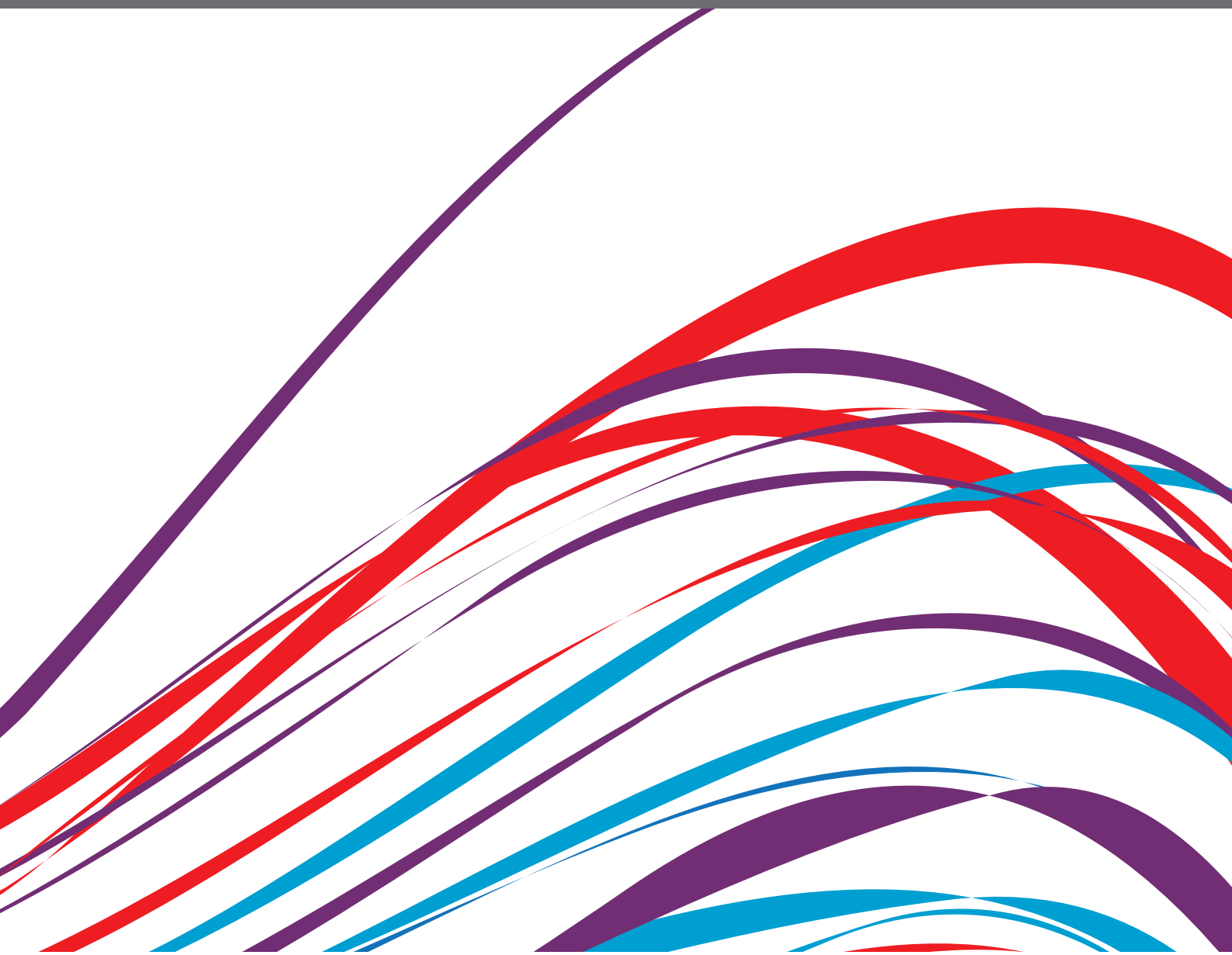
# HIGHLIGHTS IN HEART FAILURE AND TRANSPLANTATION: 2021

EDITED BY: Emma Birks and Matteo Cameli
PUBLISHED IN: Frontiers in Cardiovascular Medicine



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ISSN 1664-8714
ISBN 978-2-88974-937-9
DOI 10.3389/978-2-88974-937-9

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# HIGHLIGHTS IN HEART FAILURE AND TRANSPLANTATION: 2021

Topic Editors:
**Emma Birks,** University of Kentucky, United States
**Matteo Cameli,** University of Siena, Italy

**Citation:** Birks, E., Cameli, M., eds. (2022). Highlights in Heart Failure and Transplantation: 2021. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-937-9

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frontiers in Cardiovascular Medicine

EDITORIAL
published: 25 March 2022
doi: 10.3389/fcvm.2022.877515

# Editorial: Highlights in Heart Failure and Transplantation in 2021

*Matteo Cameli*[1]*, *Emma J. Birks*[2,3] and *Federico Landra*[1]*

[1] Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2] Division of Cardiovascular Medicine, University of Louisville, Louisville, KY, United States, [3] Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY, United States

**Keywords: heart failure, radiation, drugs, bioimpedance, seismocardiogram, machine learning, rehabilitation**

**Editorial on the Research Topic**

**Highlights in Heart Failure and Transplantation in 2021**

## SPACE TRAVELS TO ELUCIDATE RADIATION-INDUCED CV DISEASE

More than 50 years after Neil Armstrong first set foot on the moon, space travel is gaining new popularity. However futuristic this topic may seem, humankind will probably undertake space travel on a broader scale in the upcoming centuries or even decades. This means that people will need to learn how to cope with challenges related to microgravity, hypoxia, disrupted circadian rhythms, and radiation exposure. The evidence raised from radiation exposure for curative aims and nuclear disasters has led the scientific community to recognize and understand its multiple pathogenic effects on the human body's various systems, including cardiovascular one. Meerman et al. carefully examined the issue of radiation exposure related to long-distance space travel, with a particular focus on its cardiovascular effects. The pathogenic mechanisms that can lead to radiation-induced cardiovascular disease (RI-CVD), including myocardial remodeling and fibrosis, atherosclerosis, and microvascular damage, are elucidated. In addition, potential countermeasures and protection methods are reported, from physical shielding to pharmacological means.

## NEW TECHNOLOGIES READY FOR CLINICAL USE

The future is entering our lives not only by enhanced horizons but also with new technologies. Bioimpedance spectroscopy (BIS) is a non-invasive method that relies on the different electrical impedance of biological tissues to assess fluid volume status. A clinical trial by Accardi et al. showed that BIS-measured extracellular fluid was higher in patients with heart failure compared to healthy individuals and that this result was consistent with the echocardiographic parameters of fluid status, such as inferior vena cava size. It was suggested that this tool may contribute to the risk stratification of patients with heart failure and facilitate clinical decision-making both in the clinic and potentially at home. Another tool of increasing study is seismocardiography (SCG), which allows the non-invasive estimation of stroke volume, cardiac output, and myocardial contractility through cardiac and blood-induced motions transmitted to the chest surface as vibratory phenomena. In an original research article, Morra et al. show that SCG can quantify cardiac kinetic energy and continuously track its changes during an acute myocardial infarction and subsequent reperfusion. As it has already happened for atrial fibrillation with smartwatches, thanks to its ease of use SCG could potentially help in the follow-up of heart failure patients monitoring their myocardial mechanical activity.

OPEN ACCESS

***Edited and reviewed by:***
*Hendrik Tevaearai Stahel, Bern University Hospital, Switzerland*

***Correspondence:**
*Matteo Cameli*
*matteo.cameli@yahoo.com*
*Federico Landra*
*f.landra@student.unisi.it*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *16 February 2022*
***Accepted:*** *21 February 2022*
***Published:*** *25 March 2022*

***Citation:***
*Cameli M, Birks EJ and Landra F (2022) Editorial: Highlights in Heart Failure and Transplantation in 2021. Front. Cardiovasc. Med. 9:877515. doi: 10.3389/fcvm.2022.877515*

## MACHINE LEARNING FOR DISEASE COURSE PREDICTION

Above all the technological advances that are presented to us nowadays, the one that is playing an increasingly prominent role is with no doubt machine learning. Machine learning is a branch of artificial intelligence that uses statistical methods to enhance the performance of an algorithm to identify patterns in data. Fahmy et al. used machine learning for predicting heart failure progression in a huge cohort of patients affected by hypertrophic cardiomyopathy (HCM). Heart failure progression was defined as worsening in NYHA class, a drop in left ventricular ejection fraction, need for septal reduction procedure, and/or indication for heart transplantation. A set of 17 clinical and imaging variables, also confirmed by an independent validation dataset, were identified as the most important predictors of progressive heart failure in HCM patients.

## ADVANCES IN HEART FAILURE UNDERSTANDING AND TREATMENT

Besides new technologies, an important branch of research remains the one whose aim is to identify biological molecules with a potential clinical application for diagnostic and prognostic purposes. This is the case with Big Endothelin-1, the prepropeptide of endothelin-1 (ET-1), the most potent endogenous vasoconstrictor, which has been recently recognized as an independent predictor of short-term adverse events in acute decompensated heart failure by Mo et al. The predictive value of big ET-1 was comparable to NT-proBNP; moreover, the combined use of the two molecules increased the predictivity of the primary outcome, defined as a composite of in-hospital death, cardiac arrest, and utilization of mechanical circulatory support. Many articles also take into account chronic heart failure and much interest addresses the more ambiguous categories, namely heart failure with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF). Regarding the latter, Abramov and Parwani criticized the tendency to gather all patients with preserved ejection fraction under a unique definition, since this group of patients is very heterogeneous. These authors suggest not focusing on the cutoffs identified by the recently introduced diagnostic score algorithms (HFA-PEFF and $H_2$FPEF) but instead trying to understand the underlying pathophysiology to come to better management decisions. The other equivocal category is HFmrEF. Patients can fall into this subgroup even though they may have different backgrounds. The diction "mildly reduced" implies that the ejection fraction used to be normal before. However, since ejection fraction is a dynamic state, an improvement is also possible, which underlies the emerging concept of recovered/improved ejection fraction. Therefore, HFmrEF could be "mildly reduced" as much as "mildly recovered" ejection fraction. Zhang et al. demonstrated that HFmrEF patients with previously preserved ejection fraction have worse outcomes compared to those with a previously reduced ejection fraction. Definitions of heart failure are continuously evolving as well as therapeutic options. Pascual-Figal et al. have undertaken a comprehensive review on Sacubitril-Valsartan, a game-changer drug not only in the field of HFrEF.

## PREVENTION AND REHABILITATION: NEVER TOO EARLY, NEVER TOO LATE

Drugs are not the only way of managing heart failure. Huang et al. undertook an interesting systematic review on the effects of Tai Chi exercise among adults with chronic heart failure, which shows potential as a cardiac rehabilitation discipline thanks to its low-intensity, making it suitable for people with poor exercise tolerance. Finally, diametrically opposite to rehabilitation and of equal importance, there is prevention for people with cardiovascular risk factors. It is a common opinion that prevention and rehabilitation will cover more and more space in the following decades to ensure a better quality of life and at the same time improve health care sustainability. Among the most common cardiovascular risk factors, there is diabetes, with more than 500 million people affected worldwide. Chadalavada et al. analyzed an enormous UK dataset and found that mortality and heart failure risk were almost doubled in people with diabetes compared to those without it, this being more evident for female patients.

## FUTURE DIRECTIONS

We get better and better at identifying risk factors for diseases' development and progression, at predicting their course, and deploying increasingly effective therapies at the right time. For the whole spectrum of time frames in heart failure course, we know what to do in order to either prevent it or improve the prognosis and quality of life of our patients. Research continuously casts light on previously unsolved dilemmas in clinical management.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

**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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frontiers in Cardiovascular Medicine

REVIEW
published: 12 February 2021
doi: 10.3389/fcvm.2021.631985

# Myocardial Disease and Long-Distance Space Travel: Solving the Radiation Problem

*Manon Meerman[1,2], Tom C. L. Bracco Gartner[1,2], Jan Willem Buikema[2,3], Sean M. Wu[4], Sailay Siddiqi[5], Carlijn V. C. Bouten[6], K. Jane Grande-Allen[7], Willem J. L. Suyker[1] and Jesper Hjortnaes[2,8]**

[1] Division Heart and Lung, Department of Cardiothoracic Surgery, University Medical Center Utrecht, Utrecht, Netherlands, [2] Regenerative Medicine Center Utrecht, University Medical Center Utrecht, Utrecht, Netherlands, [3] Department of Cardiology, University Medical Center Utrecht, Utrecht, Netherlands, [4] Division of Cardiovascular Medicine, Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA, United States, [5] Department of Cardiothoracic Surgery, Radboud University, Nijmegen, Netherlands, [6] Department of Biomedical Engineering, Technical University Eindhoven, Eindhoven, Netherlands, [7] Department of Bioengineering, Rice University, Houston, TX, United States, [8] Division Heart and Lung, Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, Netherlands

Radiation-induced cardiovascular disease is a well-known complication of radiation exposure. Over the last few years, planning for deep space missions has increased interest in the effects of space radiation on the cardiovascular system, as an increasing number of astronauts will be exposed to space radiation for longer periods of time. Research has shown that exposure to different types of particles found in space radiation can lead to the development of diverse cardiovascular disease via fibrotic myocardial remodeling, accelerated atherosclerosis and microvascular damage. Several underlying mechanisms for radiation-induced cardiovascular disease have been identified, but many aspects of the pathophysiology remain unclear. Existing pharmacological compounds have been evaluated to protect the cardiovascular system from space radiation-induced damage, but currently no radioprotective compounds have been approved. This review critically analyzes the effects of space radiation on the cardiovascular system, the underlying mechanisms and potential countermeasures to space radiation-induced cardiovascular disease.

**Keywords: radiation-induced cardiovascular disease, cardiovascular system, space radiation, long-distance space travel, experimental studies, countermeasures, HZE ions, heart failure**

OPEN ACCESS

***Edited by:***
*Susumu Minamisawa, Jikei University School of Medicine, Japan*

***Reviewed by:***
*Yasuhiro Ikeda, Yamaguchi Prefectural Grand Medical Center, Japan*
*Willian Abraham da Silveira, Queen's University Belfast, United Kingdom*

***Correspondence:**
*Jesper Hjortnaes*
*j.hjortnaes@lumc.nl*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *21 November 2020*
***Accepted:*** *11 January 2021*
***Published:*** *12 February 2021*

***Citation:***
*Meerman M, Bracco Gartner TCL, Buikema JW, Wu SM, Siddiqi S, Bouten CVC, Grande-Allen KJ, Suyker WJL and Hjortnaes J (2021) Myocardial Disease and Long-Distance Space Travel: Solving the Radiation Problem. Front. Cardiovasc. Med. 8:631985. doi: 10.3389/fcvm.2021.631985*

## KEY POINTS

- Exposure to components of space radiation beyond the low Earth Orbit can have damaging effects on the cardiovascular system, including myocardial remodeling and fibrosis and (micro)vascular damage;
- Several mechanisms of space-radiation induced CVD have been elucidated through experimental studies, such as endothelial dysfunction, increased cellular apoptosis, increased oxidative stress, induction of inflammation and decreased DNA methylation;
- To date, there are no effective measurements to protect astronauts that travel beyond the low Earth Orbit from this damaging type of radiation, and more research should be aimed at finding new methods of protection;
- Current data on this topic is derived from experimental animal or cell culture studies that have significant limitations. Future research should focus on incorporating new techniques, such as the "heart-on-a-chip."

# INTRODUCTION

Since mankind first set foot on the Moon in 1969, the National Aeronautics and Space Administration (NASA) and other space agencies have been working together to expand human space travel into deep space, with the ultimate goal of landing on Mars (1). Consequently, more astronauts will face the serious health risks associated with traveling into deep space. Determining the risks faced by these future space explorers is crucial. Currently, exposure to space radiation is considered one of the most important limiting factors for long-distance space travel (2). Space radiation exposure is linked to the development of cancer and diseases of the central nervous system (CNS) (3). However, over the last few years, there has been growing concern about the effects of space radiation on the cardiovascular system (CVS). Therefore, further research into the effects of space radiation on the development of cardiovascular disease is critical in order to understand and predict the effects of long distance space travel. The aims of this review are to summarize the current knowledge on the effects of space radiation on the cardiovascular system and to discuss potential countermeasures to the development of space radiation-induced cardiovascular disease.

## The Space Environment

### Space Radiation

In space, astronauts encounter space radiation consisting of galactic cosmic rays (GCR) and solar particle events (SPE) (4, 5). GCR originate outside our solar system and can interact with the Earth's atmosphere, producing showers of secondary particles (5, 6). These rays are mainly composed of high-energy protons ($^{1}$H), together with alpha particles (helium nuclei, $^{2+}$He), minimal-hazard electrons and positrons and HZE ions [high (H) charge (Z) and energy (E) ions] (7, 8). HZE ions include all nuclei with atomic numbers > 2, of which carbon ($^{12}$C), oxygen ($^{16}$O), magnesium ($^{24}$Mg), silicon ($^{28}$Si) and iron ($^{56}$Fe) are the most prominent (6, 9). Of all the components of GCR, HZE ions are considered the most hazardous to the human body since they can be highly penetrating and can produce secondary particles when they interact with shielding materials like the spacecraft or spacesuit (10). The other component of space radiation, SPE or "proton storms," are occasionally produced by the Sun and contain large plasma clouds consisting of low- to medium-energy protons, which mostly contain less than a few hundred GeV of kinetic energy (4, 6, 7, 11). Proton exposure doses due to SPE can occur at doses up to 1.5 Gy/h, while GCR exposure occurs at lower dose rates (1.3 mGy/day) (9). The doses that humans are exposed to in space are significantly higher than the radiation exposure humans encounter on Earth, which is estimated to be around 3.1 mSv per year (5).

Radiation can cause damage in proteins, RNA, and DNA in two ways, either directly by direct energy absorption or indirectly via the production of reactive oxygen species (ROS) from the radiolysis of water molecules (4, 8). The amount of biological damage caused by radiation exposure does not only depend on the dose, but also on the type of radiation the target is exposed to. Different types of radiation can be distinguished by the amount of energy transferred to the target material as an ionizing particle passes through, called linear energy transfer (LET). In general, the higher the mass of the ionizing particle, the higher the LET. While the human body is normally exposed to low LET radiation (x-, β- or γ-radiation) on Earth, in space it encounters high LET radiation in the form of HZE ions (3, 12). Two characteristics of high LET radiation make it more hazardous to the human body than low LET radiation. First, radiation types with higher LET produce ion and radical clusters that are close together. Consequently, when a beam of high LET radiation passes through strands of DNA, it typically causes more biological damage than low LET radiation since it induces genomic lesions densely packed around the track of the radiation beam. This is called "clustered DNA damage" (4, 12). These DNA lesions include single- and double-strand breaks, interstrand crosslinks and base modifications. If not repaired, these lesions can result in mutations, chromosome exchanges, carcinogenesis and apoptotic cell death (4, 13). Second, because of the highly ionizing and penetrating capacity of high LET radiation, much lower magnitude physical doses are needed to induce these effects compared to low LET radiation (13). Because the HZE-component of space radiation is more important in deep space beyond the low Earth Orbit (LEO), studying the cardiovascular risks of exposure to this type of radiation is important in light of the current vision to send humans to the Moon and eventually Mars (1, 10).

## Radiation-Induced Cardiovascular Disease (RICVD)

According to a fundamental law in radiobiology ("*Law of Bergonie and Tribondeau,*" 1906), the adult heart has historically been considered a relatively radioresistant organ because of the low proliferation rates of cardiomyocytes (∼1% annually) (14). However, research has shown that this perception is not true and that instead the cardiovascular system is indeed very sensitive to radiation (13). Exposure to various types of radiation as described above therefore can lead to radiation-induced cardiovascular disease (RICVD), involving the development of new cardiovascular disease (CVD) or the exacerbation of existing CVD (15). RICVD can either develop within weeks as an acute complication of radiation exposure, mostly being acute pericarditis (12, 16–18), but it can also develop over a longer period of time as chronic RICVD (16, 17). Chronic RICVD is generally progressive and involves multiple disorders of the heart and vasculature, such as myocardial remodeling and fibrosis, accelerated development of atherosclerosis, cardiomyopathies, valve abnormalities, arrhythmias and conduction disorders (12, 13, 16, 17, 19). Retrospective observational studies show that these effects can develop over more than 10–15 years after exposure (13, 16, 17).

RICVD is a well-known complication of radiation therapy in patients treated for thoracic malignancies, such as malignant lymphomas (Hodgkin or Non-Hodgkin lymphoma) or breast

**Abbreviations:** GCR, galactic cosmic rays; HZE, high charge (Z) and energy (E); LET, linear energy transfer; LEO, low Earth Orbit; SPE, solar particle events.

and lung cancer (18, 20–23). Radiotherapy treatment for these kinds of malignancies involves exposure of the heart and thoracic vessels (aorta, carotid and coronary arteries) to incidental doses of low LET radiation, which may cause RICVD (21). For instance, a study on Hodgkin's Lymphoma (HL) survivors showed a 3- to 5-fold higher incidence of several types of CVD compared to the general population. They also showed that ∼66–80% of heart disease in the HL population was due to radiation exposure during radiotherapy (20). RICVD after breast and lung cancer treatment has also been intensively studied (22, 23). Fortunately, cardiac complications after radiotherapy are currently less common due to modifications in radiotherapy techniques (18).

Besides being observed in patients treated for cancer, RICVD has also been detected in other groups with high exposure to radiation, such as Japanese atomic bomb survivors or occupationally exposed groups, such as the Mayak workers, Chernobyl emergency workers and radiologists before the 1950s (24–26). Cardiovascular morbidity and mortality in >86,000 Japanese atomic bomb survivors, who received radiation doses of 0–4 Gy, have been studied in the Hiroshima-Nagasaki Life Span Study (LSS). This study showed a significantly increased risk for heart disease such as myocardial infarction and an increase in cardiovascular disease risk of 14% per Gy exposure (18, 25, 27).

Taken together, data from these studies demonstrate the development of RICVD in groups with excess exposure to radiation. Yet, care should be taken to extrapolate the data from these groups to astronauts, a highly unique cohort. As discussed above, space radiation is significantly different from radiation encountered on Earth in terms of radiation quality and dose rates. Moreover, cancer patients are generally less healthy than astronauts before exposure, giving rise to potential confounders that might influence the risk of CVD determined in the studies mentioned above (10). Another important consideration is the fact that most astronauts have traveled into space within LEO, while the only astronauts that currently have explored space beyond LEO are the astronauts from the Apollo program. Altogether, it remains difficult to estimate the exact risks astronauts will face during future deep space exploration.

With NASA's current plans to expand human space exploration, more humans will be exposed to the space environment beyond LEO in the near future. A study by Delp et al. reported a 4–5 times higher risk of CVD in Apollo astronauts compared to astronauts who never traveled beyond LEO (28). However, Elgart et al. showed no increased risk of CVD in this population (29). Nonetheless, the group size is limited and these studies therefore both have significant statistical limitations. These conflicting results, combined with the fact that space radiation is currently considered the greatest limiting factor for long-distance space travel (30), emphasize the need for further research into the occurrence of RICVD in astronauts that travel beyond LEO. To date, several experimental studies using different types of animal models have investigated the effects of space radiation on the CVS. The data from these studies will be summarized in the following paragraphs.

# SPACE RADIATION-INDUCED CARDIOVASCULAR DISEASE

## Cardiac Alterations

Myocardial remodeling is a key underlying factor in heart failure; this pathological remodeling includes damage to cardiomyocytes and myocardial fibrosis (31). Myocardial fibrosis is a complicated process which leads to the accumulation of extracellular matrix (ECM) in the myocardium, resulting in a stiffened heart muscle (31). In RICVD, myocardial remodeling and fibrosis are important underlying mechanisms (18). Therefore, these changes may also influence RICVD after exposure to HZE ions in space radiation. To our knowledge, several experimental studies using animal models showed signs of the development of myocardial remodeling or fibrosis after exposure to HZE ions such as protons or $^{56}$Fe ions, but not after exposure to $^{16}$O ions or γ-radiation (32–35) (**Table 1**).

Several murine models have demonstrated cardiac remodeling following radiation. Yan et al. first demonstrated the development of progressive cardiac hypertrophy up to 3 months in proton-irradiated hearts (0.5 Gy, from C57Bl/6NT mice), as indicated by an increase in left ventricular (LV) posterior wall thickness (PWth), decreased LV end-diastolic pressure (LVEDP), increased ejection fraction % (EF%) and increased minimum pressure change in the ventricle during the cardiac cycle (expressed as $dP/dt_{min}$). The development of cardiac hypertrophy was confirmed by the increased activity of NFATc4, a marker for cardiac hypertrophy signaling (32). These changes were also observed in mice exposed to $^{56}$Fe ions (0.15 Gy, 1 GeV/n), but these hearts decompensated earlier and developed systolic and diastolic dysfunction after 1 month, suggesting a stronger effect of $^{56}$Fe ions compared to protons (32). Another study further confirmed myocardial remodeling of the murine heart induced by exposure to $^{56}$Fe ions (0.5 Gy, 600 MeV/n) (35). Two common features of myocardial remodeling were both observed in the irradiated hearts, namely increased collagen deposition and increased numbers of myofibroblasts, indicated by higher α-SMC actin levels (35). However, these changes did not occur if these hearts were primed with low dose protons (0.1 Gy, 150 MeV), suggesting a potential protective effect of protons on the heart (35). The most recent study on the effects of exposure to $^{56}$Fe ions and protons on the murine heart showed that irradiation with a single low dose of $^{56}$Fe ions (0.15 Gy, 1 GeV/n), followed by 3 doses of protons (0.17 Gy, 1 GeV), caused early hemodynamic alterations of cardiac function 1 month post-exposure (33). These alterations progressed into the development of cardiac fibrosis after 3 months, suggesting synergistic effects of $^{56}$Fe ion and proton exposure on the cardiovascular system (33).

Yet, some studies have shown that not all particles found in space radiation have fibrotic effects on the myocardium. Seawright et al. reported no changes suggestive of myocardial remodeling and fibrosis in the hearts of C57Bl/6J mice exposed to a continuous low dose of γ-radiation (0.01 cGy/h, cumulative dose of 0.04 Gy), as indicated by a lack of change in α-SMC actin levels, collagen type III content or total collagen composition (36). Another recent publication from the same group showed

**TABLE 1 |** Overview of experimental animal studies on the effects of space radiation on the CVS.

| Radiation dose (Gy); exposure type | Animal model | Results | Ref. |
|---|---|---|---|
| **HEART** | | | |
| **HZE ions** | | | |
| Iron ($^{56}$Fe) | | | |
| 0.15 Gy, 1 GeV/n; WBE | Male C57Bl/6NT mice, aged 8-10 months | Early systolic and diastolic decompensation (after 1 month) and cardiac hypertrophy (after 3 months), as indicated by an increase in LV posterior wall thickness (PWth), LV end-diastolic pressure (LVEDP), $dP/dt_{min}$, ejection fraction % (EF%) and NFATc4 activity. | (32) |
| 0.5 Gy, 600 MeV/n; WBE | Male C57BL/6 mice, aged 10 weeks | Myocardial remodeling, as indicated by increased collagen deposition and α-SMC actin levels. | (35) |
| Oxygen ($^{16}$O) | | | |
| 0.1–1.0 Gy, 600 MeV/n; WBE | Male C57Bl/6J mice, aged 6 months | Myocardial remodeling in the LV, as indicated by dose-dependent increases in the 75 kDa type III collagen cleavage product and increased α-SMC actin levels. No development of cardiac fibrosis. | (34) |
| **Protons ($^{1}$H)** | | | |
| 0.5 Gy, 1 GeV; WBE | Male C57Bl/6NT mice, aged 8–10 months | Cardiac hypertrophy (after 3 months) as indicated by an increase in LV posterior wall thickness (PWth), LV end-diastolic pressure (LVEDP), $dP/dt_{min}$, ejection fraction % (EF%) and NFATc4 activity. | (32) |
| 1 Gy, 1 GeV; WBE | Male C57Bl/6J mice, aged 6 months | Decreased LV α-SMC actin levels | (34) |
| **γ-radiation** | | | |
| Continuous exposure to γ-radiation, 21 days: 0.01 cGy/h, cumulative dose 0.04 Gy; WBE | Female C67Bl/6J mice, aged 6 months | No changes suggestive of myocardial remodeling and fibrosis | (36) |
| Single exposure; 1.0 and 3.0 Gy; WBE | Male C57Bl/6J mice, aged 6 months | Myocardial remodeling in the LV, as indicated by an increase in the 75 kDa type III collagen cleave product and increased α-SMC actin levels. No development of cardiac fibrosis. | (34) |
| **Consecutive exposure of different ions** | | | |
| 0.15 Gy, 1 GeV/n $^{56}$Fe + 3 × 0.17 Gy, 1 GeV $^{1}$H; WBE | Male C57Bl/6NT mice, aged 8–10 months | Cardiac hypertrophy and diastolic dysfunction (after 1 month) and increased cardiac fibrosis (after 3 months), as indicated by increased LVEDP and NFATc4 activity. | (33) |
| 0.1 Gy, 150 MeV $^{1}$H + 0.5 Gy, 600 MeV/n $^{56}$Fe; WBE | Male C57Bl/6J mice, aged 10 weeks | No changes suggestive of myocardial remodeling | (35) |
| **VASCULATURE** | | | |
| **HZE ions** | | | |
| Iron ($^{56}$Fe) | | | |
| 0.1–0.2 Gy; targeted exposure of the orbital region | Female B6CF1 mice, aged 4 months | Degenerative changes in coronary arteries: smooth muscle degeneration with fibrosis and ECM accumulation in the tunica media. | (37) |
| 2.0 and 5.0 Gy, 600 MeV/n; targeted exposure of the upper aortic tree | Male apoE$^{-/-}$ mice, aged 10 weeks | Accelerated development of atherosclerosis: increased atherosclerotic areas (especially at the aortic root), larger necrotic cores and thickening of the carotid intima. | (38) |
| 1.0 Gy, 1 GeV/n; targeted exposure of the aorta | Male Wistar rats, aged 3–4 months | Increased aortic stiffness and chronic vascular dysfunction. | (39) |
| **γ-radiation** | | | |
| 1.0 and 3.0 Gy; WBE | Male C57BL/6 J mice, aged 6 months | Increased collagen deposition in abdominal aorta. | (34) |

*α-SMC actin, alpha smooth muscle cell actin; ECM, extracellular matrix; Gy, Gray; LV, left ventricle; LVEDP, left ventricle end-diastolic pressure; NFATc4, nuclear factor of activated T-cells cytoplasmic 4, a marker for cardiac hypertrophy signaling; WBE, whole body exposure.*

no effects of exposure to $^{16}$O ions (0.1–1.0 Gy, 600 MeV/n) or γ-radiation (0.5–3 Gy) on the development of myocardial fibrosis (34). However, they did identify some signs of myocardial remodeling in the left ventricle in response to $^{16}$O- or γ-radiation, as shown by an increase of a 75-kDa cleave product of type III collagen and α-SMC actin levels (34). In the same study, proton irradiation also showed decreased α-SMC actin levels, again suggestive of a protective effect of protons on myocardial remodeling (34).

From these studies, we can conclude that there is definitely an effect of exposure to $^{56}$Fe ions, the most prominent heavy ion found in space radiation, on myocardial remodeling, hypertrophy and fibrosis in mice. However, the exact effects of proton irradiation are still unknown, since different doses

(0.5 vs. 0.1 Gy) of protons seem to have different effects on the myocardium (32, 34, 35). The potential interplay between different particles found in space radiation is also of concern.

## Vascular Alterations

### Atherosclerosis

Atherosclerosis is an important topic in RICVD since it has been shown that in groups exposed to higher doses of radiation than the general population, there was a significantly higher prevalence of myocardial infarction (MI) caused by atherosclerosis of the coronary arteries (18, 24–27, 38). Yu et al. reported accelerated development of atherosclerosis after exposure of different areas of the aorta of apolipoprotein E-deficient (apoE$^{-/-}$) mice to 2–5 Gy of $^{56}$Fe ions (38). They observed increased atherosclerotic areas in these targeted regions of the aorta, whereas no changes were observed in the non-targeted areas, demonstrating a local, non-systemic effect of $^{56}$Fe ion irradiation on the murine aorta. This effect seemed to be the greatest at the aortic root, demonstrating that this site may be the most sensitive to this type of radiation. The lesions also showed larger necrotic cores, which is associated with instability of plaques and higher risk of thrombogenic complications such as MI or ischemic stroke (40). The authors also detected thickening of the carotid intima after exposure to $^{56}$Fe ions, indicating that injury to the arterial wall indeed occurred (38). These findings indicate that exposing the cardiovascular system to one of the most prominent components of space radiation, $^{56}$Fe ions, may cause significant development of atherosclerosis and its associated complications.

### Microvascular Damage

Arrhythmias and conduction disorders after radiation exposure are not as well studied as other types of RICVD, but some studies suggest that these conditions develop due to microvascular damage. Microvascular damage might cause these conditions as a result of direct damage to the sinoatrial (SA) of atrioventricular (AV) nodes or to cardiomyocyte conduction abnormalities (41). Yang et al. observed degenerative changes in coronary arteries from mice after local irradiation with 0.1–0.2 Gy of $^{56}$Fe ions. These changes involved smooth muscle degeneration with fibrosis and accumulation of extracellular matrix in the tunica media (37). In a study by Soucy et al., exposure of rat aortas to 1 Gy of $^{56}$Fe ions led to a significant increase in aortic stiffness and the development of chronic vascular dysfunction by xanthine oxidase (XO)-dependent ROS production and nitroso-redox imbalance, of which the latter has been linked to the development of heart failure (39, 42). Last, a recent study demonstrated a small but significant increase in collagen deposition in the abdominal aorta of C57Bl/6J mice after exposure to γ-rays (1 and 3 Gy) (34). Data from these studies suggest the role of microvascular damage and vascular dysfunction as a cause for the development of CVD after space radiation exposure.

## Biology of Space Radiation-Induced CVD

To understand how space radiation affects the CVS and to define potential countermeasures, it is important to unravel its underlying mechanisms. An investigation into potential mechanisms is a fairly limited endeavor, as a broad sense of the pathophysiology of space radiation-induced CVD remains to be elucidated. The current knowledge gained from experimental animal studies on the potential mechanisms, will be discussed below with the results summarized in **Figure 1**.

### Endothelial Dysfunction

The functional capacity of the endothelium is believed to play a central role in the development of RICVD, partly since endothelial dysfunction is associated with a proinflammatory and profibrogenic environment (12, 35). For this reason, the majority of previous radiation studies (cell culture and animal models) have focused on endothelial cells. Lauk et al. first showed that in cardiac epithelial cells from irradiated Wistar and Sprague-Dawley rats, loss of alkaline phosphatase (AP) activity, a marker of functional epithelium, occurred before the development of myocardial generation and symptoms of heart disease (43). Such findings have motivated further research into the effects of space radiation on the endothelium. For example, Soucy et al. irradiated targeted segments of rat aortas with 1 Gy (1 GeV/n) of $^{56}$Fe ions (39). The irradiated regions showed signs of dysfunctional endothelium, as measured by a diminished endothelium-dependent relaxation, compared to the non-irradiated parts. This development was linked to increased xanthine oxidase (XO) activity and ROS production and decreased nitric oxide (NO) production (39). Another feature of endothelial dysfunction is an imbalance in the thrombomodulin (TM) system. TM is a transmembrane glycoprotein found in endothelial cells and has anti-fibrinogenic and anti-inflammatory properties. Expression of TM can be used to assess endothelium functionality, since TM is cleaved off the endothelial cell surface during the development of endothelial cell dysfunction. Ramadan et al. found increased cardiac TM levels after irradiation with 0.5 Gy of $^{56}$Fe ions (35). Despite the link between the TM-system and endothelial dysfunction, identifying the precise role of TM in RICVD will require more intensive study.

### Cellular Apoptosis and Senescence

Irradiation of cardiac tissue has been previously shown to cause apoptotic cell death of various cardiovascular cell types, including cardiomyocytes, cardiac myofibroblasts, conducting and vascular tissues (16). Apoptosis has been associated with myocardial damage and is therefore an important subject to study in research on the effects of space radiation on the CVS (19). In a study conducted with 300 MeV/n $^{28}$Si ions, irradiated murine hearts showed higher levels of apoptotic cell death and inflammation up to 6 months after exposure, as measured by increased levels of cleaved poly(adenosine diphosphate-ribose) polymerase (PARP), a marker for apoptotic cell death (19). In other reports, a study using $^{56}$Fe ions showed increased levels of apoptotic cell markers after radiation exposure, as shown by an increase in the ratio of cleaved caspase 3 to the full caspase 3 protein (35). Even though $^{28}$Si and $^{56}$Fe ions have been shown to cause significant apoptosis in murine hearts, these effects were not observed after exposure to $^{16}$O ions (34). It is therefore plausible to conclude that the occurrence of apoptosis after exposure to heavy ions is radiation

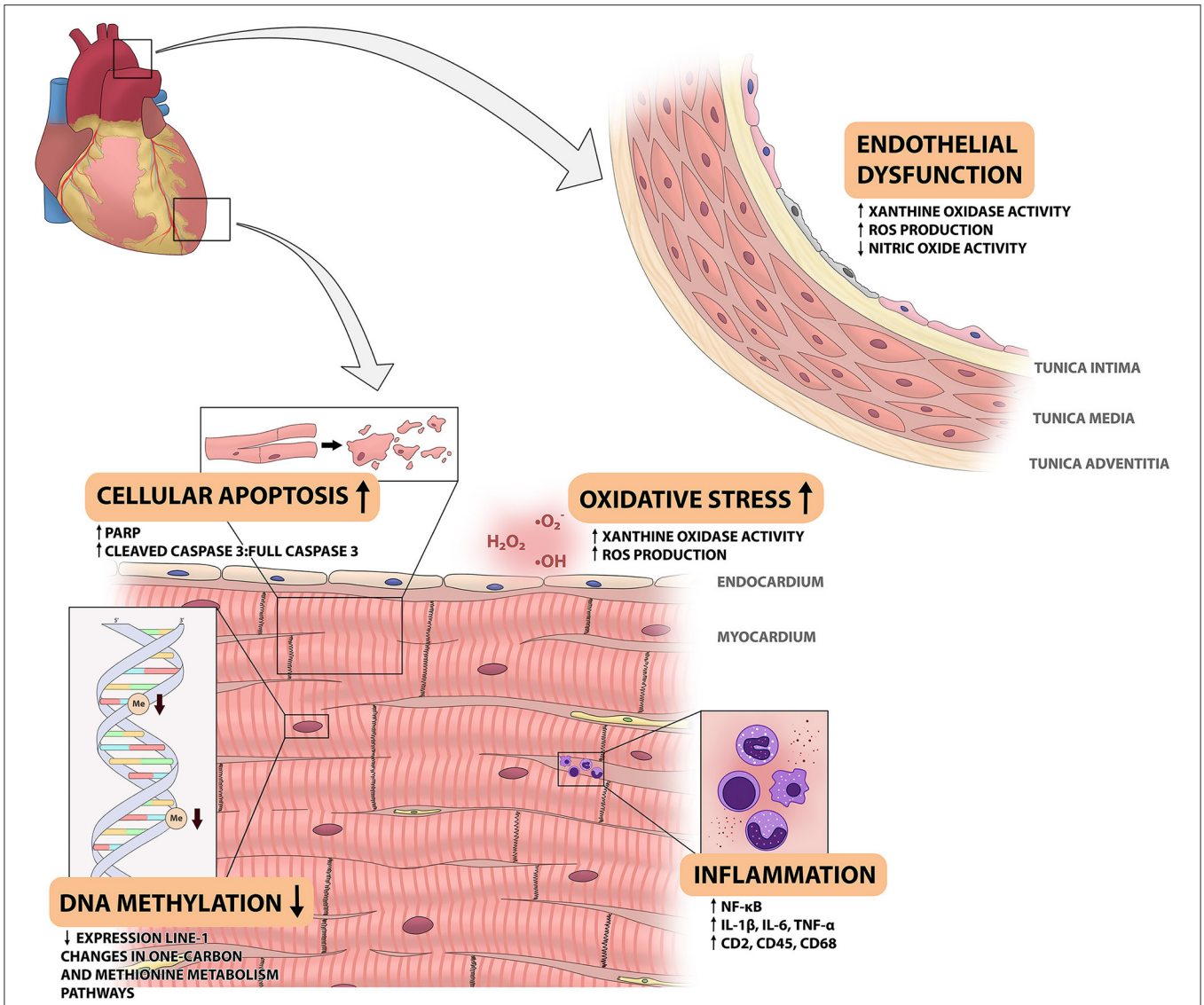


**FIGURE 1 |** Overview of space radiation-induced changes in the cardiovascular system. This figure shows the changes that have been observed in the cardiovascular system of animal models that are exposed to different components of space radiation. Space radiation has been shown to cause endothelial dysfunction in the aortic wall, as shown on the right. In the myocardium, exposure to space radiation has several effects. It leads to influx of immune cells and increased NF-kB activity, increased reactive oxygen species (ROS) production and xanthine oxidase (XO) activity, increased cellular apoptosis and decreased DNA methylation levels. IL, interleukin; ROS, reactive oxygen species; PARP, poly adenosine diphosphate-ribose polymerase.

type-specific and does not occur after exposure to every heavy ion found in space.

## Inflammation

The immune system is involved in atherogenesis and myocardial remodeling and fibrosis, with important roles for macrophages, lymphocytes, mast cells and pro-inflammatory cytokines (10, 31). How the immune system contributes to the development of space radiation-induced CVD is therefore an important question. Tungjai et al. demonstrated the induction of a chronic inflammatory state in the hearts of CBA/CaJ mice up to 6 months after exposure to $^{28}$Si ions, as indicated by persistently increased levels of NF-κB and associated pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (19). Chronic activation of NF-κB has been shown to affect the cardiovascular system negatively by stimulating the production of pro-inflammatory cytokines, which can lead to chronic inflammation, cell death and heart failure (44). After exposure to $^{56}$Fe [0.5 Gy, 600 MeV/n (34, 35) or 15 cGy, 1 GeV/n (45)] and $^{16}$O ions (0.1–1.0 Gy, 600 MeV/n), C57Bl/6J mice demonstrated increased cardiac levels of mast cell tryptase, the T-lymphocyte marker CD2 and the monocyte/macrophage marker CD68. Conversely, an increase in the leukocyte marker CD45 was only observed after $^{16}$O radiation (34, 35). Besides, cardiomyocytes isolated

from $^{56}$Fe irradiated mice (15 cGy, 1 GeV/n) showed increased activity of inflammatory and free-radical scavenging pathways, as demonstrated by time-dependent changes in gene expression. Taken together, these findings suggest that exposure of the murine heart to heavy ions found in space radiation can lead to induction of a chronic inflammatory state, which is associated with decreased cardiac function caused by oxidative stress and apoptotic cell death, induced by the release of pro-inflammatory cytokines, superoxide, nitric oxide, and other signaling molecules (36, 45).

### Oxidative Stress

Radiation exposure can damage the cardiovascular system via oxidative stress in multiple ways, of which an excellent summary can be found in Takahashi et al. (46). Since cardiomyocyte membranes are very rich in phospholipids that are sensitive to ROS, oxidative stress is an important mechanism in radiation's damaging effects (16). Several studies in which cultured cardiomyocytes were exposed to free radicals, as produced during exposure to radiation, have shown depressed contractile function, structural abnormalities, enhanced levels of phospholipid peroxidation, impaired energy production, and increased resting tension (16, 47). Furthermore, other physical stimuli in space—in addition to radiation—lead to oxidative stress, resulting in upregulated expression of oxidative enzymes and downregulated expression of anti-oxidative enzymes (46). A recent study identified one gene, FYN, that is upregulated after exposure to oxidative stress caused by space radiation and that reduces ROS levels (3). This pathway might function as an intrinsic mechanism to protect the cardiovascular system against the damaging effects of ROS. However, this putative mechanism has thus far only been observed in murine cardiomyocytes and human endothelial cells (HUVECs), so it would be interesting to see if this mechanism also occurs in whole organisms, such as mice. Overall, the exact role of oxidative stress requires further attention since there are currently limited studies who describe its effects on pathogenesis of space radiation-induced CVD.

### DNA Methylation

There is increasing interest in the role of DNA methylation, an epigenetic mechanism with an important role in cellular homeostasis, in the pathogenesis of CVD (48, 49). Emerging evidence suggests that space radiation, in part, exerts its effects on the cardiovascular system through alterations in DNA methylation, especially in repetitive elements of the genome (49, 50). In studies on DNA methylation, retrotransposon LINE-1 is often used as a marker for global DNA methylation levels since it is the most prevalent repetitive element in mammalian genomes (51).

Animal studies have shown that exposure of the murine heart to $^{56}$Fe ions, $^{16}$O ions, and protons leads to hypomethylation and decreased expression of repetitive elements such as LINE-1 (49, 50). Koturbash et al. also observed changes in components of the one-carbon and methionine metabolism pathway. These pathways are involved in DNA methylation via the synthesis of the methyl groups used in the methylation process, namely S-adenosylmethionine (SAM) (52). These changes in the methionine cycle have been suggested to impair DNA methylation, therefore intensifying the primary effects of space radiation on DNA methylation. Lastly, altered DNA methylation may serve as an early biomarker for space radiation exposure, since changes in DNA methylation are observed months after the initial exposure (36, 49, 50). This might give rise to personalized treatment based on the level of altered DNA methylation after exposure. However, the exact link between the level of exposure to space radiation, the amount of altered DNA methylation and the development of CVD has not been established yet.

## Potential Countermeasures and Protection Methods

Since space radiation exposure is considered to be the most important limiting factor for long-distance space travel, new methods of radiation protection or scavenging have to be developed in order to guarantee astronauts' safety during future space missions. There are two possible approaches for radiation protection in space. One of them is providing a physical barrier between the astronaut and space radiation by means of shielding materials. Another is the administration of radioprotective pharmacological agents. Both approaches will be discussed below.

### Shielding

Currently, the only protection method against space radiation is by the use of radiation shielding since increasing the distance from the radiation source is impossible and the amount of time exposed to space radiation cannot be limited any further if the goal is to extend space missions into deep space (2, 6). However, radiation shielding is not easily achieved in space. Current shielding methods are sufficient in protecting against space radiation inside the LEO, but are not suitable for the space environment beyond the LEO (6). The main problem regarding radiation shielding in deep space is the production of secondary particles when HZE ions encounter shielding materials such as the spacecraft (10). Research has shown that although shielding against SPE could be effective, it is currently not yet possible to shield against GCR effectively. There have been speculations that active shielding, which comprises the generation of electromagnetic fields to avert cosmic rays, might be interesting in protecting against GCR, but this technique is not applicable in practice yet (6).

### Pharmacological Protection

Because of the lack of adequate shielding possibilities, there has been increasing interest in the use of pharmacological compounds to limit the damaging effects of space radiation. Generally, such compounds can be divided into three categories, including radioprotectors (which decrease or prevent tissue damage before exposure), radiomodulators (which increase baseline resistance to radiation exposure) and radiomitigators (which limit or prevent tissue damage after exposure) (53). Over the past few years, several candidate drugs and antioxidants with such properties have been examined in the context of protection against space radiation exposure.

### *Drugs*

Since the effects of space radiation on the human cardiovascular system and its mechanisms have not been fully elucidated, very few compounds have been evaluated as of yet in a simulated space radiation environment. The angiotensin converting enzyme (ACE) inhibitor captopril seems to be able to reduce radiation-induced cardiopulmonary complications in animal models, but data are limited (53). However, it has been argued that ACE inhibitors would make poor prophylactic agents in the astronaut population because of severe side-effects in the space environment, such as decreased renal perfusion and angioedema (53). The use of the xanthine-derivative pentoxifylline combined with α-tocopherol showed beneficial effects on myocardial fibrosis and left ventricular function in animal models, but these results have not been reproduced in a model of space radiation yet (54). Statins showed promising results on reducing radiation-induced atherosclerosis, but conflicting results have been published (17). Other compounds that have been evaluated without any success have been discussed elsewhere and are beyond the scope of this review (8, 53). In conclusion, no safe pharmacological compounds are currently identified to use as prophylaxis in astronauts exposed to space radiation, motivating an ongoing search for suitable compounds.

### *Antioxidants*

The antioxidant family forms a promising group of potential radioprotectors. As aforementioned, exposure to space radiation is associated with oxidative stress because of the production of ROS in the interaction between HZE ions and water in biological tissues (4, 46). Antioxidants are enzymatic or non-enzymatic substances that limit the amount of ROS in normal tissue by removing these ROS in several steps, thereby preventing the possible damaging interactions between ROS and DNA (47). Thus, antioxidants have been of interest for treatment of CVD for years and might also serve as prophylaxis against space radiation-induced oxidative stress (8, 55). Kennedy et al. showed that combined doses of the antioxidants N-acetyl cysteine (NAC), ascorbic acid (vitamin C), α-lipoic acid (a type of vitamin B), coenzyme Q10, vitamin E succinate, sodium ascorbate and L-selenomethionine (SeM) were able to reduce oxidative stress in cultured cells. They also irradiated rats and mice with $^{56}$Fe ions (0.5 Gy, 1 GeV/n), γ-rays or protons (both 3 Gy), which led to a significant decrease in total antioxidant status (TAS). After the animals were fed with a diet supplemented with various combinations of the above mentioned antioxidants, TAS increased significantly and even returned to normal pre-radiation exposure levels when combined with the Bowman-Birk Inhibitor Complex (BBIC; a protease inhibitor derived from soy beans) (8). Amifostine, a radioprotective agent that is already being clinically used in cancer patients, also showed cardioprotective effects after single doses of radiation exposure in rats, but currently has too many side-effects to be used by astronauts (56). Furthermore, hydrogen therapy in the form of hydrogen-enriched water or hydrogen gas inhalation could be another way to protect astronauts from oxidative stress since hydrogen showed strong antioxidant properties in several studies. However, data on hydrogen therapy is still limited (57). Next to the administration of exogenous antioxidants, certain diets can also be used to manipulate the endogenous antioxidant balance. Beets, green vegetables, tomatoes and milk- and yeast-derived foods contain certain compounds that can have antioxidant properties as well, as discussed earlier by Hughson et al. (10). Additionally, there has also been some interest in certain diets that have proven to be beneficial to the cardiovascular system, such as calorie-restricted and low-sodium diets (10).

The use of antioxidants in space faces several limitations. The reduction of ROS through antioxidant use in animal models is reportedly accompanied by increased chronic inflammation of the cardiac tissue, which is also known to be associated to the development of CVD (3). It will be important to determine if this also occurs in the human cardiovascular system. Another important limitation, as discussed by Hughson et al., is the possible interaction between antioxidants and the high (100%) oxygen concentrations that astronauts are briefly exposed to during extravehicular activities (10). An increase in inhaled oxygen concentration could lead to decreased antioxidant and radioprotective properties (10). Also, few studies have been conducted regarding the underlying mechanisms of the ROS-reducing capacity of antioxidants after space radiation exposure. Last, implementing the suggested diet changes in astronauts is also challenging since the cardiovascular effects of the space environment are not the only factors to take into consideration. For example, a calorie-restricted diet is not suitable for astronauts since they exercise daily and face bone and muscle atrophy as a result of prolonged microgravity, which requires a specialized diet high in calories as a countermeasure (10).

In conclusion, current data on the efficacy of antioxidants in reducing or preventing space radiation-induced CVD is not sufficient to introduce them as radioprotective agents in astronauts. Even though some studies in animal and cell culture models show promising results, we still face several limitations regarding the implementation of these compounds in practice. However, in the future these compounds may function as radioprotective substances in combination with other radioprotective measures to prevent astronauts from space radiation-induced CVD.

## CONCLUDING REMARKS

Research on the cardiovascular effects of space radiation has increased significantly over the last few years. For space agencies, this field of research is crucial to estimate the health risks astronauts will face during and after long-distance space travel beyond the LEO. Furthermore, understanding the pathophysiological mechanisms of space radiation-induced CVD should lead to better ways to protect astronauts from these conditions. These results also have implications for life on Earth, as they can contribute to a better understanding of CVD on Earth, with and without radiation exposure.

However, there are several limitations regarding current research on the effects of space radiation on the CVS. First, a well-known complication of exposure of the heart to radiation is damage to the heart valves, which may result in valve stenosis

of regurgitation (58). However, none of the studies discussed in this review have focused on the changes in valve structure and function after exposure to components of space radiation. Yu et al. do report increased development of atherosclerosis, especially in the aortic root, which could also affect the aortic valve (AV) (38). Yet, AV structure and function was not included in their analysis. Considering the fact that valvular disease is an important contributor to the global cardiovascular disease burden (59, 60), future studies should also focus on the consequence of space radiation exposure to the heart valves.

Another limitation involves the scarcity of epidemiological data on the incidence of CVD after long-distance space travel in humans, since only the Apollo crew traveled beyond the LEO, and their exposures were quite short. Even though Delp et al. reported a significantly increased risk of CVD in the group of Apollo astronauts (28), their results have been criticized by other researchers because of several limitations in their methods (10, 61). For example, they did not account for confounding factors that might influence the development of CVD in the Apollo astronauts and did not include other space missions and radiation exposures (10). Besides, another study showed no increased risk of CVD in this group (29).

Because of the lack of data in humans, the effects of space radiation are currently most commonly investigated using cultured cell lines and animal models, which both have their individual limitations. Wnorowski et al. recently reported on the effects of microgravity on the structure and function human-induced pluripotent stem cell-derived cardiomyocytes that were cultured in the International Space Station (ISS) (62). However, the biggest disadvantage of such models is the inability to study biological processes in a living, complex organism that is more similar to human beings, which is possible with animal models (63). However, animal models also have their limitations. To study the pathophysiology of atherosclerosis, atherosclerosis-prone mouse models such as the apolipoprotein E-deficient (apoE$^{-/-}$) model have to be used since regular mouse models are relatively resistant to atherosclerosis (64). This susceptibility makes it challenging to translate these results to healthy astronauts who lack any prior cardiovascular risk factors. Furthermore, a major limitation of apoE$^{-/-}$ mice is the lack of thrombogenic complications and plaque rupture (65). Indeed, all of the animal models used in the studies discussed above have limitations. To our knowledge, no studies have been conducted with larger animal models that might better resemble the human cardiovascular system and pathogenesis of atherosclerosis (64, 65). Nonetheless, the discussed studies do show that components of space radiation cause significant damage to the cardiovascular system, which has to be further explored in future studies.

Another important limitation in current space radiation research is the possibility of mimicking the space radiation environment on Earth. The studies discussed above used single ions such as $^{56}$Fe or $^{16}$O ions, but in space astronauts will encounter different particles simultaneously or consecutively. In some studies it was already observed that the combined exposure to different particles had different effects on the cardiovascular system (33–35). To gain more precise insights into the cardiovascular effects of exposure to radiation in deep space, new methods must be developed to study the combined exposure to different particles. Additionally, several HZE ions are currently understudied. Even though $^{56}$Fe ions account for around 20% of the biological damage caused by HZE ions, very few studies have investigated the effects of other ions on the cardiovascular system, such as $^{28}$Si or $^{16}$O ions (19, 34). To our knowledge, no studies using magnesium ions ($^{24}$Mg) have been conducted yet, even though this ion is also part of the HZE-component of space radiation. Future research should focus on the combined exposure of different heavy ions found in space radiation beyond the LEO and more attention should be drawn to currently understudied ions such as oxygen, magnesium and silicon ions. The facilities of the NASA Space Radiation Laboratory (New York, USA) and the knowledge and experience of its researchers could be of great value in future research on this topic (66).

Lastly, space radiation is not the only limiting factor for long-distance space travel. To examine the exact changes the CVS undergoes in the space environment, other factors such as prolonged microgravity, hypoxia and disrupted circadian rhythms should also be considered. This is especially important since altered blood flow patterns, oxidative stress and sleep deprivation are all recognized as cardiovascular risk factors, and may therefore add to the increased risk of spaceflight-associated CVD (67). However, the effects of these other space-specific factors are outside of the scope of this review. Research in which exposure to space radiation is combined with these other space-specific factors should yield the most reliable results on the effects of the space environment on the development of CVD. Unfortunately, this type of research has not yet been conducted at the present time.

The abovementioned limitations show that both conventional cell culture platforms and animal models are not suitable for studying the effects of space radiation on the human CVS. Conventional *in vitro* cell culture platforms are not able to mimic the complex and dynamic environment of the CVS, while the CVS of the animal models used in the discussed studies are significantly different from the human CVS, which makes translating these results into humans difficult. A potential interesting alternative approach is the implementation of the "organ-on-a-chip" technology into this field of research. "Organs-on-chips" are able to incorporate different types of human cardiovascular cells in a model that is able to recapitulate the near-physiological environment of the human heart. These models have also been of great interest in the field of drug discovery and screening, which could aid in the development of new protective measures against space radiation exposure (68, 69). Also, these models would enable researchers to study the combinatorial effects of space radiation exposure with other space-specific factors such as hypoxia, which would mimic the space environment more accurately. To our knowledge, no studies into the effects of space radiation on the human CVS have been conducted using "organs-on-chips" yet. However, these models show great promise and future research should focus on implementing such models into their experimental setup.

Despite the abovementioned limitations, data from the experimental studies discussed in this review show that the cardiovascular system is undoubtedly very sensitive to the

damaging effects of space radiation. These results emphasize the need for better protective measures as more astronauts will travel into deep space. Yet, no effective compounds have been approved. Since the mechanisms of space radiation-induced CVD are slowly being unraveled, future research should focus on identifying compounds that interfere with these mechanisms. Besides, the potential benefit of antioxidants should be further explored and tested in human models such as the "organ-on-a-chip" in order to translate these results into practice. Before any recommendations can be made regarding the administration of pharmacological compounds or antioxidants to astronauts who will travel beyond the LEO, further research must be performed into the underlying mechanisms and pharmacological characteristics such as the optimal dose, side-effects and possible interactions of these compounds, in order to safely protect our astronauts. In summary, data gained from experimental animal studies show that several components of space radiation, such as HZE ions and protons, can have serious harmful effects on the CVS and therefore can lead to the development of space radiation-induced CVD. Since the rising interest in the effects of space radiation on the CVS in the last few years, few studies on this topic have been published to date, and we might have only seen a small aspect of the effects of space radiation on the CVS. One of the main questions that arises from the plans to expand human space exploration to Mars is whether the risks astronauts face during and after these future space missions outweigh the benefits of long-distance space travel. With current knowledge gained from animal and cell culture studies, it is not yet possible to answer this question. However, we now know that if the human CVS responds to space radiation in any similar way to the murine cardiovascular system, long-distance space travel can lead to several serious types of CVD and therefore affect the astronauts' health tremendously. Thus, future research should be focused on determining the exact effects of space radiation on the CVS, unraveling the underlying pathological mechanisms, and designing countermeasures in order to protect our future space explorers to the fullest extent possible.

## AUTHOR CONTRIBUTIONS

MM and JH wrote the manuscript. CB, TBG, JB, SW, SS, KG-A, and WS contributed to editing the final version of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the Innovation and the Netherlands CardioVascular Research Initiative (CVON): The Dutch Heart Foundation (2017T040), Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development, and the Royal Netherlands Academy of Science.

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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.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 08 March 2021
doi: 10.3389/fcvm.2021.603319

# Quantification of Cardiac Kinetic Energy and Its Changes During Transmural Myocardial Infarction Assessed by Multi-Dimensional Seismocardiography

*Sofia Morra[1*†], Lorenzo Pitisci[1,2*†], Fuhong Su[2], Amin Hossein[3], Jérémy Rabineau[3], Judith Racape[4], Damien Gorlier[3], Antoine Herpain[2,5], Pierre-François Migeotte[3], Jacques Creteur[5] and Philippe van de Borne[1]*

[1] Department of Cardiology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, [2] Experimental Laboratory of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, [3] Laboratory of Physic and Physiology (LPHYS), Université Libre de Bruxelles, Brussels, Belgium, [4] Research Center in Epidemiology, Biostatistics and Clinical Research, School of Public Health, Université Libre de Bruxelles (ULB), Brussels, Belgium, [5] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

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**Edited by:**
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***Correspondence:**
Sofia Morra
sofia.morra@erasme.ulb.ac.be
Lorenzo Pitisci
lorenzo.pitisci@ulb.be

[†] These authors have contributed equally to this work

**Specialty section:**
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

**Received:** 06 September 2020
**Accepted:** 08 February 2021
**Published:** 08 March 2021

**Citation:**
Morra S, Pitisci L, Su F, Hossein A, Rabineau J, Racape J, Gorlier D, Herpain A, Migeotte P-F, Creteur J and van de Borne P (2021) Quantification of Cardiac Kinetic Energy and Its Changes During Transmural Myocardial Infarction Assessed by Multi-Dimensional Seismocardiography. Front. Cardiovasc. Med. 8:603319. doi: 10.3389/fcvm.2021.603319

**Introduction:** Seismocardiography (SCG) records cardiac and blood-induced motions transmitted to the chest surface as vibratory phenomena. Evidences demonstrate that acute myocardial ischemia (AMI) profoundly affects the SCG signals. Multidimensional SCG records cardiac vibrations in linear and rotational dimensions, and scalar parameters of kinetic energy can be computed. We speculate that AMI and revascularization profoundly modify cardiac kinetic energy as recorded by SCG.

**Methods:** Under general anesthesia, 21 swine underwent 90 min of myocardial ischemia induced by percutaneous sub-occlusion of the proximal left anterior descending (LAD) coronary artery and subsequent revascularization. Invasive hemodynamic parameters were continuously recorded. SCG was recorded during baseline, immediately and 80 min after LAD sub-occlusion, and immediately and 60 min after LAD reperfusion. *i*K was automatically computed for each cardiac cycle ($iK^{CC}$) in linear ($iK_{Lin}$) and rotational ($iK_{Rot}$) dimensions. *i*K was calculated as well during systole and diastole ($iK^{Sys}$ and $iK^{Dia}$, respectively). Echocardiography was performed at baseline and after revascularization, and the left ventricle ejection fraction (LVEF) along with regional left ventricle (LV) wall abnormalities were evaluated.

**Results:** Upon LAD sub-occlusion, 77% of STEMI and 24% of NSTEMI were observed. Compared to baseline, troponins increased from 13.0 (6.5; 21.3) ng/dl to 170.5 (102.5; 475.0) ng/dl, and LVEF dropped from 65.0 ± 0.0 to 30.6 ± 5.7% at the end of revascularization (both $p < 0.0001$). Regional LV wall abnormalities were observed as follows: anterior MI, 17.6% (three out of 17); septal MI, 5.8% (one out of 17); antero-septal MI, 47.1% (eight out of 17); and infero-septal MI, 29.4% (five out of 17). In the linear dimension, $iK^{CC}_{Lin}$, $iK^{Sys}_{Lin}$, and $iK^{Dia}_{Lin}$ dropped by 43, 52, and 53%, respectively ($p < 0.0001$, $p < 0.0001$, and $p = 0.03$, respectively) from baseline to the end of reperfusion. In the

rotational dimension, $iK_{Rot}^{CC}$ and $iK_{Rot}^{Sys}$ dropped by 30 and 36%, respectively ($p = 0.0006$ and $p < 0.0001$, respectively), but $iK_{Rot}^{Dia}$ did not change ($p = 0.41$). All the hemodynamic parameters, except the pulmonary artery pulse pressure, were significantly correlated with the parameters of *iK*, except for the diastolic component.

**Conclusions:** In this very context of experimental AMI with acute LV regional dysfunction and no concomitant AMI-related heart valve disease, linear and rotational *i*K parameters, in particular, systolic ones, provide reliable information on LV contractile dysfunction and its effects on the downstream circulation. Multidimensional SCG may provide information on the cardiac contractile status expressed in terms of *i*K during AMI and reperfusion. This automatic system may empower health care providers and patients to remotely monitor cardiovascular status in the near future.

**Keywords: seismocardiography, kinetic energy, acute myocardial infarction, animal model for acute coronary syndrome, cardiac monitoring**

## INTRODUCTION

Ballistocardiography (BCG) and seismocardiography (SCG) record the micro-vibrations produced rhythmically by velocities and accelerations of blood mass flowing across cardiac chambers and main vessels as a consequence of cardiac mass contraction, with micro-accelerometers and gyroscopes placed on the body surface (1–3). There is growing evidence that BCG and SCG may provide additional relevant information on cardiovascular status beyond those already acquired by means of universally accepted current diagnostic devices. Indeed BCG and SCG reliably estimate stroke volume (SV) and cardiac output (CO) (2, 4), myocardial contractility expressed as $dP/dt_{max}$ in animal models (5), as well as the clinical status of heart failure patients (6).

As a result, this evidence fuels the curiosity of scientific and medical researchers who actively inquire on the potential of BCG and SCG signals to assess cardiovascular mechanical changes during acute myocardial infarction (AMI) (5, 7–9). Indeed the BCG and SCG signals profoundly change during AMI, and, according to previous studies, metrics secured from it enable the identification of an impairment of regional myocardial contraction due to acute ischemia with specificity of 80% (7) to 92% (9) and sensitivity of 89% (7) to 94% (9). When combined with the electrocardiogram (ECG), the SCG empowers the capability of detection of coronary artery disease during an exercise stress test, yielding a positive predictive value of 88% and a negative predictive value of 80% (10).

Recently, a multi-dimensional BCG combined with a multi-dimensional SCG, called kinocardiograph (KCG), has been introduced and, differently from many previous devices which record signals only in one dimension, the KCG records both three-dimensional (3D) linear acceleration and 3D angular velocity signals by means of linear and rotational channels (2, 11). Using specific algorithms, kinetic energy and its temporal integral ($iK$) can be computed from the BCG and SCG waveforms as scalar parameters, both in a linear ($iK_{Lin}$) and in a rotational ($iK_{Rot}$) dimension (2, 12).

Three-axes linear micro-accelerometers have already been shown useful in the early detection of experimental AMI (7–9, 13, 14). However, whether non-invasive accelerometers and gyroscopes recording signals in multiple (linear and rotational) dimensions can be affected by hemodynamic changes during acute myocardial infarction and reperfusion is not known. Recently, non-invasive techniques based on micro-accelerometers and gyroscopes exploring rotational velocities and accelerations produced by heart contraction have been introduced (15–17): rotational velocities measured using non-invasive tri-axial gyroscopes provide information on several mechanical events occurring during a contractile cycle as compared to echocardiography (16). The rotational kinetic energy obtained from tri-axial gyroscopes can accurately identify the first and the second peak of the SCG (15). Rotational, rather than linear, kinetic energy accounts for about 70% of the total cardiac energy produced during a contractile cycle, and it significantly drops after prolonged cardiac deconditioning, mainly due to a decrease in the rotational twist of the LV (18). Measuring the rotational accelerations and kinetic energy may contribute to a more in-depth and global analysis of cardiac function seen through the windows of micro-accelerations since the rotational motion of the heart along its longitudinal axis is crucial in assuring its pumping function (19).

Using an animal model for AMI, the present investigation aims (1) to track modifications of linear and rotational *i*K computed from the accelerations signals of non-invasive and multidimensional SCG during coronary artery sub-occlusion, (2) to follow these changes during the reperfusion period, and (3) to study the association of linear and rotational *i*K with invasive hemodynamic parameters. The hypothesis tested is that experimental AMI and reperfusion profoundly alter multi-dimensional SCG signals and its derived scalar parameters.

## MATERIALS AND METHODS

### Study Protocol

The present study was approved by the Institutional Ethics Committee on Animal Welfare from the Faculty of Medicine of the Université Libre de Bruxelles (ULB, Brussels, Belgium) (acceptance number: 654N). Animal care and handling were in accordance with the National Institute of Health Guidelines.

The procedure consisted in the proximal left anterior descending coronary artery (LAD) sub-occlusion by means of angioplasty semi-compliant balloon inflation for 90 min, followed by deflation and subsequent reperfusion (RE) for 60 min. A 3-min-length SCG was recorded during the steady state (baseline, BSL) preceding the LAD sub-occlusion and then at different time points during sub-occlusion and reperfusion, specifically at the onset of LAD sub-occlusion ($AMI_{t0}$) at 80 minutes of AMI ($AMI_{t80}$), at the onset of RE ($RE_{t0}$), and at 60 min of RE ($RE_{t60}$). Each record was remotely acquired with a tablet and sent *via* Bluetooth to the main server for further signal processing. To evaluate the amount of myocardial necrosis, the authors measured the serum troponin levels at the onset of LAD sub-occlusion and after revascularization: the difference between troponins measured 5 h after RE and troponins measured at the onset of LAD sub-occlusion was named Delta (Δ) troponin. Echocardiography was performed at baseline and after revascularization, and the left ventricle ejection fraction (LVEF) along with regional left ventricle (LV) wall abnormalities were evaluated by a trained operator.

## Animal Preparation and Experimental Procedure

The animals have been put on fasting for 18 h before the experiment was started, with unrestricted access to water. Twenty-one 50-kg crossbreed Landrace/Large White adult swine, of either sex, were premedicated with intramuscular neck injection of 5 mg/kg azaperone and 1.5 mg/kg midazolam. A 14-G peripheral venous line was placed into an ear vein to provide vascular access, and a 4.5-Fr arterial catheter (Leader-Cath, Vygon, France) was inserted in the left common femoral artery for invasive arterial pressure monitoring and blood sample collection. A three-lead surface ECG was connected to the hemodynamic monitoring display (SC9000, Siemens, Germany). The animals underwent endotracheal intubation following induction of anesthesia with an intravenous injection of 3 μg/kg sufentanil, 1 mg/kg propofol, and 0.5 mg/kg of rocuronium. A central venous access for drug infusion was obtained via a three-lumens central venous line inserted into the right external jugular vein (Edwards LifeSciences©, California, USA). General anesthesia and analgesia were achieved using continuous inhalation of 1.8 to 2.5% sevoflurane of minimal alveolar concentration (MAC) and continuous infusion of sufentanil 1 to 4 μg/kg/h, adapted according to the response to painful stimulations, in association with 1 to 2 mg/kg/h rocuronium continuous infusion to avoid shivering.

Sevoflurane is the most popular volatile agent used to induce general anesthesia, thanks to its safety profile (20, 21): it has low myocardial depressant effect (22); it does not alter the A–H interval, His-Purkinje conduction time (H–V interval), and ventricular conduction time (H–S interval) (23). It is associated with higher hemodynamic stability and fewer arrhythmic events compared to other volatile agents (24). Since it has no effect on the cardiac conduction system, sevoflurane can also be used in cardiac electrophysiological procedure (25). Additionally, at clinical concentrations of this drug, despite the reduction of peripheral vascular resistance, the cardiac output is preserved (26, 27), as well as coronary blood flow (21).

Mechanical ventilation was performed in a volume-controlled mode (Primus®, Draëger, Germany) with tidal volume of 8 ml/kg and a positive end-expiratory pressure set at 5 cm $H_2O$.

A 7 Fr introducer was inserted into the left external jugular vein, and a pulmonary artery catheter (CCO; Edwards LifeSciences©, California, USA) was advanced in a pulmonary artery for continuous cardiac output (CO), right heart pressures, and mixed venous oxygen saturation ($SVO_2$) monitoring. A 5 Fr introducer (Terumo Corporation, Japan) was inserted into the right internal carotid artery, and a coronary guide catheter (Sherpa JL4™, Medtronic, Belgium) was positioned into the left coronary ostium under fluoroscopic guidance with iodinate contrast media angiogram (Xenetix 350®, Guerbet, France). Through this latter step and after an intracoronary bolus of 200 μg dinitrate isosorbide to prevent coronary spasm, pressure and a Doppler flow wires (ComboWire®, Volcano Corporation, Belgium) were placed distally into the mid LAD. Two 5 Fr introducers (Terumo Corporation, Japan) were inserted into the left carotid artery and left femoral artery, where high-fidelity left ventricular pressure—volume catheter (Transonic®, France) and aortic arch catheter (Transonic®, France) were placed.

ECG, pressure and volume signal, CO, and respiratory rate were recorded using a data acquisition software (Notocord-HEM™, France), allowing subsequent offline analysis. The animals were administrated with 300 mg amiodarone, followed by continuous infusions of 900 mg/24 h and 7,500 units of unfractionated heparin, followed by a continuous infusion of 2,000 units/h.

A semi-compliant angioplasty balloon (Trek, Abbott, Belgium) was inserted over the wire into the proximal LAD and was inflated to reduce coronary flow by 60% of the baseline value for 90 min. After 90 min of ischemia, 200 mg of aspirin was administrated intravenously, and the balloon was deflated, allowing reperfusion to occur according to the best current clinical managing of ACS (28). Once the balloon was deflated, the effectiveness of reperfusion was confirmed by the recovery of intracoronary blood flow velocity. Three swine died, during the procedure, from refractory ventricular arrythmias, which occurred within the first 30 min from coronary occlusion.

## Sham Group

A sham group of another experimental procedure (Ethical Committee acceptance number: 641N), following the same protocol of general anesthesia and instrumentation of the animal, was used as a reference to rule out the possible depressant effect of general anesthesia on the hemodynamic parameters. This sham group was composed of three crossbreed Landrace/Large White adult swine (weight: 41, 31, and 46 kg), all undergoing the same general anesthesia protocol and instrumentation that we used in the present investigation. The hemodynamic parameters of each animal were followed at three different timepoints: during BSL, at 2 h (T1), and at 4 h (T2) of steady state, while no intervention was realized. These data show a reduction by ±5 mmHg of mean arterial pressure, concomitant to the experimental setting

(**Supplementary Table 1**). Additionally, no arrhythmic events were observed.

Since the results from a sham group were already available in our laboratory, the local ethical committee for animal care considered it unnecessary to add a sham group in the present investigation.

## Accelerometric Signal Acquisition and Processing

The KCG consisted of two modules, each containing MEMS accelerometers and gyroscope sensors (LSM6DSL, STMicroelectronics). One module was placed over the sternum to record local precordial vibrations (SCG); the other one was placed immediately below and externally to the left iliac crest to record one-lead ECG signal. The device was controlled remotely with a tablet connected *via* Bluetooth and collected a one-lead ECG and a linear (Lin) and a rotational (Rot) three-axes SCG. Details about this methodology have been described previously (2, 12). Observations from unpublished results demonstrate that SCG measurements are reliable and reproducible using different sensors and that the metrics of linear and rotational *i*K are comparable.

Assuming that the cardiovascular system equates a Newtonian system, scalar metrics can be obtained from velocity and acceleration signals measured with the SCG in the linear and rotational dimensions and transmitted to the body surface as vibratory phenomena. The height and weight of the animal are used to assess inertial parameters. Knowing the acceleration of an object with a given mass $m$ and the vector force ($\overrightarrow{F}$), the kinetic energy ($K$) can be calculated according to Equations (1) and (2) for the linear components and to Equations (3) and (4) for the rotational components.

$$\overrightarrow{F}\,(t) = m\overrightarrow{a}\,(t) \tag{1}$$

$$K_{Lin}\,(t) = \frac{1}{2}m(v_x^2\,(t) + v_y^2\,(t) + v_z^2\,(t)) \tag{2}$$

where $m$ is the mass of the object, $K_{\mathrm{Lin}}$ is the linear kinetic energy, $v_x$, $v_y$, and $v_z$ are components of the measured velocity vector $\overrightarrow{v}$, and $\overrightarrow{F}$ is the force vector.

For the rotational components, the scalar metrics are calculated according to Equations (3) and (4).

$$\overrightarrow{\tau}\,(t) = I.\,\overrightarrow{\alpha}\,(t) \tag{3}$$

$$K_{Rot}(t) = \frac{1}{2}(I_{xx}\omega_x^2\,(t) + I_{yy}\omega_y^2\,(t) + I_{zz}\omega_{zz}^2\,(t)) \tag{4}$$

where $\overrightarrow{\tau}$ is the torque of force, $I$ is the momentum of inertia of the object, $\overrightarrow{\alpha}$ is the angular acceleration, $K_{\mathrm{Rot}}$ is the rotational kinetic energy, $I_{xx}$, $I_{yy}$, and $I_{zz}$ are the orthogonal components of the momentum of inertia $I$ of the object, and $\omega_x$, $\omega_y$, and $\omega_z$ are the components of the measured angular velocity $\overrightarrow{\omega}$.

The time integral of $K_{\mathrm{Lin}}$ and $K_{\mathrm{Rot}}$ over the cardiac cycle (CC) was computed for the SCG as in Equations (5) and (6).

$$iK_{Lin} = \int_{CC} K_{\mathrm{Lin}}(t).dt. \tag{5}$$

$$iK_{Rot} = \int_{CC} K_{\mathrm{Rot}}(t).dt. \tag{6}$$

Data were acquired at BSL, at $\mathrm{AMI}_{\mathrm{t0-t80}}$, and at $\mathrm{RE}_{\mathrm{t0-t60}}$ and then exported and analyzed offline using a toolbox developed in MatLab version 9.5 R2018b (Mathworks®). The operator was selecting a 60-s-width artefact-free temporal window of consecutive beats. The beats were automatically identified based on the automatic identification of the peak ECG-R wave. Ensemble averaging (EA) on all beats over the selected time period was performed, and the scalar parameters of $iK_{Lin}$ and $iK_{Rot}$ were automatically computed. This method of sampling and averaging generated an averaged SCG signal which best fits the shape of a cardiac cycle. Additionally, EA was used to partially remove motion artifacts from the signals.

The P, Q, R, S, and T waves on the ECG were automatically identified and used as reference points for the identification of the electrical cardiac cycle. The sum of QRS and ST segments identifies the systolic phase (Sys) of the cardiac cycle; the sum of the TP' segment (the period from the T wave of the current beat $N$ to the P wave of the next beat $N + 1$) with the P'Q' segment (the period from the P wave of the beat $N + 1$ to the Q wave of the beat $N + 1$) identifies the diastole (Dia) of the cardiac cycle. The sum of PQ, QRS, ST, and TP' defined a whole CC. One record had to be ruled out from final analysis because of technical failure during the signal processing.

Several factors can contaminate the BCG and SCG signals, such as respiration, involuntary movements, and cough. To reduce contamination signals from artifacts, an automatic outlier detection was applied on beats that would generate too large energies, possibly due to the involuntary movement of the subject such as coughing or deglutition or movements of the extremities. If the *i*K of a heartbeat was higher than five times the median of the respective kinetic energy of the five previous beats, the *i*K of the concerned heartbeat was considered as compromised by a motion artefact and classified as abnormal.

Respiration might influence the BCG and SCG signals in three different ways: by producing a wandering of the baseline as a result of chest movement, by modifying the amplitude of SCG due to intra-thoracic pressure variation, and through the induced RR interval changes during the respiratory cycle. To avoid contamination signal from respiratory movement, a high-pass filter was applied to the signals.

## Statistical Analysis

Statistical analysis was performed using STATACorp® for Windows. GraphPad PRISM® version 5.01 and MatLab version 9.5 R2018b (Mathworks Inc.®) were used for graphing figures on Windows.

Normality of data distribution was assessed graphically and by using the Kolmogorov–Smirnov test. According to the distribution, data were expressed as mean ± standard deviation

(±SD) if normally distributed or as median and interquartile range if not [$P_{25}$-$P_{75}$].

To evaluate the effect of AMI and reperfusion on SCG signals, a generalized mixed model was used, taking time as the fixed factor, followed by multiple comparison whenever a significant effect was found. Bonferroni's correction was applied to account for multiple comparisons.

The pulse pressures of LV, aortic, femoral, and pulmonary artery pressures were calculated as the difference between systolic and diastolic pressures (29). Generalized linear mixed model was used to associate the pulse pressures and CO with the parameters of *iK*.

Spearman's rank correlation was used to assess the association of *iK* parameters with Δ troponins and the LVEF. Correlations were calculated between *i*K parameters and LVEF computed at the end of the procedure ($RE_{t60}$).

*P*-values <0.05 were considered as statistically significant.

## RESULTS

Upon LAD sub-occlusion, 77% (thirteen out of 17) of STEMI and 24% (four out of 17) of NSTEMI were observed.

Compared to baseline, troponins increased from 13.0 (6.5; 21.3) ng/dl to 170.5 (102.5; 475.0) ng/dl and LVEF dropped from 65.0 to 30.6 ± 5.7% at the end of revascularization (both $p < 0.0001$). Regional LV wall abnormalities were observed as follows: anterior MI, 17.6% (three out of 17); septal MI, 5.8% (one out of 17); antero-septal MI, 47.1% (eight out of 17); and infero-septal, 29.4% (five out of 17). The animals did not disclose valve diseases at baseline, and there were no AMI-related valve diseases throughout the study.

Modifications of heart rate (HR), CO, systolic and diastolic LV pressures (PLV Sys and PLV Dia, respectively), systolic and diastolic aortic pressures (PAo Sys and PAo Dia, respectively), systolic and diastolic femoral pressures (Pfem Sys and Pfem Dia, respectively), and systolic and diastolic pulmonary artery pressures (PAP Sys and PAP Dia, respectively) during LAD sub-occlusion and reperfusion are reported in **Table 1**.

**Figure 1** reports the modifications of pulse pressures of the same hemodynamic variables: LV pulse pressure (LV PP), aortic pulse pressure (Ao PP), femoral pulse pressure (Fem PP), and pulmonary artery pulse pressure (PA PP). The results are presented also in **Supplementary Table 2**.

HR increased by 19% from baseline to the end of reperfusion ($P_{ALL} = 0.0001$), while CO, systolic PLV, systolic PAo, and systolic Pfem decreased ($P_{ALL} = 0.0005$, $P_{ALL} = 0.005$, $P_{ALL} = 0.005$, and $P_{ALL} < 0.0001$, respectively).

According to a multiple-comparison analysis, the HR increased between $AMI_{t0}$ and $RE_{t60}$ ($p = 0.02$); CO dropped from 5.5 to 4.7 l/min from BSL to $AMI_{t80}$ and $RE_{t0}$ (both $p = 0.002$) and dropped further to 4.4 l/min at $RE_{t60}$ compared to BSL ($p < 0.0001$); the systolic pressures of LV and aorta both dropped by 16 and 19%, respectively; between BSL and $AMI_{t0}$ ($p = 0.01$ and $p = 0.03$, respectively) by 16 and 26%, respectively; between BSL and $AMI_{t80}$ ($p = 0.002$ and $p = 0.003$, respectively) by 16 and 15%, respectively, between BSL and $RE_{t0}$ ($p = 0.001$, $p = 0.002$, respectively), and by 16 and 15% between BSL and $RE_{t60}$ ($p = 0.003$ and $p = 0.036$, respectively). The systolic femoral pressure dropped between BSL and $AMI_{t0}$ (18%), $AMI_{t80}$ (19%), and $RE_{t0}$ (15%) ($p < 0.0001$, $p = 0.004$, and $p < 0.0001$, respectively).

When considering the pulse pressures of the above mentioned hemodynamic variables shown in **Table 1**, LV PP, Ao PP, and Fem PP decreased by 13, 20, and 21% from baseline to the end of reperfusion, respectively ($P_{ALL} = 0.0007$, $P_{ALL} < 0.0001$, and $P_{ALL} < 0.0001$, respectively). According to a multiple-comparison analysis, the Ao PP and the Fem PP dropped at $AMI_{t0}$ (both $p = 0.01$), at $AMI_{t80}$ ($p < 0.0001$ and $p = 0.002$, respectively), and at $RE_{t0}$ (both $p < 0.0001$) compared to BSL. The modifications of pulse pressures during the LAD sub-occlusion and reperfusion are shown in **Figure 1** and are reported in **Supplementary Table 3**.

**Figure 2** depicts the modifications of parameters of *iK* in the linear and rotational dimensions during the procedure.

All parameters of *iK*, except $iK_{Rot}^{Dia}$, decreased during LAD sub-occlusion and reperfusion. In the linear dimension, $iK_{Lin}^{CC}$, $iK_{Lin}^{Sys}$, and $iK_{Lin}^{Dia}$ dropped by 43, 52, and 53%, respectively ($P_{ALL}$ <0.0001, $P_{ALL} < 0.0001$, and $P_{ALL} = 0.03$, respectively) from

**TABLE 1 |** Modification of hemodynamic parameters during left anterior descending occlusion and reperfusion.

| Time | HR (bpm) | CO (L/min) | PLV Sys (mmHg) | PLV Dia (mmHg) | PAo Sys (mmHg) | PAo Dia (mmHg) | Pfem Sys (mmHg) | Pfem Dia (mmHg) | PAP Sys (mmHg) | PAP Dia (mmHg) |
|---|---|---|---|---|---|---|---|---|---|---|
| BSL | 74 ± 14 | 5.3 ± 1.1 | 96 ± 8 | 3 ± 6 | 94 ± 6 | 55 ± 6 | 98 ± 20 | 52 ± 14 | 36 ± 5 | 16 ± 4 |
| $AMI_{t0}$ | 77 ± 14 | 5.1 ± 0.8 | 80 ± 9* | 5 ± 4 | 78 ± 10* | 47 ± 10 | 80 ± 17‡ | 47 ± 14 | 29 ± 6 | 14 ± 4 |
| $AMI_{t80}$ | 85 ± 18 | 4.7 ± 0.85† | 80 ± 6* | 5 ± 4 | 79 ± 7* | 50 ± 8 | 79 ± 22* | 46 ± 16 | 33 ± 4 | 16 ± 3 |
| $RE_{t0}$ | 87 ± 18 | 4.7 ± 0.64† | 81 ± 7* | 5 ± 4 | 80 ± 8* | 49 ± 9 | 83 ± 22‡ | 47 ± 17 | 33 ± 4 | 16 ± 4 |
| $RE_{t60}$ | 89 ± 17*[a] | 4.4 ± 0.96‡ | 82 ± 7* | 5 ± 3 | 80 ± 9* | 49 ± 11 | 86 ± 18 | 50 ± 11 | 33 ± 11 | 15 ± 5 |
| PALL value | 0.0001 | 0.0001 | 0.005 | ns | 0.005 | ns | 0.0001 | ns | ns | ns |

*BSL, baseline; $AMI_{t0--t80}$, acute myocardial infarction at t0 and t80, respectively; $RE_{t0--t60}$, reperfusion at t0 and t60, respectively; HR, heart rate; PLV Sys and PLV Dia, systolic and diastolic LV pressures, respectively; PAo Sys and PAo Dia, systolic and diastolic aortic pressures, respectively; Pfem Sys and Pfem Dia, systolic and diastolic femoral pressures, respectively; PAP Sys and PAP Dia, systolic and diastolic pulmonary arterial pressures, respectively.*

*Results from multiple-comparison analysis account for comparison of the different timepoints against BSL. Data are presented as mean ± SD.*

*$^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.0001$.*

*[a]Comparison is significant against AMIt0.*

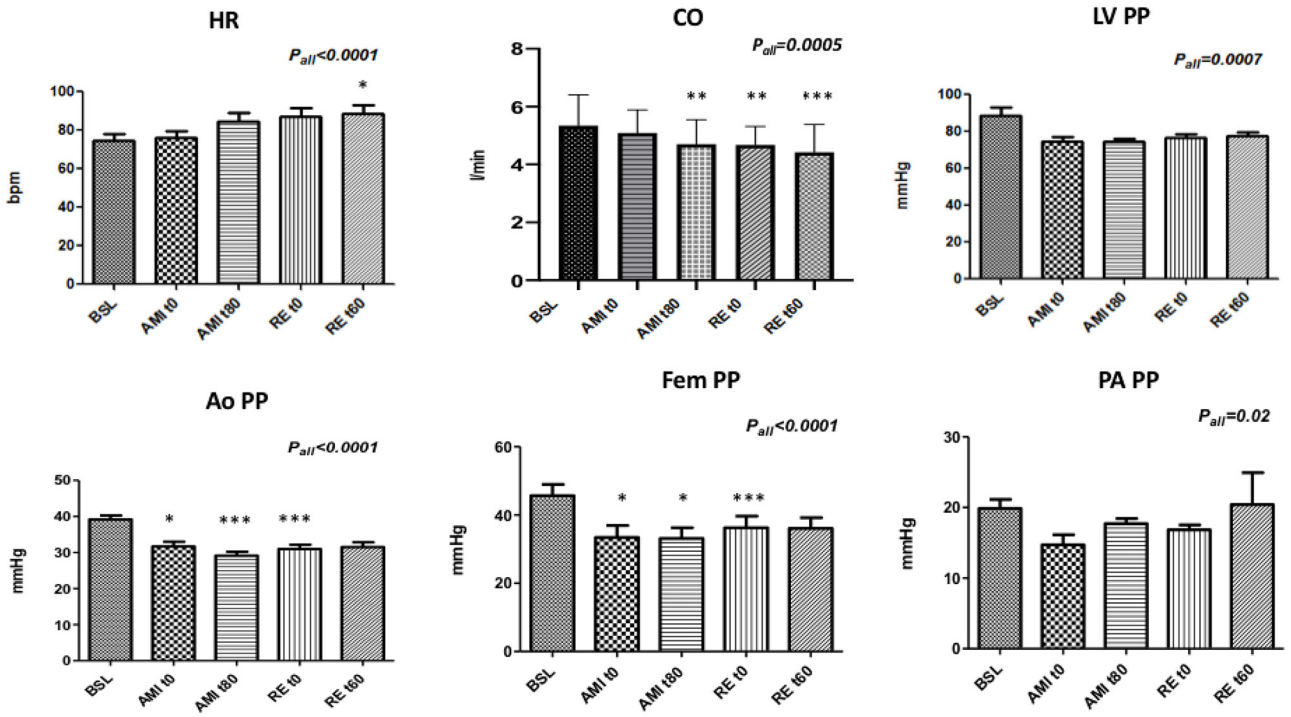


**FIGURE 1 |** Modifications of HR, CO, and pulse pressure parameters during coronary sub-occlusion and reperfusion. HR, heart rate; CO, cardiac output; LV PP, pulse pressure of LV pressure; Ao PP, pulse aortic pressure; Fem PP, femoral pulse pressure; PA PP, pulse pressure of pulmonary artery pressure; BSL, baseline; $AMI_{t0-t80}$, acute myocardial infarction at t0 and t80, respectively; $RE_{t0-t60}$, reperfusion at t0 and t60, respectively. A generalized mixed model was used, with time as the fixed factor. The level of significance was set at 0.05. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.0001$. Data are presented as mean ± SEM for each variable ($N = 17$).

baseline to the end of reperfusion. In the rotational dimension, $iK^{CC}_{Rot}$ and $iK^{Sys}_{Rot}$ dropped by 30 and 38%, respectively ($P_{ALL} = 0.0006$ and $P_{ALL} < 0.0001$, respectively).

According to multiple comparisons, $iK^{CC}_{Lin}$ dropped by 20, 30, and 43% at $AMI_{t0}$, $RE_{t0}$, and $RE_{t60}$, respectively, compared to BSL ($p = 0.01$, $p = 0.007$, and $p = 0.0009$, respectively); $iK^{Sys}_{Lin}$ dropped by 33, 45, and 52% at $AMI_{t0}$, $RE_{t0}$, and $RE_{t60}$, respectively, compared to BSL ($p = 0.003$, $p = 0.008$, and $p = 0.002$, respectively); $iK^{Dia}_{Lin}$ dropped by 53% from BSL to $RE_{t60}$ ($p = 0.005$). With regards to the rotational parameters of *i*K, $iK^{CC}_{Rot}$ dropped by 20, 30, and 30% at $AMI_{t0}$, $RE_{t0}$, and $RE_{t60}$, respectively, compared to BSL ($p = 0.01$, $p = 0.01$, and $p = 0.003$, respectively); $iK^{Sys}_{Rot}$ dropped by 25, 38, and 38% from BSL to $AMI_{t80}$, $RE_{t0}$, and $RE_{t60}$, respectively ($p = 0.008$, $p = 0.003$, and $p < 0.0001$, respectively).

**Figure 3** shows a representative case of modifications of *iK* during coronary occlusion and reperfusion for one animal.

**Table 2** shows the generalized linear model used to associate pulse pressure parameters and CO with parameters of *iK*. All of the hemodynamic parameters, except PA PP, were significantly related to the parameters of *iK*, with a positive direction of association. LV PP was positively associated with $iK^{CC}_{Lin}$, $iK^{Sys}_{Lin}$, $iK^{Dia}_{Lin}$, $iK^{CC}_{Rot}$, and $iK^{Sys}_{Rot}$ ($p < 0.0001$, $p < 0.0001$, $p = 0.03$, $p < 0.0001$, and $p < 0.0001$, respectively); $iK^{CC}_{Lin}$, $iK^{Sys}_{Lin}$, $iK^{CC}_{Rot}$, and $iK^{Sys}_{Rot}$ were positively associated with the Ao PP ($p < 0.001$, $p < 0.001$, $p = 0.008$, and $p = 0.001$, respectively) and Fem PP ($p = 0.01$, $p = 0.005$, $p = 0.05$, and $p = 0.01$, respectively). Although these associations were positive and significant, they were still indirect, as shown by the too wide confidence intervals. The CO was also found to correlate with parameters of *i*K, especially with $iK^{CC}_{Lin}$, $iK^{Sys}_{Lin}$, $iK^{CC}_{Rot}$, and $iK^{Sys}_{Rot}$, with a positive direction of association ($p = 0.002$, $p < 0.0001$, $p = 0.004$, and $p < 0.0001$, respectively).

The parameters of *iK* have been associated to the Δ troponins and to the LVEF obtained at the end of the procedure ($RE_{t60}$), but no significant associations were observed (**Tables 3**, **4**, respectively).

## DISCUSSION

We reported for the first time the direct evidence that non-invasive, multi-dimensional SCG can quantify the cardiac kinetic energy and continuously track its changes during AMI and reperfusion in a closed chest swine model of AMI. We have previously highlighted the potential of micro-accelerations and gyroscopes in providing reliable information on the contractility status of the heart (2, 30): as found in previous study, metrics of *iK* are able to follow changes in cardiac contractility with high accuracy and were related to SV and CO (2); the increased

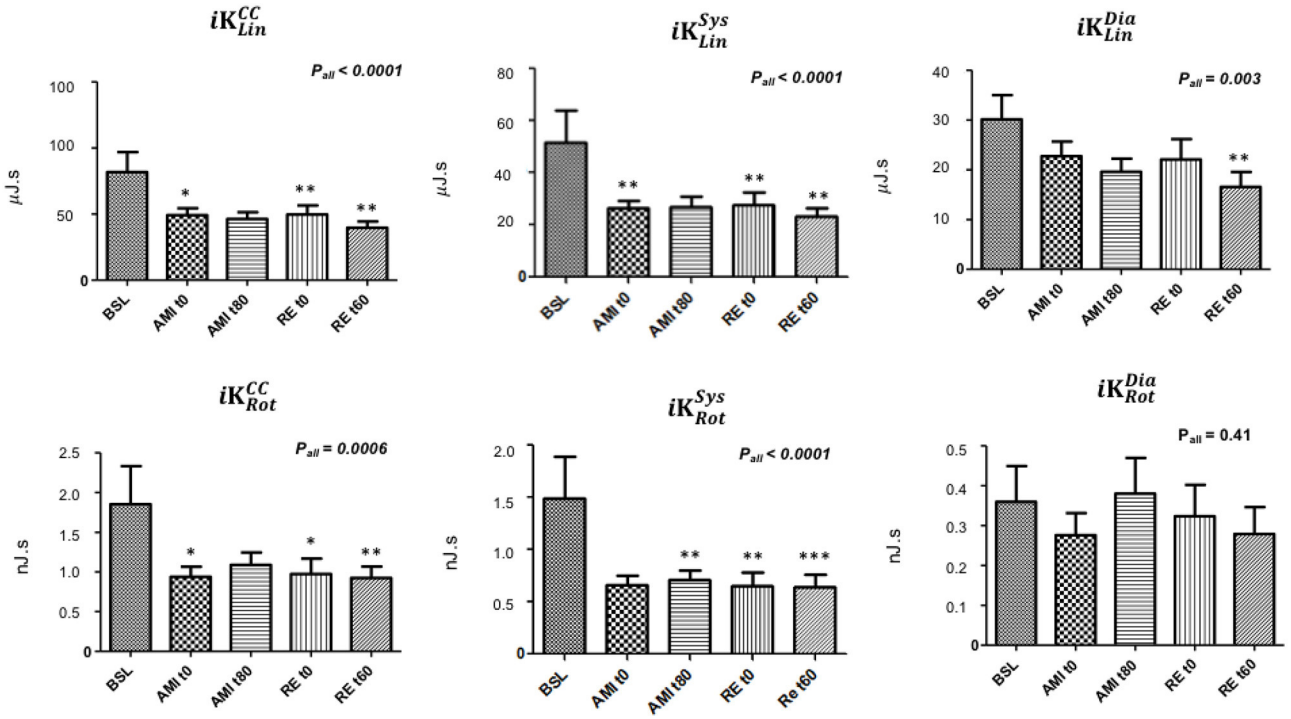


**FIGURE 2 |** Modifications of parameters of *iK* during coronary sub-occlusion and reperfusion. $iK^{CC}_{Lin}$, $iK^{Sys}_{Lin}$, $iK^{Dia}_{Lin}$, *iK* of seismocardiography (SCG) in the linear dimension computed over the whole cardiac cycle (CC), the systolic phase (Sys), and the diastolic phase (Dia), respectively; $iK^{CC}_{Rot}$, $iK^{Sys}_{Rot}$, $iK^{Dia}_{Rot}$, *iK* of SCG in the rotational dimension computed over the whole CC, Sys, and Dia, respectively; BSL, baseline; $AMI_{t0-t80}$, acute myocardial infarction at t0 and t80, respectively; $RE_{t0-t60}$, reperfusion at t0 and t60, respectively. A generalized mixed model was used, with time as the fixed factor. The level of significance was set at 0.05. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.0001$. Data are presented as mean ± SEM for each variable ($N = 17$).

cardiac kinetic energy measured with micro-accelerometers and gyroscopes was directly related to the rise of sympathetic nerve traffic during an end-voluntary maximal apnea (31); signals acquired with multi-dimensional SCG and BCG could monitor cardiac deconditioning in astronauts during simulated microgravity (32). With the present research, we demonstrate, for the first time, that the cardiac kinetic energy recorded with multi-dimensional non-invasive SCG, along with hemodynamic and echocardiographic findings, drops during AMI compared to normal cardiac inotropic state and does not improve during coronary reperfusion (33), likely reflecting a reduced left ventricular function of ischemic origin and further confirmed by the rise of plasma troponin levels and the drop of LVEF associated with regional LV wall abnormalities, which persisted despite revascularization. After sudden coronary artery occlusion, the unsupplied myocardium loses its ability to shorten and lengthen, and myocardial contractile function drastically drops (34). With relief of ischemia and reestablishment of coronary blood flow, there is a persistent wall motion abnormality despite reperfusion and viable myocytes (35). The sudden drop of *iK* observed immediately after coronary occlusion likely reflects the ischemic dysfunction due to supply lost, and the persistent drop of *iK* during reperfusion likely reflects further the myocardial reperfusion injury (33, 35). These conclusions are further supported by the drop of LVEF and the rise of plasma troponins at the end of revascularization and further corroborated by modifications of hemodynamic parameters showing the same trend of *i*K parameters during the experimental AMI.

Acute activation of sympathetic nervous system following AMI has been previously described in several investigations (36): the acute surge of catecholamines observed during prolonged acute myocardial ischemia (longer than 10 min at least) can reach plasma concentrations as high as 1,000 times of normal plasma levels, especially in cardiogenic shock (37), and such high concentrations are cardiotoxic, potentially inducing myocardial necrosis (38), with myocardial detrimental effect (37). Thus, the cardiotoxic effect of catecholamines secondary to sympathetic overactivity may be evoked as an additional mechanism contributing to the persistent drop of LVEF and *i*K parameters after reperfusion.

Previous authors extensively investigated the utility of micro-accelerometers and gyroscopes as diagnostic tools for acute ischemic myocardial impairment (7–9), and results are all in favor to suggest the potential of micro-accelerometers and gyroscopes in the early detection of myocardial dysfunction of ischemic origin. Backer et al. used the SCG to detect myocardial impairment on nine swine and differentiate ischemia from hypovolemia as causes of myocardial dysfunction (7); Elle and colleagues used a three-axes accelerometer sensor on three anesthetized swine to recognize regional myocardial ischemia early following LAD surgical occlusion and found that the acceleration signals dropped by 40% at only 130 s after

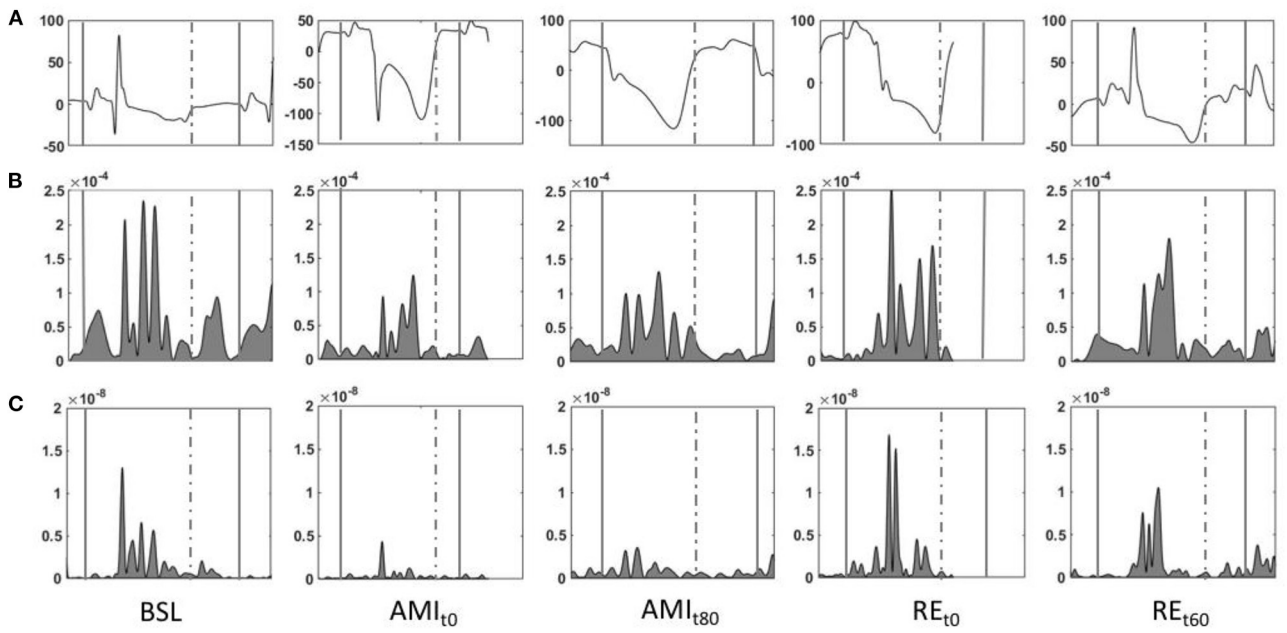


**FIGURE 3 |** Representative figure showing the evolution of waveforms of *i*K computed from the seismocardiography (SCG) signals during the experimental procedure, specifically during baseline (BSL), $AMI_{t0}$, $AMI_{t80}$, $RE_{t0}$, $RE_{t60}$. The two solid lines [from the beginning of the P wave of beat *n* to the beginning of the P wave of beat *n* + 1 on the synchronous electrocardiogram (ECG)] denote the *i*K computed over the whole cardiac cycle ($iK_{CC}$). The waveforms between the solid line and the dotted line (from the beginning of the P wave to the end of the T wave of beat *n* on the synchronous ECG) represent the *i*K of the systolic wave ($iK_{Sys}$). The waveforms between the dotted line and the solid line (from the end of the T wave of beat *n* to the beginning of the P wave of beat *n* + 1 on the synchronous ECG) represent the *i*K of the diastolic phase ($iK_{Dia}$). **(A)** ECG. **(B)** *i*K in the linear dimension. **(C)** *i*K in the rotational dimension. Linear **(B)** and rotational **(C)** *i*K drop at the onset of coronary sub-occlusion ($AMI_{t0}$), compared to BSL, remains far below baseline values during the whole duration of AMI ($AMI_{t80}$) and returns to normal level during reperfusion ($RE_{t0-t60}$). BSL, baseline; AMI t0-t80, acute myocardial infarction at t0 and t80, respectively; RE t0-t60, reperfusion at t0 and t60, respectively; *i*K, integral of kinetic energy (J·s).

coronary occlusion; Halvorsen et al. operated on 14 anesthetized swine a LAD surgical occlusion for 60 s while recording the velocities of LV wall with a three-axes accelerometer and reported that myocardial wall regional impairment is accompanied by concurrent changes in accelerometer velocities both during systole and relaxation (9). They further demonstrated the potential of accelerometers in the detection of myocardial ischemia in patients undergoing cardiac surgery (13).

The present investigation strongly reinforces and complements the previous ones by adding several novelties. First, we used three-axial sensors in three cardinal axes provided with linear and rotational channels to obtain a multi-dimensional assessment of blood flow and cardiac function with six degrees of freedom. Second, we applied Newtonian equations on acceleration signals to compute the scalar parameters of kinetic energy and its temporal integral *iK* for each contractile cycle in order to quantitatively measure the cardiac kinetic energy produced during a contractile cycle as well as during the systolic and diastolic phases (2, 11, 39). Third, we demonstrated that the fall of cardiac *iK* following LAD sub-occlusion is maintained for the whole duration of the coronary occlusion and does not improve during reperfusion. The fall of *i*K parameters is likely of ischemic origin as suggested by the rise of plasma troponins and by the drop of LVEF along with regional LV wall abnormalities, which persist at the end of the experimental procedure. Fourth, changes of *iK* parameters during the whole procedure were positively correlated with changes of invasive pulse pressures and CO, which fell as well during acute myocardial infarction, showing the same evolution pattern of *i*K parameters. Fifth, the drop of *iK* observed during occlusion and reperfusion was not related to the infarct size as estimated by early troponins release nor to the severity of myocardial contraction as estimated by the LVEF. Sixth, associations between *i*K and invasive pulse pressures are observed only with left-side pulse pressures, that is, LV PP, Ao PP, and Fem PP, but not with PA PP. Seventh, we used a closed-chest porcine model of AMI, which represents a valuable and suitable surrogate for myocardial infarction in humans (40). Reduction by 60% of coronary blood flow, induced by using a coronary balloon, was enough to trigger electrical, metabolic, and mechanical modifications of cardiac function as demonstrated by ST segment abnormalities, the rise of cardiac troponins, and the drop of LVEF along with regional LV wall abnormalities. Additionally, the sample size accounted for 17 out of 21 pigs that is far larger compared to previous investigations (5, 8, 9, 13). This observation makes the authors believe that, in this very context of experimental AMI with acute LV regional dysfunction and no concomitant AMI-related heart valve disease, linear and rotational *i*K parameters, in particular systolic ones, provide

**TABLE 2 |** Associations between pulse pressures and cardiac output with parameters of *i*K in the linear and rotational dimensions.

| | LV PP (mmHg) | | | Ao PP (mmHg) | | | Fem PP (mmHg) | | | PA PP (mmHg) | | | CO (L/min) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Coefficient** | **95% CI** | ***p*-value** | **Coefficient** | **95% CI** | ***p*-value** | **Coefficient** | **95% CI** | ***p*-value** | **Coefficient** | **95% CI** | ***p*-value** | **Coefficient** | **95% CI** | ***p*-value** |
| SCG Lin CC (μJ·s) | 0.14 | 0.07; 0.2 | <0.0001 | 0.06 | 0.03; 0.09 | <0.001 | 0.09 | 0.02; 0.15 | 0.01 | 0.002 | −0.001; 0.005 | 0.29 | 8.1 | 3.0; 13.2 | 0.002 |
| SCG Lin Sys (μJ·s) | 0.02 | 0.08; 0.3 | <0.0001 | 0.08 | 0.04; 0.11 | <0.001 | 0.12 | 0.03; 0.19 | 0.005 | 0.002 | −0.001; 0.006 | 0.16 | 11.7 | 5.6; 17.8 | <0.0001 |
| SCG Lin Dia (μJ·s) | 0.2 | 0.02; 0.37 | 0.03 | 0.05 | −0.04; 0.14 | 0.26 | 0.04 | −0.14; 0.22 | 0.65 | −0.001 | −0.009; 0.007 | 0.78 | 2.2 | −11.2; 15.6 | 0.75 |
| SCG rot CC (nJ·s) | 4.40 | 2.08; 6.72 | <0.0001 | 1.49 | 0.4; 2.60 | 0.008 | 2.28 | 0.02; 4.53 | 0.05 | 0.06 | −0.35; 15.2 | 0.22 | 2.5 | 0.8; 42.0 | 0.004 |
| SCG Rot Sys (nJ·s) | 5.56 | 2.89; 8.22 | <0.0001 | 2.16 | 0.9; 3.37 | 0.001 | 3.32 | 0.7; 5.89 | 0.01 | 0.08 | −0.03; 0.18 | 0.14 | 3.5 | 1.5; 5.4 | <0.0001 |
| SCG Rot Dia (nJ·s) | 6.10 | −3.03; 15.2 | 0.19 | −3.36 | −8.32; 1.60 | 0.18 | −3.35 | −13.3; 6.63 | 0.51 | −0.08 | −0.5; 0.36 | 0.72 | −0.7 | −7.8; 6.2 | 0.83 |

*iK SCG Lin-Rot, integral of kinetic energy of seismocardiography in the linear and rotational dimension, respectively; CC–Sys–Dia, cardiac cycle–systolic phase–diastolic phase; LV PP, left ventricle pulse pressure; Ao PP, aortic pulse pressure; Fem PP, femoral pulse pressure; PA PP, pulmonary artery pulse pressure.*

**TABLE 3 |** Spearman's correlation between delta troponins and parameters of *i*K.

| ***N* = 17** | ***iK*$_{cc}$** | ***iK*$_{Sys}$** | ***iK*$_{Dia}$** |
|---|---|---|---|
| **Linear dimension** | | | |
| Δ Troponins | $r = -0.32$, $p = 0.23$ | $r = -0.12$, $p = 0.66$ | $r = -0.36$, $p = 0.2$ |
| **Rotational dimension** | | | |
| Δ Troponins | $r = -0.17$, $p = 0.53$ | $r = 0.06$, $p = 0.8$ | $r = -0.16$, $p = 0.56$ |

*iK$_{CC}$, iK$_{Sys}$, iK$_{Dia}$: iK of seismocardiography computed over the whole cardiac cycle (CC), the systolic phase (Sys), and the diastolic phase (Dia), respectively.*

**TABLE 4 |** Spearman's correlation between LVEF and parameters of *i*K.

| ***N* = 17** | ***iK*$_{cc}$** | ***iK*$_{Sys}$** | ***iK*$_{Dia}$** |
|---|---|---|---|
| **Linear dimension** | | | |
| LVEF | $r = -0.24$, $p = 0.41$ | $r = -0.48$, $p = 0.09$ | $r = 0.10$, $p = 0.74$ |
| **Rotational dimension** | | | |
| LVEF | $r = -0.30$, $p = 0.3$ | $r = -0.30$, $p = 0.31$ | $r = -0.43$, $p = 0.13$ |

*iK$_{CC}$, iK$_{Sys}$, iK$_{Dia}$, iK of seismocardiography computed over the whole cardiac cycle (CC), the systolic phase (Sys), and the diastolic phase (Dia), respectively; LVEF, left ventricle ejection fraction.*

reliable information on LV contractile dysfunction and its effects on the downstream circulation.

As explained above, the automatic identification of P, Q, R, S, and T waves on the ECG allowed for the identification of the cardiac cycle on the SCG waveforms. By combining these reference points, the systolic and diastolic phases can also be identified (12). The present investigation reported also the different impact of AMI on systolic and diastolic SCG waveforms. Indeed while the *iK* during the systolic phase dropped during coronary sub-occlusion and reperfusion both in linear and rotational dimensions, the *iK* during the diastolic phase seems to be less influenced by the ischemic event, showing a modest significant drop in the linear dimension and no changes at all in the rotational dimension. This makes the authors believe that an acute ischemic cardiac event with predominant systolic dysfunction has a deep impact mainly on the systolic SCG waveforms rather than the diastolic ones. The authors speculate that the diastolic component of *i*K may reflect more the filling functions of the LV rather than its contractile properties. To further corroborate this viewpoint, the diastolic *iK* was not associated with any of the pulse pressure parameters nor the CO, except the linear diastolic *i*K with the LV PP, but with a weak significance.

Even though critical differences exist between our technique and those used by our predecessors (7–9, 13, 14) (i.e., non-intrusive device, remotely controlled system, automatic analysis, use of linear and rotational channels, computation of scalar parameters from acceleration signals), our observations further confirm the core concept that micro-accelerometers and gyroscopes can reliably monitor cardiovascular changes occurring during AMI and reperfusion.

Spaccarotella et al. have recently demonstrated that smartwatches ECG can detect ST segment elevation and

depression with high sensitivity and specificity compared to a standard 12-lead ECG, and this might empower the earlier detection of ECG abnormalities in patients with acute coronary syndrome (41).

We presented a device capable of computing the integral of kinetic energy of a contractile cycle recorded with micro-accelerometers and gyroscopes, with the aim to provide information on the mechanical activity of the heart. We previously demonstrated the capability of this device to follow changes of cardiac contractility in different conditions as already mentioned (2, 12, 31, 32, 42). With the present investigation, we add that this device can detect an acutely failing heart of ischemic origin by providing a parameter of kinetic energy. An important possible application of this renewed technology is the follow-up of patients with myocardial dysfunction in the mid-long term after an acute ischemic event. Thanks to the easy-to-use properties of the device, cardiac patients might be empowered to follow their own medical conditions, as it is already the case with atrial fibrillation diagnosed with smartwatches. To our knowledge, markers of myocardial mechanical function are not provided by the smartwatches currently in use, and we believe that this device may complement the existing ones by adding the cardiac kinetic energy as a new parameter of myocardial mechanical function and thus may prove useful to track changes in myocardial mechanical activity of heart failure patients in the near future.

Of course, this device must not be considered as a competitor to traditional standards and guidelines universally used for cardiac patient's follow-up but as a complement to them.

## Limitations

Some limitations need considerations. Because of marked differences in anatomy, heart, and vessel orientation, the effects of myocardial infraction in humans are likely to differ in the three axes investigated in this study, but the observations on the *iK* parameters which include the three axes should remain valid. We also cannot report on the effects of AMI on multidimensional BCG in this study because of marked differences in body mass distribution between the experimental animal model that we investigated and the human beings to which the original prototype was made for (2, 11).

Indeed because of technical limitations during the experimental procedure, mainly the recumbent position of the animal, the BCG sensor was placed externally to the left iliac crest and not close to the body center of mass (lower back of the animal) as recommended (2, 11). Placing the BCG module in this wrong position means that the recorded signals cannot be considered as BCG ones. The authors were not able to place this module over the lumbar lordosis curve for the following reasons: the recumbent position of the animal and the consequent difficulties to place the device under it and the difficulty to access this region and to promptly remove the device whenever a cardiac arrest for ventricular arrythmias occurred and prompt defibrillation was required. Indeed whenever resuscitation was required, the device was promptly removed, and easy accessibility to it was mandatory for the sake of the safety of the operators and the animal.

Despite the fact that this technique has not been standardized yet with large-scale-based studies so that no normal values of kinetic energy can be provided, this limitation was encompassed with the repeated-measures study design, where each animal was its own control. The same study design was adopted in our previous works (2, 12, 31, 32, 42).

With regard to the experimental procedure, some readers may arise concerns that the observed cardiovascular modifications might be due to general anesthesia, specifically to sevoflurane (43) and azaperone (44). However, the authors are confident to conclude that the cardiovascular modifications occurring during the experimental procedure were likely attributable to acute myocardial ischemia and not to general anesthesia for several reasons: first, the drop by $\pm 5$ mmHg of the mean arterial pressure observed in the sham group cannot explain the large reduction in the mean systemic blood pressure that we observed during myocardial infarction, and this allowed the authors to rule out the depressant effect of general anesthesia on the hemodynamic parameters; second, sevoflurane has higher hemodynamic stability and fewer arrhythmic events compared to other volatile agents (24), and sevoflurane inhalation was within normal range (1.8 to 2.5% of MAC); third, since azaperone has a duration of action of 2 to 3 h in young pigs with a peak within the first 30 min (45) and since the procedure was started after 4 h at least of steady state, the effects of this drug on systemic circulation cannot be considered as responsible for the observed hemodynamic impairment after AMI; and fourth, the rise of troponin levels and the drop of LVEF associated with regional LV wall abnormalities which persist after reperfusion are all in favor to suggest that hemodynamic impairment and reduction of *i*K parameters were a direct consequence of acute myocardial ischemia and not of anesthetic agents.

We did not find any change in the left ventricle diastolic pressure during the experimental procedure. The authors attribute this phenomenon to the effect of the mechanical ventilation with a positive end-expiratory pressure of 5 cm $H_2O$, which induces a fall in transpulmonary flow and thus in the venous return to the LV, with the global effect of reducing the LV preload (46).

The study design was conceived to induce a cardiogenic shock. Since in swine only 25% of LV mass is supplied by the right coronary artery and 25% by the left circumflex artery, occluding these arteries would have probably not induced a cardiogenic shock. Further studies should be designed to assess the consequences of less extensive MI on SCG signals.

The observational period after reperfusion is relatively short; however, the study design was initially conceived to determine whether and how acute myocardial infarction and reperfusion affect the SCG signals and the derived parameters with no additional observational period. The positive and encouraging results obtained with this pivotal study set another step toward the validation of this renewed technique in the context of acute coronary diseases and undoubtedly justify further research on the long-term effect of MI on SCG signals.

Despite the limitations described above, this study further reinforces the need to investigate on the utility of micro-accelerations and gyroscopes in the detection of acute myocardial infarction on patients in real life and their potential as monitoring tools for the assessment of cardiovascular function following an acute ischemic cardiac event.

## CONCLUSIONS

To our knowledge, this is the first study to demonstrate the potential of non-intrusive, multi-dimensional SCG to monitor in real time the functional status of cardiac muscle during AMI with predominant systolic dysfunction followed by coronary reperfusion and to provide a quantitative assessment of cardiac kinetic energy computed from acceleration signals. Thanks to its easy-to-use properties, this automatic and remotely controlled system may empower healthcare providers and patients to monitor cardiovascular status in real life and may help to remotely detect any cardiac functional abnormalities early. Of course, this device must not be considered as a competitor to traditional standards and guidelines universally used for a cardiac patient's follow-up but as a complement to them.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

## ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Ethics Committee on Animal Welfare from the Faculty of Medicine from the Université Libre de Bruxelles (ULB, Brussels, Belgium) (Acceptation Number: 654N).

## AUTHOR CONTRIBUTIONS

PvdB and SM conceived the idea and the design of the study. LP designed the animal model of AMI and carried out the whole experimental procedure supported by FS and obtained all the invasive hemodynamic parameters data. AHo provided the technical support and designed the specific Toolbox in MathLab for the correct extrapolation of all metrics from SCG. SM had full access to all data in the present investigation, extrapolated all SCG data, and takes responsibility for the integrity of the data and the accuracy of the data analysis. AHe was responsible for the experimental procedure on the sham group and provided the results for the sham group. JRac performed statistical analysis. SM and LP drafted the manuscript. All authors revised the manuscript critically for important intellectual content, proofread, and made corrections to this manuscript.

## FUNDING

This work was supported by the Fonds Erasme pour la Recherche Biomedicale, of the Erasme hospital, Université Libre de Bruxelles (SM, LP); by the Académie Royale de Médecine Belgique (SM); by the FNRS, Fond National pour la Recherche Scientifique, Fédération Wallonie Bruxelles, Belgium (SM, JRa); by the Fonds pour la Chirurgie Cardiaque (LP); by a grant from the European Space Agency and the Belgian Federal Scientific Policy Office (PRODEX PEA 4000110826) (AHo, DG, P-FM).

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.603319/full#supplementary-material

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**Conflict of Interest:** P-FM, DG, and AHo declare having direct ownership of shares in Healthcare Company.

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.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 11 March 2021
doi: 10.3389/fcvm.2021.629268

# Elevated Plasma Big Endothelin-1 at Admission Is Associated With Poor Short-Term Outcomes in Patients With Acute Decompensated Heart Failure

*Ran Mo, Yan-min Yang*, Li-tian Yu, Hui-qiong Tan and Jun Zhu*

*State Key Laboratory of Cardiovascular Disease, Emergency and Intensive Care Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

**Objective:** We aimed to evaluate the association between plasma big endothelin-1 (ET-1) at admission and short-term outcomes in acute decompensated heart failure (ADHF) patients.

**Methods:** In this single-center, retrospective study, a total of 746 ADHF patients were enrolled and divided into three groups according to baseline plasma big ET-1 levels: tertile 1 (<0.43 pmol/L, $n = 250$), tertile 2 (between 0.43 and 0.97 pmol/L, $n = 252$), and tertile 3 (>0.97 pmol/L, $n = 244$). The primary outcomes were all-cause death, cardiac arrest, or utilization of mechanical support devices during hospitalization. Logistic regression analysis and net reclassification improvement approach were applied to assess the predictive power of big ET-1 on short-term outcomes.

**Results:** During hospitalization, 92 (12.3%) adverse events occurred. Etiology, arterial pH, lactic acid, total bilirubin, serum creatine, serum uric acid, presence of atrial fibrillation and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were positively correlated with plasma big ET-1 level, whereas systolic blood pressure, serum sodium, hemoglobin, albumin, and estimated glomerular filtration rate were negatively correlated. In multivariate logistic regression, tertile 3 compared with tertile 1 had a 3.68-fold increased risk of adverse outcomes [odds ratio (OR) = 3.681, 95% confidence interval (CI) 1.410–9.606, $p = 0.008$]. However, such adverse effect did not exist between tertile 2 and tertile 1 (OR = 0.953, 95% CI 0.314–2.986, $p = 0.932$). As a continuous variable, big ET-1 level was significantly associated with primary outcome (OR = 1.756, 95% CI 1.413–2.183, $p < 0.001$). The C statistic of baseline big ET-1 was 0.66 (95% CI 0.601–0.720, $p < 0.001$). Net reclassification index (NRI) analysis showed that big ET-1 provided additional predictive power when combining it to NT-proBNP (NRI = 0.593, $p < 0.001$).

**Conclusion:** Elevated baseline big ET-1 is an independent predictor of short-term adverse events in ADHF patients and may provide valuable information for risk stratification.

**Keywords: acute decompensated heart failure, big endothelin-1, NT- pro B-type natriuretic peptide, short-term prognosis, intensive care**

OPEN ACCESS

***Edited by:***
*Chris J. Pemberton, University of Otago, New Zealand*

***Reviewed by:***
*Stefania Paolillo, University of Naples Federico II, Italy*
*Timothy Prickett, University of Otago, New Zealand*

****Correspondence:***
*Yan-min Yang*
*fuwaiyym@126.com*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *14 November 2020*
***Accepted:*** *01 February 2021*
***Published:*** *11 March 2021*

***Citation:***
*Mo R, Yang Y-m, Yu L-t, Tan H-q and Zhu J (2021) Elevated Plasma Big Endothelin-1 at Admission Is Associated With Poor Short-Term Outcomes in Patients With Acute Decompensated Heart Failure. Front. Cardiovasc. Med. 8:629268. doi: 10.3389/fcvm.2021.629268*

# INTRODUCTION

Acute decompensated heart failure (ADHF) is one of the most common and life-threatening diseases in the clinic, causing a high mortality and readmission rate (1). Recent data suggest that the in-hospital mortality for ADHF patients is nearly 3%, whereas the rehospitalization rate exceeds 50% within 6 months (2–4). In addition, the incidence of acute heart failure (AHF) syndrome has increased markedly in the last decades parallel to the aging of the population, a fact that caused a significant disease and economic burden. Therefore, it is essential to identify high-risk ADHF patients at admission and reasonably allocating limited hospital resources to deal with the most urgent situations (5).

Clinical and biochemical determinants of ADHF prognosis have been extensively studied, including age, blood lactate, serum creatinine, heart rate, liver function, serum sodium, and cardiovascular comorbidities. Among them, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the most widely used laboratory index to evaluate the severity and prognosis of ADHF. In the recent three decades, the endothelin system has been found to play a central role in the pathophysiology of many cardiovascular diseases, including hypertension (6), atherosclerosis (7), coronary artery disease (CAD) (8), and pulmonary arterial hypertension (PAH) (9). Endothelin-1 (ET-1) is the most potent vasoconstrictor, which is produced from the prepropeptide, big ET-1, by endothelin converting enzymes. With a longer half-life time in the peripheral circulation than ET-1, big ET-1 is now considered more suitable for clinical surveillance and prognostic evaluation. However, in the setting of ADHF, the prognostic role of baseline plasma big ET-1 still remains unclear. Thus, the present study aimed to investigate whether elevated plasma big ET-1 at admission is associated with worse short-term outcomes in patients with ADHF and compare its prognostic ability with NT-proBNP. We hypothesized that big ET-1 was a potential factor for improving the risk stratification of ADHF.

# MATERIALS AND METHODS

## Study Population

This is a retrospective observational study. From January 2014 to December 2018, a total of 746 patients diagnosed with ADHF who were admitted to the intensive care unit (ICU) from the emergency department (ED) at Fuwai Hospital were enrolled in the present study. All participants met the most recent European guidelines for the diagnosis of AHF (10), and ADHF was defined as exacerbation of chronic heart failure (CHF) with worsening symptoms needed intensive care. Additional inclusion criteria for the analysis were: (1) age $\geq$18 years, (2) ADHF as the first-listed diagnosis, and (3) available baseline big ET-1 level. The following criteria excluded patients from the study: known diagnosis of malignancy, ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction as the leading reason for admission because acute myocardial infarction has a totally different pathogenesis, whereas reperfusion treatment itself plays an important role on both short-term and long-term prognoses. However, patients with combined coronary heart disease (CHD) with CHF who were hospitalized for exacerbation of HF without indications for reperfusion therapy were also included in our study. All clinical data were collected from the electronic medical records. The study was approved by the ethics committee of Fuwai Hospital and was conducted in accordance with the Declaration of Helsinki.

## Data Collection

In patients who entered the study, the detailed baseline data were obtained from their medical records including demographic characteristics, chronic health status, body mass index (BMI), vital signs, and comorbidities. The classification of AHF was in accordance with 2016 European Society of Cardiology (ESC) guidelines (10). The etiology of ADHF was consistent with personal ED records, and the primary diagnosis was adopted when patients had several different pathologies. Vital signs were defined as systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body temperature measured at the ED. The following laboratory tests were assessed and recorded at admission:

- arterial blood gas: arterial pH, arterial partial pressure of oxygen ($PaO_2$), and lactate concentration
- hematology: white blood cell (WBC) count, hemoglobin (Hb) concentration, and hematocrit (HCT)
- Serum electrolytes: sodium, potassium
- Liver and renal functions: plasma albumin, total bilirubin (TBIL), serum uric acid (SUA), and serum creatinine (Scr), and the Chinese version of the Modification of Diet in Renal Disease (MDRD) equation was applied to calculate the participants' estimated glomerular filtration rate (eGFR) (11).
- High sensitivity troponin I (hs-TNI) and NT-proBNP.

The presence of atrial fibrillation (AF) and bundle branch block (BBB) was evaluated by 12-lead electrocardiography, and left ventricular ejection fraction (LVEF) as well as estimated pulmonary arterial systolic pressure (PASP) were measured by experienced physicians using echocardiography. The LVEF was calculated by the modified Simpson's biplane rule.

## Study Grouping and Outcomes

Venous blood samples were drawn from all patients immediately on admission according to standard venous blood specimen collection procedures. To measure the concentration of plasma big ET-1, the medical examination center utilized a highly sensitive and specified Big ET-1 ELISA Kit (BI2008 2H; Biomedica, Wien, Austria). The normal range was $<$0.25 pmol/L. After a brief analysis of selected patients, we divided them into three groups according to the value of plasma big ET-1: tertile 1 ($<$0.43 pmol/L, $n = 250$), tertile 2 (between 0.43 and 0.97 pmol/L, $n = 252$), and tertile 3 ($>$0.97 pmol/L, $n = 244$).

The primary outcome of interest was a composite endpoint defined as: (1) in-hospital death, (2) cardiac arrest occurring during hospitalization, and (3) utilization of mechanical support devices including extracorporeal membrane oxygenation (ECMO). The secondary outcome was all-cause mortality or listed for heart transplantation (HTx).

## Statistical Analysis

For baseline characteristic information, categorical variables were expressed as frequencies (percentages), and continuous variables were expressed as means ± standard deviations (SD) or medians with quartiles if they were not in the normal distribution. Normality was calculated using the Shapiro–Wilk W-test. A log-data transformation was applied to fit skewed distributions to normal distributions, such as eGFR, hs-TNI, and NT-proBNP. Variance analysis was adopted to compare baseline continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables among tertile 1, tertile 2, and tertile 3. Factors related to plasma big ET-1 level were assessed by Spearman correlation analysis. Univariate logistic regression was used to evaluate the predictive power for short-term outcomes of big ET-1 and other clinical parameters, whereas odds ratios (ORs) and their 95% confidence intervals (95% CIs) were displayed. Then, based on univariate analysis, several statistically significant predictors were included in multivariate logistic regression model with a forward stepwise selection algorithm. Subsequently, in order to test the predictive power of big ET-1, we performed receiver-operating characteristic (ROC) curve and used the optimal cut-off value of baseline NT-proBNP to recategorize the patients (group 1: NT-proBNP <14,873 pg/ml, $n = 654$; group 2: NT-proBNP $\geq$ 14,873 g/ml, $n = 92$). The area under the curve (AUC), net reclassification index (NRI), and integrated discrimination improvement (IDI) were calculated to further compare the prediction performance of these two parameters.

The software package SPSS version 25.0 (IBM Corporation, New York, NY, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA) were utilized for statistical analysis. All statistical tests were two-tailed, with a $p < 0.05$ considered statistically significant. Graphs were generated using the software GraphPad Prism 8.0.

# RESULTS

## Baseline Characteristics

The baseline characteristics of total participants and different groups were shown in **Table 1**. The mean age of the study population was 58.3 ± 16.6 years, and female only accounted for 28.3%. Age and sex distribution showed no statistical difference in the three groups. In total, 707 (94.8%) patients were categorized as congestive AHF. Two hundred nine (28%) participants had diabetes mellitus, and 34.3% had AF on the electrocardiogram. The top three causes for ADHF were ischemic heart disease (42.4%), cardiomyopathy (32.8%), and valvular disease (13.4%). Patients in tertile 2 and tertile 3 had lower SBP ($p = 0.016$), faster HR ($p = 0.002$), and apparently more manifestations of AF ($p < 0.001$) as well as pulmonary hypertension ($p < 0.001$). For blood laboratory test, those who had elevated big ET-1 were more likely with higher levels of arterial pH ($p = 0.018$), lactic acid ($p = 0.008$), TBIL ($p < 0.001$), SUA ($p < 0.001$), Scr ($p < 0.001$), hs-TNI ($p < 0.001$), and NT-proBNP ($p < 0.001$). In the meantime, they had significant lower levels of serum sodium ($p < 0.001$), Hb ($p < 0.001$), albumin ($p < 0.001$), and eGFR ($p < 0.001$).

## Correlations of Variables With Big ET-1

The results of bivariable correlation analysis were listed in **Table 2**. The following parameters were significantly associated with big ET-1 level on admission: etiology ($r = 0.086$, $p = 0.019$), SBP ($r = -0.088$, $p = 0.016$), arterial pH ($r = 0.102$, $p = 0.006$), lactic acid ($r = 0.145$, $p = 0.001$), serum sodium ($r = -0.112$, $p = 0.002$), Hb ($r = -0.146$, $p < 0.001$), albumin ($r = -0.097$, $p = 0.008$), TBIL ($r = 0.354$, $p < 0.001$), Scr ($r = 0.246$, $p < 0.001$), SUA ($r = 0.336$, $p < 0.001$), eGFR ($r = -0.124$, $p = 0.001$), NT-proBNP ($r = 0.438$, $p < 0.001$) and presence of AF ($r = -0.152$, $p < 0.001$). Among these factors, log-transformed NT-proBNP had the best correlation.

## Outcomes and Multivariate Logistic Regression

The clinical outcomes classified by the big ET-1 groups were shown in **Figure 1**. During hospitalization, 92 (12.3%) primary composite endpoints occurred, of whom 90 (12.1%) patients suffered from in-hospital death, 29 (12.1%) suffered cardiac arrest, and 7 (0.9%) received mechanical support devices therapy. Furthermore, 25 (3.4%) critically-ill patients were listed for HTxs. The tertile 2 and tertile 3 groups had significantly higher rates in both composite primary outcomes (6.4 vs. 8.7 vs. 22.1%, $p < 0.001$) and in-hospital mortality (6.4 vs. 8.7 vs. 21.3%, $p < 0.0001$). However, there was no statistical difference of HTx among the three groups (4.0 vs. 2.8 vs. 3.4%, $p = 0.773$).

Relations between baseline factors and outcomes were shown in **Table 3**. In the univariate regression, congestion, big ET-1, SBP, DBP, HR, lactic acid, WBC count, albumin, TBIL, SUA, Scr, log-transformed eGFR, and log-transformed NT-proBNP were, respectively, related to the primary composite endpoint. When involving all the parameters into multivariate logistic regression, plasma big ET-1 and WBC count (OR = 1.297, 95% CI 1.186–1.420, $p < 0.001$) were independent risk factors. The highest big ET-1 group compared with the lowest had a 3.68-fold increased risk of adverse outcomes during hospitalization (OR = 3.681, 95% CI 1.410–9.606, $p = 0.008$). Interestingly, such risk did not persist if patients were in tertile 2 compared with those who belonged to tertile 1 (OR = 0.953, 95% CI 0.314–2.986, $p = 0.932$). As a continuous variable, big ET-1 level was also significantly associated with primary outcome (OR = 1.756, 95% CI 1.413–2.183, $p < 0.001$) and in-hospital death (OR = 1.734, 95% CI 1.394–2.158, $p < 0.001$) but not for HTx (OR = 0.931, 95% CI 0.558–1.552, $p = 0.784$).

## Predictive Values of Big ET-1 and NT-proBNP

ROC curves of big ET-1 and NT-proBNP at admission were shown in **Figure 2**. As categorical variables, the C statistics were 0.66 for the big ET-1 groups (95% CI 0.601–0.720, $p < 0.001$) and 0.628 for the NT-proBNP groups (95% CI 0.560–0.696, $p < 0.001$) (**Figure 2B**). When these two parameters were included as continuous variables, the AUC values were 0.685 for big ET-1 level (95% CI 0.628–0.743, $p < 0.001$) and 0.667 for log-transformed NT-proBNP (95% CI 0.584–0.752, $p < 0.001$) (**Figure 2A**). The NRI and IDI analyses were performed

**TABLE 1 |** Baseline characteristics based on big ET-1 tertiles.

| Variables | Total ($n$ = 746) | Tertile 1 ($n$ = 250) | Tertile 2 ($n$ = 252) | Tertile 3 ($n$ = 244) | $p$-value |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 58.3 ± 16.6 | 58.1 ± 15.8 | 59.9 ± 16.5 | 56.9 ± 17.4 | 0.112 |
| Sex (female, %) | 211 (28.3%) | 77 (30.8%) | 69 (27.4%) | 65 (26.6%) | 0.547 |
| ADHF type (congestion, %) | 707 (94.8) | 241 (96.4) | 240 (95.2) | 226 (92.6) | 0.155 |
| **Etiology of HF ($n$, %)** | | | | | **0.005** |
| Ischemic heart disease | 316 (42.4) | 121 (48.4) | 103 (40.9) | 92 (37.7) | |
| Valvular disease | 100 (13.4) | 30 (12.0) | 43 (17.1) | 27 (11.1) | |
| Cardiomyopathy | 245 (32.8) | 75 (30.0) | 70 (27.8) | 100 (41.0) | |
| Immune disorders | 25 (3.4) | 11 (4.4) | 9 (3.6) | 5 (2.0) | |
| Inflammatory damage | 16 (2.1) | 4 (1.6) | 7 (2.8) | 5 (2.0) | |
| Congenital heart disease | 27 (3.6) | 9 (3.6) | 8 (3.2) | 10 (4.1) | |
| Aortic disease | 2 (0.3) | 0 (0.0) | 1 (0.4) | 1 77 (0.4) | |
| Pulmonary heart disease | 15 (2.0) | 0 (0.0) | 11 (4.4) | 4 (1.6) | |
| **Vital signs** | | | | | |
| BMI (kg/m$^2$) | 24.08 ± 4.51 | 24.43 ± 4.29 | 23.68 ± 4.42 | 24.13 ± 4.79 | 0.186 |
| **SBP (mmHg)** | **117 ± 42** | **122 ± 66** | **116 ± 21** | **112 ± 21** | **0.016** |
| DBP (mmHg) | 72 ± 14 | 73 ± 12 | 73 ± 15 | 70 ± 13 | 0.039 |
| Temperature (°C) | 36.4 ± 4.0 | 36.6 ± 6.6 | 36.4 ± 0.4 | 36.3 ± 2.2 | 0.702 |
| **Heart rate (bpm)** | **79 ± 18** | **76 ± 16** | **81 ± 18** | **80 ± 21** | **0.002** |
| **Comorbidities** | | | | | |
| Smoking (n, %) | 385 (51.6) | 131 (52.4) | 130 (51.6) | 124 (50.8) | 0.940 |
| Drinking (n, %) | 309 (41.4) | 107 (42.8) | 101 (40.1) | 101 (41.4) | 0.826 |
| **Diabetes mellitus ($n$, %)** | **209 (28)** | **56 (22.4)** | **68 (27.0)** | **85 (34.8)** | **0.008** |
| **Laboratory test** | | | | | |
| **Arterial pH** | **7.44 ± 0.13** | **7.43 ± 0.20** | **7.44 ± 0.08** | **7.46 ± 0.06** | **0.018** |
| $PaO_2$ (mmHg) | 87 ± 24 | 88 ± 21 | 86 ± 25 | 88 ± 26 | 0.709 |
| **Lactic acid (mmol/L)** | **1.8 ± 1.0** | **1.6 ± 0.8** | **1.7 ± 0.7** | **2.0 ± 1.3** | **0.008** |
| **Serum sodium (mmol/L)** | **135.66 ± 11.08** | **137.35 ± 9.29** | **136.20 ± 5.15** | **133.37 ± 15.89** | **<0.001** |
| Serum potassium (mmol/L) | 4.23 ± 5.04 | 4.10 ± 0.49 | 3.97 ± 0.53 | 4.63 ± 8.79 | 0.304 |
| WBC count (×10$^9$/L) | 7.70 ± 5.62 | 7.25 ± 2.12 | 7.53 ± 3.12 | 8.35 ± 9.03 | 0.078 |
| **Hemoglobin (g/L)** | **136.3 ± 24.8** | **145.4 ± 22.3** | **134.1 ± 24.5** | **129.5 ± 24.9** | **<0.001** |
| Hematocrit | 0.62 ± 5.44 | 0.45 ± 0.26 | 0.41 ± 0.07 | 1.01 ± 9.51 | 0.393 |
| **Albumin (g/L)** | **40.0 ± 15.5** | **43.3 ± 24.8** | **38.7 ± 6.05** | **37.9 ± 15.5** | **<0.001** |
| **Total bilirubin (μmol/L)** | **29.54 ± 21.33** | **21.61 ± 14.72** | **28.07 ± 20.08** | **39.15 ± 24.42** | **<0.001** |
| **Uric acid (μmol/L)** | **534.2 ± 179.0** | **469.8 ± 142.6** | **509.2 ± 166.3** | **626.1 ± 188.3** | **<0.001** |
| **Creatinine (μmol/L)** | **110.6 ± 51.3** | **95.4 ± 31.6** | **108.6 ± 50.5** | **128.4 ± 62.1** | **<0.001** |
| **hs-TNI (μg/L)** | **0.039 (0.020–0.088)** | **0.028 (0.020–0.063)** | **0.039 (0.020–0.077)** | **0.052 (0.022–0.129)** | **<0.001** |
| **eGFR (ml/min/1.73 m$^2$)** | **63.16 (43.36–89.26)** | **71.93 (52.50–96.93)** | **61.00 (43.46–85.76)** | **58.74 (36.91–82.65)** | **<0.001** |
| **NT-proBNP (pg/ml)** | **5,124 (2,195.2–11,450.17)** | **2,184.37 (1,091.2–4,620.00)** | **5,226.00 (2,880.15–9,101.80)** | **9,544.40 (4,953.10–14,343.64)** | **<0.001** |
| **Echocardiography** | | | | | |
| LVEF (%) | 37.1 ± 13.0 | 37.5 ± 11.9 | 37.2 ± 13.7 | 36.6 ± 13.4 | 0.710 |
| **PASP >30 mmHg (n, %)** | **195 (26.1)** | **31 (12.4)** | **62 (24.6)** | **102 (41.8)** | **<0.001** |
| **Electrocardiogram** | | | | | |
| **Atrial fibrillation (n, %)** | **255 (34.3)** | **66 (26.5)** | **84 (33.5)** | **105 (43.2)** | **<0.001** |
| Bundle branch block (n, %) | 178 (24.1) | 57 (23.1) | 62 (24.8) | 59 (24.3) | 0.899 |

*Bold items are statistically significant.*

to compare the predictive powers of big ET-1 and NT-proBNP (**Supplementary Data 1**). Plasma big ET-1 proved to have similar risk stratification as NT-proBNP, the representative indicator for HF patients (NRI = 5.40%, 95% CI −0.16–0.27, $p$ = 0.627; IDI = 2.53%, 95% CI −0.002–0.053, $p$ = 0.072). When adding big ET-1 levels to baseline NT-proBNP, the C statistics for primary

**TABLE 2 |** Bivariable correlation between big ET-1 and clinical variables.

| Variables | r | *p*-value |
|---|---|---|
| Etiology | 0.086 | 0.019 |
| SBP | −0.088 | 0.016 |
| Arterial pH | 0.102 | 0.006 |
| Lactic acid | 0.145 | 0.001 |
| Serum sodium | −0.112 | 0.002 |
| Hemoglobin | −0.146 | <0.001 |
| Albumin | −0.097 | 0.008 |
| Total bilirubin | 0.354 | <0.001 |
| Creatinine | 0.246 | <0.001 |
| Uric acid | 0.336 | <0.001 |
| Lg eGFR | −0.124 | 0.001 |
| Lg NT-proBNP | 0.438 | <0.001 |
| Atrial fibrillation | 0.152 | <0.001 |

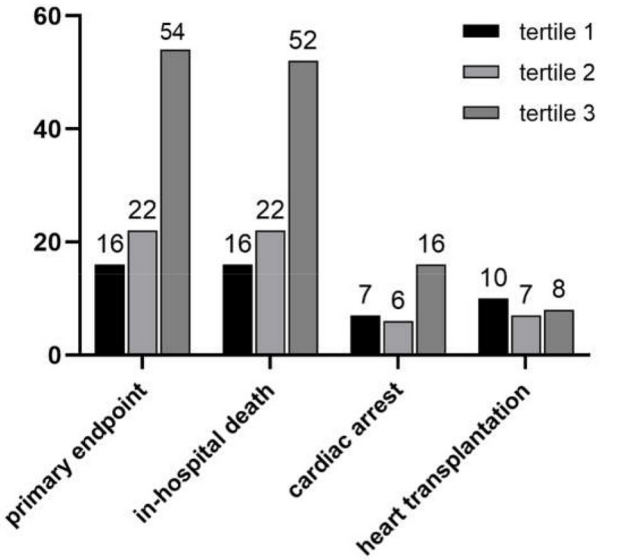


**FIGURE 1 |** Clinical outcomes based on big ET-1 tertiles.

outcomes increased to 0.704 (95% CI 0.644–0.764, $p < 0.001$) and 0.701 for in-hospital death (95% CI 0.640–0.762, $p < 0.001$). A total of 17% of patients were correctly reclassified (NRI = 0.593, 95% CI 0.38–0.81, $p < 0.001$; IDI = 0.0185, 95% CI 0.001–0.0036, $p = 0.035$) (**Supplementary Data 2**). However, none of the parameters were found to be associated with HTx.

## DISCUSSION

In the present study of Chinese patients in a single heart center ICU setting, we found that plasma big ET-1 was significantly related to the elevated risk of short-term adverse outcomes for ADHF patients who were firstly admitted to the ED. Such predictive power still existed after adjusting other clinical indicators. Moreover, baseline big ET-1 provided additional prognostic information to that yielded only by NT-proBNP. Therefore, big ET-1 as a new and practical biomarker might aid in the identification of ADHF patients at risk for the incidence of in-hospital death, cardiac arrest, or use of mechanical support devices.

Endothelin was first identified in 1988 (12), and the pathophysiological effects of the endothelin system have subsequently been investigated in various conditions including the cardiovascular system (13). ET-1 is recognized as the most potent and long-lasting vasoconstrictor. ET-1 can be synthesized and secreted in many cell types including cardiac myocytes, hepatocytes, kidney epithelial cells, WBCs, macrophages, and endothelial cells (14). Circulating ET-1 produced biological effect *via* binding to two specific receptors, namely, ETA and ETB (15). In heart failure settings, ETA is up-regulated, whereas ETB is down-regulated, causing negative inotropic and proarrhythmic effects. On the one hand, ET-1 stimulates cardiac remodeling by inducing inflammation and renin–angiotensin–aldosterone system. On the other hand, ET-1 also promotes the formation of norepinephrine with vasopressin (13).

A growing number of evidences suggest that elevated plasma big ET-1 level is a significantly independent predictor for CAD (8, 16), cardiomyopathy (17, 18), AF (19), and PAH (20). Several studies aimed at exploring the clinical effect of the endothelin system in heart failure. In CHF, cumulative results have demonstrated that ET system activation is linked to CHF presence, progression, and increased morbidity (21–23). Masson et al. measured baseline plasma big ET-1 levels of 2,359 stable and symptomatic HF patients and found that the circulating concentration of big ET-1 was an independent predictor of long-term all-cause mortality, but its prognostic value was weaker than BNP (24). Perez et al. reported the close associations between continuously measured ET-1 and both in-hospital and long-term outcomes in AHF patients (25). However, existing studies did not clarify the predictive power of plasma big ET-1, as the precursor of ET-1 with a more stable and accurate measurement, for short-term adverse events in critically-ill ADHF patients. In our study, we enrolled 746 consecutive ADHF patients admitted to the ICU and calculated that the AUC for baseline big ET-1 in predicting adverse in-hospital events was 0.66. Interestingly, when bringing big ET-1 and NT-proBNP into multivariable analysis, big ET-1 instead of NT-proBNP was significantly related to short-term outcomes. Besides, through NRI approach, our result indicated that baseline big ET-1 owned similar stratification capacity with NT-proBNP.

Moreover, our study suggested that arterial pH, lactic acid, TBIL, Scr, SUA, and presence of AF and NT-proBNP were positively correlated with plasma big ET-1 level. Conversely, SBP, serum sodium, Hb, albumin, and eGFR were negatively correlated. These findings revealed that the strong endothelin system activation reflected not only cardiac function but also renal and liver functions and personal nutritional status. The important biological functions of this comprehensive indicator in multiple organs were consistent with previous works (13, 24, 26, 27).

**TABLE 3 |** Predictor of primary endpoint in uni- and multivariate logistic regression.

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Big ET-1 | | <0.001 | | 0.001 |
| Tertile 2 | 1.399 (0.716–2.732) | 0.326 | 0.953 (0.314–2.986) | 0.932 |
| Tertile 3 | 4.157 (2.305–7.497) | <0.001 | 3.681 (1.410–9.606) | 0.008 |
| Age (years) | 0.990 (0.978–1.003) | 0.142 | | |
| Gender | 0.939 (0.575–1.532) | 0.801 | | |
| Congestion (%) | 0.380 (0.179–0.809) | 0.012 | | |
| Etiology | | 0.191 | | |
| BMI ($kg/m^2$) | 0.972 (0.922–1.024) | 0.288 | | |
| SBP (mmHg) | 0.983 (0.972–0.994) | 0.002 | | |
| DBP (mmHg) | 0.964 (0.948–0.981) | <0.001 | | |
| Temperature (°C) | 0.962 (0.883–1.049) | 0.381 | | |
| HR (bpm) | 1.012 (1.001–1.024) | 0.036 | | |
| Smoking (%) | 1.537 (0.94–2.400) | 0.059 | | |
| Drinking (%) | 0.995 (0.638–1.549) | 0.981 | | |
| DM (%) | 0.683 (0.405–1.154) | 0.154 | | |
| Arterial pH | 0.301 (0.067–1.357) | 0.118 | | |
| $PaO_2$ (mmHg) | 1.005 (0.996–1.013) | 0.276 | | |
| Lactic acid (mmol/L) | 1.636 (1.293–2.071) | <0.001 | | |
| Serum sodium (mmol/L) | 0.993 (0.978–1.008) | 0.371 | | |
| Serum potassium (mmol/L) | 0.996 (0.943–1.051) | 0.881 | | |
| WBC ($\times 10^9$/L) | 1.138 (1.069–1.212) | <0.001 | 1.297 (1.186–1.420) | <0.001 |
| Hb (g/L) | 0.995 (0.987–1.004) | 0.287 | | |
| HCT | 0.210 (0.001–4.514) | 0.319 | | |
| Albumin (g/L) | 0.961 (0.931–0.997) | 0.031 | | |
| TBIL (μmol/L) | 1.018 (1.009–1.027) | <0.001 | | |
| SUA (μmol/L) | 1.003 (1.002–1.004) | <0.001 | | |
| Scr (μmol/L) | 1.009 (1.006–1.013) | <0.001 | | |
| hs-TNI (μg/L) | 1.006 (0.980–1.033) | 0.637 | | |
| Lg eGFR | 0.287 (0.108–0.766) | 0.013 | | |
| Lg NT-proBNP | 3.079 (1.706–5.557) | <0.001 | | |
| LVEF (%) | 1.008 (0.991–1.024) | 0.359 | | |
| PASP >30 mmHg | 1.276 (0.791–2.057) | 0.317 | | |
| AF | 0.898 (0.561–1.438) | 0.655 | | |
| BBB | 0.742 (0.424–1.298) | 0.296 | | |

Although big ET-1 showed a satisfactory predictive power for the composite endpoint, it cannot accurately predict HTxs. The candidacy for HTx was assessed carefully in Fuwai Hospital. Elderly and frail patients with ADHF who failed optimal medical management and mechanical circulatory support often suffered from malnutrition, immune dysfunction, and multiple organ failure. They were obviously unsuitable for operations. It was understandable that the baseline big ET-1 level was unparallel to the consideration of HTx. Secondly, the selection for HTx was associated with economic conditions, social support, and psychological condition.

Endothelin receptor antagonists (ERAs) have been one of the hot focuses in cardiovascular diseases especially in PAH. Disappointedly, ERAs were found to be less satisfactory as a therapy for HF. The randomized intravenous Tezosentan study failed to show a significant improvement in composite primary endpoint in ADHF with acute coronary syndrome patients, but symptomatic hypotension was more frequent in the treatment group (28). Another randomized double-blind trial demonstrated that Bosentan did not improve clinical long-term outcomes in severe CHF patients but caused early and important fluid retention (29). Big ET-1 assessment may identify a subgroup of ADHF patients who benefit from treatment targeting the endothelin system. More solid evidence is needed in ERAs treating ADHF with high plasma big ET-1 level.

The following were several limitations in the present study. First, our database consisted of a cohort of patients from a single cardiovascular hospital, and the study population included only Chinese patients. The participants evaluated were limited to patients admitted only to the ICU, and ADHF patients who were then admitted to other wards were not enrolled.

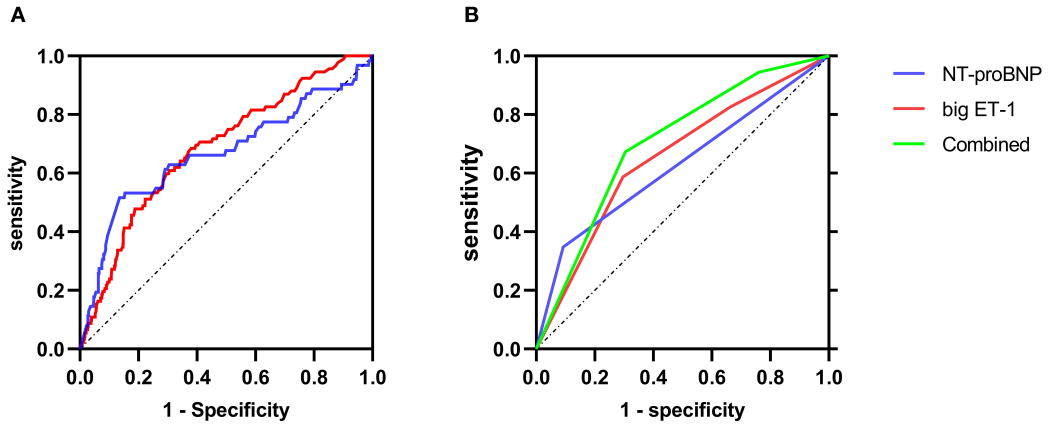


**FIGURE 2 |** ROC curves of primary endpoint predicted by NT-proBNP and big ET-1. **(A)** The ROC curves when big ET-1 and NT-proBNP were analyzed as continuous variables. **(B)** The ROC curves when big ET-1and NT-proBNP were analyzed as categorical variables, respectively, and the ROC curve for the combination of big ET-1 and NT-proBNP.

The results should be carefully interpreted when applied to a larger population. Second, the primary endpoint was in-hospital death or cardiac arrest or clinical application of mechanical support devices. Due to the lack of follow-ups after discharge, the predictive ability of baseline plasma big ET-1 for post-charge prognosis was still unknown. Third, the individual clinical data were collected at admission without taking acute-phase managements into account, such as the widely used inotropic or diuretic drugs for ADHF, which might influence admission laboratory test results. Considering the incompleteness and availability of past medical history in practical ED settings, we lacked information on baseline HF treatments, which might interfere with the big ET-1 prognostic power.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

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

## AUTHOR CONTRIBUTIONS

RM collected the clinical data, did the analysis, and drafted the manuscript. Y-mY and JZ helped design the study, collect the clinical data, and also revised this manuscript. L-tY and H-qT participated in designing and guiding the study to assure it run as intended. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

We wish to thank all the patients who agreed to participate in this single-center study and all relevant investigators from Fuwai Hospital for their help in providing clinical data.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.629268/full#supplementary-material

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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.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 18 March 2021
doi: 10.3389/fcvm.2021.589267

# The Effects of Tai Chi Exercise Among Adults With Chronic Heart Failure: An Overview of Systematic Review and Meta-Analysis

*Jinke Huang[1], Xiaohui Qin[2], Min Shen[3], Yanjuan Xu[1] and Yong Huang[4]**

[1] The Second Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou, China, [2] Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, [3] Department of Neurology, Zhejiang Provincial Hospital of Chinese Medicine, Hangzhou, China, [4] School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China

**Background:** Tai chi (TC) is a popular form of exercise among adults with chronic heart failure (CHF), yet services are greatly underutilized. The aim of the current study was to identify and summarize the existing evidence and to systematically determine the clinical effectiveness of Tai Chi in the management of CHF using a systematic overview.

**Methods:** Both English and Chinese databases were searched for systematic reviews (SRs)/meta-analyses (MAs) on TC for CHF from their inception to June 2020. The methodological quality, reporting quality, and risk of bias of SRs/MAs were assessed using Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and Risk of Bias in Systematic reviews (ROBIS), respectively. The evidence quality of outcome measures was assessed by the Grades of Recommendations, Assessment, Development and Evaluation (GRADE).

**Results:** Six SRs/MAs using a quantitative synthesis to assess various outcomes of TC in CHF were included in this overview. The methodological quality, reporting quality and risk of bias of the SRs/MAs and the evidence quality of the outcome measures are generally unsatisfactory. The limitations of the past SRs/MAs included the lack of either the protocol or registration, the list of excluded studies, and the computational details of meta-analysis were inadequately reported. The critical problems were that qualitative data synthesis relied on trials with small sample sizes and critical low quality.

**Conclusions:** TC may be a promising complementary treatment for CHF. However, further rigorous and comprehensive SRs/MAs and RCTs are required to provide robust evidence for definitive conclusions.

**Keywords: Tai Chi, heart failure, overview, AMSTAR-2, PRISMA, GRADE, ROBIS**

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***Edited by:***
*Filippo M. Sarullo, Ospedale Buccheri la Ferla Fatebenefratelli, Italy*

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*Kristen M. Tecson, Baylor Scott & White Research Institute (BSWRI), United States*

***Correspondence:**
*Yong Huang*
*nanfanglihuang@163.com*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *14 August 2020*
***Accepted:*** *26 February 2021*
***Published:*** *18 March 2021*

***Citation:***
*Huang J, Qin X, Shen M, Xu Y and Huang Y (2021) The Effects of Tai Chi Exercise Among Adults With Chronic Heart Failure: An Overview of Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:589267. doi: 10.3389/fcvm.2021.589267*

## INTRODUCTION

Heart failure (HF) is a serious clinical syndrome caused by a variety of structural and functional cardiac disorders that result in the inability of the heart to meet the body's needs (1). At least 26 million people suffer from HF worldwide, and the prevalence is increasing owing to an aging population (2). Moreover, HF imposes a significant economic burden, which is estimated

at $108 billion per annum (3). Due to its high morbidity and mortality, HF has become a public health problem that seriously affects patients' health (2). Dyspnea and fatigue are two of the most debilitating symptoms in patients with chronic heart failure (CHF) (4); these individuals frequently experience low exercise tolerance, poor quality of life (QoL), and recurrent hospitalizations and are at greater risk for morbidity and mortality (5, 6).

Exercise-based cardiac rehabilitation is an effective means to improve the QoL of patients with CHF with improved exercise tolerance and fewer CHF-related hospitalizations reported (6, 7). In addition, cardiac rehabilitation in CHF patients helps prevent social isolation (5). Moreover, cardiac rehabilitation (with exercise training at its core) has become an important recommendation in clinical guidelines (8). As a low-intensity, low-impact physical activity that originated from China, Tai Chi (TC) is suitable for older adults to perform, including those with poor exercise tolerance or chronic health conditions (9). It is believed that TC may be a promising adjunct to exercise-based cardiac rehabilitation in adults with CHF (10).

A literature search yielded several published systematic reviews (SRs)/meta-analyses (MAs), and the results revealed that the application of TC in the management of CHF has already been addressed. Although SRs/MAs are important tools to guide evidence-based clinical practice, their quality has been criticized in multiple medical fields (11, 12). An overview of SRs/MAs is a relatively new method to synthesize the outcomes of multiple SRs/MAs, appraise their quality and to attempt resolve any discordant outcomes (13). The aim of this study was to assess the scientific quality of past SRs/MAs regarding the application of TC in the management of SRs/MAs using a systematic overview.

# METHODS

The current study adheres to the guidelines for systematic reviews according to the Cochrane Handbook (14), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15). The literature search, literature selection, data extraction, and quality evaluation were done by both two reviewers independently and any inconsistencies were resolved through consensus or by consulting an experienced third reviewer.

## Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) study design: SRs/Mas based on random control trails (RCTs) in which the participants were patients with CHF and were diagnosed according to any internationally recognized clinical guidelines; (b) intervention: TC combined with conventional medication (CM) vs. CM alone; (c) outcomes: 6-min walk distance (6MWD), QoL (applying the Minnesota Living with Heart Failure Questionnaire, MLHF), serum B-type natriuretic peptide or N-terminal pro brain natriuretic peptide (BNP or NT pro-BNP), left ventricular ejection fraction (LVEF), peak oxygen uptake (peak $VO_2$), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate(HR). Non-RCT SRs/MAs, repeated publications, review comments, conference abstracts, editorials, and guidelines were excluded.

## Search Strategy

We searched PubMed, EMBASE, the Cochrane Database of Systematic Reviews, Web of Science, China National Knowledge Infrastructure, Sino-Med, Chongqing VIP, and Wanfang Data databases from inception to June 2020. We used the following search strategy: (heart failure OR cardiac failure OR decompensation heart OR myocardial failure) AND (Tai Chi OR Tai Ji) AND (systematic review OR meta-analysis) as subject word and random word for all fields.

## Eligibility Assessment and Data Extraction

The titles and abstracts of all articles were screened firstly, and potentially eligible articles were retrieved for perusal in full text. A standardized form was designed to extract the following information from each eligible review: first author, publication year, country, number of RCTs enrolled, quality assessment tool for RCTs enrolled, interventions in treatment and control groups, outcome measures, data synthesis methods, and main conclusions.

## Review Quality Assessment

Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) (16) was used to assess the methodological quality of each SR/MA based on the following domains: (a) preparation for review, (b) search for and selection of primary studies, (c) data coding and reporting, (d) data synthesis. It consists of 16 items, and seven of them were critical domains. Each item was evaluated using three evaluation options, yes (indicating high quality), partial yes (partial quality) or no (poor quality).

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (15) was applied to assess report quality of each SR/MA based on the following domains: (a) title, (b) abstract, (c) introduction, (d) methods, (e) results, (f) discussion, (g) funding. It consists of 27 items focusing on the reporting of methods and results in a meta-analysis.

Risk of Bias in Systematic reviews (ROBIS) (17) was used to assess the risk of bias of each SR/MA based on the following domains: (a) Phase 1 assessing relevance, (b) Phase 2 covers 4 domains through which bias may be introduced into an SR: Domain 1 "study eligibility criteria," Domain 2 "identification and selection of studies," Domain 3 "data collection and study appraisal" and Domain 4 "synthesis and findings," (c) Phase 3 assesses the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the phase 2 domains.

**Abbreviations:** TC, Tai chi; CHF, chronic heart failure; SR, systematic review; MA, Meta-analysis; AMSTAR-2, Assessing the Methodological Quality of Systematic Reviews 2; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROBIS, Risk of Bias in Systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, random control trails; CM, conventional medication; 6MWD, 6-min walk distance; Qol, quality of life; MLHF, Minnesota Living with Heart Failure Questionnaire; BNP, B-type natriuretic peptide; NT pro-BNP, N-terminal pro brain natriuretic peptide; LVEF, left ventricular ejection fraction; peak $VO_2$, peak oxygen uptake; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

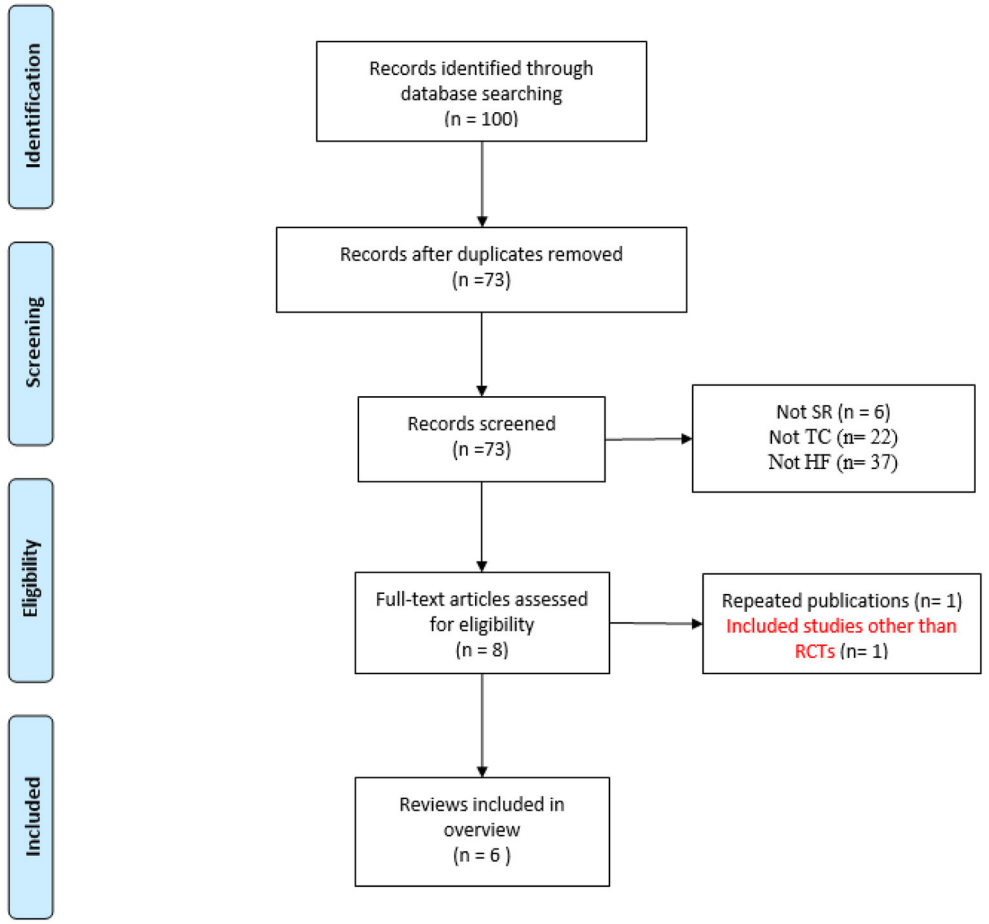


**FIGURE 1 |** Flow diagram of the literature selection process.

The Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) (18) was used to assess the evidence quality of each outcome measure enrolled in these SRs/MAs based on the following domains: (a) risk of bias (that is study limitations), (b) inconsistencies, (c) indirectness, (d) inaccuracy, (d) publication bias.

## Data Synthesis and Presentation

A narrative synthesis was used in this overview. The characteristics and results of each SR/MA as well as the results of AMSTAR 2, PRISMA and ROBIS were summarized by tabulation and figures. The GRADE evidence profile and summary of findings table were generated by using the GRADE pro GDT online software.

# RESULTS

## Results on Literature Search and Selection

A total of 100 records were identified through electronic search. After duplicates were removed, the titles and abstracts of 92 records were screened. Afterwards, 8 manuscripts were included for full-text reading, of which 2 studies were excluded because 1 record was a repeated publication and the other included studies that were not strictly RCTs. Finally, 6 SRs/MAs (19–24) were included in the current overview. The flowchart of the study selection is shown in **Figure 1**.

## Description of Included Reviews

The 6 included SRs/MAs were published between 2013 and 2020, including 5 articles from China and 1 from America. Four articles were published in English and the remaining 2 were in Chinese. All reviews included only RCTs and conducted a meta-analysis. The number of RCTs included in each MA ranged from 4 to 11, and individual study sample sizes ranged from 229 to 904. The quality assessment scales of the original studies varied: 1 used Downs and Black Quality Index checklist, 4 used Cochrane risk of bias criteria, 1 adopted the modified Jadad scale. The intervention measures were TC plus CM in the treatment group, and CM alone in the control group. The detailed study characteristics are presented in **Table 1**.

**TABLE 1 |** Review characteristics.

| Author, year (Country) | Trials (subjects) | Treatment intervention | Control intervention | Quality assessment | Main results |
|---|---|---|---|---|---|
| Taylor-Piliae and Finley (19) (American) | 6 (229) | TC + CM | CM | Downs and Black Quality Index checklist | Among adults with CHF, TC was effective in improving exercise capacity and QoL, with less depression and B-type natriuretic peptide levels observed, when compared with controls. TC is a safe form of exercise and can be easily integrated into existing cardiac rehabilitation programs. Further research is needed with rigorous study designs and larger samples before widespread recommendations can be made. |
| Li et al. (20) (China) | 7 (4,46) | TC + CM | CM | Cochrane criteria | TC can significantly improve the heart function and quality of life for the patients with heart failure, and this treatment could be applied to the rehabilitation process of patients with stable heart failure. |
| Wei et al. (21) (China) | 10 (689) | TC + CM | CM | Cochrane criteria | The current evidence shows that TC is feasible for patients with heart failure as it has positive effects on life quality, physiological functions. Due to the limited quality and quantity of included studies, the above conclusion should be validated by more high quality studies. |
| Ren et al. (22) (China) | 11 (656) | TC + CM | CM | Cochrane criteria | TC could improve 6MWD, quality of life and LVEF in patients with HF and may reduce BNP and HR. However, there is a lack of evidence to support TC altering other important long-term clinical outcomes so far. Further larger and more sustainable RCTs are urgently needed to investigate the effects of TC. |
| Gu et al. (23) (China) | 10 (904) | TC + CM | CM | Cochrane criteria | Despite heterogeneity and risk of bias, this meta-analysis further confirms that TC may be an effective cardiac rehabilitation method for patients with chronic heart failure. Larger, well-designed RCTs are needed to exclude the risk of bias. |
| Pan et al. (24) (China) | 4 (242) | TC + CM | CM | Jadad | TC may improve quality of life in patients with CHF and could be considered for inclusion in cardiac rehabilitation programs. However, there is currently a lack of evidence to support TC altering other important clinical outcomes. Further larger RCTs are urgently needed to investigate the effects of TC. |

## Results on Review Quality Assessment

### Methodological Quality

The results of AMSTAR-2 assessment are presented in **Table 2**. Since all SRs/MAs had more than one critical weakness (items 2, 4, 7, 9, 11, 13, and 15), their qualities were rated critically low. The key factors affecting the quality of the SRs/MAs on the AMSTAR-2 were the following: none of the SRs explicitly stated that the review methods were established before the conduct of the review and justified significant deviations from the protocol; none of the SRs provided a list of excluded studies and justified the exclusions.

### Report Quality

The results of PRISMA checklist assessment are presented in **Table 3**. The results showed that the reporting was relatively complete, the section of title, abstract, introduction, and discussion were all well-reported (100%), but there were still some reporting flaws in other section. In section of methods, Q5 (topic of protocol and registration), and Q15 (risk of bias across studies) were reported inadequately (<50%); in section of results, Q22 (risk of bias across studies), Q23 (additional analyses) were reported inadequately (66.7%); in section of funding, Q27 (funding) was reported inadequately (33.3%). More details are summarized in **Table 3**.

### Risk of Bias

For ROBIS, all SRs/MAs were at low risk in Phase 1 (assessing relevance), Domain 1 (study eligibility criteria) and Domain 3 (collection and study appraisal). All SRs/MAs were at high risk in Domain 2 (study eligibility criteria). Five SRs/MAs were rated low risk in Domain 4 (synthesis and findings), and 6 low risk in Phase 3 (risk of bias in the review). More details are presented in **Table 4**.

### Evidence Quality

The results of GRADE assessment are presented in **Table 5**. The 6 SRs/MAs included 29 outcomes related to the effectiveness of TC for CHF. Among these outcome indicators, the quality of evidence was high in 1, moderate in 4, low in 15 and very low in 9. Risk of bias ($n = 19$) was the most common of the downgrading factors, followed by inconsistency ($n = 17$), imprecision ($n = 16$), publication bias ($n = 9$) and indirectness ($n = 0$).

### Outcomes and Efficacy Evaluation

A narrative synthesis was conducted for exercise capacity, QoL, BNP, NT pro-BNP, LVEF, peak $VO_2$, SBP, DBP, and HR, as at least 2 studies assessed these outcomes. When TC was compared with controls, a significant effect for better QoL in all reviews (19–24), a significant effect for better exercise capacity in 5 reviews (19–23), a significant effect for lower BNP or NT pro-BNP in 5 reviews

**TABLE 2 |** Result of the AMSTAR-2 assessments.

| Author, year | AMSTAR-2 | | | | | | | | | | | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 | |
| Taylor-Piliae and Finley (19) | Y | PY | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | N | CL |
| Li et al. (20) | Y | PY | Y | PY | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | N | CL |
| Wei et al. (21) | Y | PY | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | N | N | CL |
| Ren et al. (22) | Y | PY | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | CL |
| Gu et al. (23) | Y | PY | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | CL |
| Pan et al. (24) | Y | PY | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | N | CL |

*Y, Yes; PY, partial Yes; N, No; CL, Critically low; L, Low; H, High.*

**TABLE 3 |** Result of the PRISMA assessments.

| Section/Topic | Items | Taylor-Piliae and Finley (19) | Li et al. (20) | Wei et al. (21) | Ren et al. (22) | Gu et al. (23) | Pan et sl. (24) | Compliance (%) |
|---|---|---|---|---|---|---|---|---|
| Title | Q1. Title | Y | Y | Y | Y | Y | Y | 100% |
| Abstract | Q2. Structured summary | Y | Y | Y | Y | Y | Y | 100% |
| Introduction | Q3. Rationale | Y | Y | Y | Y | Y | Y | 100% |
| | Q4. Objectives | Y | Y | Y | Y | Y | Y | 100% |
| Methods | Q5. Protocol and registration | N | N | N | N | N | N | 0% |
| | Q6. Eligibility criteria | Y | Y | Y | Y | Y | Y | 100% |
| | Q7. Information sources | Y | Y | Y | Y | Y | Y | 100% |
| | Q8. Search | Y | PY | Y | Y | Y | Y | 83.3% |
| | Q9. Study selection | Y | Y | Y | Y | Y | Y | 100% |
| | Q10. Data collection process | Y | Y | Y | Y | Y | Y | 100% |
| | Q11. Data items | Y | Y | Y | Y | Y | Y | 100% |
| | Q12. Risk of bias in individual studies | Y | Y | Y | Y | Y | Y | 100% |
| | Q13. Summary measures | Y | Y | Y | Y | Y | Y | 100% |
| | Q14. Synthesis of results | Y | Y | Y | Y | Y | Y | 100% |
| | Q15. Risk of bias across studies | N | Y | N | Y | Y | Y | 33.3% |
| | Q16. Additional analyses | N | Y | Y | Y | Y | Y | 83.3% |
| Results | Q17. Study selection | Y | Y | Y | Y | Y | Y | 100% |
| | Q18. Study characteristics | Y | Y | Y | Y | Y | Y | 100% |
| | Q19. Risk of bias within studies | Y | Y | Y | Y | Y | Y | 100% |
| | Q20. Results of individual studies | Y | Y | Y | Y | Y | Y | 100% |
| | Q21. Synthesis of results | Y | Y | Y | Y | Y | Y | 100% |
| | Q22. Risk of bias across studies | N | Y | N | Y | Y | Y | 66.7% |
| | Q23. Additional analysis | N | Y | Y | Y | Y | Y | 66.7% |
| Discussion | Q24. Summary of evidence | Y | Y | Y | Y | Y | Y | 100% |
| | Q25. Limitations | Y | Y | Y | Y | Y | Y | 100% |
| | Q26. Conclusions | Y | Y | Y | Y | Y | Y | 100% |
| Funding | Q27. Funding | N | N | N | Y | Y | N | 33.3% |

(19–23), a significant effect for better LVEF in 4 reviews (20–23), a significant effect for better HR in 1 review (22). However, no significant difference in peak $VO_2$, SBP, and DBP between the TC and controls in 2 reviews (21, 24). More details are presented in **Table 5**.

# DISCUSSION

A systematic overview of SR/MA is a comprehensive research approach for reassessing a comprehensive collection of SRs/MAs related to the same disease or health problem (25). An overview enables a more comprehensive integration of evidence, thus providing clinicians with higher quality evidence (25). Although there are an increasing number of publications of SR/MA on TC for CHF, the quality of those publications taken together has not been assessed until now. Therefore, an overview of this issue is needed. A literature search revealed that no overview of TC for CHF has been published to date.

## Summary of Main Findings

As a form of low-intensity physical activity originating in China, TC has gained popularity in Western countries as an

**TABLE 4 |** Result of the ROBIS assessments.

| Reviews | Phase 1 | Phase 2 | | | | Phase 3 |
|---|---|---|---|---|---|---|
| | Assessing relevance | Domain 1: study eligibility criteria | Domain 2: identification and selection of studies | Domain 3: collection and study appraisal | Domain 4: synthesis and findings | Risk of bias in the review |
| Taylor-Piliae and Finley (19) | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Li et al. (20) | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Wei et al. (21) | ☺ | ☺ | ☹ | ☺ | ☹ | ☺ |
| Ren et al. (22) | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Gu et al. (23) | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Pan et al. (24) | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |

☺, *low risk;* ☹, *high risk.*

alternative form of exercise in recent decades. Publications of SRs/MAs on TC for CHF is increasing annually. The included SRs/MAs on TC for CHF in this current overview were published from 2013 to 2020, and 83.3% of them were published after 2017, possibly indicating that TC has begun to attract attention as an alternative form of exercise for CHF. This overview included 6 SRs/MAs, all of which reached positive conclusions of TC for CHF; however, the authors did not want to draw firm conclusions due to the small size of the included RCTs or their low quality. Moreover, according to the evaluation results of AMSTAR-2, PRISMA, ROBIS, and GRADE, the quality of the SRs/MAs and the evidence quality of the outcome measures are generally unsatisfactory, indicating that the results of included SRs/MAs may be very different from the real situation. Therefore, based on the above findings of past SRs/MAs, we cannot draw a firm conclusion on TC for CHF, but results suggest that TC is a promising complementary treatment for CHF.

## Implications for Practice and Research

Dyspnea and fatigue limit exercise capacity in CHF patients, leading to progressive deconditioning and exercise intolerance, resulting in a vicious cycle of worsening dyspnea and fatigue (24). Furthermore, various physical and emotional symptoms that CHF patients experience could limit their physical and social activities and result in poor QoL. Therefore, Cardiac rehabilitation (with exercise training at its core) is highly desirable for patients with CHF (8). TC is a promising adjunct to exercise-based cardiac rehabilitation for adults with CHF (10). As a mind-body integrated exercise, TC including mind peace, breath flow, body movement, could activate the natural self-healing ability, evoke the balanced release of endogenous neurohormones and various natural health recovery mechanisms, thereby improving cardiac collateral circulation and increasing activity tolerance (26). Moreover, as a moderate intensity exercise, TC could improve the degree of parasympathetic nerve, inhibit sympathetic nerve activity, increase the coronary collateral circulation, cardiac stroke volume, and cardiac output, thereby achieving increased LVEF (22). The mechanism of TC practice may be to maintain the balance of "Yin" and "Yang," which was a contradiction of unity. When CHF patients perform TC, they should pay attention to the regulation of body shape, spirit and significance, and qi, so that the body enters a relaxed state; this could be achieved by adjusting the balance of autonomic nerves and reduce the sympathetic nervous tension, thereby adjusting breathing, slowing HR and improving the strength and body reactivity (22). Therefore, TC may inhibit adrenergic nervous system, decrease sympathetic nervous system, and slow HR to improve CHF.

Assessment of various aspects of the included SRs/MAs using the AMSTAR-2, PRISMA, and ROBIS identified areas for common improvement. For example, they all ignored the need to register the protocol, provided a list of excluded studies. Though the quality was unsatisfactory, meanwhile it also means that there was much room to address the quality during the SRs/MAs process. For evidence quality with GRADE, we found that risk of bias within the original RCTs was the most common of the downgrading factors in the included SRs/MAs, all of the outcome indicators were demoted because of the limitations caused by bias in random, distributive hiding or blind. Therefore, the assessment results may help guide future high-quality studies.

## Strength and Limitations

To the best of our knowledge, this current study is the first systematic overview to explore the evidence of TC for CHF. Based on the current results, the quality of the SRs/MAs and evidence quality of outcome indicators are presented cleanly, which may have certain reference value for the clinical practice and research of TC in the treatment of CHF. However, due to the generally low quality of SRs/MAs and outcome indicators, firm conclusions were impossible to draw, caution is warranted when recommending Tai Chi as a complementary treatment for CHF.

**TABLE 5 |** Results of evidence quality.

| Review | Outcomes | Certainty assessment | | | | | | | No. of patients | | Relative effect (95% CI) | *P*-value | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of trails | Design | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Experimental | Control | | | |
| Taylor-Piliae and Finley (19) | 6-MWT | 5 | Rct | No | No | No | Serious[c] | No | 135 | 134 | SMD 0.353 (0.041, 0.664) | 0.026 | ⊕⊕⊕⊕○ Moderate |
| | QoL | 5 | Rct | No | No | No | Serious[c] | No | 135 | 134 | SMD −0.671 (−0.864, −0.370) | 0.000 | ⊕⊕⊕⊕○ Moderate |
| | BNP | 4 | Rct | No | No | No | Serious[c] | No | 103 | 103 | SMD −0.333 (−0.604, −0.062) | 0.016 | ⊕⊕⊕⊕○ Moderate |
| Li et al. (20) | LVEF | 3 | Rct | No | Serious[b] | No | Serious[c] | No | 128 | 108 | MD 8.38 (6.98, 9.78) | <0.0001 | ⊕⊕⊕○○ Low |
| | 6-MWT | 5 | Rct | No | No | No | No | No | 161 | 151 | SMD 0.85 (0.61, 1.08) | <0.0001 | ⊕⊕⊕⊕⊕ High |
| | QoL | 4 | Rct | No | Serious[b] | No | Serious[c] | No | 131 | 122 | SMD −1.10 (−1.91, −0.29) | 0.008 | ⊕⊕⊕○○ Low |
| | NT-proBNP | 2 | Rct | No | No | No | Serious[c] | Serious[d] | 45 | 45 | SMD −12.14 (−23.78, −0.50) | 0.04 | ⊕⊕⊕○○ Low |
| Wei et al. (21) | QoL | 7 | Rct | Serious[a] | Serious[b] | No | No | No | 279 | 270 | MD −9.37 (−13.09, −5.65) | <0.0001 | ⊕⊕⊕○○ Low |
| | 6-MWT | 7 | Rct | Serious[a] | Serious[b] | No | No | No | 277 | 267 | MD 40.37 (9.48, 71.27) | 0.01 | ⊕⊕⊕○○ Low |
| | LVEF | 5 | Rct | Serious[a] | Serious[b] | No | No | No | 212 | 202 | MD 7.89 (3.01, 12.77) | 0.002 | ⊕⊕⊕○○ Low |
| | BNP | 5 | Rct | Serious[a] | No | No | No | No | 162 | 162 | MD −10.75 (−13.20, −8.30) | <0.0001 | ⊕⊕⊕⊕○ Moderate |
| | Peak $VO_2$ | 3 | Rct | Serious[a] | No | No | Serious[c] | Serious[d] | 73 | 73 | MD 0.29 (−1.23, 1.81) | 0.71 | ⊕⊕○○○ Very low |
| | SBP | 4 | Rct | Serious[a] | No | No | Serious[c] | Serious[d] | 80 | 81 | MD −2.81 (−8.52, 2.90) | 0.33 | ⊕⊕○○○ Very low |
| | DBP | 3 | Rct | Serious[a] | No | No | Serious[c] | Serious[d] | 70 | 71 | MD 0.37 (−3.73, 4.48) | 0.86 | ⊕⊕○○○ Very low |
| Ren et al. (22) | 6-MWT | 7 | Rct | Serious[a] | Serious[b] | No | No | No | 241 | 233 | WMD 65.29 (−32.55, 98.04) | <0.001 | ⊕⊕⊕○○ Low |
| | QoL | 7 | Rct | Serious[a] | Serious[b] | No | No | No | 236 | 230 | WMD −11.52 (−16.5, −6.98) | <0.001 | ⊕⊕⊕○○ Low |
| | BNP | 5 | Rct | Serious[a] | Serious[b] | No | No | No | 133 | 133 | SMD −1.08 (−1.91, −0.26) | <0.001 | ⊕⊕⊕○○ Low |
| | LVEF | 5 | Rct | Serious[a] | Serious[b] | No | No | No | 200 | 180 | WMD 9.94% (6.95, 12.93) | <0.001 | ⊕⊕⊕○○ Low |
| | HR | 2 | Rct | Serious[a] | No | No | Serious[c] | Serious[d] | 38 | 38 | WMD −2.52 (−3.49, −1.55) | <0.001 | ⊕⊕○○○ Very low |

*(Continued)*

**TABLE 5 |** Continued

| Review | Outcomes | Certainty assessment | | | | | | | No. of patients | | Relative effect (95% CI) | *P*-value | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of trails | Design | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Experimental | Control | | | |
| Gu et al. (23) | 6-MWT | 10 | Rct | Serious[a] | Serious[b] | No | No | No | 344 | 379 | WMD 51.01 (30.49, 71.53) | <0.001 | ⊕⊕⊕○○ Low |
| | QoL | 8 | Rct | Serious[a] | Serious[b] | No | No | No | 280 | 318 | WMD −10.37 (−14.43, −6.32) | <0.001 | ⊕⊕⊕○○ Low |
| | LVEF | 7 | Rct | Serious[a] | Serious[b] | No | No | No | 283 | 306 | WMD 7.72% (3.58, 11.89) | 0.003 | ⊕⊕⊕○○ Low |
| | BNP | 6 | Rct | Serious[a] | Serious[b] | No | No | No | 178 | 221 | SMD −1.01(−1.82, −0.19) | 0.02 | ⊕⊕⊕○○ Low |
| Pan et al. (24) | 6-MWT | 3 | Rct | Serious[a] | No | No | Serious[c] | No | 95 | 95 | MD 46.73 (−1.62, 95.09) | 0.06 | ⊕⊕⊕○○ Low |
| | QoL | 3 | Rct | No | Serious[b] | No | Serious[c] | No | 90 | 92 | WMD −14.54 (−23.45, −5.63) | 0.001 | ⊕○○○○ Very low |
| | BNP | 2 | Rct | No | Serious[b] | No | Serious[c] | Serious[d] | 45 | 45 | MD −61.16 (−179.27, −56.95) | 0.31 | ⊕⊕○○○ Very low |
| | SBP | 2 | Rct | Serious[a] | Serious[b] | No | Serious[c] | Serious[d] | 55 | 57 | MD −1.06 (−13.76, 11.63) | 0.87 | ⊕○○○○ Very low |
| | DBP | 2 | Rct | Serious[a] | Serious[b] | No | Serious[c] | Serious[d] | 55 | 57 | MD −0.08 (−3.88, 3.73) | 0.97 | ⊕○○○○ Very low |
| | Peak $VO_2$ | 2 | Rct | No | No | No | Serious[c] | Serious[d] | 65 | 65 | MD 0.19 (−0.74, 1.13) | 0.68 | ⊕○○○○ Very low |

*CI, Confidence interval; WMD, weighted mean difference; MD, mean difference; SMD, standardized mean difference.*

[a] *The experimental design had a large bias in random, distributive findings or was blind.*

[b] *The confidence interval overlap less, the heterogeneity test P was very small, and the* $I^2$ *was larger.*

[c] *The Confidence interval was not narrow enough, or the simple size is too small.*

[d] *Funnel graph asymmetry, or fewer studies were included and there may have been greater publication bias.*

## CONCLUSION

TC may be a promising complementary treatment for CHF. However, the quality of past SRs/MAs is limited, further rigorous, comprehensive SRs/MAs and RCTs that adhering to the guidelines are required to provide robust evidence for definitive conclusions.

## DATA AVAILABILITY STATEMENT

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

## AUTHOR CONTRIBUTIONS

JH planned and designed the study, and drafted the manuscript. MS and XQ screened potential studies and extracted data from the included studies. MS, XQ, and YX assessed the reviews. YH provided guidance on the overview methodology. All authors read, critically reviewed, and approved the final manuscript as submitted.

## ACKNOWLEDGMENTS

The authors thank all investigators and supporters involved in this study.

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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.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 06 April 2021
doi: 10.3389/fcvm.2021.658726

# Women With Diabetes Are at Increased Relative Risk of Heart Failure Compared to Men: Insights From UK Biobank

*Sucharitha Chadalavada[1,2‡], Magnus T. Jensen[1,3†], Nay Aung[1,2†], Jackie Cooper[1†], Karim Lekadir[4†], Patricia B. Munroe[1†] and Steffen E. Petersen[1,2*§]*

[1] William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, United Kingdom, [2] Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, London, United Kingdom, [3] Department of Cardiology, Copenhagen University Hospital Amager & Hvidovre, Hvidovre, Denmark, [4] Artificial Intelligence in Medicine Lab (BCN-AIM), Departament de Matemàtiques and Informàtica, Universitat de Barcelona, Barcelona, Spain

OPEN ACCESS

**Edited by:**
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***Correspondence:**
Steffen E. Petersen
s.e.petersen@qmul.ac.uk

†These authors have contributed equally to this work

‡First author

§Senior author

**Specialty section:**
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

**Received:** 26 January 2021
**Accepted:** 23 February 2021
**Published:** 06 April 2021

**Citation:**
Chadalavada S, Jensen MT, Aung N, Cooper J, Lekadir K, Munroe PB and Petersen SE (2021) Women With Diabetes Are at Increased Relative Risk of Heart Failure Compared to Men: Insights From UK Biobank. Front. Cardiovasc. Med. 8:658726. doi: 10.3389/fcvm.2021.658726

**Aims:** To investigate the effect of diabetes on mortality and incident heart failure (HF) according to sex, in the low risk population of UK Biobank. To evaluate potential contributing factors for any differences seen in HF end-point.

**Methods:** The entire UK Biobank study population were included. Participants that withdrew consent or were diagnosed with diabetes after enrolment were excluded from the study. Univariate and multivariate cox regression models were used to assess endpoints of mortality and incident HF, with median follow-up periods of 9 years and 8 years respectively.

**Results:** A total of 493,167 participants were included, hereof 22,685 with diabetes (4.6%). Two thousand four hundred fifty four died and 1,223 were diagnosed or admitted with HF during the follow up periods of 9 and 8 years respectively. Overall, the mortality and HF risk were almost doubled in those with diabetes compared to those without diabetes (hazard ratio (HR) of 1.9 for both mortality and heart failure) in the UK Biobank population. Women with diabetes (both types) experience a 22% increased risk of HF compared to men (HR of 2.2 (95% CI: 1.9–2.5) vs. 1.8 (1.7–2.0) respectively). Women with type 1 diabetes (T1DM) were associated with 88% increased risk of HF compared to men (HR 4.7 (3.6–6.2) vs. 2.5 (2.0–3.0) respectively), while the risk of HF for type 2 diabetes (T2DM) was 17% higher in women compared to men (2.0 (1.7–2.3) vs. 1.7 (1.6–1.9) respectively). The increased risk of HF in women was independent of confounding factors. The findings were similar in a model with all-cause mortality as a competing risk. This interaction between sex, diabetes and outcome of HF is much more prominent for T1DM ($p = 0.0001$) than T2DM ($p = 0.1$).

**Conclusion:** Women with diabetes, particularly those with T1DM, experience a greater increase in risk of heart failure compared to men with diabetes, which cannot be explained by the increased prevalence of cardiac risk factors in this cohort.

**Keywords: diabetes, heart failure, sex, prospective, UK biobank, epidemiology, cardiovascular, prognosis**

# INTRODUCTION

Globally, more than 500 million people have diabetes and its prevalence (6–7% in the UK) is expected to increase (1). The risk of all-cause mortality is doubled in individuals with diabetes compared to those without diabetes, with cardiovascular disease being the leading cause of death (2, 3). Approximately £3billion of the £10billion total cost of diabetes to the National Health Service (NHS) is associated with the cardiovascular complications of diabetes, and this figure is projected to increase to almost double in the next 20 years (4). Accelerated heart failure (HF) is a common manifestation of cardiovascular disease in people with diabetes and can occur independently of macrovascular coronary disease (5–7). In fact, non-ischaemic cardiomyopathy is the earliest and most common cardiovascular complication in people with diabetes (8).

Diabetic cardiomyopathy was first described in the 1970s (9) and is referred to as a process that affects cardiac structure and function independent of age and cardiovascular risk factors, or events which can lead to diastolic or systolic heart failure. The European Society of Cardiology has recently recognized this as a special subset of heart disease (10).

A consistent pattern has emerged revealing a prominent sex difference in the risk of developing HF from diabetes. In a recent meta-analysis of 12 million individuals, the risk of HF related to type 1 diabetes was more than 5-fold higher in women but only 3.5 times higher in men compared to individuals without diabetes. Similarly the risk of HF related to type 2 diabetes was 9% higher in women than in men (11). While the meta-analysis showed a consistent pattern, the data included were heterogenous from multiple studies with unharmonized data and therefore did not allow for further exploration of relevant contributing factors.

Using UK Biobank, a prospective population cohort study, and its large-scale detailed individual participant information, we investigated the association between presence of diabetes, sex, and risk of heart failure. We hypothesized that the increased relative risk of heart failure associated with diabetes in women compared to men would persist despite accounting for detailed individual level characteristics. We also investigate mortality as an endpoint but it not the primary focus of this study.

# METHODS

## Study Population

The UK Biobank was a prospective population study of half a million people aged 40–69 years when recruited between 2006 and 2010. The data collected, and summary of the characteristics can be viewed on the UK Biobank's website (www.biobank.ac.uk).

This study includes the entire UK Biobank cohort after excluding 30 participants who withdrew from the study before analysis of data (502,506). Participants diagnosed with Diabetes Mellitus (DM) after enrolment were also excluded from the study ($n$ = 9,339). The UK Biobank population was stratified as our exposure into non-diabetes, type 1 diabetes, and type 2 diabetes by the method previously suggested (12).

## Ethics

This study complies with the Declaration of Helsinki. The study was covered by the ethical approval for UK Biobank studies from the National Health Service National Research Ethics Service on June 17, 2011 (Ref 11/NW/0382) and extended on May 10, 2016 (Ref 16/NW/0274) with informed consent obtained from all participants.

## Study Design

The start of the study was recorded as the date of attending the first assessment for the UK Biobank study. Age of diabetes diagnosis was recorded from self-reported data and where missing supplemented using Hospital Episode Statistics (HES) data. If the diagnosis of diabetes was made after the participant attended the first assessment for the study, then these participants were excluded from the study. Time dependent co-variate analysis was considered to include participants that developed diabetes after enrollment. However, ultimately abandoned as this is reported to introduce serious bias when used with competing risk analysis (13). Additionally, the results did not differ when using diabetes as time-dependent or fixed variable, thus further supporting use of diabetes as a fixed variable.

The endpoints of death and heart failure were derived from HES data with dates recorded to provide censor dates. All-cause mortality and incident heart failure, as our outcomes, were derived in the whole UK Biobank population.

We extracted possible confounders for the effect of diabetes on the outcomes all-cause mortality and incident heart failure. Co-morbidities including hypertension, and hypercholesterolaemia were defined using a combination of self-reported data and supplemented with the medication history (see **Appendix A** for further details). Defining those with coronary artery disease included self-reported data, HES data and included hospital admissions with angina as well as any coronary event or intervention. Coronary disease is considered to be an important confounder in this study; therefore, a robust definition was made to have a broad capture of individuals with any clinically significant coronary disease in order to reduce any residual confounding.

Sex, ethnicity, smoking and alcohol were recorded from self-reported data fields. Smoking and alcohol status were categorized into never, previous and current use status. The use of diabetic oral medication or insulin use was derived from the self-reported medication use field.

Body Mass Index (BMI) recorded from calculated BMI based on their first assessment of height and weight. Participants' level of physical activity was calculated using frequency (number of days/week) and duration (minutes/d) of walking, moderate intensity, and vigorous-intensity exercise. A continuous value for the amount of physical activity, measured in metabolic equivalent minutes/week (METs), was calculated by weighting different types of activity (walking, moderate, or vigorous) by its energy requirements using values derived from the IPAQ study (International Physical Activity Questionnaire)(14). This was then further categorized according to the World Health Organization recommendation for physical activity (15) and were

**TABLE 1 |** Participants' characteristics.

| | Control | Participants with diabetes | *P*-value | Type 1 DM | | Type 2 DM | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Total, n | 470,482 | 22, 685 | | 2,626 | | 20,059 | | |
| **Demographics** | | | | | | | | |
| Age at enrolment (years), mean (sd) | 56 (8.1) | 60 (7.1) | <0.001 | 57 (8.2) | | 60 (6.9) | | <0.001 |
| Female sex, *n* (%) | 260,743 (55%) | 8,531 (38%) | <0.001 | 1,123 (43%) | | 7,408 (37%) | | <0.001 |
| Ethnicity, *n* (%) | | | <0.001 | | | | | <0.001 |
| Caucasian | 444,873 (94.5%) | 19,638 (87%) | | 2,395 (91.2%) | | 17,243 (85.9%) | | |
| Afro-Caribbean | 6,994 (1.5%) | 752 (3.3%) | | 72 (2.8%) | | 680 (3.4%) | | |
| South-Asian | 6,405 (1.4%) | 1,252 (5.5%) | | 74 (2.8%) | | 1,178 (5.9%) | | |
| Other | 12,210 (2.6%) | 1,043(4.2%) | | 85 (3.2%) | | 958 (4.8%) | | |
| **Lifestyle factors** | | | | | | | | |
| Smoking *n* (%) | | | <0.001 | | | | | <0.001 |
| Never | 258,631 (55%) | 10, 189 (45%) | | 1,325 (50.5%) | | 8,864 (44.2%) | | |
| Previous | 159,907 (34%) | 9,763 (43%) | | 940 (35.8%) | | 8,823 (44%) | | |
| Current | 49,462 (10.5%) | 2,506 (11%) | | 343 (13%) | | 2,163 (10.8%) | | |
| Unknown | 2,482 (0.5%) | 227 (1%) | | 18 (0.7%) | | 209 (1%) | | |
| Alcohol *n* (%) | | | <0.001 | | | | | 0.12 |
| Never | 19,586 (4.2%) | 2,031 (9%) | | 206 (7.8%) | | 1,825 (9.1%) | | |
| Previous | 15,780 (3.3%) | 1,712 (7.5%) | | 202 (7.7%) | | 1,510 (7.5%) | | |
| Current | 433,683 (92.2%) | 18,823 (83%) | | 2,208 (84.1%) | | 16,615 (82.8%) | | |
| Unknown | 1,433 (0.3%) | 119 (0.5%) | | 10 (0.4%) | | 109 (0.6%) | | |
| Physical activity – meeting or above WHO recommendation (%) | 279,296 (59%) | 10767 (47%) | <0.001 | 1,409 (54%) | | 9,444 (47%) | | 0.018 |
| BMI, median, kg/m$^2$, (IQR) | 26.5 (24.0–29.6) | 30.6 (27.3–34.7) | <0.001 | 27.4 (24.4–31.1) | | 31.0 (27.8–35.0) | | <0.001 |
| **Medical background** | | | | | | | | |
| Duration of diabetes mellitus, median years, y, (IQR) | 0 (0–0) | 14 (11–19) | NA | Male: 28 (18–41) | Female: 27 (17–40) | Male: 14 (11–18) | Female: 13 (10–17) | <0.001 |
| Hba1c (mmol/mol), median (IQR) | 35 (33–37) | 51 (44–60) | <0.001 | Male: 59 (50–68) | Female: 61 (54–70) | Male: 51 (44–59) | Female: 50 (44–58) | <0.001 |
| Diagnosed/treated for coronary artery disease | 18,324 (3.9%) | 3,947 (17.4%) | <0.001 | 400 (15.2%) | | 3,547 (17.7%) | | 0.002 |
| Diagnosed/treated for hypertension | 121,005 (25.7%) | 15,709 (69.2%) | <0.001 | 1,496 (57%) | | 14,213 (70.9%) | | <0.001 |
| Diagnosed/treated for hyperlipidaemia | 70,100 (14.9%) | 14,789 (65.2%) | <0.001 | 1,469 (55.9%) | | 13,320 (66.4%) | | <0.001 |

*WHO, World Health Organization; BMI, body mass index; IQR, interquartile range; Hba1c, glycated hemoglobin; SD, standard deviation.*

subdivided into below recommendation, above recommendation or meets recommendation.

## Statistical Analysis

The UK Biobank population were first divided into those with and without diabetes. Those without diabetes were the reference group for comparison in all analyses. A univariate analysis was carried out to assess mortality differences in those with diabetes and those without diabetes. Kaplan-Meier analysis was used to demonstrate these results. The associations of DM, type of DM stratified by sex with endpoints were analyzed using a multivariate cox regression model. The covariates included in the model were age, BMI, smoking and alcohol status (current, previous, never or unknown), ethnicity, hypertension, hypercholesterolaemia and coronary disease. The proportional hazards assumption was tested for all models using the Schoenfeld residuals. The assumption was violated when prevalent coronary artery disease was included as a covariate and so a stratified model was fitted. The significance of the differential associations between diabetes and sex with outcomes were tested using an interaction term. The 95% confidence interval for the difference in coefficients for men vs. women in each model was obtained with bootstrapping (1,000 times). For heart failure a competing risk analysis was conducted using a Fine and Gray competing risks model (16) to assess any impact of informative censoring as those dying from other causes may also have higher heart failure risk. A sensitivity analysis was also performed where any participants with coronary disease were excluded. The competing risk analysis support the results from the multivariate cox models. We also performed secondary sensitivity and mediation analysis. All analyses were performed with R studio version 1.2 (17). The R packages used for statistical analysis include the "survival," "boot," and "regmedint" packages.

# RESULTS

A total of 493,167 participants were included in this study. A total of 22,685 participants (4.6%) had prevalent diabetes at the start of the study. The population was further divided by sex with 260,743 (55%) female participants without

diabetes and 8,531 (38%) female participants with diabetes. HF occurred in 6,137 participants (1,223 with DM and 4,914 without DM) and 19,590 participants died (2,454 with DM and 17,136 without DM). For heart failure, the median follow-up was 8 years (IQR 7–9 years) and for all-cause mortality, the median follow-up was 9 years (IQR 8–10 years).

## Baseline Characteristics

Overall, the type 2 diabetes sub-group was older with a higher BMI and higher cholesterol levels compared to the control group (**Table 1**). In contrast, the median BMI of those with type 1 diabetes was only marginally increased compared to those without diabetes and the average age was the same as for the control group without diabetes. The duration of diabetes was longer in type 1 diabetes compared to type 2 diabetes, which is expected since they are diagnosed at a younger age. The participants with diabetes had a lower proportion of participants that either met or exceeded the World Health Organization (WHO) recommended level of physical activity. As expected, diabetes was associated with a higher prevalence of coronary disease, diagnosed hypertension, and hyperlipidaemia.

## Diabetes and All-Cause Mortality

A univariate analysis showed that those with diabetes have had a two-fold higher risk of mortality compared to individuals without diabetes. Men were found to have a lower survival probability compared to women in both groups—with and without diabetes. These results are demonstrated in **Figure 1**. In the multivariate analysis—diabetes was associated with almost double the mortality risk compared to those without diabetes (**Figure 2**). Further analysis showed that the excess risk of mortality in patients with diabetes is slightly higher in women compared to men (**Supplementary Table 1**).

## Diabetes and Heart Failure

Similarly, examining the relationship between diabetes status and incident heart failure, a multivariate analysis showed those with diabetes were at almost double the risk of heart failure compared to those without (**Figures 2**, **3**).

## Sex Differences in Risk of Heart Failure

**Figure 4** demonstrates the risk of heart failure for men and women with and without diabetes in the UK Biobank population, with models adjusted for our pre-defined confounding variables. The population was stratified into sex, and the association with incident heart failure was examined for type 1 diabetes, type 2 diabetes and all individuals with diabetes. As shown, there was an increased risk of heart failure with diabetes in both men and women, with absolute risk of events increased in men. Relative risk estimates were higher for type 1 diabetes than type 2 diabetes and, interestingly, the effect of diabetes was greater for women than for men. For women, the risk of heart failure associated with diabetes from the multivariate model, type 1 and type 2 combined, was 22% higher than for men, with hazard ratios of 2.2 (95% CI: 1.9–2.5) and 1.8 (1.7–2.0) respectively ($p$-value for interaction = 0.007). When stratified into type 1 and type 2 diabetes the risk of heart failure associated with type 1 diabetes was 88% higher in women

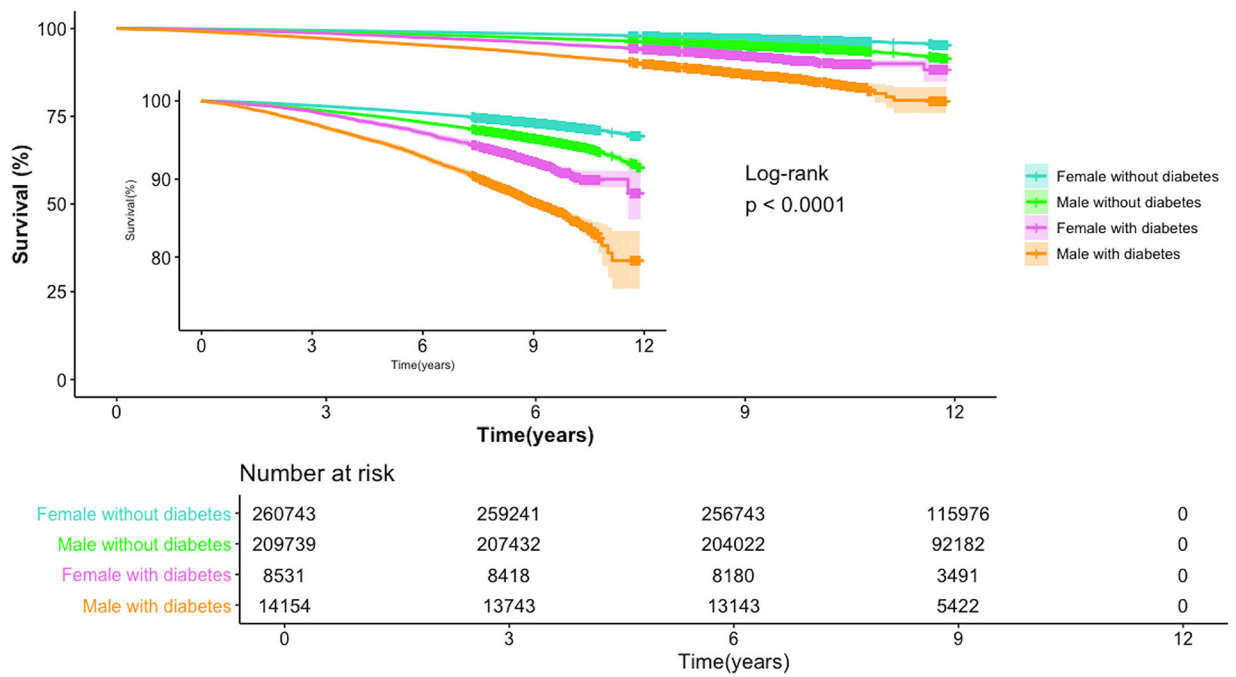


**FIGURE 1 |** The risk of all-cause mortality according to sex and presence of diabetes.

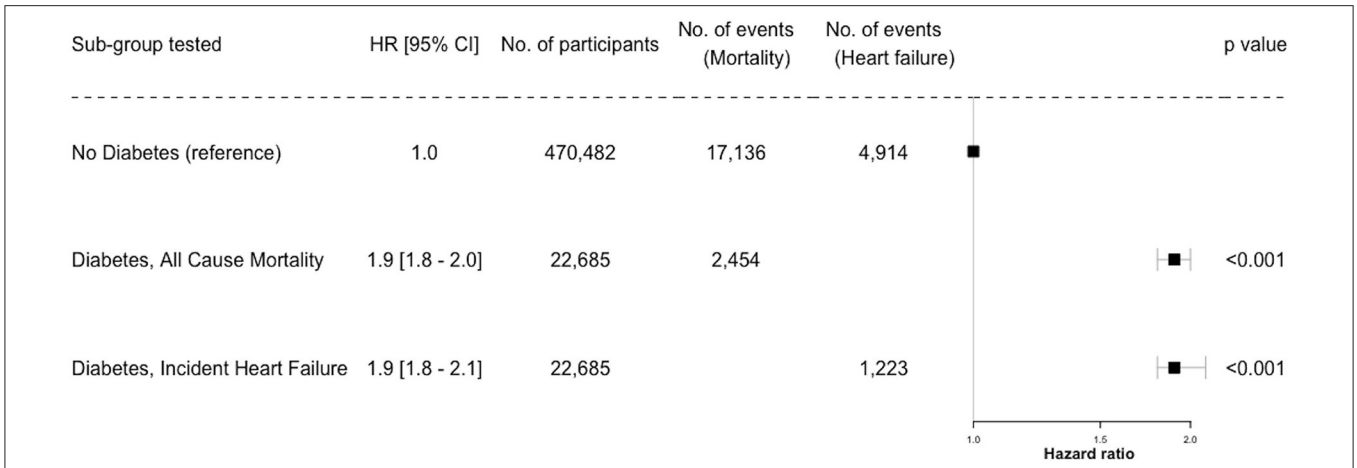


**FIGURE 2 |** Risk of All-Cause Mortality and Incident Heart Failure in Diabetes. HR, hazard ratio (95% confidence interval shown).

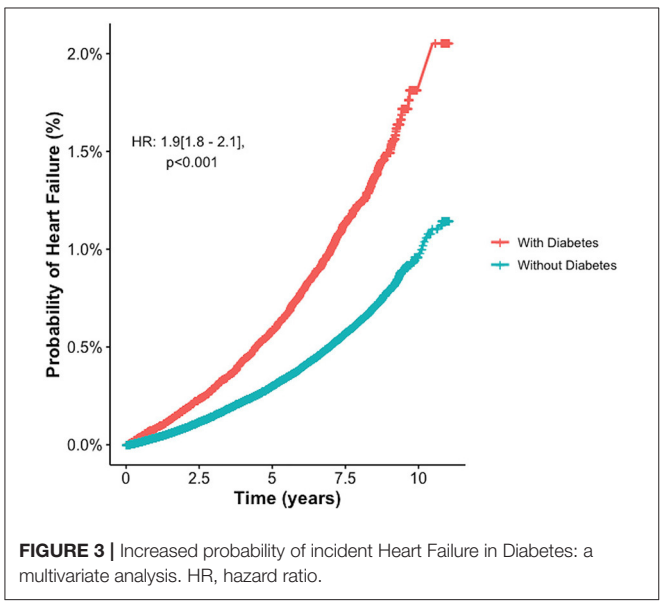


**FIGURE 3 |** Increased probability of incident Heart Failure in Diabetes: a multivariate analysis. HR, hazard ratio.

compared to men (hazard ratios 4.7 (3.6–6.2) vs. 2.5 (2.0–3.0), interaction $p = 0.0001$), while the risk of heart failure for type 2 diabetes was 17% higher in women compared to men (hazard ratios 2.0 (1.7–2.3) vs. 1.7 (1.6–1.9), interaction $p = 0.10$). Overall, findings were similar in the competing risk analyses indicating that the increased risk associated with type 1 diabetes in women remains even after accounting for the effect of all-cause mortality as a competing risk. The bootstrap analysis of the difference between coefficient of men and women in different sub-groups confirms the interaction term analysis.

A sensitivity analysis excluding individuals with coronary artery disease showed that the hazard ratios were still higher for women with diabetes than men, however, the significant interaction effect seen in the other analysis was not demonstrated (**Figure 4**). The reason for this was thought to be due to the lower number of events observed once those with coronary disease were removed. Further clarification was sought using mediation analysis which showed coronary disease may not have any mediatory effect in men with diabetes but in women with diabetes: 20% (19.1–20.9) mediatory effect is seen (see **Supplementary Table 2**).

## DISCUSSION

Men with diabetes have an increased absolute risk of heart failure events. However, the main finding of the present paper is that in women, the relative risk of suffering from heart failure for diabetes compared to those without diabetes is higher than in men, despite adjusting and stratifying for confounding variables. Although coronary disease has a minimal mediatory effect, it does not explain the majority of the excess risk of heart failure seen in women. Interestingly, the increased risk is particularly prominent in women with type 1 diabetes. The competing risk analysis in women with type 1 diabetes highlighted that the increased risk of heart failure remains after accounting for the effect of all-cause mortality as a competing risk. For type 2 diabetes the multivariate cox analysis shows the same trend where women are at increased risk of suffering from heart failure compared to men, however, the interaction between sex and heart failure was not statistically significant.

Although heart failure is the main focus of this study, a multivariate analysis showed that the excess risk of mortality in patients with diabetes is higher in women compared to men (**Supplementary Table 1**). This finding is supported by previous large cohort studies, which had found that women with diabetes had increased rates of cardiovascular and renal events as causes of death (18, 19).

This study is the largest to investigate the potential factors contributing to sex dependent difference in risk of heart failure associated with diabetes. The findings are in agreement with the results from a large meta-analysis consisting of 12 million people which was showing that having diabetes increased the risk of heart failure in women more than in men, an effect which was strongest when looking at type 1 diabetes (11). However, in the present study, we could take potential confounding factors into consideration, thereby significantly strengthening the observations. Our findings therefore suggest that the increased

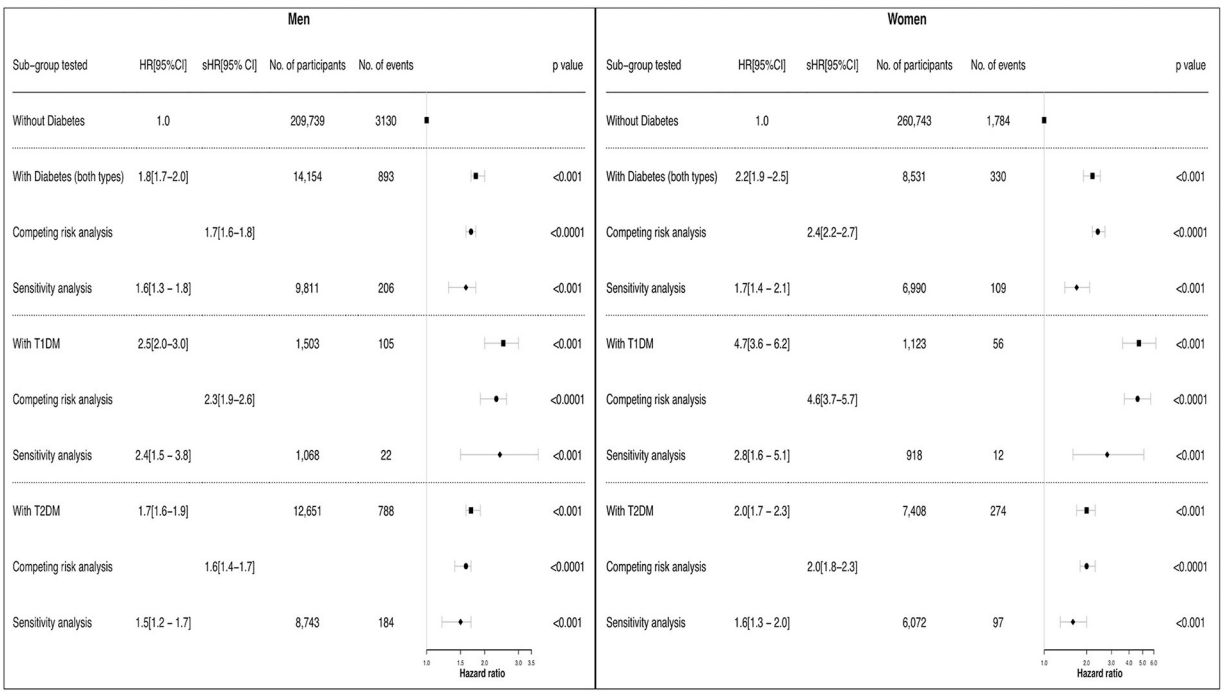


**FIGURE 4 |** Association between Diabetes, Gender and Incident of Heart Failure – multivariate, competitive risk and sensitivity analysis. Forest plot demonstrating risk of HF between men and women for each subset of participants with diabetes. The multivariate cox models were adjusted for age, ethnicity, hypertension, hypercholesterolaemia, smoking, BMI, alcohol status with coronary artery disease stratified. Interaction term between sex and heart failure is significant in the T1DM group ($p = 0.0001$) and for the overall diabetes group ($p = 0.007$). Interaction term for sex and heart failure in T2DM is $p = 0.1$. Competing risk confirms the trend seen in the multivariate analysis, and indicates that the increased risk in women especially with T1DM is significant enough to be above all-cause mortality. T1DM, type 1 diabetes; T2DM, type 2 diabetes; HR, hazard ratio; sHR, sub-distribution hazard ratio.

risk of heart failure associated with diabetes in women compared to men is not fully explained by confounding factors, but is likely a biological difference in the effect of diabetes on cardiac function in women compared to men, most notably in those with type 1 diabetes.

A widely suggested mechanism is that the increased risk in heart failure in women is secondary to the increased risk of coronary heart disease established in other studies (20, 21). The mediation analysis shows that coronary disease does have a mediatory effect on the outcome of heart failure in women with diabetes, but cannot fully account for the excess risk seen through multivariate cox regression analysis where coronary disease and other confounding variables are accounted for.

In summary, these findings may suggest that diabetes is a discrete cause of heart failure and affects women more than men, particularly in type 1 diabetes.

Sex based differences in cardiac physiology in the healthy population have been observed (22). After puberty, it is noted that male hearts undergo greater hypertrophy than women (23). In an otherwise healthy population, aging leads to an increase in septal thickness in both men and women, but the left ventricular diameter is noted to increase only in men (24) and results in loss of myocardial mass due to loss of myocytes. This loss is thought to result in compensatory hypertrophy of remaining myocytes in men, whereas myocyte mass and size are preserved in healthy women (25). These cellular changes may result in women having better diastolic function and preserved systolic function compared to men (24). Furthermore, in a healthy population, the mechanisms of cardiac adaption to exercise have been shown to be inherently different in male and female hearts despite the end result being an increase in cardiac output (26, 27). These differences in cardiac physiology and function are mostly lost in post-menopausal women (22). This would suggest that sex hormones play a role in the development and maintenance of normal cardiac function in healthy women, which is possibly reliant on a greater degree of elasticity (diastolic function). Diastolic dysfunction is a hallmark of diabetic cardiomyopathy (28). Therefore, it is possible that the benefits inferred by sex-based differences in healthy women are opposed or reduced in women with diabetes. The loss of diastolic function has a greater detrimental effect on female hearts compared to men. This may be a potential explanation for the findings of the prior metanalysis and this study.

It has also been suggested that women may be worse affected than men because they are traditionally noted to have worse glycaemic and cardiac risk factor control (29, 30). However, in this cohort the HbA1c levels are well-matched between men and women. Additionally, the traditional cardiac risk factors were adjusted for in the regression model. Therefore, the findings of this study do not support the theory that additional risk women with diabetes face is attributed to poorer glycaemic control and risk factor management.

### Interaction Between Sex, Diabetes and Heart Failure

The interaction between sex and diabetes on risk of heart failure for type 1 diabetes is statistically significant, unlike in type 2 diabetes. A recent study supports these findings and has also demonstrated certain imaging markers that are prognostic indicators of outcome for women with type 1 diabetes compared to men (31). This suggests that there are mechanisms to investigate that may correlate to the epidemiological findings of this study. Although both types of diabetes are characterized by hyperglycaemia, they are very different conditions in terms of pathophysiology and effect on cell metabolism (32), which could account for the difference seen between the two groups in this study. In addition, those with type 1 diabetes have often been diagnosed at a younger age and therefore have had a longer duration of disease which may also be responsible for the difference seen between the risk of heart failure in type 1 diabetes compared to type 2 diabetes. There has been some suggestion that insulin therapy itself may cause cardiac dysfunction and this could contribute to the excess risk of heart failure amongst those with diabetes (33, 34). This could potentially be an explanation for the increased risk in type 1 diabetes compared to type 2 diabetes. However, current literature in support of this theory is limited to animal models and explored in relation to insulin excess generated in the metabolic intolerance state in type 2 diabetes.

There is also some evidence suggesting that there are sex specific differences in telomerase activity in the heart and other molecular mechanisms, which may lead to the difference in disease expression amongst men and women with diabetes (35–37).

Overall, the evidence from this large study suggests that an independent process (diabetic cardiomyopathy) may be a potential mechanism that leads to the excess risk of heart failure in women with diabetes. Our recent study has shown that there are structural and functional changes associated with those with diabetes independent of coronary artery disease in the UK Biobank population (38). This study was performed using the CMR images from the first 5,000 participants that were scanned as part of the imaging study.

## LIMITATIONS

One of the limitations in this study, however, is that the HbA1c is a measurement taken at enrolment for the participants in UK Biobank and does not necessarily reflect long term glycaemic control. The generalizability of the findings of this study to the general population may also be a limitation. Participants in the UK Biobank are volunteers who are motivated and actively participated in this study, and therefore are generally recognized as having increased health awareness, resulting in the overall cohort being "healthier" than the general population. However, if excess risk in people with diabetes and women with diabetes can be detected in this population, then it could be surmised that this excess risk is even more likely to be present in the general population. Finally, the type of heart failure that participants are diagnosed with is not distinguished, therefore we cannot separate the outcomes of HF with reduced ejection fraction and HF with preserved ejection fraction in this study.

## CONCLUSIONS

Both men and women with diabetes are more likely to develop heart failure compared to their non-diabetic counterparts, however for women this excess risk is significantly greater than for men. This finding is more significant for type 1 diabetes than type 2 diabetes. The increased relative risk for women cannot be explained solely by factors such as increased prevalence of coronary artery disease and other cardiac risk factors. Therefore, diabetic cardiomyopathy, myocardial dysfunction related to diabetes, is a potential contributor, which affects women more than men. In order to identify this condition and develop sex specific treatment strategies, further research is needed to first establish the cardiac phenotype of diabetic cardiomyopathy and the sex differences within this phenotype. Defining this condition will allow for screening and treatment strategies to be developed and targeted.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: http://www.ukbiobank.ac.uk/register-apply/.

## AUTHOR CONTRIBUTIONS

SC is the first author and was involved in the conceptualization, data collation, data analysis, and manuscript preparation. MJ, NA, JC, KL, and PM have all contributed equally to this work and involved in data analysis and manuscript preparation. SP is the senior author and has supervised all aspects of the study and contributed to the manuscript preparation. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no. 825903 (euCanSHare project). NA was supported by a Wellcome Trust Research Training Fellowship (wellcome.ac.uk; 203553/Z/Z) and now recognizes the National Institute for Health Research (NIHR) Integrated Academic Training programme which supports his Academic Clinical Lectureship post. SP and PM acknowledge support from the National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Center at Barts.

## ACKNOWLEDGMENTS

Data access was granted through UK Biobank (UKB) access application 2964.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.658726/full#supplementary-material

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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.

**Appendix A |**

| Variable in study | Definition within UK Biobank database |
|---|---|
| Ethnicity | Derived from self-reported questionnaire participants answer at first assessment. |
| Smoking history | Derived from self-reported questionnaire participants answer at first assessment where participants answered if they were a current, previous, never smoked, or prefer not to answer. |
| Alcohol history | Derived from self-reported questionnaire participants answer at first assessment where participants answered if they were a current, previous, never smoked, or prefer not to answer. |
| Hypertension | Derived from self-reported questionnaire given to UK Biobank participants and HES data. This was supplemented with data on those participants taking anti-hypertensive medications. |
| Coronary disease | Derived from self-reported questionnaire given to UK Biobank participants and HES data including ICD 10 codes 120 – 125. In addition, any participants with hospital admission for coronary intervention (percutaneous or surgical bypass grafting) were also recorded to have coronary disease. |
| Hypercholesterolaemia | Derived from self-reported questionnaire given to UK Biobank participants. This was supplemented with data on those participants taking statin medication. |
| Heart Failure | Derived from self-reported questionnaire given to UK Biobank participants and HES data including ICD code 150. |
| Diabetic medication | Derived from self-reported medication, supplemented with data on patients self-reported to be on insulin or those started on insulin within a year of diabetes diagnosis. |

frontiers in Cardiovascular Medicine

CLINICAL TRIAL
published: 07 April 2021
doi: 10.3389/fcvm.2021.636718

# Clinical Utility of Fluid Volume Assessment in Heart Failure Patients Using Bioimpedance Spectroscopy

*Andrew J. Accardi*[1]*, *Bradley S. Matsubara*[2], *Richelle L. Gaw*[3], *Anne Daleiden-Burns*[4] and *James Thomas Heywood*[4]

[1] Department of Emergency Medicine, Scripps Memorial Hospital Encinitas, Encinitas, CA, United States, [2] ImpediMed, Inc., Carlsbad, CA, United States, [3] ImpediMed Limited, Brisbane, QLD, Australia, [4] Heart Failure Recovery and Research Program, Scripps Memorial Hospital La Jolla, La Jolla, CA, United States

**Background:** Bioimpedance spectroscopy (BIS) is a non-invasive method used to measure fluid volumes. In this report, we compare BIS measurements from patients with heart failure (HF) to those from healthy adults, and describe how these point-of-care fluid volume assessments may be applied to HF management.

**Methods and results:** Fluid volumes were measured in 64 patients with NYHA class II or III HF and 69 healthy control subjects. BIS parameters including extracellular fluid (ECF), intracellular fluid (ICF), total body water (TBW), and ECF as a percentage of TBW (ECF%TBW) were analyzed. ECF%TBW values for the HF and control populations differed significantly (49.2 ± 3.2% vs. 45.2 ± 2.1%, respectively; $p < 0.001$); both distributions satisfied criteria for normality. Interquartile ranges did not overlap (46.7–51.0% vs. 43.8–46.4%, respectively; $p < 0.001$). Subgroup analyses of HF patients who underwent transthoracic echocardiography showed that impedance measurements correlated with inferior vena cava size (Pearson correlation −0.73, $p < 0.0001$). A case study is presented for illustrative purposes.

**Conclusions:** BIS-measured ECF%TBW values were significantly higher in HF patients as compared to adults without HF. We describe three strata of ECF%TBW (normal, elevated, fluid overload) that may aid in clinical risk stratification and fluid volume monitoring of HF patients.

**Clinical Trial Registration:** COMPARE 96 www.ClinicalTrials.gov; IMPEL 96 www.ClinicalTrials.gov; Heart Failure at Home 96 www.ClinicalTrials.gov, identifier: NCT02939053; NCT02857231; NCT04013373.

**Keywords: heart failure, bioimpedance spectroscopy, extracellular fluid, total body water, case study**

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*Gaetano Ruocco,*
*Regina Montis Regalis Hospital, Italy*

***Reviewed by:***
*Guido Pastorini,*
*Regina Montis Regalis Hospital, Italy*
*Stefano Coiro,*
*Hospital of Santa Maria della Misericordia in Perugia, Italy*

***Correspondence:**
*Andrew J. Accardi*
*accardi.andrew@scrippshealth.org*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *01 December 2020*
***Accepted:*** *12 March 2021*
***Published:*** *07 April 2021*

***Citation:***
*Accardi AJ, Matsubara BS, Gaw RL, Daleiden-Burns A and Heywood JT (2021) Clinical Utility of Fluid Volume Assessment in Heart Failure Patients Using Bioimpedance Spectroscopy. Front. Cardiovasc. Med. 8:636718. doi: 10.3389/fcvm.2021.636718*

## INTRODUCTION

Heart failure (HF) affects ∼26 million people worldwide, with the prevalence increasing as the population ages (1). In the United States alone, HF affects an estimated 6.2 million individuals (2). This condition places a substantial burden on health care systems with high rates of hospitalizations, readmissions, and outpatient visits. Despite advances in treatment and monitoring, HF-related mortality remains high (1). Patients with stable ventricular function and unchanged medications can still decompensate, resulting in recurrent hospitalizations (3). Once hospitalized, up to 25% of HF patients are readmitted within 30 days (4, 5).

**TABLE 1 |** ECF and TBW correlation coefficients for BIS measurements vs. gold-standard dilution techniques.

| First author, publication year [reference] | Study population | Correlation coefficient |
|---|---|---|
| **Correlation between extracellular fluid (ECF) measured by bioimpedance spectroscopy (BIS) and bromide dilution** | | |
| Birzniece, 2015 (13) | Healthy athletes | $r = 0.84$ |
| Van De Ham, 1999 (14) | Renal transplant patients | $r = 0.87$ |
| **Correlation between total body water (TBW) measured by bioimpedance spectroscopy (BIS) and deuterium oxide dilution** | | |
| Cicone, 2019 (15) | Healthy individuals | $r = 0.93$ |
| Kerr, 2015 (16) | Resistance trained individuals | $r = 0.90$ |
| Moon, 2009 (17) | Overfat and obese individuals | $r = 0.96$ |
| Moon, 2008 (18) | Healthy individuals | $r = 0.98$ |
| Van De Ham, 1999 (14) | Renal transplant patients | $r = 0.94$ |

**TABLE 2 |** Clinical studies enrolling HF patients and healthy control subjects.

| Clinical study description | *N* | Gender (female, male) | Age (years) |
|---|---|---|---|
| New York Heart Association Class III HF patients measured daily at home over 30 days | 2 | 0F, 2M | 70.5 ± 2.1 |
| New York Heart Association Class III HF patients measured 3 times per week in clinic over 30 days | 12 | 5F, 7M | 65.0 ± 15.6 |
| New York Heart Association Class II and III HF patients recently discharged from hospitalization due to decompensated HF measured daily at home for 45 days | 50 | 23F, 27M | 70.2 ± 15.1 |
| Healthy university population 40 years or older measured at a single clinic visit | 13 | 8F, 5M | 48.8 ± 8.8 |
| Healthy university population 40 years or older measured at a single clinic visit | 25 | 11F, 14M | 47.9 ± 9.7 |
| Healthy general population 40 years or older measured at a single clinic visit | 31 | 18F, 13M | 57.8 ± 11.3 |
| **Combined populations** | ***N*** | **Gender (female, male)** | **Age (years)** |
| Heart Failure Patients (HF-pop) | 64 | 28F, 36M | 69.3 ± 14.8 |
| Healthy Control Subjects (CON-pop) | 69 | 37F, 32M | 52.5 ± 11.2 |

Bioimpedance spectroscopy is a non-invasive method used to assess fluid volume status. The electrical impedance of biological tissue is measured in response to an alternating current across a spectrum of 256 frequencies. An electrical current applied to the body will conduct primarily through fluid due to its low resistivity (6). Impedance values are then used to quantify intracellular fluid (ICF), extracellular fluid (ECF), and total body water (TBW), as well as other fluid and tissue parameters (7). BIS has enabled improved discrimination of fluid overload from HF as a cause of dyspnea, and is sensitive to changes in both pulmonary and peripheral edema (8–12). In addition, BIS measurements of ECF (13, 14) and TBW (14–18) have also been shown to correlate strongly with gold-standard bromide and deuterium oxide dilution methods, respectively (**Table 1**). BIS measurements have also been shown to correlate well with echocardiographic indicators of fluid overload (inferior vena cava size, right atrial pressure, and pulmonary artery systolic pressure) (19). The purpose of this report is to compare point-of-care bioimpedance spectroscopy (BIS) measurements from patients with HF to those from healthy adults, and to describe the range of BIS-derived ECF%TBW values in a clinically relevant way.

# MATERIALS AND METHODS

## Clinical Study Participants

In order to characterize BIS parameters in individuals with and without HF, observational data from six clinical studies utilizing BIS were evaluated (years of data collection: 2017-2019). A total of 64 patients with New York Heart Association (NHYA) Class II or III HF were enrolled across three clinical studies and combined to form a population for HF patients (HF-pop): two patients (ClinicalTrials.gov identifier NCT02939053) were clinically stable NYHA Class III men with CardioMEMS pulmonary artery pressure monitors who performed daily BIS measurements at home for 30 days; 12 patients (NCT02857231) were clinically stable and had BIS measurements taken two or three times per week in an outpatient advanced HF clinic over a 30-day period; 50 patients (NCT04013373) were enrolled within 72-h after discharge from a hospitalization for acute decompensated HF and took daily BIS measurements at home over 45 days. A total of 69 self-reported healthy control subjects aged 40 years or more were enrolled across three different clinical studies and combined to form a control population (CON-pop). A summary of these populations is provided in **Table 2**.

All contributing clinical studies received the approval of an Independent Review Board (IRB) or Ethics Committee (EC), and all participants provided written informed consent. Per BIS device instructions for use, individuals were excluded if they were amputees, had metallic implants, or implanted devices such as pacemakers or implantable cardioverter defibrillators (ICDs). Potential subjects were also excluded if they were pregnant, breast feeding, or had other comorbidities that could result in fluid overload; namely, renal failure (dialysis dependent at the time of enrollment), nephrotic syndrome or nephrosis, lymphedema, chronic liver failure or cirrhosis, and thrombophlebitis or deep vein thrombosis of the extremities (within 90 days prior to enrollment).

## Bioimpedance Spectroscopy Measurements

BIS measurements were performed using the SOZO device (ImpediMed Limited, Brisbane, Australia). The device (**Figure 1**) measures the resistance and reactance at 256 frequencies from 3 to 1,000 kilohertz (kHz). It is a mains-powered device that takes octopolar measurements using stainless-steel hand and foot plates in a standing or seated position. A measurement

**FIGURE 1 |** SOZO device. As shown, the device is configured to perform bioimpedance spectroscopy (BIS) measurements with the subject in a standing position. Bare hands and feet must be in direct contact with the electrodes (i.e., no shoes, socks, stockings, or gloves), and metallic/electronic items should be removed. BIS measurement and fluid status reporting takes ∼30 s.

takes ∼30 s and is performed at the point-of-care. BIS has been used to assess small changes in lymphatic fluid in order to detect subclinical lymphedema in cancer survivors (20–23). Other applications include use in venous insufficiency, kidney failure, and evaluation of malnutrition/hydration status (24–27). The SOZO system has been cleared by the United States Food and Drug Administration (FDA) for use in monitoring fluid in HF patients.

In each study, BIS measurements were simultaneously taken of both arms, both legs, and right and left sides of the body

as per the manufacturer's instructions for use. All participants were weighed using digital scales to the nearest 0.1 kg, and had their height recorded to the nearest centimeter using a wall or stand-mounted stadiometer. In the case of the HF-pop patients, multiple measurements were taken either daily at home or several times per week in a clinic over a monitoring period of up to 45 days. All CON-pop measures were taken in triplicate during a single clinic visit.

## Transthoracic Echocardiography

A subgroup of 12 HF-pop patients enrolled in the IMPEL clinical study (ClinicalTrials.gov identifier NCT02857231) underwent transthoracic echocardiography (TTE). At each clinic visit, limited TTE was performed by licensed echocardiographers and reviewed by Board-certified cardiologists to obtain echocardiographic measurements of inferior vena cava (IVC) size and estimates of right atrial pressure (RAP). According to recommendations by the American Society of Echocardiography (ASE), RAP values were categorized into three groups: group 1 included any RAP below 8 mmHg, group 2 included values of 8-14.99 mmHg, and group 3 included all values equal to 15 mmHg. The ASE has defined a normal RAP as 3 mmHg, intermediate as 8 mmHg, and high as 15 mmHg (19).

## Data Processing and Statistical Analysis

Prior to analysis, all BIS measurements were reviewed for suitable quality. This was done by assessing the quality of the fit of the raw impedance data to the recognized semi-circular Cole plot of biological tissue (28). Only data that met pre-defined criteria for measurement quality were used to calculate $R_0$ (the resistance of ECF, at theoretical 0 kHz) and $R_{inf}$ (the resistance of TBW, at theoretical infinite kHz) for each measure. These values were converted to absolute ECF and TBW volumes using the Hanai mixture theory implemented in the manufacturer's software and then the ECF%TBW was calculated. ECF and TBW are calculated independently (using $R_0$ and $R_{inf}$, respectively); as such, the use of ECF/TBW expressed as a percentage allows for indexing.

Because the number of and interval between BIS measurements taken during clinical studies varied, the data was standardized to include one representative measurement per subject. Based on previous work which demonstrated low variability in a healthy population over time, the average of 3 measures in a single clinic visit was used for the healthy control individuals (22). The HF patients were tracked over multiple days with multiple measurements; to mitigate issues associated with repeated measures per patient, the median BIS value for each HF patient was used.

Calculations were performed using MedCalc version 11.6.1.0. Unless otherwise specified, results are presented as means ± standard deviations, and/or medians with quartiles and ranges. Statistical significance was defined as a $p$-value $< 0.05$.

Plots of ECF%TBW, ECF, ICF, TBW, and patient weight vs. time are presented for a patient enrolled in the Heart Failure at Home study (ClinicalTrials.gov NCT04013373). The timeline is annotated for symptoms, signs, medication changes, and significant clinical events (e.g., rehospitalizations for HF) and is presented in **Figure 5**. Investigators were blinded to BIS values, so management was per standard of care.

# RESULTS

Participant age, physical characteristics, and BIS-derived fluid volumes are summarized in **Table 3**. HF-pop patients were significantly older than CON-pop subjects (median ages 71.4 and 50.0 years, respectively; $p < 0.001$), and had significantly higher body mass indices (BMI, 29.5 ± 6.1 vs. 25.9 ± 4.0 kg/m$^2$, respectively; $p = 0.0001$). There were no significant differences in ICF or TBW.

**TABLE 3 |** Age, physical characteristics, and bioimpedance spectroscopy measurements.

| | Healthy control subjects | | | | | | Heart failure patients | | | | | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* = 69 (32 males, 37 females) | | | | | | *N* = 64 (36 males, 28 females) | | | | | | |
| | | Quartiles | | | | | | Quartiles | | | | | |
| | Mean ± SD | Min | 25th | Median | 75th | Max | Mean ± SD | Min | 25th | Median | 75th | Max | |
| Age (years) | 52.5 ± 11.2 | 40.0 | 43.0 | 50.0 | 61.0 | 77.0 | 69.3 ± 15.0 | 28.0 | 59.9 | 71.4 | 79.6 | 96.0 | <0.001 |
| Height (cm) | 171.6 ± 8.2 | 150.5 | 165.1 | 171.5 | 177.8 | 190.5 | 167.8 ± 11.7 | 147.3 | 157.5 | 167.6 | 177.8 | 188.0 | 0.0347 |
| Weight (kg) | 76.6 ± 15.0 | 46.0 | 65.9 | 75.4 | 84.5 | 121.3 | 83.2 ± 19.0 | 37.6 | 70.8 | 80.3 | 99.2 | 133.8 | 0.0263 |
| BMI (kg/m$^2$) | 25.9 ± 4.0 | 17.9 | 23.3 | 25.6 | 27.6 | 39.4 | 29.5 ± 6.1 | 17.3 | 25.0 | 28.7 | 33.3 | 49.5 | 0.0001 |
| Body $R_0$ (Ohms) | 664.8 ± 97.6 | 486.0 | 602.7 | 648.6 | 735.6 | 927.6 | 591.4 ± 121.4 | 363.0 | 503.7 | 561.1 | 663.6 | 928.7 | 0.0002 |
| Body $R_{inf}$ (Ohms) | 491.9 ± 81.4 | 347.4 | 426.0 | 488.8 | 540.8 | 715.0 | 470.4 ± 103.9 | 306.0 | 394.0 | 453.5 | 525.3 | 835.6 | 0.1881 |
| ECF (liters) | 18.2 ± 4.1 | 11.7 | 14.9 | 18.0 | 20.7 | 29.5 | 20.0 ± 5.4 | 8.9 | 15.3 | 19.5 | 24.1 | 33.2 | 0.0299 |
| ICF (liters) | 22.0 ± 4.5 | 14.0 | 18.8 | 21.1 | 25.7 | 36.3 | 20.6 ± 5.2 | 7.8 | 16.4 | 19.9 | 23.8 | 33.6 | 0.0912 |
| TBW (liters) | 40.2 ± 8.4 | 25.8 | 33.7 | 38.0 | 46.2 | 65.7 | 40.6 ± 10.2 | 16.6 | 32.6 | 39.9 | 48.2 | 63.8 | 0.8046 |
| ECF%TBW (%) | 45.2 ± 2.1 | 41.5 | 43.8 | 44.8 | 46.4 | 50.0 | 49.2 ± 3.2 | 43.2 | 46.7 | 48.8 | 51.0 | 56.5 | <0.001 |
| ICF%TBW (%) | 54.8 ± 2.1 | 50.0 | 53.6 | 55.2 | 56.2 | 58.5 | 50.8 ± 3.3 | 43.5 | 48.9 | 51.2 | 53.3 | 56.9 | <0.001 |

*BMI, body mass index; $R_0$, resistance at zero Hertz; $R_{inf}$, resistance at infinite Hertz; ECF, extracellular fluid; ICF, intracellular fluid; TBW, total body water; ECF%TBW, extracellular fluid as a percentage of total body water; ICF%TBW, intracellular fluid as a percentage of total body water.*

**TABLE 4 |** Baseline systemic blood pressure, heart rate, and concomitant medications for heart failure patients.

| **Parameter ($n = 61$)*** | **Mean ± SD** |
|---|---|
| Systolic blood pressure (mmHg) | 120.0 ± 16.8 |
| Diastolic blood pressure (mmHg) | 71.1 ± 12.4 |
| Heart rate (beats per minute) | 76.9 ± 12.3 |
| **Concomitant medication ($n = 63$)^** | **Count (percentage)** |
| ACEI/ARB | 24 (38%) |
| Digoxin | 8 (13%) |
| Beta-blocker | 53 (84%) |
| HCN channel blocker | 3 (5%) |
| Sacubitril/Valsartan | 7 (11%) |
| MRA | 27 (43%) |
| Diuretic | 52 (83%) |

**Not available for three patients.*
*^Not available for one patient.*
*mmHg, millimeters of mercury; SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCN, hyperpolarization-activated cyclic nucleotide-gated; MRA, mineralocorticoid receptor antagonist.*

**Table 3** shows that significant differences ($p < 0.05$) exist between the CON-pop and HF-pop for body $R_0$, ECF, ECF%TBW, and ICF as a percentage of TBW (ICF%TBW) measures. Given that clinicians are familiar with the ECF%TBW metric and the fact there is published use of this parameter, it was further analyzed. Baseline systemic blood pressure, heart rate, and concomitant medications are summarized in **Table 4**.

## Extracellular Fluid as a Percentage of Total Body Water

The distribution of BIS-derived ECF%TBW measurements for both CON-pop and HF-pop satisfied criteria for normality (Chi-square test, $P = 0.4623$ and $P = 0.9262$, respectively) (29). ECF%TBW was significantly higher for HF-pop as compared to CON-pop (49.2 ± 3.2% vs. 45.2 ± 2.1%, respectively; $p < 0.001$); interquartile ranges did not overlap (46.7–51.0% vs. 43.8–46.4%, respectively; $p < 0.001$). These distributions are shown graphically in **Figure 2** (histogram and cumulative frequency curves) and **Figure 3A** (box-and-whisker plots). Based on these distributions, three clinical strata of ECF%TBW are shown in **Figure 3B**. The bottom three CON-pop quartiles define the "Normal" stratum (41.5–46.4%), "Fluid Overload" is defined by the highest HF-pop quartile (51.0–56.5%), and the "Elevated" stratum falls in between. Of note, the CON-pop maximum was 50.0%, so no healthy subject's ECF%TBW measurement exceeded the 51.0% threshold for fluid overload.

## Echocardiographic Subgroup Analysis

The subgroup analysis of IMPEL clinical study patients (ClinicalTrials.gov identifier NCT02857231) is presented in **Figure 4**. These 12 HF patients underwent serial (two or three times weekly) transthoracic echocardiography (TTE). Both left and right leg $R_0$ impedance measurements were correlated with inferior vena cava size (Pearson correlation −0.73, $p$-value < 0.0001 for each leg) and TTE categories of estimated right atrial pressure (RAP).

## Clinical Case Study (Figure 5)

This patient is an 87 year-old man with NYHA class III heart failure with reduced left-ventricular ejection fraction (35–40%), and a history of hypertension, atrial fibrillation, and chronic kidney disease. ECF%TBW was markedly elevated (56.7%) upon study entry, and the patient was readmitted to the hospital on study day 5. After a skilled nursing facility (SNF) stay, home monitoring resumed on study day 30. His ECF%TBW remained very high (57.0%), and bumetanide dose increases between study days 30 and 49 had minimal effect on fluid volumes and weight. Metolazone was started on study day 64, and the patient responded with a reduction in ECF%TBW to 52.7% on study day 76. He then left the study briefly only to be re-enrolled after his second readmission for heart failure. When BIS measurements resumed on study day 87, his ECF%TBW had risen to 54.7%. Metolazone therapy was reinitiated, and clinical, fluid volume, and weight stability was finally achieved by study day 115. The ECF%TBW strata shown in **Figure 3B** are based on population data and should be interpreted in clinical context. This patient was almost exclusively >51% (fluid overloaded state); achieving normal fluid status (41.5–46.4%) is an unrealistic goal in this case. With unblinded, real-time BIS data, it's likely that his caregivers would have recognized persistent fluid overload at the time of study entry as his ECF%TBW was 56-57%, markedly elevated even for this patient. An ECF%TBW of 50% and an ECF volume of 16 liters turned out to be reasonable targets in this case; a future goal of fluid monitoring in HF would be to identify and maintain target fluid volumes more quickly than is currently possible with weight tracking alone.

# DISCUSSION

Monitoring strategies and development of novel markers to guide HF management remain elusive (30, 31). Current standards of care to assess volume status include monitoring patient weight, physical exam findings, and resolution of symptoms. These methods are often insensitive and may not provide adequate warning of impending decompensation (32). Implanted pulmonary artery pressure monitoring systems have been shown to decrease rates of hospitalization and improve quality of life (33–35), but require an invasive procedure for implantation with associated risks and cost. Accurate tracking of fluid volume fluctuations has been shown to be helpful for the individualized management of diuretic therapy, which remains a cornerstone of HF management (36, 37).

Formulae for calculating estimated plasma volume status (ePVS) have been shown to correlate well with gold-standard radioisotope assay measures of plasma volume (PV). Examples include Strauss' formula (for change in ePVS), Duarte's formula [ePVS = (100 – hematocrit (%) / hemoglobin (g/dL)], and the Hakim formula [ePVS = ((actual PVS – ideal PV) / ideal PV) * 100]. These calculations utilize hematocrit, hemoglobin, and body weight and thereby avoid the complex, costly, and logistically challenging radioisotope quantification of PV.

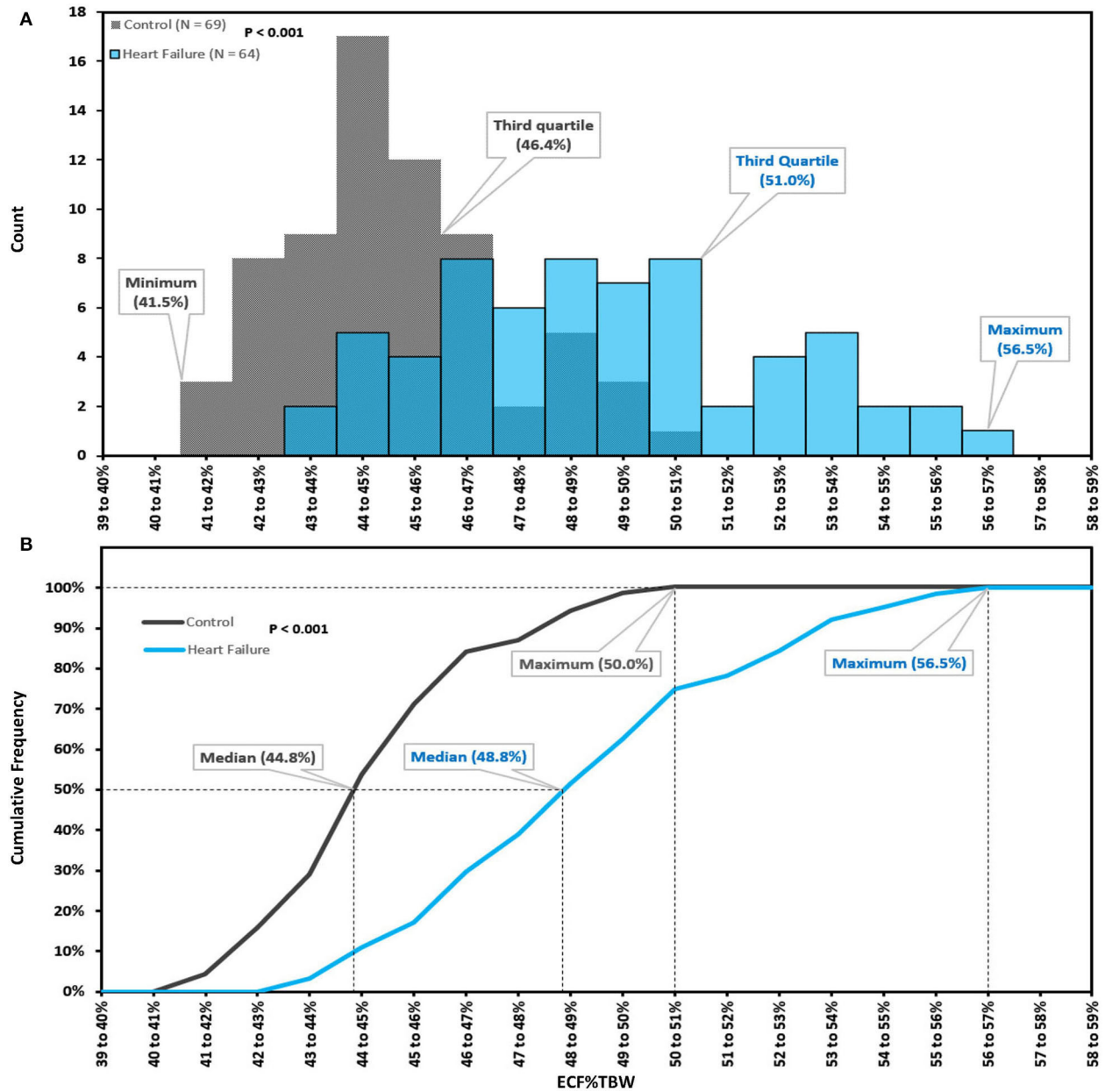


**FIGURE 2 |** Extracellular fluid percentage of total body water; histogram **(A)**, cumulative frequency curves **(B)**. Extracellular fluid percentage of total body water (ECF%TBW) for Healthy Control Subjects (CON-pop, *N* = 69, shown in gray) and Heart Failure Patients (HF-pop, *N* = 64, shown in blue); histogram **(A)**, and cumulative frequency curves **(B)**.

Reliance upon "dry" body weight—which is difficult to measure in the setting of heart and/or kidney failure—is a potential limitation of the Hakim formula. Associations of ePVS with clinical outcomes in heart failure were recently reviewed by Kobayashi et al. (38) who conclude that initial data are encouraging and warrant investigation in adequately powered prospective clinical trials.

Bedside lung ultrasound (LUS) is a relatively new method used to assess pulmonary congestion. Sonographic evaluation of the antero-lateral chest can detect extravascular lung fluid imaged as "B-lines." Mottola et al. (39) used LUS to evaluate pulmonary edema in a single-center observational study of 36 patients during the early post-operative period following kidney transplant surgery. Horton and Collins (40) suggest that LUS may help discriminate between cardiogenic and non-cardiogenic causes of dyspnea in the emergency department.

In the present report, based on measurements from HF and healthy control populations, we describe three strata of

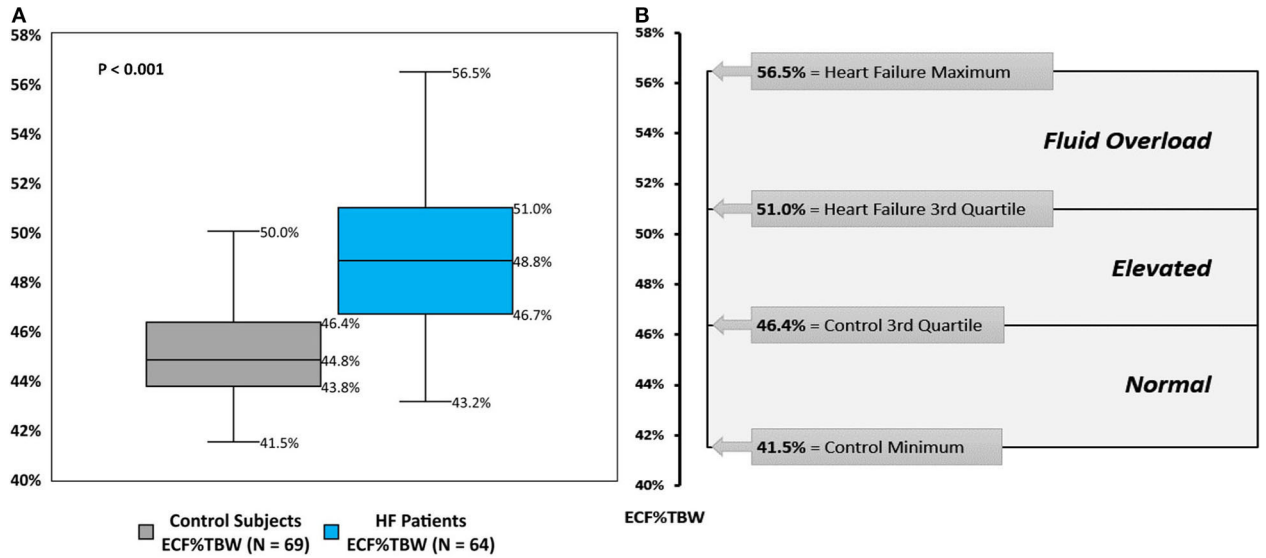


**FIGURE 3 |** Extracellular fluid percentage of total body water; box-and-whisker plots **(A)**, and clinical strata **(B)**. **(A)** box-and-whisker plots for bioimpedance spectroscopy-derived extracellular fluid percentage of total body water (ECF%TBW) for Healthy Control Subjects (CON-pop, gray plot) and Heart Failure Patients (HF-pop, blue plot). **(B)** Normal, bottom three CON-pop quartiles; Elevated, bound by CON-pop 3rd quartile and HF-pop 3rd quartile; Fluid Overload, highest HF-pop quartile.

BIS-measured ECF%TBW (**Figure 3B**) that may contribute to clinical risk stratification and may serve as a tool to help facilitate future outcomes research. BIS is rapid (∼30 s per measurement) and non-invasive, so results can be used in real-time to assist with clinical decision making at the bedside, in the clinic, and potentially at home. Real-time availability is not practical with traditional ECF%TBW determination methods such as DEXA that requires a scan with ionizing radiation, and heavy water or bromide dilution that require special reagents and blood draws. This report is not intended to directly compare BIS to these techniques, but rather to describe a clinically relevant way to quantify fluid volume status.

By way of comparison to previously published data, mean and standard deviation values of ECF%TBW from this report's control population (45.2 ± 2.1%) are in keeping with National Health and Nutrition Examination Survey (NHANES) reference data for adults aged 50-59 years (47.2 ± 2.0% for women, and 41.7 ± 1.6% for men) (41). Additionally, our 51.0% BIS-derived ECF%TBW threshold for fluid overload closely approximates the 50.0% cut-off defined by Sergi et al. who used gold-standard methods of DEXA, deuterium oxide dilution, and bromide dilution. In their publication, ECF%TBW values in excess of 50.0% were independently associated with a 10-fold higher likelihood of fluid retention (odds ratio of 10, with 95% confidence interval 3.3–30.3) (42). Indeed, the highest control population ECF%TBW value we measured was 50.0%; this provides further justification for the 51% BIS-based ECF%TBW threshold for fluid overload.

Liu et al. describe 6-month prognostic value for multi-frequency bioelectrical impedance analysis (MFBIA) in patients hospitalized for acute HF using an ECF/TBW cut-off value of 0.390 (39.0%); this so-called "edema index" was derived from 6-frequency MFBIA performed in 58 HF patients (43). We used a BIS technique that measures impedance over a spectrum of 256 frequencies thereby enabling Cole analysis for more accurate determination of $R_0$ and $R_{inf}$, and therefore more accurate ECF, TBW, and ECF%TBW (44). BIS provides a more direct, individualized measure of ECF and TBW than other bioimpedance approaches (45). This difference in measurement technique likely accounts for the discrepancy in thresholds for fluid overload between MFBIA and BIS.

We found other BIS-derived parameters, such as $R_0$ and ECF, showed statistically significant differences between HF and control populations (**Table 3**). In our TTE subgroup analysis, $R_0$ measurements from both lower extremities were shown to correlate well with TTE-measured IVC size (Pearson correlation−0.73, **Figure 4**) and estimated right atrial pressure, metrics that are used clinically to evaluate preload and filling pressure. This suggests that BIS may be able to provide similar information without the cost, time, and sonographic scanning expertise needed to perform TTE. The strong correlation between impedance and IVC size provides evidence from an external measure (TTE) that BIS tracks preload over a broad range of values (IVC sizes from ∼0.5 to 4.2 cm).

ECF is an absolute quantity (liters) that depends on patient size and is therefore more informative if tracked over time for a given individual. ECF%TBW, however, is normalized (as a percentage) allowing it to be applied across populations and enabling clinically relevant stratification as show in **Figure 3**. ECF%TBW values >51.0%, consistent with fluid overload, were measured in the highest quartile of our HF-pop patients and

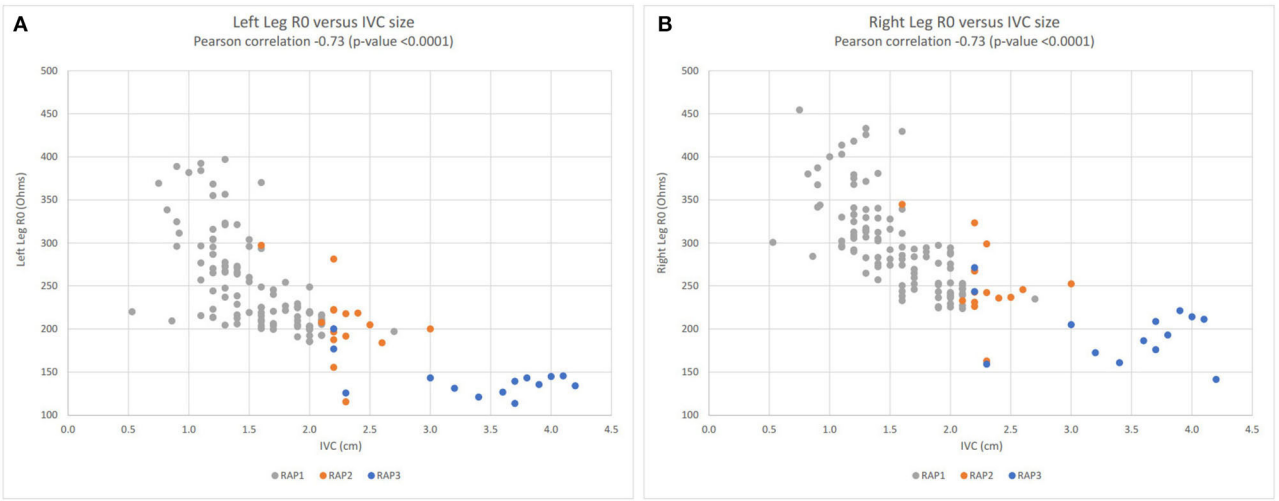


**FIGURE 4 |** Lower extremity $R_0$ impedance measurements vs. inferior vena cava (IVC) size; left leg **(A)**, right leg **(B)**. Left leg **(A)** and right leg **(B)** scatter plots for $R_0$ impedance vs. inferior vena cava (IVC) size for the subgroup of 12 heart failure patients enrolled in the IMPEL clinical study (ClinicalTrials.gov identifier NCT02857231). Right atrial pressure (RAP) categories: RAP1 in gray (<8 mmHg), RAP2 in orange (8–14.99 mmHg), and in blue RAP3 (15 mmHg). $R_0$ impedance is inversely related to extracellular fluid volume. Hence, in both legs, lower impedance values are associated with larger IVC size and higher right atrial pressures. $R_0$, resistance at zero Hertz; IVC, inferior vena cava; RAP, right atrial pressure; cm, centimeter.

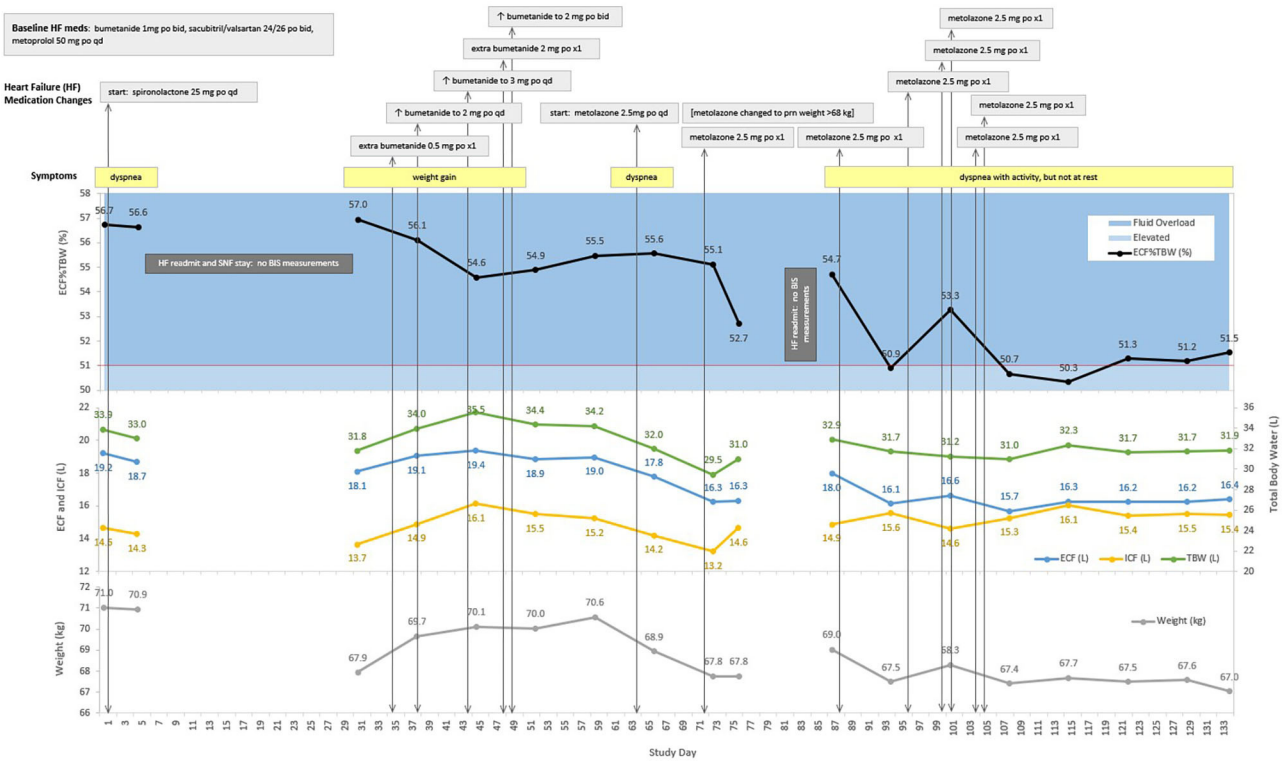


**FIGURE 5 |** Case Study: 87 year-old man with two heart failure readmissions. ECF, extracellular fluid; ICF, intracellular fluid; TBW, total body water; ECF%TBW, extracellular fluid as a percentage of total body water; mg, milligram; po, oral; qd, daily; L, liters; kg, kilograms; BIS, bioimpedance spectroscopy; SNF, skilled nursing facility. The red line at 51% ECF%TBW indicates the transition from elevated fluid volume to fluid overload.

in none of our CON-pop subjects. The next stratum (elevated: 46.4–51.0%) contains the HF-pop's interquartile range and the CON-pop's highest quartile; in this stratum, ECF%TBW and ECF tracking over time and reliance on symptoms/signs/labs are reasonable approaches. HF patients with ECF%TBW measurements falling into the normal stratum (41.5–46.4%) are likely compensated from a fluid status perspective because this range corresponds to the bottom three CON-pop quartiles. Lastly, ECF%TBW measurements <41.5% warrant further evaluation; for instance, repeat measurement for confirmation, and other assessments for potential volume depletion (e.g., orthostatic blood pressure measurement, blood urea nitrogen and creatinine laboratory values, etc.).

## Clinical Setting and Case Study

Given that the BIS device used in this report (**Figure 1**) operates while the test subject is sitting or standing without contacting metal and/or electronic objects, use in the intensive care setting is impractical. For these patients, volume status can be monitored invasively *via* pulmonary artery catheterization, and for whom fluid intake and loss is carefully tracked. BIS technology, however, may play a role in the following settings: (a) emergency departments (EDs) and urgent care centers; (b) risk stratifying HF patients at the time of hospital discharge based on the extent of residual congestion; (c) longitudinal management in clinic and skilled nursing facilities; and (d) assessing at-risk HF populations for health care managers and chief medical officers.

- Because the ED (40) and urgent care settings rely upon rapid, quantitative measures, bioimpedance-based assessment of fluid status may help facilitate triage of patients presenting with dyspnea (46). BIS measurements obtained in the ED—by serving as a point of comparison—may assist in the next phase of care if admission is required.
- HF patients, when admitted to the hospital, usually need diuresis, but knowing when sufficient decongestion has been achieved can be challenging (47). Currently, physical exams, weights, and echocardiographic measures are used to assess hydration; however, despite use of these methods, 30-day readmission rates remain high. BIS-measured ECF%TBW at the time of hospital discharge may help identify patients at high-risk of readmission owing to persistent congestion.
- In the outpatient setting, providers currently struggle with quantifying the extent of congestion. BIS may help distinguish between patients that are managed appropriately from those who may need an adjustment to their medication regimen. (47). As shown in **Figure 4**, BIS measurements correlate strongly with ultrasound-measured inferior vena cava size which has been used in clinic to manage diuresis and identify early fluid overload. Unfortunately, ultrasound is labor-intensive, requires a skilled operator, and is not always available.
- As more HF patients enter alternative payment models for care, objective measures of wellness are sought. A recent study of more than 500,000 patients (48) identified leg impedance measures as an independent risk factor for clinical deterioration; hence, BIS measurements at a population level may eventually help identify at-risk individuals. By directing resources to patients who pose the greatest risk for decline, healthcare systems can better meet the demand for high-yield care.

The case study presented in this report (**Figure 5**) is intended to provide an example of how BIS-derived fluid volume measures may be used to aid in monitoring patients with HF. It shows that ECF%TBW and ECF volume targets can be identified for heart failure patients [point (c), above]. This case also shows that patients may be discharged from hospitalizations for decompensated HF with substantial residual congestion [point (b), above]; this occurred on three occasions for this patient on study day 1 (ECF%TBW of 56.7%), day 30 (57.0%), and day 87 (54.7%).

## Limitations

As shown in **Table 3**, the CON-pop was younger than the HF-pop (median age 50.0 vs. 71.4 years, respectively). Aging is associated with a decrease in total body water and intracellular fluid due to decreases in muscle mass (42). Despite the difference in age, the current data-set demonstrates no significant difference between the ICF or TBW volumes measured between the two populations. This suggests that the populations are sufficiently matched for the purposes of this report. An age discrepancy would be more concerning in a randomized comparative efficacy trial; the intent of this report, however, is to use observational data to describe ECF%TBW values in health and HF. One of our goals was to identify healthy adult subjects to provide a range of normal ECF%TBW values; comorbidities increase with age, hence a younger control population is difficult to avoid. We set an age minimum of 40 years in order to age match the populations to the extent that was possible. Another objective was to describe higher ECF%TBW values characteristic of patients living with HF. In order to minimize confounders, individuals with hepatic or renal failure, nephrotic syndrome, lymphedema, and/or deep vein thrombosis/ thrombophlebitis were excluded. Consequently, ECF%TBW elevations were most likely due to fluid overload from known NYHA Class II or III HF rather than other causes. Finally, the degree of ECF%TBW elevation in our HF population is greater than what would be expected from advanced age alone. The highest ECF%TBW reported in NHANES III was 47.3 $\pm$ 2.0% for women aged 70–79 years (41), which is lower than the ECF%TBW we observed in our HF population (49.2 $\pm$ 3.2%).

Modest sample size and observational data collection are also potential limitations. Nevertheless, the number of control and heart failure ECF%TBW measurements was sufficient to yield statistically significant ($p < 0.001$) separation in distributions with non-overlapping interquartile ranges (**Figure 3A**). We report on 64 HF patients which, given that BIS use in HF is relatively new, is larger than HF sample sizes from previously published studies that range from five (8) to fifty (11) HF participants. The clinical strata we describe in this report represent an initial step toward quantifying fluid status in HF at the point-of-care. Refinements to account for factors such as

gender, age, and HF severity/etiology should be considered as additional data are accrued. Laboratory data (e.g., hematocrit, hemoglobin, electrolytes, and natriuretic peptide levels) and detailed information regarding left ventricular ejection fraction were not collected. These limitations will be addressed by future clinical research that should also include evaluation of outcomes (e.g., 30-day readmission rates, mortality, health care costs, etc.) based on BIS-informed HF management.

## CONCLUSION

BIS-measured ECF%TBW values were significantly higher in HF patients as compared to adults without HF. We describe three strata of ECF%TBW that include a range of normal values (41.5–46.4%) and a threshold (>51.0%) consistent with fluid overload. Other parameters, such as ECF volume and $R_0$, also differed between HF and control populations. As more data are accumulated, our results suggest that BIS measurements may provide a unique additional tool to aid in clinical decision making; however, additional BIS data controlling for confounding risk factors impacting HF will be helpful in clarifying how BIS can optimally be applied in the overall management of HF patients.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because proprietary clinical study data are reported in this article. Requests to access the datasets should be directed to bmatsubara@impedimed.com.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western IRB (Central) Scripps IRB (Scripps Memorial Hospital). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

AA: conceptualization, methodology, investigation, and writing—original draft. BM: data curation, visualization, writing—original draft, and review and editing. RG: methodology, software, formal analysis, and writing—original draft. AD-B: project administration and writing—review and editing. JH: conceptualization, investigation, writing—review and editing, and supervision. All authors: contributed to the article and approved the submitted version.

## FUNDING

The studies described herein were sponsored by ImpediMed, Inc., a corporation with an office at 5900 Pasteur Court, Suite 125, Carlsbad, CA 92008, USA; a wholly owned subsidiary of ImpediMed Limited, Unit 1, 50 Parker Court, Pinkenba, QLD 4008, Australia.

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**Conflict of Interest:** AA, AD-B, and JH provide consultancy services to ImpediMed. BM and RG are employees of ImpediMed. As funder of this clinical research, ImpediMed provided no-cost access to bioimpedance spectroscopy devices for use in accordance with clinical trial protocols. ImpediMed also provided funding for clinical trial-related costs and third-party data management and biostatistical support.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 13 May 2021
doi: 10.3389/fcvm.2021.647857

# Machine Learning for Predicting Heart Failure Progression in Hypertrophic Cardiomyopathy

*Ahmed S. Fahmy*[1], *Ethan J. Rowin*[2], *Warren J. Manning*[1,3], *Martin S. Maron*[2] *and Reza Nezafat*[1]*

[1] *Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, United States,* [2] *Division of Cardiology, Hypertrophic Cardiomyopathy Center, Tufts Medical Center, Boston, MA, United States,* [3] *Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, United States*

**Background:** Development of advanced heart failure (HF) symptoms is the most common adverse pathway in hypertrophic cardiomyopathy (HCM) patients. Currently, there is a limited ability to identify HCM patients at risk of HF.

**Objectives:** In this study, we present a machine learning (ML)-based model to identify individual HCM patients who are at high risk of developing advanced HF symptoms.

**Methods:** From a consecutive cohort of HCM patients evaluated at the Tufts HCM Institute from 2001 to 2018, we extracted a set of 64 potential risk factors measured at baseline. Only patients with New York Heart Association (NYHA) functional class I/II and LV ejection fraction (LVEF) by echocardiography >35% were included. The study cohort ($n$ = 1,427 patients) was split into three disjoint subsets: development (50%), model selection (10%), and independent validation (40%). The least absolute shrinkage and selection operator was used to select the most influential clinical variables. An ensemble of ML classifiers, including logistic regression, was used to identify patients with high risk of developing a HF outcome. Study outcomes were defined as progression to NYHA class III/IV, drop in LVEF below 35%, septal reduction procedure, and/or heart transplantation.

**Results:** During a mean follow-up of 4.7 ± 3.7 years, advanced HF occurred in 283 (20% out of 1,427) patients. The model features included patients' sex, NYHA class (I or II), HCM type (i.e., obstructive or not), LV wall thickness, LVEF, presence of HF symptoms (e.g., dyspnea, presyncope), comorbidities (atrial fibrillation, hypertension, mitral regurgitation, and systolic anterior motion), and type of cardiac medications. The developed risk stratification model showed strong differentiation power to identify patients at advanced HF risk in the testing dataset (c-statistics = 0.81; 95% confidence interval [CI]: 0.76, 0.86). The model allowed correct identification of high-risk patients with accuracy 74% (CI: 0.70, 0.78), sensitivity 80% (CI: 0.77, 0.83), and specificity 72% (CI: 0.68, 0.76). The model performance was comparable among different sex and age groups.

OPEN ACCESS

***Edited by:***
*Gaetano Ruocco,*
*Regina Montis Regalis Hospital, Italy*

***Reviewed by:***
*Mara Gavazzoni,*
*University Hospital Zürich, Switzerland*
*Kristen M. Tecson,*
*Baylor Scott and White Research Institute (BSWRI), United States*

***Correspondence:**
*Reza Nezafat*
*rnezafat@bidmc.harvard.edu*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *30 December 2020*
***Accepted:*** *29 March 2021*
***Published:*** *13 May 2021*

***Citation:***
*Fahmy AS, Rowin EJ, Manning WJ, Maron MS and Nezafat R (2021) Machine Learning for Predicting Heart Failure Progression in Hypertrophic Cardiomyopathy. Front. Cardiovasc. Med. 8:647857. doi: 10.3389/fcvm.2021.647857*

**Conclusions:** A 5-year risk prediction of progressive HF in HCM patients can be accurately estimated using ML analysis of patients' clinical and imaging parameters. A set of 17 clinical and imaging variables were identified as the most important predictors of progressive HF in HCM.

**Keywords: heart failure, hypertrophic cardiomyopathy, machine learning, risk factors, risk stratification**

## SUMMARY

Heart failure (HF) progression is the most common adverse disease consequence in hypertrophic cardiomyopathy. However, identification of at-risk patients is currently limited and predominantly relies on identifying dynamic left ventricular outflow tract obstruction, which has limited specificity and does not allow for tailored treatment planning. A few recent studies investigated the prognostic value of individual HF risk factors (e.g., left ventricular function or longitudinal strain), each with limited sensitivity and specificity. To our knowledge, no study has reported a risk stratification model for progressive HF in HCM. In this study, we present a prediction model to identify individual HCM patients who are at high risk of developing advanced HF symptoms. Our model allows personalization of individual patients' clinical course and enables the potential development of future studies investigating earlier treatment in high-risk patients to determine if this can improve patient outcomes.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease with sudden cardiac death as the most visible and devastating consequence (1–4). Much attention has been placed on the identification of HCM patients at risk for sudden death, allowing for a mature sudden death risk stratification strategy that identifies the vast majority of at-risk individuals (3, 5). However, the most common adverse consequence of HCM is the development of advanced heart failure (HF) symptoms, occurring in 35–50% of patients and leading to substantial function disability and reduced quality of life (6–8).

The mechanism of exertional disability in HCM is predominantly secondary to dynamic left ventricular (LV) outflow tract (LVOT) obstruction occurring either at rest or with provocation, with these patients at higher risk for progressive symptoms (9–11), while nonobstructive patients are at substantially lower risk for symptom progression. However, risk stratification of patients based on the LVOT obstruction falls short of specificity needed for accurate disease management and treatment planning. For example, there is limited ability to stratify patients with LVOT obstruction who are at high risk for development of HF, as compared to those who survive to advance ages with no or mild symptoms. In contrast, nonobstructive HCM patients are considered at lower risk for development of advanced HF. However, medical therapy for patients with symptomatic nonobstructive HCM is limited and patients who develop advanced HF symptoms may ultimately require cardiac transplant as the only definitive treatment option (5, 9).

Few recent studies investigated the potential prognostic value of individual imaging and clinical parameters such as LV structural and functional parameters, cardiopulmonary exercise testing parameters, serum biomarkers, and global longitudinal strain (12–14). However, there is still a limited ability to predict HF progression in HCM and there is a need for a HF risk prediction model that allows more comprehensive evaluation of the patients' clinical parameters. Machine learning (ML) algorithms provide a powerful tool for learning complex relationships between the risk predictors and outcomes from a representative sample of the patients. ML-based models have been used to predict cardiovascular events with improved accuracy and generalizability compared to traditional risk predictors (15–19). Several studies showed that further improvement can be achieved by combining a number of ML models in an ensemble utilizing their versatile characteristics (15, 20, 21). In this study, we present an ML-based HF risk prediction model in HCM patients. To avoid arbitrarily selecting a specific ML model, we followed a systematic approach to build an ensemble of models that can learn the association between HF risk and clinical and imaging risk markers. We report the performance metrics of each individual model in the ensemble to illustrate the designing steps rather than providing a rigorous comparison of the different models.

## MATERIALS AND METHODS

### Study Population and Outcome

The database of the HCM Institute at Tufts Medical Center (Boston, MA) containing data from 2,732 consecutive patients with HCM from June 2001 to Dec 2018 was interrogated. Data records for 880 patients (32%) with advanced HF symptoms at baseline (defined by New York Heart Association (NYHA) functional class III or IV) ($n = 863$), heart transplantation ($n = 1$), or septal reduction procedure ($n = 11$) or with LV ejection fraction by echocardiography <35% ($n = 5$) were excluded. Data on the most recent status of HF were obtained up to December 30, 2019, in 1,427 (77% of 1,852) patients by hospital visit or telephone contact with patients, family members, and referring physicians. Study outcomes were defined as progression in HF

**Abbreviations:** ADB, Adaptive boosted decision trees classifier; AUC, Area under curve of the receiving operator characteristics; CI, 95% Confidence interval; CMR, Cardiovascular magnetic resonance imaging; GBC, Gradient boosted decision trees classifier; HCM, Hypertrophic cardiomyopathy; HF, Heart failure; LA, Left atrium; LG, Logistic regression classifier; LV, Left ventricle; LVOT, Left ventricle outflow tract; ML, Machine learning; NYHA, New York Heart Association; NN, Neural networks; RF, Random forests; SVM, Support-vector machine.

symptoms from NYHA functional classes I/II to classes III/IV, drop in LV ejection fraction to <35%, having underwent septal reduction procedure, or having had (or added to the waiting list of) heart transplantation during follow-up. The mean ± SD follow-up duration from initial clinical evaluation at the Tufts Medical Center to the earliest of progression to class III/IV date or most recent contact was 4.7 ± 3.7 years. The average time to advanced HF symptoms in our cohort was 2.7 ± 2.6 years. The clinical diagnosis of HCM was based on two-dimensional transthoracic echocardiographic identification of otherwise unexplained hypertrophied non-dilated LV (wall thickness ≥13 mm) (3, 22). Patients had been referred for targeted subspecialty evaluations, including diagnosis, risk stratification, and treatment. Patients with phenocopies of HCM (e.g., Fabry disease, LAMP2 cardiomyopathy, PRKAG2, or amyloidosis) were excluded. This study was approved by the institutional review board at Tufts Medical Center, allowing a retrospective review of medical records and granting a waiver of informed consent in accordance with 45 CFR 46.116(d).

## Potential Risk Predictors

The model was built using potential clinical, demographic, and imaging risk markers ($n = 64$; **Supplementary Table 1**) measured at the time of initial patient evaluation including (1) baseline demographics (e.g., age and sex); (2) HF risk factors (e.g., symptoms of fatigue, dyspnea, and syncope); (3) imaging data (e.g., echocardiography LV ejection fraction, LA size, and maximum wall thickness); (4) cardiac medications (e.g., beta blocker and calcium channel blocker); and (5) comorbidities (e.g., hypertension, atrial fibrillation, stroke, and implantable cardiac device). A risk factor representing obstructive (or non-obstructive) HCM was defined by a LV outflow tract (LVOT) gradient ≥30 mmHg at rest or with provocation (i.e., exercise or Valsalva maneuver). Nonobstructive HCM was identified by a LVOT gradient <30 mmHg both at rest and with provocation. Categorical variables were replaced by an integer ranging from 0 to the maximum number of categories (as indicated in **Supplementary Table 1**). Variables with >5% missing data were not included. Missing measurements of the included variables were imputed using the *k*-nearest neighbor method, with *k* set to 1 to preserve the original variability in data distribution (23).

For the purpose of developing the HF risk model, the patients were split into three subsets (**Figure 1**): (1) development subset (713 patients (50%); (2) model-selection subset (142 patients (10%); and (3) independent-validation subset (572 patients (40%). Stratified random sampling was used to split the data such that the ratio of positive to negative HF outcomes was the same in all subsets.

## Risk Predictor Selection

The set of most important clinical variables was selected using the least absolute shrinkage and selection operator (LASSO) (24). To determine the optimal number of features, LASSO feature selection was repeated to select the best *k* features (with *k* ranging from 1 to 40). For each value of *k*, a logistic regression model was developed and evaluated using a 10-fold cross-validation scheme. In this scheme, the development dataset is split into 10 disjoint subsets, where nine subsets were used for training the model and one subset is used for model evaluation. The process was repeated 10 times to try all possible 10 different selections of training-evaluation subsets. The average model performance [measured by the area under the curve (AUC) of the receiving operating characteristics (ROC), or c-statistics] over the 10 repetitions was used to determine the optimal number, *k*, and specify the most important clinical variables.

## Model Selection

The development subset was used to train and optimize six different state-of-the-art ML classifiers: logistic regression (LG), random forests (RF), support-vector machines (SVM), gradient boosted decision trees (GBC), adaptive boosted decision trees (ADB), and neural networks (NN). Ten-fold cross-validation was used to determine the optimal model parameters. Each resulting model was then evaluated using the model-selection subset (142 patients) to determine the best model. An ensemble of the three best-performing models was used as the final HF risk stratification model. The outputs of models comprising the ensemble were merged using logistic regression. The final ensemble output was a normalized probability value (i.e., from 0 to 1) representing the patient's risk to develop HF outcome.

## Model Testing and Performance Evaluation

The final optimal models were used to predict the HF risk for the patients in the independent validation dataset. The models output a value representing the probability that a patient develops advanced HF symptoms within a 5-year follow up interval. We used AUC (or c-statistics) to estimate the discriminatory power of the model to identify patients at risk of progressive HF. An arbitrary operating point represented by a probability of 50% was used to identify patients at high risk of HF and used to compute the F1 score, sensitivity, specificity, and accuracy of each model. The contribution of each input variable to the model output for each patient (i.e., probability of developing progressive HF) was assessed by the Shapley values (25). Shapley values approximate the impact of removing the variable on the model prediction while taking into account the interactions among all variables. Model development was done using Python-V3.7 (Python Software Foundation, Fredericksburg, VA) and Scikit-learn Ver-0.23.2 (scikit-learn.org) on a PC with Quadro K620 graphics processing unit (Nvidia, Santa Clara, CA). For Shapley value computations, we used the SHapley Additive exPlanations (SHAP) analysis library (26). The final model is available at https://doi.org/10.7910/dvn/ffnlpe for external validation by other researchers.

## Statistical Data Analyses

Data are displayed as mean ± SD for continuous variables and as proportions for categorical variables. The Student (two-sample) *t*-test was used to assess statistical significance for continuous variables and *z*-test for comparing population proportions. AUC, sensitivity, specificity, and average F1 score were used to evaluate the model performance. Parametric estimation for the variance was used to compute the 95% confidence interval (CI), and a $p \leq 0.05$ was considered significant (reported as two-sided).

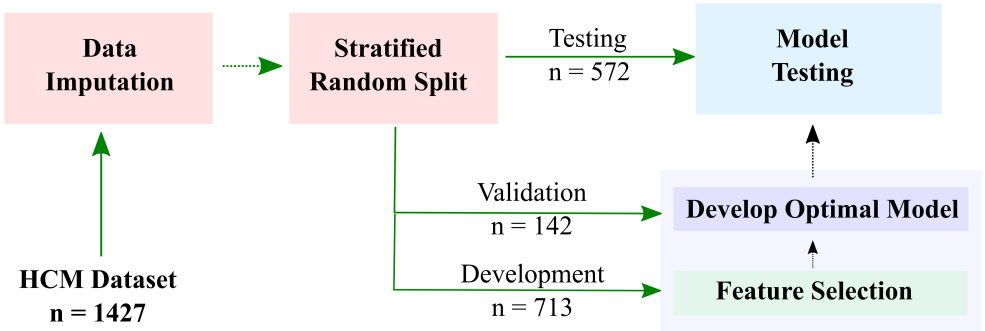


**FIGURE 1 |** Workflow of developing a machine learning-based model for predicting risk of heart failure (HF) in hypertrophic cardiomyopathy (HCM) patients. Datasets are imputed and split into development (50%), model-selection (10%), and independent-validation (40%) subsets. The development subset is used to select the most important features, and the validation subset is used for model optimization. The final HF stratification model is then used to predict HF risk in the testing subset.

Statistical calculations were performed with the Matlab statistical toolbox (version R2018b, Mathworks, Natick, MA).

## RESULTS

The mean age of the patients included in this study ($n$ = 1,427; 69% men) was 52 ± 17 years with a mean follow-up time of 4.7 ± 3.6 years (median 3.7 years). The baseline characteristics of the patient cohort are shown in **Table 1**. Twenty-three features (of 64) showed a non-zero importance score using LASSO feature selection analysis (**Figure 2**). The optimal number of important features that maximized HF risk stratification performance (c-statistics) in the development subset was 17 features (**Table 1**). Four classifiers yielded the highest three AUC scores: LG (0.79), GBC (0.79), NN (0.78), and SVM (0.78) (**Table 2**). An ensemble of LG-GBC-SVM was used as the final prediction model. The final model showed strong power to differentiate low- from high-risk patients in the testing subset (572 patients) with AUC = 0.81 [95% CI: 0.76–0.86] (**Figure 3**). The model showed accuracy of 74% [95% CI: 0.70–0.78], sensitivity of 80% [95% CI: 0.77–0.83], and specificity of 72% [95% CI: 0.68–0.76] (**Table 3**). The model performance metrics for the different age and sex subgroups was comparable and showed overlapped 95% CI, as indicated in **Table 3**. SHAP analysis showed that obstructive HCM and NYHA functional class II were associated with higher risk compared to non-obstructive HCM and NYHA functional class I (**Figure 4**). Also, presence of HF symptoms (dyspnea, fatigue, syncope, and presyncope) or abnormal heart function or structure (e.g., reduced LV ejection fraction, increased wall thickness, septal anterior motion, and mitral regurgitation) increased the risk of developing progressive HF. Also, three cardiac medications (Coumadin, beta blockers, and calcium channel blockers) showed an association with increased HF risk while the angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) was associated with low HF risk. Additionally, risk of progressive HF was higher in males and patients with history of atrial fibrillation and/or without hypertension (**Figure 4**).

## DISCUSSION

We present an ML-based study to develop and test a prediction model for progressive HF in HCM. There has previously been limited ability to predict HF risk in HCM as a number of disease features appear to impact symptom progression limiting accuracy of traditional prediction models. In our study, an ensemble of machine learning classifiers, including logistic regression, is used to accurately predict the risk of progressive HF over an average of a 5-year follow-up period. The most significant variables in our models included clinical and imaging variables that have previously been individually linked to progressive HF in HCM, but with limited accuracy. Thereby, the ability to predict progressive HF symptoms appears to be related to an interaction of these variables. We initially included all 64 measured risk factors to determine if specific symptoms (e.g., dyspnea, fatigue, or chest pain) were predictive of the development of advanced HF over time. This allowed the final model to include risk factors that are not completely independent. For example, both dyspnea and NYHA class were significant factors in the model. While dyspnea is included as part of NYHA class evaluation, notably a number of other factors ultimately play into the determination of NYHA class (e.g., degree of effort leading to dyspnea and degree of fatigue with exertion). In our cohort, 68 patients with dyspnea were in NYHA class I while 56 patients without dyspnea were in NYHA class II. All machine learning techniques studied in this work, except random forests, showed comparable accuracy (77–79%) for predicting the endpoints. An ensemble of the three best models showed a slightly higher accuracy (80%). Although the study endpoints included LV ejection fraction depression and cardiac transplantation, the small number of events during our follow-up period ($n$ = 3 and 1, respectively) does not allow separate prediction of these events. Prediction of these events separate from progression of the NYHA class requires longer follow-up periods and a larger patient cohort to account for the low incidence rate of these events.

Our results demonstrate that the model performance is comparable in male and female patients. Also, there was no statistical significance in performance among the different age

**TABLE 1 |** Baseline clinical characteristics for the hypertrophic cardiomyopathy (HCM) patients at initial clinical assessment.

| | Model input | ALL ($n$ = 1,427) | HF– ($n$ = 1,144) | HF+ ($n$ = 283) | $p$-value |
|---|---|---|---|---|---|
| Male, *n* (%) | Yes | 985 (69) | 818 (72) | 167 (59) | <0.001 |
| Age at HCM diagnosis (years), mean ± SD (median) | No | 45 ± 18 (48) | 45 ± 18 (48) | 46 ± 18 (48) | 0.55 |
| NYHA functional class | Yes | | | | |
| I, *n* (%) | | 794 (56) | 733 (64) | 61 (22) | <0.001 |
| II, *n* (%) | | 633 (44) | 411 (36) | 222 (78) | <0.001 |
| Family history of HCM, *n* (%) | No | 369 (26) | 296 (26) | 73 (26) | 0.98 |
| Family history of sudden death secondary to HCM, *n* (%) | No | 154 (11) | 41 (4) | 28 (10) | 0.58 |
| Family history of end-stage HCM, *n* (%) | No | 41 (3) | 31 (3) | 10 (4) | 0.49 |
| Obstructive HCM, *n* (%) | Yes | 747 (52) | 525 (45) | 229 (81) | <0.001 |
| LV outflow tract gradient (mmHg), mean ± SD (median) | No | 19 ± 5 (17) | 15 ± 32 (0) | 34 ± 41 (0) | <0.001 |
| Mid-cavity LV obstruction gradient (mmHg), mean ± SD (median) | No | 3 ± 12 (0) | 3 ± 12 (0) | 2 ± 12 (0) | 0.52 |
| Maximum LV wall thickness (mm), mean ± SD (median) | Yes | 19 ± 5 (17) | 18 ± 4 (17) | 20 ± 5 (19) | <0.001 |
| LV ejection fraction (%), mean ± SD (median) | Yes | 64 ± 5 (65) | 63 ± 5 (65) | 64 ± 6 (65) | 0.29 |
| LV EDD (mm), mean ± SD (median) | No | 42 ± 7 (42) | 42 ± 7 (42) | 41 ± 7 (41) | <0.001 |
| LV ESD (mm), mean ± SD (median) | No | 27 ± 6 (26) | 27 ± 6 (26) | 26 ± 5 (25) | 0.002 |
| LV apical aneurysm, n (%) | No | 42 (3) | 40 (4) | 2 (1) | <0.001 |
| LA diameter (mm), mean ± SD (median) | No | 40 ± 7 (40) | 40 ± 7 (40) | 42 ± 7 (41) | 0.001 |
| Systolic anterior motion, *n* (%) | Yes | 927 (68) | 681 (63) | 246 (89) | <0.001 |
| Mitral regurgitation, *n* (%) | Yes | 562 (39) | 410 (36) | 152 (54) | <0.001 |
| NSVT seen on ambulatory monitor, *n* (%) | No | 137 (10) | 120 (26) | 17 (6) | 0.008 |
| Syncope, *n* (%) | Yes | 139 (10) | 100 (9) | 37 (13) | 0.046 |
| Fatigue, *n* (%) | Yes | 198 (14) | 125 (11) | 73 (26) | <0.001 |
| Presyncope, *n* (%) | Yes | 71 (5) | 47 (4) | 24 (8) | 0.014 |
| Dyspnea, *n* (%) | Yes | 645 (45) | 417 (39) | 226 (80) | <0.001 |
| Hypertension, *n* (%) | Yes | 461 (32) | 379 (33) | 82 (29) | 0.17 |
| Atrial fibrillation, *n* (%) | Yes | 203 (14) | 158 (14) | 51 (18) | 0.24 |
| Patients with ICD placed prior to initial visit, *n* (%) | No | 159 (11) | 117 (10) | 42 (15) | 0.045 |
| Appropriate ICD therapy prior to initial visit, *n* (%) | No | 17 (1) | 11 (1) | 6 (2) | 0.20 |
| Resuscitated cardiac arrest prior to initial visit, *n* (%) | No | 24 (2) | 19 (2) | 5 (2) | 0.91 |
| Medications—beta blocker, *n* (%) | Yes | 807 (57) | 610 (53) | 197 (70) | <0.001 |
| Medications—calcium channel blocker, *n* (%) | Yes | 290 (20) | 212 (19) | 78 (28) | 0.002 |
| Medications—ACEi/ARB, *n* (%) | Yes | 309 (22) | 266 (23) | 43 (15) | 0.001 |
| Medications—coumadin, *n* (%) | Yes | 80 (6) | 56 (5) | 24 (8) | 0.044 |

*Data represents n (%) or mean ± SD (median). HF+, patients developed heart failure during follow-up (i.e., positive HF outcome); HF–, patients without HF outcome; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; ICD, implantable intracardiac defibrillator; LA, left atrium; LV, left ventricle; EDD, end diastolic diameter; ESD, end systolic diameter; LVOT, left ventricular out flow tract; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SD, standard deviation.*

groups. However, the model average discriminating power, measured by AUC, was relatively high (≥0.81) in patients within the 20–60-year-old groups compared to the other two groups. This may be explained by the generally high representation of patients in this age range in our dataset (62%). We also note that the limited number of positive events in the youngest age group does not allow reliable prediction of HF, which was indicated by the wide 95% CI.

Progressive and advanced HF development is the most common adverse pathway in HCM. With the availability of mature strategy for identification of patients at risk for sudden death and utilization of ICDs for sudden death prevention, HF has become the most common cause of HCM death. While most HCM patients will have a benign clinical course without HF progression, there has been an inability to identify at-risk patients, leading to uncertainty from treating clinicians as to which patients are in need for more aggressive therapy and closer clinical follow-up. Similarly, there has been uncertainty for patients regarding their disease-related natural history and individual risk. The present model allows for clarification of an individual risk and allows for a more personalized treatment approach regarding both need for closer clinical follow-up and more aggressive treatment. For example, the model can identify individual patients who may develop advanced HF with relatively high sensitivity (80%) and specificity (72%). This can open the opportunity for adopting more aggressive treatment to improve clinical outcomes in higher-risk individuals and closer follow-up. Meanwhile, it can offer a substantial reassurance that

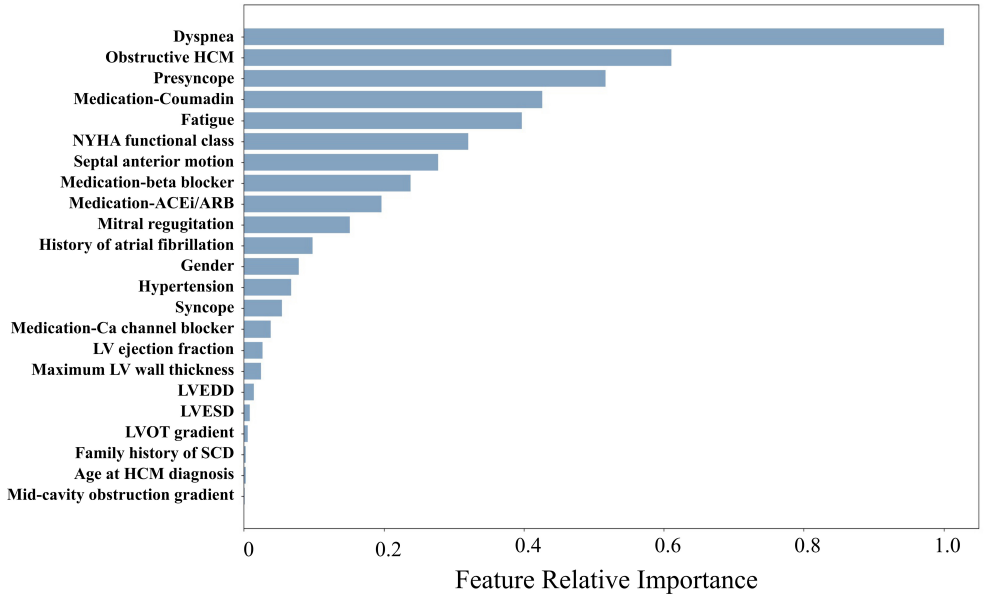


**FIGURE 2 |** Relative importance scores for the risk factors included in the study (only factors with nonzero scores are displayed).

**TABLE 2 |** Performance evaluation of the different machine learning models using the model-selection dataset (143 patients; 28 positive heart failure outcomes).

| Classifier type | AUC | ACC | Sn | Sp | F1 score |
|---|---|---|---|---|---|
| Neural networks (NN) | 0.78 | 0.68 | 0.82 | 0.65 | 0.64 |
| Support vector machines (SVM) | 0.78 | 0.69 | 0.75 | 0.68 | 0.63 |
| Random forests | 0.67 | 0.70 | 0.21 | 0.93 | 0.59 |
| Gradient boosted DT (GBC) | 0.79 | 0.69 | 0.64 | 0.70 | 0.62 |
| Adaptive boosted DT | 0.77 | 0.79 | 0.14 | 0.95 | 0.54 |
| Logistic regression (LG) | 0.79 | 0.71 | 0.71 | 0. 71 | 0.65 |
| LG + GBC + NN | 0.79 | 0.71 | 0.71 | 0.71 | 0.65 |
| LG + GBC + SVM | 0.80 | 0.71 | 0.71 | 0.71 | 0.65 |

*DT, decision trees; AUC, area under the receiver operating characteristic curve; ACC, accuracy; Sn, sensitivity; Sp, specificity.*

low-risk patients are unlikely to need interventional procedures over a 5-year period. However, we note that the presented model is developed based on a 5-year follow-up period and may not be accurate to predict HF beyond 5 years. The lack of established HF stratification models in HCM does not allow benchmarking of our model. However, we note that the stratification power and accuracy of our model are comparable to those reported for established sudden cardiac death risk stratification models (27–29).

While the impact of medical therapy to change the natural history of HCM remains controversial without data to routinely support implementation (9, 30), a more targeted approach to initiation of medical therapy specifically in patients identified at higher risk is deserving of a further study. This is particularly relevant given the ongoing research into novel therapeutic interventions in HCM, including myosin modulators which may prove more powerful treatments to alter HCM phenotype and prevent disease progression (31).

Our study has a number of limitations. First, our HF prediction model is designed to accommodate a typical clinical protocol implemented by a single medical center and is not tested using data acquired using different protocols. Also, given the longitudinal nature of our cohort with patients seen and evaluated over a 15-year period, more novel potential risk markers, such as serum biomarkers or mechanical deformation parameters such as global longitudinal strain (12), are not available but may offer additional dimensions to the model. Additionally, not every patient in this study was followed for the full 5-year term and patients who did not develop HF symptoms during the follow-up period were treated as not having the outcome of interest, which could bias the model.

In conclusion, our machine learning model allowed for accurate identification of HCM patients at risk for HF progression within a 5-year follow-up period. The model is based on 17 significant risk factors including imaging parameters (e.g., LVOT obstruction, septal anterior motion,

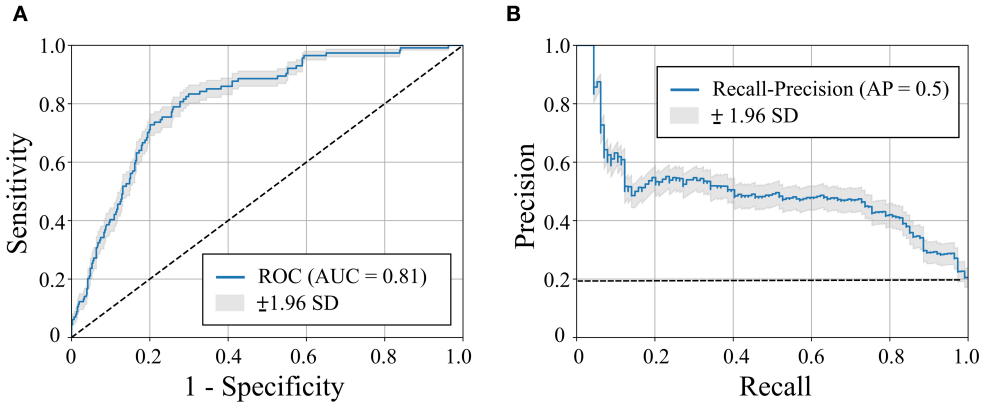


**FIGURE 3 |** Receiver operating characteristic (ROC) curve **(A)** and recall-precision curve **(B)** for the machine learning-based heart failure (HF) risk stratification in hypertrophic cardiomyopathy patients ($n = 572$). Dashed line represents pure-chance stratification AUC = 0.5 in **(A)** or precision = ratio of HF outcomes in the dataset (=20%) **(B)**. AUC = area under the curve. AP, average precision; SD, standard deviation.

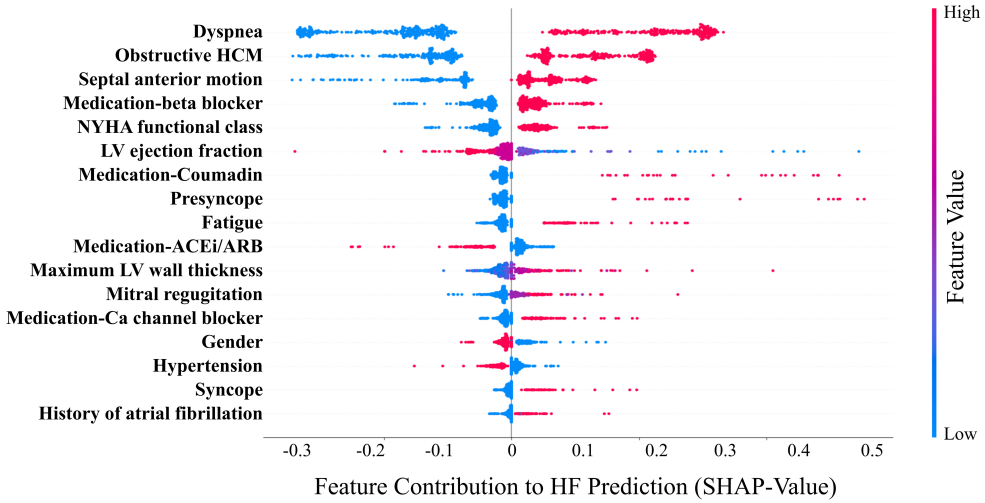


**FIGURE 4 |** Relative contribution (SHAP-values) of the model variables ($n = 17$) to heart failure (HF) prediction. Each point in the graph indicates the contribution of the corresponding clinical variable to the HF prediction of one patient. Ca, calcium; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers. HCM, hypertrophic cardiomyopathy; LV, left ventricle; NYHA, New York Heart Association.

**TABLE 3 |** Performance evaluation of the ensemble model using the independent-validation dataset.

| | AUC | ACC | Sn | Sp | F1 score |
|---|---|---|---|---|---|
| **All patients** ($n^*$ = 572; 114 HF+) | 0.81 [CI: 0.76–0.86] | 0.74 [CI: 0.70–0.78] | 0.80 [CI: 0.77–0.83] | 0.72 [CI: 0.68–0.76] | 0.68 [CI: 0.64–0.72] |
| **Female** ($n$ = 188; 55 HF+) | 0.76 [CI: 0.68–0.84] | 0.69 [CI: 0.62–0.76] | 0.80 [CI: 0.74–0.86] | 0.64 [CI: 0.57–0.71] | 0.67 [CI: 0.60–0.74] |
| **Male** ($n$ = 384; 59 HF+) | 0.81 [CI: 0.74–0.88] | 0.76 [CI: 0.72–0.80] | 0.75 [CI: 0.71–0.79] | 0.76 [CI: 0.72–0.80] | 0.66 [CI: 0.61–0.71] |
| **Age[#]: < 20 years** ($n$ = 76; 14 HF+) | 0.78 [CI: 0.63–0.93] | 0.82 [CI: 0.73–0.91] | 0.71 [CI: 0.61–0.81] | 0.84 [CI: 0.76–0.92] | 0.73 [CI: 0.63–0.83] |
| **Age: 20–40 years** ($n$ = 139; 26 HF+) | 0.84 [CI: 0.74–0. 94] | 0.74 [CI: 0.67–0.81] | 0.85 [CI: 0.79–0.91] | 0.72 [CI: 0.65–0.79] | 0.68 [CI: 0.60–0.76] |
| **Age: 40–60 years** ($n$ = 229; 46 HF+) | 0.81 [CI: 0.73–0.89] | 0.72 [CI: 0.66–0.78] | 0.85 [CI: 0.80–0.90] | 0.69 [CI: 0.63–0.75] | 0.68 [CI: 0.62–0.74] |
| **Age: ≥ 60 years** ($n$ = 128; 27 HF+) | 0.77 [CI: 0.66–0.88] | 0.65 [CI: 0.57–0.73] | 0.78 [CI: 0.71–0.85] | 0.61 [CI: 0.53–0.69] | 0.61 [CI: 0.53–0.69] |

**n* represents number of patients (of 572 patients in the testing subset). [#]Age at diagnosis of hypertrophic cardiomyopathy. HF+, positive heart failure outcomes; CI: 95% confidence interval; AUC, area under receiver operating characteristic curve; ACC, accuracy; Sn, sensitivity; Sp, specificity.*

and LV ejection fraction), cardiac medications (e.g., beta-blockers and coumadin), and physical symptoms of heart failure (e.g., dyspnea and fatigue). This may allow personalization of individual patients' clinical course into clinical practice and closer clinical follow-up in high-risk individuals. In addition, the developed models allow the opportunity for future research on implementation of earlier disease-specific treatment in high-risk patients to determine if this can prevent symptom progression and improve outcomes.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study was subjected to the following licenses/restrictions: Participant data used in this study are not publicly available at present. The source code of the machine learning algorithm implementation and the final (trained) model was available at https://doi.org/10.7910/dvn/ffnlpe.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board at Tufts Medical Center, allowing retrospective review of medical records and granting a waiver of informed consent in accordance with 45 CFR 46.116(d). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

MM and RN: guarantor of integrity of entire study. ER and MM: data acquisition. AF: algorithm implementation. AF and ER: statistical analysis. AF, ER, and RN: literature research. ER, WM, MM, and RN: clinical studies. Underlying data was accessed and verified by AF, ER, and RN. All authors conceptualization and formulation of study design and overall goals, data curation and analysis/interpretation, manuscript drafting, editing, or manuscript revision for important intellectual content, approval of final version of submitted manuscript, and agreement to ensure any questions related to the work are appropriately resolved.

## FUNDING

RN was supported by National Institutes of Health 5R01HL127015, 1R01HL154744, 5R01HL129185, and 1R01HL129157-01A1 (Bethesda, MD, USA); American Heart Association (AHA) 15EIA22710040 (Dallas, TX, USA). AF was supported by the AHA Institute for Precision Cardiovascular Medicine 19AIML34850090.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.647857/full#supplementary-material

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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.

frontiers in Cardiovascular Medicine

OPINION
published: 10 June 2021
doi: 10.3389/fcvm.2021.665424

# Diving Into the Diagnostic Score Algorithms of Heart Failure With Preserved Ejection Fraction

*Dmitry Abramov* and Purvi Parwani*

*Loma Linda University Health, Loma Linda, CA, United States*

**Keywords: heart failure, heart failure with a preserved ejection fraction, comorbidities, diagnosis, geriatrics**

Due to an aging population, heart failure with preserved ejection fraction (HFpEF) is on the rise. Yet this condition remains difficult to characterize and diagnose. There have been two recently proposed risk scores for the evaluation and diagnosis of patients with suspected HFpEF (1, 2). These include the European Society of Cardiology (ESC) consensus recommendation for the diagnosis of HFpEF (HFA-PEFF score) (1) and the $H_2$FPEF (2) score. The $H_2$FPEF score was developed from evaluation of patients with dyspnea and identified that obesity, hypertension, atrial fibrillation, pulmonary hypertension, older age (>60 years old), and evidence of elevated filling pressures on echocardiogram were associated with invasively confirmed elevation of filling pressures used as the gold standard for the HFpEF diagnosis. The HFA-PEFF score from the ESC is based on expert consensus and refers to a multi-step evaluation process of patients with dyspnea to diagnose HFpEF. The scoring systems aim to replace current simpler and phenomenological American College of Cardiology/American Heart Association definitions of HFpEF, which relies on signs and symptoms of heart failure, evidence of abnormal diastolic parameters, and preserved ejection fraction. This opinion piece offers concerns over attempts to protocolize a vastly heterogenous group of patients using diagnostic scoring systems.

## CO-MORBIDITIES ARE THE RULE

The HFA-PEFF algorithm suggests that evaluation of patients with dyspnea begin with ruling out cardiac and non-cardiac comorbid conditions that may mimic heart failure. Specifically, the algorithm targets coronary artery disease, lung disease, and anemia as comorbidities that need to be ruled out, but identifies obesity, diabetes, and atrial fibrillation as common risk factors in patients with HFpEF. However, teasing out the contribution of various comorbidities, including those that either mimic or are consistent with HFpEF, may be difficult in practice and have limited clinical implication (3).

The presence of one or more comorbid conditions like coronary artery disease, atrial fibrillation, hypertension, diabetes, renal insufficiency, pulmonary hypertension, anemia, obesity, and lung disease often defines older patients in the Western world. These comorbidities can be associated with fluid retention and dyspnea on exertion, which can mimic the signs and symptoms of heart failure. Many of these conditions, such as obesity, atrial fibrillation, systemic and pulmonary hypertension, and old age, have been specifically associated with elevated filling pressures at rest or with exercise as defined by the $H_2$FPEF score (2). However, is there a need to label these comorbidities and their associated symptoms as garden variety HFpEF? Or, should the diagnosis and management of conditions associated with dyspnea and volume overload primarily focus on the comorbidities themselves?

These are key questions because calling the effects of these conditions HFpEF may distract caregivers from the management of the causal comorbidity. Indeed, older patients with multiple

OPEN ACCESS

***Edited by:***
*Gaetano Ruocco,*
*Regina Montis Regalis Hospital, Italy*

***Reviewed by:***
*Guido Pastorini,*
*Regina Montis Regalis Hospital, Italy*
*Francesca Valentini,*
*Azienda USL Toscana Sud Est, Italy*

****Correspondence:***
*Dmitry Abramov*
*dabramov@llu.edu*

***Specialty section:***
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

***Received:*** *08 February 2021*
***Accepted:*** *19 April 2021*
***Published:*** *10 June 2021*

***Citation:***
*Abramov D and Parwani P (2021) Diving Into the Diagnostic Score Algorithms of Heart Failure With Preserved Ejection Fraction. Front. Cardiovasc. Med. 8:665424. doi: 10.3389/fcvm.2021.665424*

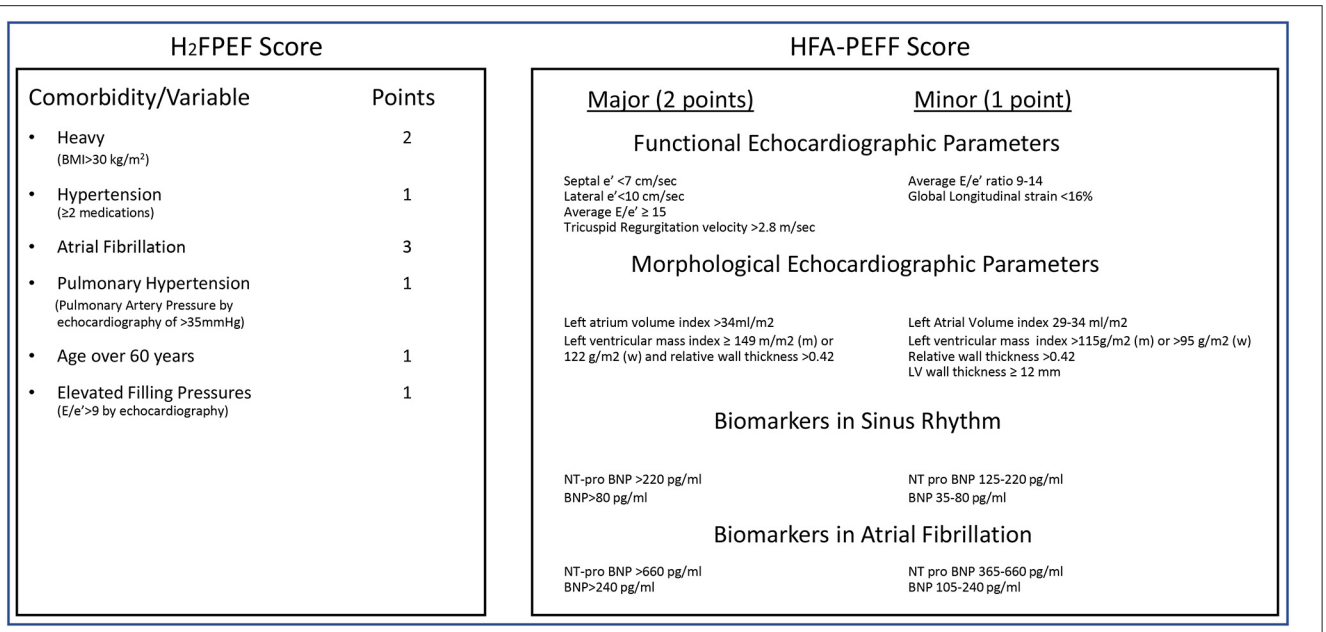


**FIGURE 1 |** Scoring algorithms for HFpEF diagnosis. $H_2$FPEF score: Patient gets points based on presence of comorbidity/variable. Low probability of HFpEF (0–1 points), Intermediate Probability of HFpEF (2–5 points), High probability of HFpEF (6–9 points). HFA-PEFF score: Each category is assessed, and patients get points if meeting a major or minor criteria. Intermediate score (2–4 points), High score consistent with HFpEF (≥ 5 points).

comorbidities are complex to evaluate and manage. The focus on the search for the HFpEF diagnosis may take the focus away from the in-depth evaluation, management, prevention, and discussion surrounding the comorbidities themselves. Medical care should always be directed at the true cause of illness, and treatment of co-morbidities has been suggested as the primary treatment of HFpEF (4). Patients with more severe manifestations of comorbidities may also have a worse prognosis, and comorbidities have been strongly associated with outcomes in patients with HFpEF (5). The prognostic implications of the HFpEF diagnosis, and the HFA-PEFF/$H_2$FPEF scores (6), may therefore be due to comorbidity burden rather than a particular cardiac pathology.

## INTEGER SCORES/INVASIVE EVALUATION FOR A DIAGNOSIS OF A COMPLEX SYNDROME

Both the HFA-PEFF and the $H_2$FPEF algorithms rely on a scoring system to assess the likelihood of HFpEF (See **Figure 1**). While the $H_2$FPEF score relies mostly on comorbidities, the HFA-PEFF scoring system is based on echocardiographic structural and functional parameters as well as natriuretic peptides. There are many challenges to the idea that an integer score, particularly as expressed in the HFA-PEFF algorithm, will help the care of complex patients.

First, the commonly used echocardiographic parameters for the diagnosis of HFpEF—diastolic abnormalities in mitral inflow and tissue Doppler as well as structural atrial enlargement or ventricular hypertrophy—have significant limitations as part of diagnostic algorithms (7) and echocardiographic subsets of HFpEF trials demonstrate a high number of patients with normal or only mildly abnormal diastolic/structural parameters. Despite these limitations, the HFA-PEFF score ultimately turns on echocardiographic structural and functional parameters with precise cut-offs to differentiate patients meeting normal, minor, and major criteria. However, strict precision in the measurement and interpretation of diastolic echocardiographic parameters may be difficult, which can complicate subsequent patient management. Based on the scoring system, many patients will score in the intermediate range, where the diagnostic algorithm becomes more complex and further evaluation with exercise diastolic stress testing or invasive hemodynamics at rest and/or with exercise is indicated (8).

Early experience with application of the diagnostic scores demonstrate significant discrepancy between the $H_2$FPEF and the HFA-PEFF scores, with about a third or more of the patients with falling into the intermediate score range (6, 9). In this community, this may lead many older and frail patients who are being evaluated for HFpEF to be subjected to invasive or exercise testing as part of the guideline evaluation algorithms. Diastolic or invasive stress testing is not widely available in the community. There is also a lack of data on the feasibility, safety, efficacy, and cost effectiveness of advanced testing in the community for this common cohort of patients, and it is therefore unclear whether the benefits of pursuing complex testing outweigh the risks. Guidelines should reserve complex and invasive testing for tertiary care centers in patients who have atypical presentations, and the complex and invasive approach

| Trial | PEP-CHF[18] | CHARM-Preserved[17] | I-PRESERVE[15] | TOPCAT[16] | PARAGON[13] | DIG-PEF[14] |
|---|---|---|---|---|---|---|
| Therapy | Perindopril | Candesartan | Irbesartan | Spironolactone | Sacubitril/Valsartan | Digoxin |
| Key Enrollment Criteria | EF>40% plus Structural Cardiac Abnormalities | EF>40% | EF≥45%, | EF≥45% and HF hospitalization or elevated BNP | EF≥45%, elevated BNP plus Structural Cardiac Abnormalities | EF>45% |
| Size | 850 | 3023 | 4128 | 3445 | 4822 | 988 |
| Key Primary Endpoint | Mortality or HF Hospitalization | Cardiovascular death or HF hospitalization | Mortality or cardiac hospitalization | Cardiovascular death, HF hospitalization | Cardiovascular death or HF hospitalization | HF death or HF hospitalization |
| Enrolled NYHA Class | Class I-II: 75%<br>Class III-IV: 25% | Class II: 61%<br>Class III-IV: 39% | Class II: 21%<br>Class III-IV: 79% | Class I-II: 67%<br>Class III-IV: 33% | Class I-II: 80%<br>Class III-IV: 20% | Class I-II: 77%<br>Class III-IV: 23% |
| Comorbidity Burden | HTN 79%<br>AF 20%<br>DM 20%<br>MI 27% | HTN 65%<br>DM 28%<br>AF 29%<br>MI 45% | HTN 89%<br>MI 24%<br>AF 29%<br>DM 28% | HTN 92%<br>AF 36%<br>DM 33%<br>MI 26%<br>COPD 12%<br>CKD 39% | HTN 96%<br>AF 33%<br>DM 44%<br>MI 22% | HTN 60%<br>MI 50%<br>DM 28% |
| Primary Outcome Rates Or Rate/100-yr* | 23.6% perindopril<br>25.1% placebo | 22% Candesartan<br>24.3% Placebo | 10.0 Irbesartan*<br>10.5 Placebo | 18.6% spironolactone<br>20.4% placebo | 12.8 Sacubitril-Valsartan*<br>14.6% Placebo | 21% Digoxin<br>24% Placebo |
| Primary Outcome | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |
| Other Comments | Improved HF hospitalization and Improved walk distance | Greater benefit with lower EF.<br>Improved hospitalization | Neutral overall | Greater benefit with lower EF | Greater benefit in women and EF below median (≤57%) | Trend for improved hospitalization but more angina |

**FIGURE 2 |** Key clinical trials involving patient with HFpEF.

is unlikely to be either feasible or beneficial for most patients in the community who have dyspnea associated with multiple comorbidities and intermediate diagnostic scores. Additionally, many asymptomatic patients in an elderly cohort demonstrated intermediate or high-risk scores by the scoring systems (6), which may increase the risks of further diagnostic testing based on non-specific symptoms and scores alone.

## RETHINKING THE LABEL "HFpEF"

Finally, the application of the term "heart failure" to label this heterogenous syndrome deserves re-evaluation. As the doctor-patient relationship continues to evolve, there is an increased focus on optimizing communication to improve a shared understanding of illness. Part of this process may require the evolution of terms such as "heart failure" that may cause harm when interpreted by patients (10–12). The labeling of these findings as heart failure in clinical practice may lead to negative patient perception, especially since uncertainty exists about the underlying causal etiology of abnormal echocardiographic or lab findings which may not result from a "failing" heart.

The focus on optimizing terminology is particularly important because the diagnosis of HFpEF, regardless of the diagnostic algorithm, may not offer much change in management unless a specific comorbidity or disease process directly amenable to clinical management (i.e., cardiac amyloidosis) is identified. Importantly, a thorough evaluation of patient signs/symptoms (such as dyspnea or BNP elevation) and echocardiographic abnormalities (such as atrial enlargement or ventricular hypertrophy) can include specialist referral, ischemic evaluation, strain echocardiography, cardiac MRI, genetic testing, or other indicated testing which can lead to specific management decisions without the need to first establish a general HFpEF diagnosis. The multiple neutral clinical trials in patients with presumed HFpEF further suggest that the approach to diagnosis and management deserves re-evaluation (**Figure 2**) (13–18). The use of integer scores for clinical trial selection or quality metrics may face similar difficulties due to grouping of a heterogeneous cohort of patients.

## CONCLUSION

Much work is needed to optimize the diagnosis and management of a heterogeneous group of patients presenting for evaluation of dyspnea and volume overload. Future evaluation and management should focus on characterization of patient populations into subgroups based on underlying pathophysiology (19, 20). Under a targeted approach to diagnosis and management, patients with comorbidities such as diabetes, chronic kidney disease, or lab abnormalities such as BNP elevation, may be candidates for future clinical trials or novel medication classes without complex diagnostic evaluation. Likewise, patients with recurrent fluid overload manifested by hospitalizations for pulmonary edema may be candidates for implantable pressure monitoring systems without necessitating a search for a specific heart failure diagnosis.

Evaluation and treatment targets based on atrial, microvascular, endothelial, and sympathetic nervous system dysfunction will continue to evolve, and these may lead to additional terminology and clinically meaningful diagnostic algorithms. In the meantime, diagnostic and management algorithms should be optimized with patients in mind, with less focus on heart failure terminology or dichotomous diagnostic cutoffs and more focus on understanding the pathophysiology of illness and obtaining management options that improve quality of life.

## AUTHOR CONTRIBUTIONS

DA and PP conceived and wrote the manuscript. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

The authors acknowledge Dr. John Mandrola for his help with the manuscript.

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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.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 03 August 2021
doi: 10.3389/fcvm.2021.697221

# Heart Failure With Midrange Ejection Fraction: Prior Left Ventricular Ejection Fraction and Prognosis

*Xinxin Zhang[1†], Yuxi Sun[1†], Yanli Zhang[1], Feifei Chen[1], Shuyuan Zhang[1], Hongyan He[1], Shuang Song[1], Gary Tse[1,2*] and Ying Liu[1*]*

[1] Heart Failure and Structural Cardiology Ward, The First Affiliated Hospital of Dalian Medical University, Dalian, China, [2] Kent and Medway Medical School, Canterbury, United Kingdom

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**Edited by:**
Yasuhiro Ikeda,
Yamaguchi Prefectural Grand Medical Center, Japan

**Reviewed by:**
Makoto Takei,
Keio University, Japan
Masashi Kanemoto,
Saiseikai Yamaguchi General Hospital, Japan
Kenichi Hongo,
Jikei University School of Medicine, Japan

***Correspondence:**
Ying Liu
yingliu.med@gmail.com
Gary Tse
garytse86@gmail.com

[†] These authors have contributed equally to this work and share first authorship

**Specialty section:**
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

**Received:** 26 April 2021
**Accepted:** 29 June 2021
**Published:** 03 August 2021

**Citation:**
Zhang X, Sun Y, Zhang Y, Chen F, Zhang S, He H, Song S, Tse G and Liu Y (2021) Heart Failure With Midrange Ejection Fraction: Prior Left Ventricular Ejection Fraction and Prognosis. Front. Cardiovasc. Med. 8:697221. doi: 10.3389/fcvm.2021.697221

**Aims:** Evidence-based guidelines for heart failure management depend mainly on current left ventricular ejection fraction (LVEF). However, fewer studies have examined the impact of prior LVEF. Patients may enter the heart failure with midrange ejection fraction (HFmrEF) category when heart failure with preserved ejection fraction (HFpEF) deteriorates or heart failure with reduced ejection fraction (HFrEF) improves. In this study, we examined the association between change in LVEF and adverse outcomes.

**Methods:** HFmrEF patients with at least two or more echocardiograms 3 months apart at the First Affiliated Hospital of Dalian Medical University between September 1, 2015 and November 30, 2019 were identified. According to the prior LVEF, the subjects were divided into improved group (prior LVEF $< 40\%$), stable group (prior LVEF between 40 and 50%), and deteriorated group (prior LVEF $\geq 50\%$). The primary outcomes were cardiovascular death, all-cause mortality, hospitalization for worsening heart failure, and composite event of all-cause mortality or all-cause hospitalization.

**Results:** A total of 1,168 HFmrEF patients (67.04% male, mean age $63.60 \pm 12.18$ years) were included. The percentages of improved, stable, and deteriorated group were 310 (26.54%), 334 (28.60%), and 524 (44.86%), respectively. After a period of follow-up, 208 patients (17.81%) died and 500 patients met the composite endpoint. The rates of all-cause mortality were 35 (11.29%), 55 (16.47%), and 118 (22.52%), and the composite outcome was 102 (32.90%), 145 (43.41%), and 253 (48.28%) for the improved, stable, and deteriorated groups, respectively. Cox regression analysis showed that the deterioration group had higher risk of cardiovascular death (HR: 1.707, 95% CI: 1.064–2.739, $P = 0.027$), all-cause death (HR 1.948, 95% CI 1.335–2.840, $P = 0.001$), and composite outcome (HR 1.379, 95% CI 1.096–1.736, $P = 0.006$) compared to the improvement group. The association still remained significant after fully adjusted for both all-cause mortality (HR = 1.899, 95% CI 1.247–2.893, $P = 0.003$) and composite outcome (HR: 1.324, 95% CI: 1.020–1.718, $P = 0.035$).

**Conclusion:** HFmrEF patients are heterogeneous with three different subsets identified, each with different outcomes. Strategies for managing HFmrEF should include previously measured LVEF to allow stratification based on direction changes in LVEF to better optimize treatment.

**Keywords: heart failure, mid-range ejection fraction, prior, left ventricular ejection fraction, prognosis**

# INTRODUCTION

Heart failure (HF) represents the final common pathway of different cardiac diseases and is a major cause of death among the elderly in many countries (1–4). Currently, risk management and treatment of HF mainly depend on current left ventricular ejection fraction (LVEF) in clinical practice (5, 6). In the latest European Society of Cardiology (ESC) guideline, HF was divided into HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF) based on LVEF (7). HFmrEF patients are encountered with an increasing frequency in contemporary HF clinics (8). The latest data show that the prevalence of HFmrEF in hospitalized patients ranged from 13 to 26% (9–11), while the prevalence in outpatients varied from 9 to 21% (12–17). Nevertheless, previous studies mostly focused on HFrEF and HFpEF, with less attention paid to HFmrEF until now (18, 19). Consequently, less is known regarding the clinical characteristics of patients with HFmrEF, and with limited evidence on which to base recommendation for therapy (20).

Indeed, LVEF can be dynamic as the condition of the patient changes. To date, many investigators have been devoting to working on LVEF transition, exploring the incidence, predictors, and associations with outcomes of changes in LVEF in HF patients (21, 22). Some investigators have suggested that HFmrEF patients do not represent a distinct group, but rather represent a heterogeneous group of HFrEF and HFpEF patients, in whom a change in LVEF resulted in their being categorized as a unique subset of HF patients. In their view, HFmrEF represents a transitional state, and can easily progress to HFpEF or HFrEF. However, it must be pointed that transition into the HFmrEF category may also occur by either deterioration or improvement of LVEF. Up to now, there are few studies available describing their characteristics and clinical outcomes. In this study, we examined the association between changes in LVEF and adverse outcomes.

# MATERIALS AND METHODS

## Study Population

This retrospective cohort study was approved by the institutional review board of the First Affiliated Hospital of the Dalian Medical University. The inclusion criteria were patients admitted for acute decompensated HF at the First Affiliated Hospital of Dalian Medical University between September 1, 2015 and November 31, 2019. The exclusion criterion was a lack of prior echocardiography for comparison. Details of clinical characteristics, comorbidities, drug therapies, laboratory values, and echocardiography findings of the subjects were collected and recorded from Yidu Cloud. All procedures were conducted in accordance with the Declaration of Helsinki. As this was a retrospective research, no informed consents can be obtained.

## Classification of HF Cases

We classified current HFmrEF patients as having (1) improved group (defined as any previously documented LVEF $< 40\%$), (2) stable group (defined as all previously documented LVEF between 40 and 50%), and (3) deteriorated group (defined as at least one previously documented LVEF $\geq 50\%$). The study flow chart was shown in **Figure 1**.

## Clinical Definitions

HF is defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion (23). According to echocardiographic data, patients with an EF from 40 to 50% were categorized as HFmrEF.

## Adverse Outcomes

Cardiovascular death, all-cause death, and hospitalization for worsening HF were determined using the Yidu Cloud with complete follow-up through November 30, 2020. The composite endpoint was defined as all-cause hospitalization or all-cause mortality. If these data were unavailable, the status was ascertained by a telephone calling to the patients.

## Statistical Analysis

Statistical analysis was performed using SPSS Statistical Software, Version 22.0 (SPSS Inc., Chicago, IL, USA). Patients' characteristics were summarized with continuous variables expressed as means ± standard deviation and categorical variables presented as frequencies and percentages. Measurement data with a non-normal distribution were expressed as the median (interquartile range). The Kruskal-Wallis test was used for multi-group comparisons, and single-factor ANOVA was used for inter-group comparison. Characteristics were compared across HFmrEF groups using analysis of variance or chi-square tests, as appropriate. Kaplan-Meier analysis was used to describe the cumulative incidence of adverse events, and the long-rank test was used to compare differences.

Univariate and multivariate Cox proportional hazards regression models were used to investigate the risk factors of the endpoints. Covariates selected for multivariate Cox analysis come from either the one with a significance of $P < 0.05$ in the univariate analysis or the one that had been proven to greatly affect the prognosis of HF (**Supplementary Tables 1, 2**), including age, male, coronary artery disease, hypertension, diabetes mellitus, cerebrovascular disease, ICD, beta-blockers, ACEI/ARB/ARNI, spironolactone, loop diuretics, aspirin, statins, nitrates, hemoglobin, BNP, creatinine, plasma sodium, d-dimer, and time interval. The hazard ratios (HR) and 95% confidence intervals (CI) compare clinical outcomes of cardiovascular death, all-cause death, hospitalization for worsening HF, and composite event of all-cause hospitalization or all-cause mortality for stable group compared with improved group (unadjusted and fully adjusted) and deteriorated group compared with improved group (unadjusted and fully adjusted). All *P*-values represent the significance of the HRs for stable group compared with improved group or deteriorated group compared with improved group. All values were two-tailed, and $P < 0.05$ was considered statistically significant.

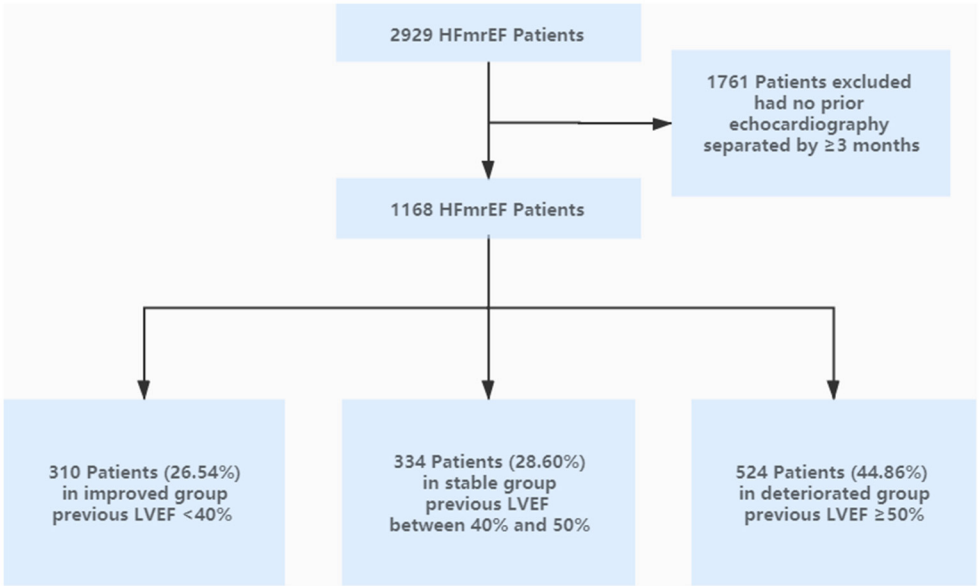


**FIGURE 1 |** Flow diagram of patient flow.

# RESULTS

## Demographic and Clinical Characteristics

Of 2,929 patients who had physician-diagnosed HFmrEF at our institution during September 1, 2015 and November 30, 2019, 1,761 patients were excluded due to the lack of availability of an echocardiogram separated by >3 months apart for comparison. A total of 1,168 patients were included (67.04% male, mean age 63.60 ± 12.18 years). The percentages of improved, stable, and deteriorated group were 310 (26.54%), 334 (28.60%), and 524 (44.86%), respectively. The flow chart indicating the inclusion and exclusion criteria was shown in **Figure 1**.

The baseline characteristics were shown in **Table 1**. In brief, patients in improved group were younger, had a higher proportion of males, and had a lower frequency of coronary artery disease, cancer, and hypertension compared with those in stable and deteriorated groups. There was no statistical difference in the proportion of NYHA class III–IV between the three groups at the prior echocardiogram. By contrast, improved group showed relative lower prevalence of NYHA class III–IV at the time of inclusion compared to the remaining two groups. Regarding medical therapies, patients in improved group were more likely to take angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)/angiotensin receptor neprilysin inhibitor (ARNI), beta-blockers, spironolactone, loop diuretics, and CRT compared to patients in the remaining two groups. As for laboratory data, the level of white blood cell, hemoglobin, platelet count, uric acid, and BNP in the improved group were significantly higher than other two groups. The average time interval between the two echocardiogram was 16 months. The interval in the deteriorated group was longer than that of the remaining two groups. Prior echocardiography findings showed that patients in improved group had higher left ventricular diameter and left atrial diameter, whereas with lowest value of interventricular septal thickness. Echocardiography findings at the time of inclusion indicated LVEF in all three subgroups fluctuated between 40 and 50, and the value of LVEF in deteriorated group was higher than that of improved group. Moreover, improved group still had the highest left ventricular diameter among the three subgroups; nevertheless, there was no statistical significance across the three groups for the remainder of the parameters.

## Clinical Outcomes

Over a median follow-up of 40.00 [25.00–53.00] months, there were 208 patients (17.81%) deaths, and the percentages of improved, stable, and deteriorated group were 35 (11.29%), 55 (16.47%), and 118 (22.52%), respectively. Five hundred patients met the composite endpoint (42.81%), and the number were 102 (32.90%), 145 (43.41%), and 253 (48.28%) for the improved, stable, and deteriorated groups, respectively. Kaplan-Meier analysis showed that the mortality and composite outcome in improved group was significantly lower than that in stable and deteriorated groups (**Figures 2**, **3**). However, there was no statistical difference in the rates of cardiovascular death and hospitalization for worsening HF among the three subsets (**Supplementary Figures 1, 2**).

Cox regression analysis indicated that the deteriorated group showed a significantly higher risk of composite endpoint compared with patients in improved group (HR 1.379, 95% CI 1.096–1.736, $P = 0.006$). This difference was mainly due to trends toward increased risk of all-cause mortality (HR 1.948, 95% CI 1.335–2.840, $P = 0.001$). The association remained significant after adjustment for potential confounders for both mortality (HR = 1.899, 95% CI 1.247–2.893, $P = 0.003$) and

**TABLE 1 |** Baseline demographics and clinical characteristics of the enrolled heart failure patients stratified by the directional change in LVEF.

| Characteristics | All patients ($n$ = 1,168) | Improved group ($n$ = 310) | Stable group ($n$ = 334) | Deteriorated group ($n$ = 524) | $P$-value |
|---|---|---|---|---|---|
| Age (years) | 63.60 ± 12.18 | 60.08 ± 13.08$^{\Psi\dagger}$ | 62.92 ± 12.10$^{*\dagger}$ | 66.11 ± 11.09$^{*\Psi}$ | <0.0001 |
| Male (*n*, %) | 783 (67.04%) | 226 (72.90%)$^{\dagger}$ | 237 (70.96%)$^{\dagger}$ | 320 (61.07%)$^{*\Psi}$ | 0.0004 |
| Systolic blood pressure (mmHg) | 136.2 ± 23.33 | 133.0 ± 22.22$^{\dagger}$ | 136.3 ± 23.25 | 138.0 ± 23.86$^{*}$ | 0.0118 |
| Diastolic blood pressure (mmHg) | 80.46 ± 13.77 | 81.85 ± 14.11$^{\dagger}$ | 80.77 ± 13.23 | 79.43 ± 13.84$^{*}$ | 0.0437 |
| Heart rates | 82.21 ± 22.02 | 85.76 ± 21.03$^{\dagger}$ | 82.60 ± 22.87 | 79.85 ± 21.79$^{*}$ | 0.0009 |
| Body weight (kg) | 73.77 ± 13.26 | 75.84 ± 15.13$^{\dagger}$ | 74.38 ± 13.10 | 72.22 ± 11.97$^{*}$ | 0.0037 |
| Body mass index (kg/m$^2$) | 26.15 ± 4.034 | 26.66 ± 4.1 | 25.29 ± 3.70 | 26.27 ± 4.15 | 0.5814 |
| Prior NYHA class III–IV (*n*, %) | 322 (27.56%) | 84 (27.10%) | 95 (28.44%) | 143 (27.29%) | 0.9126 |
| NYHA class III–IV at the time of inclusion (*n*, %) | 406 (34.76%) | 89 (28.70%)$^{\Psi\dagger}$ | 130 (38.92%)$^{*}$ | 187 (35.68%)$^{*}$ | 0.0204 |
| **Comorbidities** | | | | | |
| Coronary artery disease (*n*, %) | 633 (54.20%) | 148 (47.74%)$^{\Psi\dagger}$ | 187 (55.99%)$^{*}$ | 298 (56.87%)$^{*}$ | 0.0258 |
| Atrial fibrillation (*n*, %) | 310 (26.54%) | 67 (21.61%) | 93 (27.84%) | 150 (28.63%) | 0.0699 |
| Cancer (*n*, %) | 52 (5.65%) | 10 (3.26%)$^{\dagger}$ | 15 (4.49%) | 41 (7.82%)$^{*}$ | 0.0116 |
| Cerebrovascular disease (*n*, %) | 179 (15.33%) | 36 (11.61%) | 55 (16.47%) | 88 (16.79%) | 0.1055 |
| Diabetes mellitus (*n*, %) | 414 (35.45%) | 97 (31.29%) | 125 (37.43%) | 192 (36.54%) | 0.1980 |
| Hypertension (*n*, %) | 719 (61.56%) | 166 (53.55%)$^{\Psi\dagger}$ | 211 (63.17%)$^{*}$ | 342 (65.27%)$^{*}$ | 0.0027 |
| **Therapy** | | | | | |
| ACEI/ARB/ARNI (*n*, %) | 652 (55.82%) | 187 (60.32%)$^{\dagger}$ | 197 (58.98%)$^{\dagger}$ | 268 (51.15%)$^{*\Psi}$ | 0.0139 |
| Aspirin (*n*, %) | 683 (58.48%) | 176 (56.77%) | 209 (62.57%) | 298 (56.87%) | 0.1982 |
| Beta-blockers (*n*, %) | 885 (75.77%) | 266 (85.81%)$^{\Psi\dagger}$ | 267 (79.94%)$^{*\dagger}$ | 352 (67.18%)$^{*\Psi}$ | <0.0001 |
| Digoxin (*n*, %) | 154 (13.18%) | 62 (20.00%)$^{\dagger}$ | 36 (10.78%)$^{*}$ | 56 (10.69%)$^{*}$ | 0.0002 |
| Loop diuretics (*n*, %) | 432 (36.99%) | 145 (46.77%)$^{\Psi\dagger}$ | 121 (36.23%)$^{*}$ | 166 (31.69%)$^{*}$ | <0.0001 |
| Nitrates (*n*, %) | 438 (37.50%) | 103 (33.23%)$^{\Psi}$ | 144 (43.11%)$^{*}$ | 191 (36.45%) | 0.0280 |
| Spironolactone (*n*, %) | 596 (51.03%) | 227 (73.23%)$^{\Psi\dagger}$ | 173 (51.80%)$^{*\dagger}$ | 196 (37.40%)$^{*\Psi}$ | <0.0001 |
| Statins (*n*, %) | 763 (65.33%) | 197 (63.55%) | 235 (70.36%) | 331 (63.17%) | 0.0726 |
| Warfarin (*n*, %) | 226 (19.35%) | 55 (17.74%)$^{\dagger}$ | 52 (15.57%)$^{\dagger}$ | 119 (22.71%)$^{*\Psi}$ | 0.0252 |
| Pacemaker (*n*, %) | 81 (6.93%) | 14 (4.52%) | 22 (6.59%) | 45 (8.59%) | 0.0784 |
| ICD (*n*, %) | 18 (1.54%) | 8 (2.58%) | 5 (1.50%) | 5 (0.95%) | 0.1825 |
| CRT (*n*, %) | 22 (1.88%) | 14 (4.52%)$^{\Psi\dagger}$ | 5 (1.50%)$^{*}$ | 3 (0.57%)$^{*}$ | 0.0002 |
| **Laboratory values** | | | | | |
| White blood cell (10∧9/L) | 7.655 ± 3.135 | 8.061 ± 3.386$^{\dagger}$ | 7.595 ± 3.007 | 7.452 ± 3.042$^{*}$ | 0.0231 |
| Hemoglobin (g/L) | 136.9 ± 21.64 | 141.1 ± 21.85$^{\Psi\dagger}$ | 136.9 ± 20.66$^{*}$ | 134.4 ± 21.77$^{*}$ | <0.0001 |
| Platelet (10∧9/L) | 208.7 ± 66.64 | 222.4 ± 80.98$^{\Psi\dagger}$ | 202.0 ± 59.32$^{*}$ | 205.0 ± 60.34$^{*}$ | 0.0001 |
| Creatinine (μmol/L) | 76.00 (62.00, 97.00) | 79 (64.25, 99.00) | 76.00 (63.00, 98.00) | 74.00 (61.00, 95.00) | 0.6160 |
| UA (μmol/L) | 409.4 ± 138.0 | 440.9 ± 161.1$^{\Psi\dagger}$ | 412.5 ± 131.9$^{*}$ | 390.3 ± 124.5$^{*}$ | <0.0001 |
| $Na^+$ (mmol/L) | 141.7 ± 3.130 | 141.6 ± 3.169 | 141.6 ± 3.021 | 141.7 ± 3.179 | 0.7728 |
| Glu (mmol/L) | 6.351 ± 2.614 | 6.370 ± 2.853 | 6.373 ± 2.489 | 6.326 ± 2.560 | 0.9619 |
| D-dimer (μg/L) | 420 (210.0, 970.0) | 410 (210.0, 970.0) | 410 (190.0 880.0) | 455.0 (230.0, 1,025) | 0.2193 |
| BNP level (ng/L) | 317.5 (119.9, 779.4) | 506.7 (183.5, 1,168)$^{\dagger}$ | 337.4 (127.0, 922.1)$^{\dagger}$ | 231.2 (90.40, 517.9)$^{*\Psi}$ | <0.0001 |
| **Echocardiography parameters** | | | | | |
| Time interval (months) | 16.00 (7.250, 29.00) | 12.00 (6.000, 26.00)$^{\dagger}$ | 13.50 (7.000, 27.00)$^{\dagger}$ | 19.00 (10.00, 31.00)$^{*\Psi}$ | <0.0001 |
| **Prior echocardiography findings** | | | | | |
| Left ventricular ejection fraction (%) | 46.26 ± 10.57 | 32.41 ± 5.626$^{\Psi\dagger}$ | 43.61 ± 2.711$^{*\dagger}$ | 56.16 ± 3.088$^{*\Psi}$ | <0.0001 |

*(Continued)*

**TABLE 1** | Continued

| Characteristics | All patients ($n$ = 1,168) | Improved group ($n$ = 310) | Stable group ($n$ = 334) | Deteriorated group ($n$ = 524) | $P$-value |
|---|---|---|---|---|---|
| Left ventricular diameter (mm) | 53.52 ± 7.875 | 59.69 ± 7.213$^{\Psi\dagger}$ | 54.22 ± 6.706$^{*\dagger}$ | 49.61 ± 6.466$^{*\Psi}$ | <0.0001 |
| Left atrial diameter (mm) | 42.44 ± 7.225 | 44.02 ± 6.313$^{\Psi\dagger}$ | 42.64 ± 6.711$^{*\dagger}$ | 41.44 ± 7.838$^{*\Psi}$ | <0.0001 |
| Interventricular septal thickness (mm) | 10.68 ± 1.914 | 10.38 ± 1.661$^{\Psi\dagger}$ | 10.80 ± 1.951$^{*}$ | 10.78 ± 2.007$^{*}$ | 0.0103 |
| E/e′ | 13.02 ± 5.621 | 13.46 ± 5.383 | 13.47 ± 6.075 | 12.38 ± 5.372 | 0.0534 |
| **Echocardiography findings at the time of inclusion** | | | | | |
| Left ventricular ejection fraction (%) | 43.75 ± 2.875 | 43.35 ± 2.874$^{\dagger}$ | 43.70 ± 2.757 | 44.02 ± 2.925$^{*}$ | 0.0047 |
| Left ventricular diameter (mm) | 53.92 ± 6.604 | 56.24 ± 6.259$^{\Psi\dagger}$ | 54.78 ± 6.759$^{*\dagger}$ | 51.84 ± 6.076$^{*\Psi}$ | <0.0001 |
| Left atrial diameter (mm) | 42.85 ± 6.782 | 42.28 ± 6.630 | 43.52 ± 6.433 | 42.77 ± 7.079 | 0.0682 |
| Interventricular septal thickness (mm) | 10.76 ± 1.998 | 10.55 ± 1.871 | 10.73 ± 2.153 | 10.90 ± 1.960 | 0.0568 |
| E/e′ | 13.07 ± 5.628 | 12.19 ± 5.645 | 13.18 ± 5.344 | 13.49 ± 5.770 | 0.0668 |

*NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; BNP, B-type natriuretic peptide; Glu, glucose; UA, uric acid; E/e′, mitral Doppler early velocity/mitral annular early velocity. * is compared with Improved group $P < 0.05$, Ψ is compared with Stable group $P < 0.05$, † is compared with Deteriorated group $P < 0.05$.*

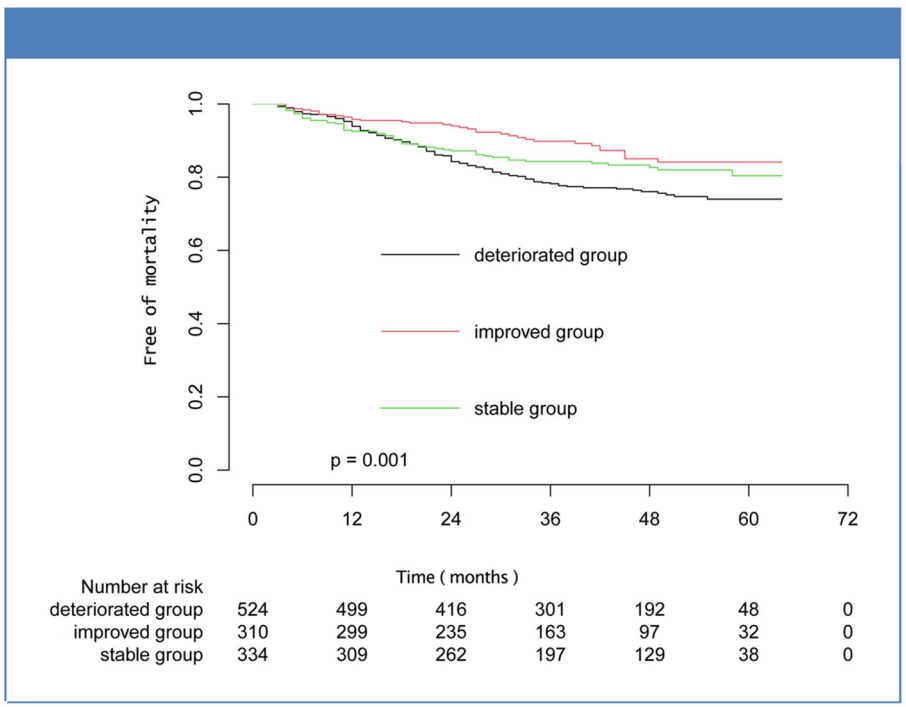


**FIGURE 2 |** Kaplan-Meier curves for mortality for the subsets of heart failure with midrange ejection fraction.

composite outcome (HR: 1.324, 95% CI: 1.020–1.718, $P = 0.035$). Moreover, compared to improved group, deteriorated group also experienced a 1.71-fold increase in risk of cardiovascular death (HR: 1.707, 95% CI: 1.064–2.739, $P = 0.027$), albeit not reaching statistical significance in fully adjusted analysis. As with outcomes for hospitalization for worsening HF, HRs between the three subgroups did not show statistical differences. In addition, no significant differences in outcomes between patients in the improved and stable groups were seen for any of the endpoints in either unadjusted or fully adjusted analysis. The results were shown in **Figure 4**.

## DISCUSSION

This study demonstrated that HFmrEF patients were a heterogeneous group of patients comprised of at least three different subsets. Additionally, the characteristics and clinical

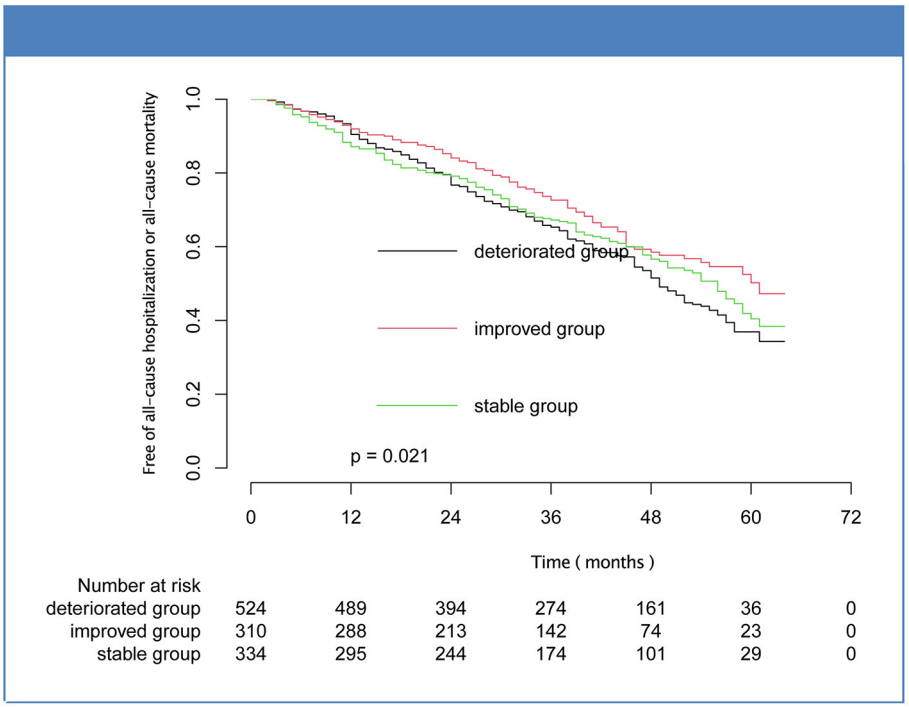


**FIGURE 3 |** Kaplan-Meier curves for composite outcome of mortality or hospitalization for the subsets of heart failure with midrange ejection fraction.

outcomes of HFmrEF patients among subgroups defined by the prior directional changes in LVEF are significantly different.

Risk stratification in HF is an important clinical problem (24, 25). Previous studies have elucidated that the demographics of patients with HFmrEF lied in between those of HFpEF and HFrEF patients, but in general were more similar to HFpEF patients, with a heavier burden of hypertension and atrial fibrillation/flutter (10, 12, 13, 26). Nevertheless, HFmrEF also resembled HFrEF showing a higher burden of ischemic heart disease (9, 27–29). In our study, we found that the HFmrEF cohort suffered from a heavy burden of comorbidities, such as hypertension (61.56%), coronary heart disease (54.20%), and atrial fibrillation/flutter (26.54%). Our research also indicated that the characteristics of patients within HFmrEF subgroup were significantly different from the HFrEF and HFpEF subgroups. For example, patients in the deteriorated group were older, more female, and more likely to have hypertension, which were features consistent with HFpEF. By contrast, the deteriorated cohort had higher prevalence of coronary artery disease, which was in keeping with a HFrEF phenotype.

Regarding treatment, previous literatures suggested that HFmrEF patients received a mixture of medications indicated for both HFrEF and HFpEF patients (30, 31). Indeed, our study found that HFmrEF patients were prescribed medications recommended for HFrEF (digoxin, ACEI or ARB) as well as for HFpEF (calcium channel blockers). In our cohort, more than 50% patients received the traditional first-line agents of beta-blockers, ACEI/ARB, and aldosterone antagonist. Moreover, we found that patients in the improved group were more likely to take beta-blockers, ACEI/ARB/ARNI, spironolactone, and CRT than patients in the remaining two groups. The reason may be that neurohormonal blocking agents were only recommended for the patients with HFrEF but not HFpEF in HF management guidelines. Overall, these discrepancies underscored the considerable heterogeneity between patients in the HFmrEF population.

Notably, prior studies illustrated that the prognosis of HFmrEF patients was distinct from those of HFrEF and HFpEF. A 5-year follow-up of mortality showed that all-cause mortality in HFmrEF was higher than the rate of HFpEF patients, but lower than that of HFrEF patients (32, 33). However, HFmrEF mortality at 1 year after discharge was similar to that of HFpEF (10, 34, 35). The findings from four community-based longitudinal cohorts showed that age was an important clinical predictor of new onset HFmrEF (27). Meanwhile, a latest separate study demonstrated age ≥80 years was associated with a higher risk of mortality within 1 year following discharge in the HFmrEF group compared with other HF types (35). In this study, our results also identified age as an independent risk factor for both mortality and composite outcome. Moreover, we found the adverse events of patients with HFmrEF varied considerably between subgroups and the clinical course was closely associated with the directional changes in LVEF that brought them into the mid-range. Unsurprisingly, patients in deteriorated group had a worse prognosis compared to other HFmrEF phenotypes, with a remarkably increased risk of a median follow-up of 40.00 months mortality and hospitalization, indicating the urgent need for careful follow-up of this group. The unfavorable outcomes may

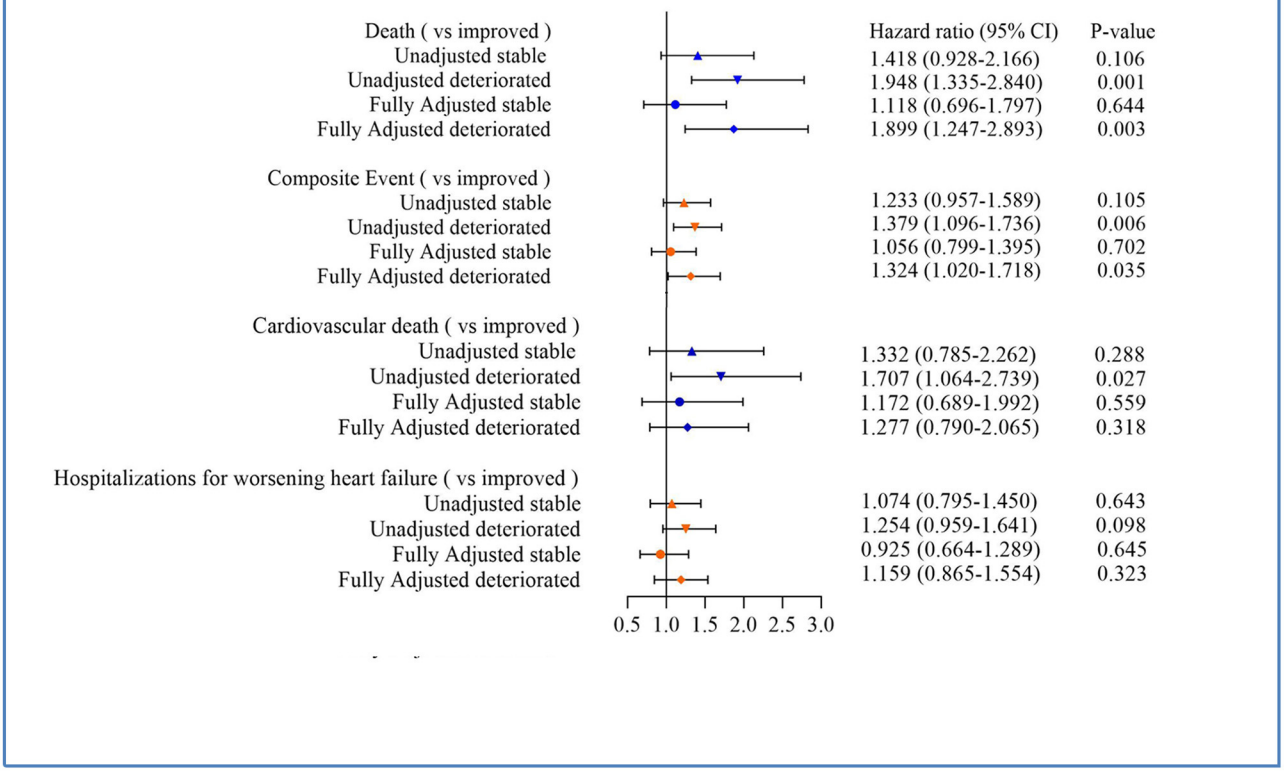


**FIGURE 4 |** Forest plot of clinical outcomes in HFmrEF subgroups.

be related to a large reduction of LVEF and a substantial increase in LV diameter in deteriorated group. The adverse alternations in cardiac structure and function are most likely due to the lower usage of guideline-directed medical therapy and the relatively high prevalence of coronary artery disease, as coronary artery disease was always associated with higher risk of mortality and worsening LVEF. In the large Improve Heart Failure Therapies in the Outpatient Setting registry, patients without prior myocardial infarction and non-ischemic HF etiology were both associated with a >10% improvement in LVEF (36).

These findings suggested that for HFmrEF patients, previous changes in the direction of LVEF may provide important prognostic value, and clinicians should consider previous changes in LVEF when devising treatment plans.

## Limitations

Nevertheless, we must note that this study still has several limitations. Firstly, considering the single-center nature of our study, the findings may not be generalizable to other settings. Secondly, the interval between the prior echocardiogram and the inclusion to the study was not exactly the same. Patients with echocardiography assessments within a short time period might have been less likely to exhibit a change in EF category. Although multivariate Cox regression models were applied to adjust for the interval between echocardiography assessments, residual confounding might have been a limitation. Thirdly, we can only obtain the medical record of patients hospitalized at our center, and we have no way of confirming when HF was first diagnosed, as this might have taken place at other hospitals. Thus, in this study, not every patient's echocardiogram time relative to initial HF diagnosis can be clearly recorded. Lastly, clinical outcomes were ascertained mainly depending on a telephone calling to the patients. Therefore, only a small number of patients in this cohort underwent the last follow-up echocardiography. In the near future, a large prospective cohort or a randomized-controlled study is necessary to understand the characteristics and evaluate the effects of drugs in HFmrEF population.

## Conclusions

In conclusion, differences in the prevalence of risk factors and underlying etiology may generate different effects on LVEF transition, and thus different outcomes. The condition of HFpEF to HFmrEF is a dangerous and complex pathological process, which always implied worse clinical outcomes. These findings would remind clinicians to pay more attention to previous echocardiography results in HFmrEF patients, and to consider the impact of direction changes in LVEF on the prognosis of patients when planning management strategies.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Dalian Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

XZ and YS were responsible for collecting clinical data and writing the paper. YZ and FC assisted YS in collecting data and conducting telephone follow-up. HH helped YZ with the follow-up. SS and SZ were responsible for the statistical analysis. YL and GT were responsible for revising the paper and determining the research direction. All authors were involved in the drafting or revision of the manuscript.

## FUNDING

This work was supported in part by National Science Foundation of China (No. U1908209).

## ACKNOWLEDGMENTS

We would like to thank all the staff for their outstanding efforts in this work, especially those responsible for follow-up and statistics. The authors would like to thank Yidu Cloud (Beijing) Technology Co. Ltd. for their assistance in data searching, extraction, and processing.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.697221/full#supplementary-material

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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.

frontiers in Cardiovascular Medicine

REVIEW
published: 11 November 2021
doi: 10.3389/fcvm.2021.754499

# Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review

*Domingo Pascual-Figal[1,2*†], Antoni Bayés-Genis[3,4,5†], Paola Beltrán-Troncoso[6†], Pedro Caravaca-Pérez[5,7,8†], Alicia Conde-Martel[9†], Maria G. Crespo-Leiro[10,11†], Juan F. Delgado[5,7,8†], Javier Díez[5,12,13,14†], Francesc Formiga[15] and Nicolás Manito[16*†]*

[1] Cardiology Department, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [2] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain, [3] Heart Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [4] Department of Medicine, Centro de Investigación Biomédica en Red, Enfermedades Cardiovasculares, Autonomous University of Barcelona, Barcelona, Spain, [5] Centro de Investigación Biomédica en Red, Enfermedades Cardiovasculares, Carlos III Institute of Health, Madrid, Spain, [6] Hospital de Viladecans, Barcelona, Spain, [7] Cardiology Service, Hospital Universitario 12 de Octubre, Madrid, Spain, [8] Faculty of Medicine, Complutense University of Madrid, Madrid, Spain, [9] Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas, Spain, [10] Advanced Heart Failure and Heart Transplant Unit, Cardiology Department, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain, [11] Institute of Biomedical Research (INIBIC), A Coruña, Spain, [12] Cardiovascular Diseases Programme, Centre of Applied Medical Research, University of Navarra, Pamplona, Spain, [13] Departments of Nephrology, Cardiology, and Cardiac Surgery, University of Navarra Clinic, Pamplona, Spain, [14] Navarra Institute for Health Research, Pamplona, Spain, [15] Internal Medicine Department, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain, [16] Heart Failure and Heart Transplantation Unit, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain

Heart failure (HF) is a clinical syndrome characterized by the presence of dyspnea or limited exertion due to impaired cardiac ventricular filling and/or blood ejection. Because of its high prevalence, it is a major health and economic burden worldwide. Several mechanisms are involved in the pathophysiology of HF. First, the renin-angiotensin-aldosterone system (RAAS) is over-activated, causing vasoconstriction, hypertension, elevated aldosterone levels and sympathetic tone, and eventually cardiac remodeling. Second, an endogenous compensatory mechanism, the natriuretic peptide (NP) system is also activated, albeit insufficiently to counteract the RAAS effects. Since NPs are degraded by the enzyme neprilysin, it was hypothesized that its inhibition could be an important therapeutic target in HF. Sacubitril/valsartan is the first of the class of dual neprilysin and angiotensin receptor inhibitors (ARNI). In patients with HFrEF, treatment with sacubitril/valsartan has demonstrated to significantly reduce mortality and the rates of hospitalization and rehospitalization for HF when compared to enalapril. This communication reviews in detail the demonstrated benefits of sacubitril/valsartan in the treatment of patients with HFrEF, including reduction of mortality and disease progression as well as improvement in cardiac remodeling and quality of life. The hemodynamic and organic effects arising from its dual mechanism of action, including the impact of neprilysin inhibition at the renal level, especially relevant in patients with type 2 diabetes mellitus, are also reviewed. Finally, the evidence on the demonstrated safety

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**Edited by:**
*Gaetano Ruocco,*
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**Reviewed by:**
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*Azienda USL Toscana Sud Est, Italy*

***Correspondence:**
*Domingo Pascual-Figal*
*dpascual@um.es*
*Nicolás Manito*
*nml@bellvitgehospital.cat*

*† These authors have contributed equally to this work*

**Specialty section:**
*This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine*

**Received:** *06 August 2021*
**Accepted:** *06 October 2021*
**Published:** *11 November 2021*

**Citation:**
*Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Pérez P, Conde-Martel A, Crespo-Leiro MG, Delgado JF, Díez J, Formiga F and Manito N (2021) Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review. Front. Cardiovasc. Med. 8:754499. doi: 10.3389/fcvm.2021.754499*

and tolerability profile of sacubitril/valsartan in the different subpopulations studied has been compiled. The review of this evidence, together with the recommendations of the latest clinical guidelines, position sacubitril/valsartan as a fundamental pillar in the treatment of patients with HFrEF.

**Keywords: heart failure, heart failure with reduced ejection fraction, sacubitril/valsartan, ARNI, neprilysin inhibition**

## INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by the presence of dyspnea or limited exertion due to impaired cardiac ventricular filling and/or blood ejection (1). Because of its high prevalence, it is a major health and economic burden worldwide (2, 3).

Within neurohormonal regulation, there are different mechanisms that contribute to and modulate the key pathways that trigger HF: the autonomic nervous system, the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide (NP) system (4). In patients with HF, the RAAS is over-activated, causing vasoconstriction, hypertension, elevated aldosterone levels and sympathetic tone, and eventually cardiac remodeling (4). However, an endogenous compensatory mechanism, the NP system is also activated, albeit insufficiently to counteract the RAAS effects. Since NPs are degraded by the enzyme neprilysin, it was hypothesized that its inhibition could be an important therapeutic target in HF (5). However, inhibition of neprilysin alone results in reflex activation of the RAAS, so pharmacological development of neprilysin inhibition has been carried out in combination with simultaneous inhibition of the RAAS (5).

Sacubitril/valsartan is the first of the class of dual neprilysin and angiotensin receptor inhibitors (ARNI) (6). Its efficacy in reducing the combined risk of death from cardiovascular (CV) causes or hospitalization for HF was demonstrated in the PARADIGM-HF study [Prospective Comparison of ARNI with Angiotensin-Converting Enzyme Inhibitors (ACEI) to Determine Impact on Global Mortality and Morbidity in HF], a randomized, double-blind study involving 8,442 outpatients with symptomatic HF [New York Heart Association (NYHA) class II–IV] in patients with left ventricular ejection fraction (LVEF) $\leq$40% (5). Patients were randomized to receive sacubitril/valsartan 200 mg/12 h or enalapril 10 mg/12 h, in addition to treatment considered optimal in systolic HF. The study was stopped prematurely after a mean follow-up of 27 months, due to the overwhelming clinical benefit of sacubitril/valsartan over enalapril found in the pre-specified interim analysis (5). More recently, the PIONEER-HF [Comparison of Sacubitril/Valsartan vs. Enalapril on Effect on N-terminal pro b-type natriuretic peptide (NT-proBNP) in Patients Stabilized from an Acute HF Episode] and TRANSITION [Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HF With Reduced Ejection Fraction (HFrEF) Patients After an Acute Decompensation Event] trials demonstrated that early administration of sacubitril/valsartan during hospitalization improves prognostic markers and reduces the risk of rehospitalization relative to enalapril (7, 8). Accordingly, the latest guideline updates from academic associations, such as the American College of Cardiology in January 2021 or the Canadian Society of Cardiology, recommend sacubitril/valsartan as the angiotensin antagonist of choice in HF patients with HFrEF (9–11). In the recent HF Congress 2021 from the European Society of Cardiology, a novel framework for treatment implementation has been proposed, recommending the four "pharmacological pillars" [sacubitril/valsartan, beta blockers, mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 inhibitors] for the treatment of HFrEF to be introduced in parallel, early in the patient pathway (12, 13). In terms of pharmacoeconomic value, in most countries sacubitril/valsartan has shown to be a better cost-effective therapy for HFrEF than the comparator (14).

This article reviews in detail the demonstrated benefits of sacubitril/valsartan in the treatment of patients with HFrEF, both in terms of mortality reduction and disease progression, cardiac remodeling and quality of life (5, 7, 8). The hemodynamic and organic effects arising from its dual mechanism of action, including the impact of neprilysin inhibition at the renal level, especially relevant in patients with type 2 diabetes mellitus (T2DM), are also reviewed (15). Finally, the evidence on the demonstrated safety and tolerability profile of sacubitril/valsartan in the different subpopulations studied has been compiled (7, 8, 16–18).

## MORTALITY, SUDDEN DEATH, AND VENTRICULAR ARRHYTHMIAS

### Reduced Mortality in HF Patients

The PARADIGM-HF study demonstrated a clear and early benefit of sacubitril/valsartan compared to enalapril, with a 20% relative risk reduction in the combined primary endpoint of CV death and HF hospitalization (HR 0.80 95% CI 0.73–0.87 $p < 0.001$), as well as in the individual components of the primary endpoint. These results contrast with those of many pivotal studies of ACEI/angiotensin II receptor antagonists (ARA II) (SOLVD-T, CHARM-Alternative, EMPHASIS-HF, ATLAS, HEAAL) where the reduction is more pronounced in HF hospitalizations than in CV death (19). In addition, ARNI reduced the risk of death from any cause by 16% [Hazard ratio (HR) 0.84 95% CI 0.76–0.93 $p < 0.009$] and improved quality of life. The benefits were consistent across all pre-specified subgroups analyzed (5), including age groups (17).

## Reduction of CV Mortality Due to Sudden Death

Following the initial publication of PARADIGM-HF, a specific and very detailed analysis of the mode of death was conducted and adjudicated by a blinded independent committee (19). Causes of death were initially classified as CV, non-CV and unknown. CV deaths were subclassified into sudden death, death due to myocardial infarction, worsening HF, stroke or other cause of death. Sudden death was defined as unexpected death in a stable patient and was subclassified according to whether patients were seen alive 1 h or between 1 and 24 h before death. Sudden deaths in patients who were last seen alive >24 h before death were categorized separately as "apparent sudden deaths."

Of the total 1,546 patients who died in the study, there were 1,251 deaths that were considered CV (80.9%), with a 20% risk reduction observed in the ARNI vs. enalapril group (13.30 vs. 16.5%, respectively; HR 0.80 CI 9% 0.72–0.89 $p < 0.001$). Most CV deaths were sudden death (44.8%) (also in patients considered "stable" in NYHA class I and II) or HF-related (26.5%). In both cases, a reduction in the risk of death of 20 and 21%, respectively, was observed in the ARNI group vs. enalapril (HR 0.80 95% CI 0.68–0.94 $p = 0.008$ and HR 0.79 95% CI 0.64–0.98 $p = 0.034$) (19).

For sudden deaths (both resuscitated and non-resuscitated), a 22% risk reduction was observed in patients in the ARNI treatment arm compared to enalapril. The magnitude of this effect did not differ in patients with or without an implantable defibrillator (ICD). Notably, this incremental benefit in reducing sudden death with ARNI over the active comparator enalapril was also observed in patients receiving optimal treatment with beta-blockers (93%) and MRA (55%). Both drugs are known to reduce all-cause mortality and sudden death (20), and interestingly, in patients with an ICD, in whom the reduction of sudden death with ARNI reached 50% (19). Additionally, this protective effect on sudden death had not been observed with ACEIs or ARA II. Thus, the SOLVD study showed a reduction in mortality from HF progression with enalapril vs. placebo, but not of sudden death (20).

## Effect on Ventricular Arrhythmias

The effect of ARNIs on ventricular arrhythmias was evaluated in a prospective, observational study in a cohort of 120 patients with HFrEF and an ICD with remote monitoring capability (21). Patients in the study were treated with an ARNI for 9 months after having previously been on ramipril or valsartan for 9 months. All arrhythmic events during the 9 months before and 9 months after the switch to ARNI were analyzed: appropriate shocks, non-sustained ventricular tachycardia (NSVT) and supraventricular tachycardia (SVT), ventricular extrasystolic load and percentage of biventricular pacing, where indicated. The patients, most of whom were in NYHA class II, experienced clinical improvement, reduced NT-proBNP levels, improved left ventricular remodeling (increase in ejection fraction of ∼5 points), and a significant reduction in arrhythmic load after switching to ARNI. Specifically, patients had fewer episodes of SVT (≥ 30 beats or treated with the ICD) or NSVT (≥ 4 beats and < 30 s) and an 80% reduction in appropriate ICD shocks (0.8 vs. 6.6% $p < 0.002$). Additionally, patients had fewer ventricular premature beats, leading to an increase in the percentage of biventricular pacing (from 95% ± 6% to 99% ±1%, $p < 0.02$) in patients on cardiac resynchronization therapy (21).

Conversely, patients with ventricular arrhythmias had higher NT-proBNP levels ($p < 0.0001$), and the reduction of arrhythmic load correlated with the grade of NT-proBNP improvement (21). Previous studies have shown that elevated NP levels are independent predictors of sustained ventricular arrhythmias and ICD shocks. Likewise, appropriate ICD shocks have been associated with increased mortality, so ARNI would be beneficial in both cases.

## Mechanism of Action of ARNIs in Mortality Reduction

There are two main mechanisms that can lead to sudden death. The first is sustained ventricular tachycardia, that is typically presented in patients with mild HF symptoms and underlying ischemic etiology, which can be treated by ICD implantation. The second mechanism is an acute mechanical failure of the left ventricle (LV), which manifests on the electrocardiogram as bradyarrhythmia, asystole or electromechanical dissociation. Regardless of the mechanism, a common underlying pathogenesis involves adverse left ventricular remodeling with interstitial fibrosis and myocardial distension, which promotes a pro-arrhythmic substrate and may trigger cascade failure, ending in electrical storm or mechanical collapse (22).

It has been reported that treatment with an ARNI can reduce mortality beyond treatment with beta-blockers, ACEI and MRAs, mainly due to the beneficial effects of neprilysin inhibition in reducing myocardial fibrosis and improving cardiac remodeling (wall stress, inflammation, hypertrophy and cell death), as well as its anti-arrhythmic effect through sympathetic inhibition and the increase of enkephalins, endorphins and bradykinin (**Figure 1**) (23–25).

Thus, in patients with HFrEF, sacubitril/valsartan has shown vs. enalapril a further reduction in all-cause mortality, CV mortality (including sudden death) and HF hospitalization, as well as improving patient quality of life, irrespective of age (5, 17, 19). In addition, switching from treatment with ramipril or valsartan to treatment with an ARNI has been shown to reduce episodes of both SVT and NSVT, as well as ventricular premature beats (21). The beneficial effects observed with ARNIs on cardiac remodeling, as well as their anti-arrhythmic effect, would stem from their primary mechanism of action by inhibiting neprilysin (23, 24).

# CLINICAL PROGRESSION: HOSPITALIZATION AND REHOSPITALIZATION

HF is a chronic and progressive disease, in which related hospitalizations represent a symptomatic event that identifies disease progression and impaired prognosis, with an increased

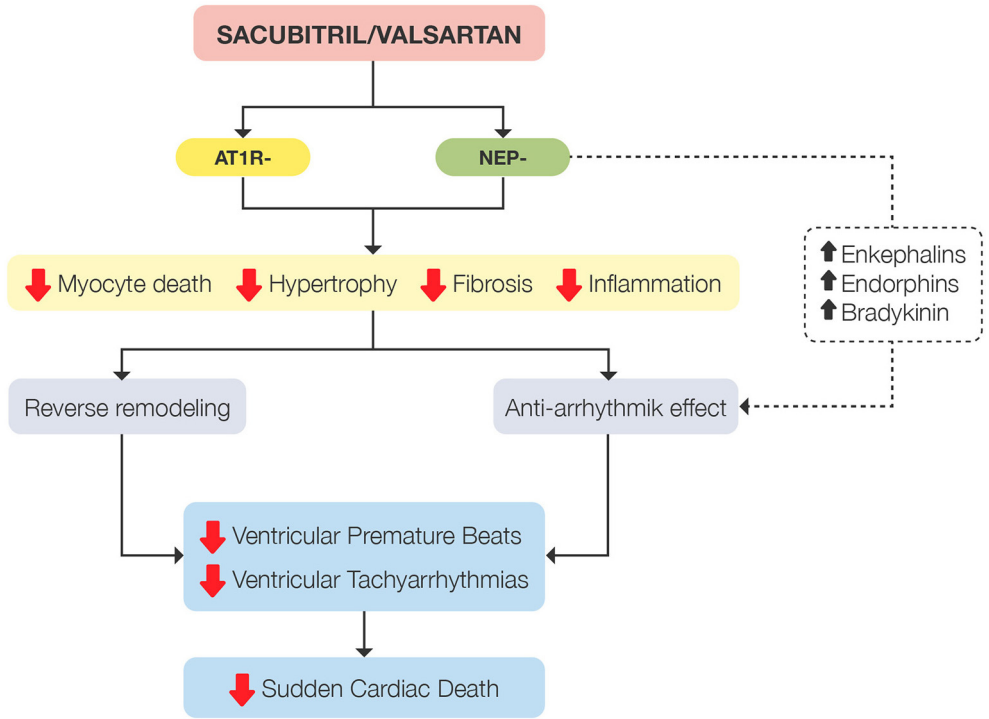


**FIGURE 1 |** Summary of mechanisms involved in reducing the sudden death rate demonstrated by sacubitril/valsartan. AT1R-, angiotensin type 1 receptor inhibition; NEP-, neprilysin inhibition.

risk of death in both the short and long-term (26, 27). After the first hospitalization for HF, patients enter in a vulnerable phase in which they are prone to readmissions. Having overcome this early vulnerable period, patients may enter in an apparent "stable" phase. However, after a variable amount of time, patients will suffer recurrent episodes of worsening HF leading to readmissions that anticipate death. Indeed, the higher the number of hospitalizations, the shorter the survival time. Therefore, hospitalizations due to worsening HF are the main signal of disease progression and impaired prognosis. This lifetime course is well-observed in registries in different populations (27–29).

## Prevention of Hospitalizations in Chronic HFrEF

In the PARADIGM-HF trial, after a median follow-up of 27 months, patients in the sacubitril/valsartan group had 23% fewer hospitalizations for worsening HF ($P < 0.001$). This reduction was irrespective of baseline patient characteristics, including prior HF hospitalization, and sacubitril/valsartan prevented both the first HF hospitalization and recurrent HF hospitalizations (30). It is significant that such reduction in risk was observed shortly after initiating sacubitril/valsartan, and the reduction in HF hospitalization was evident within the first 30 days after randomization (40% risk reduction, $P = 0.027$) (31). In case of hospitalization for HF during the study, patients on sacubitril/valsartan had lower rates of early readmission for HF, which was already significant in the early phase after discharge: at 30 days (risk reduction of 38%, $p = 0.006$) and at 60 days (risk reduction 32%, $p = 0.013$) (32). Consequently, sacubitril/valsartan – compared with enalapril – reduced the risk of recurrent hospitalizations for HF by 33% ($p < 0.001$), which was more prominent in the early vulnerable period after discharge (33).

## Prevention of Hospitalization in Acutely Decompensated HF

The PIONEER-HF study included patients hospitalized with HFrEF, who were randomized to sacubitril/valsartan or enalapril soon after admission (median of 68 h). After discharge, fewer patients treated with sacubitril/valsartan were readmitted for HF at 8 weeks (8.0%) compared to enalapril (13.8%). This meant a risk reduction of 44% ($p = 0.005$) with a number necessary to treat of 13 to prevent 1 HF readmission at 8 weeks (7). This study provided the first evidence about the tolerability and safety of initiating sacubitril/valsartan in hospital. Indeed, there were no differences between sacubitril/valsartan and enalapril in terms of secondary side effects, including hypotension. Tolerability of sacubitril/valsartan initiated in hospital has also been confirmed in the TRANSITION study. This trial compared pre-discharge and post-discharge initiation of sacubitril/valsartan, and no differences were found in either the ability to attain target doses

of sacubitril/valsartan at 10 weeks or in the occurrence of side effects (8). In fact, both trials included patients with *de novo* HF and those naïve for ACEI or ARA II for the first time; populations not included in PARADIGM-HF. The observed clinical benefit for these populations was similar in PIONEER-HF, and tolerability was similar or even better in terms of side effects and achieved doses.

Considering the PIONEER-HF and TRANSITION studies together, an in-hospital initiation should be preferred to prevent readmissions in the early vulnerable period after discharge. This recommendation is reinforced by the open-label extension of PIONEER-HF that showed that after both arms were on sacubitril/valsartan, the survival curves remained separate due to the significant reduction of rehospitalization risk in the early period after discharge.

## Relationship Between HF Hospitalization and Disease Progression

Apart from the ability of sacubitril/valsartan to reduce the risk of hospitalization for HF – the main feature of HF progression – other findings also suggest an effect of the ARNI in the severity of decompensations, the risk of outpatient worsening HF and meaningful myocardial biomarkers. Indeed, fewer patients treated with sacubitril/valsartan experienced worsening HF episodes not requiring hospitalization, defined as intensification of medical treatment for HF (16% risk reduction, $P = 0.003$) or an emergency department visit for worsening HF without hospitalization (34% risk reduction, $P = 0.001$) (31). This protective effect is relevant because worsening HF in an outpatient setting is associated with a worse prognosis, indicating HF progression (34).

When hospitalization was required, patients receiving sacubitril/valsartan were less likely to require intensive care (18% risk reduction, $P = 0.005$), to receive intravenous positive inotropic agents (31% risk reduction, $P < 0.001$), and to need implantation of a HF device or cardiac transplantation (22% risk reduction, $P = 0.07$) (31).

This protective effect is supported from a pathophysiological point of view, given that biomarkers reflecting myocardial stretch (NT-proBP) and necrosis [high-sensitivity Troponin T (hsTnT)] were also reduced and related to the net clinical benefit (7, 35). Indeed, patients with an early phase of disease as well as *de novo* HF patients seemed to obtain a greater benefit in terms of biomarkers, as suggested in a sub analysis from the TRANSITION study (36).

Finally, as the main consequence of halting disease progression, CV death (HR 0.80, 95% CI 0.72–0.89, $P < 0.001$), and specifically death due to worsening HF (HR 0.79, 95% CI 0.64–0.98, $P = 0.034$) were reduced in patients receiving sacubitril/valsartan compared to enalapril (19). Nevertheless, this beneficial effect was not observed in patients with advanced HFrEF (37).

Therefore, the accumulated evidence supports sacubitril/valsartan compared to enalapril prevents HF progression based on its ability to reduce worsening HF, hospitalizations and rehospitalizations, shortly after treatment initiation and in the mid to long term (**Figure 2**). These positive effects observed in clinical trials lead to the expert recommendation of initiating sacubitril/valsartan in patients hospitalized with HFrEF in order to prevent rehospitalizations and HF progression in this high-risk population (11).

# CARDIAC REMODELING AND NEPRILYSIN INHIBITION

Cardiac remodeling is intrinsically related to the progression of HFrEF (38). It is secondary to the compensatory mechanisms that are triggered by a myocardial injury or stress. Molecular, genetic, cellular, and interstitial changes manifest as an increase in volume, alteration of shape (from elliptical to spherical), and progressive dysfunction of the LV (38). Cardiac remodeling leads to an increase in CV morbidity and mortality: a 10% decrease in LVEF has been associated with a 73% increase in the risk of death from chronic HF (39). In contrast, patients with reverse cardiac remodeling show a decrease in mortality: a 15% reduction in left ventricular end systolic volume index has been associated with a 68% reduction in mortality (40).

Because medical treatment effecting cardiac remodeling is key to preventing the progression of ventricular functional impairment and in turn improving the prognosis of patients with HFrEF (41), it should be initiated early. ACEI (42), angiotensin receptor blocker II (ARB II) (43), and MRA (44) slow the progression of damaging cardiac remodeling, whereas beta-blockers (45), cardiac resynchronization therapy (46) and ARNI (25) induce reverse cardiac remodeling, achieving a significant decrease in ventricular volumes and an increase in LVEF.

## Effects of Sacubitril/Valsartan on the Pathophysiology of Myocardial Remodeling

One of the key mechanisms of sacubitril/valsartan is increased bioavailability of circulatory and myocardial nitric oxide, which leads to an increase in cyclic guanosine monophosphate (cGMP) and the activation of the protein kinase G. The final effect is reduced systemic oxidative stress, apoptosis, and hypertrophy, accompanied by antiplatelet and antithrombotic effects (47). Regarding protection in acute myocardial infarction, experimental studies have shown that sacubitril/valsartan offers superior benefits to valsartan in the short and long term. It significantly reduces the size of the infarction and the progression of post-acute myocardial infarction cardiac remodeling by suppressing pro-inflammatory cytokines and the degradation of the extracellular matrix. This prevents LV dysfunction and reduces the associated symptoms of HF.

A systems biology analysis provided mechanistic data at the molecular level on the synergistic activity of sacubitril/valsartan in cardiac remodeling in HF and after acute myocardial infarction. This analysis showed effects on the reduction of cell death, hypertrophy, contractile dysfunction, and extracellular matrix remodeling (**Figure 3**) (48). As previously mentioned, extracellular matrix and fibrosis promote adverse ventricular remodeling and dysfunction, and trigger severe

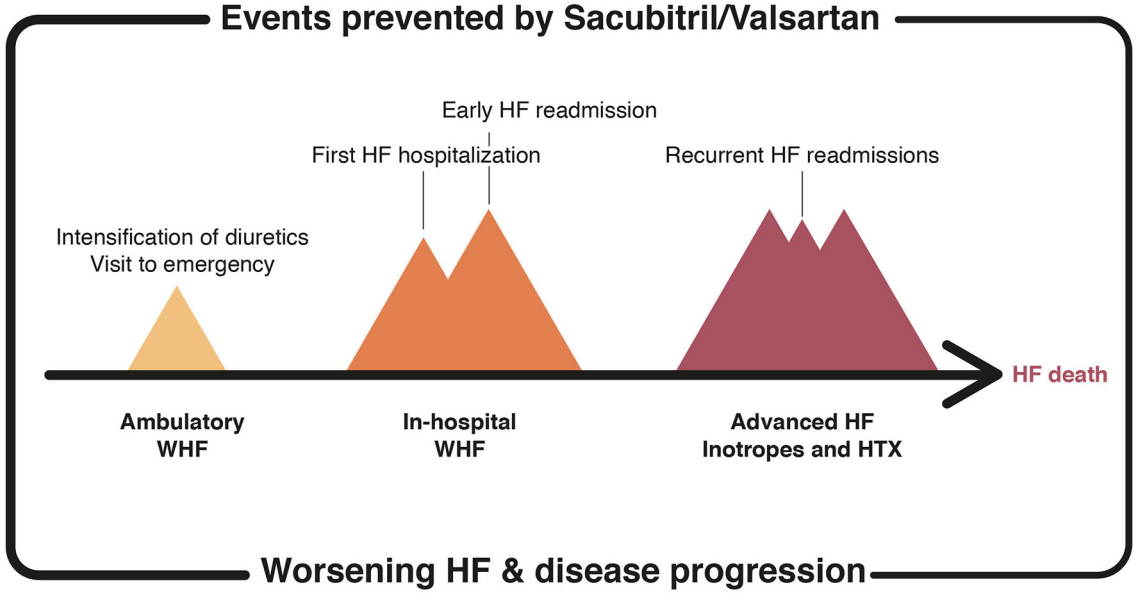


**FIGURE 2 |** HF-related events prevented by the treatment with sacubitril/valsartan. HF, heart failure; WHF, worsening HF; HTX, heart transplantation.

ventricular arrhythmias and sudden death in HF. A substudy of PARADIGM-HF trials analyzed the effect of sacubitril/valsartan on biomarkers of extracellular matrix homoeostasis and collagen synthesis and their relationship with clinical events. Increased baseline profibrotic activity was observed in patients with HFrEF and a greater reduction in CV death or hospitalization for HF, the greater the decrease in soluble tumorigenicity suppressor 2 (sST2) or metallopeptidase inhibitor 1 (TIMP-1) compared to baseline levels (49). Sacubitril/valsartan significantly reduced levels of aldosterone, soluble tumorigenicity suppressor, matrix metallopeptidase 9 (MMP-9), TIMP-1, and procollagen type 1 amino-terminal propeptide (P1NP) (**Figure 3**) at 8 months' treatment compared to enalapril. To date, the only other treatment that has been shown to decrease any profibrotic biomarker are MRAs (N-terminal propeptide of procollagen type III). Finally, a pre-specified secondary analysis of the PROVE-HF study showed that the initiation of treatment with sacubitril/valsartan produced a rapid (before 14 days) and significant increase in atrial natriuretic peptide (ANP) correlated with a subsequent increase in urinary cGMP (50).

## Effects of Sacubitril-Valsartan on Cardiac Geometry and Function

The earliest effect in chronic patients was recorded in the EVALUATE-HF study: a significant reduction in left ventricular end systolic and end diastolic volumes (LVESV and LVEDV) of the left atrial volume index (LAVI) and E/e' ratio compared with enalapril was observed at 12 weeks (51). Another prospective study carried out with a blind echocardiographic analysis showed improvement in systolic and diastolic function after 4 months of substituting ACEI/ARB II for sacubitril/valsartan in patients with chronic HFpEF previously optimally treated (100% ACEI/ARB II, 95% beta-blockers, 82% MRA, 56% RCT). The mean increase in EF was greater than 5 points, along with significant reductions in LVESV and LVEDV and a reduction in the degree of mitral insufficiency (MI) and in the proportion of patients with a restrictive filling pattern (52). Functional MI is a direct consequence of cardiac remodeling due to worsening ventricular geometry. Additionally, it facilitates the progression of cardiac remodeling, inducing worse clinical evolution and prognosis. The PRIME study in patients with symptomatic HF and functional MI also showed a significant reduction in MI and ventricular volumes without significant changes in blood pressure at 12 months, in this case compared to valsartan (53).

The open study PROVE-HF (54) included patients with *de novo* HF, who had not been previously treated with ACEI/ARB II, with low levels of NT-proBNP, and with submaximal doses of sacubitril/valsartan, at a mean of 50 months (more than 4 years) from the diagnosis of HF. The mean baseline concentration of NT-proBNP was 816 pg/ml and presented a rapid, early (mostly during the first 14 days) and sustained reduction, reaching 455 pg/ml at 12 months (25). The most relevant finding was a mean increase of 9.4 points in LVEF at 12 months, from 28.2 to 37.8%, with 25% of patients presenting an increase $\geq$13.4 points. In the subgroup of naïve or *de novo* patients, the mean increase was 12.8 points. Based on these findings, the recent American Heart Association/American College of Cardiology expert consensus recommends deferring the decision to implant an ICD in patients in whom reverse remodeling is expected to continue to progress beyond the usual 3 months (9). All other echocardiographic parameters (indexed LVESV and LVEDV, LAVI, E/e' ratio, and

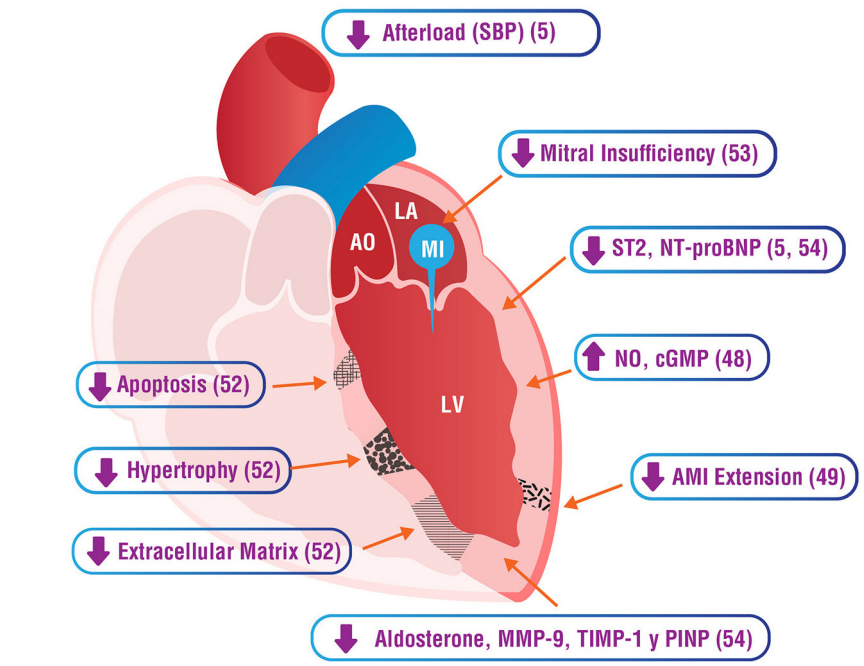


**FIGURE 3 |** Summary of mechanisms of sacubitril/valsartan enhancement of ventricular remodeling. AO, aorta; LA, left atrium; LV, left ventricle; MI, mitral insufficiency; cGMP, cyclic guanosine monophosphate; NO, nitric oxide; sST2, soluble suppression of tumorigenesis-2; Nt-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; AMI, acute myocardial infarction; MMP-9, matrix metallopeptidase 9; TIMP-1, tissue inhibitor of metalloproteinase-1; PINP, aminoterminal propeptide of type I collagen.

LV mass index) also progressively and significantly improved (25). The speed and magnitude of the increase in ANP was seen to be associated with a greater increase in LVEF and a decrease in the LAVI Furthermore, the speed and magnitude of the reduction in NT-proBNP and the indexed LVESV showed an impact on clinical prognosis: the probability of hospitalization for HF or death was significantly higher in patients in whom these parameters did not fall below the mean at 3 and 6 months, respectively, compared to those that did (odds ratio = 2.03; CI 95%, 1.25–3.30; $p < 0.001$) (55).

The effect on reverse cardiac remodeling when sacubitril/valsartan was used to treat hospitalized patients compared to ACEI/ARB II was even more striking: there was a mean increase in LVEF of 7.5 points at 3 months' follow-up, an improvement of 42% in *Global Longitudinal Strain* compared with 1% in ACEI/ARB II and a significant reduction in LVESV and LAVI (56).

Finally, significant changes were also found in the remodeling of the right ventricle 12 months after substituting ACEI/ARB II for sacubitril/valsartan (57). All this points to the effect of reverse cardiac remodeling of sacubitril/valsartan in patients with HFrEF. In the PARADISE-MI study (58), sacubitril/valsartan did not significantly reduce the rate of MACE compared with ramipril following acute myocardial infarction, but there were consistent findings that support incremental clinical benefits of sacubitril/valsartan over ACEI since the rate of the composite primary endpoint was 10% lower (59).

In any case, an improvement in cardiac remodeling should not result in a dose reduction or termination of medical treatment, since it has been seen that the suspension of medical treatment leads to the reappearance of cardiac remodeling and HF (60).

In conclusion, cardiac remodeling is one of the determining pathophysiological mechanisms in the progression of HF and is intrinsically related to a HF prognosis (38). The precocity and magnitude of reverse cardiac remodeling is related to reduced clinical events: hospitalization for HF and CV death (40). Because of its antifibrotic, antihypertrophic, and antiapoptotic effect, sacubitril/valsartan induces early, significant and clinically meaningful reverse cardiac remodeling that is not seen in treatment with ACEI/ARB II – even in patients with several years of HF development (25, 55).

## HEMODYNAMIC EFFECTS OF NEPRILYSIN INHIBITION

The hemodynamic effects of neprilysin inhibition were first studied with candoxatrilate, an inhibitor that increases endogenous levels of ANP. First studies showed that

administration of this peptide increased natriuresis and inhibited the sympathetic nervous system, with transient reductions in plasma vasopressin, aldosterone levels, and plasma renin activity, improving the hemodynamic profile of patients with HFrEF (61). Acute exposure to a dose of candoxatrilate in patients with severe HF resulted in reduced ventricular filling pressures: decreased pulmonary capillary pressure, right atrial pressure and pulmonary pressures, and slightly increased cardiac output (61). These hemodynamic effects were mainly explained by the greater reduction in preload vs. afterload, as there were no significant changes in systemic vascular resistances (61). This neutral effect on systemic vascular resistance could be due to the non-selective nature of neprilysin, which also inhibits the degradation of vasoconstrictor molecules such as angiotensin II, endothelin 1 and noradrenaline, with a consequent increase in their circulating levels that counteract the vasodilatory effects of NPs (62). These observations suggested that the combination of neprilysin inhibition with RAAS inhibition could enhance the beneficial effects of both molecules and avoid deleterious effects (4) (**Figure 4**).

Omapatrilat was the first dual inhibitor of neprilysin and angiotensin-converting enzyme (ACE). Its hemodynamic effects were investigated in a randomized, double-blind, placebo-controlled study in 369 patients with HFrEF in functional class II-IV (63). After the first dose, pulmonary capillary pressure and systemic vascular resistances were significantly reduced, an effect that was maintained at 12 weeks of treatment. These acute vasodilatory effects were accompanied by an increase in circulating levels of NPs such as ANP, b-type natriuretic peptide (BNP) or adrenomedullin. Increased plasma levels of potentially deleterious hormones such as endothelin-1 and noradrenaline, possibly due to sympathetic release reflecting the reduction in blood pressure, were observed initially, but normalized with chronic use. Despite these favorable effects on ventricular preload and afterload, no significant acute or chronic changes on cardiac index were observed. The development of omapatrilat was discontinued due to safety concerns regarding an increased risk of angioedema (63).

Sacubitril/valsartan is the first of the ARNI class, in which neprilysin inhibition is coupled with blockade of the angiotensin AT1 receptor. As previously discussed, its efficacy in reducing the combined risk of death from CV causes or hospitalization for HF in patients with HFrEF was demonstrated in the PARADIGM-HF study, which was prematurely stopped because it exceeded the threshold of a clearly significant benefit (5).

At the hemodynamic level, sacubitril/valsartan treatment causes vasodilation, reduction of blood volume and increases renal sodium and water excretion by reducing aldosterone production (4). The hemodynamic impact of sacubitril/valsartan use was further evaluated in a prospective study by implanting a monitoring device in patients with HFrEF, which showed a significant reduction in pulmonary diastolic pressure, a surrogate marker of pulmonary capillary pressure, even at low doses of the drug, which did not change significantly with increasing dose (64). The use of sacubitril/valsartan has also been associated with a beneficial effect on reverse remodeling in patients with HFrEF, improving ejection fraction, left ventricular diameter and volume compared to treatment with ACEI or ARA II in a meta-analysis (65) and more recently in the PROVE-HF with evident improvement after 12 months of treatment (25).

The potent systemic vasodilator effects produced by dual inhibition with sacubitril/valsartan in patients with arterial hypertension result in a marked reduction in blood pressure, with a preferential effect on systolic blood pressure (SBP) compared to diastolic blood pressure, providing an additional improvement in pulse pressure reduction. In addition, it shows a good safety profile, making it a promising molecule to treat arterial hypertension (66).

In the presence of HFrEF, low SBP levels are associated with poor prognosis. In addition, patients with a low SBP number represent a high-risk group for adverse events, so these patients often do not receive disease-modifying drugs (16). In a sub-analysis of the PARADIGM-HF study on the effect of sacubitril/valsartan on SBP (16), a more beneficial effect was observed with sacubitril/valsartan vs. enalapril, which was cross-sectional across the different prespecified SBP categories. It is important to note that the effect on blood pressure was significantly lower in patients with the lowest SBP $<$ 110 mm Hg), while the beneficial effect was more defined in these same patients with lower SBP. While 25.5% of patients with SBP $<$ 110 mmHg treated with sacubitril/valsartan experienced an episode of hypotension (vs. 13.7% with enalapril), only 1.3% discontinued sacubitril/valsartan compared to 1% who discontinued enalapril. In the overall SBP categories for the two treatments, $\leq$1% of patients discontinued the study (16). Thus, the sacubitril/valsartan combination has been shown to improve prognosis, including patients with persistent low SBP compared to enalapril, reducing mortality and morbidity in these patients (16).

These data suggest that, in patients with HFrEF, the presence of hypotension not accompanied by evidence of poor perfusion (cerebral, renal or peripheral) does not represent a reason not to initiate treatment with drugs that may modify the prognosis of the disease, such as sacubitril/valsartan. The lower limit of SBP for treatment with this combination established in the product datasheet is 100 mmHg, although in the PARADIGM-HF study it was 95 mmHg, and in clinical practice it is used at even lower SBP in selected patients (16).

In conclusion, sacubitril/valsartan treatment exerts beneficial hemodynamic effects, including vasodilatation and blood volume reduction, with increased renal sodium and water excretion (4). It also has a beneficial effect on cardiac remodeling, improving ventricular preload and afterload (65). Its use leads to a reduction in blood pressure, preferentially SBP and a greater reduction the lower the initial SBP and has been shown to improve prognosis in all SBP groups, including patients with persistently low SBP, compared to enalapril (16).

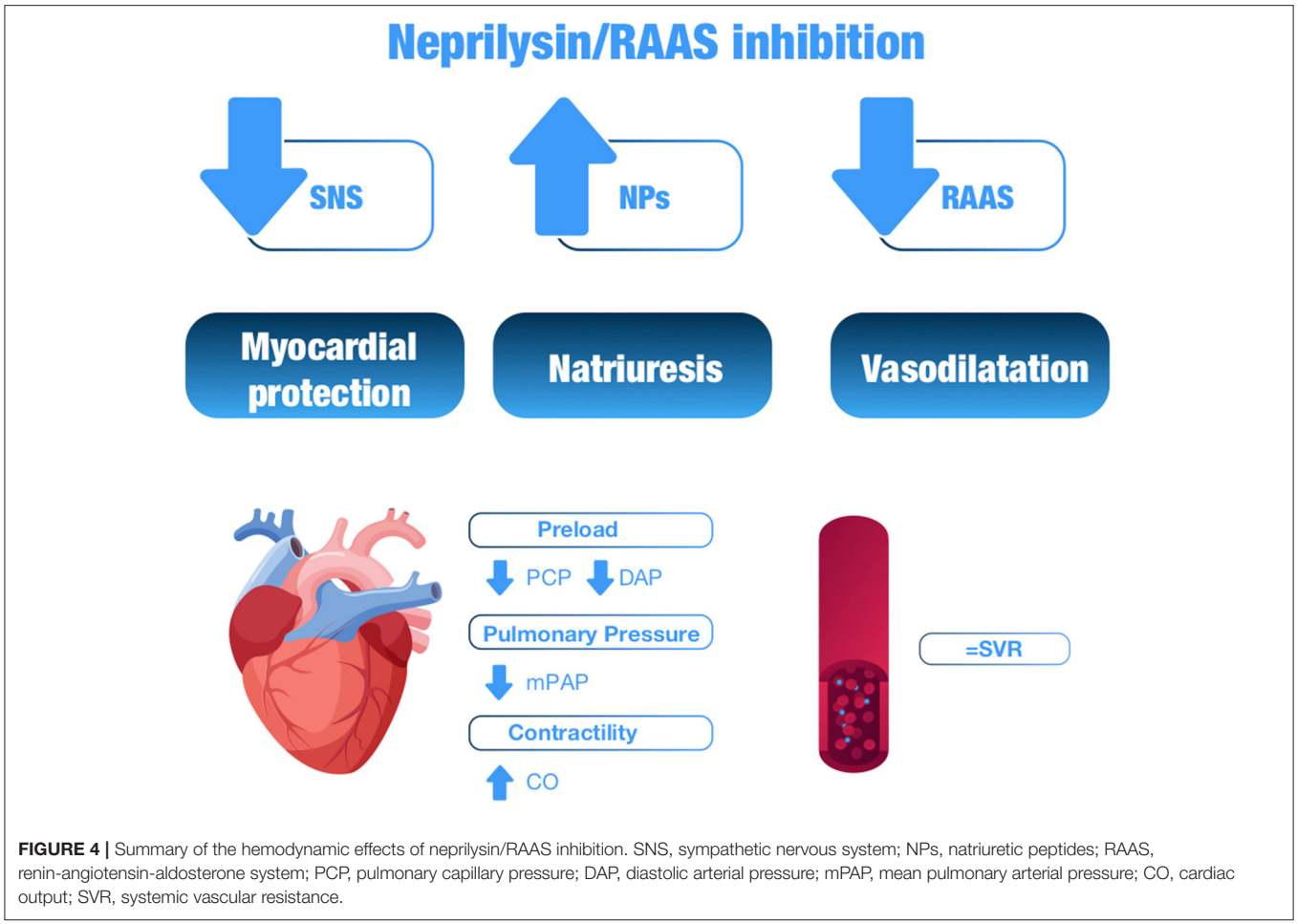


**FIGURE 4 |** Summary of the hemodynamic effects of neprilysin/RAAS inhibition. SNS, sympathetic nervous system; NPs, natriuretic peptides; RAAS, renin-angiotensin-aldosterone system; PCP, pulmonary capillary pressure; DAP, diastolic arterial pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance.

Therefore, low SBP levels should not be an obstacle to initiating sacubitril/valsartan treatment.

## BIOMARKERS: NPS, TROPONINS, AND ST2

### HF Biomarkers

HF biomarkers can be classified as prognostic, pharmacodynamic, or predictive; a single biomarker can be valuable in all three conditions. A prognostic biomarker provides information on the likely course of HF in an untreated individual or in an individual treated with conventional therapies. A predictive biomarker is one that can be used to identify individuals who are most likely to respond to a given therapy (e.g., sacubitril/valsartan). Lastly, pharmacodynamic biomarkers measure the effect of a drug on the disease state itself (67). For example, changes in circulating NT-proBNP levels are reflective of HF severity, and therefore blood NT-proBNP levels have been proposed as a surrogate endpoint to test the efficacy of sacubitril/valsartan.

Several HF biomarkers have been proposed according to the pathologic process they indicate (68). In the current review, we will focus on NPs (indicative of myocardial stretch), cardiac troponins (reflective of myocyte injury), and circulating ST2 (a multidimensional biomarker surrogate of stretch, inflammation, and extracellular matrix remodeling that some investigators call the 3-in-1 biomarker) These three biomarkers are already incorporated into the American Heart Association/American College of Cardiology guidelines for HF: NPs and troponins with IA indication, and ST2 with IIb indication (69).

### NT-ProBNP

As expected, the biomarker substudy of PARADIGM-HF revealed neprilysin inhibition with sacubitril/valsartan increased levels of both urinary cGMP and plasma BNP. In contrast, in comparison with enalapril, patients receiving sacubitril/valsartan had consistently lower levels of NT-proBNP (reflecting reduced cardiac wall stress) throughout the trial (31). The contrasting effects of sacubitril/valsartan on the two types of NPs are a key finding, because the levels of the two peptides characteristically parallel each other during the course of HF. However, because BNP (but not NT-proBNP) is a substrate for neprilysin, levels of BNP reflect the action of the drug, whereas levels of NT-proBNP will reflect the cardioprotective effect of the drug.

Zile et al. reported that 1 month after randomization, 24% of the baseline NT-proBNP levels >1,000 pg/ml had fallen to ≤1,000 pg/ml. Risk of the primary endpoint was 59% lower in patients with a decrease of NT-proBNP to ≤1,000 pg/ml than in those without such a reduction. One month after randomization, median NT-proBNP was significantly lower in sacubitril/valsartan-treated patients than in enalapril-treated patients and fell to ≤1,000 pg/ml in 31% of patients treated with sacubitril/valsartan vs. 17% of enalapril-treated patients. Similar results were seen when the partition value was set at a reduction in NT-proBNP ≤750 and ≤500 pg/ml; sacubitril/valsartan was nearly twice as likely as enalapril to cause a meaningful reduction in NT-proBNP (35).

In the PIONEER-HF trial, the NT-proBNP was used as a candidate pharmacodynamic biomarker of neprilysin inhibition-based therapy monitoring. The primary efficacy outcome was the time-averaged proportional change in NT-proBNP concentration from baseline through weeks one, four, and eight. The investigators found that among patients with HF with HFrEF who were hospitalized for acute decompensated HF, the initiation of sacubitril/valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy (-46.7 vs.−25.3%, respectively), which was significant at 1 week after randomization (7). Further insight on the rapid NT-proBNP response to sacubitril/valsartan has been recently provided by a *post-hoc* analysis of the TRANSITION study, which showed a statistically significant decline of NT-proBNP levels just within a few days after in-hospital initiation of sacubitril/valsartan compared to those who initiated optimized standard of care therapy (28 vs. 4% decrease) (70). We must point out two issues regarding the effect of sacubitril/valsartan on NT-proBNP concentrations: the precocity, few days in the TRANSITION *post-hoc* analysis, 1 week in PIONEER-HF and 4 weeks in PARADIGM, reflecting a rapid decrease of myocardial wall stress; and the close association with a lower risk of adverse clinical events, reflecting the meaningful relationship between cardiac protection and clinical evolution.

Similarly, NT-proBNP was used as the surrogate endpoint in the PARAMOUNT (Prospective comparison of ARNI with ARA II on Management of HF with preserved ejection fraction) trial in patients with HF and preserved ejection fraction, in which sacubitril/valsartan reduced NT-proBNP to a greater extent than valsartan at 12 weeks and was well-tolerated (71).

## HsTnT

Cardiomyocyte necrosis releases Troponin I or Troponin T (cardiac isomers of proteins from the troponin-tropomyosin complex) into the circulation, where they are typically useful in the detection of myocardial ischemia. However, both troponins are also elevated in the blood of patients with HF, and therefore have been appropriately studied regarding their ability to predict HF and their utility in determining prognosis in patients with established HF.

Patients receiving sacubitril/valsartan had significantly lower levels of hsTnT (reflecting reduced cardiac injury) compared to enalapril, in both ambulatory patients (PARADIGM-HF trial) and patients hospitalized with decompensated HF (PIONEER-HF trial). It should be highlighted that even very low levels of troponin release reflect ongoing myocardial injury (possibly related to increased wall stress), and even small increases in the levels of troponin reflect a higher risk of HF progression (31). Therefore, sacubitril/valsartan initiation prevented myocardial injury (as reflected by troponin release) and consequently HF progression.

## ST2

ST2 is a receptor from the interleukin-1 family with two gene forms – soluble (sST2) and transmembrane (ST2L). Like other biomarkers, blood ST2 levels can predict mortality and new onset HF (72, 73). Soluble ST2 is associated with cardiac remodeling and fibrosis.

In PARADIGM-HF, O'Meara et al. compared ST2 levels between treatment groups (sacubitril/valsartan vs. enalapril) at baseline and at 1 and 8 months post-randomization. Sacubitril/valsartan reduced ST2 levels at both one and eight months, whereas enalapril did not. This finding held when ST2 was evaluated as a continuous variable, as well as when it was evaluated as the percentage of patients above or below the FDA threshold of 35 ng/ml (or any other threshold evaluated). Changes in ST2 level from baseline to 1 month were associated with the subsequent risk of major outcomes, even when corrected for baseline ST2 concentration, clinical covariates, NT-proBNP, hsTnT, and randomized treatment (74).

Zile et al. extended these data to incorporate additional extracellular matrix regulation biomarkers. The authors observed that at baseline, the profibrotic biomarkers aldosterone, ST2, tissue TIMP-1, galectin 3, PINP and N-terminal propeptide of procollagen type III were higher, and biomarkers associated with collagen degradation such as MMP-2 and MMP-9, were lower than published reference control values. Eight months after randomization, aldosterone, ST2, TIMP-1, MMP-9, PINP, and N-terminal propeptide of procollagen type III had decreased more in the sacubitril/valsartan group than in the enalapril group. Changes from baseline to 8 months in ST2 and TIMP-1 were associated with changes in outcomes. These data suggest that a mechanism by which sacubitril/valsartan may exert a beneficial outcome in HFrEF patients may be related to a reduction in profibrotic signaling (49).

In summary, biomarker studies using PARADIGM-HF data showed that treatment with sacubitril/valsartan decreased those meaningful biomarkers in patients with HFrEF: NT-proBNP, hsTnT, and ST2 (**Figure 5**). Remarkably, the recently developed Barcelona Bio-HF risk calculator incorporates these three biomarkers in addition to clinical variables, comorbidities, and treatments (drugs and devices). The 2.0 version of the Barcelona Bio-HF risk calculator (bcnbiohfcalculator.org) is externally validated with the PARADIGM-HF cohort (75) and may be a valuable addition for doctors to incorporate these biomarkers into their daily clinical practice for the stratification of patient risk.

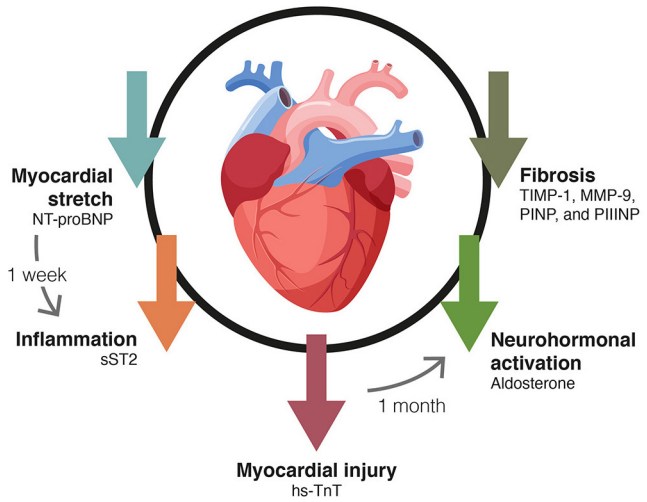


**FIGURE 5 |** Effect of the treatment with sacubitril/valsartan on HF biomarkers. Nt-proBNP, N-terminal pro b-type natriuretic peptide; sST2, soluble tumorigenicity suppressor 2; hs-TnT, high-sensitivity troponin T; TIMP-1, metallopeptidase inhibitor 1; MMP-9, matrix metallopeptidase 9; PINP, aminoterminal propeptide of type I collagen; PIIINP, N-terminal propeptide of procollagen type III.

# RENAL IMPACT OF NEPRILYSIN INHIBITION

## Mechanistic Effects of the Renal Impact of Neprilysin Inhibition

The increased renal bioavailability of NPs secondary to neprilysin inhibition results in a number of effects: (1) (i) direct inhibition of sodium reabsorption in the inner medullary collecting duct; (ii) inhibition of angiotensin II stimulated sodium reabsorption in the proximal tubule; (iii) direct vasodilatation of the afferent arteriole; (iv) reversal of norepinephrine mediated afferent vasoconstriction; (v) attenuation of angiotensin II induced vasoconstriction of the efferent arteriole; (vi) increase of the glomerular capillary ultrafiltration coefficient secondary to both relaxation of the contractile intraglomerular mesangial cells that increases the filtration surface and enhancement of endothelial permeability and capillary hydraulic conductivity; (vii) direct inhibition of renin release from juxtaglomerular (granular) cells; and (viii) inhibition of the V2 receptor mediated action of vasopressin in the collecting ducts (76). Other consequences of increased renal bioavailability of NPs secondary to neprilysin inhibition include reduction in renal damage (e.g., inflammation and cell death) and attenuation of renal remodeling (e.g., glomerulosclerosis and tubulointerstitial fibrosis) that develop in conditions of kidney injury (77).

## Clinical Consequences of the Renal Impact of the Neprilysin Inhibition

### Heart Failure

Findings from several clinical studies support that, despite dramatic increases in circulating NP concentrations, chronic HF represents a state of reduced effectiveness of the renal (and extrarenal) NP system with potential implications for therapy with neprilysin inhibition (78).

A meta-analysis using data from three HFrEF trials that compared combined neprilysin/RAAS inhibition with RAAS inhibition alone (IMPRESS [omapatrilat vs. lisinopril], OVERTURE [omapatrilat vs. enalapril], and PARADIGM-HF [sacubitril/valsartan vs. enalapril]) showed that combined neprilysin/RAAS inhibition was associated with a reduced incidence of renal dysfunction or elevation in serum creatinine, and less pronounced decline of glomerular filtration rate (GFR) (79). Although blood pressure dropped more in the neprilysin/RAAS inhibition groups in these studies than in the RAAS inhibition groups, GFR was better preserved.

In the PARADIGM-HF trial, the decrease in eGFR during follow-up was lower with sacubitril/valsartan compared with enalapril (-1.61 ml/min/1.73 $m^2$/year vs.−2.04 ml/min/1.73 $m^2$/year; $p < 0.001$). A greater increase in urinary albumin/creatinine ratio was observed, but in a range not clinically meaningful (1.20 mg/mmol vs. 0.90 mg/mmol; $p < 0.001$) (80). The benefit of sacubitril/valsartan on CV death or HF hospitalization was not modified by renal parameters and, compared to enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved CV outcomes, even in patients with chronic kidney disease (CKD). Of interest, in the PARADIGM-HF trial, levels of urinary cGMP were higher during treatment with sacubitril/valsartan than with enalapril (31). Furthermore, the incremental renal benefit of sacubitril/valsartan in patients with T2DM from the PARADIGM-HF trial, which was twice as large as in those without T2DM, is not solely explained by the benefit on the clinical course of HF and other not well-known mechanisms (18). This benefit is really relevant, given that patients without diabetes who have chronic HF experienced a decline in eGFR that was twice as rapid as the general population, and the coexistence of diabetes further doubled the rate of deterioration in eGFR (18).

A potential interpretation of the major renal effects of combined neprilysin/RAAS inhibition in stable HF can be the following (81). Enhanced renal bioavailability of NP (as assessed by the increase in urinary cGMP) in addition to further reducing systemic blood pressure and renal perfusion pressure induces a preferential vasorelaxation of the afferent arteriole and a relative vasoconstriction of the efferent arteriole. The consequent decrease in pre-glomerular resistances and increase in post-glomerular resistances contribute to increasing intracapillary hydraulic pressure despite decreased renal perfusion pressure, which in turn increases filtration fraction and preserves GFR in a reduced blood pressure setting. The increased intracapillary hydraulic pressure possibly combined with a direct effect of NP on the glomerular barrier may increase albumin ultrafiltration with consequent albuminuria. Additionally, the maintenance of GFR and the inhibition of tubular reabsorption by NP facilitate natriuresis and diuresis.

### Chronic Kidney Disease

The UK HARP-III trial compared the effects of sacubitril/valsartan and irbesartan on renal function and

other outcomes among patients with CKD (82). Over 12 months, sacubitril/valsartan had similar effects on GFR and albuminuria to irbesartan, but it had the additional effect of lowering blood pressure and cardiac biomarkers (troponin I and NT-proBNP). Allocation to sacubitril/valsartan produced a non-significant 9% reduction in study-average albuminuria. Although the renal effects were not encouraging, the effects on blood pressure and cardiac biomarkers supported the hypothesis that sacubitril/valsartan might reduce the risk of CV events (and in particular those related to HF) among patients with CKD, irrespective of established CV disease. The safety outcomes in the UK HARP-III trial also support further investigation of this hypothesis. More recently, a multicenter observational study evaluating the effects of the concomitant administration of sacubitril/valsartan and an sodium-glucose co-transporter 2 inhibitor on the renal function in patients with T2D and HFrEF, demonstrated a similar renal safety profile at mid-term as reported with both drugs given separately, without any significant or clinical relevant changes in eGFR (83).

In summary, neprilysin/RAAS inhibition and the associated increase in NP availability determines a plethora of renal benefits in terms of functional adaptations and structural remodeling (**Figure 6**). These effects would explain the lower decline of renal function observed in patients with HF and represent a promising approach in chronic renal insufficiency.

## METABOLIC EFFECTS: T2DM AND URIC ACID

### HF and T2DM

HF and T2DM share risk factors and pathophysiological mechanisms that favor coexistence (84–86). It has been documented that patients with HF have a four times higher prevalence of T2DM than patients without HF, with the proportion being even higher in patients hospitalized for HF (86). In fact, the severity of HF, as defined by the daily dose of loop diuretics, has been directly related to the risk of developing T2DM (87), which leads to a worse prognosis, both in terms of mortality and readmissions (84–86). Moreover, the risk of developing HF is 2.5 times higher in patients with T2DM, and hospitalization for HF is higher in diabetic patients compared to non-diabetic patients (86).

Moreover, the risk of developing HF is 2.5 times higher in patients with T2DM, and hospitalization for HF is higher in diabetic patients compared to non-diabetic patients. Similarly, in clinical trials, all HF drugs and devices were equally effective regardless of the presence or absence of T2DM (86). Interestingly, it was noted that dual inhibition of the RAAS and neprilysin may lead to better glycemic control (15, 88).

This is suggested by the results of a *post-hoc* analysis of the PARADIGM-HF study, which included 3,778 patients with HFrEF and known diabetes (98% T2DM) or an HbA1c $\geq$6.5%, who were randomized to receive either enalapril or sacubitril/valsartan. At a 1-year follow-up, a greater reduction in HbA1c concentrations was observed in the sacubitril/valsartan group compared to the enalapril group (0.26 vs. 0.16%, $p = 0.0023$) (15). This greater reduction with sacubitril/valsartan treatment was maintained at the 3-year follow-up ($p = 0.0055$). Also, 29% fewer patients in the sacubitril/valsartan group needed to start insulin (7 vs. 10%, $p = 0.0052$) or oral antidiabetic treatment ($p = 0.073$) (15).

The PARADIGM-HF data have also made it possible to assess the effect of neprilysin inhibition on the course of kidney disease in patients with T2DM (18). A sub-study showed that even in patients already receiving high doses of RAAS-blocking drugs, additional neprilysin inhibition slows the decline in estimated GFR (follow-up of up to 44 months), especially in patients with diabetes (0.6 mL/min per 1.73 $m^2$ yr vs. 0.3 mL/min per 1.73 $m^2$ yr; $p = 0.038$). This more marked effect in patients with diabetes could not be explained by glycaemic control and occurred despite a modest increase in proteinuria in patients treated with sacubitril/valsartan (18). The clinical benefits described would be justified by the role of neprilysin inhibition in glucose homeostasis (89–91), increasing plasma levels of various peptides such as GLP-1 (neprisilin inactivates up to 50% of GLP-1 released into circulation), NP, cGMP and bradykinin, which can improve insulin sensitivity (**Figure 7**). Additionally, NPs promote lipid mobilization from adipose tissue, increase postprandial lipid oxidation, promote adiponectin release and increase muscle oxidative capacity (91). Increased urinary cGMP concentrations, especially low in diabetic patients, have also been linked to the renal benefits of NPs (18).

In another study of 73 HF patients, 16 of whom had diabetes, switching from an ACEI or ARA II to an ARNI for 3 months resulted in a decrease in plasma neprilysin activity. This was associated with a reduction in fructosamine levels, a marker of protein glycation in diabetic and non-diabetic patients, indicating rapid action on glycaemic control with the use of ARNI (90).

However, in monotherapy, neprisilin inhibitors increase levels of angiotensin II and enzymes such as dipeptidyl peptidase-4, resulting in reduced efficacy of inhibition, or concomitant elevation of other neprisilin substrates (adrenomedullin, endothelin1, glucagon, etc.) which may promote insulin resistance and pancreatic beta-cell dysfunction (91). For this reason, it is preferable to administer neprisilin inhibitors in dual therapy as ARNIs (91).

Recently, the DAPA-HF study has shown that dapagliflozin administration in patients with HFrEF, with or without DM2, results in a significant reduction vs. placebo in the risk of worsening HF or CV death, which remains constant in patients who received sacubitril/valsartan treatment (92). Similarly, the EMPEROR-Reduced study has shown that empagliflozin significantly reduces the primary composite endpoint of HF hospitalization rate and CV death vs. placebo, with no difference compared to the sacubitril/valsartan treatment group (93). These results suggest that the two drugs have different and potentially synergistic biological effects.

### HF and Uric Acid

Uric acid is a marker of oxidative stress that induces inflammation, impairs endothelial function, and activates the RAAS, which may be associated with myocardial damage and worse outcome in HF patients (94–96). Renal insufficiency and

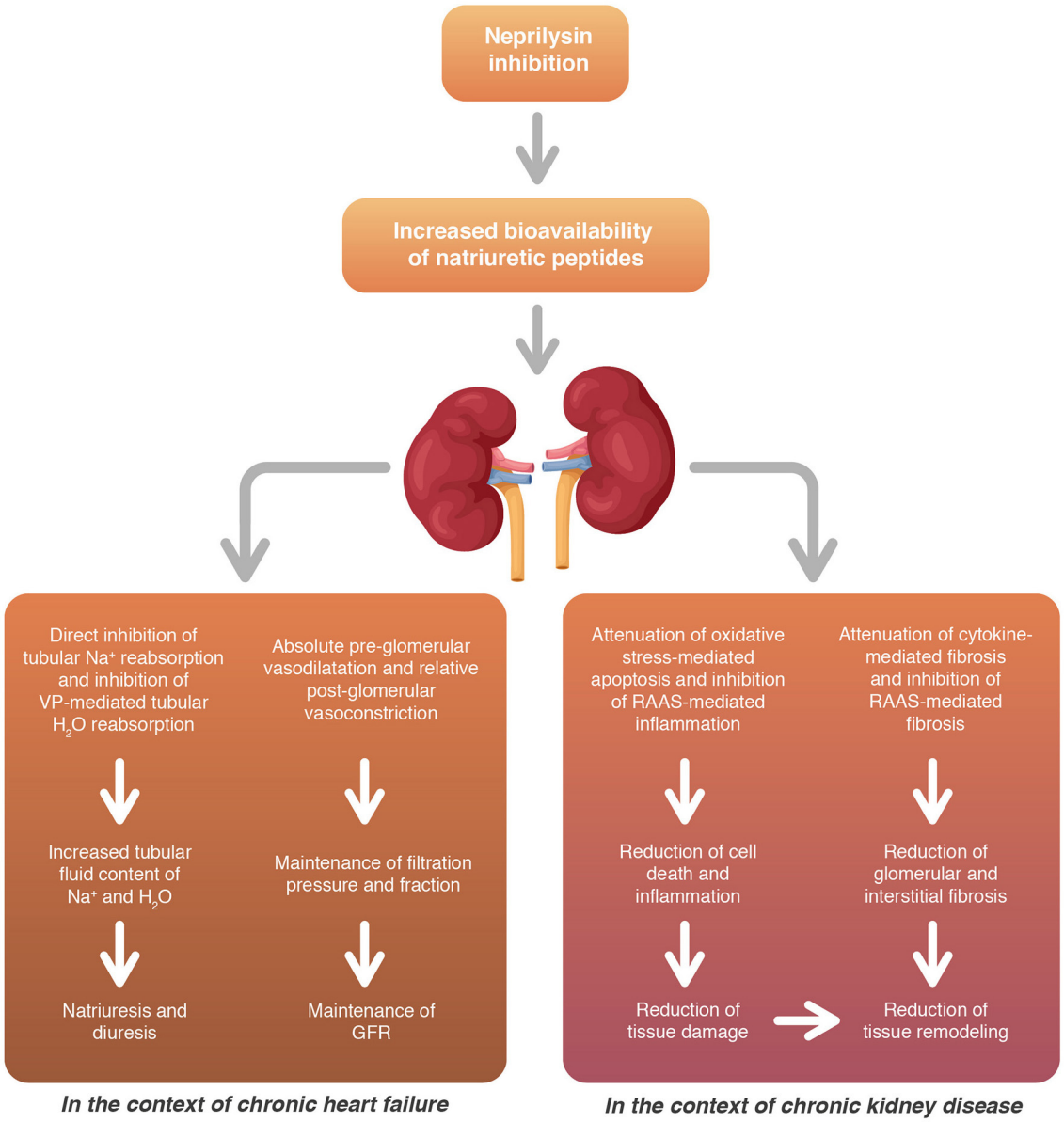


**FIGURE 6 |** Neprilysin/RAAS inhibition provides several renal benefits both in terms of functional adaptations and structural remodeling. RAAS, renin-angiotensin-aldosterone system; GFR, glomerular filtration rate; VP, vasopressin.

the use of diuretics also increase the concentration of uric acid due to alterations in its excretion (94). In PARADIGM-HF, UA was an independent predictor of worse outcomes. Compared with enalapril, sacubitril/valsartan reduced UA by 0.24 mg/dL and improved clinical outcomes irrespective of UA levels (96).

In conclusion, the use of ARNI in HF patients has shown a better metabolic profile than enalapril treatment. In a sub-analysis of the PARADIGM-HF study with patients with HFrEF and T2DM, treatment with sacubitril/valsartan resulted in lower HbA1C concentrations and reduced need for both insulin and oral antidiabetic drugs compared to the group treated with enalapril (15). Similarly, sacubitril/valsartan treatment has been shown to reduce UA levels and the improved CV outcomes demonstrated in the PARADIGM-HF study compared to enalapril occurred independently from UA levels (96).

## QUALITY OF LIFE AND FUNCTIONAL CAPACITY

### Quality of Life

HF patients have a severely impaired health-related quality of life (HRQOL). As the VIDA-IC (97) study demonstrated, patients with HF and systolic dysfunction suffer from a higher limitation of mobility and a higher incidence of symptoms

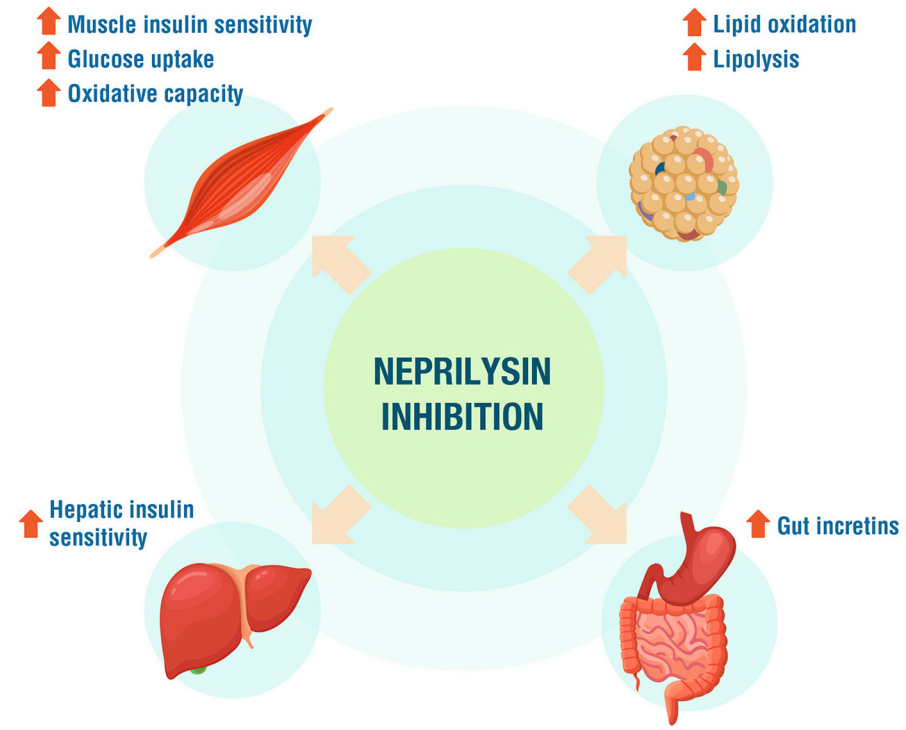


**FIGURE 7 |** The role of neprilysin inhibition in glucose homeostasis. GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic peptide; PYY, peptide YY; CCK, cholecystokinin; VIP, vasoactive intestinal polypeptide. Adapted from Esser and Zraika (91).

such as pain/discomfort and anxiety/depression compared to other chronic diseases perceived as very disabling, e.g., cancer and Alzheimer's disease. Therefore, understanding the impact of therapeutic interventions beyond mortality or hospitalizations is a priority, especially from the patient's perspective.

In the PARADIGM-HF study, sacubitril/valsartan was shown to improve quality of life over enalapril from month 4 post-randomization using the Kansas City Cardiomyopathy Questionnaire. This difference was sustained over 36 months of follow-up (98). This improvement was consistent across the 8 domains explored. An important aspect was the buffering effect of sacubitril/valsartan on the decline in quality of life associated with HF hospitalization compared to enalapril (98).

Since physical and social activities are typically the most limited in HF patients, a specific secondary analysis was performed on the effect of sacubitril/valsartan relative to enalapril on these aspects of quality of life. Patients on sacubitril/valsartan had better adjusted scores on most physical and social activities at 8 months compared to those on enalapril. These scores were sustained at 36 months (99). The greatest comparative improvements were found in domestic activities and sexual relations (**Figure 8**). Overall, the improvement in patients treated with sacubitril/valsartan would be equivalent to a difference of ∼9 years of aging compared to those treated with enalapril. In turn, a sub-analysis showed that non-fatal events worsen HRQOL (100), therefore preventing these events with sacubitril/valsartan would prevent the associated deterioration in HRQOL.

In summary, we can state that improving HRQOL is a target of increasing interest when evaluating new therapies in HF. So far, the first-line drugs that have been shown to improve disease prognosis have had mixed results with respect to HRQOL, starting with beta-blockers, which do not improve HRQOL, to the mixed results seen with ACEIs or ARA II. However, sacubitril/valsartan has been shown to improve quality of life in HF patients consistently over enalapril, especially in terms of physical activity and social relationships.

## Functional Capacity

Quality of life is strongly associated with intolerance to physical exertion, a pivotal symptom of HF. The assessment of functional capacity in healthcare practice is routinely performed using the NYHA functional classification, and significant improvements in NYHA functional class were reported in PARADIGM-HF (5). Nevertheless, it has limitations due to its subjectivity and lack of


**FIGURE 8 |** Effect of sacubitril/valsartan relative to enalapril on different components of quality of life[99]. KCCQ, Kansas City cardiomyopathy questionnaire; MTS, meters; 6minWT, 6-minute walk test; VO2, Oxygen uptake.

reproducibility compared to objective assessments using the 6-miwalk test (6MWT) (101) or the cardiopulmonary exercise test (102), the latter is considered to be the reference standard.

The 6MWT is a simple and inexpensive tool that helps predict morbidity and mortality. In the BIOSTAT-CHF study, walking 240 m or less at the baseline assessment was shown to be more predictive of mortality than age (>75 years), diabetes, chronic renal failure or previous stroke. Conversely, for every 50 m "lost" at 9 months, the risk of mortality and hospitalizations increased by 8% and the risk of mortality by 14%. Functional capacity gains of 30–50 m at 6MWT are considered clinically meaningful as they are associated with significant improvements in NYHA functional class and HRQOL. Regarding cardiopulmonary ergometry, a 6% increase in peak $VO_2$ is associated with an 8% reduction in CV mortality or HF hospitalizations and a 7% reduction in all-cause mortality (103).

The effect of sacubitril/valsartan on objective functional capacity has been explored in several observational studies. In a cohort of 58 patients, after 1 month with sacubitril/valsartan (104), patients were able to walk 41.8 meters further, which represented an increase of 14% over baseline (104). In another cohort of 16 patients treated with sacubitril/valsartan and assessed by cardiopulmonary ergometry (105), peak $VO_2$ increased significantly at 30 days by 0.92 ml/min/kg, corresponding to an increase of 7.9% compared to baseline, and respiratory efficiency also showed a significant improvement after 1 month, with a 9.1% reduction in $VE/VCO_2$ slope (**Figure 8**) (105). A third study in a larger cohort ($n = 99$) (106), showed a significant improvement of 17% in peak $VO_2$ and a 7% reduction in $VE/VCO_2$ slope. Finally, in a prospective study of 37 consecutive patients with advanced HF on the waiting list for heart transplantation, significant improvement in NYHA class, peak $VO_2$ and 6MWT was observed after 1 year of treatment, while no statistical differences were observed during the year prior to starting sacubitril/valsartan (107). In turn, a significant reduction in depressive symptomatology related to improvements in the 6MWT was observed independently of other variables (age, sex, antidepressant treatment, $VO_2$ maximum, NT-proBNP, systolic pulmonary artery pressure, NYHA class) (107). The relationship between depression, a common problem in patients with CV disease, and increased mortality, excess disability, increased health expenditure, and reduced quality of life has been previously described (108).

In conclusion, there is sufficient evidence that sacubitril/valsartan has a positive and clinically significant impact on quality of life and functional capacity. These measures are highly relevant from the patient perspective and may also improve adherence to this life-saving therapy. It should be a priority in clinical practice to incorporate the patient's perspective through objective assessments of these parameters, both in the evaluation of new therapeutic interventions and in day-to-day clinical care.

## SAFETY: RENAL FAILURE, HYPERKALEMIA, HYPOTENSION, ANGIOEDEMA, IN OUTPATIENTS AND HOSPITALIZED PATIENTS

The safety and tolerability of sacubitril/valsartan is well-established in both clinical trials and real-life clinical practice. The more relevant adverse events related to treatment with drugs in HF and with sacubitril/valsartan are discussed below (**Table 1**).

### Renal Insufficiency

Sacubitril/valsartan has shown a more favorable renal safety profile than enalapril (5). The PARADIGM-HF study found that both the elevation of serum creatinine $\geq$ 2.5 mg/dl and the

**TABLE 1 |** Side effects in the PARADIGM-HF and PIONEER-HF trials.

| | PARADIGM-HF (5) n (%) | | | PIONEER-HF (7) n (%) | | |
|---|---|---|---|---|---|---|
| | **S/V (*N* = 4,817)** | **Enalapril (*N* = 4,212)** | ***P*** | **S/V (*N* = 440)** | **Enalapril (*N* = 441)** | **RR (CI 95 %)** |
| Symptomatic hypotension | 588 (14.0) | 388 (9.2) | <0.001 | 66 (15.0) | 56 (12.7) | 1.18 (0.85–1.64) |
| Elevated creatinine ≥2.5/mg/dL* or Impaired renal function ǂ | 139 (3.3)* | 188 (4.5)* | 0.007 | 60 (13.6) ǂ | 65 (14.7) ǂ | 0.93 (0.67–1.28) |
| Elevated $K^+$ > 5.5 mmol/L | 674 (16.1) | 727 (17.3) | 0.15 | 51 (11.6) | 41 (9.3) | 1.25 (0.84–1.84) |
| Elevated $K^+$ > 6 mmol/L | 181 (4.3) | 236 (5.6) | 0.007 | — | — | — |
| Angioedema | 19 (0.4) | 10 (0.2) | 0.13 | 1 (0.2) | 6 (1.4) | 0.17 (0.02–1.38) |
| Discontinuation of treatment due to side effects | (10.7) | (12.3) | 0.03 | 51 (11.5) | 45 (10.1) | NS |

*eGFR, estimated glomerular filtration rate.*

*ǂImpaired renal function defined as an increase in creatinine concentration ≥ 0.5 mg/dL and decrease in estimated GFR ≥ 25%.*

*NS, not significant.*

**Elevated creatinine in the PARADIGM study.*

progression of renal function deterioration were less frequent with sacubitril/valsartan vs. enalapril (80). The magnitude of the benefit of sacubitril/valsartan on renal function was twice as high in patients with T2D vs. patients without T2D (18). This nephroprotective effect was observed despite the fact that patients treated with sacubitril/valsartan had higher hypertension and increased albumin/creatinine ratio in urine (18, 80). The number of patients who discontinued sacubitril/valsartan due to adverse renal events was half compared to enalapril (0.7 vs 1.4%; $p = 0.002$), and fewer than half in CKD patients (1.1 vs 2.6%; $p = 0.008$) (80). In patients hospitalized with acute HF in the PIONEER-HF trial (7), the frequency of renal function impairment did not differ [13.6 vs. 14.7%; RR 0.93 (0.67–1.28)].

Sacubitril/valsartan was also evaluated in patients with CKD and albuminuria (but not HF) vs. irbesartan, including patients with eGFR of 20 to 60 mL/min/1.73m$^2$. There were no differences in eGFR at 12 months, but sacubitril/valsartan added significant reductions in levels of cardiac biomarkers (82). Successful use of sacubitril/valsartan in eGFR of <30 mL/min/1.73m$^2$ has also been reported in real life patients (109). Sacubitril/valsartan seems therefore safe in patients with more advanced CKD, a scenario where the use of ACE inhibitors is very limited.

## Hyperkalemia

The PARADIGM-HF study (5) found that severe hyperkalemia (serum potassium of >6 mEq/L) was less frequent with sacubitril/valsartan than with enalapril (4.3 vs. 5.6%; $p = 0.007$), while no significant differences were found in the PIONEER-HF study (7).

Concomitant use of MRA is recommended by clinical practice guidelines to reduce morbidity and mortality in patients with symptomatic HFrEF, but it associates an increased risk of hyperkalemia. A sub-analysis of patients treated with MRA in the PARADIGM-HF study (110) found that the annual incidence of severe hyperkalemia was lower with sacubitril/valsartan vs. enalapril, both in patients already receiving MRA (2.2 vs. 3.1%; $p = 0.02$) or those who initiated MRA (2.3 vs. 3.3%; $p = 0.003$). In addition, patients receiving sacubitril/valsartan and MRA had fewer temporary or permanent discontinuations of MRA than those treated with enalapril (111). All these data suggest that sacubitril/valsartan associates a lower risk of hyperkalemia, even when combined with ARM, compared with ACEI or ARB (110).

## Arterial Hypotension

Symptomatic hypotension was the most frequent adverse event reported with sacubitril/valsartan, in clinical trials (5, 7) and real life (109). In the PARADIGM-HF trial (5), sacubitril/valsartan was associated with a higher frequency of symptomatic hypotension (14 vs. 9.2% enalapril; $p < 0.001$), but did not result in a higher rate of drug withdrawal (0.9 vs. 0.7%, $p = 0.38$). The beneficial effect observed with sacubitril/valsartan vs. enalapril, however, was constant across the different pre-established SBP categories, and greater in those patients with lower SBP below 110 mm Hg (16).

Hypotension should not preclude initiation and titration of sacubitril/valsartan in elderly patients (aged >75 years), as there was no interaction between age and treatment on its rate, it did not lead to a higher rate of discontinuation and the benefit obtained was independent of age (17).

In the PIONEER-HF study (82), symptomatic hypotension did not differ significantly between sacubitril/valsartan and enalapril [15% vs. 12.7%; RR 1.18 (0.85–1.64)] in hospitalized patients, with similar low withdrawal rates in both groups (2.5%). Hypotension did not influence the benefits of sacubitril/valsartan vs. enalapril (80). A slower titration is recommended in the presence of hypotension, as it is associated with a higher rate of achieving target doses (111).

## Angioedema

Both in the PARADIGM-HF (5) (0.5% sacubitril/valsartan and 0.2% enalapril, $p = 0.13$), and the PIONEER-HF (82) studies (0.2% sacubitril/valsartan and 1.4% with enalapril, RR 0.17; 0.02–1.38), angioedema was rarely seen, with no significant differences between groups. In all studies, sacubitril/valsartan was started at least 36 h after discontinuation of enalapril to minimize the risk of angioedema.

### Tolerance

In the PARADIGM-HF study drug tolerance was adequate, and permanent discontinuation due to adverse events was very low and less frequent with sacubitril/valsartan vs. enalapril (10.7 vs. 12.3%, $p = 0.03$) (5). A recent meta-analysis affirmed that patients with HFpEF who received sacubitril/valsartan had a lower rate of serious adverse events vs. the ACEI/ARB control group (RR 0.89; CI 95%, 0.86–0.93) (112). In patients with acute decompensated HF, early initiation of sacubitril-valsartan or enalapril were associated with similar rates of discontinuation (11.5 vs. 10.1%, p not significant) (7) When initiated in stable patients before discharge, sacubitril/valsartan showed an even lower discontinuation rate (7.1%) (8).

To summarize, sacubitril/valsartan has been shown to be safe in patients with HFrEF, both in the outpatient and the in-hospital settings, with a more favorable renal safety profile vs. enalapril, including a lower risk of renal impairment and severe hyperkalemia. It should be expected a slightly higher risk of hypotension, but not severe hypotension. Considering the clinical benefits, initiation of sacubitril/valsartan must be recommended before discharge in hospitalized HFrEF patients.

## DISCUSSION

In patients with HFrEF, treatment with sacubitril/valsartan has been shown to be cost-effective (14) and superior to enalapril in reducing all-cause and cardiovascular mortality, including sudden cardiac death and HF death, as well as in reducing the rate of HF hospitalization and rehospitalization (5). Initiation of ARNI is also associated with an early significant benefit, compared to treatment with enalapril, in both the chronic and the acute setting (7, 8). Sacubitril/valsartan administration has been shown to be safe and well-tolerated in a wide range of HFrEF patients, and associated with a significant improvement in quality of life measures (99, 100).

There are several related mechanisms that explain this wide benefit, and they include both cardiac and extracardiac protective effects. At the cardiac level, a major mechanism is the modulation of the NP system, leading to a reduction in myocardial stress, inflammation and cell death, which in turn leads to improved parameters of cardiac function and remodeling (24, 25, 65). At the extracardiac level, favorable vascular (4), metabolic (15, 96) and renal effects (18, 80) also make a significant contribution, leading to greater vascular protection and a lower risk of diabetes and renal impairment, as well as better tolerance and persistence over other beneficial treatments (5, 7, 112).

In conclusion, there is sufficient evidence to affirm that sacubitril/valsartan is the first-line therapeutic option in patients with HFrEF, compared to isolated RAAS inhibition.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

A non-conditioned grant by Novartis Spain was acknowledged.

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**Conflict of Interest:** This publication received a non-conditioned grant by Novartis, providing non-conditioned support for medical writing. The authors also declare the following competing interests: DP-F has received personal fees, non-financial support, and/or research grants from Novartis, Astra

Zeneca, Boehringer Ingelheim, Roche, Rovi, Vifor, Abbot, Pfizer, Servier, and Medtronic. AB-G has received fees from lecturing and/or advise from Abbott, Astrazeneca, Boehringer Ingelheim, Novartis, Vifor, Roche Diagnostics, and Critical Diagnostics. PB-T and AC-M has received consultant and/or speaker fees from Novartis and Rovi. FF has received honoraria for lectures/consultancy from Novartis and Rovi.

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