



Building medical knowledge from real world registries: The case of heart failure



Alberto Aimo^{a,b,*}, Chiara Seghieri^c, Sabina Nuti^c, Michele Emdin^{a,d}

^a Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy

^b Cardiology Division, University of Pisa, Italy

^c Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy

^d Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy

ARTICLE INFO

Article history:

Received 29 March 2018

Accepted 30 March 2018

Available online 10 April 2018

Heart failure (HF) is a leading cause of morbidity and mortality worldwide [1]. Over the years, many randomized controlled trials (RCTs) have laid the foundations of current management of HF patients, although many recommendations still do not rely on RCTs or meta-analyses. The lowest level of evidence in Guidelines is assigned when recommendations rely on expert consensus opinion, small and/or retrospective studies, or clinical registries [2]. While the main purpose of clinical registries is not to inform Guideline recommendations, clinical registries may still be underused in HF research. This is suggested by the fact that, out of 659 papers referenced in the same Guidelines, only 10 (1.5%) were registries, mostly dedicated to specific treatment options (MitraClip, subcutaneous defibrillators, or left ventricular assist device), instead of the broad population of HF patients [2].

In general, RCTs assess a carefully selected subpopulation of patients with a specific disease; or treated with specific therapies or management modalities (for example, natriuretic peptide-guided therapy for HF patients). The patients enrolled have particular characteristics that ensure internal validity at the expense of external validity and representation [3]. By contrast, registries typically include unselected patients with a disease, thus considering larger populations of patients than RCTs, and allowing more realistic predictions of outcomes in the real-world setting. When carefully conducted, registry-based research may constitute a reliable, invaluable tool to translate findings from RCTs into high-quality evidence that can guide routine clinical practice. For example, registry-based studies can allow to identify problems in physicians' adherence to recommendations and inpatients' compliance with

instructions, underlying drawbacks in medical training, patient education, and healthcare organization [3]. Standardized national registries can also be used to compare the disease management between several different countries, and to derive estimates of mortality, morbidity and resource utilization. Moreover, clinical registries allow to search for unwarranted variations in clinical practice across geographic areas, i.e. variations that cannot be explained by disease type or severity or by patient preferences [4]. Clinical registries then lead to the generation of hypotheses for RCTs, and may guide the process of improvement of healthcare systems [3]. The shortcoming of registries include the heterogeneity of available data, the need for quality check, the long times for data collection, the costs and the organizational efforts needed. When considering the specific HF setting, it has been proposed that HF registries should meet the following requirements: the ability to provide long-term prospective updated evidence that may also be used for cost analyses, proper representation of HF populations, and constant interactions with RCTs [3]. However, it is also true that in the last few years, administrative healthcare databases have become important resources for population-based research in addition to their function of providing the administrative support for which they were first developed. Moreover, in the era of information technology, the linkage among different administrative databases (such as hospital or ambulatory records, drug registries, etc.) provides the possibility to assess patient treatment along different care pathways, and the evolution of patient management over time [3]. Overall, HF registries are very promising tools for clinical research, and an overview of the studies deriving from these registries seems worthwhile.

In the present issue of the Journal, Du and Colleagues review existing observational studies from HF registries carried out in at least one of the 35 Organization for Economic Co-operation and Development (OECD) members, i.e. from high-income countries [5]. Two hundred and two observational studies were published from 2002 to March 2017, with a number increasing over years. The Swedish HF registry (SwedeHF) had the most publications ($n = 24$), followed by the Acute Decompensated Heart Failure National Registry (ADHERE) and Get With The Guidelines-HF Quality Improvement Registry (GWTG-HF). The vast majority of papers (98%) were observational cohort studies, and 2% were economic studies. Median sample size was 5152 patients. The most often reported outcome was all-cause mortality (91%), followed by hospital admission (17%), and length of stay (15%). The socio-

DOI of original article: <https://doi.org/10.1016/j.ijcha.2018.02.006>.

* Corresponding author at: Scuola Superiore Sant'Anna and Cardiology Division, University of Pisa, Piazza Martiri della Libertà, 33, Pisa, Italy.

E-mail addresses: albertoaimo@libero.it, a.aimo@santannapisa.it (A. Aimo).

economic status was considered in 33% of studies, and life-style factors in 45%. The Authors also propose that “existing observational studies from HF registries in OECD countries apply a number of advanced statistical methods to enable the minimization of bias and limitations of RWD [real world data], which in turn improve their validity and reliability,” although the information provided in the paper (number of studies performing Kaplan-Meier curves, Chi-square test, etc.) does not actually allow the reader to come to the same conclusions [5].

The Authors should be congratulated for their attempt to provide a comprehensive view on HF registries through the screening of 6706 titles from five electronic databases [5]. However, several limitations can be outlined. For example, the choice to focus on wealthy countries is not explained by the Authors, and led to the exclusion of important registries such as the Indian Trivandrum Heart Failure Registry [6] and the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) [7], representative of diverse medical realities. Moreover, study classification lacks in detail: most notably, chronic and acute HF, despite being very different conditions, could not be clearly distinguished based on the information provided in the original manuscripts [5]. Even more important, the analysis was basically not informative on the impact of HF registries on healthcare organization, clinical research, therapy decision-making and patients quality of care improvement process. Indeed, as correctly noted by the Authors, “the quality of the published studies [...], evaluation of risk of bias and the effect of research results on HF recommendation guidelines” remain to be elucidated [5].

Nevertheless, the paper by Du and Colleagues has the merit to remind of the relevance of HF registries, which have either reached national scales (e.g. the SwedeHF [8] or the HF section of the PINNACLE registry) [9], or derived from multinational collaborations (e.g. the ESC HF registry [10]). Continuously running prospective representative data, collected with registries but also with administrative data, with the flexibility to adapt to the evolution of clinical knowledge and practice and with periodic reporting would represent invaluable

tools to improve the quality of care provided, patient outcomes, and the overall socioeconomic burden of the HF syndrome.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] E. Braunwald, The war against heart failure: the lancet lecture, *Lancet* 385 (2015) 812–824.
- [2] P. Ponikowski, A.A. Voors, S.D. Anker, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC, *Eur. Heart J.* 37 (2016) 2129–2200.
- [3] J. Parissis, D. Farmakis, F. Triposkiadis, Heart failure registries: how far can we go? *Eur. J. Heart Fail.* 18 (2016) 626–628.
- [4] P.A. Soden, S.L. Zettervall, T. Curran, et al., Regional variation in patient selection and treatment for lower extremity vascular disease in the vascular quality initiative (VQI), *J. Vasc. Surg.* 65 (2017) 108–118.
- [5] X. Du, A. Khamitova, M. Kyhlstedt, S. Sun, M. Sengoelge, Utilisation of real-world data from heart failure registries in OECD countries – a systematic review, *Int. J. Cardiol. Heart Vasc.* (2018) (in press).
- [6] S. Harikrishnan, G. Sanjay, T. Anees, et al., Clinical presentation, management, in-hospital and 90-day outcomes of heart failure patients in Trivandrum, Kerala, India: the Trivandrum heart failure registry, *Eur. J. Heart Fail.* 17 (2015) 794–800.
- [7] A. Damasceno, B.M. Mayosi, M. Sani, et al., The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries, *Arch. Intern. Med.* 172 (2012) 1386–1394.
- [8] A. Jonsson, M. Edner, U. Alehagen, U. Dahlström, Heart failure registry: a valuable tool for improving the management of patients with heart failure, *Eur. J. Heart Fail.* 12 (2010) 25–31.
- [9] P.N. Peterson, P.S. Chan, J.A. Spertus, et al., Practice-level variation in use of recommended medications among outpatients with heart failure: insights from the NCDR PINNACLE program, *Circ. Heart Fail.* 6 (2013) 1132–1138.
- [10] A.P. Maggioni, U. Dahlström, G. Filippatos, et al., EURObservational research Programme: the heart failure pilot survey (ESC-HF pilot), *Eur. J. Heart Fail.* 12 (2010) 1076–1084.