Editorial

Evolving mortality and clinical scenarios in HCM: Where are we?

Hypertrophic cardiomyopathy (HCM) is a quite common genetic heart disease with a prevalence of 1:500 in the general population [1]. It has been 65 years since the disease was first described, and tremendous progress has been made in understanding the natural history and clinical management of HCM, so that our perception of the disease has progressively changed. As opposed to what believed in the past, it is now evident that patients with HCM in many cases can lead normal lives, and only a minority has serious disease-related complications. In the past two decades, the introduction of septal reduction therapies, associated to heart transplantation (HTx) and ventricular assist devices (VADs) have changed the prognosis of even the most critically ill patients. Furthermore, advances in arrhythmic risk stratification have enabled an increasingly better selection of candidates to implantable defibrillators (ICDs), mostly in primary prevention. As a consequence, a significant reduction in sudden cardiac deaths (SCD), which often affect younger HCM-patients, has been obtained and the overall reduction in HCM-related mortality decreased from 1.5%/year in the 1990s to a current estimated mortality of 0.5%/year [2,3]. The above therapeutic strategies had not only affected the life expectancy, but probably also the main clinical scenarios encountered in clinical practice, particularly regarding the end of life of patients with severe forms of HCM.

On this bases, Zampieri M. et al. conducted a retrospective analysis [4], published in this issue of International Journal of Cardiology, to describe the death patterns of patients with HCM based on age, disease stage and clinical scenarios. From a registry population of 1461 HCM-patients researchers recruited a cohort of 161 patients who died between 2000 and 2020, with a follow-up of at least one year. The Authors are to be complimented for the comprehensiveness of the data collected, as a current picture of these data on such a large population was lacking in the contemporary literature. Overall, 64% of patients in the cohort died from HCM-related complications, including heart failure (HF), which resulted as the leading cause of death, and SCD. These patients were on average younger than those who died from causes unrelated to HCM. Patients were also stratified according to the stage of disease presentation into three groups: “classic phenotype,” “adverse remodeling,” and “overt dysfunction,” as previously described [5]. This stratification seems to be a useful tool to better identify the disease trajectory of HCM patients and thus to optimize treatment strategies and timing. In fact, advanced stages of the disease would suggest an increased risk of progression to heart failure, warranting closer follow-up and a more aggressive treatment approach.

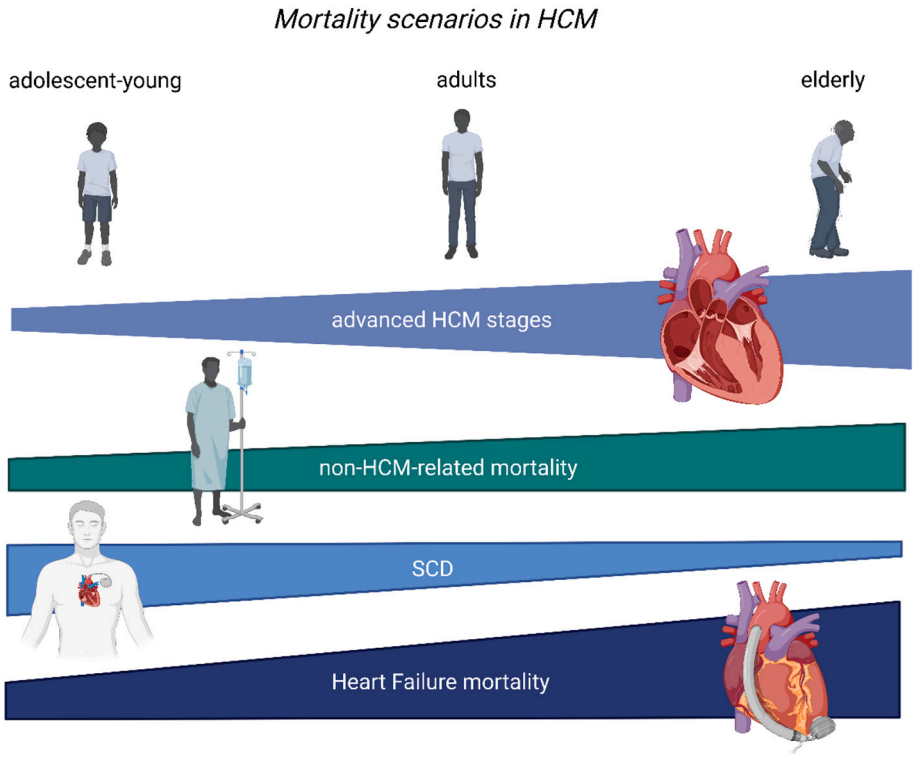
Patients who died from HCM-related causes had a median age 8 years lower than those who died from non-CMD-related causes. This is probably guided by the statistical contribution of SCD, which accounted for 22% of total deaths in the analysis and involved patients with a median age of 44 years, compared with the median age of 70 years for patients who died of heart failure. Furthermore, according to the stage of disease presentation, the prevalence of SCD followed a progressively decreasing gradient from less severe to more severe stages of disease. Even with the limitation of the long enrolment period, which ranged two decades, it emerges how the burden of SCD still remains an important factor in reducing the life expectancy of patients with HCM. Furthermore, although not the most frequent, SCD is the cause of death with the greatest social impact, because it affects younger patients and at a more socially active age. Several studies on HCM arrhythmic risk stratification in various countries of the world have led to the creation and subsequent implementation of algorithms for selecting the best candidates to ICD implantation, reported in the European and American guidelines [6,7]. However, the great heterogeneity of clinical scenarios of HCM not infrequently leaves patients, especially those at low-to-moderate risk, in a “gray zone” of recommendation, where the choice for ICD implantation remains arbitrary [8]. In addition, a recent analysis highlighted the scenario of different defibrillator implantation policies worldwide, with significant differences in the cumulative incidence of ICD implantation in primary prevention between U.S. and non-U.S. countries, with no significant difference in SCD [9]. The results of the study by Zampieri et al. further stress the need to optimize the arrhythmic risk stratification as one of the targets of the future research. In this challenge, the

implementation of innovative tools, including advanced CMR and artificial intelligence for processing complex data, and promises in the field of genetics could bring important contributions in the future.

Most deaths in patients with HCM, however, were preceded by a slow progression of the disease to advanced stages and occurred due to refractory HF in older patients. In most cases, symptoms are caused by outflow tract obstruction, which is observed in 70% of patients, and are usually progressive but reversible with septal reduction therapies, while current drug therapy has so far shown only modest evidence in preventing disease progression [8]. The first-in-class disease-specific drug Mavacamtem has shown benefit in patients with symptomatic obstructive HCM, but it is currently available only in the U.S. and has a rather limited therapeutic window [10]. In addition, a smaller but not negligible number of HCM patients develop a restrictive diastolic pathophysiology or left ventricular systolic dysfunction with refractory HF. In these cases, LVAD and HTx represent the last available therapies. In this context the choice of optimal timing for invasive treatments is relevant. Indeed, in the study by Zampieri et al., deaths from HF were clustered around a median age of 70 years, after a median time from HCM diagnosis of 21 years. Older age would therefore limit the access of these patients to invasive interventions such as heart transplantation.

In conclusion, studies like that by Zampieri et al. are important to shed some light into the heterogeneous, complex, and changing universe of HCM and fuel considerations on the basis of which to set up epidemiological and hopefully prospective studies for new therapies in the next future, towards precise diagnoses, targeted therapies, and individualized follow-up strategies.

Image: main causes of death in patients with HCM, according to age and stage of presentation. From the analysis of Zampieri et al. HCM-related complications accounted for 64% of mortality in patients with HCM, with heart failure as the leading cause. Sudden cardiac death was the main cause of death in young, low-stage patients (HCM: Hypertrophic Cardiomyopathy; SCD: Sudden Cardiac Death).



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