Precision medicine in heart failure no longer a visual theory but a realistic opportunity

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Over the last decades, major advances in the understanding of pathophysiology in a wide spectrum of cardiovascular diseases provided several effective pharmacological and non-pharmacological therapies [1]. Along with novel rehabilitation and follow up strategies, these advances have improved the survival rate of cardiac diseases, globally, and contributed generally to a significant increase in life expectancy [2]. As a consequence, there is a parallel increase of patients suffering from challenging and multifaceted syndromes such as heart failure (HF). HF is a recognised pandemic disease, with a progressively increasing prevalence in the aging population [3]. It is a major public health issue, considering both its social and economic implications. HF patients are characterised by a high level of complexity because of the advanced age and the presence of multiple relevant comorbidities requiring dedicated polytherapy [1]. Therefore, overall mortality of HF patients is still unacceptably high, exceeding that of several neoplasms, carrying a risk of approximately 10% at 12 months from clinical onset [4].

Despite the complexity of the syndrome, the clinical management and available therapeutic strategies in patients with HF currently rely mainly on a classification predominantly based on the left ventricular ejection fraction (EF). Patients with EF $<40\%$ are defined as HF with reduced EF (HFrEF) and those with EF $>50\%$ as HF with preserved EF (HFrEF). Patients with an EF ranging from 40% to 50% are classified as HF with "midrange" EF (HFmEF) and represent a poorly characterised and dynamic category that includes features of both the HFrEF and HFpEF spectra [1,5]. However, EF could be dynamic over time, with tailored therapy [6]. About 40% of patients with non-ischemic dilated cardiomyopathy (DCM) experience a significant left ventricular reverse remodeling [7] under evidence-based medical therapy, in some cases leading to normalization of systolic function and reclassification in HFpEF. Similarly, although having an apparent better long-term evolution, up to 17% of patients with DCM and HFmrEF develop HFrEF despite appropriate therapy because of progressive DCM [8]. Finally, some patients with HFpEF for several years can experience a relevant loss of cardiomyocytes and the development of HFrEF due to some environmental factors (such as myocarditis, arrhythmias or myocardial infarction [MI]) or to the intrinsic progressive nature of the heart disease. Therefore, recent onset and long-standing HF, ischemic and non-ischemic HF regardless of the etiology, could all be characterized in the same category, despite carrying a different risk of cardiovascular events.

The continuous effort aimed to improve the global management and outcome of patients with HF should probably be based on the deep and individual characterization of those patients, in support of a clinical strategy looking beyond the EF. The paper by Kobayashi et al. [5], published in this issue of the *European Journal of Internal Medicine*, fits into this perspective. In a representative and large study population, the Authors demonstrate the ischemic HF with the most unfavorable prognostic significance compared to other HF etiologies and, further, they identify renal failure as the comorbidity able to confer the highest risk of worsening HF syndrome. Furthermore, the article confirms the relatively well-known concept that neuro-hormonal therapy should be systematically up-titrated at maximal tolerated dosages, regardless of the etiology [9].

In ischemic cardiomyopathy, the development of myocardial scar provides a structural substrate which confers an increased risk of HF or ventricular arrhythmias, potentially leading to sudden cardiac death. In addition, despite successful coronary flow restoration, revascularization acts only on epicardial arteries and some degree of microvascular ischemia could persist. Conversely, patients with non-ischemic etiology represent a more heterogeneous subgroup where different cardiac substrates confer variable risk profiles. Finally, the global risk of major events in HF patients is not entirely driven by cardiovascular factors, but may be predominantly related to the presence and severity of non-cardiac comorbidities. For these reasons, patients affected by HF require a multidisciplinary approach dealing with either the specific cause prompting HF or the presence of several comorbidities in order to ensure a tailored therapy and clinical management, contributing to increasing the survival and, wherever feasible, the quality of life of the patients.

The study of Kobayashi et al. [5] is a notable example of how deeply the path towards precision medicine has been undertaken in the setting of HF so far and, probably, represents the new frontier for cardiovascular research in the years to come. This holds true both for clinical research and basic research in pursuit of novel drugs capable of interacting with specific inter- and intra-cellular networks [10,11].

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Beside many remarkable aspects, the paper by Kobayashi et al. [5] is not devoid of limits. The most relevant limit is represented by the relative poor characterization of patients with non-ischemic and non-valvular DCM, a disease affecting mainly young adults and frequently associated with a complex inflammatory or genetic background [12]. This heterogeneous subgroup of patients is substantially different from the setting of ischemic cardiomyopathy. The frequent presence of removable factors favoring decompensated non-ischemic HF should be systematically considered in this group of patients as they represent a crucial therapeutic goal, namely hypertension in hypertensive heart disease, rhythm control in tachy-induced cardiomyopathy, resynchronization in dyssinchrony-induced cardiomyopathy, alcohol removal in toxic cardiomyopathy [12]. Conversely, in patients affected by ischemic cardiomyopathy, the irreversible loss of working myocardium following an acute MI and the progressive replacement fibrosis leading to significant arrhytmogenic potential, represent major determinants of a particularly poor cardiovascular outcome. However, looking closely, even the subgroup of patients with ischemic heart disease is highly heterogeneous, including those undergoing coronary artery revascularization (both by percutaneous intervention and coronary artery bypass), those with no treatable coronary artery disease, those having stenosis of epicardial coronary arteries and those suffering from microvascular dysfunction. Finally, patients with HFpEF were under-represented in the study population and, consequently, no solid conclusions could be drawn for this subgroup. The phenotypic spectrum of non-ischemic HFpEF comprises patients suffering from a wide variety of cardiac etiologies and extra-cardiac comorbidities, characterized by high levels of heterogeneity. Anyway, the abovementioned limits are inevitable as either non-ischemic DCM and ischemic cardiomyopathy or HFpEF are “umbrella” terms comprising several different etiologies. These findings point out the crucial need of a novel approach to HF patients in the next future, based on a patient-oriented characterization, including gender medicine towards the model of precision medicine providing treatments for the specific disease, prompting HF syndrome, even in the setting of genetically determined diseases [13].

The section dealing with comorbidities is of great importance because this represents a pivotal issue in the clinical management of patients with HF, beyond left ventricular systolic function and the specific underlying etiology. Even from this point of view, the paper by Kobayachi et al. [5] is a valuable model of the advantages of adopting multidisciplinary and, at the same time, organ-targeted (i.e. cardiology, neurology, nephrology) strategy of management. A well-known interaction exists between HF and comorbidities promoting a vicious cycle facilitating maintenance and progression of patient's clinical status [14]. In case of multiple comorbidities, patients’ conditions obviously reach higher levels of complexity. In particular, patients with HFpEF compared to HFrEF might have the same mortality burden as the outcome is substantially influenced by the presence and severity of non-cardiac comorbidities. The prevalence of obesity and arterial hypertension has been reported higher in HFpEF, carrying a subsequent risk of non-cardiac events [15]. Renal failure is a recognized predictor of poor outcome in patients with HF and it emerges as the most unfavorable among several comorbidities in the present study [5]. Progressive renal failure represents the main factor limiting the introduction and the up-titration of anti-neurohormonal therapy. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors (ARNI) and mineralcorticoid receptor antagonists are the cornerstone of evidence-based medical treatment in HF, but they are burdened by significant renal toxicity. Furthermore, renal and cardiac failure cannot always be clearly distinguished, especially considering the delicate interaction between the kidneys and the heart enclosed in the so-called “cardio-renal syndrome [16]. The kidneys represent the crossroads where multiple damaging factors act together even before the HF clinical onset as in the case of uncontrolled arterial hypertension and diabetes mellitus. Furthermore, hemodynamic imbalance due to HF results in renal hypoperfusion and progressive decline in glomerular filtration rate. Once cardio-renal syndrome is established, it is extremely challenging, and sometime impossible, to understand which of these two organs mainly drives the failure of the other one.

In conclusion, the presence of significant comorbidities, the specific etiology underlying cardiac disease and the possibility to reach the maximal evidence-based dose of anti-neurohormonal therapy emerge as the key determinants of HF patients’ outcome, also with the reduction of hospitalization risk for decompensated HF. Although enrolling patients with lower median age compared to those included in the present study [5], the PARADIGM Trial [17] testing ARNI therapy and the DAPA-HF trial [18] testing Dapagliflozin, demonstrated a significant increase in overall survival and, moreover, reduction in the risk of hospitalization for HF. Noteworthy, in a post-hoc analysis from the PARADIGM trial focusing on renal function, ARNI therapy was associated with a lower rate of decline in glomerular filtration rate compared to enalapril therapy, despite a small and clinically non-relevant increase in microalbuminuria [19].

Considering the abovementioned findings, physicians dealing with the clinical management of HF patients are required to progressively acquire multidisciplinary competence in fields of medicine and to be part of a team including non-cardiologists, working together to pursue the most specific and effective treatments for patients. Nowadays, we are in all probability experiencing a real turning point in the management of patients with HF. Great efforts of the medical community should be made in an attempt to achieve a model of individualized medicine directed at characterizing the single patient, taking into account his/her specific cardiac disease and comorbidities. Following in the footsteps of the present study [5], over the next years, cardiovascular research would probably aim at deriving prognostic multi-parametric models based on patient's gender, comorbidities, genetic profile and etiologic characterization of cardiac diseases. In this perspective, current basic research is developing novel molecules acting on specific mechanisms that are impaired by peculiar genetic mutations [20] and that represent the foundation for a proper translation of precision medicine from a theoretical standpoint to a concrete opportunity, possibly applicable into everyday clinical practice in the decades ahead.

Declaration of Competing Interest

None

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