Circulation: Heart Failure

SPECIAL REPORT

Toward a Universal Definition of Etiologies in Heart Failure: Categorizing Causes and Advancing Registry Science

Anubha Agarwal, MD, MSc*; Jasper Tromp, MD, PhD*; Wael Almahmeed, MD; Christiane Angermann, MD; Chanchal Chandramouli, PhD; Hyunjai Cho, MD; Don-Ju Choi, MD; Albertino Damasceno, MD, PhD; Gerasimos Filippatos, MD; Gregg C. Fonarow, MD; Sivadasanpillai Harikrishnan, MD, DM; Lars Lund, MD, PhD; Fred Masoudi, MD; George A. Mensah, MD; Asad Pathan, MD; Pablo Perel, MD, PhD; Fausto Pinto, MD, PhD; Antonio Luiz Ribeiro, MD, PhD; Stuart Rich, MD; Yasuhiko Sakata, MD, PhD; Karen Sliwa, MD, PhD; Johan Sundstrom, MD, PhD; Renee Wong, PhD; Clyde Yancy, MD, MSc; Kelvin Yiu, MD; Jian Zhang, MD; Yuhui Zhang, MD; Carolyn S.P. Lam, MBBS, PhD†; Gregory A. Roth, MD, MPH†; The Global Heart Failure Roundtable Group

ABSTRACT: Heart failure (HF) is a well-described final common pathway for a broad range of diseases however substantial confusion exists regarding how to describe, study, and track these underlying etiologic conditions. We describe (1) the overlap in HF etiologies, comorbidities, and case definitions as currently used in HF registries led or managed by members of the global HF roundtable; (2) strategies to improve the quality of evidence on etiologies and modifiable risk factors of HF in registries; and (3) opportunities to use clinical HF registries as a platform for public health surveillance, implementation research, and randomized registry trials to reduce the global burden of noncommunicable diseases. Investment and collaboration among countries to improve the quality of evidence in global HF registries could contribute to achieving global health targets to reduce noncommunicable diseases and overall improvements in population health.

Key Words: global health ■ heart failure ■ registries

Heart failure (HF) is a well-described final common pathway for a broad range of diseases; however, substantial confusion exists regarding how to describe, study, and track these underlying etiologic conditions.[1,2] We will review current approaches to categorizing the causes of HF to improve clarity and best practices for clinical care and research, with a particular focus on challenges for global health and equity.

The global prevalence of HF has increased over the last three decades and is a significant challenge for global health.[3,4] Substantial research efforts have focused primarily on diagnosis, treatment, and prognosis of HF with inadequate attention toward HF prevention.[5,6] The lack of standardization of etiologies of HF in clinical registries worldwide and their differentiation from coexisting comorbidities significantly impedes HF prevention and management.

Here, we describe (1) the overlap in HF etiologies, comorbidities, and case definitions as currently used in HF registries led or managed by members of the Global HF Roundtable; (2) strategies to improve the quality of evidence on etiologies and modifiable risk factors of HF in registries; and (3) opportunities to use clinical HF

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Correspondence to: Greg A. Roth, MD, MPH, Institute of Health Metrics and Evaluation, Population Health Bldg/Hans Rosling Center, 3980 15th Ave NE, Seattle, WA 98195. Email rothg@uw.edu

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*A. Agarwal and J. Tromp contributed equally as cofirst authors.

†C.S.P. Lam and G.A. Roth contributed equally as cosenior authors.

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Nonstandard Abbreviations and Acronyms

GBD	global burden of disease
HF	heart failure
WHO	World Health Organization

registries as a platform for public health surveillance, implementation research, and randomized registry trials to reduce the global burden of noncommunicable diseases.[7]

Etiologies, Comorbidities, and Case Definitions of HF

The collection of comorbidities, HF risk factors, past medical history, and related data in HF registries remains idiosyncratic while specific case definitions are absent or unaligned. To better understand the current state of HF surveillance, we asked participating registry leaders to provide current demographic data of enrolled participants and case report form details.[5,8–29] The Figure shows an overview of selected registries, led by investigators participating in this viewpoint, which were largely region-specific (eg, Asian Sudden Cardiac Death in Heart Failure, The European Society of Cardiology Heart Failure Long-Term Registry, the Sub-Saharan Africa Survey of Heart Failure, Gulf CARE), country-specific (eg, Get With The Guidelines-Heart Failure, Change the Management of Patients With Heart Failure registry, National Cardiovascular Data Registry Practice Innovation and Clinical Excellence, Indian National HF Registry) or state/city-specific (eg, Kerala HF Registry, Trivandrum HF Registry) and include participants from each World Health Organization region. We acknowledge that this is not a comprehensive listing of all available registries, but a selected group. There remains a lack of local data on HF in many countries within each World Health Organization region, which is a key limitation as countries from the same World Health Organization region may have different HF profiles and outcomes. The prospective reporting-form-based registries range in size from 1006 participants in the Sub-Saharan Africa Survey of Heart Failure to over 110 000 participants in 30 Swedish Heart Failure Registry, and the mean age of participants ranges from 52 years in Africa (the Sub-Saharan Africa Survey of Heart Failure)

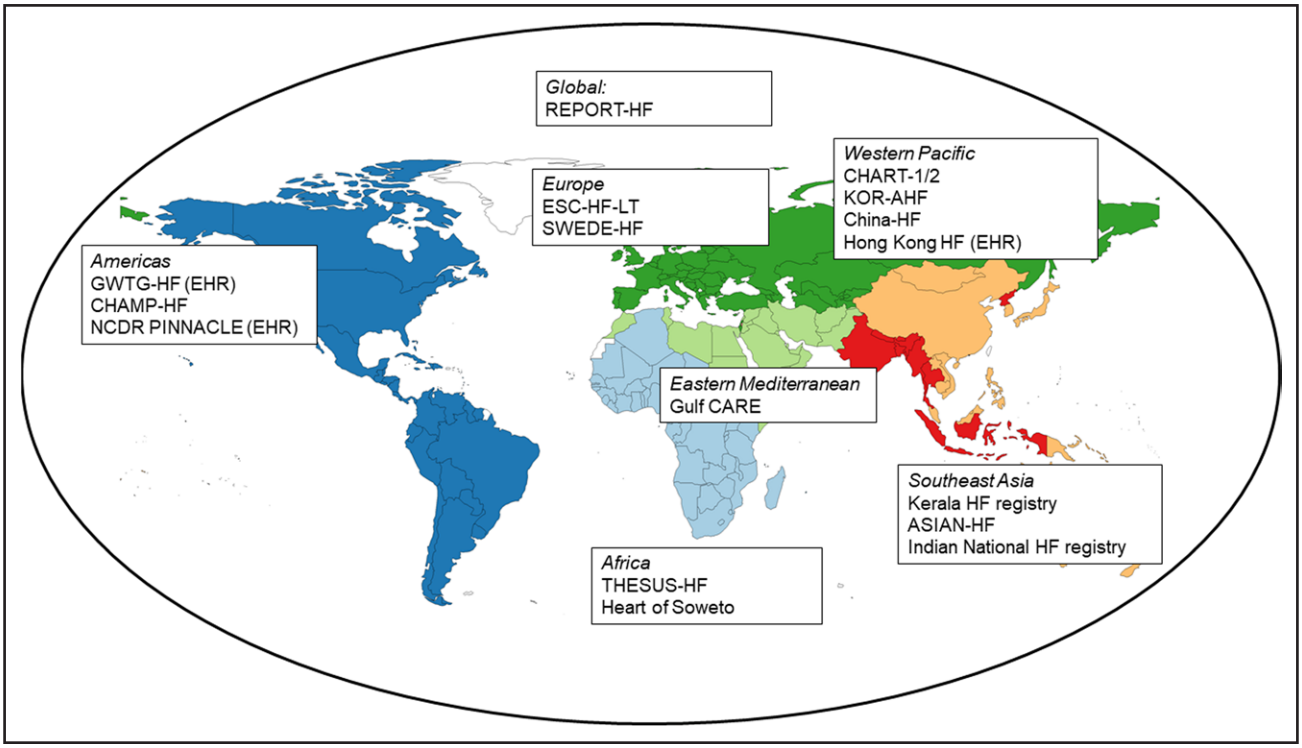

Figure. Representative global heart failure registries by World Health Organization geographic regions.
ASIAN-HF[22] indicates Asian Sudden Cardiac Death in Heart Failure; CHAMP-HF,[18] Change the Management of Patients With Heart Failure Registry; CHART-1/2,[23] Chronic Heart Failure Analysis and Registry in the Tohoku District; ESC-HF-LT,[10–12] The European Society of Cardiology Heart Failure Long-Term Registry; Gulf CARE,[25,26]; Gulf Acute Heart Failure Registry; GWTG-HF,[16] Get With The Guidelines-Heart Failure; NCDR PINNACLE,[14,15] National Cardiovascular Data Registry Practice Innovation and Clinical Excellence; REPORT-HF,[5] International Registry to Assess Medical Practice With Longitudinal Observation for Treatment of Heart Failure; SWEDE-HF,[30] Swedish Heart Failure Registry; and THESUS-HF,[27] the Sub-Saharan Africa Survey of Heart Failure.

to 75 years in Europe (30 Swedish Heart Failure Registry; Table S1).[11,29] The proportion of women enrolled in prospective reporting-form-based registries ranges from 27% in Asian Sudden Cardiac Death in Heart Failure to 51% in the Sub-Saharan Africa Survey of Heart Failure.[24,29]

Some HF registries exclusively enrolled participants hospitalized for HF, such as International Registry to Assess Medical Practice with Longitudinal Observation for Treatment of Heart Failure or the China Heart Failure Registry while others enrolled outpatients (eg, CHART-2). While some differences in registry participants (eg, age) reflect the demographic characteristics in the general population from each country or region, others (eg, sex) may not and instead reflect potential biases in participation or access to care in health system-based registries. Differences in inclusion criteria, site selection (eg, hospital versus primary health care centers), level of detail of collected data, and the need for informed consent limits the potential of prospective reporting-form-based HF registries to serve as tools for public health surveillance. Retrospective electronic health record-based registries such as National Cardiovascular Data Registry Practice Innovation and Clinical Excellence (United States), or clinical data analysis and reporting system (Hong Kong) are often a better representation of the real world. However, comparisons across these electronic health record-based registries are limited by the lack of standardization of definitions of HF etiologies and comorbidities (Table S2).

There is substantial variation in the number and definition of etiologies and comorbidities captured across registries (Table S2; Figure S1). Some registries are continuous ongoing registries, whereas others are snap-shot or periodic. Two major HF registries (Get With The Guidelines-Heart Failure, Asian Sudden Cardiac Death in Heart Failure) initially demarcate etiologies of HF into ischemic and nonischemic categories with subsequent subcategories within nonischemic cardiomyopathy. The most common causes of HF, including ischemic heart disease and hypertension, are represented in most but not all registries. There is marked variability for other etiologies of HF, including an emphasis on rheumatic heart disease, HIV cardiomyopathy, Chagas disease, and endomyocardial fibrosis in regions where these HF etiologies are prevalent.[31,32] Several important etiologies of HF, including right HF, peripartum cardiomyopathy, and cardiotoxicity cardiomyopathy, are not commonly captured.[33–35] Right HF may coexist in many patients with HF.[36] Notably, there are key differences in case definitions of HF etiologies, potentially leading to inconsistencies in primary data collection within registries and comparisons across registries (Table 1). For example, a patient may not meet the defined case criteria for ischemic heart disease in the Sub-Saharan Africa Survey of Heart Failure without evidence from angiography, imaging, or stress test diagnosis. In the Indian National HF Registry, the same patient may be classified as having HF due to ischemic heart disease based on the broader case definition. Furthermore, there may be overlapping definitions for ischemic cause versus history of myocardial infarction in the same registry. Iron deficiency—with or without anemia—is also a common comorbidity that may play an etiologic role in HF severity.[37] This example illustrates the significant clinical overlap between HF etiologies, HF risk factors, and coexisting comorbidities. These varying, vaguely defined, and frequently missing case definitions of HF etiologies can lead to significant challenges in assessing HF risk factors to guide HF prevention efforts.

Improving the Quality of Evidence in Registries

For most patients with HF, treatment with guideline-directed medical therapy is guided by ejection fraction regardless of underlying cause. But, for HF prevention, standardized case definitions of HF etiologies are essential for systematically assessing HF risk and clinical course and allocating public health resources to HF prevention. The current proposal for standardizing the definition of HF etiologies is part of a broader paradigm shift in large-scale research to harmonize global data sources for discovery across HF cohorts to guide prevention efforts.[38,39] The global burden of disease (GBD) proposes categorizing HF etiologies according to the pathophysiologic or causal mechanism leading to HF (Table 2). This GBD list attempts to standardize the definition of HF etiologies. Recognizing the often-complex nature of HF in clinical practice, the list enables combining multiple etiologies according to a standardized definition. For example, a patient with ischemic heart disease may also have chronic kidney disease leading to concurrent ischemic and volume overload cardiomyopathy. Assigning a risk factor as an cause versus a comorbidity can be arbitrary and a matter of clinical judgement. Based on the clinical context, HF may be clinically determined to be attributed to specific cardiomyopathies such as ischemic or valvular cardiomyopathy, or associated with risk factors such as hypertension or diabetes. Hypertension, one of the most common risk factors for HF worldwide, is an example where the distinction between cause and comorbidity is often unclear in registries (Table S2). Hypertension as a comorbidity in patients with HF is relevant as the measured blood pressure impacts the current management of a patient, whereas identification of hypertension as an cause of HF, hypertensive heart disease, can also guide prevention efforts. This initial categorization in the GBD HF etiologies list, as with registry data collection, is not exhaustive and a category of other cardiomyopathy is included. Because

Table 1. Examples of Different Case Definitions of Selected Heart Failure Etiologies in Selected Registries

	HF Registries WHO Region					
HF etiologies	REPORT-HF[5] Global	ESC-HF-LT[10] Europe	CHART-2[23] Western Pacific	THESUS-HF[27] Africa	Indian National Heart Failure Registry[19] Southeast Asia	SWEDE-HF[30] Europe
Ischemic heart disease	Heart failure post-MI, post-bypass, post-PCI, or post-angiography	Ischemic heart disease with angiography Ischemic heart disease without angiography	History of previous CAD or MI diagnosed by attending cardiologists, investigator determined	Major epicardial coronary artery >70% obstruction, and history of acute MI with wall motion abnormalities, and stress testing diagnosis	Coronary heart disease is a common term for the buildup of plaque in the heart's arteries that could lead to heart attack	Ischemic heart disease, investigator determined
Dilated cardiomyopathy	Any cardiomyopathy, investigator determined	Dilated CM unknown cause vs genetic CM	Dilated cardiomyopathy in the absence of CAD/MI, investigator determined	Dilated cardiomyopathy, investigator determined	Dilated cardiomyopathy, investigator determined	Dilated cardiomyopathy, investigator determined
Hypertensive heart disease	Hypertensive cardiomyopathy, investigator determined	Arterial hypertension, investigator determined	Hypertension in the absence of ischemic heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, significant valvular heart disease, and other cardiomyopathies, investigator determined	Hypertensive cardiomyopathy, investigator determined	Not included	Hypertensive cardiomyopathy, investigator determined

CAD indicates coronary artery disease; CM, cardiomyopathy; ESC-HF-LT, The European Society of Cardiology Heart Failure Long-Term Registry; MI, myocardial infarction; PCI, percutaneous coronary intervention; REPORT-HF, International Registry to Assess Medical Practice with Longitudinal Observation for Treatment of Heart Failure; SWEDE-HF, Swedish Heart Failure Registry; THESUS-HF, the Sub-Saharan Africa Survey of Heart Failure; and WHO, World Health Organization.

the GBD study is reproduced annually, its list of HF etiologies can be refined through subsequent iterations by the GBD collaborative network and feedback from the broader research community. The GBD study provides at least one approach to standardizing case definitions for HF etiologies and an opportunity to improve and harmonize the estimation of HF drivers globally, leading to greater tailoring of HF prevention efforts for specific countries or regions.

Public Health Surveillance and Platform for Clinical Studies and Implementation Science

HF registries offer a mechanism for ongoing surveillance of evolving and emerging HF risk factors to improve the quality of life, reduce hospital care, and lower health costs at the local, regional, and international levels.[40,41] These registries could play an essential role in improving our understanding of the way coronavirus disease 2019 (COVID-19) may be altering patterns of HF around the world and the disproportionate impact COVID-19 has on subsets of patients with HF.[42,43] For HF registries to be a valuable tool for public health, standardization of HF etiologies and protocol case definitions is needed and would facilitate pooling estimates across regions and globally. With sufficient alignment, HF registries could become a platform for implementation research to design targeted interventions to mitigate HF risk factors, treat or prevent HF, and improve population health.[44] The Sustainable Development Goal 3.4, to reduce noncommunicable disease mortality by 1/3 by 2030, remains ambitious in the face of rising cardiovascular mortality rates around the world.[45] Cooperation and harmonization across existing HF registries, as represented by the Global HF Roundtable, offers one avenue for improving cardiovascular public health efforts around the world by generating new hypotheses and correlations for further research.

CONCLUSIONS

There is a need to link the underlying etiologies of HF and antecedent risk factors with clinical HF phenotypes, with the goal of improving prevention, treatment, and control of HF. One step toward this goal would be for HF registries to harmonize their assessment of risk factors including socioeconomic status indicators, past medical history, HF etiologies, and case definitions. The GBD HF etiologies list is an initial attempt at categorizing the causes of HF, focusing on global public health and prevention. Increased efforts are needed to improve public health surveillance of HF disease burden, emerging HF risk factors, and strengthening of the global health approach for HF prevention and management. Investment and collaboration among countries to improve the quality of evidence in global HF registries could contribute to achieving global health targets to reduce noncommunicable diseases and overall improvements in population health.

Table 2. Global Burden of Disease Heart Failure Etiologies List

Pathophysiologic grouping	Cause
Ischemic cardiomyopathy	Ischemic heart disease
Pressure overload of the left heart	Hypertensive heart disease Calcific aortic valve disease
Pulmonary heart disease	COPD Interstitial lung disease and pulmonary sarcoidosis Coal-workers' pneumoconiosis Silicosis Asbestosis Other pneumoconiosis Pulmonary arterial hypertension
Valvular and congenital cardiomyopathy	Congenital heart abnormalities Other nonrheumatic valvular diseases Degenerative mitral valve disease Rheumatic heart disease
Primary myocardial disease	Myocarditis
Toxic cardiomyopathy	Alcoholic cardiomyopathy Cocaine use disorders Amphetamine use disorders
Infectious disease	Chagas Endocarditis
Stress, tachycardia, and high-output mediated cardiomyopathy	Thyroid disorders G6PD deficiency Thalassemia's Other hemoglobinopathies and haemolytic anaemias Atrial fibrillation Stroke
Volume overload syndromes	Chronic kidney disease Cirrhosis and other chronic liver diseases
Other etiologies	Other cardiovascular and circulatory disorders Other cardiomyopathy

COPD indicates chronic obstructive pulmonary disease.

ARTICLE INFORMATION

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Affiliations

Washington University in St. Louis School of Medicine, MO (A.A.). Saw Swee Hock School of Public Health, National University of Singapore and National University Health System (J.T.). Heart and Vascular Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates (W.A.). Comprehensive Heart Failure Center, University Hospital Wuerzburg, Germany (C.A.). National Heart Centre Singapore and Duke-NUS Medical School (C.C.). Seoul National University Hospital, Korea (H.C., D.-J.C.). Eduardo Mondlane University, Maputo, Mozambique (A.D.). University of Washington, Seattle (G.A.R.). University of Cyprus, School of Medicine and National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Greece (G.F.). Ronald Reagan UCLA Medical Center, Los Angeles, CA (G.C.F.). Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India (S.H.). Karolinska University Hospital, Stockholm, Sweden (L.L.). University of Colorado School of Medicine at the Anschutz Medical Campus, Aurora (F.M.). Center for Translation Research and Implementation Science, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (G.A.M.). Tabba Heart Institute Karachi, Pakistan (A.P.). London School of Hygiene and Tropical Medicine, United Kingdom (P.P.). Santa Maria University Hospital, University of Lisbon, Portugal (F.P.). Hospital das Clinicas and School of Medicine, Unversidade Federal de Minas Gerais, Belo Horizonte, Brazil (A.L.R.). Northwestern University Feinberg School of Medicine, Chicago, IL (S.R., C.Y.). Tohoku University Graduate School of Medicine, Sendai, Japan (Y.S.). National Cerebral and Cardiovascular Center, Suita, Japan (Y.S.). University of Cape Town, South Africa (K.S.). Uppsala University, Sweden (J.S.). Heart Failure and Arrhythmias Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (R.W.). Institute of Cardiovascular Science and Medicine, Hong Kong University, Hong Kong and Department of Medicine, University of Hong Kong-Shenzhen Hospital, China (K.Y.). Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (J.Z., Y.Z.). National Heart Centre Singapore, Singapore (C.S.P.L.). Duke-NUS Medical School, Singapore and University Medical Centre Groningen, the Netherlands (C.S.P.L.).

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Supplemental Material

Tables S1 and S2
Figure S1
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