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**Title:** Has the “epidemic” of heart failure has been replaced by a tsunami of co-morbidities?

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The epidemiology of heart failure has been described as an “epidemic” (1). Rates of hospitalisations for heart failure were rising in populations around the world. However, faster and more effective treatment for myocardial infarction and more effective treatment of other causes of heart failure such as hypertension has since led to a progressive fall in the incidence and first hospitalisation rate for heart failure in many countries(2–5). Multiple randomized controlled trials now document which pharmacological and device therapies improve morbidity and mortality in heart failure with reduced ejection fraction. As a result, we have seen progressive improvements in survival accompanying these reductions in hospitalization rates. In the current issue of the *European Journal of Heart Failure*, Schmidt *et al* (6) report the epidemiology of heart failure from an analysis of hospital discharge records in Denmark over a 30 year period. They confirm many of the trends described above by other investigators; rates of first hospitalisations for heart failure are falling and survival continues to improve. Confirming trends over time, and in different populations, is important to ensure that we continue to understand the natural history of heart failure and detect any new trends. But despite these reassuring trends, Schmidt *et al* (6) do report some data, consistent with other European and non-European data, that is worrying, and merits our attention. Namely the steady or increasing prevalence of heart failure and growing prevalence of co-morbidities.

The trends in co-morbidities reflect the clinical experience of any specialist who cares for patients with heart failure. No longer is the typical patient with heart failure a man presenting a few months after a large anterior myocardial infarction they were lucky to survive. More commonly, it is an elderly man, or woman, with multiple co-morbidities. These co-morbidities present their own challenges in terms of treatment, for example

diabetes mellitus. The co-morbidities may influence the ability of the heart failure specialist to prescribe therapies that improve the prognosis of heart failure, the classic example being renal impairment and the inhibitors of the renin-angiotensin-aldosterone system. These co-morbidities also have their own influence on prognosis (7). One of the successes in the prevention of heart failure is the increasing age of the patients who present with heart failure. Median age at presentation to hospital for the first time increased by 2 years in the Danish cohort. The proportion of patients presenting at age 80 years or over increased by 6% while the proportion of those in the 60-79 year old age group fell. However, with this increase in the age at presentation, there has been a corresponding increase in the burden of co-morbidities. Co-morbidities increase with age and complicate the treatment of heart failure. Although established and newer therapies for heart failure with reduced ejection fraction are consistently beneficial across the spectrum of age(8–10), the use of evidence based therapies may drop with advancing age and greater burden of co-morbidity(11). It is difficult therefore to predict what may happen at a population level when all of these trends and associations converge. Schmidt *et al* do present data on the common co-morbidities and trends in two of these are worthy of greater scrutiny; atrial fibrillation and diabetes.

For instance the prevalence of type 2 diabetes mellitus (T2DM) is rising in patients with heart failure as it is in the general population. A diagnosis of T2DM increases the risk of death in patients with HF. While Schmidt *et al* (6) did find that the prevalence of T2DM increased year on year, the authors concede that the prevalence of T2DM was lower than other Western countries but similar to other patient groups in Denmark. The risk of death was higher in those with diabetes, as is to be expected from prior studies, but satisfyingly first hospitalisations for heart failure fell in this group. This might be considered unexpected

as recently there has been great concern that the treatments used to control blood glucose in T2DM may increase the risk of heart failure hospitalisation (12) and efforts have concentrated on ensuring new therapies do not cause heart failure. Therefore, despite many reasons to suspect that there may be unfavourable trends in those with diabetes, the opposite was reported. With recent evidence that new therapies for the treatment of diabetes can reduce heart failure hospitalisations (13) we hope that this trend may continue and it will be important to confirm this.

While overall survival has improved, gains in survival have not been equally distributed amongst patients with different co-morbidities. The absolute and relative reductions in mortality were smaller in those with atrial fibrillation compared to other co-morbidities such as myocardial infarction. Recent meta-analysis of the betablocker trials conducted in heart failure have suggested that betablockers may only reduce mortality and morbidity in patients with heart failure who are in sinus rhythm (14). Certainly this would seem to fit with the trends in population level survival reported by Schmidt *et al* (6), this group is not experiencing the same gains as others. Those with T2DM have also not seen particularly large reductions in mortality. This again would fit with there being no therapies available during the study period that convincingly reduce morbidity and mortality in T2DM. So while the prognosis of HF has improved the prognosis of T2DM has not. This is of course, all speculation. Without population level data on prescribing rates we can only speculate on the myriad of potential interacting explanations for these trends. It will be important to continue to monitor these trends as newer therapies and data indicate that mortality can be altered by pharmacotherapy in patients with T2DM (13). What is however highlighted by

these data is the need to involve multiple specialists (diabetes, respiratory and renal experts) in the care of patients with heart failure.

While there are worrying trends in individual co-morbidities, perhaps the greatest concern is the increase in the total burden of co-morbidities over time. The proportion of patients with one or more co-morbidity rose from 34 to 43%. Survival at 5 years in those with 2 or more co-morbidities was an appalling 22%, 50% had died within 1 year. As the population with heart failure ages, and the number of co-morbidities increase, these statistics should worry any heart failure specialist. Despite successes in the treatment of heart failure they highlight the truly terrible prognosis of patients when we look outside of the highly selected cohorts of patients recruited into randomised controlled trials. But is it fair to blame all of these statistics on the treatment of patients with multiple co-morbidities or is there another explanation?

Schmidt *et al* (6) note that in common with many epidemiological datasets they did not have information on ejection fraction. This weakness is unfortunate, as it may explain why some these trends have been observed. Co-morbidities are common in those with heart failure with preserved ejection fraction (7). Could these trends simply reflect an increasing prevalence of heart failure with preserved ejection fraction? Without data on ejection fraction it is difficult to say. However, we might speculate that this may be the case.

Finally, it is worth reflecting on the impact of registry based data such as these. Northern European countries such as Denmark have been at the forefront of the systematic collection of health data by public health care systems which cover the entire population and country.

The foresight of those who initiated these electronic systems is to be commended, as they continue to provide valuable epidemiological data. However, most population registries are from Northern Europe or North America and we have little information about heart failure from the rest of the world (15). Even within Europe the populations are heterogeneous. There are significant within and cross country variations and inequalities in the financing, organisation, access, delivery, quality and effectiveness of cardiac care in Europe(16). Therefore, secular trends in Denmark may not be applicable to many of the countries in Europe and even less so to other countries across the world. What is clear is that registry based studies are going to become more common as health care systems adopt and integrate e-health technology (17). Through the integration of high quality registries on treatment of patients with outcome data such as hospitalisations and death registers, markers of the quality of care of patients can be examined, developed and subsequently improved (18).

Although registries hold much promise, and their use is likely to change radically, we must be mindful of the trends that are demonstrated through their interrogation. The growing problem of co-morbidities is an issue that heart failure specialists will have to deal with. The scale and impact of this issue means that we cannot ignore it and we must incorporate it into the treatment of our patients if we are to improve the prognosis of patients with heart failure.

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