Classification of heart failure: A farewell to ejection fraction?

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How it all started

In 1789, the English physician William Withering, inspired by an old herb woman in Shropshire, published his seminal monograph, "An account of the Foxglove and some of its medical uses with practical remarks on dropsy, and other diseases," (1) in which he described the clinical effects of an extract of the foxglove plant on patients with a condition that he called dropsy; thus, the first, albeit potentially toxic, remedy for heart failure was established. Withering observed that after ingesting his herbal extract, patients with dropsy started to urinate and edema regressed. He realized that this condition was due to water retention, but he was far from today's understanding of heart failure.

With the advent of imaging techniques, initially chest X-ray imaging, then ventriculography, echocardiography, and eventually nuclear techniques and cardiac magnetic resonance imaging, many patients with such a condition were found to have large hearts with poor pump function. As no other parameter was available, changes on the volume of the ventricles, i.e., ejection fraction, became the center of interest for the assessment of patients with what we know today as heart failure. Since then the left ventricular ejection fraction (LVEF) was the focus in this patient population–is LVEF still appropriate? Let us start to look at the beginning of evidence-based heart failure management!

Pump failure

Researchers started to characterize patients with heart failure as having pump failure. They specifically focused on those with an LVEF below 40% and performed a series of seminal trials in this patient population. Research was not based on specific pathophysiological reasoning, but was carried out as an attempt to reach high rates of major cardiovascular events (MACE)–indeed, MACE can only be reduced significantly if a large number of events are to be expected –and a low LVEF undoubtedly predicts MACE (Fig. 1) (2).

The first trial was the CONSENSUS Trial that tested enalapril, an angiotensin-converting enzyme (ACE) inhibitor in patients with severe heart failure, showing a marked reduction in MACE and mortality (3). Several other trials have investigated ACE inhibitors with similar results in lower-risk patients with heart failure. Initially, beta blockers were considered contraindicated in heart failure until a courageous pioneer, Finn Waagstein et al. (4), from Göteborg, Sweden, provided evidence that it may actually be beneficial. Indeed, heart failure leads to an overactivation of the sympathetic nervous system that may be detrimental for the heart and circulation. Indeed, against all odds, a series of trials with metoprolol (5), bisoprolol (6), and carvedilol (7, 8) all showed marked reductions in MACE and mortality. Finally, mineralocorticoid receptor antagonists, such as spironolactone (9) and later eplerenone (10), further reduced death and hospitalizations. This was the standard guideline therapy until cardiac resynchronization therapy (CRT) provided devices that are able to improve symptoms and outcomes in patients with heart failure (11). More recently, new drugs such as angiotensin-neprilysin inhibitors [ARNI (12)] and sodium-glucose transport type 2 inhibitors such as empagliflozin (13) or dapagliflozin (14) showed remarkable additional beneficial effects on top of what have been achieved so far in patients with heart failure, regardless of the presence or absence of diabetes. Finally, cyclic guanylyl cyclase activators provided small reduction in MACE (15).

While all these interventions inhibited mainly neurohumoral activation and peripheral vasoconstriction and thereby unloaded the heart and/or reduced renal water and sodium retention,

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all attempts to stimulate the failing heart, not only with phosphodiesterase inhibitors (16), but also with other compounds, counterintuitively increased, rather than decreased, mortality despite their beneficial hemodynamic and symptomatic effects. In contrast, in a most recent trial, the novel cardiac myosin activator Omecamtiv Mecarbil improved cardiac performance on top of the standard therapy, but the effect size on MACE was undesirably small (17). Nevertheless, the management of patients with heart failure with reduced ejection fraction (HFrEF) is a true achievement that led to a marked improvement of the quality of life of such patients and clinical outcomes, with a continuously declining incidence of heart failure hospitalizations, MACE, and mortality, including sudden death (18).

From a failing heart to a stiff heart

Moreover, patients with heart failure may have normal or near-normal LVEF with typical symptoms such as breathlessness, reduced exercise capacity, as well as pulmonary and peripheral edema. Although outcomes are quite better in heart failure with preserved ejection fraction (HFpEF) than in HFrEF, these conditions are still associated with a significant number of MACE and death (Fig. 1) (19). Therefore, the most recent ESC Guidelines on the Management of Acute and Chronic Heart Failure, published in 2016, suggested to classify patients with heart failure into those with HFpEF, heart failure with mid-range ejection fraction (HFmrEF), and HFrEF (Table 1) (20).

However, while classical medications and CRT were a real success in patients with HFrEF, all these measures were not effective in patients with HFpEF (21). Similarly, the TopCat trial using spironolactone in patients with HFpEF did not attain its primary end point (22). However, a subanalysis revealed that those with ejection fraction <60% did indeed benefit from spironolactone, while those with true HFpEF, i.e., ejection fractions >60%, did not (Fig. 2) (23).

Similarly, the most recent PARAGON Trial using ARNI provided neutral results overall, except in patients with HFmrEF (24, 25), suggesting that these patients have an early or mild form of HFrEF rather than a specific condition such as HFmrEF or even HFpEF. Thus, the initial categorization needs to be reconsidered based on these recent trials.

From lumping to splitting

Initially, as we saw, all patients with HFrEF were lumped together, regardless of their etiology, be it ischemic or non-ischemic in nature–but it worked so far. However, it was not a personalized approach, as it did not consider the underlying cause of heart failure, individual characteristics, specific natural course, and MACE risk of a patient. Thus, we must move from lumping to splitting to develop a more individualized approach in the management of HFrEF (26).

Indeed, categorization of patients with reduced pump function based on LVEF alone is a very crude criterion. In fact, LVEF

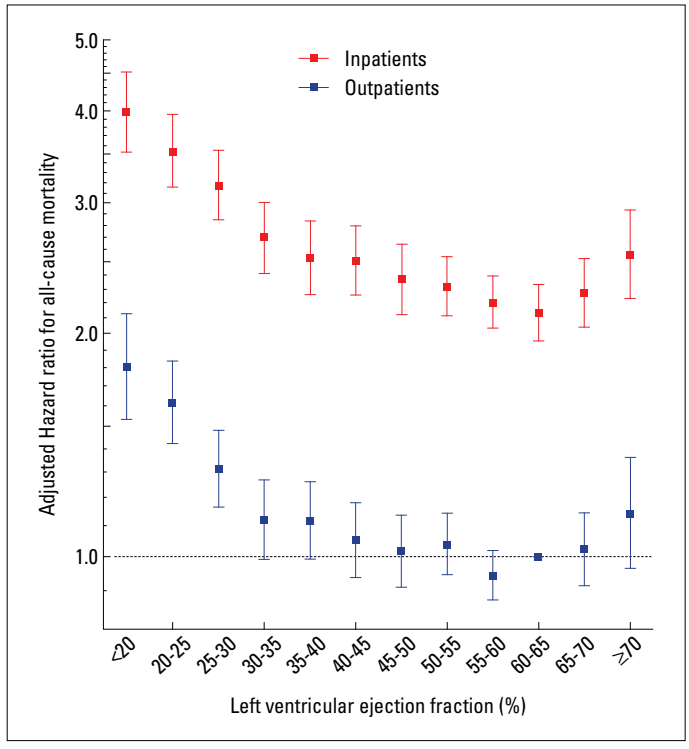

Figure 1. Relation of left ventricular ejection fraction with mortality (2)

Table 1. Categorization of heart failure according to the ESC Guidelines on the Management of Acute and Chronic Heart Failure (20)

Type of HF	HFrEF	HFmrEF	HFpEF
Criteria			
1	Symptoms±signs*	Symptoms±signs*	Symptoms±signs*
2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
3	–	1. Elevated levels of natriuretic peptides*;	1. Elevated levels of natriuretic peptides*;
		2. At least one additional criterion:	2. At least one additional criterion:
		a. Relevant structural heart disease (LVH and/or LAE).	a. Relevant structural heart disease (LVH and/or LAE).
		b. Diastolic dysfunction (for details see section 4.3.2).	b. Diastolic dysfunction (for details see section 4.3.2).

*Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics. LVEF - left ventricular ejection fraction; HF - heart failure; HFrEF - heart failure with reduced ejection fraction; HFmrEF - heart failure with mid-range ejection fraction; HFpEF - heart failure with preserved ejection fraction

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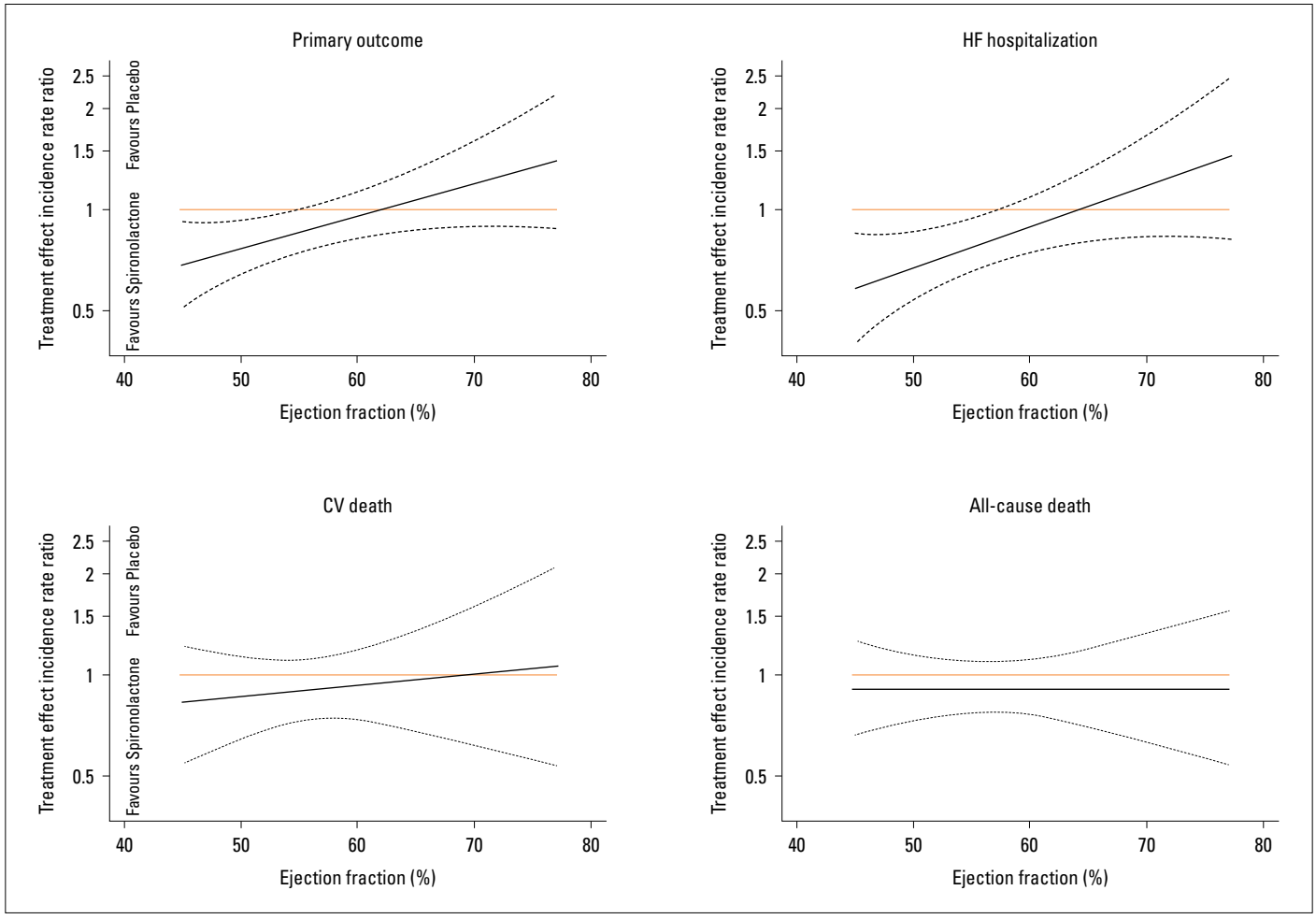

Figure 2. Relation between left ventricular ejection fraction and outcomes of the TopCat trial (23)

only describes one aspect of the phenotype, i.e., the change in the volume during the cardiac cycle, and does not reflect the pump function of the heart. For instance, LVEF may grossly overestimate the true pump function in the presence of moderate and, in particular, severe mitral regurgitation. Furthermore, a classification based only on LVEF does not consider the underlying cause of heart failure, e.g., toxins, genetics, and hemodynamics, which markedly affect clinical outcomes and the effectiveness of heart failure therapy. For instance, patients with HFrEF who underwent chemotherapy do not respond well to current treatment modalities, while other forms of dilated cardiomyopathy do.

From phenotype to genotype

Indeed, genetic maps that summarize genetic mutations of patients with various forms of dilated cardiomyopathy have been published (Fig. 3) (27). These maps made it possible to perform a more personalized evaluation of patients with dilated cardiomyopathy. Certainly, some patients, particularly those with laminin mutations, have worse outcome than others and may require an implantable cardioverter defibrillator, while patients with other forms of dilated cardiomyopathy may not. Thus, while all cases of HFrEF due to a dilated cardiomyopathy were taken together, more recently, splitting has been an achievement in this patient population. Importantly, LVEF is not the main, or only, predictor of outcomes in such patients, because genetic mutations determine whether such patients die of pump failure or die suddenly from fatal arrhythmias or are at risk for both. Indeed, while sudden cardiac death overall is less common in non-ischemic than in ischemic cardiomyopathy (28), the degree of fibrosis, rather than LVEF, might become an important risk predictor for sudden cardiac death. Clearly, LVEF <40% or 35% alone is an insufficient criterion for ICD implantation, particularly in dilated cardiomyopathy. On the contrary, increasing evidence support the prognostic role of myocardial fibrosis (29).

Beyond ejection fraction

As LVEF only measures volumes during systole and diastole and is markedly affected by the degree of regurgitation through an increasingly leaky mitral valve, we have to rely on other imaging techniques to correctly assess myocardial performance. New imaging technologies that focus on longitudinal and circumferential strains and other load-independent diameters of pump function may be a genuine advantage in assessing patients with mitral regurgitation beyond LVEF. Furthermore, more advanced

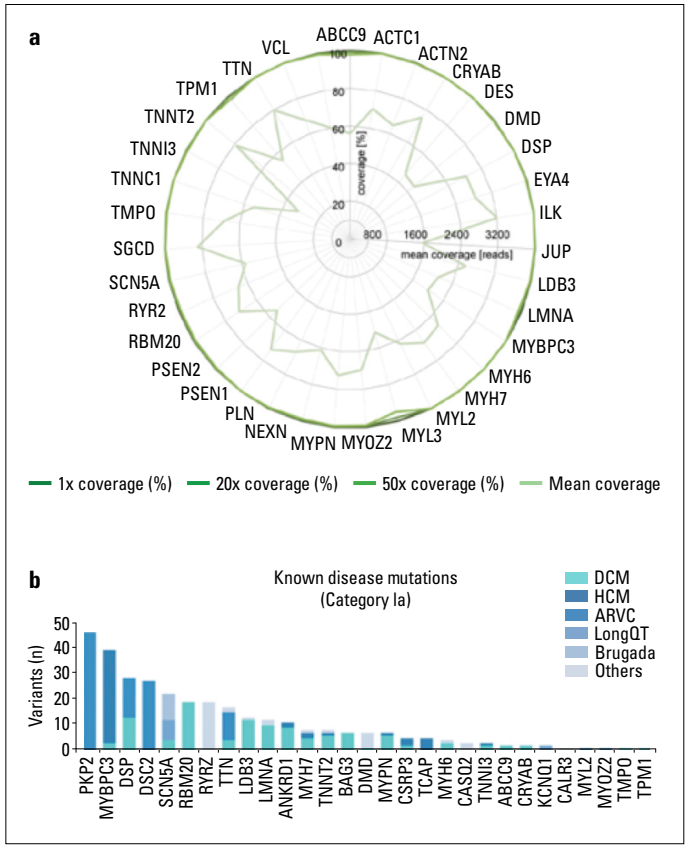

Figure 3. Atlas of the clinical genetics of human dilated cardiomyopathy (27)

technique such a diffusion tensor imaging (30) may provide much deeper insights into myocardial performance, for instance, in hypertrophic cardiomyopathy (31) and congenital heart disease (32), and possibly many others, as such imaging technique considers myocardial microstructure, fiber orientation, and strain rather than mere changes in volume.

Conclusion

As we move from lumping to splitting, heart failure management becomes more sophisticated and precise for patients and more interesting for physicians. First, we must reconsider the classification of heart failure solely based on LVEF: HFrEF should be defined as an LVEF <60%, as all such patients respond in a similar fashion to current evidenced-based therapy with ACE inhibitors, angiotensin II receptor blockers, ARNIs and beta blockers, mineralocorticoid antagonists, and CRT and ARNIs. HFmrEF is an early or mild-to-moderate form of HFrEF, not a separate entity, and therefore should be abandoned. Within this spectrum of reduced LVEF, the underlying cause is an increasingly important factor in determining the risk of MACE and the requirements of and response to therapy.

In contrast, patients with HFpEF, i.e., those with LVEF>60%, symptoms of heart failure, and moderately increased natriuretic peptides, are a heterogeneous group that does require further research. At this point, we know that transthyrethin amyloid heart disease is a distinct entity amenable to novel drugs such as tafamidis (33). In addition, for hypertrophic cardiomyopathy, specific drugs such as mavacamten, a cardiac myosin inhibitor, raises hopes in symptomatic patients (34). Patients with hypertensive LV remodeling and HFpEF are rather candidates for aggressive antihypertensive treatment with RAS inhibitors or ARNIs. In patients with fibrotic stiff hearts, mineralocorticoid antagonists and, in the future, antifibrotic therapies might be appropriate. Thus, as we move from lumping to splitting, we may provide personalized drug therapy to the benefit of our patients with heart failure.

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