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# Challenges of evaluating chronic heart failure and acute heart failure events in research studies using large health care databases

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ABSTRACT

Epidemiological studies on heart failure (HF) using large health care databases are becoming increasingly frequent, as they represent an invaluable opportunity to characterize the importance and risk factors of HF from a population perspective. Nevertheless, because of its complex diagnosis and natural history, the heterogeneous use of the relevant terminology in routine clinical practice, and the limitations of some disease coding systems, HF can be a challenging condition to assess using large health care databases as the main source of information. In this narrative review, we discuss some of the challenges that researchers may face, with a special focus on the identification and validation of chronic HF cases and acute HF decompensations. For each of these challenges, we present some potential solutions inspired by the literature and/or based on our research experience, aimed at increasing the internal validity of research and at informing its interpretation. We also discuss future directions on the field, presenting constructive recommendations aimed at facilitating the conduct of valid epidemiological studies on HF in the coming years.



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> "In clinical trials, when a specific uniform definition is lacking, the concurrence between the initial and adjudicated assessment of heart failure is lower than is the case with adjudications of myocardial infarction and/or stroke. This lack of concurrence illustrates the challenges investigators face in classifying heart failure events and underlines the importance of a standardized definition of event."
>
> [Hicks et al *Circulation* 2014[1]]

Large health care databases (eg, administrative or claims databases) have become one of the most appealing tools for clinicians, researchers, and health care systems managers to evaluate scientific research questions with public health importance and/or relevance to routine clinical practice. The large size of these databases allows maximizing precision and conducting key subgroup analyses with sufficient statistical power. Also, data are readily available for research purposes, and findings of these studies are often generalizable to large groups of individuals—or even to the whole population of a given territory. Because of these and other advantages,[2-4] research studies using large health care databases are likely to become more and more frequent in the coming years.

Heart failure (HF) is considered one of the pandemics of our time[5] and represents a great burden for patients, societies, and health care systems.[5-8] Because of its relevance, HF is increasingly becoming a frequent condition of interest in a number of epidemiological studies, such as evaluations of its frequency within a given area[9,10] or of the health care resource use associated with the disease.[11,12] HF has also become a relevant end point in many studies, for example, postauthorization pharmacoepidemiological evaluations of drugs potentially associated with an increased risk of HF events.[13-16]

Because of its complex diagnosis, natural history, and terminology, HF can be, however, a challenging condition to assess using large health care databases. Indeed, researchers may find it more complex to define HF than other cardiovascular outcomes such as acute myocardial infarction (AMI)[1,17] or stroke.[1,18] Importantly, as for any observational research, bias also represents a threat to the validity of studies using large health care databases.[2,4,19] In this context, HF involves specific nuances that may pose additional complexity to the design of this research.

In this narrative review, we discuss some of the challenges that researchers may face when conducting epidemiological studies on HF using large health care databases as the key source of information. These include the heterogeneity and inconsistent use of the terminology relative to HF in routine clinical practice, the limitations of some disease coding systems, the difficulties to define chronic heart failure (CHF) cases, and the challenges when identifying acute HF decompensation events, among others (Table I). For each of these complexities, we present potential solutions aimed at maximizing internal validity. These include not only considerations regarding the diagnostic codes that should be used to identify cases/events but also study design features that should be taken into consideration when conducting this type of research. Finally, we discuss future directions in the field, aimed at stimulating debate and research on this relevant topic.

## Background: definition and natural history of HF

Compared to other cardiovascular end points, the natural history of HF is slightly more complex, as it can include asymptomatic phases; acute decompensations; and chronic, stable periods. Investigators need to be aware of these nuances, as they may have direct implications for the design and interpretation of epidemiological research.

In their 2016 guidelines, the European Society of Cardiology stressed the notion of HF as a syndrome, "characterized by typical 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 a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress".[20] This definition is consistent with the concepts included in the American College of Cardiology/American Heart Association HF guidelines.[21]

Figures 1 and 2 summarize the typical natural history scenarios for patients with HF. Most of the time (Figure 1, scenario A ["delayed"]), individuals initially develop a structural/functional abnormality of the heart (eg, ventricular hypertrophy), but the typical HF signs/symptoms are not present. At this stage, by definition, the patient does not qualify as an "HF patient"[20,21] yet is *at risk of* HF.[21] Later in time, some of these patients may eventually develop clinically overt HF; when this happens, they are considered to have CHF for the rest of their life.

An alternative debut may occur in some patients (Figure 1, scenario B ["abrupt"]) in which there is a sudden, acute injury of the heart (eg, extensive AMI) that leads to the abrupt development of HF signs and symptoms. Although some of these patients may fully recover from the acute episode (eg, some cases of acute myocarditis[22,23]), in many of them, some HF signs/symptoms will remain, and the patient will be considered to have CHF.[20]

Regardless of the type of presentation, once CHF is present (Figure 2), patients typically alternate periods of clinical stability, in which they can have an almost normal life and the disease is managed with oral pharmacotherapies and lifestyle modifications, with acute deteriorations ("decompensations") requiring hospitalization or management in specialized clinics/daycare facilities (eg, administration of intravenous therapies).[20,21] This natural history lasts until the patient dies, which is often caused by the disease (CHF has a high 5-year mortality[24]) or from other comorbidities, which often cluster in these patients.[9,25] Some patients may have an excellent response to CHF therapies (eg, patients in which a New York Heart Association functional class I is achieved; patients in which congestive symptoms are relieved for long periods of time; or patients in which the left ventricle ejection fraction [LVEF] is normalized after titration of β-blocker therapy); however, these patients typically remain being considered CHF patients, and follow-up is often done by cardiologists/CHF specialists.

Alternatively, some patients may be treated with left ventricle assist devices and/or undergo heart transplantation, resulting in a marked improvement of their prognosis. Nevertheless, the proportion of patients in which these therapies are used is currently small. Also, these patients are also typically followed by CHF specialists. Importantly, from an epidemiological research standpoint, the use of such therapies is typically considered a censoring event in most studies.

## HF-specific terminological issues with implications for epidemiological research

The pathophysiology and features of HF are currently object of active scientific research,[26] resulting in an evolving body of knowledge. This, together with the complex natural history described above, results in a rich, rapidly changing terminology. As an example, terms such as

**Table I**
Complexities and challenges when studying HF using large administrative health care databases

| |
|---|
| Natural history: |
| Complex natural history, with structural/functional abnormalities typically preceding in time the onset of HF |
| Once CHF is established, phases of stability alternate with acute decompensations. |
| Terminological issues: |
| Heterogeneous, ever evolving terminology |
| Clinical complexity and heterogeneity; inconsistent use of HF terminology in routine clinical practice |
| Limited granularity of some disease coding systems |
| Lack of consistency between some coding systems and the latest terminology supported by scientific societies |
| Definition of CHF: |
| The nuances of the distinction structural/functional abnormalities of the heart versus syndromic HF may not be evident to all clinicians/those involved in coding. |
| The validity of CHF recorded diagnoses may be low, particularly of those generated in primary care settings. |
| Identification of acute HF decompensations: |
| Patients with severe HF decompensations tend to be hospitalized, whereas milder episodes tend to be managed in outpatient settings; however, this varies across centers/areas. |
| The type of events included in the study (first ever/first event during the study period) can have implications for the interpretation of study results and their generalizability. |
| With some coding systems, disentangling the actual reason for the hospitalization in patients with CHF (HF decompensation vs other reason) can be challenging. |
| HF decompensations may be hard to characterize even for clinicians, particularly in old patients with multiple comorbidities. This may result in limited validity of the original clinical information and in heterogeneous coding practices. |

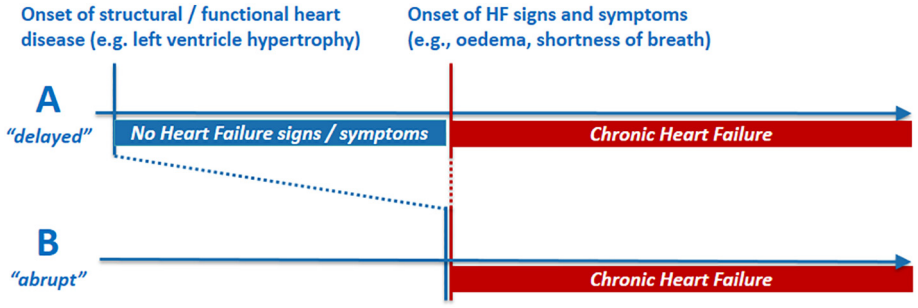


**Figure 1.** Presentation of HF: typical debut scenarios. In both scenarios, the horizontal axis represents time (blue arrow), and the vertical bars represent key clinical milestones within the natural history of HF. Scenario **A** ("delayed"): The structural/functional abnormality of the heart, which puts the patient at risk of developing HF (American College of Cardiology/American Heart Association stage B), precedes in time the onset of syndromic HF. Scenario **B** ("abrupt"): The structural/functional abnormality of the heart and the onset of syndromic HF happen very close in time/simultaneously.

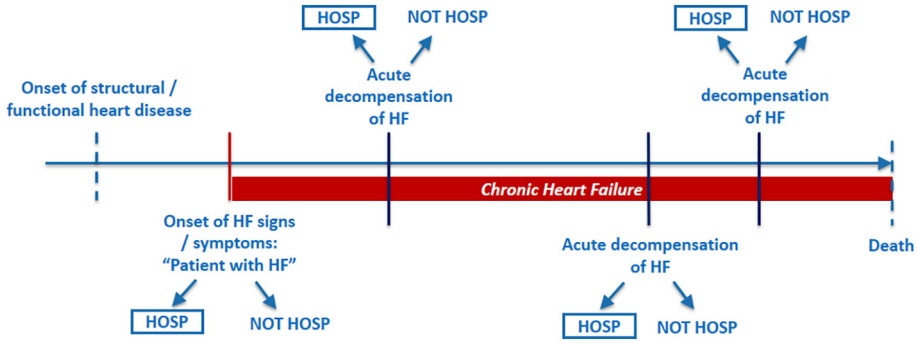


**Figure 2.** Typical natural history of patients with CHF. The horizontal axis represents time (blue arrow), and the vertical bars represent key clinical milestones within the natural history of HF. Once CHF is present, the patient alternates periods of clinical stability and acute decompensations of the disease, which may require hospitalization or may be managed in ambulatory settings. *HOSP*, hospitalization.

*diastolic heart failure*,[27] which is included in several *International Classification of Diseases* (*ICD*) classifications, is already considered obsolete compared to the more recent terms *HF with preserved ejection fraction* and *HF with midrange ejection fraction*.[20,21,28,29]

Also, it must be noted that the diagnosis of HF events in routine clinical practice can be challenging.[20,21,30-32] This can be particularly true for mild acute HF decompensations in patients with multiple comorbidities, leading to a heterogeneous description of such events in discharge reports. In addition, because of the frequent coexistence of other, severe comorbidities, HF patients can be managed in internal medicine wards, geriatric medicine units, or emergency departments, among others[33,34] (ie, not necessarily in cardiology wards), which adds an additional layer of clinical and terminological heterogeneity. Likely as a consequence of these factors, the terminology relevant to HF is currently not completely standardized in routine clinical practice, nor is it used consistently across sites, departments, and health care professionals.

Finally, the limited granularity specifically for HF of some widely used disease coding systems, such as *ICD, 10th Revision* (*ICD-10*), represents an additional challenge for researchers. In this sense, the *ICD, Ninth Revision,* and *ICD-10, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) systems provide much more detail than the original *ICD-9* and *ICD-10* classifications, as the former include specific codes for chronic, acute, and acute over chronic HF events (Table II). Importantly, different sources of data within a given health care database (eg, hospital data, primary care data) may use different disease coding systems, resulting in additional complexity.

**Table II**
Comparison between *ICD-10* (2016 version) and *ICD-10-CM* (2018 version) I50 codes for HF

| *ICD-10* (2016 version) | *ICD-10-CM* (2018 version) |
|---|---|
| I50.0 Congestive heart failure | |
| I50.1 Left ventricular failure | I50.1 Left ventricular failure, unspecified |
| | I50.20 Unspecified systolic (congestive) heart failure |
| | I50.21 Acute systolic (congestive) heart failure |
| | I50.22 Chronic systolic (congestive) heart failure |
| | I50.23 Acute on chronic systolic (congestive) heart failure |
| | I50.30 Unspecified diastolic (congestive) heart failure |
| | I50.31 Acute diastolic (congestive) heart failure |
| | I50.32 Chronic diastolic (congestive) heart failure |
| | I50.33 Acute on chronic diastolic (congestive) heart failure |
| | I50.40 Unspecified combined systolic (congestive) and diastolic (congestive) heart failure |
| | I50.41 Acute combined systolic (congestive) and diastolic (congestive) heart failure |
| | I50.42 Chronic combined systolic (congestive) and diastolic (congestive) heart failure |
| | I50.43 Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure |
| | I50.810 Right heart failure, unspecified |
| | I50.811 Acute right heart failure |
| | I50.812 Chronic right heart failure |
| | I50.813 Acute on chronic right heart failure |
| | I50.814 Right heart failure due to left heart failure |
| | I50.82 Biventricular heart failure |
| | I50.83 High output heart failure |
| | I50.84 End stage heart failure |
| | I50.89 Other heart failure |
| I50.9 Heart failure, unspecified | I50.9 Heart failure, unspecified |

**Table III**
Methodological approaches aimed at maximizing the validity of studies on HF using large administrative health care databases

| Focus is on CHF | Focus is on acute HF decompensations |
|---|---|
| Use customized definitions adapted to research question, type of data available, study population, and features of coding system | |
| Inform definitions with prior (validation) studies | |
| Perform sensitivity analyses using alternative definitions | |
| Prioritize data sources with coding systems granular for HF and/or with access to free text comments (if research question is not area or database specific) | |
| Include clinical qualifiers in the study case definition, such as chronic loop diuretic use | Restrict to inpatient cases if focus is on severe events; include also outpatient cases if focus is on any HF decompensation events |
| | Consider the pathophysiological mechanisms potentially linking the exposure under evaluation and HF events |
| | Consider conducting both “first event ever” and “first event during the study period” analyses |
| | Validate study end points with clinical records/GP questionnaires |
| | Consider CHF patient registries/cohort studies for specific research questions |

*GP*, General practitioner.

*General potential solutions for researchers*

It is important to note that, because clinical information (eg, presence of specific signs/symptoms) or test results (eg, levels of specific biomarkers) are usually not available in this type of databases, research studies have a strong reliance on the diagnostic, procedural, and medication codes recorded in the databases.

In this context and provided the aforementioned issues, rather than using uniform lists of diagnostic codes to identify HF cases across studies, researchers may want to use customized definitions, taking into consideration relevant study features such as the study aims, the type of data available in the database, the coding system in place, or the feasibility of validating HF events, among other considerations, to maximize the internal validity of the definitions. Also, use of data sources with granular coding systems could be prioritized, although this may not be an option if the research question applies to a specific geographic area and validation studies are needed to better characterize their validity.

Indeed, results from prior studies reporting validity measures can help inform definitions and database choices.[35-37] In addition, sensitivity analyses using alternative case definitions may provide complementary information, as well as valuable insights on the robustness of the study findings. In this sense, beyond diagnosis codes, additional items such as biomarkers or other clinical features can be considered for inclusion in the case definition in those databases in which this information is available.[37] Finally, validation of potential HF cases, when feasible, may have a large impact on internal validity.

Further discussion on the specific challenges that researchers may face when conducting studies on HF using large health care databases, as well as on the implementation of these solutions, is presented in the following sections and is summarized in Table III.

## Research challenge #1: identifying CHF cases

Researchers may be specifically interested in defining CHF as their condition of interest[9-12] or as a component of the study end point in studies assessing acute decompensations in patients with CHF. The usual approach to identify conditions in studies using large health care databases is to create an operational definition combining a specific list of diagnosis codes, which are then automatically searched for in the database using an electronic algorithm.

For CHF, however, the accurate identification of cases may be a bit more challenging than for other conditions. First, the nuances of the distinction between presence of structural/functional abnormalities of the heart (eg, dilated cardiomyopathy, mitral regurgitation) and syndromic HF may be overseen during the diagnosis/coding process and/or may not be fully captured by the disease coding system in place. Second, studies have shown that the validity of CHF diagnoses may be low, particularly when generated in primary care settings.[38,39] In this context,

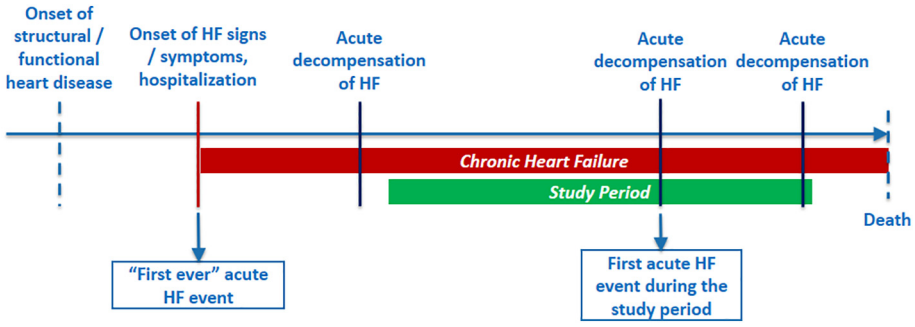


**Figure 3.** Example of the potential interplay between the study period of a hypothetical epidemiological study and the natural history of a patient with HF. The horizontal axis represents time (blue arrow), and the vertical bars represent key clinical milestones within the natural history of HF. In this specific example, the first acute HF event during the patient's lifetime and the first acute HF decompensation during the study period differ. This patient would be excluded from the study population in a study restricted to "first ever" acute HF events.

inclusion of such potential cases in a study without further evaluation may bias the study findings.[40]

*Potential solutions for researchers*

Some of the solutions discussed above may be helpful when defining CHF cases in a study using large health care databases. Specifically, because it may be hard to decide whether codes such as "I42.0 Dilated cardiomyopathy" (*ICD-10*) should be included in the case definition, a reasonable approach may be to use several definitions, as this may provide additional, complementary information. Information from prior validation studies[38,39] can also help inform this decision.

Another reasonable approach to increase validity may be to include additional qualifiers in the case definition of CHF. For example, patients with CHF are typically treated with oral loop diuretics (eg, furosemide) even during periods of clinical stability.[20,21] Thus, incorporation of this criterion as part of the CHF definition[12,25] may increase specificity and exclude cases in which structural abnormalities are not accompanied with syndromic HF. Strategies such as this may be particularly useful in very large databases with thousands of potential CHF cases in which individual validation may not be feasible. If used, the impact of any additional qualifiers in the number of cases identified should be reported.

Similarly, in databases in which test results are available, incorporation of levels of biomarkers such as the N-terminal pro–B-type natriuretic peptide (NT-ProBNP) or of imaging parameters such as the LVEF may markedly strengthen the study case definitions. Unfortunately, this information is currently not available in a systematic way in most large health care databases.

## Research challenge #2: acute HF decompensations: where should we search for the events?

Accurate identification of acute HF decompensations in patients with CHF can be also challenging for researchers using information from large health care databases.

The first complexity that must be taken into account when identifying this type of events is the setting (eg, in-hospital, outpatient) in which they are managed. For AMI or stroke, currently, all diagnosed patients are expected to be hospitalized[41,42]; consequently, in epidemiological studies in which AMI and stroke are the events of interest, an operational definition combining a hospitalization and a list of relevant diagnosis codes[43,44] would be expected to accurately capture almost all relevant events, except those dying before arrival to the hospital.

HF, on the other hand, is also heterogeneous with regard to the clinical management of the acute decompensations.[20,21] Severe decompensations may require inpatient stays, whereas milder episodes may be managed in outpatient settings such as hospital clinics or daycare facilities. This, however, varies across health care areas and centers, depending mainly on the availability of specific ambulatory resources for HF patients.[20,21,45-47]

*Potential solutions for researchers*

In view of this heterogeneous management, for acute HF decompensation events, complex operational definitions may be required, intended to capture not only inpatient events but also events managed in the ambulatory setting. Alternatively, researchers may prefer to restrict their study to inpatient events alone, as this may operate as a more "specific" case definition, or ambulatory care information may not be available in the specific database. Nevertheless, it should be noted that the study findings would not apply to all HF decompensations but only to the most severe episodes. Management plans for CHF patients are progressively prioritizing the use of ambulatory care resources and reduction of hospitalizations,[48-50] and this should be progressively taken into consideration in future studies involving this patient population.

## Research challenge #3: timing of acute HF decompensations and implications for study interpretation

In many epidemiological studies assessing acute, nonfatal cardiovascular end points, such as AMI or stroke, the focus is on the *first ever* occurrence of the event of interest.[51-54] This approach is used particularly in etiological studies to avoid interferences between the treatments initiated after a first event and the association under evaluation.[55]

Nevertheless, provided the natural history of HF, in which a given patient may have several acute decompensations within their life span,[20,21] researchers will have to decide whether they are interested in "first ever" acute HF events, in "first events during the study period," or in any events (Figure 3). This decision is important because it has direct implications for the research question being evaluated, for the interpretation of the study results, and for their generalizability.

A "first event ever" design excludes from the study population any patients with acute HF decompensations recorded before study entry. Such design allows assessing whether an exposure of interest causes structural/functional abnormalities of the heart (which may eventually or abruptly lead to syndromic HF) and/or whether the exposure increases the risk of syndromic HF in individuals who already have such abnormalities. Of note, because many patients with CHF and multiple comorbidities (in whom clinical ascertainment of acute HF decompensations can be challenging—see challenge #4) would be removed from the study population, this approach would increase the specificity of the potential acute HF events captured. On the other hand, such exclusion may limit the generalizability of the study findings.

On the other hand, a design evaluating first events *during the study period* would include a larger, more heterogeneous study population. This design would also allow assessing whether the exposure of interest increases the risk of acute HF decompensations in patients with CHF,

including those who already had prior decompensations. Also, the findings of such design may be more generalizable, although the validity of the events captured may be lower than using a "first event ever" approach.

*Potential solutions for researchers*

Researchers should be aware of these nuances and make this decision informed by the specific study aims, the potential pathophysiological mechanisms involved, and the characteristics of the population under study, among other considerations. If feasible, implementation of both designs (first ever, first during the study period) could be considered, as this may provide complementary information, including insights on the mechanisms behind the association under evaluation. Alternatively, a "first during the study period" design including a subgroup analysis stratified by preexisting CHF may also be very informative. It must be noted, however, that identification of "first ever" events may be challenging in databases in which the amount of historical information available is limited.

## Research challenge #4: differentiating acute HF decompensations from chronic conditions in patients with multiple comorbidities

The clinical context of acute HF decompensations must also be taken into consideration when designing a research study using large health care databases. Specifically, older CHF patients typically have several other comorbidities (eg, chronic obstructive pulmonary disease, anemia, chronic kidney disease[25]), and the acute HF decompensation (which is often mild) happens in the context of other acute processes (eg, infections, acute renal failure). In these patients, who are becoming increasingly frequent given the aging of the general population[56] and of the CHF population in particular,[25,57] the HF decompensation component, when present, may not necessarily be listed as the primary discharge diagnosis.

This, together with the fact that the granularity of some coding systems can be very limited for HF and the fact that some diagnosis codes are used to refer to both stable CHF and acute decompensations (eg, *ICD-10* code "I50x. Congestive heart failure"[36] [Table II]), can make it hard to disentangle, using the information captured by health care databases, whether a patient with a code relevant to HF in a discharge report was hospitalized for an acute HF decompensation or had stable CHF and was hospitalized for another reason (ie, the HF code corresponds to a comorbidity diagnosis).

*Potential solutions for researchers*

In view of this complexity, validation of study end points appears as a key approach to increase the accuracy of the potential events identified by electronic algorithms.[15,16,58] In those instances in which review of medical records or other clinical information is not feasible, communication between the study team and the primary care treating doctors (eg, via general practitioner questionnaires[14,59]) may allow to obtain valuable information about the clinical details of the episode. Both approaches are typically used in pharmacoepidemiological studies to increase (or at least evaluate) the validity of the acute events included in the analyses.[14-16,58,59]

Also, sensitivity analyses using alternative definitions and under different assumptions may provide complementary information, to be integrated and interpreted in the context of the research question being assessed. For example, a sensitivity analysis could only include those cases in which the HF code is listed as the primary discharge diagnosis or exclude as acute HF decompensations those cases in which, despite the presence of a HF diagnosis, the primary discharge code refers to an acute process/procedure very unlikely to coexist in a patient initially hospitalized for an HF decompensation, for example, an orthopedic surgery.

Prioritizing the use of databases with granular coding systems may also aid the accurate identification of acute HF events. The same applies to databases in which the information from free text comments can be accessed for research purposes.[58] Alternatively, large registries of patients with HF such as the Acute Decompensated Heart Failure National Registry[60] or the European Society of Cardiology Heart Failure Long-Term Registry,[61] which include not only thousands of patients with CHF but also detailed information on key clinical variables such as left ventricular ejection fraction, could be considered, as they may be more appropriate than health care databases to test some specific research questions. However, access to these registries by external researchers may be limited, and use of already existing, large health care databases for research purposes may be more efficient than creating new registries.

Finally, other study designs such as population-based cohort studies (eg, the Multi-Ethnic Study of Atherosclerosis), in which exhaustive baseline evaluations are conducted and in which incident events are identified using detailed clinical data and adjudicated, may be more appropriate to respond to specific research questions, for example, questions related to the pathophysiology of the disease or analyses stratified by LVEF.[62,63]

## Future directions

In a context of aging populations in most countries,[56] HF is likely to keep growing as a highly relevant public health issue in the coming years and, consequently, as the focus of epidemiological research. In parallel, the availability of large health care databases for research purposes is expected to keep expanding too. The combination of these 2 phenomena is likely to boost the frequency of HF studies using this type of databases, and efforts should be made to maximize the validity of these evaluations as much as possible.

A first step toward this goal should be the development and implementation of an international diagnostic and terminological consensus for HF, to be used consistently across sites, departments, and units. Clinical practice guidelines provide clear definitions and descriptions of the natural history of the disease[20,21]; nevertheless, homogeneous use of such terminology is still an unmet need, and additional efforts are needed. In this sense, clinicians should become increasingly aware of the potential use for research purposes of the information generated during patient care.

Second, widely used coding systems should be informed by recent clinical practice guidelines and by experts. This would harmonize the language used by clinicians and researchers with that used in health care documents and databases, facilitating the implementation of a homogeneous terminology.

Third, appropriate use of diagnosis codes should be encouraged and incentivized as means to maximize the completeness and validity of the information being recorded. In the absence of adequate training and incentives, general or less specific codes would be expected to be prioritized (if any) over more granular, informative codes, the choice of which may be perceived as harder and time consuming. These first 3 initiatives would also increase comparability across studies.

Fourth, efforts should be made to increase the availability of laboratory test data (eg, levels of NT-ProBNP) and of other test results (eg, LVEF) in large health care databases, as incorporation of this information to study case/event definitions would markedly increase the validity of the definitions being used and therefore of the research being conducted.

Fifth, implementation of some of the strategies discussed in this review (Table III) may help ameliorate some of these challenges, inform study design decisions, and aid the interpretation of research findings. Nevertheless, formal research is needed to better understand the advantages and disadvantages of the different approaches. Similarly, further validation studies are also needed to better understand the pros and cons of different HF case identification strategies, including

novel approaches such as regression models, machine learning methodologies,[64] or electronic medical record–driven phenotyping algorithms, which use structured and unstructured information, such as the algorithms developed by eMERGE Network.[65,66] Some of these are already being used for clinical purposes in a number of centers.

Sixth, dissemination by researchers of the definitions and lists of codes used to define HF in their studies may be very informative for other groups. Also, communication of the challenges identified when conducting this type of research as well as of the approaches used to minimize bias will help increase the overall quality of the research being conducted.

Finally, novel clinical and epidemiological scenarios in the coming years will require developing updated research methods and definitions. For example, expanded use of left ventricle assist devices and longer survival of these patients will likely lead to new research questions specifically referred to this patient population. In this context, adequate identification of such therapies in the algorithms and adequate recording in the databases will be key to maximizing internal validity.

## Conclusions

Research studies on HF using large health care databases represent an invaluable opportunity to characterize the features and risk factors of HF from a population perspective. Nevertheless, the natural history and specific terminological features of HF result in challenges that increase the complexity of this research. As these studies become increasingly available, awareness of these complexities becomes crucial, as it may help inform study design decisions and definitions, stress the need for validation efforts, and ultimately maximize internal validity.

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