Title: Geographic variation in heart failure – a matter of celebration or condemnation?

Authors:

Pardeep S Jhund [1]

Affiliations

1. BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

Correspondence:

Pardeep S Jhund

BHF Glasgow Cardiovascular Research Centre,

Institute of Cardiovascular and Medical Sciences,

University of Glasgow,

Glasgow, UK

Tel:+44 141 330 1672

Fax: +44 141 330 6955

Email: pardeep.jhund@glasgow.ac.uk

Keywords: heart failure, epidemiology, geographic variation, comorbidities

Word count: 1247

Geographic variations in outcomes in patients with heart failure have been of great interest recently. Recent secondary analyses of clinical trials have suggested that geographic variation in outcomes in heart failure may be important for heart failure with preserved but not reduced ejection fraction (1,2). This has led to much discussion of the implications of conducting multinational clinical trials which take place in countries that are geographically distinct with differing health care systems (3,4). In contrast, the epidemiology of heart failure clearly varies by geographic region. It also varies within region by level of income of the individual countries (5). However, in contrast to clinical trials that hold data on many countries from all regions of the world, epidemiological data from many regions are still lacking. Data from Western Europe and North America predominate the literature. While data from other parts of Europe, Africa, the Middle East, Asia, Australasia/Pacific and Central/South America do exist (6-10), they are generally lacking by comparison. This has been due, in part, to the lack of infrastructure and large epidemiological datasets in many of these regions. However, with the increasing use of information technology in health care systems around the world, more and more data is being generated for the heart failure community to analyse and interpret. In the current issue of the *European Journal of Heart Failure* data from a national hospitalisation database in Slovenia provides a valuable insight into the epidemiology of heart failure in the relatively understudied area of Central Europe (11).

In a study of hospitalisation rates for heart failure in Slovenia (a country with a population of just over 2 million people) Omersa and colleagues examine the rate of hospitalisation for heart failure and their trends between 2004 and 2012 (11). They report that the

standardised rate of hospitalisation for heart failure was much higher than has previously been described in other country level epidemiological datasets. As discussed by authors, this may in part be due to the older age of the Slovenian population, but it likely reflects other more complex differences. Potential explanations include admission thresholds and biases, reporting biases for the diagnosis of heart failure and differences in the availability of services such as heart failure nurse networks that can help reduce hospitalisations. Although no data on prescribed therapies was available, differences in the use of evidence based therapies and devices may further explain this discordance in hospitalisation rates. It may be easy to conclude that altering health care systems or additional interventions might change these rates, but it must be recognised that what is found to be effective in one region may not be as easy to institute or effective in another region (or even within a region) (12). Understanding the local epidemiology of heart failure and the underlying causes behind the trends is therefore crucial before embarking on changes to a health care system.

In an effort to explain the trends observed, Omersa *et al* (11) present data on the distribution of comorbidities and their associations with outcomes. It is not surprising that the burden of comorbidities was high, nor that comorbidities were associated with higher hospitalisation rates and mortality. However, the distribution of comorbidities was very different to many of the prior epidemiological studies. Rates of ischaemic heart disease were generally lower, and hypertension higher, than prior studies from elsewhere in Europe. This may represent a markedly different distribution of the risk factors and aetiology of heart failure in Central as opposed to Northern Europe (5). The data from Omersa *et al* are not outliers either. The EuroHeart survey described a gradation in the prevalence of comorbidities from East to West Europe (13). This would certainly fit with

position Slovenia occupies within Europe, with rates of ischaemic heart disease in keeping with its neighbours to the west, but lower than that of countries to the east. Or it may simply reflect a survival bias; those with ischaemic heart disease in Slovenia may not live long enough to develop heart failure. While the data should always be examined for potential explanations for differences with the published literature, it is not always easy. Given the broad number of potential aetiologies and risk factors, identifying, tracking and interpreting trends in these other factors using other data sources, is necessary to fully understand the epidemiology of heart failure in a region.

It is important to acknowledge the role that comorbidities play in the burden of heart failure. The crude numbers are perhaps the most interesting aspect of the study. In the database of hospitalisations there were 2.4 million hospitalisations. Hospitalisations where heart failure was the primary cause of admission accounted for 2% of these admissions and readmissions for heart failure did not change over time. Hospitalisations in patients with heart failure for non-heart failure reasons i.e. due to comorbid diagnoses, accounted for 4% of hospitalisations and these readmissions increased over the study period. Therefore, approximately 6% of all hospitalisations in the country were due to heart failure or occurred in a patient with heart failure. This is possibly due to the higher burden of comorbidities in patients with heart failure but also improvements in survival and the removal of the competing risk of death. Whatever the underlying reason it is clear that the burden of ill health that these patients carry and place on the health care system in Slovenia, is huge.

Understanding the epidemiology of heart failure in countries outside of Western Europe and North America is important. While data are influenced by local factors, any data has

implications for the wider region from which the data are derived and regions across the world. As more clinical trials are conducted in more areas of the world, data are needed to help plan recruitment and estimate potential event rates. Although we may seek to remove or minimise geographic variation in clinical trials, in epidemiological studies we should embrace such differences. As long as we take time to understand these differences they present local and international clinicians with an opportunity to further the understanding of a disease that still exerts a heavy burden on individuals and health care systems.

References

1. Kristensen SL, Kober L, Jhund PS, Solomon S, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJV. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. *Circulation*. 2015;131:43–53.

2. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau J-L, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.

3. Rossignol P, Zannad F. Regional Differences in Heart Failure With Preserved Ejection Fraction Trials. *Circulation*. 2015;131:7-10

4. Pitt B, Gheorghiade M. Geographic variation in heart failure trials: time for scepticism? *Eur J Heart Fail*. 2014;16:601-2.

5. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int J Cardiol.* 2013;168:1186-94.

6. AlHabib KF, Elasfar AA, Alfaleh H, Kashour T, Hersi A, AlBackr H, Alshaer F, AlNemer K, Hussein GA, Mimish L, Almasood A, AlHabeeb W, AlGhamdi S, Alsharari M, Chakra E, Malik A, Soomro R, Ghabashi A, Al-Murayeh M, Abuosa A. Clinical features, management, and short- and long-term outcomes of patients with acute decompensated heart failure: phase I results of the HEARTS database. *Eur J Heart Fail*. 2014;16:461-9.

7. Sani MU, Davison BA, Cotter G, Sliwa K, Edwards C, Liu L, Damasceno A, Mayosi BM, Ogah OS, Mondo C, Dzudie A, Ojji DB, Voors AA. Renal dysfunction in African patients with acute heart failure. *Eur J Heart Fail*. 2014;16:718-28.

8. Sulaiman K, Panduranga P, Al-Zakwani I, Alsheikh-Ali AA, AlHabib KF, Al-Suwaidi J, Al-Mahmeed W, AlFaleh H, Elasfar A, Al-Motarreb A, Ridha M, Bulbanat B, Al-Jarallah M, Bazargani N, Asaad N, Amin H. Clinical characteristics, management, and outcomes of acute heart failure patients: observations from the Gulf acute heart failure registry (Gulf CARE). *Eur J Heart Fail*. 2015;17:374-84.

9. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail*. 2015;17:884-92.

10. Harikrishnan S, Sanjay G, Anees T, Viswanathan S, Vijayaraghavan G, Bahuleyan CG, Sreedharan M, Biju R, Nair T, Suresh K, Rao AC, Dalus D, Huffman MD, Jeemon P; Trivandrum Heart Failure Registry. 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*. 2015;17:794-800.

11. Omersa D, Farkas J, Erzen I, Lainscak M. National trends in heart failure hospitalization rates in Slovenia 2004– 2012. *Eur J Heart Fail*

12.Hebert K, Quevedo HC, Gogichaishvili I, Nozadze N, Sagirashvili E, Trahan P, Kipshidze N, Arcement LM. Feasibility of a heart failure disease management program in eastern Europe: Tbilisi, Georgia. *Circ Heart Fail.* 2011;4:763-9.

13. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme —a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24:442-63.