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Review Article

Challenges for the Generation of Real-World Evidence in Heart Failure in Europe

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Abstract

Heart failure (HF) constitutes a substantial health burden in Europe and, indeed, globally, warranting improvements in disease management strategies. Real-world evidence (RWE) research is a useful tool that can guide treatment intervention and preventative strategies if based on large, comprehensive data sources, covering a wide variety of patient demographics and clinical characteristics. However, some inherent challenges associated with HF that influence the generation of RWE in Europe are those relating to diagnosis and disease management. Despite the availability of evidence-based guidelines for HF treatment, heterogeneity in the HF population and disease course can contribute to variation in the management of HF in routine clinical practice globally, making interpretation of real-world data difficult. In this review, we summarise and discuss these challenges in the context of ways in which they affect the generation of RWE in HF. Addressing these matters could see greatly increased usability of RWE in HF, which could translate into improvement in treatment interventions and best practice of patient care.

Keywords: *Real-World Evidence; Heart Failure; Europe; Disease Management; Registry*

Abbreviations

AI: Artificial Intelligence; EF: Ejection Fraction; EHR: Electronic Health Records; EORP: EURObservational Research Programme; ESC: European Society of Cardiology; EUROHEART: European Unified Registries on Heart care Evaluation and Randomised Trials; FDA: Food and Drug Administration; HF: Heart Failure; HFA: Heart Failure Association; HFimpEF: Heart Failure with Improved Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; ICD: International Classification of Diseases; LVEF: Left Ventricular Ejection Fraction; MDT: Multi-Disciplinary Team; NYHA: New York Heart Association; QCC: Quality of Care Centres; RCT: Randomised Controlled Trials; RRCT: Registry-Based Randomised Controlled Trial; RWD: Real-World Data; RWE: Real-World Evidence; SPIRRIT-HFpEF: Spironolactone Initiation Registry Randomized Interventional Trial in HFpEF; UK: United Kingdom; US: United States

Introduction

Heart failure (HF) is among the leading causes of cardiovascular morbidity and mortality worldwide, affecting 1 - 2% of adults in developed countries, with prevalence increasing to ≥ 10% in individuals aged 70 years or older. Mortality is high among patients with HF, and these patients typically have at least one other comorbidity, ultimately contributing to worsening health status [1,2]. Prolonged and

recurrent hospitalisation is typical in patients with HF, who are hospitalised for an average of 5 - 10 days, with ~60% readmitted within 12 months, most commonly for worsening HF. This has a deleterious effect on patient quality of life [3] and contributes to an immense financial burden, with HF accounting for 2-3% of all healthcare expenditure in developed countries [1].

Definition and classification of HF can differ between countries due to the complexity of the syndrome. To standardise the definition and classification, a consortium of HF societies [4] issued guidance outlining suggested HF definitions and categories. According to the report by Bozkurt., *et al*. and the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure, HF is defined as a clinical syndrome with cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by cardiac abnormalities and is confirmed by increased natriuretic peptide levels and/or evidence of pulmonary or systemic congestion [2,4]. Patients with HF are often categorised according to left ventricular ejection fraction (LVEF) function, including HF with reduced ejection fraction (EF) (HFrEF, EF of ≤ 40%), HF with mildly reduced EF (HFmrEF, EF of 41 - 49%), HF with preserved EF (HFpEF, EF of ≥ 50%), and the recently suggested HF with improved EF (HFimpEF, baseline EF ≤ 40%, followed by a ≥ 10-point increase and second measurement of > 40%). Despite improvements in LVEF to 41 - 49% or ≥ 50%, HFimpEF should be encouraged to be used as a categorisation and shouldn't be included within HFmrEF or HFpEF, since stopping HFrEF therapy in this group has a negative prognostic impact [4]. Symptoms can be relatively similar across the HF subtypes, although there are important differences in pathophysiology, treatment options and response, and prognosis, such that lower EF is being considered as an independent risk factor for mortality. The subtype of HF, along with comorbidities, contributes to increased heterogeneity in the HF population, thus necessitating an individual patient-tailored approach to treatment. Therefore, early diagnosis, and optimal and bespoke treatment based on HF subtype is of utmost importance [5,6]. However, in patients with asymptomatic HF (also known as asymptomatic left ventricular systolic dysfunction), or stage B HF, where diagnosis is challenging, early treatment initiation using HF-directed pharmacotherapy has been proven to improve outcomes [7]. There have been advances in pharmacological treatments for HFrEF, yet the residual global health burden of HF constitutes a need for improvement in disease management strategies. In a healthcare setting, real-world evidence (RWE) is an important tool that can be used to guide the development of these strategies, as it can provide information on a large population comprising patients of varying demographics, health status and comorbidities [8,9]. Heart failure, which is a highly prevalent condition, provides an expansive and heterogeneous patient population for the collection of real-world data (RWD). There are numerous sources of RWE including non-interventional studies, patient registries, electronic health record (EHR) studies, patient surveys and studies from insurance health claims databases [8]. However, in Europe, consistent capture of RWD is challenging due to differences between national health care systems, legal framework and clinical databases. In this narrative review, we focus on patient registries in Europe and provide an overview of challenges associated with the diagnosis and management of HF in the context of ways in which they influence RWE generation and interpretation, along with identifying and discussing some opportunities that may be helpful in overcoming these challenges. To the best of our knowledge, literature describing these topics is scarce; thus, we hope to raise awareness and stimulate further discussion among independent stakeholders, ultimately leading to an improvement in the generation of RWE in HF.

RWE and HF: Challenges and opportunities

Real-world evidence

In HF, RWE is a useful tool as it provides information on treatment and disease management effects, and the corresponding implications for patient care, in a setting that closely resembles routine clinical practice. Real-world data collected from registries, EHRs, claims databases, and medical and hospital records are a source of observational prospective and/or retrospective studies for the generation of RWE [10]. The generalisability of RWE allows healthcare decision-makers to use RWD to monitor treatment patterns and improve best practice in care for patients [11]. It is not surprising that there is a growing interest from healthcare regulatory authority bodies such as the European Medicines Agency and Food and Drug Administration (FDA), to consider RWE to inform approval decisions for new treatments [12].

Patient registries are an essential source of RWD collected during routine clinical practice and, as such, they can be used to drive best practice in HF management, ultimately improving patient outcomes [13,14]. Furthermore, registries provide valuable information on national compliance to regional guidelines, along with potential reasons for poor adherence [15,16]. This information helps to determine the effectiveness of treatments in specific populations, which can lead to better-informed decisions for interventions.

The SwedeHF registry is, arguably, one of the most renowned registries in the HF field in Europe. It includes the majority of hospitals providing care for patients with cardiac-related disease in Sweden. Enrolment in the SwedeHF registry is associated with improvements in cardiovascular medications and subsequent reductions in all-cause mortality, and RWD from SwedeHF have contributed to a greater understanding of HF phenotypes, particularly in distinguishing between HFpEF and HFmrEF [14,15]. Importantly, SwedeHF has been used to investigate the efficacy of a novel disease intervention in a registry-based randomised controlled trial (RRCT), Spironolactone Initiation Registry Randomized Interventional Trial in HFpEF (SPIRRIT-HFpEF) [17]. Registry-based randomised controlled trials use data gathered by registries for rapid patient enrolment, baseline data collection and straightforward follow-up. As such, they are less costly than the traditional randomised controlled trials (RCTs), allowing for enrolment of a large number of heterogeneous patients with more varied characteristics than patients participating in RCTs, thus increasing generalisability of the outcomes [18]. However, the subgroups of patients with chronic HF and various morbidities might be utilized to prevent generalisability of the results, if needed. Although the success of SwedeHF is attributable to several components, a key contributing factor is that it can link with other databases, such as the National Patient Registry and Statistics Sweden, which provide additional comorbidity and socioeconomic data, respectively. However, it should be noted that aspects of the Swedish healthcare system enable such links. Therefore, the development of similar data infrastructure is needed in other countries to enable greater data harmonisation [19].

A challenge for other European countries in the generation of reliable and robust RWD relates to the legal framework affecting access to data and data sharing following the implementation of the General Data Protection Regulation. To ensure appropriate data privacy, patient consent and standardised data anonymisation techniques are required when developing registries [9]. Cardiology registries in Europe, including a Swedish quality-of-care registry SWEDEHEART, the Netherlands Heart Registration and the United Kingdom (UK)-based NICOR registry, successfully ensure patient privacy by having dedicated data control personnel, encrypted data storage, and data pseudonymisation techniques [20]. However, this may be more challenging for international studies, particularly those using administrative databases, which are not developed for research purposes and may have added language and translation barriers [21]. Indeed, with the rise of big data-driven healthcare, substantial increases in security breaches, including attempted hacking and ransomware, have been recorded [22]. As such, patient privacy and security will likely pose a challenge in the era of big data, and future RWE studies will need to develop innovative techniques to overcome this, while ensuring that the appropriate and necessary laws are strictly adhered to. Moreover, developing, conducting, and interlinking registries needs globally accepted standards and definitions to ensure optimal data input. However, HF classifications are constantly evolving as we learn more about the disease, adding further challenges in the formation of registries and the interpretation of RWD.

Diagnosis of HF

The clinical manifestations of HF vary greatly between patients, who typically have comorbidities or non-specific symptoms, which make it difficult to isolate HF-specific signs and symptoms. This can lead to under- or misdiagnosis of HF, and misclassification of HF in databases [23]. Initially, it is normal for patients to present to their primary care physician; yet, despite the availability of evidence-based guidelines, successful diagnosis of HF in primary care is suboptimal in Europe, varying from ~70% in Germany to just ~30% in the UK. Moreover, the time to diagnosis from onset of symptoms is typically delayed and can be > 2 years. A contributing factor relates to lack of access to echocardiography in primary care. As an alternative, physicians commonly use electrocardiography, which does not account for the left ventricular dysfunction required for accurate HF diagnosis and categorisation [26,27]. Indeed, in a study of ~16,000 patients presenting in primary care with at least one of three key HF symptoms, only 39% were referred for an echocardiogram or had serum

natriuretic peptide levels tested. As such, diagnosis largely takes place during hospitalisation, despite patients presenting to their general practitioner several times prior to diagnosis [24,25]. For HFpEF, a correct diagnosis is even more challenging due to normal LVEF and a typical patient population who are older and have more comorbidities such that they present with nonspecific symptoms [26]. Therefore, evidence-based guidelines should be adhered to which recommend thorough clinical examination followed by appropriate and timely investigation to achieve an accurate diagnosis [2]. This would also help in assessing the true prevalence of HF.

According to the 2021 ESC guidelines, various diagnostic tests including electrocardiogram, measurement of natriuretic peptides, chest X-ray and transthoracic echocardiography are recommended for the assessment of patients with suspected chronic HF [2]. Non-adherence to guideline diagnostic processes can lead to misclassifications and failure to phenotype HF correctly, adding a layer of complexity when conducting RWE studies [27]. From the International Classification of Diseases codes, the codes for HF fall under ICD-8, ICD-9, and ICD-10. A meta-analysis reporting the validity of these HF diagnostic codes in administrative databases showed that, although coding is largely predictive of true HF cases, a substantial proportion (~25%) of HF diagnoses are missed due to healthcare personnel only coding for comorbidities or active conditions, such as myocardial infarction, excluding the code for chronic HF [28]. This is likely due to patients presenting with symptoms equally attributable to comorbidities, resulting in inaccuracies or incomplete diagnostic coding during diagnosis.

Similarly, analysis of HF registry data showed that ~15% of entries do not fulfil ESC diagnostic criteria for HF [29], and this number may be even greater for primary care diagnoses [30]. This, in part, is due to a lack of echocardiography examination, which is necessary to accurately diagnose HF [29]. Patients diagnosed with HF in primary care are not always categorised using the New York Heart Association (NYHA) functional classification, which describes HF according to the severity of signs and symptoms and, as such, can guide treatment decisions [2]. Evidence suggests a lack of standard methodological practice in NYHA class evaluation among physicians [31], which may be a contributing factor. Moreover, there are several other prognostic indicators, although the NYHA classification relies fully on disease symptoms [2]. Codes describing LVEF are not always included in the registry data, most likely because echocardiography is not consistently performed in primary care [32], which adds to the challenges in determining HF phenotype [33]. Indeed, evidence suggests that EHRs, such as those ubiquitously used in primary and secondary care settings, often do not capture phenotypic specific information for patients with HF [34], despite the discernible differences in causes and outcomes for patients with different HF phenotypes [35,36]. Thus, due to a lack of standardised diagnostic processes and the paucity of phenotypic data in EHRs, patients are omitted from registries or incorrectly categorised in databases, which leads to erroneous interpretation of RWD, limitations for data pooling and misalignment in registry outputs. As such, suboptimal diagnosis of HF can be a limiting factor in large RWE studies.

Management of HF

Evidence-based guidelines for treatment of HF have been established, and detail recommendations for pharmacological- and device-related HF treatment. According to the 2021 ESC guidelines, angiotensin-converting enzyme inhibitors/angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose transport protein 2 inhibitors are the cornerstone therapies for patients with HFrEF, unless the drugs are contraindicated or not tolerated. However, difficulties in the management of HF remain, affecting the interpretation of RWE [2].

Similar to HF diagnosis, a major challenge in the management of HF relates to HFpEF, which accounts for half of HF cases, and for which there has been quite recently approved treatment in Europe [37] as well as in the United States (US) FDA [38,39]. A substantial proportion of patients with HFpEF are treated with therapy recommended for HFrEF, or therapy that overlaps with treatments for comorbidities, potentially as a result of insufficient differentiation between HF subtypes, or of the current absence of HFpEF-specific HF treatment in Europe [40]. Thus, there is inconsistency in the use of treatments within the population of patients with HF.

There are geographical variations in therapeutic prescriptions for HF and underdosing of pharmacological treatment is common, possibly suggesting relatively low compliance with the guidelines. Moreover, not all of the patients with HF receive the treatment

recommended by the guidelines [41]. Approximately 70% of patients with HF do not receive the target therapy dose, despite uniform treatment recommendations and target therapy consisting of all necessary drugs as well as optimal doses, indicative of a lack of a globally implemented approach to HF management [40,42,43]. The variation in HF management introduces difficulties in the interpretation of RWD, which, in turn, can affect both healthcare decision-making and patient self-care recommendations.

Given the chronic nature of HF, long-term multi-disciplinary team (MDT) disease management programmes are important for improving patient mortality and morbidity, hospital readmissions, patient quality of life and treatment cost-effectiveness [2,3,44]. The value of these patient-centred programmes is well established in HF; however, in some European countries, their initiation and conduct have been suboptimal. In reality, there is a lack of cross-collaboration between primary care physicians and cardiovascular specialists. There are even significant delays in time between a patient presenting symptoms to their general practitioner, receiving a diagnosis, and being referred for an expert review [45]. Specialist input into the care of patients with HF is sometimes even non-existent, and approximately 30% of patients with HF are treated solely in primary care [44,46]. The fragmentation of patient care across healthcare divisions likely results in multiple data sources and fragmented patient datasets, contributing to challenges in RWD capture and interpretation. Home-based management programs, such as home telemonitoring, should be used to offer a tailored approach to address the patient's needs, in synergy with the existing healthcare facilities. It is an effective way to educate and motivate patients while also assisting with care delivery [2].

Often, patient registries enrol patients from specialist HF centres only [47], thereby excluding patients treated in primary care, where suboptimal adherence to guideline-recommended therapy is established. Outputs from RWE studies are therefore associated with residual questions about treatment efficacy, namely, whether poor treatment response is due to patient characteristics, suboptimal disease management or other reasons. Additionally, variation between databases in the definitions for HF and disease outcomes, along with multiple data systems and variability in the types of outcomes collected can cause difficulties for data harmonisation, thus affecting the feasibility of pooling datasets or linking registries [27,48]. Without widespread compliance to standardised HF definitions, combining data from different healthcare databases may contribute to a lack of large integrated datasets for HF [27].

This narrative review focused on the impact of inadequate/suboptimal diagnosis and disease management associated with HF on the generation of RWE in Europe. However, the underlying reasons for these inherent challenges have not been discussed in this review.

Future direction

Variation in registry standards across Europe, along with differences in the classification, diagnosis, and management of HF, may profoundly affect the generation and interpretation of RWD. Suboptimal diagnoses, due to misclassification and subsequent miscoding, as well as non-adherence to diagnostic guidelines, also pose a challenge for widespread leverage and implementation of RWE. Furthermore, varying management strategies, indicated through different rates of dosing and low achievement of guideline-recommended target therapy dose, suggest low adherence to disease management guidelines.

Overcoming the challenges outlined above would considerably advance the usability of HF RWE. Efforts are ongoing to implement MDT programmes across Europe, initiated by the Heart Failure Association (HFA) of the ESC, who will collaborate with national HF societies to develop accredited quality of care centres (QCC) by integrating country-adapted QCC programmes into existing health care systems. Compliance to the HFA/ESC QCC standards and definitions will be necessary for HFA accreditation, thus serving to standardise medical databases and patient care across Europe [49]. Comprehensive regional data collection initiatives, such as those introduced by the ESC, have been highly beneficial for the generation of reliable and valuable HF RWD. Launched in 2008 by the ESC, the EURObservational Research Programme (EORP) is used to monitor new HF therapy interventions and treatment patterns in Europe based on observational data. While EORP is a unique and insightful project, improvements related to quality, along with geographical and cardiovascular disease representativeness have been proposed [50]. To expand the registry programme, the European Unified Registries On Heart care Evaluation

And Randomised Trials (EUROHEART) project was developed by the ESC in 2019, aiming to improve the quality of observational data and provide a continuous collection of standardised RWD in HF. EUROHEART supports national registries using a common dataset and harmonised methodology, which allows for data pooling at both the national and international level [51]. The European Health Data and Evidence Network, another European initiative, aims to compile hospital-owned data for millions of people across Europe into one large-scale, standardised network, by converting the data to a common model [52]. Similarly, BigData@Heart, an initiative launched in 2017 by the Innovative Medicines Initiative, brings together key stakeholders in cardiovascular disease management in Europe to improve patient outcomes in HF, atrial fibrillation and acute coronary syndrome using a big data-based research platform comprising harmonised and standardised big datasets and cohorts [53].

The RRCTs have been used in Europe to generate RWE in other cardiovascular disease areas, including myocardial infarction [54], and are being implemented in HF as exemplified by the aforementioned SPIRRIT trial [17]. However, their widespread use has been limited by a lack of high-quality data and registries, along with the challenges associated with combining data from multiple national registries. The RRCTs may minimise some of the general limitations of RCTs, including cost, patient enrolment and follow-up, and generalisability, and allow stakeholders to carry out pragmatic trials comparing the effects of various treatments in a real-world setting [55]. Thus, with the initiatives outlined above providing optimal data harmonisation, there is an opportunity for RRCTs to be performed on a multinational level. On a global level, the International Consortium for Health Outcomes Measurement developed a set of standardised outcome measures in an effort to improve patient quality of life. Implementing these standard sets locally or nationally in registries and routine clinical practice would improve international data comparisons and database linking, as the definitions, coding practices and other data collection factors are standardised [56]. Widespread enrolment into these types of initiatives should greatly improve the robustness and impact of HF RWD, and subsequently guide effective treatment interventions and preventative strategies, generate broad epidemiological data, and evaluate the incorporation of evidence-based guidelines at a national level.

High-quality datasets provide an opportunity to utilise artificial intelligence, particularly machine learning and big data analytics, in the diagnosis and management of HF. Artificial intelligence can be implemented in routine clinical practice to predict risk factors and survival rates, improve diagnosis from cardiac imaging, classify patients based on phenotype, and for precision medicine [57,58]. Indeed, EHRs represent important data reservoirs amenable to big data analytics as they encompass large, heterogeneous patient populations in both primary and secondary care settings, as opposed to registries that predominantly provide insights from second-line care. For example, EHR databases have been successfully utilised to confirm age- and sex-specific associations of modifiable risk factors and comorbidities with incident HF across a large patient population with varying HF phenotypes [34]. Similarly, studies have shown that predictive modelling can be used to accurately determine HF phenotype by EF data mining from EHRs, such as insurance claims databases linked to healthcare provider networks [59]. Thus, implementing a standardised approach to generate high-quality RWD would be beneficial for the future of HF healthcare. It must also be noted that the ubiquitous implementation of the 'Findability, Accessibility, Interoperability and Reusability' data principle in RWD generation is vital to ensure maximum added and derived value in the RWE HF landscape [60].

Conclusion

The benefit of RWE in healthcare is well established, yet there is a potential for improvement in order to optimise the usability of RWE. Here, we have outlined some challenges associated with HF that influence RWD, and thus affect the generation of RWE in Europe. Intrinsic difficulties in HF diagnosis and management can contribute to omissions and misclassifications in datasets, consequently leading to difficulties in RWD interpretation. It is clear that, despite evidence-based guidelines, a unified approach to HF diagnosis and management is needed to increase patient enrolment and improve data quality and harmonisation. The lack of cross-communication between registries, and indeed within registries between contributors, also warrants improvement. Overcoming these challenges is likely to require input from all stakeholders, including patients, physicians, policymakers and payers. It is our opinion that a successful registry should foster a collaborative approach, adapting partnerships, particularly at the primary care level, and including key questions relating

to diagnosis, treatment and dose optimisation. Addressing the associated challenges and developing comprehensive registries will help to pave the way for the generation of credible and invaluable RWE in HF.

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Conflict of Interest

Vera Vesela reports current employment at Novartis Pharma AG, Basel, Switzerland; Shashidhar Rao reports current employment at Novartis Pharma AG, Basel, Switzerland; Rachel Studer reports current employment at Novartis Pharma AG, Basel, Switzerland and holds shares of the same company.

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Volume 9 Issue 5 July 2022