019) Patients treated with dapagliflozin had lowered the threats of worsening HF or/and cardiovascular-related death compared to those staying in the placebo group. However, concerns still exist regarding its cardiovascular (CV) safety. In type 2 diabetes patients with or at risk of atherosclerotic CV disease, dapagliflozin lowered the rates of CV death or hospitalization due to heart failure. (Cohen et al., 2023). Nevertheless, it did not significantly lower the incidence of major adverse cardiovascular events (MACE) compared to the placebo arm. (Wiviott et al., 2019; Palmer et al., 2021).

Sotagliflozin can block intestinal SGLT1 and renal SGLT2 glucose transporters, thereby reducing the absorption of glucose in the intestines and consequently reducing postprandial glucose and insulin concentrations, (Powell et al., 2020), By increasing the renal excretion of glucose, sotagliflozin lowers the level of glucose. Serving as an adjunct to insulin, the double-acting inhibitor of SGLT1 and SGLT2, sotagliflozin can enhance the manage of blood glucose levels in patients diagnosed with type 1 diabetes. Simultaneously, it reduces insulin dosage, promotes weight loss, significantly decreases the occurrence of severe hypoglycemia, and does not increase the probability of hypoglycemia occurrence. This enables more individuals with type 1 diabetes to meet therapeutic objectives without gaining weight within a specified period. (Sands et al., 2015; Buse et al., 2018; Danne et al., 2018; Danne et al., 2019; Rodbard et al., 2020). Additionally, oxidative stress, characterized by an excess of oxidative species, has been identified as one of the primary mechanisms contributing to the pathology of type 2 diabetes. (Andreadi et al., 2022).This process results in the production of advanced glycosylated end products (AGEs) or activation of the polyol pathway, which bind to receptors and induce the expression of adhesion molecules, impairing endothelial function and elevating the risk of cardiovascular disease. (Nakamura et al., 1993; Schmidt et al., 1995; Andreadi et al., 2023). The overproduction of reactive oxidative species (ROS) and reactive nitrogen species (RNS), or an imbalance between ROS and cellular antioxidants, contributes to the development of various diseases. (D'Autréaux and Toledano, 2007). Hyperglycemia free fatty acids (FFA), and pancreatic beta cell insulin release directly or indirectly induce the overproduction of ROS, disrupting intracellular homeostasis. (Andreadi et al., 2023). Animal model studies have identified SGLT-2i as a potent antioxidant drug capable of reducing oxidative sress by modulating the production of pro-oxidant enzymes such as Nox, eNOS, and xanthine oxidase. (Kawanami et al., 2017). Additionally, the study found that sotagliflozin significantly reduced cardiovascular outcomes compared to the control group, with a reduction from 76.3% to 51.0% in the primary outcome. (Docherty and McMurray, 2021; Andreadi et al., 2023). Among type 1 diabetes patients receiving insulin treatment, a higher percentage of patients in the sotagliflozin group achieved glycated hemoglobin levels below 7.0%, with no occurrence of severe hypoglycemia or diabetic ketoacidosis, compared to the placebo group. (Garg et al., 2017). The 2021 European Society of Cardiology (ESC) Diabetes Guidelines designate SGLT2 inhibitors as the primary recommended medication for individuals with diabetes who also have a concomitant high or very high cardiovascular risk, with a recommendation grade of IA. (McDonagh et al., 2021). Recent research indicates that, compared to a placebo, the use of sotagliflozin has demonstrated significant efficacy in reducing the overall occurrence of cardiovascular-related deaths, hospitalizations due to heart failure, and emergency visits in individuals with diabetes and those with recently worsened heart failure. (Bhatt et al., 2021b).

The latest study indicates that the T_{max} of Sotagliflozin is 3 h, and the plasma protein binding rate is as high as 97.7%. In patients with Type 2 Diabetes Mellitus (T2DM) and normal renal function, sotagliflozin's onset of action is rapidly absorbed, with $T_{1/2}$ ranging between 13.5 and 20.7 h. This extended half-life can significantly enhance the duration of efficacy compared to the 13-h duration of dapagliflozin. Therefore, administering the drug directly before breakfast and once daily can maximize its effect. (Scheen, 2015; Garcia-Ropero et al., 2018).

Therefore, the aim of this study is to offer a prospective endpoint economically, comparing the cost of preventing heart failure in diabetic patients using sotagliflozin *versus* dapagliflozin for each outcome.

2 Methods

2.1 Data source

The original data for sotagliflozin were derived from the SOLOIST-WHF clinical trial, which was sponsored by Sanofi and Lexicon Pharmaceuticals. (Bhatt et al., 2021b). The dapagliflozin's outcome data were rooted in the intervention group of adults with diabetes mellitus in the DAPA-HF study. (Petrie et al., 2020).

2.2 Primary outcome

The primary endpoint was the Cost Needed to Treat (CNT), preventing one event of hHF (Heart Failure hospitalizations) or the death of cardiovascular (composite outcome). (Mayne et al., 2006). This study was analyzed from the perspective of payment by the US healthcare payer.

2.3 Cost needed to treat/number needed to treat analysis

The Cost Needed to Treat (CNT) and the Number Needed to Treat (NNT) were introduced as an alternative way to demonstrate clinical benefit. (Thabane, 2003). The CNT was determined by the product of the annualized number needed to treat (aNNT) and the annual cost of treatment. (Mendes et al., 2017). Number Needed to Treat (NNT) signified the number of patients within a specific timeframe that one would need to treat to complete one extra study endpoint. The NNT was calculated as the reciprocal of the absolute risk reduction (ARR), presented as a decimal. We utilized drug costs in our analysis based on 75% of the US National Average Drug Acquisition Cost, as extracted in November 2023. (Data Medicaid, 2023).

2.4 Annualized number needed to treat analysis

The aARR represented the absolute difference between the annualized Absolute Risk (aAR) in the control group and the intervention group.

2.5 Secondary outcomes

Secondary outcomes included CNT to prevent one event of cardiovascular mortality (CV mortality) and all-cause mortality, considered as distinct clinical endpoints.

2.6 Sensitivity analysis

In order to assess the stability of the CNT study and reduce variations in outcomes between the RCT control and intervention groups, this study employed univariate sensitivity analysis. Analysis parameters included the event risk in the control arm of the RCTs and the annual cost associated with the interventions under compared.

To minimize the impact of drug variations in RCTs, this study simulates the annual event rates for each clinical trial drug in every clinical trial.

3 Results

3.1 Patient population

The patient demographics and heart failure with DM treatment modalities were effectively matched between the trial groups at the outset (McMurray et al., 2019; Bhatt et al., 2021b). A total of 2,747 subjects were included in this two randomized trials, as shown in Table 1. The medium follow-up was slightly shorter for Sotagliflozin (0.77 years) compared to Dapagliflozin (1.51 years). The medium age was 69 years in the Sotagliflozin group compared to 66.3 years in the Dapagliflozin group, indicating a minimal difference in mean age between the two groups of subjects. The majority of patients in both trials were white. The SOLOIST-WHF trial included patients with Hemoglobin of 7.1 and NT-proBNP (IQR) of 1816.8 pg/mL compared to Hemoglobin of 7.4 and NT-proBNP (IQR) of 1,479 pg/mL for DAPA-HF. Meanwhile, the median eGFR was 49.2% and the systolic blood pressure was 122 mmHg in the SOLOIST-WHF trial, compared to 63.9% and 121.4 mmHg in the DAPA-HF trial. Finally, the BMIs of the two groups of subjects equalized approximately.

TABLE 1 Key characteristics in the trial population.

Intervention trial	Sotagliflozin	Dapagliflozin
Number of patients with T2DM(%)	608 (100%)	2,139 (100%)
White (%)	93.3%	69.2%
Median follow-up (years)	0.77	1.51
Age (medium)	69	66.3
Female sex (%)	32.6%	22.3%
Medium Hemoglobin	7.1	7.4
Medium NT-proBNP(IQR)-pg/ml	1816.8	1,479
Medium eGFR (%)	49.2	63.9
Systolic BP	122	121.4
BMI	30.4	29.3

3.2 Annualized number needed to treat and cost needed to treat

The computations of annualized NNT and CNT are shown in Table 2, listing the concrete calculation process. Figure 1 depicts the acceptable price curve for the simulation of sotagliflozin's drug price, using 75% of the November 2023 updated NADAC for dapagliflozin as the baseline price.

3.3 Secondary outcome analysis

The CNT results of the secondary outcome are detailed in Table 3. Figures 2, 3 respectively present the results of simulating the NNT based on the calculated CNT for sotagliflozin and dapagliflozin, and the comparison between the two.

3.4 Sensitivity analysis

The outcomes of the sensitivity analysis, which involved simulating the use of different annualized event rates within the control arm according to the event rates in each of the trials, are presented in Table 4.

TABLE 2 The calculations of the number and the cost needed to treat.

Parameter	Sotagliflozin	Dapagliflozin
Number of patients in the control arm	614	1,064
Patient years of therapy in the control arm	473	1,607
Number of events-control arm	355	271
Annualized event rate-control arm	75.05%	16.86%
Number of patients- intervention arm	608	1,075
Patient years of therapy- intervention arm	468	1,623
Number of events-intervention arm (95%CI)	238 (185–302)	203 (171–244)
Annualized event rate-intervention arm (95%CI)	50.85% (39.53–64.53%)	12.51% (10.54–15.03%)
Absolute event rate reduction (annualized) (95%CI)	24.2% (10.52–35.52%)	4.35% (1.83–6.32%)
Annualized number needed to treat (95%CI)	4 (3–7)	23 (16–55)
Annual drug cost	Figure 1	$4,741
Cost needed to treat to prevent one event (95%CI)	Figure 1	$109043 ($75856–260,755)

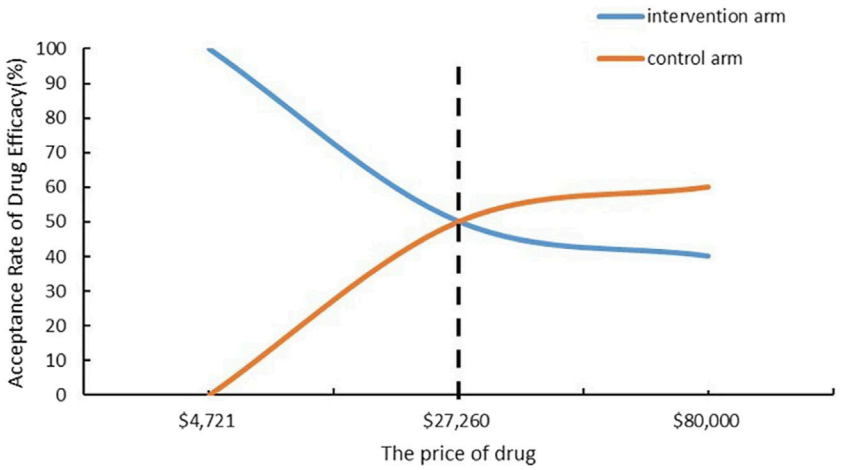

FIGURE 1
Cost-Acceptability Curve to prevent one event.

TABLE 3 Secondary of outcome analysis.

Outcome	Risk reduction		Annualized NNT		CNT	
	SOTA VS SOC	DAPA VS SOC	SOTA	DAPA	SOTA	DAPA
All-cause mortality (95%CI)	0.82 (0.59–1.14)	0.78 (0.63–0.97)	35 (16~∞)	40 (24–238)	Figure 2	$189640 ($113784~$1128358)
CV mortality (95%CI)	0.84 (0.58–1.22)	0.79 (0.63–1.01)	56 (19~∞)	50 (29~∞)	Figure 3	$237050 ($132748~∞)

4 Discussion

The 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America Guidelines for the Management of Heart Failure: (Failure, 2021): SGLT-2 inhibitors as the first choice for the therapy of heart failure, including dapagliflozin. However, as a new class of SGLT-1/SGLT-2 dual-acting inhibitors, the efficacy and safety of sotagliflozin have attracted much attention. Therefore, this study will give sound advice on clinical decision making from the following aspects.

This study determines that sotagliflozin is remarkably more effective in lowering the NNT compared to dapagliflozin for

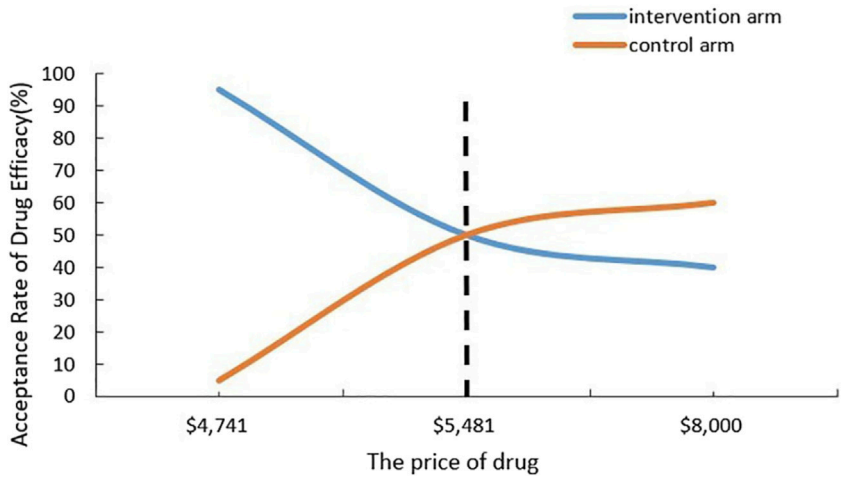

FIGURE 2
Cost-Acceptability Curve to All-cause mortality.

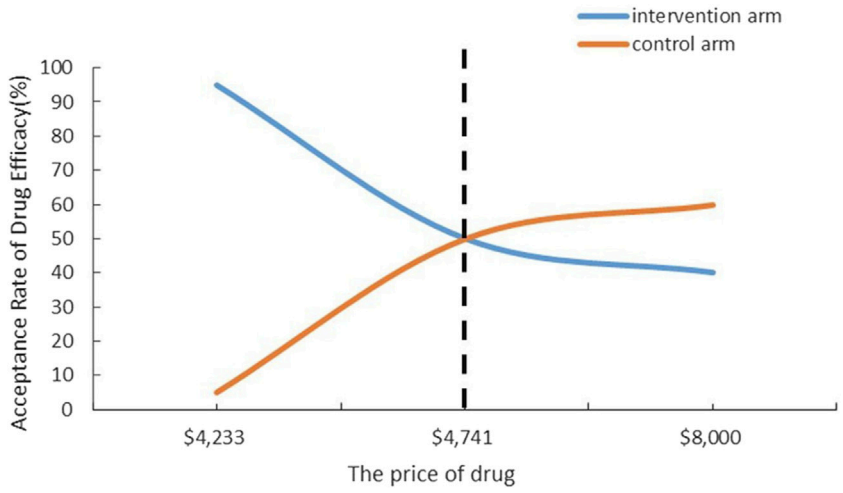

FIGURE 3
Cost-Acceptability Curve to CV mortality.

TABLE 4 Results of simulating the effect of intervention in the two RCTs.

	Value	CNT for sotagliflozin	CNT for dapagliflozin
Simulation of annualized event tare in the RCT control group	75.05% (as in SOLOIST-HF)	$18964 ($14223-$33187)	$85338 ($61633-$199122)
	16.86% (as in DAPA-HF)	$23705 ($18964-$56892)	Base-case:$109043 ($75856–260,755)

preventing one event. Refer to Table 2 for detailed information, the NNT for sotagliflozin was 4 (95% CI 3-7), whereas for the control group, it is 23 (95% CI 16-55). Notably, the NNT for the intervention group constitutes only 17.4% of that for the control group. In the calculation of the CNT, a sensitivity prediction analysis is employed, using the drug price as the baseline for the control drug and examining the indicators for the intervention group.

In Figure 1, the odds of cost acceptability for the intervention group approach 100% when both sotagliflozin and dapagliflozin are priced at $4,741. As the drug price rose to $27,260, patients' acceptance of the prices for both drugs converged, with sotagliflozin being only 17.39% of the price of dapagliflozin. This implies that within the $4,741-$27,260 price range for sotagliflozin, choosing sotagliflozin is economically superior to selecting dapagliflozin.

This analysis suggests that the CNT is lower in the sotagliflozin group compared to the dapagliflozin group, indicating its superiority in terms of monetary value. In the secondary outcome analysis, we can compare sotagliflozin and dapagliflozin regarding all-cause mortality and cardiovascular mortality. For reducing all-cause mortality, the NNT for the sotagliflozin group is 35, slightly lower than the control group's NNT of 40. Additionally, Figure 2 illustrates the economical price range for sotagliflozin, spanning from $4,741 to $5,481. This indicates that despite the price of sotagliflozin being higher than $4,741 but lower than $5,481, it is still considered economical. Nevertheless, for reducing cardiovascular mortality, the NNT of sotagliflozin is slightly higher than that of the dapagliflozin. The price sensitivity analysis reveals that sotagliflozin is considered economical only when priced below $4,741.

In the results of simulating the intervention effects in the two RCTs, the Cost-Effectiveness Ratio (CNT) for base treatment is $18,964 (95% CI $14,223-$33,187), compared to the dapagliflozin group's CNT of $855,338 (95% CI $61,633-$199,122). In this analysis, the drug price of dapagliflozin is equated with that of sotagliflozin, demonstrating a significant reduction in drug purchase expenditures. Additionally, this analysis shows a substantial decrease in medication expenses when the drug price of dapagliflozin is equated with that of sotagliflozin. Similarly, with an annualized event rate of 16.86% in the control group, the CNT is $23,707 (95% CI $18,964-$5,689,892) in the sotagliflozin group compared to $109,043 (95% CI $75,856-$2,607,555) in the dapagliflozin group.

In summary, patients receiving sotagliflozin exhibited lower incidence rates of both primary and secondary outcome events compared to those in the control group. During the SOLOIST-HF trial, the overall incidence of CV death, urgent heart failure visits, and heart failure in the control arm was 76.4%. In the experimental arm receiving sotagliflozin, the overall incidence of events was 51.3%, representing a significant reduction of 25.1%. Breaking down the primary outcome measures, the event rate for cardiovascular death in the experimental group was 8.4% compared to 9.4% in the control group, indicating a 1% reduction in occurrence. The incidence of hospitalization due to heart failure events in the experimental arm (33.7%) was markedly lower than in the control arm (51.9%). Moreover, the occurrence rate for urgent heart failure visits was decreased by 5.2%.

Dual mechanism of action of sotagliflozin may have potential clinical advantages. The kidney plays a crucial role in the body's glucose metabolism, and glucose transport in the body relies on sodium-dependent glucose transporter carriers (SGLTs). SGLT-2, primarily located in the S1 segment of the renal proximal tubule, functions as a low-affinity, high-capacity transporter. Meanwhile, its inhibitors protect pancreatic β-cell function. (Brunton, 2015). Consequently, it plays a significant role in glucose reabsorption. This phenomenon elucidates the ability of SGLT-2 inhibitors to effectively reduce blood glucose levels. Studies have found that genetic mutations in SGLT-1 can lead to severe diarrhea, even life-threatening. (van den Heuvel et al., 2002). It is probable that dual inhibitors targeting both SGLT1 and SGLT2 may provide vascular benefits similar to, or potentially surpassing, those of selective SGLT2 inhibitors. (Kashiwagi et al., 2015).Dapagliflozin is highly potent, reversible, and selectively inhibits sodium-glucose cotransporter-2, making it a widely used medication for treating type 2 diabetes mellitus. Moreover, dapagliflozin's cost-effectiveness compared to similar medications may be substantial. (McEwan et al., 2020; Nguyen et al., 2023). Additionally, genital infections are more prevalent. (Dhillon, 2019). Significant barriers hinder the adoption of SGLT2 inhibitors. However, despite the benefits and guidelines provided by the Society of Cardiology, the rates of clinical prescribing are low. (Vardeny and Vaduganathan, 2019). This is primarily attributed to a lack of understanding of the medication, concerns about introducing confusion into diabetes care, and discomfort with prescribing diabetes medications. (Gao et al., 2020). According to a systematic review, sotagliflozin demonstrated significant reduction in cardiovascular mortality, hospitalizations, and urgent HF visits due to heart failure when compared to dapagliflozin. Conversely, dapagliflozin exhibited notably significant benefits in terms of cardiovascular mortality and the worsening heart failure. (Iyer et al., 2023).

Overall, the analysis of data indicates that the benefits of sotagliflozin on heart failure and blood glucose control across the entire spectrum of renal function can be summarized in two main aspects. Firstly, sotagliflozin significantly reduces the overall incidence of CV death, heart failure hospitalizations, and urgent heart failure visits; (Bhatt et al., 2021b);Secondly, as an oral double-acting inhibitor of SGLT-1/SGLT-2, sotagliflozin markedly lowers glycated hemoglobin (HbA1c) levels in patients with alleviate to moderately severe chronic kidney disease (CKD), demonstrating significant efficacy individual with CKD. (Bhatt et al., 2021a). Relevant studies have demonstrated that sotagliflozin prevents the onset of atrial arrhythmias by additional SGLT1 inhibition. (Bode et al., 2021). However, it is associated with an increase in diarrhoea, genital infection, and volume depletion events. (Sims et al., 2018). The overall safety profile of sotagliflozin is comparable to that of that of other SGLT2 inhibitors. (Avgerinos et al., 2022).

In addition to the differences in the reported clinical outcomes of sotagliflozin and dapagliflozin, it is worth that these medications also confer cost-effectiveness that may influence their benefits. Based on DAPA-HF, this study investigated the cost-effectiveness of dapagliflozin compared to a placebo among heart failure patients with diabetes. This finding demonstrated that dapagliflozin was projected to add 0.63 (95% uncertainty interval [UI], 0.25-1.15) quality adjusted life-years (QALYs), with an incremental lifetime ratio of $42,800 (95%UI, $37,100-$50,300), resulting in an incremental cost-effectiveness ratio of $68,300 per QALY gained (95%UI, $54,600-$117,600 per QALY gained). (Isaza et al., 2021). Conversely, the use of sotagliflozin incurred an incremental lifetime ratio of $19,374 and resulted in a net gain in QALYs of 0.425, with an estimated incremental cost-effectiveness ratio of $45,596 per QALY gained based on the SOLOIST-WHF trial. (Kim et al., 2023). So dapagliflozin was linked to a net increase of 0.205 QALYs compared to sotagliflozin, with a 33.2% lower cost per QALY gained. Hence, prescribing medication maybe based on the patient's specific condition is clinically imperative.

Despite mounting evidence indicating that sotagliflozin is significantly superior to dapagliflozin in terms of both efficacy and affordability, its clinical use remains limited. This limitation partly stems from the uncertainty surrounding costs and partly from the lack of understanding of sotagliflozin. For instance, the literature we cited suggests that sotagliflozin demonstrates efficacy specifically in individuals with diabetes and worsening heart failure. This could provide healthcare professionals with the flexibility to tailor the medication to the patient's condition during decision-making analyses.

4.1 Limitation

There are several limitations of this study. First, the experimental data in this analysis were obtained from the SOLOIST-WHF trial. The trial sponsor changed from Sanofi to Lexicon Pharmaceuticals in the middle of the trial, leading to alterations in some endpoints and related parameters, such as the median duration of follow-up. Moreover, the baseline values for enrollment of subjects in the two clinical trials were less homogeneous, potentially leading to some differences in the statistics of the data.

Secondly, due to the timing of the drug launch in the intervention group, we currently lack price data for these drugs. Therefore, this analysis employs sensitivity prediction analysis, using the drug price as a baseline in the control group to analyze the indicators of the intervention group.

Finally, and most importantly, this study does not replace cost-effectiveness analyses of medicines to achieve the QALYs. The CNT and NNT in this study are calculated from the patient's median follow-up time and the odds of preventing a single event. However, using CNT and NNT for decision analyses of medicines has its limitations, as the number of treatments it requires varies with the length of follow-up. (Altman and Andersen, 1999). This explains the large difference in results between the control and intervention groups in this study. Moreover, NNT can only measure studies comparing different treatments for the same disease, (Pitt et al., 2014) i.e,., choosing the superior one of two comparable treatments. Nonetheless, NNT has been shown to be an objective, clinically relevant, descriptive, and easily interpretable measure of clinical data in several ways, particularly when applying trial results in a clinical setting, where annualized rates appear to be more effective than absolute risk reductions in assessing chronic disease. (Walter and Irwig, 2001; Greenstein and Nunn, 2004; Cazzola, 2006; Mayne et al., 2006).

5 Conclusion

In summary, dapagliflozin and sotagliflozin seem comparable in terms of safety in treating diabetes in individuals with heart failure. However, the preliminary results of this study suggest that sotagliflozin is more likely to significantly reduce the incidence of patients needed to prevent a single event and decrease medication expenses. Additionally, as a new class of SGLT-1/SGLT-2 dual-acting inhibitors, sotagliflozin markedly lowers glucose concentrations in the gastrointestinal tract. Therefore, this study supports including sotagliflozin as a therapeutic agent in relevant guidelines for treating heart failure.

Data available statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

WZ: Conceptualization, Data curation, Writing–original draft, Writing–review and editing. MY: Data curation, Writing–review and editing. GC: Conceptualization, Supervision, Writing–review and editing.

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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

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EDITED BY
Heike Wulff,
University of California, Davis, United States

REVIEWED BY
Maria Victoria Sánchez,
University of Rovira i Virgili, Spain
Mohd Yazid Abu,
Universiti Malaysia Pahang, Malaysia

*CORRESPONDENCE
Ana Paula Beck Da Silva Etges,
anabsetges@gmail.com

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Improvements in technology and the expanding role of time-driven, activity-based costing to increase value in healthcare provider organizations: a literature review

Ana Paula Beck Da Silva Etges[1,2,3]*, Porter Jones[2], Harry Liu[2], Xiaoran Zhang[2] and Derek Haas[2]

[1]PEV Healthcare Consulting, São Paulo, Brazil, [2]Avant-garde Health, Boston, MA, United States, [3]Programa de Pós-graduação em Epidemiologia da Escola de Medicina da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Objective: This study evaluated the influence of technology on accurately measuring costs using time-driven activity-based costing (TDABC) in healthcare provider organizations by identifying the most recent scientific evidence of how it contributed to increasing the value of surgical care.

Methods: This is a literature-based analysis that mainly used two data sources: first, the most recent systematic reviews that specifically evaluated TDABC studies in the surgical field and, second, all articles that mentioned the use of CareMeasurement (CM) software to implement TDABC, which started to be published after the publication of the systematic review. The articles from the systematic review were grouped as manually performed TDABC, while those using CM were grouped as technology-based studies of TDABC implementations. The analyses focused on evaluating the impact of using technology to apply TDABC. A general description was followed by three levels of information extraction: the number of cases included, the number of articles published per year, and the contributions of TDABC to achieve cost savings and other improvements.

Results: Fourteen studies using real-world patient-level data to evaluate costs comprised the manual group of studies. Thirteen studies that reported the use of CM comprised the technology-based group of articles. In the manual studies, the average number of cases included per study was 160, while in the technology-based studies, the average number of cases included was 4,767. Technology-based studies, on average, have a more comprehensive impact than manual ones in providing accurate cost information from larger samples.

Conclusion: TDABC studies supported by technologies such as CM register more cases, identify cost-saving opportunities, and are frequently used to support reimbursement strategies based on value. The findings suggest that using TDABC with the support of technology can increase healthcare value.

KEYWORDS

time-driven activity-based costing, TDABC, microcosting, technology, digital health

Introduction

Improving the quality and accuracy of cost information is among the challenges actively administered by healthcare policymakers and leaders, motivated by the transition in payment models and pressure to reduce waste in the healthcare system (Najjar et al., 2017). Especially after the COVID-19 pandemic period, when healthcare systems were expected to prove their capability to deliver care with high efficiency, making cost information available has been recognized as elementary in the continuous search for more sustainable, equitable, and excellent healthcare systems.

One of the first steps to defining strategies that can result in excellent care with financial responsibility is to determine if there are enough resources with the quality or knowledge necessary to achieve excellence in care delivery and how much it costs. Microcosting analysis supported by the time-driven activity-based costing (TDABC) method has been identified as the gold standard in the search for accurate answers to these questions (Kaplan, 2014; Keel et al., 2017; da Silva Etges et al., 2020).

Since TDABC's first applications in the healthcare field by Prof. Robert Kaplan (Kaplan, 2014), several projects worldwide have achieved favorable results measured in cost savings and value-increase opportunities, especially in the surgical field. Until 2020, systematic reviews evaluated applications of the method (Keel et al., 2017; da Silva Etges et al., 2020). Among the challenges reported in most studies was the difficulty in automating the data collection, scaling the method, and, consequently, moving from research to a digital solution that can be implemented in the hospital's routines to guide managers in their decision-making processes about delivering care with higher efficiency.

The last few years were also marked by the explosion of health tech and by the consensus of the requirement to establish data-driven organizations in healthcare that can better use real-world evidence to guide effective health policies (Kraus et al., 2021; Ebbert et al., 2023). Among the solutions identified in published articles, the CareMeasurement software (Avant-garde Health, Boston, USA) (CM) makes a demonstrated contribution to some of the problems reported by the previous TDABC systematic reviews. It allows the automation of time stamps, resource consumption data collection, and the scalability of the TDABC as a routine to manage costs and has assisted managers in taking actions with a high likelihood of providing cost savings to hospital organizations (Carducci et al., 2020; Fang et al., 2021a; Carducci et al., 2021).

This study evaluated the influence of using technology on measuring accurate costs in healthcare organizations by identifying how such technology contributed to increasing value in the most recent scientific evidence of TDABC application in surgical pathways.

Methods

This is a literature-based analysis that mainly used two data sources: the most recent systematic review that specifically evaluated TDABC studies in the surgical field, published in 2020, and all articles that mentioned the use of a CM to implement TDABC, which started to be published after 2020.

Literature search strategy

PubMed was used to confirm the most recent systematic review, specifically exploring the use of TDABC in surgical pathways. Seven articles were found when searching for systematic reviews of TDABC on PubMed. The most recent, published in 2023, is specific for interventional radiology (Bulman et al., 2023) and spine surgeries (Ali et al., 2023). In 2022, a systematic review that evaluated the cost measure of value-based healthcare but did not specifically focus on TDABC studies was published (Leusder et al., 2022). In 2019 and 2018, studies specific to joint replacement (Pathak et al., 2019) and cancer (Alves et al., 2018) were published. The other two articles represent systematic reviews focused on evaluating TDABC in healthcare not associated with a specific clinical field or including other cost methods, the first published in 2017 (Keel et al., 2017) and the most recent in 2020 (da Silva Etges et al., 2020). This last one was used to identify the manual studies in this article.

The studies using CM were also retrieved from PubMed. The search was supported by the research team from the company responsible for CM development, Avant-garde Health, who organized the studies developed using data from the software that were indexed on Pubmed and used CM to extract or analyze cost information following the TDABC principles.

Both groups only considered original articles written in English.

Data analyses

The articles from the systematic review (da Silva Etges et al., 2020) were grouped as manual, while those using CM were grouped as technology-based studies of TDABC implementation. The analysis compared the methodological aspects and accuracy of the results from both sets of articles and focused on evaluating the impact of using technology to apply TDABC. A general description, including the most frequent clinical fields and journals, was followed by three levels of information extraction: the number of cases included, the number of articles published per year, and the contributions of TDABC to achieve cost savings and redefine supply pricing and reimbursement strategies based on value.

For all microcosting articles included in the systematic review and in the group of CM articles, information on the number of cases included was extracted, and a mean number of articles that used manual methods or were supported by technology was calculated. Articles from the systematic review that were not based on a microcosting method and did not use a sample of patients were excluded from this analysis. For both groups, the number of articles published per year was computed, and the publication rates were compared.

A final analysis consisted of extracting the cost savings estimates achieved in manual and technology-based studies and contributions from the TDABC projects in redesigning more sustainable reimbursement programs. The mean cost savings were compared to evaluate the impact of technology on the hospital's capabilities to increase its financial sustainability.

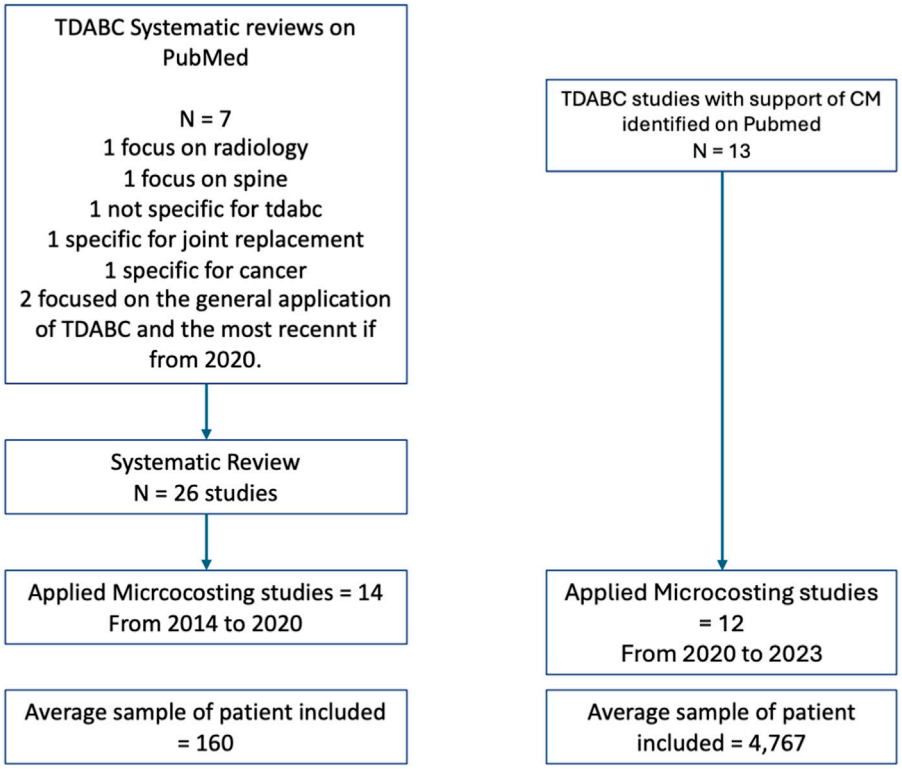

FIGURE 1
Flowchart of the studies included.

Results

Among the 26 articles included in the systematic review, only 14 were applied microcosting studies that used real-world data at a patient level to evaluate costs. These studies comprised the manual studies. All studies that reported the use of CM were microcosting and applied studies and comprised the technology-based group of articles. In the manual group, the first evidence published is from 2014, and the group accounts for 14 studies published until 2020. In the technology-based group, 13 studies were identified that had been published in three years. Among the manual studies, the average number of cases included was 160, while among the technology-based studies, the average number of cases included was 4,767. Figure 1 contains the flowchart of the studies included, and Table 1 contains the articles included in both groups, the surgical fields, and the total number of patients included.

Since TDABC implementations began to receive technological support, the contributions in terms of cost savings estimates and the generation of accurate cost information to adjust reimbursement strategies have been more frequent. In the manual group, only two articles explored the use of costs based on TDABC to define reimbursement strategies at a macro level and compared TDABC with traditional methods but did not measure the impact of the differences in hospital sustainability (Akhavan et al., 2016; Laviana et al., 2018). In contrast, five studies from the technology-based group explored potential impacts on the definition of reimbursement strategies and were able to measure variabilities in cost items (labor, supply, medication) and between technologies or patient profiles (Fang et al., 2021a; Carducci et al., 2021; Chisari et al., 2021; Fang et al., 2021e; Theosmy et al., 2021). Comparing the cost information granularity between both groups reveals that the technology has potentialized the managers' capabilities to identify the cost components responsible for the highest variabilities and, consequently, guide the efforts to adjust reimbursement strategies and deliver better care.

For cost-saving estimates, the differences observed are more concentrated in the cost variables explored and how to use them to estimate the potential economic impact at a hospital level. The manual studies focused on opportunities to reduce the length of time in the operating room and redesign surgical processes, resulting in suggestions to redefine hospital processes to reduce waste (Chen et al., 2015; Hamid et al., 2017; Odhiambo et al., 2019; Simmonds et al., 2019). The technology-based studies focused much more on variabilities and opportunities to renegotiate supply pricing and, because of the volume and cost proportions represented, estimate the important potential economic impact at the hospital and healthcare system levels (Fang et al., 2021a; Carducci et al., 2021; Chisari et al., 2021; Fang et al., 2021e; Theosmy et al., 2021). Supply cost-saving opportunities were not mentioned by the manual studies, and this seems to be where the studies that included more data encountered the highest cost-saving opportunities in surgeries that use high-cost supplies. Table 2 demonstrates how the studies from each group increased value by yielding cost savings, were used to sustain new reimbursement agreements, or explored other contributions from the TDABC.

TABLE 1 Studies included in each group, surgical field, sample, and publication year.

Group	Study	Cost-saving result	Reimbursement or supply pricing contributions	Other TDABC contributions
Manual studies	Simmonds et al. (2019)	Estimated that 57% of the overhead costs attributed to the adenotonsillectomy procedures by the relative value units (RVU) system were from equipment and implants used by different hospital services	NA	NA
	Hamid et al. (2017)	Demonstrated how the TDABC can identify inefficiencies and result in cost savings. However, the study did not estimate or measure the potential cost savings that could be achieved in the surgery studied	NA	NA
	Koehler et al. (2019)	NA	NA	Compared technologies but did not explore potential cost savings in the same care pathway
	Odhiambo et al. (2019)	Estimated that the redundant staff members in the operating room represent an additional opportunity cost of £15 per minute, which represents, on average, a potential net loss of £1,000 per additional or delayed surgery hour	NA	NA
	Laviana et al. (2018)	NA	Compared TDABC results with traditional cost methods suggesting the value of this level of information to define accurate reimbursement strategies	NA
	Balakrishnan et al. (2018)	NA	NA	Compared technologies but did not explore potential cost savings in the same care pathway
	Chen et al. (2015)	Reduced duration and costs in the emergency department (−41 min, −$23) and preoperative floor (−57 min, −$18). Same-day discharge protocol eliminated postoperative floor costs (−$306). All three interventions reduced the total direct costs by 11% ($2753.39 to $2447.68) and the duration of hospitalization by 51%	NA	NA
	Husted et al. (2018)	NA	NA	Compared technologies but do not explore potential cost savings in the same care pathway
	McCreary et al. (2018)	NA	NA	Compared technologies but do not explore potential cost savings in the same care pathway
	Akhavan et al. (2016)	NA	Compared TDABC results with traditional cost methods suggesting the value of this level of information to define accurate reimbursement strategies	NA
	Yangyang et al. (2016)	NA	NA	Demonstrated how TDABC can identify inefficiencies and result in cost savings. However, did not estimate or measure the potential cost savings that could be achieved in the surgery studied
	McLaughlin et al. (2014)	NA	NA	Demonstrated how TDABC can identify inefficiencies and result in cost savings. However, did not estimate or measure the potential cost savings that could be achieved in the surgery studied
	Yangyang et al. (2017)	NA	NA	Compared technologies but did not explore potential cost savings in the same care pathway
	da Silva Etges et al. (2019)	NA	NA	Described the step-by-step process to execute TDABC as a microcosting technique

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TABLE 1 (*Continued*) Studies included in each group, surgical field, sample, and publication year.

Group	Study	Cost-saving result	Reimbursement or supply pricing contributions	Other TDABC contributions
Technology-based studies	Carducci et al. (2021)	NA	Demonstrated the value of TDABC to make supply and labor costs transparent, suggesting that this level of transparency is necessary for the establishment of more accurate and profitable agreements with suppliers	NA
	Fang et al. (2021b)	Used accurate data from CM to evaluate the impact of implementing reference pricing (RP) for total knee arthroplasty supplies (TKS). Demonstrated that hospital costs for total knee arthroplasty (TKA) implants decreased by 16.7% after implementing RP. All the individual implant components decreased in costs	NA	NA
	Carducci et al. (2020)	NA	NA	The study focused on measuring the value index for total shoulder arthroplasty
	Carducci et al. (2020)	Determined that the implant is the most expensive cost item for all types of arthroplasties, identifying centers where it is possible to pay lower prices for implants that result in lower costs	NA	NA
	Chisari et al. (2021)	NA	Estimated the incremental cost of performing total knee arthroplasty (TKA) *versus* unicompartmental knee arthroplasty (UKA), arguing that the reimbursement for TKA should be reviewed to cover the incremental labor costs compared with UKA	NA
	Theosmy et al. (2021)	NA	Measured the differences between inpatient and outpatient TKA and compared them in terms of the reimbursement fees implemented for each type of surgery, arguing that by better adjusting the fee to the cost, it will be possible to economically benefit the healthcare system	NA
	Zachwieja et al. (2020)	Measured the potential profit increase of conducting overlapping surgeries. In the study, it was estimated to yield a potential profit increase of $1,215 per overlapping surgery in 8 h	NA	NA
	Yayac et al. (2020)	Determined that the increased cost of a cementless implant is recouped through savings in the cost of cement and supplies, as well as shorter operative times	NA	NA
	Goh et al. (2022)	Using TDABC, it was demonstrated that overall facility costs were lower in robot-assisted UKA (RA-UKA) despite a longer operative time. To facilitate wider adoption of this technology, implant manufacturers may negotiate lower implant costs based on volume commitments when robotic assistance is used. These supply cost savings appear to offset a portion of the increased costs	NA	NA
	Fang et al. (2021c)	NA	NA	Compared costs between the two groups but did not explore potential cost savings
	Fang et al. (2021d)	NA	NA	Compared costs between the two groups but did not explore potential cost savings
	Fang et al. (2021a)	NA	Demonstrated the value of TDABC to make supply and labor costs transparent, suggesting that this level of transparency is necessary for the establishment of more accurate and profitable agreements with suppliers	NA
	Fang et al. (2021e)	NA	Compared TDABC results with traditional cost methods, suggesting the value of this level of information to define accurate reimbursement strategies	NA

TABLE 2 Contributions from applying TDABC to increase value.

Group	Title	Surgery field	Number of cases included	Year
Manual studies	Comparing the real and perceived cost of adenotonsillectomy using time-driven activity-based costing (Simmonds et al., 2019)	Adenotonsillectomy	53	2019
	Determining the cost-savings threshold and alignment accuracy of patient-specific instrumentation in total ankle replacements (Hamid et al., 2017)	Ankle replacement	87	2017
	Endoscopic versus open carpal tunnel release: A detailed analysis using time-driven activity-based costing at an academic medical center (Koehler et al., 2019)	Endoscopic vs. carpal tunnel release	40	2019
	Health facility cost of Cesarean delivery at a rural district hospital in Rwanda using time-driven activity-based costing (Odhiambo et al., 2019)	Cesarean	197	2019
	Retroperitoneal *versus* transperitoneal robotic-assisted laparoscopic partial nephrectomy: a matched-pair, bicenter analysis with cost comparison using time-driven activity-based costing (Laviana et al., 2018)	Retroperitoneal *versus* transperitoneal robotic-assisted laparoscopic partial nephrectomy	355	2018
	TDABC: Lessons from an application in healthcare (Balakrishnan et al., 2018)	Endoscopic vs. carpal tunnel release	180	2018
	Time-driven activity-based costing of total knee replacement surgery at a London teaching hospital (Chen et al., 2015)	Knee replacement	20	2015
	Time-driven activity-based cost of outpatient total hip and knee arthroplasty in different set-ups (Husted et al., 2018)	Hip and knee arthroplasty	6	2018
	Time-driven activity-based costing in fracture care: is this a more accurate way to prepare for alternative payment models? (McCreary et al., 2018)	Surgical treatment of isolated ankle fractures	35	2018
	Time-driven activity-based costing more accurately reflects costs in arthroplasty surgery (Akhavan et al., 2016)	Arthroplasty surgery	677	2016
	Time-driven activity-based costing to identify opportunities for cost reduction in pediatric appendectomy (Yangyang et al., 2016)	Appendicitis surgery	149	2016
	Time-driven activity-based costing: a driver for provider engagement in costing activities and redesign initiatives (McLaughlin et al., 2014)	Neurosurgery and urology	124	2014
	Time-driven activity-based costing: a dynamic value assessment model in pediatric appendicitis (Yangyang et al., 2017)	Pediatric appendicitis	208	2017
	An 8-step framework for implementing time-driven activity-based costing in healthcare studies (da Silva Etges et al., 2019)	Bone marrow transplant	12	2019
Technology-based studies	Identifying surgeon and institutional drivers of cost in total shoulder arthroplasty: a multicenter study (Carducci et al., 2021)	Shoulder arthroplasty	1.571	2020
	Reference pricing reduces total knee implant costs (Fang et al., 2021b)	Knee replacement	7.148	2020
	Variation in the value of total shoulder arthroplasty (Carducci et al., 2020)	Shoulder arthroplasty	239	2020
	Variation in the cost of care for different types of joint arthroplasty (Carducci et al., 2020)	Arthroplasty surgery	22.215	2020
	Despite equivalent Medicare reimbursement, facility costs for outpatient total knee arthroplasty are higher than unicompartmental knee arthroplasty (Chisari et al., 2021)	Knee replacement	2.641	2020
	Is the new outpatient prospective payment system classification for outpatient total knee arthroplasty appropriate? (Theosmy et al., 2021)	Knee replacement	4.496	2020
	Overlapping surgery increases operating room efficiency without adversely affecting outcomes in total hip and knee arthroplasty (Zachwieja et al., 2020)	Knee and hip replacement	4.786	2020

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TABLE 2 (*Continued*) Contributions from applying TDABC to increase value.

Group	Title	Surgery field	Number of cases included	Year
	The use of cementless components does not significantly increase procedural costs in total knee arthroplasty (Yayac et al., 2020)	Knee replacement	2.426	2020
	Robotic-assisted versus manual noncompartmental knee arthroplasty: a time-driven activity-based cost analysis (Goh et al., 2022)	Knee replacement	265	2022
	Differences in hospital costs among octogenarians and nonagenarians, following primary total joint arthroplasty (Fang et al., 2021c)	Arthroplasty surgery	889	2021
	Episode-of-care costs for revision total joint arthroplasty by decadal age groups (Fang et al., 2021d)	Arthroplasty surgery	551	2021
	Financial burden of revision hip and knee arthroplasty at an orthopedic specialty hospital: higher costs and unequal reimbursements (Fang et al., 2021a)	Knee and hip replacement	13.946	2021
	The cost of hip and knee revision arthroplasty by diagnosis-related groups: comparing time-driven activity-based costing and traditional accounting (Fang et al., 2021e)	Knee and hip replacement	793	2021

Discussion

TDABC studies supported by technologies such as CM register more cases and deliver more precise measures to identify cost-saving opportunities, mainly based on supply variabilities. They are frequently used to redefine reimbursement strategies based on value, and potential improvements may be implemented more quickly. This suggests that the challenge of scaling the organizational capability to measure costs per care pathway at a patient level (Keel et al., 2017; da Silva Etges et al., 2020; Tsai et al., 2018) has started to receive answers from health tech companies. Healthcare leaders and policymakers should take note of how these advances impact the precision of cost information and its use as real-world data in health technology assessment processes, the continuous effort to reduce waste in healthcare, and the acceleration of implementing data-driven value-based reimbursement.

In his seminal book on health economics (Drummond et al., 2005), Prof. Michael Drummond pointed out microcosting techniques as the best strategies to provide accurate cost information for use in economic models to guide health policies and HTA processes. Several researchers have agreed that microcosting is the only way to understand and measure how each individual with a specific clinical condition is consuming resources from the healthcare system. It is not pricing, charges, or fee analyses; microcosting measures resource consumption, which should be used as a parameter to define more assertive reimbursement strategies adjusted to outcomes and clinical conditions (Tan et al., 2009). TDABC is an effective method for performing microcosting analysis (da Silva Etges et al., 2019). However, for the health economics community, the bottleneck from microcosting techniques is the capability to generate representative cost information from a population due to the complexity of data collection and analysis (Drummond et al., 2005). In an era where each day, more uses of real-world financial and clinical data are emerging and being recommended by the reglementary agencies, such as the FDA and NICE (Sherman et al., 2016; Jarow et al., 2017), high data accuracy and difficulty to scale and generate representative information represents a trade-off that deserves answers. By consolidating evidence from technology-based studies that incorporate a larger number of cases and detailed cost information, especially regarding supply consumption, this review provides a crucial starting point for implementing data-driven strategies to reduce waste, improve population health, and increase value.

The next step in affecting people's lives through improved data quality involves valuing "health" rather than "healthcare service delivered" by redefining reimbursement strategies, such as strategies based on value (Porter and Kaplan, 2016). The success of implementing value reimbursement strategies relies on the level of granularity in outcomes and cost data that stakeholders can monitor, including specific details related to patients' consumption patterns based on their clinical condition. Achieving this level of granularity requires using technology that enables the ethical and compliant sharing of data. The technology-based studies that contributed to the definition of reimbursement strategies reported how CM allowed making supply and labor costs transparent on a very detailed level. It was noted as a significant advance achieved by technology and a differential to define the agreements involving the device industry and payers. All these initiatives are recent and are in a proof-of-concept period in most countries, with a consensus that having good-quality data is a requirement for establishing effective agreements (Agarwal et al., 2020).

In the orthopedic field, implants comprise approximately 50% of surgical costs, with revision surgeries being more expensive than primary procedures (Fang et al., 2021a). Pricing strategies with suppliers have been developed to reduce costs during hospital surgical processes (Collins et al., 2017). Reliable pricing strategies require accurate and transparent data, which can be obtained using software, such as CM, that provides real-time, detailed information about individual consumption, enabling the control of payments between stakeholders.

Limitations: Although this study is innovative in its evaluation of the impact of technological advancements on measuring healthcare costs and defining reimbursement and supply pricing agreements, there are some limitations to consider. The analysis presented focused on evaluating the advances based on one disseminated technology to scale TDABC analysis in the healthcare field. Future research could use the results reported to examine emerging technologies. It is expected that the capability to compare solutions and identify benchmarks for making healthcare more effective and data-driven will improve with the advancement of digital technologies. In this future scenario, having previous review studies, such as this one, can accelerate the process of identifying evidence from specific solutions available on the market. Additionally, the cases identified in the technology-based group are from the United States, and further research is needed to evaluate the variability of the impacts of redefined agreements in different cultural contexts. Finally, this study only focuses on surgical pathways, and there is a gap in the literature regarding the implications for clinical pathways.

Conclusion

TDABC studies supported by technologies such as CM register more cases, identify cost-saving opportunities, mainly based on supply variabilities, and are frequently used to redefine reimbursement strategies based on value. Our findings suggest that using TDABC with the support of technology can accelerate the process of redefining payment agreements with suppliers and, consequently, healthcare payers, contributing to reducing waste and establishing a more financially adjusted and value-based healthcare system.

Summary points

- TDABC studies supported by technologies such as CM are registering more cases.
- Technology advances are contributing to delivering more precise measures to identify cost-saving opportunities, mainly based on supply variabilities.
- Healthcare leaders are using these advances to redefine reimbursement strategies based on value.
- TDABC, with the support of technology, can serve as a solid element to accelerate the process of redefining payment agreements with suppliers and, consequently, healthcare payers. It contributes to reducing waste and establishing a more financially adjusted and value-based healthcare system.

Author contributions

AE: conceptualization, formal analysis, investigation, methodology, supervision, validation, writing–original draft, and writing–review and editing. PJ: conceptualization, investigation, validation, and writing–review and editing. HL: supervision, validation, and writing–review and editing. XZ: formal analysis, validation, and writing–review and editing. DH: resources, supervision, validation, and writing–review and editing.

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Conflict of interest

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EDITED BY
Clara L. Rodríguez-Bernal,
Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain

REVIEWED BY
Salvador Peiró,
Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain
Colin E. Murdoch,
University of Dundee, United Kingdom

*CORRESPONDENCE
Maria Giner-Soriano,
mginer@idiapjgol.info

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Treatment of hypertension during pregnancy: a cohort of pregnancy episodes from the SIDIAP database, Catalonia, Spain

Ainhoa Gomez-Lumbreras [1], Carles Vilaplana-Carnerero [2,3,4,5], Marta Lestón Vázquez [3,6], Cristina Vedia [3,7], Rosa Morros [2,3,4,8] and Maria Giner-Soriano [2,3]*

[1]Department of Pharmacotherapy, College of Pharmacy, University of Utah, SLC, UT, United States, [2]Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain, [3]Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain, [4]Plataforma SCReN, UIC IDIAPJGol, Barcelona, Spain, [5]Departament de Medicina, Universitat de Barcelona (UB), Barcelona, Spain, [6]Àrea del Medicament i Servei de Farmàcia, Gerència d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Barcelona, Spain, [7]Servei d'Atenció Primaria Maresme, Barcelona, Spain, [8]Institut Català de la Salut, Barcelona, Spain

Introduction: Hypertension during pregnancy is one of the most frequent causes of maternal and fetal morbimortality. Perinatal and maternal death and disability rates have decreased by 30%, but hypertension during pregnancy has increased by approximately 10% in the last 30 years. This research aimed to describe the pharmacological treatment and pregnancy outcomes of pregnancies with hypertension.

Methods: We carried out an observational cohort study from the Information System for the Development of Research in Primary Care (SIDIAP) database. Pregnancy episodes with hypertension (ICD-10 codes for hypertension, I10–I15 and O10–O16) were identified. Antihypertensives were classified according to the ATC WHO classification: β-blocking agents (BBs), calcium channel blockers (CCBs), agents acting on the renin-angiotensin system (RAS agents), diuretics, and antiadrenergic agents. Exposure was defined for hypertension in pregnancies with ≥2 prescriptions during the pregnancy episode. Descriptive statistics for diagnoses and treatments were calculated.

Results: In total, 4,839 pregnancies with hypertension diagnosis formed the study cohort. There were 1,944 (40.2%) pregnancies exposed to an antihypertensive medication. There were differences in mother's age, BMI, and alcohol intake between pregnancies exposed to antihypertensive medications and those not exposed. BBs were the most used (n = 1,160 pregnancy episodes; 59.7%), followed by RAS agents (n = 825, 42.4%), and CCBs were the least used (n = 347, 17.8%).

Discussion: Pregnancies involving hypertension were exposed to antihypertensive medications, mostly BBs. We conduct a study focused on RAS agent use during pregnancy and its outcomes in the offspring.

KEYWORDS

hypertension, pregnancy-induced, pregnancy outcome, antihypertensive agents, cohort studies, electronic health records, EHR

Introduction

Hypertension disorders during pregnancy complicate between 5% and 10% of pregnancies and are among the frequent causes of feto-maternal morbimortality (Bramham et al., 2014; Williams et al., 2018; Wu et al., 2020). Hypertension during pregnancy has been associated with maternal complications such as stroke or heart failure, and in the fetus, it is associated with intrauterine growth restriction and stillbirth. Globally, hypertension during pregnancy has increased approximately 10% in the last 30 years, though the death and disability rates have decreased up to 30% (Wang et al., 2021). Hypertension can be a preexisting medical condition before the pregnancy (chronic hypertension) or be induced by the pregnancy and diagnosed after 20 weeks of gestation (gestational hypertension) (Williams et al., 2018).

The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) establish that pharmacology treatment aims to reduce maternal risk while being safe for the fetus (Williams et al., 2018). These guidelines, even with scarce evidence, recommend pharmacological treatment for those women with persistent elevation in blood pressure (BP) (≥150/95 mmHg), with some other guidelines indicating starting treatment for BP ≥ 140/90 mmHg (ACOG, 2019). However, there is no clear threshold for initiating pharmacological treatment for patients with mild hypertension (systolic BP between 140–150 and 160) (Kaimal, 2022). There are five groups of antihypertensive medications: antiadrenergic agents, β-blocking agents (BBs), diuretics, calcium channel blockers (CCBs), and those acting in the renin-angiotensin system (RAS) agents, including angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs). Women already undergoing treatment for preexisting hypertension might continue with their antihypertensive medication; however, agents acting on the renin-angiotensin system (RAS) are contraindicated due to the related adverse fetal and neonatal outcomes, and the indication is to switch the antihypertensives with awareness of the pregnancy (Brown et al., 2018; Braunthal and Brateanu, 2019).

Due to the increase in the number of pregnant women with hypertension and the potential implications of pharmacological treatments in pregnancy outcomes, we describe the antihypertensive medications used in a cohort of pregnancies with hypertension diagnoses.

Methods

This is an observational cohort study of pregnancies with hypertension diagnoses conducted with data obtained from the Information System for the Development of Research in Primary Care (SIDIAP). The SIDIAP database characteristics have been described elsewhere (Recalde et al., 2022). It contains electronic health records (EHRs) of the Primary Care Centers of the Catalan Health Institute (ICS) in Catalonia, Spain, from 2006 of up to 6 million people and almost 500,000 pregnancy episodes, most of which were followed at the sexual and reproductive healthcare services (ASSIR) of the ICS. The EHRs in ASSIR are used by gynecologists and midwives to register variables related with the sexual and reproductive health of women and follow-up of pregnancies, such as date of the last menstrual period or pregnancy start date (PSD), gestational week, date of delivery or pregnancy end date (PED), and termination outcomes. We identified a cohort of pregnancy episodes (n = 327,865) that occurred during 2011–2020 registered at the ASSIR and those pregnancy diagnoses registered in the primary care EHR through International Classification of Diseases 10th at SIDIAP (ICD-10) (WHO, 2019; Lestón Vázquez et al., 2023).

Cohort definition

A previous study from SIDIAP identified a total of 327,865 pregnancy episodes occurring during 2011–2020 (Lestón Vázquez et al., 2023). For our cohort, we included those pregnancy episodes with ICD-10 codes for hypertension (I10–I15) and gestational hypertension (O10–O16). For patients with more than one ICD-10 code for hypertension, the first one recorded was selected. Based on the date of the registered hypertension code, the pregnancy episodes were classified as chronic hypertension (codes before the PSD) and gestational hypertension (those registered during the pregnancy episode).

Only completed pregnancy episodes were considered, meaning only those pregnancies starting after the study period start date (1 Jan 2011) and completed by the end of the study period (30 June 2020).

Antihypertension medication exposure

The antihypertensive medications were grouped and defined by the WHO ATC classification as follows: antiadrenergic agents (C02), diuretics (C03), BB (C07), CCB (C08), and RAS agents (C09) (WHO Collaborating Centre for Drug Statistics Methodology, 2022).

SIDIAP pharmacy invoice data were used to define drug exposure. Invoices of those antihypertensive medications prescribed between the previous month and the PSD up to the month preceding the PED were considered to occur during the pregnancy episode. All prescriptions issued in primary care and ASSIR centers of drugs reimbursed by the Spanish National Health System that are dispensed in a community pharmacy produce a register in the invoice data. Pregnancies with at least two invoices for an antihypertensive medication were considered exposed.

Variables

The demographic characteristics, MEDEA socioeconomic index (Domínguez-Berjón et al., 2024), body mass index (BMI), smoking status, and alcohol intake were considered from 12 months before PSD up to PED. The number of pregnancies by woman was considered if occurring during the study period (2011–2020), with no distinction made regarding pregnancies with multiple fetuses.

Statistical analysis

Sample size and study power

We did not anticipate any specific number of pregnancies as we used all the pregnancy episodes with a diagnosis of hypertension.

TABLE 1 Baseline characteristics of all the hypertension pregnancy episodes classified according to the antihypertensive medication exposure.

Total cohort (4,839 pregnancy episodes)	Exposed to antihypertensive drugs N = 1,944	Not-exposed to antihypertensive drugs N = 2,895	*p*
Mother age (mean, SD) at PSD	36.0 (5.2)	34.2 (5.5)	<0.001
Obesity (ICD-10 code + BMI≥30)	686 (35.3)	788 (27.2)	<0.001
Mother's socioeconomic status (MEDEA)[a]			
Rural	337 (17.3)	508 (17.5)	0.004
Urban (U)	177 (9.1)	254 (8.8)	
U1	152 (7.8)	311 (10.7)	
U2	255 (13.1)	399 (13.8)	
U3	271 (13.9)	433 (15.0)	
U4	320 (16.5)	458 (15.8)	
U5	431 (22.2)	530 (18.3)	
Smoking habit[a]	359 (18.5)	548 (18.9)	0.830
Alcohol consumption[a]	180 (9.3)	184 (6.4)	<0.001
CKD (ICD-10 code: N18)	28 (1.4)	15 (0.5)	0.001
Parity number			
1st	1,689 (87.2)	2,432 (84.0)	0.006
2nd	211 (10.9)	383 (13.2)	
≥3rd or more	37 (1.9)	80 (2.8)	
Hypertension			
chronic	1,425 (73.3)	1,553 (53.6)	<0.001
gestational	519 (26.7)	1,342 (46.4)	
Live births	1,510 (77.7)	2,394 (82.7)	<0.001
Average of gestation duration (weeks mean, IQR)	39.0 (36.0-40.0)	38.0 (30.3-39.6)	<0.001
Preterm births (ICD-10th code)	331 (17.0)	356 (12.3)	<0.001

[a]variable up to 12 months before PSD. SD, standard deviation; PSD, pregnancy start day; ICD-10, International Classification of Diseases 10th version; BMI, body mass index; MEDEA, Mortalidad en áreas pequeñas Españolas y Desigualdades socioEconómicas y Ambientales; REF CKD, chronic kidney disease; IQR, interquartile range.

Main analysis

We calculated descriptive statistics for pregnancy characteristics and antihypertensive medication exposure [mean and standard deviation (SD), median and interquartile range (IQR), or percentages].

Results

From the 327,865 pregnancy episodes identified in SIDIAP, a total of 4,839 (1.5%) pregnancy episodes were included in our study cohort. This cohort was built with pregnancy episodes with hypertension diagnosis during the study period (2011–2020). In Table 1 it can be seen that the cohort had 1,944 (40.2%) pregnancy episodes exposed to an antihypertensive medication. Mothers were older in the exposed group (mean age in years 36.0, SD 5.2) than in the non-exposed group (34.2, SD 5.5). The rate of obesity was higher in the exposed group (35.3% vs. 27.2%). Almost three-quarters (73.3%) of the exposed pregnancies had chronic hypertension (diagnosis registered before the PSD) compared to half of the non-exposed pregnancies (53.6%). There was a higher rate of live-birth pregnancies among pregnancies that were not exposed to drugs (82.7% vs. 77.7%) and, on average, live birth pregnancy duration was 1 week longer in the non-exposed group than in the exposed group (mean 39.0 weeks, IQR 36.0–40 vs. 38.0 weeks, IQR 30.3–39.6, respectively). To see all the baseline characteristics of the pregnancy episodes, please see Table 1.

From the non-exposed pregnancy cohort, there were 529 (18.3%) cases with just one invoice of an antihypertensive medication, which did not meet the criteria for exposure. These were predominantly in the third trimester (n = 301 pregnancies, 56.9%), followed by the first one (n = 194 pregnancies, 36.7%). For these single-invoice pregnancies, BBs were leading the list (n = 301 pregnancies, 56.9%). To see the complete description of cases that were considered not exposed though with one invoice of an antihypertensive, see Supplementary Table S1.

BBs (n = 1,160 pregnancies, 59.7%) were the most frequently used agents, followed by RAS agents (825 pregnancies, 42.4%). CCBs were the least used (347 pregnancies, 17.8%). The combination of antihypertensive treatments across all the pregnancy trimesters shows BB and RAS agents (155 pregnancy episodes, 8.0%) as the most-used combination, followed by BB agents and antiadrenergic (98 pregnancies, 5.0%). The complete description of the frequency of exposure to the different antihypertensives and combinations through the pregnancies can be seen in Figure 1, and to see the

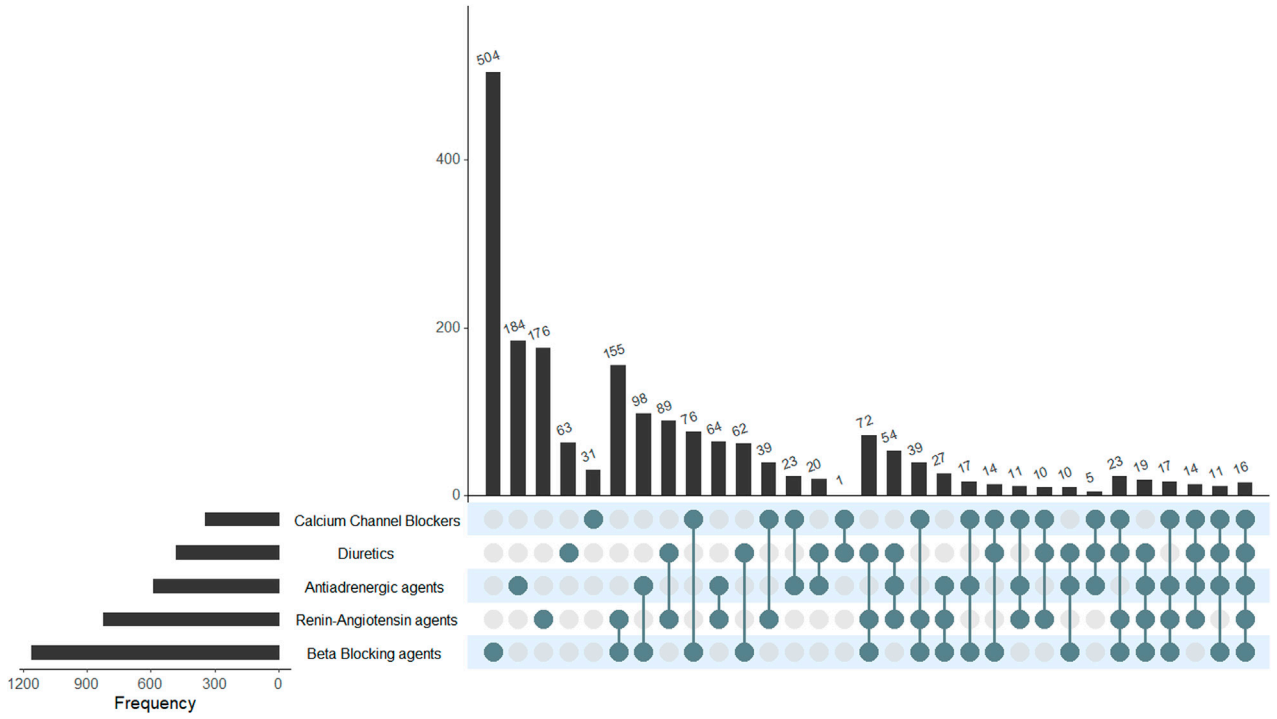

FIGURE 1
Antihypertensive drugs (and combinations) used across the cohort of exposed pregnancies. This is a two-way reading chart to show the total of unique and combinations of antihypertensive drugs that were used in the pregnancy episodes. Pharmacological groups are shown on the left, with horizontal bars representing the frequency of the pharmacological groups used in monotherapy or in combination. As an example, BB in the horizontal bar shows that they were used in 1,160 episodes, and the longest vertical bar shows the most frequently used treatment, which were BBs alone (n = 504). The most common combination of drugs was RAS + BB, and it is represented in the sixth vertical bar (N = 155).

most-used agents for each antihypertensive group, see Supplementary Table S2.

Figure 2A (gestational hypertension) and 2b (chronic hypertension) showed a decrease in exposure during the second trimester. In gestational hypertension (Figure 2A), exposure increased 96.5% from the second to the third trimester, while a 37.3% increase is shown in chronic hypertension pregnancies (Figure 2B). Chronic hypertension pregnancies decreased by 70.5% in exposure to RAS agents from the first trimester to the third (601–177). BBs were the most-used agents across all trimesters for both chronic and gestational hypertension pregnancies.

Discussion

In this observational cohort study of pregnancy episodes with hypertension in Catalonia, Spain, during 2011–2020, our results showed that more than half of the pregnancies with hypertension diagnosis had no exposure to antihypertensive medications. Among pregnancy episodes with chronic hypertension, almost three-quarters were exposed to antihypertensives, and approximately a quarter of the gestational hypertension episodes were exposed to antihypertensive agents too. The most-used antihypertensives were BBs, and the least-used ones were CCBs. Combinations of antihypertensives were not frequent.

Mothers exposed to antihypertensives were on average 2 years older than those not exposed. Older women are at more risk of hypertension during pregnancy (Khalil et al., 2013). Obesity has previously been associated with hypertension during pregnancy, with up to a three-fold increased risk; accordingly, in our study, the rate of obese women was higher in the exposed pregnancies (Mission et al., 2015). In the literature, these risks have been defined and associated with hypertension during pregnancy (Assis et al., 2008; Poon et al., 2010). Both cohorts, exposed and not exposed, showed a low rate of pregnancy episodes with chronic kidney disease (CKD) (<2%). Among women with childbearing potential, the average rate of CKD is 4%, and our rates seem consistent. We found a higher rate of CKD among those exposed to antihypertensives compared to the non-exposed ones, probably because they have more advanced CKD in need of antihypertensive treatment (Coresh et al., 2007).

Clinical guidelines recommend maintaining pharmacological treatment in women with chronic hypertension when pregnant, except for RAS agents, as they have been associated with adverse perinatal outcomes (Al Khaja et al., 2014; Garovic et al., 2022). Our results showed higher use of antihypertensives in the first trimester among pregnancies with chronic hypertension, in agreement with the guidelines; however, to date, there is no consensus on the BP values to start antihypertensive medication for pregnancies with BP < 160/90 mmHg. Two recently published meta-analyses have shown better outcomes for pregnancies receiving antihypertensive medications, and a network meta-analysis showed that even if all antihypertensives reduce the risk of severe hypertension, labetalol

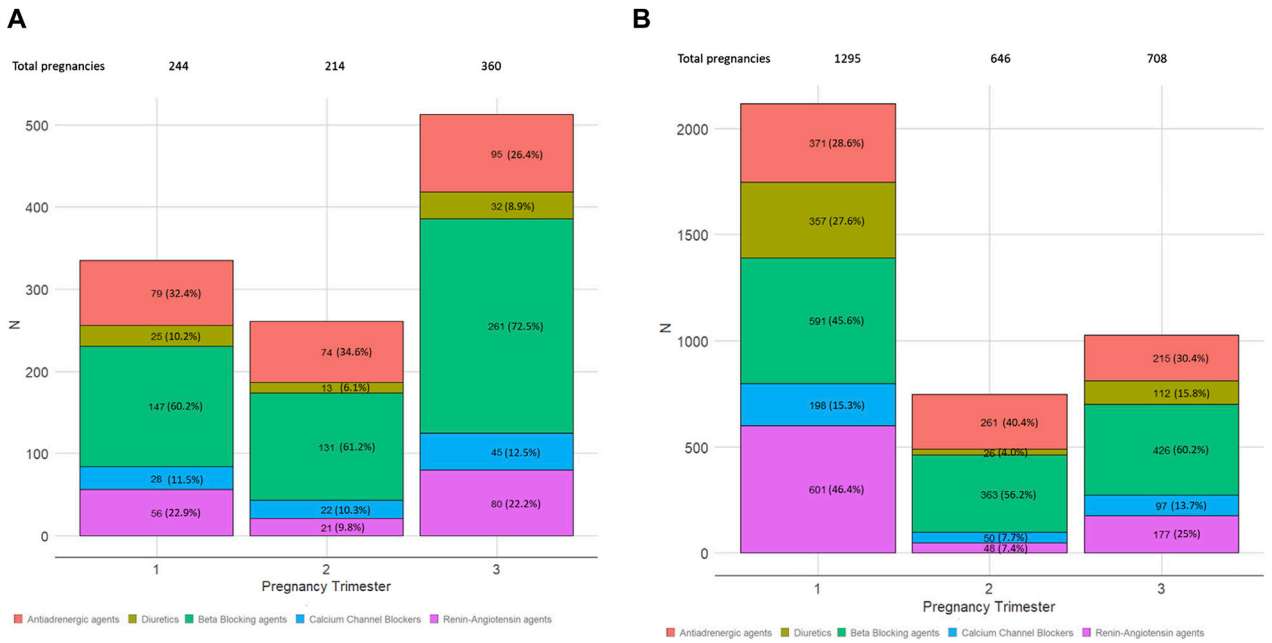

FIGURE 2
Distribution of the number of pregnancies exposed to the different antihypertensive groups by the trimester of gestation. Each bar represents the three pregnancy trimesters. The five colored boxes represent the pharmacological groups, with the number of episodes and percentage inside each box: antiadrenergic agents, diuretics, beta blocking agents, calcium channel blockers, and renin–angiotensin agents. **(A)** Gestational hypertension exposure. **(B)** Chronic hypertension exposure.

may also decrease proteinuria/preeclampsia and fetal/newborn death (Bone et al., 2022; Attar et al., 2023). The boundaries for BP values for when to start medication are uncertain, making this area suitable for shared decision making (SDM), with some research focusing in developing tools for SDM in women with moderate hypertension (Whybrow et al., 2022).

Our results showed a decrease in the exposure to antihypertensives in the second trimester. During the pregnancy-related physiologic changes, BP usually decreases from the baseline values during the second trimester and increases during the third. These changes in BP may lead to a decision to stop treatment in the second trimester; it is reflected in our results (Sanghavi and Rutherford, 2014).

The reduction in the exposure in chronic hypertension pregnancies by the third trimester might be explained by an early referral of high-risk pregnancies to obstetric departments in hospital settings, with no data in the primary care and ambulatory obstetric settings, as prescriptions from hospital providers were not available. Gestational hypertension pregnancies increased exposure by the third trimester, probably due to the higher BP measures during advanced pregnancy.

The most-used antihypertensive medications during pregnancy were BBs, recommended by obstetric guidelines for non-urgent treatment, where the oral BB labetalol and the antiadrenergic central agent methyldopa are the first-line recommended therapies (Brown et al., 2018; Braunthal and Brateanu, 2019). Our results on the most used group are similar to those of a UK cohort study and a US one, where BBs were the most prescribed agents during pregnancy (Cea Soriano et al., 2014; Garcia et al., 2023). For the second trimester of pregnancy, the UK study showed diuretics as the second most-used group, while in our study, for both chronic and gestational hypertension pregnancies, they were antiadrenergic agents. A French study found CCBs and RAS agents as the second most used after BBs (Lailler et al., 2023). Over a decade ago, another US cohort study described antihypertensive nifedipine (33%), a CCB agent, and methyldopa (26%), an antiadrenergic agent, as the most common drugs (Andrade et al., 2008). A more recent cohort study in North Carolina, US, from 2007 to 2017 showed that BBs (79.2%) were the most used, followed by CCBs (31.8%), with labetalol and nifedipine being the most used agents in these groups (Garcia et al., 2023).

Surprisingly, almost half of the pregnancies were exposed to RAS agents (overall 42.4%), though decreasing by trimester. Our rates of exposure to RAS agents by the third trimester (257, 24%) were higher than those in a UK study (12.5%), but they were much higher than those in a French one (0.7%) (Cea Soriano et al., 2014; Lailler et al., 2023). There is a US cohort study that did not mention any exposure to RAS agents while studying different hypertension disorders (chronic included) (Garcia et al., 2023). RAS should be discontinued as soon as possible with awareness of pregnancy, as continuing exposure through pregnancy has been related to malformations, and this may explain the decrease in their use as pregnancy progresses (Al Khaja et al., 2014; Ahmed et al., 2018).

Several studies have tried to show the association between antihypertension and preterm birth. A meta-analysis of eight randomized controlled trials comparing hypertension treatment to control showed protection of preterm birth (OR 0.69; 95% CI, 0.59–0.82) (Chen et al., 2023). In contrast, the meta-analysis of 16 observational studies found a higher OR (2.23, 95% CI 1.96–2.53) for preterm birth for women with chronic hypertension compared to normotensive, a four times greater odds of medically

indicated preterm birth (ORadj 4.76, 95% CI 3.55–6.14) but no association between chronic hypertension and spontaneous preterm birth (ORadj 1.44, 95% CI 0.74–2.80) (Al Khalaf et al., 2021). In 2014, a Cochrane systematic review including 49 trials and over 4,000 pregnant women concluded no effect on the incidence of preterm births of treated mild–moderate hypertension (Abalos et al., 2018).

It remains unclear if treating hypertension resulted in a negative effect on pregnancy outcomes or if the higher risk of preterm birth could be caused by the severity of hypertension. It might be possible that elective delivery could be indicated in those with worse hypertension control and more antihypertensive treatment.

Limitations

We aimed to describe the use of antihypertensive agents during pregnancy in patients with hypertension disorders considering EHR data potential misclassification in time and specific diagnosis, which was the reason why we classified hypertension as chronic or gestational by the time hypertension diagnosis was registered and not by the specific definition. For hypertension, the BP levels are of relevance, but we did not have BP values, which might have helped in a more accurate classification of hypertension and its severity (Chen et al., 2020). We did not account for multiple pregnancies; these pregnancies have been associated with a higher risk for hypertension and preterm elective delivery (Sibai et al., 2000). To avoid exposure misclassification, we defined hypertension medication exposure by two invoices, considering that just one invoice could be an error, especially when just in the second trimester, or not be accurate for the initial and end terms of the pregnancy. However, exposure misclassification in pharmacoepidemiologic studies conducted with databases has frequently been reported (Prada-Ramallal et al., 2019).

Conclusion

We have described the antihypertensives used in a Catalan cohort of pregnancy episodes that shows that BBs are prescribed the most, which is in line with worldwide guidelines. Pregnancies were exposed to RAS agents, which deserves further detailed study, as does its implications in the offspring. Considering women already on RAS treatment prior to gestation, physicians may explain the risk of conception while on treatment with these agents.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the IDIAP Jordi Gol Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the need for consent was waived by the Research Ethics Committee of IDIAPJGol as it was deemed unnecessary according to European legislation (Regulation (EU0) 2016/679).

Author contributions

AG-L: conceptualization, funding acquisition, investigation, writing–original draft, and writing–review and editing. CV-C: data curation, formal analysis, funding acquisition, investigation, methodology, visualization, writing–review and editing. ML: funding acquisition, investigation, visualization, writing–original draft, and writing–review and editing. CV: conceptualization, funding acquisition, investigation, supervision, and writing–review and editing. RM: conceptualization, funding acquisition, investigation, supervision, writing–review and editing. MG-S: conceptualization, funding acquisition, investigation, writing–original draft, and writing–review and editing.

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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/fphar.2024.1346357/full#supplementary-material

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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Krzysztof Dyrbuś,
Silesian Center for Heart Diseases, Poland
Guy Friedrich,
Innsbruck Medical University, Austria

*CORRESPONDENCE
Kristen Kopp,
k.kopp@salk.at

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Implementation of risk-based lipid-lowering therapies in older (age ≥ 65 years) and very-old adults (age ≥ 75 years) with ischemic heart disease in the greater Salzburg region

Kristen Kopp[1]*, Lukas J. Motloch[1,2,3], Bernhard Wernly[4], Alexander E. Berezin[1], Victoria Maringgele[5], Anna Dieplinger[6], Uta C. Hoppe[1] and Michael Lichtenauer[1]

[1]Department of Internal Medicine II, Division of Cardiology, Paracelsus Medical University, Salzburg, Austria, [2]Department of Internal Medicine II, Salzkammergut Klinikum, OOEG, Voecklabruck, Austria, [3]Department of Cardiology, Kepler University Hospital, Medical Faculty, Johannes Kepler University, Linz, Austria, [4]Institute for General-, Family- and Preventive Medicine, Paracelsus Medical University, Salzburg, Austria, [5]Department of Psychiatry, Psychotherapy and Psychosomatics, Paracelsus Medical University, Salzburg, Austria, [6]Institute for Nursing and Practice, Paracelsus Medical University, Salzburg, Austria

Introduction: European guidelines recommend the implementation of lipid-lowering therapies (LLTs) in adults (≥ 65 years) with established atherosclerotic cardiovascular disease (ASCVD) and for risk-based primary prevention in older adults (≤ 75 years), yet their use in very-old adults (> 75 years) is controversial, discretionary, and oriented on the presence of risk factors. The aim of this retrospective study is to assess guideline-directed LLT implementation and low-density lipoprotein cholesterol (LDL-C) target achievement in high-/very-high-risk older/very-old adults (65–74 and ≥ 75 years) at presentation for ST-segment elevation myocardial infarction (STEMI) and also to assess evidence-based care delivery to older adults in our region.

Methods: All STEMI patients with available LDL-C and total cholesterol presenting for treatment at a large tertiary center in Salzburg, Austria, 2018–2020, were screened (n = 910). High-risk/very-high-risk patients (n = 369) were classified according to European guidelines criteria and divided into cohorts by age: < 65 years (n = 152), 65–74 years (n = 104), and ≥ 75 years (n = 113).

Results: Despite being at high-/very-high-risk, prior LLT use was < 40% in the total cohort, with no significant difference by age. Statin monotherapy predominated; 20%–23% of older/very-old adults in the entire cohort were using low-/moderate-intensity stains, 11%–13% were using high-intensity statins, 4% were on ezetimibe therapy, and none were taking proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. In the secondary prevention cohort, 53% of older/very-old patients used prior LLTs. Significantly higher percentages of older/oldest ASCVD patients (43% and 49%) met LDL-C targets < 70 mg/dL compared to patients < 65 years (29%; p = 0.033), although just 22% and 30% of these older groups attained stricter LDL-C targets of < 55 mg/dL. Low LLT uptake (16%) among older adults aged 64–74 years for primary prevention resulted in 17% and 10% attainment of risk-based LDL-C targets <

70 mg/dL and < 55 mg/dL, respectively. Oldest adults (≥ 75 years) in both primary and secondary prevention groups more often met risk-based targets than older and younger adults, despite predominantly receiving low-/moderate-intensity statin monotherapy.

Conclusion: Secondary prevention was sub-optimal in our region. Less than half of older/very-old adults with established ASCVD met LDL-C targets at the time of STEMI, suggesting severe care-delivery deficits in LLT implementation. Shortcomings in initiation of risk-based LLTs were also observed among high-/very-high-risk primary prevention patients < 75 years, with the achievement of risk-based LDL-C targets in 10%–48% of these patients.

KEYWORDS

older adults, low-density lipoprotein cholesterol, lipid-lowering therapy, guidelines, ST-segment elevation myocardial infarction, very-high risk

1 Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide and in Europe, claiming some 1.8 million lives in the European Union annually (Timmis et al., 2020), with ischemic heart disease followed by stroke as the most prevalent CVD condition (Vaduganathan et al., 2022). CVD poses a major burden not only to the individual patient but also to health systems, being the highest healthcare cost component in the European Union. It accounts for 11% of EU health expenditure and an estimated €282 billion in annual costs (Luengo-Fernandez et al., 2023), thus making prevention to reduce CVD risk an essential health policy priority. Atherothrombotic coronary artery disease (ASCVD) is a root cause of type I myocardial infarction (Thygesen et al., 2018). Underlying the development of ASCVD is the retention of low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein B-containing lipoproteins within the artery walls (Ference et al., 2017). As well-described in the literature, increased LDL-C values are causally linked to ASCVD development, and inversely, lower LDL-C values are correlated with a lower risk of future adverse cardiovascular (CV) events (Boekholdt et al., 2014; Ference et al., 2017). Every 1 mmol/L or 38.7 mg/dL absolute reduction in LDL-C corresponds to approximately a 10% reduction in all-cause mortality and an estimated 21% reduction in the occurrence of major adverse vascular events (Cholesterol Treatment Trialists CTT Collaboration et al., 2010).

Age is a relevant factor for CVD development, and increasing age is associated with higher rates of adverse CVD events (Stoll et al., 2020). Age is also considered a primary driver of risk, as age equals cumulative exposure time to risk factors (Mach et al., 2020). According to a 2022 American Heart Association publication, older adults ≥ 75 years in the US are disproportionately affected by ischemic heart disease and account for 30%–40% of all hospitalized patients with acute coronary syndrome (ACS) and the majority of ACS deaths (Damluji et al., 2023). Although the last decade has witnessed a decline in CVD death rates in developed countries due to better prevention and treatment, a paradoxical increase in CVD burden in older adults is expected due to the demographic shift and expansion of populations aged 65 years and older, increased life expectancy, and larger populations of older adults with a history of CVD taking optimal therapies (Dai et al., 2016).

A large body of evidence has shown that use of statins and cholesterol absorption inhibitors such as ezetimibe produces significant reductions in vascular events in patients with established ASCVD across all age groups, as well as in primary prevention in older adults ≤ 75 with high-/very-high-risk CVD profiles (Catapano et al., 2016; Ouchi et al., 2019; Mach et al., 2020; Lettino et al., 2022). The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) in their jointly issued *Guidelines for the Management of Dyslipidemias* in 2016, and upgraded in 2019, thus recommend first-line treatment with statins for people aged > 65 years with established ASCVD in the same way as for younger patients to achieve risk-based LDL-C targets (Catapano et al., 2016; Mach et al., 2020), with the introduction of ezetimibe recommended if LDL-C targets remain unmet on the maximally tolerated statin dose (Mach et al., 2020). Newer classes of drugs such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) may be considered in primary prevention and recommended in secondary prevention if targets are not achieved despite the use of statin–ezetimibe combination therapies, although data on their use in older adults are limited (Mach et al., 2020; Nanna et al., 2023). While the 2016 and 2019 ESC/EAS *Guidelines* provided a scoring system (Systematic Coronary Risk Estimation, SCORE) to calculate the 10-year cumulative risk of a fatal CVD event, a new SCORE-OP (older persons) published in 2021 now supports clinicians for implementation of LLT in older adults ≥70 years in primary prevention (SCORE2-OP working group and ESC Cardiovascular risk collaboration et al., 2021). However, certain patient groups are identified as high-/very-high risk without the need for risk calculation and thus are targeted for LDL-C-lowering and lifestyle interventions (Catapano et al., 2016; Mach et al., 2020). Guideline-recommended LDL-C target levels are based on total individual CV risk with the necessary follow-up evaluation of treatment responses, as responses vary according to the individual (Boekholdt et al., 2014; Corn et al., 2023).

However, LLT use in very-old adults > 75 years is contentious, especially in primary prevention in patients without ASCVD or modifiable CVD risk factors, in part due to less robust data in this age group but also due to other considerations such as multi-morbidity, frailty, cognitive impairment, polypharmacy, impaired renal function, safety (prevented outcomes versus side effects), quality of life, and longevity (Lettino et al., 2022).

The concept of time to benefit (TTB) versus time to harm (TTH) has emerged with respect to implementation of preventative LLTs and prioritization of multiple therapies in older and multi-morbid individuals (Holmes et al., 2013). Some authors have reconsidered the appropriateness of statin prescription in older individuals, arguing that the benefit of statin treatment should guide clinical decisions and citing the Cholesterol Treatment Trialists Collaboration meta-analysis showing that a standard reduction of cholesterol in patients age > 75 years would lead to an absolute risk reduction of 0.6% per year with a resultant number needed to treat (NNT) of 167 to prevent one vascular event per year of therapy (Cholesterol Treatment Trialists CTT Collaboration et al., 2010; Ruscica et al., 2018). Meta-analyses of several large primary prevention lipid trials (ASCOT-LLA, JUPITER, HOPE, and CARDS trials) describe NNTs ranging from 21 to 62 to prevent the occurrence of one adverse CV event that may include nonfatal MI, stroke, or CV death with use of atorvastatin or rosuvastatin in older individuals (> 60, 65, or ≥ 70 years) (Ruscica et al., 2018) A recent meta-analysis of LDL-lowering in 244,090 patients published in the *Lancet* in 2020, however, found an unequivocal reduction in the risk of vascular events with both statin and non-statin LDL-C lowering treatments, reducing the incidence of the endpoints CV death, myocardial infarction, stroke, and coronary revascularization both in patients ≥75 years and <75 years and in primary as well as secondary prevention (Gencer et al., 2020).

The goal of primary and secondary prevention in older as well as younger patients is to prevent or delay the progression of ASCVD with manifestations such as myocardial infarction, stroke, critical limb ischemia, or CV death. Prevention of events potentially results not only in increased longevity and maintenance of functional status but also an improved quality of life for patients, in addition to potential reduction in healthcare system burden and costs.

1.1 Study aims

The aims of the study are 1) to assess the use of risk-based, guideline-recommended LLT among older adults aged 65–74 years and very-old adults ≥75 years with and without medical history of ASCVD at the time of presentation for STEMI in our region, 2) to contribute knowledge about the use of statin-based treatments, especially in the oldest adults ≥ 75 years as described in "Gaps in the Evidence" in the ESC/EAS Guidelines for the Management of Dyslipidemias, and 3) to determine risk-based LDL-C target achievement in a real-world STEMI population with a focus on older and very-old adults meeting high- and very-high-risk criteria.

2 Methods

2.1 Study design

All patients (n = 964) presenting with ST-segment elevation myocardial infarction (STEMI) between 1 January 2018 and 31 December 2020 at a single, large tertiary care center in Salzburg, Austria, were screened for this retrospective study. Our center functions as the primary 24/7 regional cardiac care provider, providing cardiac catheterization services to patients from the State of Salzburg (2023 population: 568,000) as well as the greater region, including parts of the States of Upper Austria, Styria, Tirol (Austria), and Bavaria, Germany.

The inclusion criteria are as follows: STEMI patients aged ≥ 18, with available LDL-cholesterol (LDL-C, mg/dL) and total cholesterol (TC, mg/dL) values drawn during baseline hospitalization for STEMI (n = 910). Patients (n = 54) without available LDL-C and/or TC values were excluded.

Patients with available LDL-C and TC values (n = 910) were then screened for the presence of high-/very-high-risk criteria, as described in the 2016 and the 2019 *ESC/EAS Guidelines for the Management of Dyslipidemias*, the current guidelines during the time of enrollment. A total of 324 patients met ESC/EAS high-risk or very-high-risk criteria when they presented for STEMI. Patients were stratified by age, and a description of age classification is provided in Section 2.2. The achievement of guideline-recommended, risk-based LDL-C targets (2016 and 2019) was then analyzed in all age groups. For patient inclusion and cohort stratification, see Figure 1.

A sub-analysis of patients with and without prior ASCVD was performed to assess the differences in guideline recommendations for LLT use by age and medical history conditions. Additionally, as severe kidney disease (eGFR <30 mL/min/1.73 m^2) may affect prescription, dosing, and uptake of LLT, and as impaired renal function is common in older and very-old adults, a sub-analysis of all high-risk/very-high-risk patients with and without severe CKD was done.

Prior LLT in use at the time of admission for STEMI was recorded for all patients. Current daily use of 40 or 80 mg of atorvastatin or 20 or 40 mg of rosuvastatin constituted high-intensity statin use, while moderate-/low-intensity statin use was defined as current daily use of lower doses of atorvastatin, < 40 mg/day; rosuvastatin, <20 mg/day; or use of any other statins/doses (simvastatin, pravastatin, and fluvastatin in our study). Ezetimibe use in combination with statins or alone, use of PCSK9 inhibitors, and use of any other lipid-lowering therapy were recorded, although fibrates were the only non-statin/non-ezetimibe LLT in use among STEMI patients in this study.

To determine the presence of high-risk or very-high-risk characteristics, medical history was collected for all patients (see detailed description in Section 2.3). Laboratory parameters drawn during baseline hospitalization for STEMI included TC, triglycerides, HDL-C, non-HDL-C, LDL-C, HbA1C, CRP, eGFR, and cardiac markers such as high-sensitivity troponin T (hs-cTnT) and creatinine kinase (CK).

2.2 Patient age classification

Age is considered a major risk factor for CVD, yet the age cutoffs described in the literature and international guidelines are arbitrary, and the term "older adult" has been applied to individuals aged > 65 years, > 70 years, and > 75 years. The current definition according to the United Nations for older adults is a person ≥ 65 years of age (United Nations, 2023), while the World Health Organization (WHO) defines them as ≥ 60 years of age (World Health Organization, 2017). The ESC/EAS 2016 guidelines loosely use the term "older adults" without specifically defining its meaning,

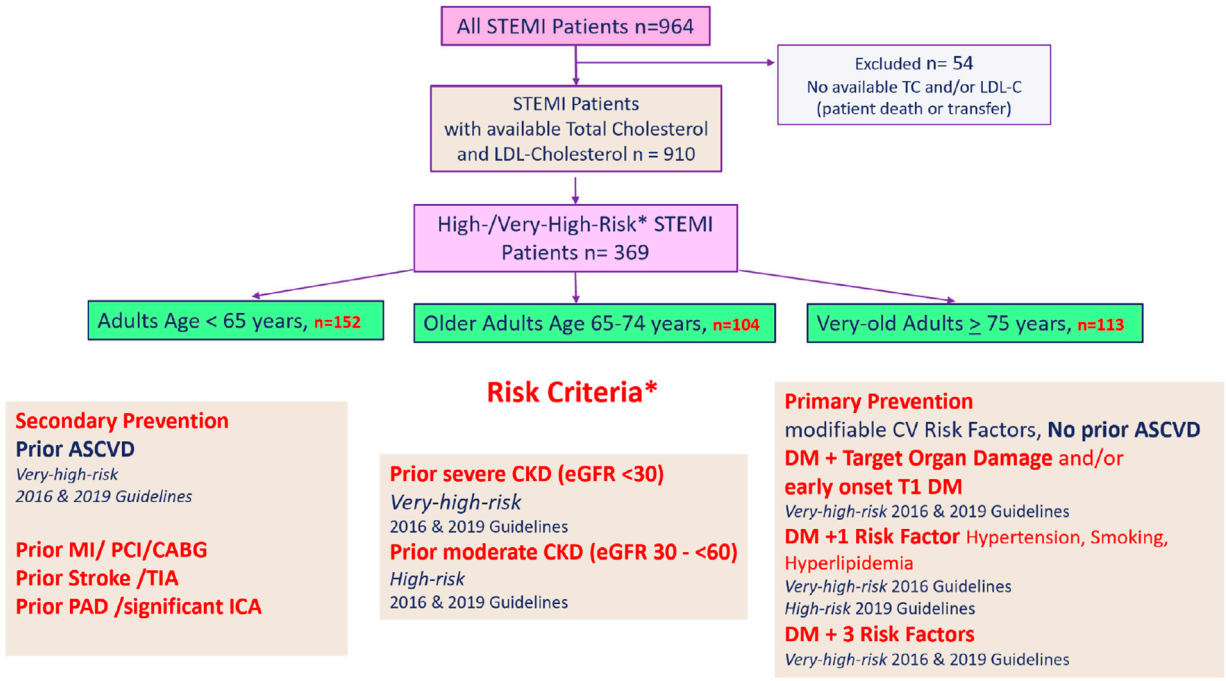

FIGURE 1
Patient inclusion and cohort stratification. STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol mg/dL; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; PAD, peripheral arterial disease; ICA, internal carotid artery stenosis; CKD, chronic kidney disease; DM, diabetes mellitus; T1 DM, type I diabetes mellitus.

although citing literature using the age cutoffs, 65, 70, and 75 years (Catapano et al., 2016). The revised 2019 ESC/EAS guidelines used more specific terminology and defined older people as those > 65 years old, here recommending statin use in older people with ASCVD in the same way as for younger patients (secondary prevention) (Mach et al., 2020). The 2019 guidelines also utilized an age cutoff of 75, recommending risk-based statin use in patients aged ≤ 75 years (1A recommendation) and consideration of their use in high-risk/very-high-risk patients > 75 years of age, although a IIb/B recommendation was given due to gaps in evidence. Based on cutoffs of 65 and 75 years, we selected the following age cutoffs and terminology for use in our study: adults < 65 years, older adults aged 65–74 years, and very-old adults ≥ 75 years.

2.3 Patient risk classification and risk-based LDL-C targets

The period under consideration in our study (2018–2020) witnessed a change in the guidelines, both with respect to risk classification and guideline-directed, risk-based LDL-C targets. Both the 2016 and 2019 ESC/EAS guidelines defined patients with overt, documented ASCVD, either clinical or unequivocal on imaging, as having a very-high 10-year risk of fatal CVD. These include patients with previous myocardial infarction (MI) and/or coronary revascularization, previous stroke, or transient ischemic attack (TIA) and those with peripheral arterial disease (PAD) or significant internal carotid artery stenosis as seen on imaging. Patients with prior severe chronic kidney disease (CKD) with eGFR < 30 min/mL/1.73 m^2 are also classified as very-high risk in both guideline years (Catapano et al., 2016; Mach et al., 2020). Additionally, diabetes mellitus (DM) patients with evidence of target organ damage, defined as microalbuminuria, retinopathy, or neuropathy, and/or early onset Type I DM (>20 years), and/or DM II patients presenting with three major risk factors such as smoking, hypertension, and hyperlipidemia are considered very-high risk for a fatal CVD event in both guidelines (Catapano et al., 2016; Mach et al., 2020). No risk score calculation is needed for patients with one or more of these very-high-risk criteria, and these patients will always qualify for medical LLT and lifestyle intervention. Patients with medical history of any of the aforementioned criteria were thus classified as very-high risk in our study.

With respect to guideline-directed risk-based LDL-C targets for very-high-risk patients, the 2016 Guidelines set an LDL-C target of < 70 mg/dL, while the revised 2019 ESC/EAS guidelines were more stringent, reducing the target to <55 mg/dL and urging "the lower the better" prevention strategies. Hence, both LDL-C cut-offs have been analyzed in our study.

Regarding risk classification in other DM patient groups, DM II patients presenting with just one additional risk factor such as hyperlipidemia (HLP), hypertension (HTN), or smoking are described in the 2016 Guidelines as very-high risk; however, DM plus a single risk factor was down-classified to high risk only in the 2019 Guidelines (Catapano et al., 2016; Mach et al., 2020). We therefore also included patients with high-risk criteria in our analysis due to guideline revision. Patients with DM but without end-organ damage, patients with moderate CKD (eGFR 30–59 mL/min/1.73 m^2), and patients with TC > 310 mg/dL are also considered high-risk in both guideline years and are included in our study

population. The risk factor familial hypercholesterolemia (FH) was not captured in our database, and while FH patients with established ASCVD are included by default, those without may not be captured (see limitations in Section 4.6). The 2016 and 2019 ESC/EAS Guidelines recommended LDL-C targets of <100 mg/dL and <70 mg/dL, respectively, for high-risk patients (Catapano et al., 2016; Mach et al., 2020), and therefore, these cutoffs were included in our analysis.

2.4 Measurement of LDL-C

All laboratory parameters were analyzed at the University Institute for Medical-Chemical Laboratory Diagnostics at the University Clinic Salzburg at the time of admission for STEMI. Plasma LDL-C concentration was determined using a c702 module of the Roche Cobas® 8000 Analyzer (Roche Diagnostics Mannheim, Germany) according to the current manufacturer's instructions. LDL-C was calculated using the Friedewald formula when triglyceride levels were <275 mg/dL; otherwise, a direct method of measurement of LDL-particle numbers was applied. According to EASC/EAS guidelines, both calculated and direct measurements of LDL-C show good alignment Ference et al., 2017. However, it must be noted that the reliability of the Friedewald LDL-C calculation may be influenced by a non-fasting state. Additionally, plasma LDL-C and LDL particle concentrations can become discordant in patient populations with certain comorbidities such as diabetes or hypertriglyceridemia; thus, ESC/EAS guidelines recommend analyzing non-HDL-C (Catapano et al., 2016; Mach et al., 2020). Due to the presence of these comorbidities in many high-/very-high-risk patients and because fasting status could not be reliably determined upon admission for STEMI, non-HDL-C values were therefore provided for all patients.

2.5 Estimating the glomerular filtration rate

The CKD–EPI formula was used to estimate the glomerular filtration rate (eGFR, mL/min/1.73 m^2) (Levey et al., 2009).

2.6 Statistical analyses

All analyses were descriptive, and the data were summarized by age groups. A Shapiro–Wilk test confirmed the unequal distribution of data. A chi-square test was thus applied for categorical variables, which are reported as numbers and percentages. A Wilcoxon rank-sum test was applied for continuous variables. Here, data are reported as the median and interquartile range (IQR). A p-value < 0.05 is considered statistically significant. Stata/BE 18.0 software was used for statistical analysis (StatCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StatCorp LLC, United States).

2.7 Data extraction

Data were extracted from STEMI hospitalization charts, and admission, discharge, and laboratory reports were found in the ORBIS electronic medical records system (Agfa Healthcare, version 08043301.04110DACHL) and the medical records archiving system (Krankengeschichten Archiv System, Uniklinikum Salzburg, Softworx by Andreas Schwab ™, 2008) of the University Clinic Salzburg, Austria, and entered pseudo-anonymously into an Excel database.

2.8 Ethics declaration

The Ethics Commission of the State of Salzburg, Austria, approved this study on 12 April 2021 (EK-Nr. 1038/2021) and determined that no patient informed consent was required due to the retrospective study design. The data were handled in accordance with the Declaration of Helsinki and according to Good Clinical Practice (ICH-GCP).

3 Results

3.1 High-/very-high-risk older adults (65–74 years) and very-old adults (≥ 75 years)

Table 1 illustrates patient characteristics for all high-risk/very-high-risk patients (n = 369) for the entire STEMI cohort by age. Women comprised 14%, 26%, and 41% of the < 65 year, 65–74 year, and ≥ 75 year populations, respectively (p < 0.001). With respect to behavioral risk factors, high active smoking rates were observed in younger adults aged <65 years (59%) and in older adults aged 65–74 years (24%), exceeding the 2019 Austrian national average of 21% and the EU average of 18.4% daily active smokers (OECD, 2021). A greater number of former smokers were observed among older adults (29%) and very-old adults (27%) (p < 0.001). The median BMI of each age cohort was 28, 27, and 26 (p < 0.001), thus meeting the WHO classification of overweight (BMI 25 to <30 kg/m^2), with the upper quartile of patients aged < 65 years and aged 65–74 years meeting the classification of obesity (World Health Organization Fact, 2023).

Among classic CV risk factors, previously diagnosed hypertension was most common, occurring in 77%–90% of high-/very-high-risk STEMI patients, and was most prevalent in very-old adults aged ≥ 75 years (p < 0.001). Previously diagnosed hyperlipidemia was observed in 76%–80% of STEMI patients, without significant differences between age groups (p = 0.77). Note that while hypertension was pretreated in 52%–77% of patients, again most often in very-old adults ≥75 years (p < 0.001), pretreatment of hyperlipidemia was observed in just 32%–37% of STEMI patients with no significant differences between age groups (p = 0.69).

With respect to established ASCVD at presentation for STEMI, prior coronary artery disease was observed in 30%–42% of patients, with no significant differences between age groups; prior peripheral arterial disease (PAD) and/or internal carotid arterial disease were noted in 14%–22% of patients and were more common in older and very-old adults, although the differences between age groups were non-significant (p = 0.27). Patients with previous ischemic stroke or TIA comprised 7%–19% of the STEMI patient population, and this finding of ASCVD medical history was most common in older and very-old adults (p = 0.006).

TABLE 1 Patient characteristics.

	Age < 65	Age 65–74	Age ≥ 75	*p*-value
	N = 152	*N* = 104	*N* = 113	
Age	57 (52–61)	70 (67–72)	79 (77–83)	<0.001
Gender				<0.001
Women	14% (22)	26% (27)	41% (46)	
Men	86% (130)	74% (77)	59% (67)	
BMI	28 (26–31)	27 (25–31)	26 (23–29)	<0.001
Smoking				<0.001
Current	59% (90)	24% (25)	11% (12)	
Former	14% (21)	29% (30)	27% (30)	
Hypertension	77% (116)	82% (84)	90% (102)	0.023
Hypertension pretreated	52% (78)	67% (68)	77% (87)	<0.001
Hyperlipidemia	79% (119)	80% (82)	76% (86)	0.77
Hyperlipidemia pretreated	32% (48)	37% (38)	36% (41)	0.69
Prior MI	34% (51)	27% (28)	26% (29)	0.31
Prior PCI/CABG	42% (64)	38% (39)	30% (34)	0.13
Prior Stroke/TIA	7% (10)	9% (9)	19% (21)	0.006
Prior PAD/ICA	14% (22)	18% (19)	22% (25)	0.27
Prior renal insufficiency	11% (17)	29% (30)	50% (56)	<0.001
Diabetes mellitus	52% (79)	53% (55)	40% (45)	0.079
Diabetes pretreated	29% (43)	39% (40)	26% (29)	0.042
Prior heart failure	14% (21)	12% (12)	15% (17)	0.73
LVEF %	40 (35–50)	40 (35–50)	40 (35–50)	0.67
Atrial fibrillation	3% (4)	9% (9)	21% (24)	<0.001
Cancer				0.012
Active	2% (3)	7% (7)	4% (4)	
Previous	2% (3)	7% (7)	11% (12)	
Death during STEMI hospitalization	7% (11)	10% (10)	17% (19)	0.041

ASCVD, atherosclerotic coronary vascular disease; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; PAD, peripheral arterial disease; ICA, internal carotid artery stenosis; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction.

Among other patient characteristics, medical history of CKD (eGFR <60 mL/min/1.73 m^2) was observed in 29% of older adults 65–74 years and in 50% of very-old adults ≥ 75 years, compared with 11% in adults < 65 years ($p < 0.001$). Older patients also had significantly higher rates of atrial fibrillation and active/prior cancer than patients < 65 years, although prior heart failure and left ventricular ejection fraction (40%, IQR 35–50) did not differ significantly between age cohorts. The incidence of prior diabetes mellitus, although more common in patients <75 years (52%–52% vs. 40%), was not significantly different between age groups. Compared to just 7% ($n = 6$) of younger adults, 12% ($n = 7$) of older adults and 17% ($n = 12$) of very-old adults died during hospitalization for STEMI; however, the difference in incidence between age groups was not significant ($p = 0.12$).

Laboratory values are listed by age group in Table 2. In this study, the most notable findings are significant differences observed in lipid profiles and renal function (eGFR) between age groups. Younger patients < 65 years showed highest TC (176 mg/dL, IQR 148–208) compared to adults aged 65–74 and ≥ 75 years (157 mg/dL, IQR 130–194; 152 mg/dL, IQR 129–200; $p = 0.004$), as well as highest LDL-C (103 mg/dL, IQR 76–135) compared to older adults (86 mg/dL, IQR 64–118) and oldest adults (86 mg/dL, IQR 58–121), $p = 0.004$. Parallel to higher LDL-C values, non-HDL-C was also highest in patients < 65 years compared to older and very-old adults (134 mg/dL, IQR 100–166; 108 mg/dL, IQR 82–142; and 103 mg/dL, IQR 72–146, respectively; $p < 0.001$). Additionally, significantly more patients < 65 years had triglyceride levels in excess of 275 mg/dL (15%; $p = 0.009$) compared to older and very-old

TABLE 2 Laboratory parameters.

	Age < 65	Age 65–74	Age ≥ 75	*p*-value
	N = 152	*N* = 104	*N* = 113	
Cardiac markers				
hsTnT (ng/L, IQR)	3,204 (1,185–6,353)	3,470 (1,431–6,761)	3,813 (1,359–8,025)	0.62
CK (U/L, IQR)	1,445 (642–3,023)	1,281 (599–2,832)	1,213 (525–2,159)	0.099
Lipid parameters				
Total cholesterol (mg/dL, IQR)	176 (148–208)	157 (130–194)	152 (129–200)	0.004
Triglycerides (mg/dL, IQR)	144 (102–213)	108 (71–168)	105 (77–141)	<0.001
HDL (mg/dL, IQR)	42 (35–50)	45 (37–59)	50 (40–61)	<0.001
Non-HDL (mg/dL, IQR)	**134 (100–166)**	**108 (82–142)**	**103 (72–146)**	**<0.001**
LDL (mg/dL, IQR)	**103 (76–135)**	**86 (64–118)**	**82 (58–121)**	**0.004**
Other parameters				
HbA1C (%, IQR)	6 (6–8)	6 (6–7)	6 (6–7)	0.082
CRP	3 (1–10)	3 (1–13)	4 (2–11)	0.30
eGFR	80 (67–90)	68 (50–82)	52 (41–70)	<0.001
Non-HDL				0.006
Non-HDL <85 mg/dL	16% (22)	29% (29)	33% (32)	
Non-HDL 85–99 mg/dL	9% (12)	14% (14)	12% (12)	
Non-HDL >99 mg/dL	76% (106)	57% (58)	55% (54)	
Triglycerides				0.009
Triglycerides <275 mg/dL	85% (122)	92% (93)	96% (100)	
Triglycerides ≥275 mg/dL	15% (22)	8% (8)	4% (4)	
LDL				0.022
LDL <55 mg/dL	6% (9)	17% (17)	23% (23)	
LDL 55–69 mg/dL	16% (23)	15% (15)	16% (16)	
LDL 70–99 mg/dL	25% (36)	25% (25)	24% (24)	
LDL >99 mg/dL	52% (75)	43% (43)	38% (39)	

hsTnT, high-sensitive troponin T; HDL, high-density lipoprotein; non-HDL, non-high-density lipoprotein; LDL, low-density lipoprotein. The parameters highlighted in bold are those required by ESC/EAS to determine LDL-C and non-HDL target attainment.

adults. Regarding other non-lipid parameters, while there were no significant differences between age groups for the parameters HbA1C (6%, $p = 0.082$) and CRP (3–4, $p = 0.30$), renal function (eGFR) was significantly reduced in the older and very-old adult population (80 mg/dL IQR 67–90 adults vs. 68 mg/dL IQR 50–82 older adults, 52, IQR 41–70 oldest adults; $n = <0.001$). A sub-analysis of TC and LDL-C values in patients who died versus those who survived baseline hospitalization showed no significant differences between groups: TC 162 mg/dL, IQR 128–210 vs 166 mg/dL, IQR 137–205; $p = 0.76$ and LDL-C: 81 md/dL, IQR 67–114 vs. 94 mg/dL, IQR 64–128;; $p = 0.75$.

With respect to the focus of our study, see Table 3 for the achievement of LDL-C guideline targets in older/very-old adults with high-/very-high-risk criteria at the time of presentation for STEMI.

During presentation for STEMI, 57% of older adults had an LDL-C < 100 mg/dL, the 2016 target for high-risk patients, yet just 32% of older adults had an LDL-C < 70 mg/dL, the guideline target for very-high-risk patients in 2016 and high-risk patients in 2019. Only 17% of older adults met the more stringent 2019 LDL-C target of <55 mg/dL for very-high-risk patients at the time of STEMI. With respect to secondary non-HDL targets as listed in the 2019 guidelines, 43% of older adults met high risk and just 29% met very-high-risk non-HDL guideline targets at presentation for STEMI.

Among the oldest adults aged ≥ 75 years at the time of STEMI presentation, 63% met the 2016 LDL-C < 100 mg/dL for high-risk patients, while just 39% achieved the LDL-C target of < 70 mg/dL for high-/very-high-risk patients according to the 2016 and 2019 guidelines, respectively. Approximately 23% of very-old

TABLE 3 Prior lipid-lowering therapies and ESC/EAS[a] lipid target achievement.

	Age < 65	Age 65–74	Age ≥ 75	*p*-value
	N = 152	*N* = 104	*N* = 113	
Hyperlipidemia pretreated	32% (48)	37% (38)	36% (41)	0.69
Statin intensity				0.90
Low/moderate-intensity+	16% (25)	23% (24)	20% (23)	
High-intensity*	13% (20)	11% (11)	13% (15)	
Intensity unknown	1% (2)	1% (1)	1% (1)	
Pretreatment with ezetimibe	5% (7)	4% (4)	4% (5)	0.45
Unknown	0% (0)	1% (1)	0% (0)	
Pretreatment with other LLT				0.47
Fibrate	1% (2)	1% (1)	0% (0)	
PCSK9i	0%	0%	0%	
Known statin intolerance	1% (2)	3% (3)	2% (2)	0.66
LLT target achievement				
Non-HDL				0.006
Non-HDL <85 mg/dL	16% (22)	29% (29)	33% (32)	
Non-HDL 85–99 mg/dL	9% (12)	14% (14)	12% (12)	
Non-HDL >99 mg/dL	76% (106)	57% (58)	55% (54)	
LDL				0.022
LDL <55 mg/dL	**6% (9)**	**17% (17)**	**23% (23)**	
LDL 55–69 mg/dL	**16% (23)**	**15% (15)**	**16% (16)**	
LDL 70–99 mg/dL	25% (36)	25% (25)	24% (24)	
LDL >99 mg/dL	52% (75)	43% (43)	38% (39)	

*High-intensity statins: atorvastatin ≥40 mg and rosuvastatin ≥20 mg.

+low/moderate-intensity statins: atorvastatin <20 mg, rosuvastatin <20 mg, or all other statins/doses such as simvastatin, pravastatin, and fluvastatin; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; LDL, low-density lipoprotein. The parameters highlighted in bold are those required by ESC/EAS to determine LDL-C and non-HDL target attainment.

[a]ESC/EAS Guidelines, European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias (2016 and 2019).

adults met the stricter 2019 LDL-C very-high-risk goal of <55 mg/dL. Regarding secondary non-HDL goals, 45% met high-risk and 33% met very-high-risk targets. Note that patients < 65 years had the lowest achievement of guideline targets, with just 22% having LDL-C <70 mg/dL and only 6% meeting LDL-C <55 mg/dL targets at the time of presentation for STEMI, significantly lower than achievement among older patient groups (p = 0.022). Aligning with these observations, just 25% met non-HDL secondary targets <100 mg/dL for high-risk patients and just 16% met the stringent targets for very-high-risk patients, both significantly lower than those of the older and oldest adult populations (p = 0.006).

Hyperlipidemia was pretreated in just 32%–36% of our high-risk/very-high-risk STEMI population, with no significant differences between age groups (n = 0.69) (refer to Table 3 for LLT implementation). Low-/moderate-intensity statins were the most commonly prescribed LLTs, taken by 16%, 23%, and 20% (p = 0.9) adults, older adults, and very-old adults, respectively, at the time of presentation for STEMI, but without significant differences between age groups. Just 13%, 11%, and 13% of STEMI patients in each age category were treated with high-intensity statins, and only few (5%–4%) were treated with ezetimibe, either in combination with statin therapy or alone, also without significant differences between age groups (p = 0.45). Isolated patients were taking fibrates at the time of STEMI. No patient in the entire STEMI cohort was treated with PCSK9is. Known statin intolerance was low and ranged from 1% in adults < 65 years to 3%–2% in older and very-old adults (p = 0.66).

3.2 Very-high-risk patients with previously established ASCVD

Table 4 shows the characteristics of patients with and without previously established ASCVD. Regarding patients with previously diagnosed ASCVD (see Table 4, left column), these secondary prevention patients are always considered very-high risk and thus

TABLE 4 Patient characteristics (patients with and without prior ASCVD).

Patients with prior ASCVD	Age <65	Age 65–74	Age ≥75	*p*-value	Patients without prior ASCVD	Age <65	Age 65–74	Age ≥75	*p*-value
	N = 89	*N* = 59	*N* = 70			*N* = 63	*N* = 45	*N* = 43	
Age	57 (51–61)	70 (66–73)	80 (77–83)	<0.001	Age	58 (55–61)	70 (68–72)	79 (77–83)	<0.001
Gender				<0.001	Gender				0.019
Women	12% (11)	27% (16)	40% (28)		Women	17% (11)	24% (11)	42% (18)	
Men	88% (78)	73% (43)	60% (42)		Men	83% (52)	76% (34)	58% (25)	
BMI	28 (25–31)	27 (24–31)	26 (24–29)	0.19	BMI	28 (27–32)	28 (26–32)	26 (23–29)	<0.001
Smoking				<0.001	Smoking				<0.001
Current	63% (56)	32% (19)	10% (7)		Current	54% (34)	13% (6)	12% (5)	
Former	16% (14)	24% (14)	31% (22)		Former	11% (7)	36% (16)	19% (8)	
Hypertension	76% (67)	81% (48)	91% (64)	0.041	Hypertension	79% (49)	82% (36)	88% (38)	0.46
Hypertension pretreated	52% (45)	71% (42)	79% (55)	0.001	Hypertension pretreated	70% (43)	66% (29)	65% (28)	0.084
Hyperlipidemia	85% (76)	90% (53)	83% (58)	0.52	Hyperlipidemia	70% (43)	66% (29)	65% (28)	0.81
Hyperlipidemia pre-treated	45% (39)	53% (31)	53% (37)	0.52	Hyperlipidemia pre-treated	15% (9)	16% (7)	9% (4)	0.63
Prior MI	57% (51)	47% (28)	41% (29)	0.13	Prior MI	0% (0)	0% (0)	0% (0)	
Prior PCI/CABG	72% (64)	66% (39)	49% (34)	0.009	Prior PCI/CABG	0% (0)	0% (0)	0% (0)	
Prior Stroke/TIA	11% (10)	15% (9)	30% (21)	0.008	Prior Stroke/TIA	0% (0)	0% (0)	0% (0)	
Prior PAD/ICA	25% (22)	32% (19)	36% (25)	0.30	Prior PAD/ICA	0% (0)	0% (0)	0% (0)	
Prior renal insufficiency	8% (7)	27% (16)	37% (26)	<0.001	Prior renal insufficiency	16% (10)	31% (14)	70% (30)	<0.001
Diabetes mellitus	23% (20)	36% (21)	34% (24)	0.16	Diabetes mellitus	94% (59)	76% (34)	49% (21)	<0.001
Diabetes pre-treated	13% (13)	29% (17)	20% (14)	0.29	Diabetes pretreated	49% (31)	51% (23)	35% (15)	0.048
Prior heart failure	23% (20)	15% (9)	16% (11)	0.39	Prior heart failure	2% (1)	7% (3)	14% (6)	0.042
LVEF %	40 (35–50)	42 (35–50)	40 (35–50)	0.99	LVEF %	40 (35–50)	40 (35–50)	40 (35–47)	0.33
Atrial fibrillation	3% (3)	8% (5)	27% (19)	<0.001	Atrial fibrillation	2% (1)	9% (4)	12% (5)	0.095
Cancer				0.039	Cancer				0.50
Active	2% (2)	8% (5)	14% (10)		Active	2% (1)	4% (2)	5% (2)	
Previous	2% (2)	7% (4)	4% (3)		Previous	2% (1)	7% (3)	2% (1)	
Death during hospitalization	7% (6)	12% (7)	17% (12)	0.12	Death during hospitalization	8% (5)	7% (3)	16% (7)	0.25

ASCVD, atherosclerotic coronary vascular disease; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; PAD, peripheral arterial disease; ICA, internal carotid artery stenosis; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction.

require intensive lipid-lowering therapy to meet risk-based LDL-C targets as well as lifestyle interventions for risk reduction. The majority of patients in each age group had prior ASCVD at presentation for STEMI (58.5% of patients < 65 years, *n* = 89; 56.7% of older adults 65–74 years, *n* = 59; and 61.9% of very-old adults ≥ 75 years, *n* = 70). Women represented 27% of the older adult age group and 40% of the very-old adult STEMI population with established ASCVD at the time of admission. Among modifiable risk factors, at least half of the patients in each age group were classified as overweight, with the upper quartile of adults and older adults < 75 years meeting the classification of obesity. The highest rates of active smoking were observed among adults < 65 (63%) and older adults < 75 years (32%).

Regarding ASCVD qualifying conditions, previous incidence of myocardial infarction was observed in 57% of patients < 65 years and 47% and 41% of older and very-old adults, respectively, with no

significant differences by age (p = 0.13). Prior coronary revascularization was significantly more prevalent in younger patients (72% versus 66% of older adults and 49% of very-old adults, p = 0.009). Prevalence of prior PAD/ICA did not significantly differ between age groups, although it was more common in older and very-old adults (p = 0.30). With respect to the prevalence of prior stroke or TIA, no significant differences were observed between age groups, although this medical history was more common in older (32%) and very-old adults (36%) than in adults < 65 years (25%, p = 0.3).

Older and very-old ASCVD patients more commonly had a medical history of hypertension compared to patients < 65 years (81% and 91% versus 76%, p = 0.041). The prevalence of treatment for hypertension also increased significantly with age, with just 52% of patients < 65 years on treatment for hypertension at presentation for STEMI compared to 71% among older adults and 79% (p = 0.001) of very-old adults. Equally common was the presence of hyperlipidemia in patients with prior ASCVD, yet there were no significant differences between age groups. While previous hyperlipidemia was observed in 85% of adults, 90% of older adults, and 83% of very-old adults (p = 0.52), only 45%–53% of very-high risk ASCVD patients were actually on treatment at the time of STEMI, with no significant differences observed between age groups (patients < 65 years, 45% versus older adults (53%) and very-old adults (53%); p = 0.52).

There were significant differences between age groups with respect to the occurrence of severe and moderate chronic kidney disease, an important CV risk factor, which was significantly more prevalent in older and oldest adults (27% and 37%, respectively) compared with adults < 65 years (8%, p < 0.001). While there were no significant differences in the prevalence of diabetes mellitus between age groups, older adults and very-old adults were more often previously diagnosed compared to younger patients (36% and 34% versus 23% respectively, p = 0.16). Furthermore, prevalence of prior and active cancer (p < 0.001) and atrial fibrillation (p < 0.001) was more common in older and very-old adults. Prior heart failure, in contrast, was more prevalent in younger patients aged < 65 years (23%) compared to its prevalence in 15%–16% of older and very-old adults, but this was not significant (p = 0.39). Death during STEMI hospitalization occurred in 7%–17% of patients, and although more common in older and oldest adults, the difference between age groups was non-significant.

3.3 LLTs and LDL-C target achievement in high-risk patients with prior ASCVD

The median LDL-C for this very-high-risk ASCVD population was 97 mg/dL (IQR 64, 135) in younger adults and significantly lower in older adults (77 mg/dL, IQR 58, 108) and very-old adults (77 mg/dL, IQR 51, 109) (p = 0.004). TC was 172 mg/dL (IQR 140, 210), 151 mg/dL (127, 178), and 142 mg/dL (122, 186) in younger, older, and very-old adults, respectively (p = 0.005). Regarding the achievement of risk-based lipid targets, see Table 5.

Less than half of older and very-old ASCVD patients met the 2016 guideline target LDL-C <70 mg/dL for very-high-risk patients (43% of older adults and 49% of very-old adults), with even fewer achieving the more stringent 2019 LDL-C target <55 mg/dL at the time of presentation of STEMI (22% of older adults and 30% of very-old adults). To be mentioned, significantly lower percentages of younger adults < 65 years achieved the 2016 (29%) and 2019 LDL-C targets (7%), respectively, at the time of admission for STEMI (p = 0.033). The achievement of guideline-directed non-HDL secondary targets paralleled findings for LDL-C, with 42% and 36% of older adults meeting 2019 high- and very-high-risk non-HDL targets, respectively, and 50% and 42% of oldest adults ≥ 75 years meeting high-/very-high risk non-HDL secondary targets, respectively.

Fifty-three percent of both older adults 65–74 years and oldest adults ≥ 75 years with prior ASCVD were on treatment for hyperlipidemia at the time of STEMI presentation, primarily statin monotherapy. Low- or moderate-intensity statin therapy predominated, used in 34% of older adults, 29% of very-old adults, and 21% of younger adults, with no significant differences between age groups (p = 0.66). Only 17% of older adults and 20% of the oldest adults were taking high-intensity statins at the time of STEMI presentation. Pre-treatment with ezetimibe was uncommon, with 8% of younger adults, 5% of older adults, and 7% of very-old adults taking ezetimibe either in combination with statins or as monotherapy. None of our ASCVD patients had been given PCSK9 inhibitors. Just 2%–3% of ASCVD patients had documented statin intolerance.

3.4 High-risk/very-high-risk patients without previously diagnosed ASCVD

For characteristics of patients without previously established ASCVD at the time of STEMI presentation, see Table 4, right column. Approximately 43.3% of older adults and 38.1% of very-old adults did not have a medical history of ASCVD at the time of STEMI presentation, yet other risk factors qualified them as high /very-high risk with a need for primary prevention treatment. Women represented 24% of older adults and 42% of very-old adults, yet 17% of the younger adult population (p = 0.019). Median BMI was 28 in younger and older adults and 26 in the oldest adults, meeting the criteria for overweight, with the upper quartile of younger and older adults fulfilling the classification of obesity. In contrast, the lower quartile of very-old adults had a normal weight (p < 0.001). Significantly more younger adults <65 years were active smokers (54%) compared with older adults (13%) and very-old adults (12%) (p < 0.001), although there were higher rates of previous smoking among older (36%) and very-old adults (19%). Again, hypertension was a common comorbidity in this population, observed in 79% of young adults, 82% of older adults, and 88% of very-old adults. Hypertension was pretreated in 70%, 66%, and 65% of younger, older, and very-old adults, respectively, without significant differences by age (p = 0.084). While hyperlipidemia was a common medical history finding in 70% of younger adults <65 years, 66% of older adults aged 65–74, and 65% of oldest adults ≥75 years, pretreatment was observed in just 15% 16%, and 9% of these high-risk/very-high-risk patients, respectively, with no significant differences between age groups (p = 0.63).

The most common high- or very-high-risk criteria for 10-year fatal CVD among the patient population without previously established ASCVD differed significantly by age group. Diabetes

TABLE 5 Lipid-lowering therapies and ESC/EAS[a] lipid target achievement in patients with and without prior ASCVD.

Patients with prior ASCVD	Age <65	Age 65–74	Age ≥75	*p*-value	Patients without prior ASCVD	Age <65	Age 65–74	Age ≥75	*p*-value
	N = 89	*N* = 59	*N* = 70			*N* = 63	*N* = 45	*N* = 43	
Hyperlipidemia pretreated	45% (39)	53% (31)	53% (37)	0.52	Hyperlipidemia pretreated	15% (9)	16% (7)	9% (4)	0.63
Statin intensity				0.66	Statin intensity				0.84
Low/moderate-intensity+	21% (19)	34% (20)	29% (20)		Low/moderate-intensity+	10% (6)	9% (4)	7% (3)	
High-intensity*	20% (18)	17% (10)	20% (14)		High-intensity*	3% (2)	2% (1)	2% (1)	
Intensity unknown	2% (2)	0% (0)	1% (1)		Intensity unknown	0% (0)	2% (1)	0% (0)	
Pretreatment with ezetimibe	8% (7)	5% (3)	7% (5)	0.54	Pretreatment with ezetimibe	0% (0)	2% (1)	0% (0)	0.42
Unknown	0% (0)	0% (0)	0% (0)		Unknown	0% (0)	2% (1)	0% (0)	
Pre-treatment with other LLT				0.55	Pre-treatment with other LLT				0.62
Fibrate	1% (1)	0% (0)	0% (0)		Fibrate	2% (1)	2% (1)	0% (0)	
PCSK9i	0% (0)	0% (0)	0% (0)		PCSK9i	0% (0)	0% (0)	0% (0)	
Known statin intolerance	2% (2)	3% (2)	3% (2)	0.92	Known statin intolerance	0% (0)	2% (1)	0% (0)	0.31
LLT target achievement[a]					LLT target achievement[a]				
Non-HDL				0.028	Non-HDL				0.18
Non-HDL <85 mg/dL	20% (17)	36% (21)	42% (25)		Non-HDL <85 mg/dL	9% (5)	19% (8)	18% (7)	
Non-HDL 85–99 mg/dL	10% (8)	16% (9)	8% (5)		Non-HDL 85–99 mg/dL	7% (4)	12% (5)	18% (7)	
Non-HDL >99 mg/dL	70% (58)	48% (28)	50% (30)		Non-HDL >99 mg/dL	84% (48)	70% (30)	63% (24)	
LDL				0.033	LDL				0.90
LDL <55 mg/dL	7% (6)	22% (13)	30% (19)		LDL <55 mg/dL	5% (3)	10% (4)	10% (4)	
LDL 55–69 mg/dL	22% (18)	21% (12)	19% (12)		LDL 55–69 mg/dL	8% (5)	7% (3)	10% (4)	
LDL 70–99 mg/dL	25% (21)	21% (12)	21% (13)		LDL 70–99 mg/dL	25% (15)	31% (13)	28% (11)	
LDL >99 mg/dL	46% (38)	36% (21)	30% (19)		LDL >99 mg/dL	62% (37)	52% (22)	51% (20)	

[+]low/moderate-intensity statins: atorvastatin < 20 mg, rosuvastatin < 20 mg, or all other statins/doses such as simvastatin, pravastatin, and fluvastatin; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; non-HDL, Non-high-density lipoprotein; LDL, low-density lipoprotein.

*High-intensity statins: atorvastatin ≥40 mg and rosuvastatin ≥20 mg.

[a]ESC/EAS Guidelines, European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias (2016 and 2019).

with one or more additional risk factors such as hypertension, hyperlipidemia, and/or smoking was common in 94% of younger adults < 65 years and in 76% of older adults aged 65–74 years, yet in just 49% of very-old adults ($p < 0.001$). Prior renal insufficiency, in contrast, was observed in just 16% of younger adults, 31% of older adults, and 70% of very -old adults ($p < 0.001$). In addition, very-old adults more commonly had prior heart failure (14%) compared to older adults (7%) and younger adults (2%) ($p = 0.042$). In addition, the presence of atrial fibrillation (9% and 12%, respectively) as well as a medical history of active (4%–5%) or previous (7%, 2%) cancer were more common in older and very-old adults, without significant differences between age groups. Death during hospitalization for STEMI among patients without established ASCVD did not differ significantly between age groups, although it more commonly occurred in very-old adults (17%) compared with older adults (7%) and younger adults (8%) ($p = 0.25$).

3.5 LLT and LDL-C target achievement in high-risk patients without prior ASCVD

LDL-C in high-/very-high-risk patients presenting without known ASCVD was 108 mg/dL (86, 134) in younger adults, 104 mg/dL in older adults (76, 132), and 101 mg/dL (70, 147) in

very-old adults (p = 0.58). TC was 182 (162, 206), 171 mg/dL (148, 215), and 175 mg/dL (142, 214) in these three groups, respectively (p = 0.58). Regarding the achievement of risk-based lipid targets among patients without prior ASCVD upon admission for STEMI, see Table 5, right column.

While less than half of older and very-old adults (48%) met the 2016 high-risk target LDL-C < 100 mg/dL, less than 20% of older and very-old patients in this population met the 2016 very-high-risk guideline target LDL-C <70 mg/dL (17% of older adults and 20% of very-old adults), with just 10% of older and very-old adults achieving the stricter 2019 LDL-C target <55 mg/dL at the time of STEMI presentation. Note that LDL-C target achievement was lowest among younger adults < 65 years, with 13% meeting 2016 LDL-C < 70 mg/dL and 5% meeting 2019 LDL-C target < 55 mg/dL at the time of admission for STEMI, though differences by age were not significant (p = 0.9). The achievement of guideline-directed non-HDL secondary targets was accordingly low, with just 31% and 19% of older adults meeting 2019 high- and very-high-risk non-HDL targets, respectively, and 36% and 18% of oldest adults ≥ 75 years meeting high- and very-high-risk non-HDL secondary targets, respectively.

Pretreatment for hyperlipidemia at the time of STEMI presentation was lowest in this high-risk/very-high-risk cohort of patients without previously established ASCVD at admission for STEMI. Only 16% of older adults 65–74 years and just 9% of oldest adults ≥ 75 years were taking any kind of LLT. Low- or moderate-intensity statin therapy was most common, used in 9% of older adults, 7% of very-old adults, and 10% of younger adults, with no significant differences between age groups (p = 0.84). Pretreatment with high-intensity statin therapy was rare: only 2% of older adults and 2% of oldest adults were taking high-intensity statins at the time of STEMI presentation. Pretreatment with ezetimibe was also uncommon, with 2% of older adults and no very-old adults taking ezetimibe either in combination with statins or as monotherapy at the time of STEMI presentation, with no differences between age groups (p = 0.42). None of our high-risk/very-high-risk patients without prior ASCVD had been treated with PCSK9 inhibitors, although 2% of younger and older adults were taking fibrates at the time of STEMI presentation. Documented statin intolerance was uncommon, present only in 2% of older adults but not in younger or oldest adults (p = 0.31).

3.6 LLT use and LDL-C target achievement in very-high-risk patients with severe kidney disease (<30 mL/min/1.73 m^2)

Patients with severe kidney disease, defined in both ESC/EAS Guideline years as those with eGFR <30 mL/min/1.73 m^2, are always considered to be at very-high risk of ASCVD and are at higher risk of mortality than patients with CVD alone. While the use of statins or statin–ezetimibe combination therapy is recommended in this patient group, LLT implementation may be challenging due to the need for dose adaptations and/or dose-related adverse events. For this reason, we chose to extract patients with severe CKD and perform a sub-analysis on them separately. Only a very small number of patients in our study had prior severe kidney disease without dialysis at the time of STEMI presentation (3% adults < 65 years, n = 4; 3% older adults, n = 3; and 6% very-old adults, n = 7); however, results must be viewed with caution due to the sample size. Pretreatment with low-/moderate-intensity statins was observed in just three patients (one patient in each age group), while only one older adult had prior treatment with a high-intensity statin in combination with ezetimibe. Note that three patients in this cohort had a medical history of prior myocardial infarction with revascularization and/or ischemic stroke, and one had prior PAD, therefore establishing ASCVD. Median LDL-C was 107 mg/dL (IQR 70, 157) and median non-HDL was 121 mg/dL (IQR 78, 163) at admission for STEMI, with only three patients meeting the 2016 LDL-C target of < 70 mg/dL and no patient meeting the 2019 LDL-C target of < 55 mg/dL for very-high-risk patients.

3.7 LLT use and LDL-C target achievement in high-risk/very-high-risk patients without severe kidney disease (eGFR ≥ 30 mL/min/1.73 m^2)

The ESC/EAS guidelines make specific mention with respect to LLT use in older patients with renal impairment, recommending slow up-titration of statins to meet risk-based LDL-C targets, especially as decreasing estimated glomerular filtration rate (eGFR) is clearly associated with increased CVD risk. Use of statins or statin/ezetimibe combination therapy is a 1A recommendation in patients at high- or very-high CVD risk with stage 3–5 kidney disease, yet the guidelines do urge caution with respect to dosing and potential dose-related adverse events. For this reason and as the use of statin therapies in patients with advanced CKD has been controversial, LLT prescription, use, and/or dosing may be more restrictive in patients with more severe renal impairment, thus influencing results. Therefore, we also undertook a sub-analysis of LLT uptake and LDL-C target achievement in high-risk/very-high-risk patients without severe renal disease (eGFR ≥ 30 mL/min/1.73 m^2) by age (see Table 6).

In our study, 97% of adults < 65 years, 97% of older adults aged 65–74 years, and 94% of very-old adults aged ≥ 75 years had eGFR ≥ 30 mL/min/1.73 m^2 at presentation for STEMI. The median eGFR was 80 (69, 90) in younger adults, 68 (54, 82) in older adults, and 54 (43, 71) in very-old adults. Median LDL-C in this cohort was 104 mg/dL (IQR 76, 135), 85 mg/dL (63, 115), and 81 mg/dL (56, 121) in younger, older, and very-old adults, respectively. TC values were 177 mg/dL (148, 208) in younger adults, 156 mg/dL (130, 190) in older adults, and 152 (129, 201) in very-old adults at presentation for STEMI.

Despite being at high-/very-high-risk, just 31% of younger adults, 34% of older adults, and 35% of very-old adults in this population were pretreated with LLTs at the time of admission (p = 0.74). Again, pretreatment with low-/moderate-intensity statin monotherapy was most common but was observed in just 16% of younger adults, 23% of older adults, and 20% of oldest adults (p = 0.87). High-intensity statin use upon admission for STEMI was seen in only 10% of older adults and 14% of both younger adults and very-old adults. Ezetimibe use, either alone or in combination therapy, was rare, observed in 3% of older adults and 5% of very-old adults. Known statin intolerance was low, recorded in 1%–3% of our high-risk/very-high-risk STEMI patients.

The corresponding achievement of LDL-C risk-based targets was also low, with 32% of older adults and 39% of very-old adults meeting the 2016 very-high and 2019 high-risk LDL-C target <70 mg/dL at the time of STEMI, with younger adults < 65 years having the poorest target

TABLE 6 Lipid-lowering therapies and ESC/EAS[a] lipid target achievement in patients without severe kidney disease (eGFR ≥ 30 mL/min/1.73²)[b].

	Age <65	Age 65–74	Age ≥75	*p*-value
	N = 148	*N* = 101	*N* = 106	
Hyperlipidemia pretreated	31% (46)	34% (34)	35% (37)	0.74
Statin intensity				0.87
Low/moderate-intensity+	16% (24)	23% (23)	20% (21)	
High-intensity*	14% (20)	10% (10)	14% (15)	
Intensity unknown	1% (2)	1% (1)	1% (1)	
Pretreatment with ezetimibe	5% (7)	3% (3)	5% (5)	0.44
Unknown	0% (0)	1% (1)	0% (0)	
Pretreatment with other LLT				0.59
Fibrate	1% (2)	1% (1)	0% (0)	
PCSK9i	0%	0%	0%	
Known statin intolerance	1% (2)	3% (3)	2% (2)	0.67
LLT target achievement[a]				
Non-HDL				0.007
Non-HDL <85 mg/dL	15% (21)	29% (28)	32% (30)	
Non-HDL 85–99 mg/dL	9% (12)	14% (14)	12% (11)	
Non-HDL >99 mg/dL	76% (104)	57% (56)	56% (52)	
LDL				0.015
LDL <55 mg/dL	**6% (9)**	**18% (17)**	**24% (23)**	
LDL 55–69 mg/dL	**16% (22)**	**14% (14)**	**15% (15)**	
LDL 70–99 mg/dL	25% (35)	26% (25)	23% (22)	
LDL >99 mg/dL	53% (74)	42% (41)	38% (37)	

*High-intensity statins: atorvastatin ≥40 mg and rosuvastatin ≥20 mg. The parameters highlighted in bold are those required by ESC/EAS to determine LDL-C and non-HDL target attainment.
+low/moderate-intensity statins: atorvastatin < 20 mg, rosuvastatin < 20 mg, or all other statins/doses such as simvastatin, pravastatin, and fluvastatin.
[a]ESC/EAS Guidelines, European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias (2016 and 2019).
[b]eGFR, estimated glomerular filtration rate; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; non-HDL, non-high-density lipoprotein; LDL, low-density lipoprotein.

achievement (22%) (p = 0.015). With respect to the more stringent 2019 LDL-C goal of < 55 mg/dL, just 6% of younger adults, 18% of older adults, and 24% of very-old adults met this target at the time of presentation for STEMI. Secondary non-HDL goals were also achieved in only a minority of patients. Just 43% of older adults and 44% of oldest adults met high-risk targets of < 100 mg/dL, with only 29% of older adults and 32% of very-old adults meeting the very-high-risk non-HDL target of < 85 mg/dL. Note that younger adults had the lowest achievement for both non-HDL targets (p = 0.007).

4 Discussion

4.1 Deficits in LLT implementation and LDL-C target achievement in older-/very-old adults with established ASCVD

The results of our study showed severe deficits in prior LLT use, with just 32%–36% of high-risk and very-high-risk patients on treatment for hyperlipidemia at the time of STEMI presentation, without significant differences by age group. Sub-optimal implementation of risk-based, guideline-directed therapies was observed in STEMI patients on prior treatment, both in younger adults and older adults 65–74 years and in very-old adults ≥75 years at the time of presentation for STEMI, although the severity of deficits in our study differed according to the presence or absence of prior ASCVD. As a consequence, the achievement of risk-based LDL-C targets was less than ideal in our older and very-old adult STEMI population. In our study, just over half (53%) of older and very-old ASCVD patients were pretreated with LLTs, predominantly with low-/moderate-dose statin monotherapy and ≤7% with combined ezetimibe, with just a 3% rate of statin intolerance reported. Approximately 12% and 17% of older and very-old patients with established ASCVD prior to STEMI did not survive to discharge.

A large body of evidence has underscored ESC/EAS guideline recommendations for statin use in secondary prevention in high-risk older patients > 65 years with established ASCVD in the same

way as for younger patients (Boekholdt et al., 2014; Efficacy and safety of LDL, 2015; Catapano et al., 2016; Bach et al., 2019; Mach et al., 2020). Here, the causal role of LDL-C and the benefits of lipid-lowering therapy must be emphasized. A systematic review and meta-analysis of 21,292 older patients aged ≥ 75 years from statin, ezetimibe, and PCSK9i randomized control trials (RCTs) and the 24 Cholesterol Treatment Trialists (CTT) Collaboration studies demonstrated that LDL-C lowering significantly reduced the risk of major vascular events in older patients (≥75 years) by 26% per 1 mmol/L reduction in LDL cholesterol (RR 0.74 [95% CI 0.61–0.89; $p = 0.0019$]) with no statistically significant differences compared to that in patients <75 years (0.85 [0.73–0.91; $p_{interaction} = 0.37$]) (Gencer et al., 2020). Significant reductions were seen for all included composite endpoints, such as CV death, myocardial infarction, stroke, and coronary revascularization, regardless of age. Additionally, Gencer et al. (2020) found no offsetting safety concerns that would pose a barrier to treatment.

Another meta-analysis of statin use in older patients aged ≥ 65–82 years with established CVD showed a reduction in all-cause mortality, with an estimated relative risk reduction of 22% over 5 years with the use of statins (RR 0.78, 95% credible interval CI 0.65–0.89). Moreover, a reduction of 30% was also observed in coronary heart disease mortality (RR 0.70; 95% CI 0.53–0.83); non-fatal myocardial infarction, 26% (RR 0.74; 95% CI 0.6–0.89); need for revascularization, 30% (RR 0.7; 95% CI 0.53–0.83); and occurrence of stroke, 25% (RR 0.75; 95% CI 0.56–0.94). A posterior median estimate of NNT to save 1 life was 28 (95% CI 15–56) (Afilalo et al., 2008). In our study, however, 47% of older and very-old adults with established ASCVD were not taking any LLTs at the time of admission for STEMI, suggesting either potential adherence or intolerance issues or deficits in follow-up care delivery after their first ASCVD event or diagnosis. Note that 71% and 79% of older and very-old ASCVD were taking and prescribed medications for comorbidity hypertension and thus were managed by a healthcare provider, yet risk-based LLT was not implemented in these patients despite low reported statin intolerance (3, 2%).

Of particular note is the relatively low incidence of statin intolerance (SI) observed among our real-world STEMI patients, in contrast to findings from a large, ESC/EAS meta-analysis of 176 studies in 4 million patients worldwide, which showed a 9.1% [95% CI, 8%–10%] pooled prevalence of SI, regardless of statin type, and a 5.9% [4.0%–7.0%] SI incidence when using EAS diagnostic criteria (Bytyçi et al., 2022). The authors also noted that SI incidence was significantly lower in RCTs compared to cohort studies [4.9% (4.0%–6.0%) vs. 17% (14%–19%)], an observation not aligned with our results. Especially interesting, however, was the 13% [95% CI, 2.0%–24%] SI incidence described in secondary prevention acute coronary syndrome patients, compared to the 2%–3% seen among our patients with prior ASCVD at presentation for STEMI. In a meta-regression analysis, Bytyçi et al. (2022) observed that age as a continuous variable was significantly associated with a higher SI risk [odds ratio OR 1.33, 95% CI 1.25–1.41, $p = 0.04$], yet in our study, no significant differences in SI were observed between age groups, perhaps explained by our comparatively small sample size.

According to the Cholesterol Treatment Trialists' Collaboration, more-intensive statin regimens produce a highly significant 15% further reduction in major vascular events compared to less intensive regimens, primarily through significant reductions in coronary death and non-fatal myocardial infarction (Cholesterol Treatment Trialists CTT Collaboration et al., 2010). The SAGE study (Study Assessing Goals in the Elderly) study also showed an association between high-intensity statin therapy and greater reductions in LDL-C, the occurrence of major acute cardiovascular events, and death in patients aged 65–85 years of age when compared to the use of moderate-intensity statin therapy (Deedwania et al., 2007).

However, in our study, 34% and 29% of older and very-old ASCVD patients were treated with low/moderate dose statin therapy at the time of STEMI, respectively, and just 17% and 20% of older/very-old patients were treated with high-intensity statin therapy, despite guideline recommendations encouraging up-titration of statins to meet risk-based LDL-C guideline targets (2016) or prescription of a high-intensity statin titrated to the highest tolerated dose (2019), with the addition of ezetimibe if targets are unmet (2019) in very-high-risk populations. Ezetimibe was only used in 5%–7% of our older and very-old ASCVD patients at the time of admission for STEMI. Our findings align with those of a US study of high-intensity statin and non-statin LLT use in older patients ≥ 75 years with ASCVD. In that study, 49.3% were taking any statin, with 16.6% taking a high-intensity statin, 32.7% taking a low-/moderate-intensity statin, 2.4% on ezetimibe, and a rare use of PCSK9is (0.24%) (Nanna et al., 2023). Although we cannot confirm in our retrospective study whether the observed doses were actually those most tolerated, our findings still highlight deficits in the intensification of statin therapy and/or in the expansion of therapy with ezetimibe in the majority of our older and very-old patients with established ASCVD. A secondary analysis of the IMPROVE-IT study, an RCT examining combined statin–ezetimibe therapy versus statin monotherapy in ACS patients, demonstrated that the greatest absolute risk reduction was observed among patients aged ≥75 years. Addition of ezetimibe to statin treatment was not associated with a significant increase in safety issues among the oldest patients (Bach et al., 2019).

It is important to note that none of our STEMI patients were on prior treatment with PCSK9 inhibitors, despite the 1A recommendation for their use in secondary prevention patients not meeting LDL-C targets at maximally tolerated doses of statin–ezetimibe therapy. Although PCSK9is were introduced to the Austrian market in 2016, lack of use or prescription may potentially be attributed to high costs, initially restrictive prescribing policies by social insurance carriers, or concerns about weaker evidence regarding their use in older populations underrepresented in market-entry RCTs.

Sub-optimal achievement of LDL-C targets was observed in our secondary prevention patients, aligning with the described LLT implementation deficits: only 43% of older adults and 49% of very-old adults with established ASCVD met 2016 LDL-C targets <70 mg/dL, and just 22% of older adults and 30% of very-old adults met stricter 2019 LDL-C targets <55 mg/dL at the time of presentation for STEMI. Several large European registries and observational studies, such as Da Vinci, EUROASPIRE-V, and SANTORINI studies, describe gaps between guideline recommendations and actual clinical practice (De Backer et al., 2019; Ray et al., 2021; Gouni-Berthold et al., 2022; Ray et al., 2023). Although not differentiated by age, the EU-wide observational Da

Vinci study of LLT use and LDL-C target achievement in 5,888 primary and secondary care patients noted that just 35% of the patients with established ASCVD (n = 2,794) taking moderate-intensity statin monotherapy met the 2016 targets and 16% met the 2019 targets. In contrast, 45% of ASCVD Da Vinci patients taking high-intensity statin monotherapy met 2016 and 22% met 2019 LDL-C goals, respectively, highlighting persisting deficits in LDL-C goal attainment even in those patients prescribed and taking LLTs (Ray et al., 2021). In those Da Vinci ASCVD patients taking statin–ezetimibe combination therapy, 54% met 2016 LDL-C targets and 21% achieved more stringent 2019 goals. The mean age of ASCVD patients was 68 years (SD 10), thus roughly corresponding to the age of our older and younger patient populations. As in the Da Vinci study, we observed some discrepancy between the 53% of older adults and very-old adults taking LLTs at the time of STEMI and the respective rates of LDL-C attainment. Interesting to note were higher percentages of very-old adults achieving stricter LDL-C < 55 mg/dL targets than older adults aged 65–74, and there was less of a treatment discrepancy in LDL-C target attainment in the oldest group. Observations from a Danish nationwide cohort study (n = 82,958) describe large patient-to-patient variability in LDL-C responses to statin treatment, and the authors observed that initiation of low–moderate-intensity statins was associated with greater reduction in LDL-C levels in oldest patients (age > 75) than in younger patients, both in primary and secondary prevention patients (Corn et al., 2023), offering a potential explanation for the higher treatment response in our oldest ASCVD patients. Older adults had higher plasma concentrations than younger adults, which authors suggested may be linked to greater bioavailability of statins and greater drug absorption in older patients, or to age-related changes in hepatic function, leading to increased statin exposure, or to impairment in renal function potentially affecting statin concentrations (Corn et al., 2023).

Relevant to our study were the results of the EU-wide Santorini study, which focused on LLT implementation and achievement of 2019 guideline LDL-C targets among high- and very-high-risk patients in diverse primary and secondary care settings in 14 European countries (n = 9,044), including Austria (n = 310), in 2020–2021 (Ray et al., 2023). Among the 9,044 patients enrolled in the Santorini study, the majority (73.3%) did not achieve 2019 LDL-C goals, and the median LDL-C was out of target, both in high-risk (93 mg/dL, 2.4 mmol/L) and very-high-risk patients (78 mg/dL, 2.0 mmol/L). A total of 6,954 patients (76.9%) had prior ASCVD, thus classifying them as very high-risk. Among Santorini ASCVD patients, 21.4% were not taking any LLTs at baseline, 53% were taking statin monotherapy, and just 25.6% were taking combination LLTs (Ray et al., 2023). One key message in the study was that LDL-C targets were not attained in the vast majority of very-high-risk patients, even in those using high-intensity statin monotherapy, and the authors concluded that combination therapies proven to effectively lower LDL-C levels still have not found widespread use in Europe. This finding mirrors the results of our study. The finding that 1,094 (15.7%) patients with ASCVD were incorrectly classified by their physicians as high-risk instead of very-high risk was alarming as well, indicating an underestimation of patient risk and perhaps contributing to sub-optimal LLT implementation with resultant LDL-C not at target levels (Ray et al., 2023).

In the Austrian Santorini cohort (n = 310), 26.1% of patients were not taking any LLT, 48.1% were on statin monotherapy, and 25.8% were taking combination therapies at baseline (Ray et al., 2023). The resulting out-of-target median LDL-C levels (78.1 mg/dL, 2.02 mmol/L) demonstrated sub-optimal LLT implementation among high- and very-high-risk patients (Ray et al., 2023). When compared to the total Santorini study population and Austrian sub-cohort, our real-world STEMI population had even higher LDL-C medians (82–103 mg/dL) and inversely lower rates of 2019 LDL-C target achievement in just 15%–16% of high-risk and 6%–23% of very-high-risk patients across all age groups. Severe deficits in LLT implementation were observed among our patients, as 64%–68% of high-/very-high-risk patients were not taking any LLT at presentation for STEMI, 16%–20% were taking low-/moderate-intensity statins, and just 11%–13% were taking a high-intensity statin with only 4%–5% on combination therapy, more severe deficits than observed among participants in the Santorini study, without significant differences between age groups.

4.2 Deficits in LLT implementation and LDL-C target achievement in older adults (aged 65–74) without established ASCVD

With respect to primary prevention, the 2019 guidelines recommend a risk-based approach for utilization of statins for older patients ≤ 75 years (1A recommendation) and consideration for their use in high-/very-high-risk patients >75 years (IIb/B), while the 2016 guidelines, also in place during our study period, make a general IIa/B recommendation for "consideration of their use in older adults free of CVD, particularly in the presence of risk factors hypertension, smoking, diabetes and dyslipidemia" (Catapano et al., 2016; Mach et al., 2020). In our study, just 16% of older adults aged 65–74 years without established ASCVD but with high-/very-high-risk criteria were taking LLTs for primary prevention at the time of STEMI. Nine percent of patients were taking low-/moderate-intensity statin therapy, with 2% on high-intensity statin treatment at the time of STEMI, although the statin intensity was unknown. Ezetimibe use was low at 2%. With respect to LDL-C target attainment, 48% of older patients met 2016 high-risk LDL-C targets of < 100 mg/dL, while 17% attained the 2016 very-high-risk/2019 high-risk LDL-C target of < 70 mg/dL. Just 10% of patients aged 65–74 years met the 2019 very-high-risk LDL-C target <55 mg/dL. A 2% statin intolerance was reported in this age group.

Note that 66% of these patients were on treatment for hypertension and 51% were treated for the comorbidity DM, suggesting potential care-delivery deficits with respect to low rates of risk-based LLT implementation, especially following the more direct 2019 guideline recommendations. However, with respect to the 2016 ESC/EAS IIa/B recommendation, the decision not to implement LLT may have often been a conscious one, especially amid the debate regarding the time to benefit of statin treatment in primary prevention in this age group and uncertainty about the effects of statins in older adults (Yourman et al., 2021) In a US meta-analysis evaluating the time to benefit of statin use in primary prevention, including 60,383 patients aged 50–75 years, Yourman et al. (2021) concluded that treating 100 adults without

established CV disease in this age group with a statin for 2.5 years would likely yield prevention of one MACE in one adult. In contrast, results of a British meta-analysis in 70,388 patients concluded that statins in primary prevention improve survival and reduce the risk of major CV and cerebrovascular events in people without established CVD, with equal treatment benefits across a range of clinically defined groups (men/women, older adults > 65 years, and those with DM) (Brugts et al., 2009).

4.3 LLT implementation and LDL-C target achievement in older adults (aged ≥ 75) without established ASCVD

The use of statin therapy for primary prevention in oldest adults > 75 years is contentious, especially due to multi-morbidities, frailty, polypharmacy, altered pharmacokinetics and pharmacodynamics, and safety concerns with respect to drug-related adverse events or drug–drug interactions, potentially outweighing treatment benefits. In this context, both 2016 and 2019 guidelines are careful with recommendations for initiation of statin therapy for primary prevention in oldest patients >75 years with high-/very-high-risk profiles, which "may be considered" (IIb/B) (Catapano et al., 2016; Mach et al., 2020). In our study, 9% of oldest adults with high-risk/very-high-risk profiles were on prior treatment with statin at the time of presentation for STEMI, with 7% taking low-/moderate-intensity therapy and 2% taking high-intensity therapy. No patient was using ezetimibe alone or as a combination therapy. No statin intolerance was reported. This age group had the highest rates of renal insufficiency (70%) and prior heart failure (14%), potentially influencing decisions to initiate LLT. Approximately 20% of patients in this age group had LDL-C values < 70 mg/dL and 10% had LDL-C values < 55 mg/dL at the time of presentation for STEMI.

The literature offers mixed evidence regarding the appropriateness, use, and benefit of statin therapy in oldest adults without overt ASCVD. A US Veterans observational study of 326,981 predominantly male patients ≥ 75 years free of ASCVD at baseline showed that initiation of statin therapy was significantly associated with a lower risk of all-cause and CV death (Orkaby et al., 2020). A French study evaluating the new use of statins in 7,284 patients aged ≥ 75 years to lower the risk of acute coronary syndrome or all-cause death with a 4.7-year follow-up showed that cumulative use of statins was associated with a lower risk of outcomes in primary prevention patients with modifiable risk factors as well as in secondary prevention patients, but not in primary prevention patients without modifiable risk factors (Bezin et al., 2019). However, in a meta-analysis of individual participant data from 28 RCTs, the CTT collaboration authors concluded that while statin therapy produces significant reductions in major vascular events irrespective of age, there was a less direct benefit in patients > 75 years without evidence of prior occlusive vascular disease (Gencer et al., 2020).

4.4 LLT implementation and LDL-C target attainment in the context of renal impairment

Both the 2016 and 2019 guidelines make unequivocal recommendations for statin or combined statin–ezetimibe use in patients with CKD stages 3–5 to address concurrent high ASCVD risk, yet the guidelines urge caution when dosing due to increased blood concentrations of compounds with the potential for drug-related adverse events in this population (Catapano et al., 2016; Mach et al., 2020). Among the small cohort of patients with severe CKD (eGFR < 30 mL/min/1.73 m^2) in our study, only 3 out of 14 (21%) were on treatment with a low-/moderate-intensity statin and only 1 was treated with high-intensity statin–ezetimibe combination therapy at the time of STEMI. Corresponding LDL-C target achievement was low, with 3 patients meeting the <70 mg/dL LDL-C targets and none attaining stricter < 55 mg/dl LDL-C goals. However, in a meta-analysis examining the effect of renal function on LDL cholesterol lowering in patients with severe kidney disease, the Cholesterol Treatment Trialists' Collaboration determined that statin-based therapy reduced the risk of a first major vascular event by 21% (RR 0.79, 95% CI 0.77–0.81; $p < 0.0001$) per mmol/L on LDL-C reduction (Cholesterol Treatment Trialists' CTT Collaboration et al., 2016). Reductions in LDL-C, however, became smaller with more advanced CKD. In parallel, reductions in major vascular events observed with the use of statin-based therapies became smaller as eGFR declined, with little or no benefit derived in patients on dialysis. The authors concluded that in patients with severe CKD, statin-based regimens should be selected to maximize absolute LDL-C reduction to attain maximal therapeutic benefits (Cholesterol Treatment Trialists' CTT Collaboration et al., 2016).

As severe renal impairment may influence prescribing, uptake, and dosing of statins and is often cited as the reason for drug-related adverse events, we removed patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) in a sub-analysis to determine potential effects on LLT implementation and corresponding LDL-C target achievement results in the remaining cohort, especially as prior renal insufficiency was significantly prevalent in 29% older and 50% very-old adults, both with and without prior ASCVD, compared to younger adults. However, after removing these patients, similar rates of pretreatment LLT were observed between age groups in 31%, 34%, and 35% of younger, older, and very-old adults, respectively. Rates of low-/moderate-intensity statin use were also comparable between age groups (16%, 23%, and 20%, respectively), as was the less-common use of high-intensity statins (14%, 10%, and 14%) and the rare use of ezetimibe (5%, 3%, and 5%). Significant differences in LDL-C target attainment by age were observed in this cohort, with the highest attainment of LDL-C targets < 70 mg/dL found among older (32%) and oldest adults (39%) and the achievement of stricter LDL-C targets < 55 mg/dL observed in just 18% of older and 24% of very-old adults. These results mirror the findings of our total cohort. Note that these findings allow no justification for missing, low, or non-optimized LLT implementation, as the guidelines make a 1A recommendation for statin or combined statin–ezetimibe use in patients with stages 3–5 CKD at high- or very-high CVD risk (Mach et al., 2020).

4.5 Healthcare delivery deficits

Sub-optimal implementation of guideline-directed, risk-based LLTs was seen in our study, especially among older and very-old adults with established ASCVD (secondary prevention) as well as in older adults < 75 years without prior ASCVD but with a high-/very-high-risk profile (primary prevention) at the time of presentation for STEMI.

Severe healthcare delivery deficits were observed among secondary prevention patients across all age groups. With respect to older and very-old adults with established ASCVD, most were only taking statin monotherapy and were treated with low-/moderate-intensity statins (34, 29%), despite the low achievement of LDL-C targets, meaning that dose intensity had not been optimized in many patients on prior treatment. Few of our older-/very-old very-high-risk patients were taking high-intensity statins (17, 20%), and fewer were using ezetimibe therapy (5%–7%), despite the evidence of its efficacy and recommendation for use. The percentage of patients with documented statin intolerance was low (3%) in our older/very-old populations; thus, the lack of therapy intensification cannot solely be attributed to statin intolerance. Our findings align with those of several studies describing the underuse of statins in older ASCVD populations (Ko et al., 2004).

Especially worrisome is the finding that 47% of our very-high-risk older/very-old adults with established ASCVD were not on any LLTs at the time of STEMI, despite their demonstrated efficacy in preventing subsequent events. Considering that 71% of older and 79% of very-old ASCVD patients were prescribed and taking medications for the comorbidity hypertension and were thus managed by a healthcare provider, the lack of LLT use in large percentages of these patients highlights a severe deficit in follow-up care in these very-high-risk patients after an initial ASCVD event or diagnosis. Coupling the prescription of hypertension medications and/or the prescription of medications for other comorbidities represents a strategy for improving LLT uptake. As patients in Austria are required to physically pick up prescriptions from their general practitioners or internists, the prescription of an LLT at the time of prescription for other conditions was either overlooked, adherence issues/side-effects were not addressed, or a very high risk was not recognized by a healthcare provider. In primary prevention among high-/very-high-risk patients aged 65–74 years, single digit rates of statin use were reported with low attainment of risk-based LDL-C targets, although here poor LLT implementation may be attributed to weaker 2016 guideline recommendations. However, the 2019 guidelines issued a 1A recommendation for their use in high-/very-high-risk patients aged ≤ 75. Therefore, our findings show deficits in uptake. Again, 66% of patients were concomitantly treated with medications for hypertension and 51% for diabetes mellitus, suggesting that healthcare providers were not recognizing or appropriately managing risk.

The European Society of Cardiology provides evidence-based risk prediction tools and resources for physicians and allied health professionals to align patient characteristics, clinical signs, and laboratory tests with accurate, objective prediction of risk to support appropriate treatment strategies, improve clinical outcomes, and avoid both overtreatment of low-risk individuals and undertreatment of those with higher risk (Rossello et al., 2019). Validated risk prediction tools such as the Systematic Coronary Risk Evaluation (SCORE2) model and SCORE-OP (for older persons) may be used with patients to discuss risks, tailor patient counseling, encourage adherence to medications and lifestyle changes, and facilitate shared treatment decisions (SCORE2-OP working group and ESC Cardiovascular risk collaboration et al., 2021; Rossello et al., 2019; SCORE2 working group and ESC Cardiovascular risk collaboration et al., 2021). However, some obstacles to its routine implementation in daily practice have been described, such as lack of time or the perceived simplicity of the algorithm in contrast to patient complexity, which causes resistance among some physicians (Rossello et al., 2019). Risk prediction tools allow healthcare providers to more accurately gauge risk and tailor LLT to meet risk-based LDL-C goals in ASCVD populations. Greater uptake of these tools has the potential to remedy deficits in LLT implementation and LDL-C target achievement observed in STEMI populations across all age groups.

Poor patient adherence and/or diminishing uptake of LLTs over time in older populations, often in conjunction with LLT side effects, such as statin-related muscle pain, have been reported in the literature (Cheeley et al., 2022). The ESC/EAS guidelines recommend addressing any potential statin side effects with patients and providing healthcare providers with strategies for gradual dose up-titration, the addition of ezetimibe, and/or potentially PCSK9is to achieve LDL-C targets (Mach et al., 2020). If a conscious decision to deprescribe statins was made due to polypharmacy, potential adverse reactions, and/or concerns about treatment complications, then effective alternative therapies, for example, with PCSK9 inhibitors, were not initiated in our patients, also highlighting a potential care-delivery deficit. An Italian population-based study of nearly 30,000 older patients with mean age 76.5 years described the consequence of deprescribing statins in older patients with polypharmacy, associating statin depresciption with an increase in the long-term risk of fatal and non-fatal CV outcomes, especially in high-risk patients (Rea et al., 2021).

Non-adherence to evidence-based therapies for CVD is multifactorial and has been attributed to sociodemographic, psychological, economic, and clinical factors as well as the complexity of treatment regimens, polypharmacy, and pill burden, especially common in older patients (Bramlage et al., 2017; Tamargo et al., 2022). Use of a polypill is one option to address sub-optimal drug adherence and has been shown in multiple studies to significantly improve adherence to long-term regimens (Bramlage et al., 2017). The SAGE (secondary prevention of cardiovascular disease in the elderly) demonstrated significant improvements to CVD medication adherence in older adults ≥ 65 years with a corresponding reduction in major adverse CV events 6 months post-MI through the use of a polypill compared to individual medication doses (Castellano et al., 2022). A German retrospective study of statin and ezetimibe prescribing practices in over 300,000 CVD patients also described higher LLT adherence rates when using a fixed dose statin–ezetimibe polypill versus individual pill intake, noting cardiologists were more likely to prescribe a polypill with high-intensity statins than GPs, who tended to prescribe low-to-moderate-intensity statin monotherapy, with low rates of add-on ezetimibe therapy prescription (Katzmann et al., 2022).

Mobile health (mHealth) tools offer another new modality for providing patient education and adherence support using mobile devices, such as mobile phones and other personal monitoring devices, falling loosely under the rubric of telemedicine (Gandapur et al., 2016). Automated SMS reminders, alarms, and voice messaging have been shown to increase adherence to CV medicines, with some studies describing higher percentages of correct doses, doses taken on time, and improved cumulative adherence (Park et al., 2014; Vollmer et al., 2014; Wald et al.,

2014), although study designs and sizes varied and did not specifically focus on use of mHealth tools among older adults. Note that despite the use of statins, LDL-C targets are not always achieved in all patients. A large Australian population study of 61,000 patients retrospectively examined LDL-C goal achievement among all risk groups and found that only 36% of patients on statin therapy actually met therapeutic targets (Talic et al., 2022). These findings only partially align with the observations of our study. Although 53% of our older patients with ASCVD were on treatment, just 43% met 2016 and 22% met 2019 LDL-C targets. The discrepancy between LLT use and LDL-C target achievement was less pronounced among very-old patients with established ASCVD (53% LLT use versus 49% and 30% achievement by guideline year). Our findings emphasize the importance of LDL-C follow-up measurement and the importance of therapy optimization if LDL-C targets are unmet. Follow-up control cannot be left to chance but requires policies to ensure guideline-directed therapy implementation and optimization to reduce potential future adverse CV events.

When current LLTs are inadequate or not well-tolerated, emerging alternative classes of drugs have been shown to lower LDL-C, such as the small interfering RNA injectable, inclisiran, as an alternative to PCSK9 inhibitors, or the ATP citrate-lyase inhibitor, bempedoic acid, for statin-intolerant patients, and may offer benefit, although robust data for their use in older and very-old adults are still needed (Mach et al., 2020).

Identification and follow-up of very-high-risk patients are essential not only for the control of LDL-C but also as an opportunity for management of other ASCVD risk factors, such as overweight/obesity and smoking. In our study, more than three-quarters of older STEMI patients were overweight/obese and 32% of older patients with a very-high-risk profile were actively smoking at the time of STEMI presentation, demonstrating the need for more rigorous lifestyle risk factor management in these patients.

The ESC has urged improvement in preventative care, especially through the use of secondary prevention programs (inpatient, outpatient, and long-term interventions), cardiac rehabilitation, and multidisciplinary preventive services in the community (Piepoli et al., 2016). Yet the ESC estimates that only one-third to one-half of eligible patients are referred to appropriate prevention programs, identifying barriers at the patient, healthcare provider, and healthcare system levels. At the patient level, hurdles include not receiving or understanding information from healthcare providers, lack of social support, poor psychological wellbeing, lack of access to programs, and competing work and family commitments (Piepoli et al., 2016). At the healthcare provider level, educational gaps in detailed preventive care knowledge among cardiologists, GPs, and allied healthcare specialists, a shift from longer hospital stays to less expensive outpatient treatment, leaving a limited amount of time and resources for education, inappropriate risk stratification, a lack of or inadequate post-discharge strategies to support patients, and suboptimal communication between acute care and primary care healthcare providers all contribute to inadequate referral or enrollment of patients to prevention programs (Piepoli et al., 2016). Limiting factors at the healthcare system level include a lack of available prevention centers or rehabilitation programs for all regions, a lack of minimum standards for the quality and delivery of secondary prevention programs, the need for accountability measures such as referral performance and evaluation of appropriate prescriptions of evidence-based medications at the system level, as well as the need for structured, multidisciplinary care pathway plans to be used by health services to guide the referral and management of patients qualifying for risk-based (secondary) prevention programs (Piepoli et al., 2016). Life expectancy in high-income countries for patients aged 75 is expected to be at least 10 years (Gencer et al., 2020); therefore, adequate risk control and risk reduction are essential for longevity, maintenance of functional status, and quality of life, both in the interest of patients and with respect to healthcare system costs and burden.

4.6 Limitations

Our findings should be interpreted in the context of several limitations. The main limitation was the single-center, retrospective design of our study. Therefore, our results may not reflect LLT implementation or LDL-C target achievement in older and very-old adult high-risk/very-high-risk populations in other EU regions. Yet our study serves as a healthcare delivery quality indicator in our region, and the sub-optimal implementation of guideline-directed, risk-based LLTs and poor LDL-C target achievement, especially among older/very-old patients with established ASCVD, observed in our study is a finding potentially applicable in other regions. An important limitation to be highlighted is that 54 patients or 5.6% of the entire STEMI patient population were excluded as no LDL-C and/or TC was available, despite clear guideline recommendations for clinical risk assessment during STEMI hospitalization. Lack of testing may have been caused by either patient death, staff oversight, or patient transfer out of our clinic prior to testing, partially explained in 2020 by disrupted care delivery processes at the start of the SARS-CoV-2 pandemic.

Our study had other limitations to report. Although lipoprotein-B measurement is suggested in the guidelines, this parameter is not routinely measured in STEMI patients at our hospital, however, both ESC/EAS guidelines determined risk and treatment targets using LDL-C and TC, which were the parameters used in our study. The ESC/EAS guidelines offer a scoring system for calculation of risk for 10-year fatal CVD. We did not use the SCORE calculator to solely classify patients as high/very-high risk in our retrospective study, as we could not confirm whether blood pressure measurements at the presentation for STEMI required for the SCORE calculation were performed in a harmonized way. Therefore, the actual number of high-/very-high-risk patients may be underestimated. The newer SCORE-OP, a specific calculator for determining risk in older persons, was not yet published at the time of our study and, therefore, was not used. Another potential group of very-high-risk patients not specifically captured in our study concerns those with FH, although FH patients with confirmed ASCVD were included by default. However, FH and only one major risk factor may not have been recognized as very-high risk, again possibly resulting in an underestimation of the total number of very-high-risk patients. Another limitation concerns the results of the sub-analysis in patients with severe CKD, which must be viewed with caution due to the very small sample size.

A retrospective study cannot confirm a causative effect of LDL-C exceeding guideline-recommended target levels with the presentation for

STEMI, despite the implication of LDL-C in the development of ASCVD. However, as widely documented, LDL-C reductions correlate to reductions in all-cause mortality and occurrence of major adverse cardiovascular events, such as STEMI. Our study therefore only seeks to provide insights into real-world clinical practice with respect to LLT implementation and current lipid profiles in older/very-old high-/very-high-risk patients at the time of presentation for STEMI.

5 Conclusion

Our findings demonstrate critical shortcomings in real-world clinical practice with respect to implementation and optimization of guideline-directed, risk-based LLTs among high/very-high-risk older and very-old adults at the time of presentation for STEMI, with corresponding low achievement guideline-recommended LDL-C targets. Missing or non-optimized LLT implementation was observed in many ASCVD patients, indicating care-delivery deficits in therapy optimization, especially as less than half of older and very-old adults met the 2016 LDL-C target (43, 49%) and less than one-third attained stricter 2019 LDL-C targets (22, 30%).

In primary prevention, prior treatment with LLTs and LDL-C target achievement must be examined in the context of guideline revisions and diverging recommendations for age groups < 75 years and ≥ 75 years. In high-risk/very-high-risk older patients (65–74 years), with the 2019 1A recommendation for statin or statin–ezetimibe combination therapy, 16% prior treatment with statin therapy and 2% pretreatment with ezetimibe were alarmingly low, revealing potential shortcomings in risk identification and LLT initiation by healthcare providers. The percentage of risk-based LDL-C achievement among older adults 65–74 years differed according to level of risk and guideline year, with 48% of patients meeting LDL-C targets for high-risk patients (2016 guidelines), 17% meeting very-high-risk (2016)/high-risk (2019) LDL-C targets, and 10% meeting 2019 very-high-risk LDL-C targets.

Among oldest adults ≥ 75 years without established ASCVD but with a high-risk/very-high-risk profile, prior LLT with low-/moderate-dose statin monotherapy was observed in just 9% of patients, likely due to weaker IIb/B guideline recommendations and amid contentious debate regarding LLT initiation in the context of multi-morbidity, frailty, polypharmacy, and concern for drug-related adverse events, although mounting evidence has demonstrated that LDL-C lowering significantly reduces the risk of major vascular events in older patients (≥ 75 years) without offsetting safety concerns, which would pose a barrier to treatment.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Commission of the State of Salzburg, Austria. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of the retrospective study of standard-of-care data.

Author contributions

KK: conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing–original draft, and writing–review and editing. LM: supervision, validation, and writing–review and editing. BW: formal analysis, methodology, software, and writing–review and editing. AB: writing–review and editing. VM: software and writing–review and editing. AD: supervision, validation, and writing–review and editing. UH: supervision and writing–review and editing. ML: methodology, supervision, and writing–review and editing.

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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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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Xiao Li,
Shandong Provincial Qianfoshan Hospital, China
Wasan Katip,
Chiang Mai University, Thailand

*CORRESPONDENCE
Yuhua Zhao,
zhaoyuhua1987@126.com
Zhenwei Yu,
yzw_srrsh@zju.edu.cn

†These authors have contributed equally to this work

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Is it time to recommend AUC-based vancomycin therapeutic drug monitoring only? A cross-sectional survey in China

Jieqiong Liu[1,2†], Xuan Zhang[3†], Gang Liang[1†], Jianping Zhu[1], Yi Yang[1], Ying Zheng[2], Yun Han[1,4,5], Lingyan Yu[5,6], Yuhua Zhao[7]* and Zhenwei Yu[1,5]*

[1]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2]The 903rd Hospital of PLA Joint Logistic Support Force, Hangzhou, China, [3]Northern Jiangsu People's Hospital, Yangzhou, China, [4]College of Pharmaceutical Science, Zhejiang University, Hangzhou, China, [5]Research Center for Clinical Pharmacy, Zhejiang University, Hangzhou, China, [6]The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [7]Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou, China

Background: The latest published therapeutic drug monitoring (TDM) guidelines for vancomycin recommend changing trough-based monitoring to area under the concentration-to-time curve (AUC)-based monitoring. This study aimed to evaluate the implementation status and perceptions of vancomycin AUC-based TDM in China and to determine the challenges in performing AUC-based TDM.

Methods: A nationwide cross-sectional survey was conducted in China using an online questionnaire. The questionnaire comprised a total of 25 questions with open- and closed-ended answers to collect information about the current implementation of vancomycin TDM and the participants' perceptions of these practices. The questionnaire responses were collected via the Questionnaire Star platform and analyzed.

Results: A total of 161 questionnaires were completed by 131 hospitals and were included. Approximately 59.5% (78/131) of the surveyed hospitals conducted vancomycin TDM; however, only 10.7% (14/131) of these hospitals performed AUC-based vancomycin TDM. Of the eligible participants, 58.4% (94/161) had experience with vancomycin TDM, and only 37 participants (37/161, 23.0%) had the ability to estimate the AUC, primarily through Bayesian simulation (33/161, 20.5%). The participants considered the following challenges to implementing AUC-based monitoring: (1) the high cost of AUC-based monitoring; (2) inadequate knowledge among pharmacists and/or physicians; (3) the complexity of AUC calculations; (4) difficulty obtaining AUC software; and (5) unclear benefit of AUC-based monitoring.

Conclusion: The majority of surveyed hospitals have not yet implemented AUC-based vancomycin TDM. Multiple challenges should be addressed before wide implementation of AUC-based monitoring, and guidance for trough-based monitoring is still needed.

KEYWORDS

vancomycin, survey, therapeutic drug monitoring, trough concentration, area under the concentration-time curve

Introduction

Vancomycin is a commonly used glycopeptide antibiotic in clinical practice for the treatment of serious infections caused by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Tong et al., 2015; Burns and Goldman, 2020). Vancomycin has a narrow therapeutic window and large interindividual pharmacokinetic variability; thus, therapeutic drug monitoring (TDM) has been a key approach for maximizing its therapeutic efficacy and minimizing the risk of nephrotoxicity (Perin et al., 2020). The optimal TDM practice for vancomycin is evolving but still controversial (Jorgensen et al., 2021; Lodise and Drusano, 2021). The 2009 American guideline recommends monitoring vancomycin trough concentrations in routine clinical practice, which can be used as a surrogate marker for the 24-hour area under the curve (AUC) because of the historical difficulty in estimating the AUC for vancomycin (Rybak et al., 2009). This guideline recommended a target trough concentration of 15–20 mg/L to increase the likelihood of attaining an AUC of ≥400 mg h/L (Rybak et al., 2009). However, there is increasing evidence of limitations in vancomycin trough monitoring, such as a poor linear relationship between trough concentrations and the AUC, and that trough-guided TDM possibly leads to overexposure, thereby increasing the risk of nephrotoxicity (Patel et al., 2011; Clark et al., 2019; Yamada et al., 2023). In light of these findings and the increasing accessibility of AUC estimation software, the 2020 American guideline and 2022 Japanese guideline recommended a pivotal change in vancomycin TDM target from trough to 24-hour area under the curve/minimum inhibitory concentration (AUC/MIC) or AUC (with a surrogate MIC of 1 mg/L), which is in accordance with its pharmacokinetics and pharmacodynamics profile and no longer recommended the trough guided doing (Rybak et al., 2020; Matsumoto et al., 2022). As it would be a challenge for pharmacists and physicians to estimate the AUC based on limited samples in routine clinical practice, the Chinese guideline recommended the AUC and trough concentration both for vancomycin TDM (He et al., 2020).

Currently, there is limited knowledge regarding the implementation status of AUC-based vancomycin TDM in Chinese hospitals, as well as a lack of understanding about the perceptions of pharmacists and physicians regarding AUC-guided vancomycin monitoring. Thus, we conducted this nationwide cross-sectional survey to determine the overall implementation status, perception and knowledge of AUC-based vancomycin monitoring and to identify the main difficulties in performing AUC-based TDM. The findings of this study will provide valuable evidence for determining the current extent and approach to implementing vancomycin AUC-based monitoring and provide guidance on how to further implement vancomycin monitoring in the future.

Methods

Study design

This nationwide cross-sectional survey was conducted in China using an online questionnaire. A convenient sampling approach was applied to enroll participants throughout mainland China in August 2023. The participants were invited to answer the questions through a link to the questionnaire via social media (WeChat group). Participation was voluntary, confidential, and anonymous.

The ethics committee of Sir Run Shaw Hospital, School of Medicine, Zhejiang University, reviewed the protocol and decided that ethical approval was not needed.

Questionnaire development and data collection

The questionnaire comprised a total of 25 questions with open- and closed-ended answers to collect information about the current implementation status of vancomycin TDM and the participants' perceptions of these practices. The English version of the questionnaire is available in Supplementary Table S1. This survey was created by investigators, and the questionnaire piloting was conducted by several anti-infective clinical pharmacists to assess its relevance, clarity, validity, reliability and completeness. The data collected in the survey included the participants' demographic information, the implementation status of vancomycin TDM in the participants' hospitals, the pattern of vancomycin TDM (e.g., trough-based TDM or AUC-based TDM), the participant's ability to estimate the AUC of vancomycin, the method of estimating the AUC of vancomycin (e.g., Bayesian estimation or first-order PK equations), and the participants' perceptions about changing the vancomycin TDM strategy from trough-based to AUC-based and challenges or barriers to implementing AUC-based vancomycin TDM. This questionnaire was designed with skip logic to reduce the completion time and minimize survey fatigue.

The questionnaire responses were collected via the Questionnaire Star platform (https://www.wjx.cn/), which is the largest online survey platform in China, and analyzed via Microsoft Excel 2019 (Yin et al., 2022). When "other" answers were selected for certain questions, the investigators independently reviewed the free-text responses and assessed the intent of their responses. Based on the investigators' assessments, responses with similar intent were classified together. All the results are presented descriptively as numbers and percentages.

Results

Participant characteristics

A total of 162 questionnaire responses were obtained from 131 hospitals in 20 provinces in China. One questionnaire was excluded from the final analysis because of an incomplete response. Therefore, 161 participants with complete responses were eligible and included in the analysis. The demographic characteristics of the participants and hospitals are shown in Tables 1, 2. The main participants were pharmacists from tertiary hospitals.

Implementation of vancomycin TDM

We investigated the overall implementation status of performing AUC-based TDM. Surprisingly, routine vancomycin

TABLE 1 Demographic characteristics of the participants.

Variable	Total (n = 161)
Department	
Pharmacy	138 (85.7%)
ICU	18 (11.2%)
Emergency medicine	2 (1.24%)
Others	3 (1.86%)
Position	
Pharmacist	141 (87.6%)
Physician	20 (12.4%)
Areas of specialization	
Respiratory	21 (13.0%)
Infectious diseases	49 (30.4%)
ICU	39 (24.2%)
Hematology	3 (1.86%)
General	15 (9.32%)
Others	65 (40.4%)
Experience in working	
1–3 years	17 (10.6%)
4–6 years	17 (10.6%)
7–9 years	30 (18.6%)
≥10 years	96 (59.6%)
Experience of vancomycin TDM	94 (58.4%)
Estimation AUC	
Available	37 (23.0%)

Abbreviations: ICU, Intensive Care Unit; TDM, therapeutic drug monitoring; AUC, 24-h area under the curve.

TDM was administered in only 59.5% (78/131) of the surveyed hospitals. Moreover, only 10.7% (14/131) of these hospitals used AUC-based vancomycin TDM (Table 2). Of the eligible participants, 58.4% (94/161) had experience with vancomycin TDM, and only 37 participants (37/161, 23.0%) had the ability to estimate the AUC (Table 1). The hospitals surveyed preferred a combination of the two methods of monitoring (100/161, 62.1%), and more than half of the respondents indicated that they expected to conduct or transition to AUC-based monitoring within 1 year (92/161, 57.1%), although a significant number of respondents indicated that they were not sure about the need to transition (59/161, 36.6%).

Perception about vancomycin TDM

The perceptions and knowledge of AUC-based monitoring in participants who had experience with vancomycin TDM are shown in Table 3. Participants identified patients at high risk of nephrotoxicity (74/94, 78.7%) as the preferred indications for vancomycin TDM, followed by critically ill patients (70/94, 74.5%). The most commonly accepted AUC/MIC target value for vancomycin was 400–600 (33/94, 35.1%), which was also recommended by American and Japanese guidelines. However, the appropriate AUC for vancomycin was still unclear for many people (45/94, 47.9%). In addition, participants considered the most appropriate vancomycin trough concentration targets to be 10–15 mg/L for adult patients (66/94, 70.2%) and 15–20 mg/L for adult patients with severe MRSA infections (64/94, 68.1%), which were recommended by the Chinese guidelines.

For the guidelines to change the monitoring index of vancomycin from the trough concentration to the AUC, pharmacists and physicians have varying perspectives. Of the 161 respondents, 35 pharmacists and physicians expressed their views on the current vancomycin TDM guidelines. Most of the respondents (24/35, 68.6%) supported that AUC monitoring is a more accurate and meaningful approach, which is highly conducive to individualized use in the clinic to improve therapeutic efficacy. However, a portion of the respondents (6/35, 17.1%) held a less optimistic view due to perceived complexities associated with AUC calculation and the current lack of sufficient high-quality evidence on benefits of AUC-based monitoring, thereby posing challenges for its routine implementation.

Factors influencing the AUC-based vancomycin TDM implementation

The challenges and barriers to implementing AUC-based monitoring as perceived by the participants are shown in Figure 1. Unsurprisingly, the highest barrier to implementing vancomycin TDM was the cost of AUC-based monitoring (113/161, 70.2%), which included but was not limited to Bayesian software costs, and staff training costs. Inadequate knowledge about AUC-based monitoring (105/161, 65.2%) was the second challenge. The complexity of the AUC calculations and the difficulty of obtaining AUC software were also identified as important challenges by approximately half of the participants. Furthermore, the unclear benefit of AUC-based monitoring is also an important barrier that should be considered.

Discussion

To the best of our knowledge, this is the first survey to evaluate the implementation status and perception of vancomycin AUC-based TDM in China. Our study included 131 hospitals from 20 provinces in China and could adequately reflect the status of vancomycin TDM. Based on the results of this study, vancomycin AUC-based TDM has not yet been widely implemented in clinical practice, and most hospitals still use trough-based TDM. The perceptions of pharmacists and physicians about vancomycin TDM were inconsistent with the current guidelines. Difficulties in AUC estimation and high cost were the main issues that needed to be accounted for before the implementation of AUC-based monitoring. It is too early to recommend AUC-based monitoring only in China, as well as other resource limited areas. This survey also demonstrated the dilemmas and doubts of vancomycin AUC monitoring, which may be helpful in its further implementation.

The revised vancomycin TDM guidelines, which recommend AUC-based monitoring, were published more than 3 years ago (He et al., 2020; Rybak et al., 2020; Matsumoto et al., 2022). However, this study revealed that AUC-based monitoring was still not commonly

TABLE 2 Hospital characteristics of the surveyed medical centers.

Variable	Total (n = 131)
Region	
East	93 (71.0%)
South	11 (8.40%)
Central	8 (6.11%)
North	6 (4.58%)
West	6 (4.58%)
Southwest	5 (3.82%)
Northeast	1 (0.763%)
Hospital level	
Tertiary (Grade III)	117 (89.3%)
Secondary (Grade II)	13 (9.92%)
Primary (Grade I)	1 (0.763%)
Hospital type	
General	108 (82.4%)
Specialized	22 (16.8%)
Community	1 (0.763%)
Implementation of vancomycin TDM	
TDM performed	78 (59.5%)
Trough-based TDM	64 (48.9%)
Peak and trough-based TDM	25 (19.1%)
AUC-based TDM	14 (10.7%)
TDM not performed	53 (40.5%)

Abbreviations: TDM, therapeutic drug monitoring; AUC, 24-h area under the curve.

used among Chinese hospitals. Only 10.7% (14/131) of the responding hospitals adopted AUC-based monitoring, whereas 51.9% (68/131) used conventional peak and/or trough-based monitoring. Similar situations in other countries have also been reported. A cross-sectional survey of a national health consortium performed in 2019 showed that 23.1% of responding academic medical centers performed AUC-based TDM (Kufel et al., 2019). Another survey performed in 2022, 2 years after the publication of American updated guideline, revealed that only 29.7% of the institutions had implemented an AUC dosing program in hospitals across America (Bradley et al., 2021). It can be estimated that AUC-based monitoring is uncommon in developing countries. Thus, we can see that AUC-based monitoring only, as recommended by some guidelines, seems to be unsuitable for resource limited areas.

We also investigated respondents' perceptions and knowledge of AUC-based vancomycin monitoring. It is concerning that guideline-recommended populations and TDM targets were inconsistent, which confused physicians and pharmacists. The Japanese guidelines recommend that AUC-guided TDM should be routinely used for all MRSA infections, irrespective of the severity or complexity of the infection (Matsumoto et al., 2022). Even in institutions where calculating the AUC using Bayesian methods is difficult, the use of AUC-guided dosing should be considered for patients at high risk of acute kidney injury (Matsumoto et al., 2022). Similarly, the guidelines published by the Anti-infectives Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) recommend that TDM should be indicated for all patients who are expected to receive vancomycin for longer than 48 h (Reuter et al., 2022). On the other hand, the guidelines published by the Chinese and American authors did not recommend vancomycin TDM for all patients but rather for patients at high risk of nephrotoxicity, patients with severe infections, neonates/children, and so on (He et al., 2020; Rybak et al., 2020). From the results we can see that respondents' perceptions and knowledge of vancomycin were not fully consistent with any guidelines. Pharmacists and physicians were not able to timely track the updates of guidelines and deeper understand the changing of TDM targets. Therefore, it is paramount important to establish a more precise and clearer guidance for better clinical practice.

There is uncertainty in the academic community regarding whether AUC monitoring is required for all patients. In our previous study, we found that a trough concentration of 15–20 mg/mL had a good relationship with an AUC of 400–600 mg·h/L in critically ill patients not receiving renal replacement therapy, and trough-guide TDM may be sufficient in these populations (Yu et al., 2023). The other two studies proposed a similar idea. Huang et al. developed a hybrid model of trough and AUC monitoring through plan–do–study–act (PDSA) cycles and reported that trough-based TDM was a pragmatic strategy for short-term anticipated dosing, while AUC-based TDM was the most impactful and cost-effective for patients at high risk of nephrotoxicity (Huang et al., 2021). The value of universal AUC-based monitoring was also questioned by Dilworth and Wright, who suggested that an easier and more effective way to reduce toxicity may be to focus on effective antibiotic stewardship to reduce overall prescribing rather than optimizing dosing based on limited hypothetical data (Dilworth et al., 2020; Wright et al., 2021). This evidence seems to indicate that AUC monitoring is not necessary for all patients. Therefore, high quality evidences are urgently needed for clinical decision making.

In addition, it is important to provide education or staff training to increase awareness of vancomycin TDM among pharmacists, physicians, nurses and laboratory staff, especially those using Bayesian software, to implement vancomycin TDM successfully. This education should provide personalized multimodal strategies with profession-specific content (Reuter et al., 2022). For example, physician education should focus on evidence or problem-based learning, while nurse education should include receiving clear instructions and protocols through in-service training (Van Dort et al., 2020). In contrast, for those who need to interpret the data to make dose recommendations, education based on the background and rationale for pharmacokinetics and pharmacodynamics should be provided to aid in understanding dosing decisions (Reuter et al., 2022). Furthermore, convincing studies about vancomycin TDM are needed to resolve these inconsistencies and achieve a consensus. We investigated the factors that impede the implementation of vancomycin AUC-based TDM. Unsurprisingly, participants generally identified monitoring costs as the most significant barrier. The annual cost of purchasing software, as well as subsequent software maintenance and staff training, may be enormous. However, a previous report showed that AUC monitoring was cost-neutral and could significantly reduce patient costs (Lee et al., 2020). However, this cost–benefit study did not consider the impact of empirical therapies that are common in clinical practice or the implementation fees of EMRs and staff

TABLE 3 Perceptions about implementation of vancomycin TDM.

Variable	Total (n = 94)
Indications for vancomycin TDM	
Patients at high risk of nephrotoxicity	74 (78.7%)
Critically ill patients	70 (74.5%)
Patients receiving high-dose vancomycin	64 (68.1%)
Patients with moderate to severe heart failure, or underweight patients	63 (67.0%)
Hemodynamically unstable patients	62 (66.0%)
Elderly patients (>65 years old)	62 (66.0%)
Pediatric patients, neonates	60 (63.8%)
Obese patients, burn patients	59 (62.8%)
Patients with augmented renal clearance	57 (60.6%)
Patients receiving prolonged courses of therapy (more than 3–5 days)	57 (60.6%)
Patients with MRSA infection	44 (46.8%)
All patients received vancomycin	35 (37.2%)
Others	2 (2.13%)
Vancomycin TDM target	
AUC/MIC	
400–600 in American and Japanese guidelines	33 (35.1%)
400–650 in Chinese and IATDMCT guidelines*	15 (16.0%)
Other or not sure	45 (47.9%)
Trough target	
2020 Chinese guideline	
10–15 mg/L in adult patients	66 (70.2%)
10–20 mg/L in patients with serious MRSA infections	20 (21.3%)
5–15 mg/L in pediatric patients or neonates	27 (28.7%)
2020 IATDMCT guideline	
10–15 mg/L in patients with serious MRSA infections	4 (4.26%)
2013 Japanese guideline and 2009 American guideline	
15–20 mg/L in patients with serious MRSA infections	64 (68.1%)
10–20 mg/L in adult patients	14 (14.9%)
10–20 mg/L in all infections	7 (7.45%)
Other	4 (4.26%)
AUC estimation method	
Can estimate AUC	37 (39.4%)
Bayesian modeling	33 (35.1%)
First-order PK equations with two concentrations	22 (23.4%)

Abbreviations: TDM, therapeutic drug monitoring; AUC, 24-h area under the curve; MIC, minimum inhibitory concentration; IATDMCT, International Association of Therapeutic Drug Monitoring and Clinical Toxicology; MRSA, methicillin-resistant *Staphylococcus aureus*; PK, pharmacokinetics. * Chinese and IATDMCT, guidelines suggested a AUC, target of 400–650 mg·h/L.

training; thus, the overall costs may have been underestimated (Lee et al., 2020). It is not surprising that the guidelines are more supportive of AUC-based dosing strategies than troughs are; this change would be an enormous task for hospitals, requiring significant time, effort, cost, and training (Bland et al., 2021). Therefore, we wanted to find a safe and feasible way to reduce costs and to accommodate the needs of medical institutions that are not equipped to conduct monitoring, for example, by establishing regional medical centers to centralize testing. Moreover, given that the majority of current models rely on sparsely sampled or limited datasets, a Bayesian-based vancomycin calculation website utilizing intensive sampling or a larger number of samples would significantly enhance AUC calculations. Additionally, implementing a decision tree model could effectively reduce unnecessary resource consumption.

Difficulties in the estimation of the AUC were one of the main barriers to the implementation of AUC-based monitoring. The guidelines recommend Bayesian estimation as the preferred method for calculating the AUC of vancomycin (He et al., 2020; Rybak et al., 2020; Matsumoto et al., 2022). Other methods, such as first-order PK equations, require two steady-state vancomycin concentrations, which may result in additional sampling and testing (Meng et al., 2019). Moreover, the calculation is complex. The advantage of Bayesian estimation is that the AUC of vancomycin can be estimated using trough-only data or plasma concentration data at any random time within the first 24–48 h (Rybak et al., 2020). Notably, the use of Bayesian software to calculate the vancomycin AUC and optimize the dose presupposes the use of a well-developed vancomycin population PK model as a Bayesian prior. Obviously, Bayesian programs adopting such priors are extremely rare, and most of them were developed based on sparse sampling (Aljutayli et al., 2022). On the other hand, there are differences in the clinical settings for which different software programs are applicable, so a combination of multiple software programs may be required to meet clinical needs (He et al., 2022). Furthermore, due to the heterogeneity among vancomycin population pharmacokinetic models, selecting an appropriate model for clinical use is not trivial. Models developed in a specific patient population may perform poorly when applied to more general inpatient populations or other patient populations, making them highly susceptible to bias in dosing decisions (Greppmair et al., 2023). Even for the same patient population, different models may lead to different results, which may be related to the sample size, heterogeneous study designs or assay methodology. Broeker et al. compared thirty-one published population pharmacokinetic models of vancomycin and elucidated that the relative bias and relative root mean squared error of the a priori predictions varied substantially (−122.7%–67.96% and 44.3%–136.8%, respectively) (Broeker et al., 2019). Therefore, some scholars recommend that extensive evaluation is required before applying any model to clinical patients (Guo et al., 2019).

Moreover, there is still uncertainty regarding whether the implementation of vancomycin AUC-based monitoring increases the likelihood of clinical cure. Systematic evaluation and meta-analysis revealed considerable heterogeneity in the pooled sensitivity and specificity of the vancomycin AUC/MIC ratio for predicting clinical outcomes, and the majority of these studies failed to demonstrate a relationship between the AUC/MIC and positive clinical outcomes (Dalton et al., 2020). Another retrospective study in patients with *enterococcal* infections showed that an AUC/MIC ≥400 was associated with significant differences in clinical and microbiological responses, as well as a higher rate of nephrotoxicity compared to an AUC/MIC <400 (Katip and Oberdorfer, 2021).

This study has several limitations. First, this electronic survey was widely distributed through social media (WeChat group), and

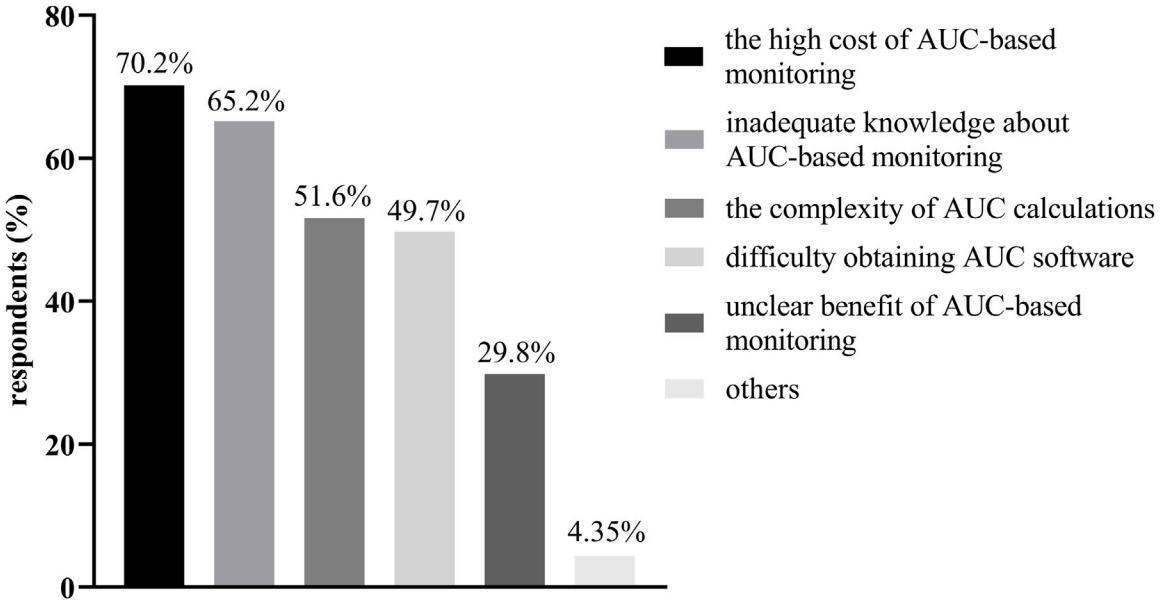

FIGURE 1
The challenges and barriers to implementing AUC-based monitoring as perceived by the participants.

we could not measure the true response rate because of the inability to know how many questionnaires were actually distributed; thus, it may introduce a non-response bias. Second, most of the hospitals surveyed in this study were tertiary care hospitals in Eastern China, and sampling bias may exist. In addition, some participants selected "other" for some questions and entered free text for clarification. The inclusion of these textual responses may still introduce bias, despite an independent review of these texts by our investigators. Furthermore, despite the considerable cost being the primary limiting factor for implementing AUC-based monitoring, we did not collect expenditure data comparing AUC-based and trough-based TDM. This aspect merits further investigation in future studies to enhance our comprehension of the feasibility of promoting AUC-guided TDM. Finally, we omitted collecting information regarding hospitals' selection of software for calculating the AUC and evaluating its reliability. Such data could serve as a reference for other hospitals intending to conduct AUC TDM in the future.

Conclusion

The majority of surveyed hospitals have not yet implemented AUC-based vancomycin TDM, especially in economically underdeveloped areas. The ability of physicians and pharmacists to estimate the AUC is also generally inadequate and requires further training. The highest ranked barrier to implementing vancomycin TDM was the cost of AUC-based monitoring, followed by the unfamiliarity of pharmacists and/or physicians. Given the low implementation rate and the lack of standardization of methods for estimating the AUC of vancomycin, it may be too early to recommend AUC-based TDM only, and trough-based monitoring is still needed. We look forward to more comprehensive analyses of vancomycin monitoring across diverse populations, and to developing a decision-tree model that will provide practical implementation strategies.

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 authors.

Author contributions

JL: Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing–original draft. XZ: Data curation, Writing–review and editing. GL: Data curation, Software, Writing–review and editing. JZ: Data curation, Writing–review and editing. YY: Data curation, Writing–review and editing. YiZ: Data curation, Writing–review and editing. YH: Data curation, Writing–review and editing. LY: Data curation, Writing–review and editing. YuZ: Project administration, Supervision, Writing–review and editing. ZY: Conceptualization, Investigation, Project administration, Validation, Writing–original draft, Writing–review and editing.

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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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Supplementary material

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EDITED BY
Ceu Mateus,
Lancaster University, United Kingdom

REVIEWED BY
Nanlin Li,
Air Force Military Medical University, China
Dechuang Jiao,
Henan Provincial Cancer Hospital, China

*CORRESPONDENCE
Tamie de Camargo Martins,
tamie.de_camargo_martins@roche.com

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The burden of systemic therapy administration route in treating HER2-positive breast cancer (for patients, healthcare professionals, and healthcare system): a systematic literature review

Luciana Castro Garcia Landeiro[1], Tamie de Camargo Martins[2]*, Ruth Bartelli Grigolon[3], Isabel Monteiro[2], Joana Bisol Balardin[3], Eduardo Padilha[2], Gilberto Amorim[4] and Stephen Stefani[5]

[1]Oncology, Oncoclínicas Group, Bahia, Brazil, [2]Roche Pharmaceuticals, São Paulo, Brazil, [3]Oracle Life Sciences, São Paulo, Brazil, [4]Oncology, Instituto D'Or de Pesquisa e Ensino (IDOR), Rio de Janeiro, Brazil, [5]Oncology, Núcleo de Avaliação de Tecnologias UNIMED Central, São Paulo, Rio Grande do Sul, Brazil

Introduction: Breast cancer (BC) is one of the leading causes of cancer and is the first cause of death from malignant tumors among women worldwide. New cancer therapies receive regulatory approval yearly and to avoid health disparities in society, the health systems are challenged to adapt their infrastructure, methodologies, and reimbursement policies to allow broad access to these treatments. In addition, listening to patients' voices about their therapy preferences is essential. We aim to investigate the administration route preferences [subcutaneous (SC) or intravenous (IV)] among patients diagnosed with HER2 positive BC and healthcare professionals (HCPs) and to investigate healthcare resources utilization (quality and quantity) for each route of administration (SC or IV) for treating those patients.

Methods: We conducted a systematic literature review focused on clinical trials and observational and economic studies, using PubMed (MEDLINE), Cochrane Library, Virtual Health Library (VHL), Scientific Electronic Library Online (SciELO), and Latin American and Caribbean Health Sciences Literature (LILACS) databases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Results: The literature review included 25 studies in the analysis. Studies have reported that patients and HCPs prefer the SC route of administration to IV because it saves time in terms of chair time, administration, and preparation and is less painful. In addition, SC administration might be a more cost-saving option when analyzing direct and indirect costs.

Discussion: As BC stands as a significant global health concern and the leading cause of cancer-related deaths in women worldwide, understanding and incorporating patient and HCPs preferences in the choice of administration route become paramount. The observed preference for SC administration not only aligns with the imperative of adapting health systems to facilitate broad access to new cancer therapies but also underscores the importance of

considering patient experiences and economic implications in shaping treatment strategies. These insights are crucial for healthcare policymakers, clinicians, and stakeholders in optimizing healthcare resources and enhancing the overall quality of BC care.

KEYWORDS

HER2, breast cancer, trastuzumab, pertuzumab, subcutaneous administration, intravenous administration

1 Introduction

Breast cancer (BC) is one of the leading causes of cancer among women worldwide, accounting for 15% of new annual female cancer cases (GBD, 2017 Causes of Death Collaborators, 2018; GBD, 2019 Diseases and Injuries Collaborators, 2020; Arzanova and Mayrovitz, 2022) and is the first cause of death from malignant tumors in women in the world (Smolarz et al., 2022). Breast cancer incidence rates have increased over the last four decades (2010–2019, 0.5% increase per year), largely driven by localized stage and hormone receptor-positive disease (Giaquinto et al., 2022). The most common and widely accepted classification of breast cancer is from an immunohistochemical perspective, based on the expression of estrogen receptor (ER), progesterone receptor (PR), and overexpression of human epidermal growth factor receptor 2 (HER2), and/or amplification of *ERBB2* gene. In this context, there are four molecular subtypes of breast cancer: 1) luminal A (ER and/or PR positive and HER2/neu negative), 2) luminal B (ER and/or PR positive and HER2/neu positive), 3) HER2-positive (ER and PR negative and HER2/neu positive), and 4) triple-negative (ER, PR, and HER2/neu negative) (Patel et al., 2020; Doğan et al., 2023).

The human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor critically involved in the carcinogenesis of the mammary gland (Moasser, 2007). Approximately 20% of - BC cases are HER2 positive (Patel et al., 2020). The study of HER2 oncogenic role and the development of drugs targeting HER2 have revolutionized breast oncology. In the context of HER2-positive early breast cancer (eBC), trastuzumab has emerged as the pivotal cornerstone in the therapeutic landscape. According to seminal studies evaluating adjuvant treatment of HER2+ eBC, the addition of trastuzumab to standard adjuvant chemotherapy halves the risk of recurrence, with a 10% absolute improvement in disease-free survival (DFS) and a 9% increase in 10-year overall survival (OS) (Slamon et al., 2011; Perez et al., 2014; Cameron et al., 2017). In HER2+ disease, as for other BC subtypes, a neoadjuvant strategy is usually preferred to the adjuvant one (Wuerstlein and Harbeck, 2017), except for small tumors (T < 2 cm), clinically node-negative. Dual HER2-targeting with pertuzumab added to chemotherapy plus trastuzumab as neoadjuvant treatment further increased pathologic complete response (pCR) rate (Schneeweiss et al., 2013; Gianni et al., 2016), and led to pertuzumab approval by both US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In the adjuvant setting, pertuzumab with trastuzumab (PH) showed a benefit in invasive DFS improvement (0.9%), most driven by the high-risk population with node-positive HER2+ eBC (Piccart et al., 2021). In the metastatic setting, most patients receive frontline dual blockade with PH combined with a taxane, followed by dual blockade maintenance (+/- endocrine treatment in tumors expressing HER) (Cardoso et al., 2020). This regimen has led to an unprecedented OS of 57 months, with more than a third of the patients being alive after 8 years (EMA, 2020; FDA, 2020; Swain et al., 2020; Mateo et al., 2022). The previous studies mentioned used intravenous PH formulation. However, subcutaneous (SC) formulations may offer several advantages compared with intravenous (IV), including shorter treatment times, a reduction in the use of healthcare resources, increased convenience for patients, and greater patient preference. In this setting, two robust clinical trials (FeDeriCa and PHranceSCa studies) demonstrated the efficacy, safety and preferences of pertuzumab and trastuzumab fixed-dose combination for subcutaneous injection (PH FDC SC) for the treatment of HER2-positive BC. The Phase 3 pivotal study FeDeriCa compared the pharmacokinetics, efficacy, and safety of PH FDC SC and IV PH in 500 patients with HER2-positive eBC in the neoadjuvant/adjuvant settings (Im et al., 2021; Tan et al., 2021). The Phase 2 PHranceSCa study (O'Shaughnessy et al., 2021) compared the preferences of patients for the administration route for PH FDC SC or PH IV at two-time points: after trying both methods of administration post-surgery, and after completion of neoadjuvant IV PH and chemotherapy. Patients could then choose SC or IV to continue for up to 18 cycles. The primary analysis showed that most patients preferred PH FDC SC (85.0% overall vs. 13.8% for IV PH; 1.3% had no preference). The two main reasons patients preferred PH FDC SC were spending less time in the clinic (42.2%) and being comfortable during administration (25.9%). Indeed, 86.9% of patients choose to continue their HER2-targeted adjunctive therapy with PH FDC SC over IV PH (13.1%) (O'Shaughnessy et al., 2021).

In the PrefHer study, both patients and healthcare professionals (HCPs) demonstrated a preference for SC trastuzumab over the intravenous IV administration method. Additionally, within this study, a prospective, observational time and motion analysis was conducted to quantitatively assess the time that patients spent in infusion chairs and the active time expended by HCPs in managing the PrefHer process. The study had a similar design to PHranceSCa and has demonstrated reductions in patient chair time and active HCP time in eight countries (De Cock et al., 2016). This time-and-motion evaluation showed that, per treatment session, SC administration via a portable syringe (comparable to a single-use injection device) reduced patient chair time (time between entering and exiting the chair infusion) versus IV infusion averaging 55.2 min (mean range of time savings across countries: 40.3–80.6 min; $p < 0.0001$). Such evidence was able to demonstrate that treatment time can also impact the quality of life (QoL) of these patients as well as the use of health resources.

Based on this data, in 2020, the FDA and EMA first approved the ready-to-use fixed-dose combination of PH for subcutaneous (SC) injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf; PH FDC SC) to treat adult patients with HER2-positive BC that has spread to other parts of the body, and for treatment of adult patients with early HER2-positive BC (EMA, 2020; FDA, 2020).

New cancer therapies receive regulatory approval yearly for biomarker-defined subsets of patients, including HER2-positive patients. However, to avoid health disparities in society, the health systems are challenged to adapt their infrastructure, methodologies, and reimbursement policies to allow broad access to these drugs for patients. Broad and equitable access to treatments will depend on the specific situation in various countries and their health systems, in addition to the specificity of patients or tumors. The affordability of new therapeutic strategies is required to ensure health systems' sustainability (Mateo et al., 2022). Moreover, such affordability is based on an accurate diagnosis. It is well known that this accuracy is impossible to achieve depending on the healthcare system. Access plans for advanced diagnostics need to be designed in a patient-centric rather than institution-centric manner. Clearly, it does not seem feasible that all healthcare institutions can adopt advanced diagnostic platforms and support teams for data interpretation. This gap is part of the problem of accessing new technologies that will provide better treatments for patients (Mateo et al., 2022).

In light of such evidence, the present review aimed to investigate the administration route preferences' (SC or IV) among patients and HCPs (doctors, nurses, psychologists and others); and to investigate the healthcare resources utilization (quality and quantity) for each route of administration (SC or IV) for treating the patients with HER2-positive BC.

2 Methods

This systematic literature review is registered with the International Prospective Register of Ongoing Systematic Reviews (Systematic review registration – PROSPERO 2023: CRD42023412349).

2.1 Literature review

The literature search was conducted using PubMed (MEDLINE), Cochrane Library, Virtual Health Library (VHL), Scientific Electronic Library Online (SciELO), and Latin American and Caribbean Health Sciences Literature (LILACS) databases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021). The reviews were performed independently by two authors (RBG and JBB) in a blinded fashion way using the Rayyan online platform (Ouzzani et al., 2016). Any discrepancies detected after unblinding were resolved by consensus between RBG, JBB, and TCM.

Our search focused on randomized clinical trials, observational studies, and systematic literature reviews that assessed: 1) patients' and HCPs' preferences, perceptions, and satisfaction with SC and IV administration route; and 2) healthcare resources utilization (quality and quantity) for treating the patients with SC and IV administration route. The target population included patients with early or metastatic HER2-positive BC (Supplementary Tables S1, S2).

2.2 Search strategy and selection criteria

We searched databases from the first publication until 30 January 2023. The search strategy followed Boolean terms for two categories of focus: 1) patients and HCP preferences, perceptions, and satisfaction; and 2) healthcare resource utilization. For each category, we had a search strategy (Supplementary Tables S3, S4).

Relevant publications from the listed references of the included articles, as well as from other systematic reviews and meta-analyses, were also assessed for eligibility. References were complemented by research on works registered on clinicaltrials.gov.

2.3 Eligibility criteria

We considered as inclusion criteria: 1) articles reporting original data; 2) human research; 3) studies with patients with early or metastatic HER2-positive BC; 4) manuscripts written in English, Spanish, French, German or Portuguese; 5) randomized clinical trials, observational studies, and systematic literature review; 6) adult patients aged equal or greater than 18 years old; 7) comparison of the outcomes between SC and IV administration route; and 8) present the outcomes related to the use of trastuzumab or the combination of PH. Regarding exclusion criteria, we considered: (1) book chapters, conference abstracts, case reports, case series, letters, comments, interviews, and narrative reviews; (5) children and adolescents; and (6) overlapped data (in this case, we included the latest published data).

2.4 Data extraction

The following variables were extracted according to a structured checklist previously prepared by the authors: 1) metadata (authorship, publication year, study design and country); 2) patients characteristics (sample size and diagnosed disease); 3) characteristics of the intervention (therapy and regimen); 4) measures used to access the outcome of interest; and 5) the outcomes of interest: patients and HCP preferences, resources used/consumed, and cost-savings.

2.5 Quality assessment

To evaluate the quality of the evidence, we used the corresponding tool for each study design: 1) Randomized clinical trials - Risk of Bias for randomized trials version 2.0 (RoB 2.0) (Sterne et al., 2019); 2) Observational studies - Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) (Sterne et al., 2016); and 3) Economic model studies - Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013).

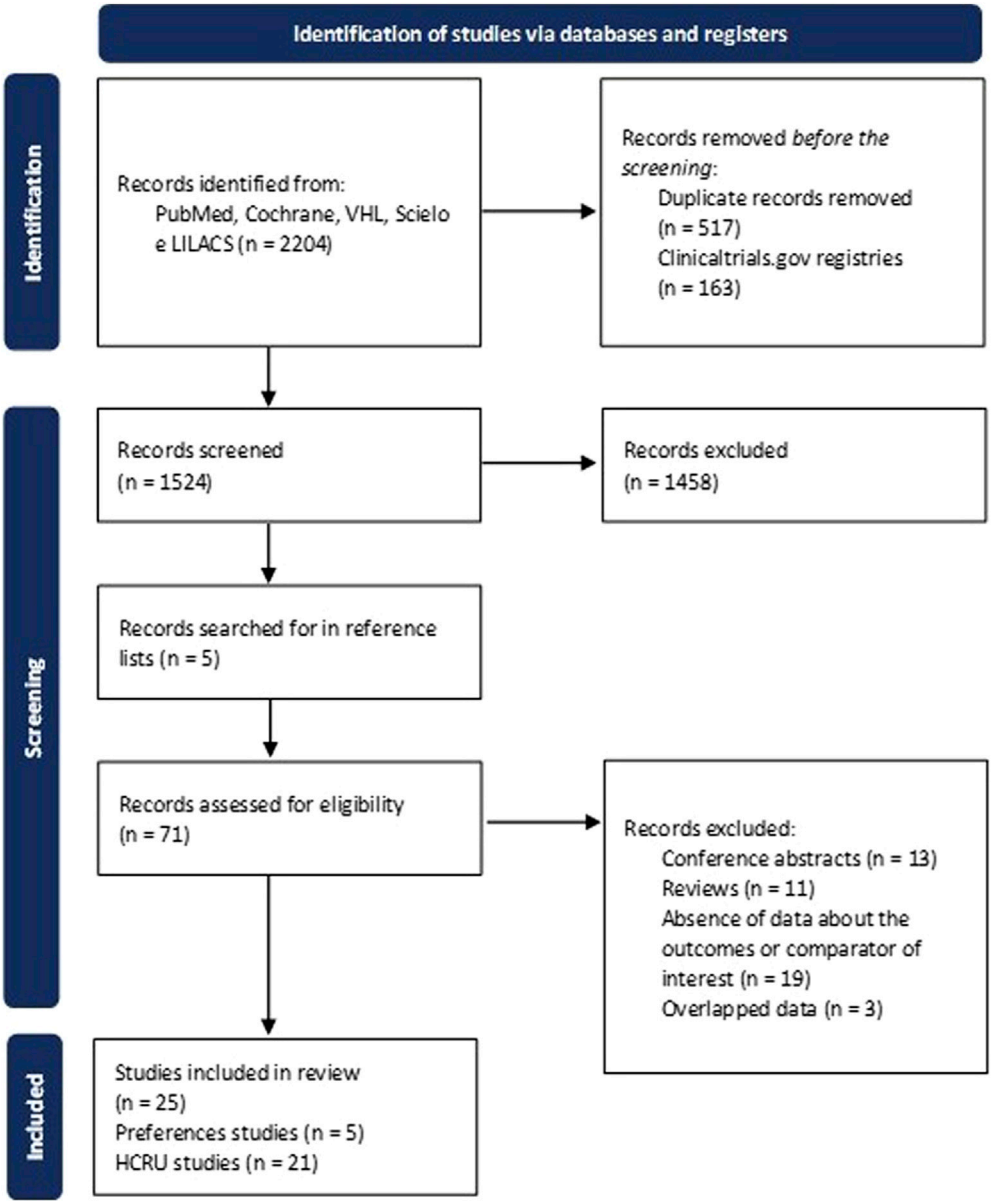

FIGURE 1
Selection of the studies flowchart. HCRU, healthcare resource utilization.

3 Results

3.1 Overview

Our systematic review yielded 1,524 studies after duplicates were removed. In a preliminary eligibility evaluation, we excluded 1,458 articles (Figure 1). In a more detailed subsequent selection phase, we excluded 46 articles for the following reasons: incorrect study design (abstracts and reviews) (n = 24); absence of data of the outcome or comparator of the interest (n = 19), and overlapped data (n = 3), meaning that we used the latest published data (Supplementary Table S5). In the end, 25 studies complied with our criteria and were included for the analyses: 5 studies for patients and HCP preferences and 21 studies for the outcomes of healthcare resource utilization. Notably, the study by O'Shaughnessy et al. (2021) (O'Shaughnessy et al., 2021), was included in both categories due to its comprehensive data on preferences and HRCU.

Table 1 and Supplementary Table S7 summarizes the characteristics of all included studies (preferences and healthcare resource utilization). In total, 25 publications were identified that described the preferences and healthcare resource utilization in terms time/resource use and/or costs associated with the comparison of SC versus IV administration for the treatment of HER2-positive BC.

Concerning the variable of healthcare resource utilization (Table 1), two publications were related to PrefHer, a multinational study conducted in eight countries (Canada, France, Switzerland, Denmark, Italy, Russia, Spain, and Turkey) (Jackisch et al., 2015; De Cock et al., 2016), 16 publications reported data from European countries (Burcombe et al., 2013; Jackisch et al., 2015; Lieutenant et al., 2015; Lazaro Cebas et al., 2017; De Cock et al., 2016; Olofsson et al., 2016;

TABLE 1 Characteristics of the included studies regarding preferences for each administration route.

Author, year	Study design	Diagnose	Therapy	Regimen	Preference measure	Sample size Sc	Sample size iv	Median age (yrs)	Main findings
Pivot et al. (2014)	Open-label, randomized study [PrefHer (NCT01401166)] - data from two cohorts	Early HER2-overexpressing breast cancer	Trastuzumab	-Neoadjuvant chemotherapy followed by SC trastuzumab (600 mg) for 18 cycles followed by IV (standard dosing) compared with the reverse; -Cohort 1: SC by injection device; -Cohort 2: SC by handheld syringe	Patients: telephone interviews and self-administered satisfaction questionnaire; HCP: satisfaction question ('All things considered with which method of administration were you most satisfied?') and perceived time savings	SC → IV: 235	IV → SC: 232	52–53	Patients Preferences: 88.9% preferred SC (415/467, 95% CI 85.7–91.6; $P< 0.0001$), 9.6% (45/467, 95% CI 7.1–12.7) preferred IV, and 1.5% (7/467, 95% CI 0.6–3.1) had no preference Main reasons: time-saving and less pain/discomfort/side effects HCPs Preferences: 77.0% preferred SC (181/235, 95% CI 71.1–82.2), 3.0% (7/235, 95% CI 1.2–6.0) preferred IV, and 20.0% (47/235, 95% CI, 15.1–25.7) had no preference
Reinisch et al. (2022)	Substudy of the phase III multicenter, randomized trial [GAIN-2 (NCT01690702)]	HER2-positive breast cancer [(neo)adjuvant chemotherapy and surgery]	Trastuzumab	-SC: 600 mg fixed dose; -IV: loading dose of 8 mg/kg and subsequent doses of 6 mg/kg 18 triweekly dosing cycles (1 year of treatment/a full treatment cycle)	Patients: validated, study-specific patient interview (PINT) questionnaires before randomization (PINT1) and after the end of cycle 8 of SC trastuzumab (PINT2)	SC thigh: 110 SC AW: 109	IV: 219	50	Patients Preferences: 83.5% (152/182) preferred SC over previous IV applications or had no preference None of the SC sites of injection were preferred over the other (thigh: N = 93 (80.6% [95% CI 72.6–88.7]); AW: N = 89 (86.5% [95% CI 79.4, 93.6]), $p = 0.322$; odds ratio (OR) 1.54 [95% CI 0.69–3.42], $p = 0.288$)
O'Shaughnessy et al. (2021)	Randomized, open-label, international, multicenter, crossover, phase II study conducted at 39 sites in 16 countries [PHranceSCa (NCT03674112)]	Early HER2-overexpressing breast cancer	PH FDC SC P+H IV	Loading doses: -IV: P IV 840 mg; H IV 8 mg/kg; -SC: PH FDC SC 1200 mg P/600 mg H in 15 mL Maintenance doses: -IV: P IV 420 mg; H IV 6 mg/kg; -SC: PH FDC SC 600 mg P/600 mg H in 10 mL	Patients: modified intention-to-treat (mITT) population - the proportion of patients who preferred PH FDC SC based on the question: "All things considered, which method of administration did you prefer?" [Patient Preference Questionnaire (PPQ)]	PH FDC SC → P + H IV: 80	P + H IV → PH FDC SC:80	47	Patients Preferences: -PH FDC SC: 85.0% (136/160) - "very/fairly strong" preference: 92.6% [the most common reasons were "requires less time in the clinic" and "feels more comfortable during administration"] -P + H IV: 13.8% (22/160) - "very/fairly strong" preference: 63.6% [the most common reasons were "feels more comfortable during administration" and "lower level of injection site pain"] Patients perceptions: -"(very) satisfied" - PH FDC SC: 88.1%; P + H IV: 67.5%; -"not at all" restricted - PH FDC SC: 71.3%; P + H IV: 34.4%; -"gained a lot of time" or "gained some time" - PH FDC SC: 60.6%; P + H IV: 4.4% HCPs Preferences:

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TABLE 1 (*Continued*) Characteristics of the included studies regarding preferences for each administration route.

Author, year	Study design	Diagnose	Therapy	Regimen	Preference measure	Sample size Sc	Sample size iv	Median age (yrs)	Main findings
									–86.9% (139/160) chose to continue with PH FDC SC after completing the crossover (arm A: 88.8% [71/80]; arm B: 85.0% [68/80])
Pivot et al. (2017)	Open label, randomized, multicenter, phase III study [MetaspHer (NCT01810393)]	Metastatic HER2-overexpressing breast cancer	Trastuzumab	-SC: 3 cycles of 600-mg fixed-dose; IV: 6 mg/kg	Patients: Patient Preference Questionnaire (PPQ); HCP: Satisfaction questionnaire	SC → IV: 47	IV → SC: 45	57.8–59.5	Patients Preferences: -SC: 85.9% (79/92; 95% CI: 78.8%–96.8%; $p < 0.001$); IV: 14.1% (13/92; 95% CI: 7.0%–21.3%); -Among patients without preference at baseline (52/89 available data) SC was the preferred administration route - SC: 88.5% (46/52; 95% CI: 79.8%–97.2%) HCPs Preferences: -SC: 63.6% were satisfied (56/88 available data; 95% CI: 53.6e73.7%)
Ciruelos et al. (2020)	Phase III, open-label, multicenter study [ChangHER (NCT01875367)]	Metastatic HER2-overexpressing breast cancer	Trastuzumab	SC: 600 mg every 3 weeks for 4 cycles -arm A (2 cycles with vial followed by 2 cycles with SID); -arm B (reverse sequence) Before starting SC, patients received an additional IV cycle	Questionnaire (the study did not report the name of the instrument)	IV→ vial → SID: 85	IV → SID → vial: 81	58–63	Patients Preference: -SC: 86.2%; IV: 6.9%; had no preference: 6.9% -arm A (vial to SID) - SC: 86.8% (95% CI 77.1–93.5); IV: 7.9% (95% CI 3.0–16.4); had no preference: 5.3% (95% CI 1.5–12.9); -arm B (SID to vial) - SC: 85.5% (95% CI 76.1–92.3); IV: 6.0% (95% CI 2.0–13.5); had no preference: 8.4% (95% CI 3.5–16.6) HCPs Preferences (nurses, medical oncologists, and others): -SC: 87.2% (95% CI 72.6–95.7); no difference: 10.3% (95% CI 2.9–24.2); failed to respond: 2.6% -The most important factors associated with the SC preference: "fewer resources required for preparation" (100%); "time saver" (97.4%); "more convenient for patients" (94.9%); and "less painful for patients" (76.9%)

HER2, human epidermal growth factor receptor 2; SC, subcutaneous; IV: intravenous; CI, confidence interval; P, Pertuzumab (Perjeta); H, trastuzumab (Herceptin); P + H IV, intravenous pertuzumab plus trastuzumab; PH FDC SC, fixed-dose combination of Perjeta and Herceptin for subcutaneous injection; HCP, healthcare professionals; AW, abdominal wall; SID, single injection device.

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Farolfi et al., 2017; Lopez-Vivanco et al., 2017; Olsen et al., 2017; Tjalma et al., 2018; Hedayati et al., 2019; Mitchell and Morrissey, 2019; O'Brien et al., 2019; Altini et al., 2020; O'Shaughnessy et al., 2021; Simoens et al., 2021). The remaining studies (n = 5) were from Costa Rica (Cordero et al., 2019), Brazil (Kashiura et al., 2019), Chile (Rojas et al., 2020), Saudi Arabia (Elsamany et al., 2020), and New Zeland (North et al., 2015). Regarding the study design, nine studies were focused in reporting a health economic model of cost-effectiveness (Tjalma et al., 2018; Hedayati et al., 2019), budget impact (Kashiura et al., 2019; Elsamany et al., 2020), cost-minimization (North et al., 2015; Cordero et al., 2019; Rojas et al., 2020), and micro-costing (Lopez-Vivanco et al., 2017; O'Brien et al., 2019). Of those, three studies had data based on the PrefHer Trial (NCT01401166) (Lopez-Vivanco et al., 2017), SafeHer Trial (NCT01566721) (North et al., 2015), and HANNAH Trial (NCT00950300) (Kashiura et al., 2019). The remaining 11 studies were designed as observational (prospective cross-sectional and cohorts) and, four of them were based on the PrefHer Trial (NCT01401166) (Burcombe et al., 2013; Jackisch et al., 2015; De Cock et al., 2016; Farolfi et al., 2017). Finally, one was the randomized, open-label, international, multicenter, crossover, phase II PHranceSCa Trial (NCT03674112) (O'Shaughnessy et al., 2021). Eleven studies specified the stage of the diagnose of the breast cancer, being eight with individuals diagnosed with HER2-positive eBC (Burcombe et al., 2013; North et al., 2015; De Cock et al., 2016; Farolfi et al., 2017; Lopez-Vivanco et al., 2017; Mitchell and Morrissey, 2019; Rojas et al., 2020; O'Shaughnessy et al., 2021) and three HER2-positive early or metastatic BC (Olofsson et al., 2016; Tjalma et al., 2018; Kashiura et al., 2019). Regarding the therapy, only one study demonstrated data regarding the combination of PH (O'Shaughnessy et al., 2021), while the others were conducted with trastuzumab. Seventeen studies reported data regarding resource utilization in terms of patient and HCP time spent to conduct the administration of the medication, while 18 studies reported data regarding the cost related to the treatment (per cycle or full-cycle treatment).

Studies related to the variable of patients' and HCPs' preferences (Supplementary Table S7), each of the five included studies were from a different randomized clinical trial: PrefHer (NCT01401166) (Pivot et al., 2014), GAIN-2 (NCT01690702) (Reinisch et al., 2022), PHranceSCa Trial (NCT03674112) (O'Shaughnessy et al., 2021), MetaspHer (NCT01810393) (Pivot et al., 2017), and ChangHER (NCT01875367) (Ciruelos et al., 2020). Two studies were conducted with individuals diagnosed with HER2-positive metastatic BC (Pivot et al., 2017; Ciruelos et al., 2020) and the remaining three were with individuals diagnosed with HER2-positive eBC (Pivot et al., 2014; O'Shaughnessy et al., 2021; Reinisch et al., 2022). As mentioned previously, only one study was conducted with the combination of PH (O'Shaughnessy et al., 2021), while the others were conducted with trastuzumab only. Most of the included studies presented data regarding patients' and HCPs' preference; one study from Reinisch et al. (Reinisch et al., 2022) (substudy of the phase III trial GAIN-2 [NCT01690702]) reported data of patients' preference only.

3.2 Main results for patients and healthcare professional preferences

Summarized results from patients and HCP preferences can be found in Figures 2, 3.

The patients and HCPs' preferences were evaluated though different measures, for example, semi-structure interviews with open questions, validated study-specific patient interview, validated preference questionnaire (Patient Preference Questionnaire [PPQ]), and satisfaction questionnaires. The output of these evaluations was demonstrated in proportion of patients and HCPs who prefer each administration route. Overall, more than 75% of the patients and HCPs preferred the SC administration route over the IV.

The main reasons demonstrated by the studies on why patients prefer SC administration route include time-savings and less pain, discomfort, and side effects (Pivot et al., 2014; O'Shaughnessy et al., 2021); HCPs agreed that SC administration route is time-savings, more convenient and less painful for patients, in addition to requiring fewer resources for preparation (Ciruelos et al., 2020). Promoting benefit in the HCPs workload, reducing drug waste, enabling shorter infusion times and observation of attack and maintenance drug doses, generating a significant reduction in patient chair time.

3.3 Main results for healthcare resource utilization

The summarized results of the healthcare resource utilization can be found in Tables 2, 3.

3.4 Healthcare professionals and patients' time

In terms of the variable's definition in the included studies, HCP (e.g., pharmacists, nurses, nursing assistants, medical staff, etc.) time includes drug preparation and administration times. Chair time refers to the period that the patients spent in the unit of care to receive the drugs (entry and exit from the infusion chair), also referred to as treatment room time, time at the unit, and hospital time. Additionally, as a patient variable, some studies report data regarding the burden of the treatment in the patients and caregivers' life, referring to time off from work and transit.

Specifically for HCP time, the studies reported that IV administration time can be two to 19 times longer than SC administration time (including loading and maintenance doses), while the preparation time for IV can be three times longer than SC. Regarding the overall HCP time (including administration and preparation time), IV administration time can be two to six times longer than SC administration time.

Regarding the patients' time spent to receive the drugs, the studies reported significant time-savings with the SC administration route. Intravenous administration makes the patient remain in the care unit for two to 13 times longer compared to SC, which also prolongs work absences by three times.

Overall, the SC administration route saves more than 40% of HCP and patients time compared to IV.

3.5 Costs related to SC compared to IV administration route

The reported costs by the included studies were based on data from time-and-motion, in which the time for specific procedures

was directly measured. Other studies reported direct costs, expressed by the resource used, for example, drugs, consumables, healthcare personnel, catheter, possible waste of the drug, structural costs, and adverse events; as well as indirect costs, expressed by the burden that this procedure imposes to patients and HCPs, like societal costs and loss of productivity. Those costs were also extrapolated for one to 5 years of treatment.

The studies from Simoens et al. (Simoens et al., 2021), Lieutenant et al. (Lieutenant et al., 2015), North et al. (North et al., 2015), Olsen et al. (Olsen et al., 2017), did not present the exact cost (in terms of values) comparison between IV and SC, but demonstrated the significant cost-saving of using the SC administration route. Specifically, the case study of Simoens et al. (Simoens et al., 2021) in Belgium healthcare center found that IV treatment was less expensive than SC for patients weighing up to 75 kg. This phenomenon occurred because the authors considered data from biosimilars to conduct the study. Kashiura et al. (Kashiura et al., 2019) demonstrated the budget impact of incorporating the SC administration route in Brazilian private healthcare system for a period of 5 years and reported a significant cost-saving compared to IV administration route (cost-savings of up to USD 176,859,259.46 for HER-2 positive eBC and up to USD 6,307,656.20 for HER-2 positive metastatic breast cancer). Hedayati et al. (Hedayati et al., 2019) demonstrated that SC administration can save USD 650,710.94 over 1 year, avoiding surgery to implant catheters (69% of cost-saving), and saving time for drug preparation (28% of cost-saving) and consumables (3% of cost-saving) involved in the procedure.

Regarding direct costs with consumables, the studies reported that the IV administration route cost two to four times more than SC; the costs of health professionals, which include the preparation and administration of the medication, are one to eight times higher in the IV administration route in comparison to SC per cycle and for full cycles (17–18 cycles); if we extrapolate these data to 3 years of treatment, these costs could be 12 times higher with the IV administration route; indirect costs vary from one to 25 times higher when using the IV administration route; structural costs are also higher with the IV administration route–which is nine times higher than with SC. Interestingly, total costs and drug and adverse event costs did not differ when comparing IV to SC administration route.

3.6 Quality assessment

In the Supplementary Figures S1, S2 and Supplementary Table S6, we demonstrated the results regarding the quality appraisal of the included studies. Overall, most of the observational studies presented low to moderate risk of bias. Only three studies demonstrated serious risk of bias due to: deviations from intended interventions and missing data (Altini et al., 2020); measurement of the outcomes (Mitchell and Morrissey, 2019); and classification of the interventions (Burcombe et al., 2013). Regarding the risk of bias of randomized controlled trials, we found that more than half of the included studies presented low to some concerns. Only two studies demonstrated high methodological risk of bias due to: randomization process (Ciruelos et al., 2020; O'Shaughnessy et al., 2021) and selection of the reported result (Ciruelos et al., 2020). The economic studies were evaluated by the CHEERS checklist. Bias was considered when the study did not report some of the mandatory item for conducting an economic study design. Overall, topics not reported by some studies were: 1) discount rate and its reason for including 2) currency, price date and conversion; 3) characteristics of heterogeneity and uncertainty; 4) specific parameters; 5) effect of uncertainty; and 6) conflict of interests.

4 Discussion

This systematic literature review focused on the benefits of biologic administration routes for the treatment of early-stage or metastatic HER-2-positive BC, regardless of the drugs administered. These benefits were evaluated through preferences reported by HCPs and patients, time spent performing this task, and cost savings. According to our study, the HCPs and patients prefer the SC administration route. Furthermore, and consistent with these findings, the SC method of administration substantially reduces the time spent by HCPs on administration and preparation, as well as patient chair time in the healthcare facility. The advantages of SC therapy are understood to include shorter treatment time, reduced use of healthcare resources, lower costs (both direct and indirect costs), greater patient convenience, and greater preference for patients and HCPs when compared to IV therapy (Pivot et al., 2013; Wynne et al., 2013; Pivot et al., 2014; De Cock et al., 2016). Another possible advantage of the SC administration route is that patients do not need to go to an infusion room; treatment can be administered by trained nurses outside the hospital setting (O'Shaughnessy et al., 2021).

In light of these considerations, the SC administration route emerges as an enticing solution, further augmented by its capacity to offer the convenience of home delivery. Administration at home reduces the risk of exposure to nosocomial infections. It is expected that, with this alternative, the QoL of patients will improve, in addition to making life easier for those who live far from a hospital or have difficulties in commuting and parking close to the hospital. This can contribute to a lower financial, family, and friends burden (Jonaitis et al., 2021). However, some countries, like Brazil, may have specific legislation that restricts the use of cancer therapies to certified units.

SC delivery systems are designed with smaller needle sizes, which can decrease pain during administration. It has been proven effective, safe, well tolerated, and generally preferred by patients and HCPs because it is less time-consuming, requires less effort and time absent from work, reduces the loss of productivity and leisure time associated with patients attending the hospital, and minimizes the discomfort associated with IV infusions. The SC route of administration, interestingly, results in the reduction of health costs related to drug administration and the use of resources and is cost saving from the societal perspective (Jonaitis et al., 2021). Another possible benefit is that central venous access devices can be removed sooner, reducing the risk of morbidity (O'Shaughnessy et al., 2021). These benefits are particularly noticeable in the context of the public health system, where human resources are limited.

It is important to highlight that the decision of the treatment and route of administration, should be shared with patients. In the

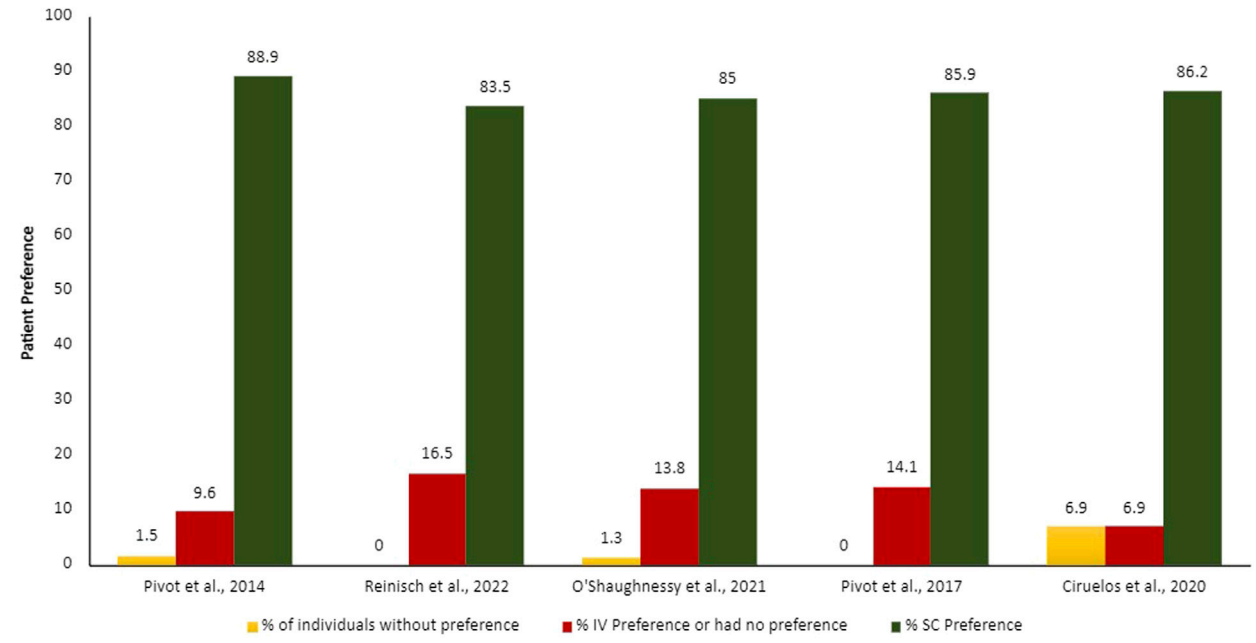

FIGURE 2
Proportion of patients' preferences according to each administration route. IV, intravenous; SC, subcutaneous.

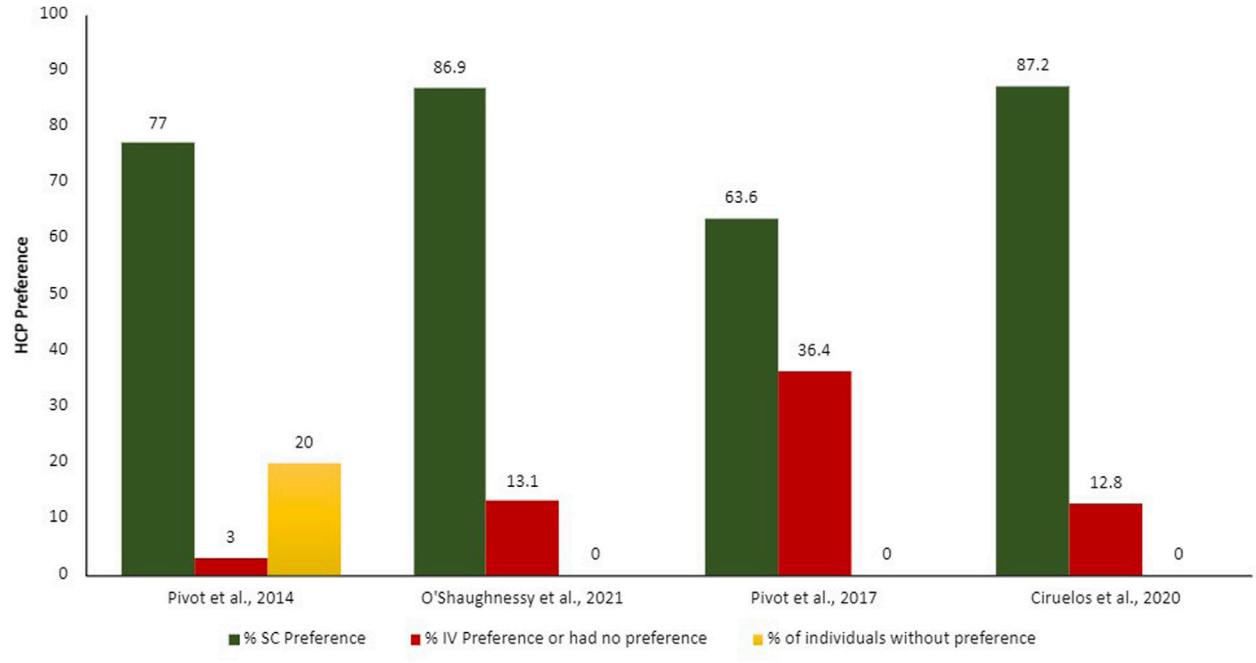

FIGURE 3
Proportion of HCPs preferences according to each administration route. IV, intravenous; SC, subcutaneous.

decision-making process, patients need to understand the relative time-related burden associated with different treatment options. Although values and preferences will vary across individuals, most patients want to minimize time toxicity. Most clinical trials do not report measures of time toxicity. This data could be used to guide patients, who might have different priorities (O'Shaughnessy et al., 2021). With respect to transition costs from IV to SC administration, the SC administration route may offer payers distinct cost advantages. Compared to IV infusions, many SC-administered drugs (e.g., rituximab and belimumab) offer direct cost savings as

TABLE 2 Summarized results regarding healthcare resource utilization in terms of time spent for patients and HCP.

Authors, year	Healthcare resource utilization (time)[a]	Relation SC:IV
Cordero et al. (2019)	Administration time	1:3
Mitchell and Morrissey (2019)	Chair-time per session	1:4
Olofsson et al. (2016)	Time off from work	1:3
	Time for the accompanying kin	1:1
Lieutenant et al. (2015)	Administration time (Loading doses Administration time (Maintenance doses)	1:4 1:2
	Transit time	1:18 to 1:6
	Manufacturing time	1:3
O'Brien et al. (2019)	Treatment room time	1:4
Lopez-Vivanco et al. (2017)	HCP time	1:2
	Chair-time	1:5
	Treatment room time	1:4
	Hospital time	1:2
North et al. (2015)	HCP time	1:2
	Chair-time	1:5
Burcombe et al. (2013)	HCP time	1:4
	Time at the unit of care	1:3
	Chair-time	1:4
Tjalma et al. (2018)	HCP time	1:6
	Hospital time	1:3
	Chair-time	1:13
Altini et al. (2020)	Administration time	1:2
	Chair-time	1:2
Farolfi et al. (2017)	Preparation time	1:3
	Administration time	1:9
Hedayati et al. (2019)	Administration time (1st session) Administration time (Subsequent sessions)	1:9 1:3
Jackisch et al. (2015)	HCP time	1:2
	Chair-time	1:3
O'Shaughnessy et al. (2021)	Chair-time	1:4 to 1:6
	Administration time	1:9 to 1:19

[a]Time was measured according to the study methodology (hours or minutes).

they do not require premedication (Heald et al., 2021). As an example of this direct cost reduction, the assessment of the budgetary impact (forecasted budget impact at 1, 2 and 3 years) of introducing rituximab SC in cancer patients in US health plans showed that changing the route of administration from IV to SC reduced total pharmacy and administration costs in the year of highest conversion rate by $223,000 (translating to a per-member-per-month [PMPM] decrease of $0.02) (Tetteh and Morris, 2014; Hansen et al., 2018). Similar findings with oncology biologics have been reported across countries despite differences in healthcare systems and payer types (Heald et al., 2021). A Brazilian study demonstrated that incorporating the SC administration route into the private system resulted in a significantly lower budgetary impact when compared to the IV administration route (Kashiura et al., 2019). It is important to mention that this study was conducted with the reference drug and the magnitude of savings can vary according to the type of drug (biosimilar or reference) and the context of the health system (public or private). Additionally, one potential challenge with SC administration is the use of fixed doses, which may not account for interpatient variability in body weight and

TABLE 3 Summarized results regarding healthcare resource utilization in terms of treatment costs.

Authors, year	Country	Healthcare resource utilization (costs)[a]	Relation SC:IV
Cordero et al. (2019)	Costa Rica	Cost per application	1:6
Mitchell and Morrissey (2019)	United Kingdom	Total cost	1:3
Olofsson et al. (2016)	Sweden	Societal treatment costs (First-time treatment occasion) Societal treatment costs (Subsequent treatment occasions)	1:1 1:1
O'Brien et al. (2019)	Ireland	Costs of Consumables (Per treatment cycle) Costs of Consumables (For a complete 17-cycle treatment) HCP Costs (Preparation and administration - Per treatment cycle) HCP Costs (Preparation and administration - For a complete 17-cycle treatment) Drug Costs (17-cycle treatment) Indirect Costs (Lost productivity for 17-cycle treatment per patient)	1:2 1:2 1:5 1:5 1:1 1:3
Lopez-Vivanco et al. (2017)	Spain	Costs of Consumables (Per treatment cycle) Costs of Consumables (For a complete 18-cycle treatment) HCP Costs (Preparation and administration - Per treatment cycle) HCP Costs (Preparation and administration - For a complete 18-cycle treatment) Drug costs (18-cycle treatment) Indirect costs (lost productivity - By patient room time) Indirect costs (lost productivity - By hospital time	1:4 1:4 1:2 1:2 1:1 1:4 1:2
Burcombe et al. (2013)	United Kingdom	Costs/patient episode (administration and preparation)	1:4
Tjalma et al. (2018)	Belgium	Total cost HCP time/patient episode Cost of consumables	1:20 1:5 1:8
Altini et al. (2020)	Italy	Total cost	1:1
Elsamany et al. (2020)	Saudi Arabia	Costs to prepare and administer the drugs formulations over 3 years Total annual costs (drug and non-drug costs) - 1st scenario Total annual costs (drug and non-drug costs) - 2nd scenario Indirect costs (lost productivity)	1:12 1:2 1:2 1:25
Lazaro Cebas et al. (2017)	Spain	Total cost	1:1
Farolfi et al. (2017)	Italy	Total cost of the drugs Direct cost/patient Outpatient clinic costs/patient Direct + Indirect costs (costs/patient)	1:1 1:1 1:9 1:1
Rojas et al. (2020)	Chile	HCP Costs (Preparation - Per treatment cycle) HCP Costs (Preparation - For a complete 18-cycle treatment) HCP Costs (Administration - For a complete 18-cycle treatment) Adverse drug reaction (ADR) treatment costs Non-medical costs Total cost	1:1 1:1 1:2 1:1 1:1 1:1

[a]Currency was standardized in United States Dollars (USD) on 27 March 2023.

surface area. This could lead to insufficient dosing in larger patients or excessive dosing in smaller patients. However, studies have shown that the fixed-dose regimen of PH FDC SC is generally well-tolerated and effective across a range of patient demographics, although careful monitoring and individual adjustments may be necessary in certain cases to optimize therapeutic outcomes (Kolberg et al., 2021).

Examining indirect costs alongside direct costs is another important consideration for some payers when comparing IV versus SC administration. A cost analysis showed that SC administration costs were 50% lower compared to the IV route, with most patients administering their own SC medications. Other indirect benefits of this administration route include shorter waiting time at the infusion unit, reduced risk of infections or other diseases (especially for patients with breast cancer who are often immunosuppressed), and reduction of direct costs of the patient (travel, occupational break). For biologics cases (IV versus SC), in direct/indirect cost analysis, excluding drug acquisition costs, SC administration appears to be the most cost-effective option for many patients (Heald et al., 2021).

In line with this information, studies have demonstrated that SC administration of biotherapeutics is a relevant alternative to IV administration in diverse disease scenarios, including inflammatory bowel disease, non-Hodgkin's lymphoma, rheumatoid arthritis, primary immunodeficiency, multiple sclerosis, etc. (Bittner et al., 2018). With the alternative of SC administration, a significant benefit is expected for patients receiving monotherapy of a biologic in the maintenance/adjuvant setting or in combination with oral chemotherapy, as there will be a reduction in the time required for frequent hospital visits. For complex dosing regimens, such as fixed-dose combinations (two or more active molecules co-formulated in the same formulation) or ready-to-use devices that deliver two or more biotherapeutics per half hour from a single SC injection, the use of SC administration can further simplify

medication administration (Bittner et al., 2018). Additionally, the SC administration route is as well-tolerated as the IV route, with comparable safety profiles. SC administration often results in localized injection site reactions, such as mild pain, redness, and swelling, which are generally manageable. In contrast, IV administration is associated with a higher incidence of systemic infusion-related reactions, including fever, chills, nausea, headaches, and potential cardiac toxicity. This data indicates that SC administration, with its lower incidence of systemic adverse effects and greater patient convenience, may be a preferable option for many patients undergoing treatment for HER2-positive breast cancer (Pivot et al., 2014; O'Shaughnessy et al., 2021).

Furthermore, the humanistic impact of SC and IV formulations of oncology therapies showed that patients have a clear preference for SC administration and report better health-related QoL (Anderson et al., 2019; Epstein, 2021). Corroborating this fact, patients reported "time savings" as the main reason for preferring SC (Gianni et al., 2010; McCloskey et al., 2023), in addition to being more comfortable, well-tolerated, safe, and less painful. HCPs were also more satisfied with SC as they perceived better clinical management and an efficient method (Marty et al., 2005; Pivot et al., 2014; Gianni et al., 2016).

Patients and HCPs are convinced that the SC administration route is more suitable for younger and employed patients, while the IV route is more suitable for older patients, especially those who refuse to inject themselves and feel safer when receiving therapy in a hospital setting (Jonaitis et al., 2021). The key drivers for switching from IV to SC administration of biologics include medical considerations (disease amelioration/stabilization, facility decongestion, patient involvement in treatment), patient considerations (preference for a more comfortable and easy-to-administer formula, self -administration, a more flexible schedule, limited reliance on medical facilities and personnel) and administrative considerations involving costs and, in some countries, insurance reimbursement (Jonaitis et al., 2021).

Nonetheless, it is important to interpret the data presented in this systematic literature review with a mindful consideration of certain limitations. Firstly, it is important to notice that the efficacy and safety profiles of the medication administered by SC and IV were assumed to be comparable (Kolberg et al., 2021). Secondly, there was some variation in times reported for IV and SC preparation and administration, which may reflect a heterogeneity concerning the methods of measuring the data and its results, for example, the time estimate methodologies, definitions of time periods, and clinical practice/hospital set up between the different participating centers. Based on this premise, it is highly essential to standardize the data measurement methodology and create uniform parameters to adequately support decision-making. Pharmacoeconomic consideration is a point of interest, but they are highly dependent on the model of reimbursement and valorization of IV and/or SC administrations and it could not be translated from one country to another. Independently, of the cost and payment considerations, the SC administration route has demonstrated benefits in terms of time and resource saving, in addition, to being preferred by the HCPs and patients (Pivot et al., 2017).

In conclusion, this systematic literature review highlighted a consistent trend in favor of SC administration across all publications, related to patients and HCP preferences. Combined data, has shown that SC administration route benefits both patients and healthcare systems (Pivot et al., 2014). These data provide supporting evidence for a practice change regarding the route of administration of the anti-HER2 therapy setting either in the adjuvant or in the metastatic setting (Pivot et al., 2017).

Author contributions

LL: Writing–review and editing, Validation, Supervision. TM: Writing–review and editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. RG: Writing–review and editing, Writing–original draft, Resources, Project administration, Methodology, Investigation, Formal Analysis, Data curation. IM: Writing–review and editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. JB: Writing–review and editing, Formal Analysis, Data curation. EP: Writing–review and editing. GA: Writing–review and editing, Validation, Supervision, Formal Analysis. SS: Writing–review and editing, Validation, Supervision, Formal Analysis, Conceptualization.

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Conflict of interest

Author LL was employed by Oncoclínicas Group. Authors TM, IM and EP were employed by Roche Pharmaceuticals. Authors RG and JB were employed by Oracle Life Sciences.

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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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1338546/full#supplementary-material

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