International REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): rationale for and design of a global registry

Gerasimos Filippatos, Sadiya Sana Khan, Andrew P. Ambrosy, John G. F. Cleland, Sean P. Collins, Carolyn S. P. Lam, Christiane E. Angermann, Georg Ertl, Ulf Dahlström, Dayi Hu, Kenneth Dickstein, Sergio V. Perrone, Mathieu Ghadanfar, Georgina Bermann, Adele Noe, Anja Schweizer, Thomas Maier and Mihai Gheorghiade

Linköping University Post Print

N.B.: When citing this work, cite the original article.

Original Publication:
http://dx.doi.org/10.1002/ejhf.262
Copyright: Oxford University Press (OUP): Policy B / Wiley: 12 months
http://www.oxfordjournals.org/

Postprint available at: Linköping University Electronic Press
http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-118239
International REgistry to assess medical Practice with IOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): rationale for and design of a global registry

Gerasimos Filippatos1, Sadiya Sana Khan2, Andrew P. Ambrosy3, John G.F. Cleland4, Sean P. Collins5, Carolyn S.P. Lam6, Christiane E. Angermann7, Georg Ertl7, Ulf Dahlström8, Dayi Hu9, Kenneth Dickstein10, Sergio V. Perrone11, Mathieu Ghadanfar12, Georgina Bermann12, Adele Noe12, Anja Schweizer12, Thomas Maier12, and Mihai Gheorghiade2*

1 Athens University Hospital Attikon, Athens, Greece; 2 Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 3 Duke University Medical Center, Durham, NC, USA; 4 National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, UK; 5 Vanderbilt University, Nashville, TN, USA; 6 National Heart Centre, Singapore; 7 University Hospital Würzburg, and Comprehensive Heart Failure Center, University of Würzburg, Germany; 8 Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; 9 Peking University People’s Hospital, Beijing, China; 10 University of Bergen, Stavanger University Hospital, Stavanger, Norway; 11 Instituto Fleni, Mendoza, Argentina; and 12 Novartis Pharma AG, Basel, Switzerland

Received 10 December 2014; revised 27 January 2015; accepted 2 February 2015; online publish-ahead-of-print 10 March 2015

Aims The clinical characteristics, initial presentation, management, and outcomes of patients hospitalized with new-onset (first diagnosis) heart failure (HF) or decompensation of chronic HF are poorly understood worldwide. REPORT-HF (International REgistry to assess medical Practice with IOngitudinal obseRvation for Treatment of Heart Failure) is a global, prospective, and observational study designed to characterize patient trajectories longitudinally during and following an index hospitalization for HF.

Methods Data collection for the registry will be conducted at ∼300 sites located in ∼40 countries. Comprehensive data including demographics, clinical presentation, co-morbidities, treatment patterns, quality of life, in-hospital and post-discharge outcomes, and health utilization and costs will be collected. Enrolment of ∼20 000 adult patients hospitalized with new-onset (first diagnosis) HF or decompensation of chronic HF over a 3-year period is planned with subsequent 3 years follow-up.

Perspective The REPORT-HF registry will explore the clinical characteristics, management, and outcomes of HF worldwide. This global research programme may have implications for the formulation of public health policy and the design and conduct of international clinical trials.

Keywords Heart failure • Hospitalized • Global • Morbidity • Mortality • Quality of life

Introduction

Heart failure (HF) is a global public health problem affecting millions worldwide.1–12 In the USA, the prevalence is 5.7 million and there are 670 000 new cases per year, while there are another 15 million people living with HF in Europe.13–15 In addition, there are >1 million admissions for HF annually in both the USA and Europe, accounting for the vast majority spent each year on HF-related care.13,14,16 However, the socio-economic burden of HF is especially worrisome in the low- and middle-income regions of...
Africa, South America, the Middle East, and Asia Pacific, where the prevalence of HF is rising rapidly and the clinical characteristics, treatment patterns, and outcomes vary substantially.\textsuperscript{12,17–23}

Several observational registries have been conducted in patients with HF (Table \textsuperscript{1}).\textsuperscript{1–12} These registries have either focused on in-patient characterization and short-term outcomes or maintained separate samples of acute HF hospitalizations and chronic HF follow-up, limiting understanding of the transition from chronic maintenance to an acute state requiring hospitalization.\textsuperscript{24,25} No prior detailed, longitudinal evaluations of long-term disease progression, healthcare utilization, and health economics on a global scale have been reported. Furthermore, while registries have been conducted to compare within-region differences in disease characteristics and outcomes, no truly international prospective registry exists with uniform data collection and systematic follow-up using a common protocol. In addition, most registries have been based on non-consecutive enrolment, which may result in a sample that is not representative of the real-world patient inflow. Clearly, there remains an unmet clinical need in HF to design and conduct a graphically representative registry to shape public policy at all levels and guide research endeavours.

Thus, REPORT-HF (International R\textsuperscript{2}egistry to assess medical Practice with iO\textsuperscript{2}ntitudinal o\textsuperscript{2}bservation for Treatment of Heart Failure), a global, prospective, and observational study initiated during index hospitalization for new-onset (first diagnosis) HF or decompensation of chronic HF designed to capture comprehensive data on clinical characteristics, management, and outcomes with longitudinal follow-up over 3 years, is proposed in order to enhance the understanding of the epidemiology of HF worldwide.

\section*{Study design}

Patients hospitalized with a primary diagnosis of new-onset (first diagnosis) HF or decompensation of chronic HF as assessed by the clinician–investigator are eligible for enrolment. Exclusion criteria include current or recent participation in a clinical trial of any investigational treatments. Each centre will implement an admission log that will also document reasons for patients not being enrolled in REPORT-HF. Each patient will be followed for 3 years or until death, withdrawal of consent, or study termination.

Prospective enrolment will take place at \textasciitilde300 hospitals in \textasciitilde40 representative countries across Europe, North and Latin America, Africa, Asia and the Pacific, and the Middle East (Figure \textsuperscript{1}). The number of participating centres for each country takes into consideration the size of its population. Investigators are asked to recruit consecutive patients within assigned enrolment intervals corresponding to an average of \textasciitilde70 patients over a period of \textasciitilde3 years. For smaller hospitals, this may translate into an open enrolment to include all patients meeting inclusion criteria, while in larger medical centres patients may be enrolled over a pre-defined period in order to ensure that the workload is manageable and that recruitment is evenly distributed across days of the week and seasons of the year. The first patient was enrolled in July 2014 and, by end of 2014, \textasciitilde60 sites from 12 countries had been initiated.

Background HF therapy will be left to the discretion of the treating physician, but all sites are encouraged to manage patients according to standard local practice as informed by current guideline-based recommendations. This study will be conducted in accordance with the Declaration of Helsinki, the protocol submitted and approved by the Institutional Review Board and/or ethics committee at each participating centre, and written informed consent obtained from all patients or a designated surrogate medical decision-maker prior to enrolment.

\section*{Data collection and follow-up}

The proposed time frame for data collection during hospitalization and post-discharge is shown in Figure \textsuperscript{2}. Clinician–investigators will enrol patients during the index admission and, with the assistance of the study coordinator, will collect data on patient demographics, past medical history (i.e. cardiac and non-cardiac co-morbidities), admission and discharge medications, vital signs and physical exam, laboratory values, acute management (i.e. HF- and cardiovascular-related therapies and procedures), and hospital course (i.e. in-hospital worsening HF and other adverse events). Pre-specified data collection points will occur at 6 months, 1 year, and annually thereafter until study completion. At each data collection point, study staff will obtain an updated medical and medication history, NYHA functional class, review of symptoms, vital status, and interval events including invasive procedures, hospitalizations, and scheduled and unscheduled office and emergency room visits. Follow-up information from study participants will be collected via telephone interviews unless a regular follow-up visit is planned at the index site according to local practice. Every effort will be made by the study personnel to obtain confirmation of the information. In addition, vital status will be supplemented using national reporting databases where available.

\section*{Patient and caregiver questionnaires}

Validated questionnaires will optionally be completed at specific time points to evaluate the quality of life (QOL) of the patient and to assess the burden placed on the caregiver (Table \textsuperscript{2}). A generic health status questionnaire [EuroQ\textsuperscript{2}OL-5 Dimensions questionnaire (EQ-SD)]\textsuperscript{26} and a HF-specific questionnaire [Kansas City Cardiomyopathy Questionnaire (KCCQ)]\textsuperscript{27} will be serially administered to the patient. The EQ-SD is a widely used, self-administered questionnaire designed to assess health status in adults. The tool assesses five dimensions indicative of QOL (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and provides a self-rated global health status using a visual analogue scale ranging from 0 (i.e. ‘worst possible health state’) to 100 (i.e. ‘best possible health state’). On the day after admission (day 2), a special (recall) version of the EQ-SD questionnaire will be administered asking the patient to describe retrospectively how he or she felt on the day of admission, while the standard EQ-SD questionnaire will be administered on day 2 (in addition to the recall version) and for the remainder of the study. The KCCQ tool is another self-administered questionnaire covering physical activity, clinical symptoms, social function, self-efficacy and knowledge, and QOL.

© 2015 The Authors. \textit{European Journal of Heart Failure} published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
## Table 1 Overview of other heart failure registries

<table>
<thead>
<tr>
<th>Registries</th>
<th>ADHERE¹</th>
<th>OPTIMIZE-HF²</th>
<th>GWTG-HF³</th>
<th>EHFS I⁴</th>
<th>EHFS II⁵</th>
<th>ESC-HF Pilot⁶</th>
<th>ESC-HF⁷</th>
<th>ATTEND⁸</th>
<th>ADHERE-AP⁹</th>
<th>ASIAN-HF¹⁰</th>
<th>ALARM-HF¹¹</th>
<th>THEUS-HF¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regions/countries</strong></td>
<td>USA</td>
<td>USA</td>
<td>USA</td>
<td>Europe²</td>
<td>Europe³</td>
<td>Europe⁴</td>
<td>Europe⁵</td>
<td>Japan</td>
<td>Asia-Pacific⁶</td>
<td>Asia-Pacific⁷</td>
<td>Multinational⁸</td>
<td>Africa²²</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>105,388</td>
<td>48,612</td>
<td>110,621</td>
<td>11,327</td>
<td>3,580</td>
<td>1892</td>
<td>12,440</td>
<td>48,420</td>
<td>10,171</td>
<td>5,000</td>
<td>4,953</td>
<td>1,006</td>
</tr>
<tr>
<td><strong>Data collection</strong></td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>60–90 days</td>
<td>–</td>
<td>3 months</td>
<td>1 year</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 years</td>
<td>6 months</td>
<td>–</td>
</tr>
</tbody>
</table>

ADHERE, Acute Decompensated Heart Failure National Registry; ADHERE-AP, Acute Decompensated Heart Failure National Registry International–Asia Pacific; ALARM-HF, Acute Heart Failure Global Registry of Standard Treatment; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; ATTEND, Acute Decompensated Heart Failure Syndromes; EHFS I, European Heart Failure Survey I; EHFS II, European Heart Failure Survey II; ESC-HF, European Society of Cardiology-Heart Failure; GWTG-HF, Get With The Guidelines-Heart Failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; OPTIMIZE-HF, Organized Program to Improve Survival and Efficacy of Treatment of Heart Failure; PROs, patient reported outcomes; THESUS-HF, The Sub-Saharan Africa Survey of Heart Failure.

¹Austria, Belgium, Czech Republic, Denmark, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, the Netherlands, UK.

²Austria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, The Netherlands, Norway, Poland, Portugal, Russia, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, UK.

³Austria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Norway, Poland, Portugal, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey.

⁴Austria, Bosnia-Herzegovina, Bulgaria, Czech Republic, Egypt, France, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden.

⁵Australia, Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand.

⁶China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand.

⁷Australia, France, Germany, Greece, Italy, Mexico, Spain, Turkey.

⁸Austria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovakia, Slovenia, Spain, Sweden.

⁹Austria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovakia, Slovenia, Spain, Sweden.

¹⁰Australia, Bangladesh, Canada, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Denmark, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Norway, Pakistan, Peru, Philippines, Portugal, Romania, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom.

¹¹Australia, China, Denmark, Germany, Greece, Italy, Mexico, Poland, Portugal, Russia, Slovakia, Slovenia, Spain.

¹²Austria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, UK.
each measured using a unique Likert scale. The KCCQ questionnaire is more extensive than the EQ-5D questionnaire and will only be administered in select countries (i.e. Germany, Spain, Russia, the UK, and the USA).

Similarly, the Work Productivity and Activity Impairment Questionnaire (WPAI)\textsuperscript{28} and the Caregiver Burden Questionnaire for Heart Failure (CBQ-HF)\textsuperscript{29} will be utilized to assess the burden placed on the caregiver. The WPAI includes six items that measure absenteeism, presenteeism, lost work productivity, and activity impairment. In contrast, the CBQ-HF consists of four domains measuring the impact of caring for HF patients on aspects of the caregiver’s daily life including physical well-being, emotional health, social life and relationships, and lifestyle.

### Statistical analysis plan

A sample size of 20,000 participants has been proposed to estimate comparisons of interest and taking into account potential losses to follow-up. In order to perform meaningful analyses comparing proportions across clinically relevant subgroups (i.e. defined by combinations of geographic area, type of admission unit, clinical characteristics, etc.), a sample size of 300 in each of the strata will...
Rationale for and design of a global registry

Table 2 Administration time points of patient and caregiver questionnaires

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Administration time points</th>
<th>Follow-up data capture points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Index hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>Day 5</td>
</tr>
<tr>
<td>Patient</td>
<td>EQ-SD</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>KCCQ</td>
<td></td>
</tr>
<tr>
<td>Caregiver</td>
<td>CBQ-HF</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>WPAI</td>
<td>X</td>
</tr>
</tbody>
</table>

EQ-SD, [EuroQol-5 Dimensions questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; CBQ-HF, Caregiver Burden Questionnaire–Heart Failure; WPAI, Work Productivity and Activity Impairment Questionnaire.

Discussion

Heart failure is a global public health problem and socio-economic burden, which may be at least partially attributable to a poor understanding of this heterogeneous syndrome. Although disease-based registries remain the primary source of real-world data on chronic medical conditions and fundamental to shaping public health policy at all levels and guiding research from bench to bedside, limitations of the available registry data include, but are not limited to, poor geographic representation, non-consecutive patient enrolment, incomplete data capture, and absent or short duration of follow-up. REPORT-HF is a global, prospective, and observational registry initiated during the index HF hospitalization with longitudinal patient follow-up of up to 3 years aiming to advance the comprehension of the epidemiology of HF worldwide.

There are several salient features of this observational study which merit further mention. REPORT-HF is the first truly global observational experience in HF, with ∼300 centres in ∼40 representative countries across Europe, North and Latin America, Africa, Asia and the Pacific, and the Middle East. In contrast, prior large-scale HF registries have primarily enrolled patients in North America and Western Europe, collectively representing only slightly more than 15% of the world’s population. In addition, previous observational experiences in HF have primarily relied on non-consecutive enrolment of patients admitted with an unequivocal primary diagnosis of HF, which may have led to a non-random sampling of lower acuity patients. Thus, this study will employ consecutive or intermittently consecutive enrolment in order to obtain a representative cohort while minimizing the workload required of study personnel.

Although data collection in registries is often limited by resource availability and variation in routine clinical practice, REPORT-HF will utilize a standard protocol and case report form across all centres including follow-up in order to provide a detailed description of clinical characteristics and management of HF patients of all levels of acuity, across the spectrum of clinical settings, and over time. In addition, REPORT-HF will provide insights into the initiation and titration of guideline-directed medical therapies over time including the initial real-world experience with promising and emerging treatment options. Most importantly, REPORT-HF will for the first time serially track outcomes including HRU (i.e. scheduled and unscheduled office appointments, emergency room visits, and hospitalizations), patient QOL and caregiver burden, and survival over a time frame of years in a geographically diverse and representative population.

In an era of globalization in cardiovascular research, the most significant contribution of REPORT-HF may be to the future design and conduct of international clinical trials, which have traditionally suffered from poor enrolment. Interestingly, post-hoc analyses of phase III clinical trial databases have found substantial geographic variation in the aetiology of HF, co-morbid disease states, background therapy, and event rates (i.e. hospitalizations and mortality) despite employing specific inclusion and exclusion criteria to select for a relatively homogeneous and enriched study population. Furthermore, there is a growing appreciation among the scientific community that failure to consider these regional differences in patient characteristics, management, and outcomes at the planning stage may impact both the response to therapy and the success or failure of pivotal trials. Thus, REPORT-HF provides...
The REPORT-HF registry is sponsored by Novartis Pharma AG.

Funding

The REPORT-HF registry is sponsored by Novartis Pharma AG.

Acknowledgements

We thank Ciara Kelly (Novartis) for assisting in the preparation of the tables and figures.

Mihai Gheorghiade (chair), Gerasimos Filippatos (co-chair), John G.F. Cleland, Sean P. Collins, Carolyn Lam Su Ping, Christiane E. Angermann, Georg Ertl, Ulf Dahlström, Dayi Hu, Kenneth Dickstein, Sergio V. Perrone, and Mathieu Ghanadan are members of the steering committee for the REPORT-HF registry.

Conflict of interest: G.F. is a member of the Steering Committee of trials sponsored by Novartis, Cardiorentis, Bayer, and Vifor. J.G.F.C. reports grants and personal fees from Novartis and Amgen, and personal fees from Trevena. S.P.C. has received research support from Cardiorentis, Cardioxy, Intersection Medical, and Novartis, and has consulted for Cardiorentis, Cardioxy, Intersection Medical, Novartis, Insys, and Abbott Point-of-Care. C.L.S.P. has received research support from Boston Scientific, Medtronic, and Vifor Pharma, and has consulted for Novartis, Bayer, AstraZeneca, and Vifor Pharma. C.E.A. receives speaker honoraria, consultancy fees, and research grants from Novartis, ResMed, Bayer, Servier, and Boehringer Ingelheim. G.E. reports personal fees from Novartis. U.D. receives consulting fees from Novartis and Vifor Pharma, and research grant from AstraZeneca. S.V.P. receives honoraria from Laboratorios Bagó S.A., Laboratorios Raffo S.A., Biotecnica Argentina, and Novartis. M.G., G.B., A.N., A.S., and T.M. are employees and shareholders of Novartis Pharma AG. M.G. is a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma, Bayer HealthCare, Cardiorentis, CorThera, Cytokinetics, CytoPhex, DebioPharm, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Inc., Johnson and Johnson, Medtronic, Merck, Novartis Pharma, Ono Pharma USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals, and Trevena Therapeutics. The other authors declare no conflict of interest.

References


2. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217–2226.


