

Changing epidemiology in patients with heart failure

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Abstract: Heart failure (HF) and type 2 diabetes mellitus (DM) are current global epidemics with increasing prevalence that show no signs of slowing down. Of particular concern is the burden that both of these disorders place on individuals and society as a whole. Individually, both are expensive in resources, have high mortality rates, and cause significant reductions in quality of life. However, 30% to 45% of patients with HF have DM, and DM is an independent risk factor for the development of progressive HF and cardiovascular death, complicating management for physicians and further raising pressures on health and social care systems. Breakthroughs in the medical management of DM and HF have reduced mortality rates, meaning that the current epidemic is largely fueled by increased prevalence of the two disorders. Of particular concern is the rise of DM in developing countries, as these areas of the world become more prosperous, with the trappings of Western civilization rapidly infiltrating their cultures. Subsequent declines in physical activity and increased consumption of refined foods, drastically removed from indigenous eating habits, are resulting in DM sweeping the globe. ■ *Heart Metab.* 2019;80:4-7

Keywords: diabetes mellitus; epidemiology; heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction

Introduction

The prevalence of type 2 diabetes mellitus (DM) and heart failure (HF) have reached epidemic proportions, generating major challenges to health and social care systems globally.^{1,2} Both conditions are associated with reduced quality of life, frequent hospitalization and are leading causes of mortality. An epidemic can reflect increased incidence, increased survival leading to increased prevalence, or both factors combined. In the case of HF and DM both increased incidence and survival have contributed to the rise in both of these disorders; it is estimated that 38 million people in the world are affected by HF,² and figures from the International Diabetes Foundation (IDF) indicate that in 2017 425 million

adults were living with DM - a figure projected to rise to 629 million by 2045.³

It is becoming increasingly understood that HF is not an independent pathology, but rather a heterogeneous group of conditions presenting with the classic symptoms of the HF syndrome: fatigue, breathlessness, and edema. Historically HF has been viewed as a failure of left ventricular (LV) contractile function, with reduced left ventricular ejection fraction (LVEF) being used to define systolic dysfunction, assess prognosis, and select patients for therapeutic interventions.⁴ However, it is now well established that HF can occur in the presence of normal or near-normal LVEF: this HF with preserved ejection fraction EF (HFpEF) now accounts for a substantial proportion of clinical cases of HF.^{5,6}

HF is frequently accompanied by a number of comorbid conditions, complicating management for physicians and contributing to worsening morbidity and mortality. These comorbidities include, but are not limited to, renal disease, obesity, anemia, and type 2 diabetes mellitus (DM). DM is an independent risk factor for the development of progressive HF and cardiovascular death,⁷⁻¹⁰ and is present in 30% to 45% of people with existing HF,¹¹ which, when combined with alarming projections for future prevalence,³ implicates DM as perhaps the most important comorbidity of all in HF.

Type 2 diabetes mellitus

Traditionally viewed as a disease of affluent Western society, DM has now spread to all four corners of the globe, and there are now more people living with type 2 diabetes in developing societies than in industrialized nations.¹² It is estimated that the number of adults with DM in the world increased from 108 million in 1980 to 425 million in 2017,^{3,12} with growth and aging of the world population, the global obesity epidemic, and the success of cardiovascular risk management and treatment being key factors in this meteoric rise.^{13,14} The spread of the DM epidemic to the developing world adds a further challenge to health care systems already under strain from contending with communicable diseases.¹ Inadequate prevention strategies, delayed diagnosis, and substandard aftercare of people with diabetes raises the risk of developing future complications such as ischemic heart disease (IHD),⁸ further increasing the burden on societies lacking sufficiently funded health care systems.

Heart failure with reduced ejection fraction

Arising as a consequence of a number of conditions impacting on LV function, including coronary artery disease, valvular heart disease, and hypertension, heart failure with reduced ejection fraction (HFrEF) remains a major cause of death and disability worldwide.² The second half of the 20th century saw little change in the incidence of HFrEF among men, a drop of one third in incidence among women and a one third decline in mortality following the onset of HF in both sexes.¹⁵ Despite positive trends in mortality, HFrEF remained deadly: 50% of patients given a diagnosis of HFrEF in the 1990s, when annual incidence in North America was around half a million cases, were dead at 5 years.

Continued advancements in our understanding of the underlying pathophysiology of HFrEF led to developments in pharmacological treatment,¹⁶⁻¹⁹ and device therapy^{20,21} which, when combined with improved post-myocardial infarction survival rates²² resulted in the first decade of the 21st century witnessing a simultaneous reduction in cardiovascular mortality and HFrEF incidence.²³⁻²⁵ However, conflicting data from a recent population-based study in the United Kingdom raises cause for concern. From 2002 to 2014, the incidence of HF decreased by 7% from 358 to 332 per 100 000 person-years. But, the number of individuals with a new diagnosis of HF increased by 12%, from an estimated figures of 170 727 in 2002 to 190 798 in 2014, largely attributed to ageing and increases in population. This was accompanied by a 23% increase in the absolute number of patients with HF in the UK, a rise from 750 127 in 2002 to 920 616 equates to a 23% increase in prevalence over this period.²⁴

Heart failure with preserved ejection fraction

The ongoing change in the HF landscape is also influenced by a higher proportion of diagnoses being attributed to HFpEF.^{5,26} Understanding the epidemiology of HFpEF has been challenging due to the heterogeneity of underlying etiology and pathophysiology, making diagnosis difficult.^{27,28} Despite this there is general consensus that prevalence of HFpEF is increasing.²⁸ A review of 31 studies conducted from 1970 to 1995 HF found between 13% and 74% (median 40%) of patients investigated for HF had HFpEF,²⁹ and following this 12 studies published from 1998 to 2003, found the prevalence of HFpEF to be between from 40% to 71% (mean 54%).^{6,30} As of yet no therapeutic intervention has proven to be effective in HFpEF³¹⁻³⁴ consequently, this increased prevalence is unlikely to change in the near future. Alongside an emphasis on multiple phenotypes of HFpEF, there is a growing consensus about HFpEF being more of a systemic disease with adverse consequences in multiple organs than one involving exclusively the heart.³⁵ A number of studies have suggested that DM is an important risk factor for all-cause mortality in patients with HFpEF^{9,36,37} identifying the presence of DM as an important phenotype of HFpEF, which may have implications for therapeutic strategies.

Conclusion

Both DM and HF represent a significant problem for society; individually both are expensive of resources and are leading causes of morbidity and mortality, but as comorbidities they result in significantly worse outcomes for an increasing number of people who suffer from both conditions. Advancements in medical therapy have shifted the landscape of both DM and HF: favorable impacts on mortality have the challenging effect of increased health care utilization, which is increasingly becoming a problem in countries with less developed and under resourced health care systems. The problems presented by DM and HF are too great for the scientific community to handle on their own; whilst emerging nations cannot be deprived of their chance to develop financially and socially, there is a desperate need for higher-level intervention, to ensure that the necessary education on lifestyle management is delivered to stem the tide of this deadly duo. ■

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REFERENCES

1. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. *Diabetes*. 2017;66(6):1432-1442.
2. Braunwald E. The war against heart failure: the Lancet lecture. *Lancet*. 2015;385(9970):812-824.
3. (IDF). T1DF. *Diabetes Facts and Figures*. 2017 [cited 2019 23/05/2019]; Available at: <https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html>. Accessed October 2019.
4. Marwick TH. Ejection fraction pros and cons: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(19):2360-2379.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355(3):251-259.
6. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004;43(3):317-327.
7. MacDonald MR, Petrie MC, Hawkins NM, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J*. 2008;29(10):1224-1240.
8. Johansson I, Edner M, Dahlström U, Näsman P, Rydén L, Norhammar A. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2014;16(4):409-418.
9. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29(11):1377-1385.
10. Cubbon RM, Adams B, Rajwani A, et al. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. *Diab Vasc Dis Res*. 2013;10(4):330-336.
11. Packer M. Heart Failure: The most important, preventable, and treatable cardiovascular complication of type 2 diabetes. *Diabetes Care*. 2018;41(1):11-13.
12. IDF. *IDF Diabetes Atlas, 8th edition*. [2017 08/07/2019]; 8: Available at: <http://www.diabetesatlas.org>. Accessed October 2019.
13. Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513-1530.
14. Rawshani A, Rawshani A, Gudbjörnsdóttir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;377(3):300-301.
15. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-1402.
16. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.
17. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation*. 2004;110(17):2618-2626.
18. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.
19. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-717.
20. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352(15):1539-1549.
21. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237.
22. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362(23):2155-2165.
23. Sidney S, Quesenberry CP, Jaffe MG, et al. Recent trends in cardiovascular mortality in the united states and public health goals. *JAMA Cardiol*. 2016;1(5):594-599.
24. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391(10120):572-580.
25. Cubbon RM, Gale CP, Kearney LC, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. *Circ Heart Fail*. 2011;4(4):396-403.
26. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *J Am Coll Cardiol Heart Fail*. 2018;6(8):678-685.
27. Kelly JP, Mentz RJ, Mebazaa A, et al. Patient selection in heart failure with preserved ejection fraction clinical trials. *J Am Coll Cardiol*. 2015;65(16):1668-1682.
28. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med*. 2016;375(19):1868-1877.
29. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol*. 1995;26(7):1565-1574.
30. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis*. 2005;47(5):320-332.

31. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006;27(19):2338-2345.
32. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53(23):2150-2158.
33. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359(23):2456-2467.
34. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362(9386):777-781.
35. Lindman BR. The diabetic heart failure with preserved ejection fraction phenotype: is it real and is it worth targeting therapeutically? *Circulation*. 2017;135(8):736-740.
36. Aguilar D, Deswal A, Ramasubbu K, Mann DL, Bozkurt B. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. *Am J Cardiol*. 2010;105(3):373-377.
37. Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation*. 2017;135(8):724-735.