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The spectrum of heart failure: value of left ventricular ejection fraction and its moving trajectories

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Heart failure may occur in patients with different pump function of the left ventricle. The ESC Guidelines have defined three patient groups, i.e. those with heart failure with preserved ejection fraction (HFpEF), those with mid-range ejection fraction (HFmrEF), and those with reduced ejection fraction (HFrEF).[1] Patients with HFrEF and an EF below 40% may have persistently reduced pump function during proper treatment or recover wholly or in part over time. In their article '**Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study**', Finlay A. McAlister and colleagues from the University of Alberta Hospital in Edmonton, Canada address this issue in 10 641 patients of which around a third had HFrEF and were followed up with two or more echocardiograms during treatment.[2] Mean EF at baseline declined from 30% to 29% on the second echocardiogram in those with persistent HFrEF, i.e. <10% improvement in EF, but improved from 26% to 46% in a third of these patients. On multivariate analysis, female gender, younger age, atrial fibrillation, cancer, hypertension, lower baseline EF, and hydralazine were associated with EF improvements ≥10%. Those patients also had lower mortality, and fewer hospitalizations, emergency room visits, left ventricular assist device (LVAD) implantations, or cardiac transplantation as compared with those with persistent HFrEF. Thus, patients with recovering HFrEF are younger, more likely to be females or hypertensives, or to have atrial fibrillation or cancer, and they do have a better prognosis compared with those with persistent HFrEF. These intriguing results are put into clinical context in an **Editorial** by Sanjay Prasad from the Royal Brompton Hospital in London, UK.[3]

In addition to effective heart failure drugs, cardiac resynchronization therapy (CRT) is increasingly used,[4] and ameleriorates symptoms and outcome in selected HFrEF patients with wide QRS complex[1,5] or those with atrial fibrillation after AV node ablation.[6] However, the very long-term outcome of such patients surviving the first few years after receiving CRT has not been clarified. In their article entitled '**Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients**', Serge Boveda from the Clinique Pasteur in Toulouse, France investigated 1775 patients with ischaemic or non-ischaemic dilated cardiomyopathy who were alive 5 years after CRT implantation, especially with regard to sudden cardiac death.[7] Over a mean follow-up of 30 months beyond the first 5 years, mortality was 27%. The annual age-standardized mortality rates of CRT-D and CRT-P patients were 40.4 and 97.2 per

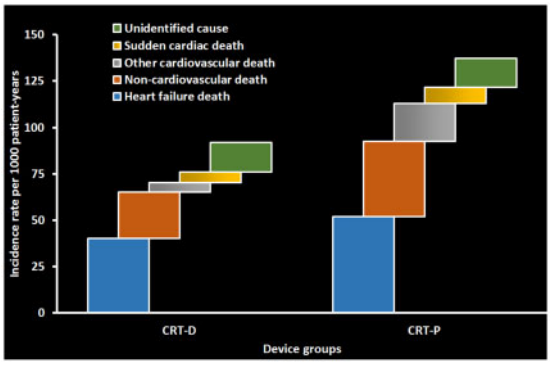

Figure 1 Incidence rate displayed by mortality cause in cardiac resynchronization therapy defibrillator and pacemaker patients. CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker (from Barra S, Duehmke R, Providencia R, Narayanan K, Reitan C, Roubicek T, Polasek R, Chow A, Defaye P, Fauchier L, Piot O, Deharo J-C, Sadoul N, Klug D, Garcia R, Dockrill S, Virdee M, Pettit S, Agarwal S, Borgquist R, Marijon E, Boveda S, on behalf of the French-British-Swedish-Czech CRT Network. Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients. See pages 2121–2127).

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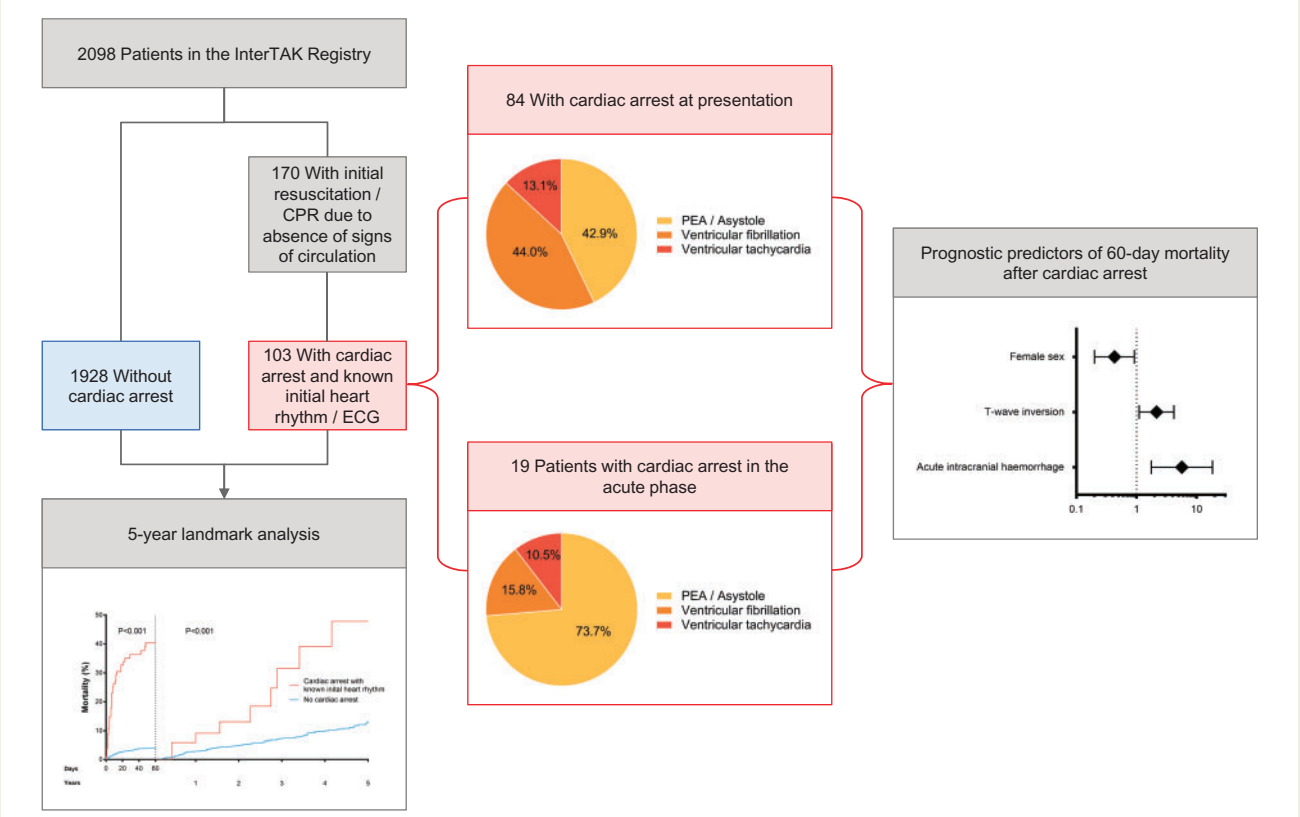

Figure 2 Cardiac arrest affects a relevant number of patients presenting with takotsubo syndrome and is associated with higher short and long-term mortality. Although typically occurring at presentation, cardiac arrest can also occur in the subsequent acute phase in patients with takotsubo syndrome. Among patients with cardiac arrest and takotsubo syndrome, simple clinical and electrocardiographic parameters may help to identify those at higher risk of death (from Gili S, Cammann VL, Schlossbauer SA, Kato K, D'Ascenzo F, Di Vece D, Jurisic S, Micek J, Obeid S, Bacchi B, Szawan KA, Famos F, Sarcon A, Levinson R, Ding KJ, Seifert B, Lenoir O, Bossone E, Citro R, Franke J, Napp LC, Jaguszewski M, Noutsias M, Münzel T, Knorr M, Heiner S, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuß G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin A, Borggrefe M, Gilyarova E, Shilova A, Gilyarov M, Horowitz JD, Kozel M, Tousek P, Widimský P, Winchester DE, Ukena C, Gaita F, Di Mario C, Wischnewsky MB, Bax JJ, Prasad A, Böhm M, Ruschitzka F, Lüscher TF, Ghadri JR, Templin C. Cardiac arrest in takotsubo syndrome: results from the InterTAK Registry. See pages 2142–2151).

1000 patient-years, respectively. Twenty-nine patients died of sudden cardiac death (14 with CRT-P, 15 with CRT-D; Figure 1), corresponding to 6.1% of all causes of death in both device groups (*Figure 1*). Specific annual sudden cardiac death rates were 8.5 and 5.8 per 1000 patient-years in CRT-P and CRT-D patients, respectively, with no significant difference between groups. Death due to progressive heart failure was the principal cause of death in around half of the patients, whereas approximately a third of deaths were due to non-cardiovascular death. Thus, progressive heart failure death still represents the most frequent cause of death in patients surviving the first 5 years after CRT implantation, while sudden cardiac death is quite rare irrespective of the presence of a defibrillator. These intruiging results are further discussed in an informative **Editorial** by John G.F. Cleland from Imperial College London in the UK.[8]

Obesity is a growing problem worldwide and associated with significant morbidity and mortality,[9] among them with an increased risk for heart failure,[10] but a reduced risk of stroke in atrial fibrillation.[11] Roux-en-Y gastric bypass or gastric sleeve are the only convincingly effective treatment modalites for morbid obesity,[12] but their long-term effects are not well described. In their article entitled '**Surgical obesity treatment and the risk of heart failure**', Kristjan Karason and colleagues from the Sahlgrenska University Hospital in Gothenburg, Sweden analysed data from the Swedish Obese Subjects study to investigate whether bariatric surgery reduces this risk.[13] They identified 4033 obese individuals with no history of heart failure, of whom 2003 underwent bariatric surgery and 2030 received usual care. During a follow-up of 22 years, heart failure occurred in 188 of the participants treated with bariatric surgery and in 266 of those receiving usual care, corresponding to a hazard ratio of 0.65. After pooling data from the two study groups, the quartile of subjects with the largest weight loss after 1 year (i.e. 41 kg) displayed the greatest risk reduction, with a hazard ratio of 0.51. Thus, compared with usual care, bariatric surgery is associated with reduced risk of heart failure in the severely obese. These clinically relevant findings

are put into context in an **Editorial** by Nicholas Finer from UCL in London, UK.[14]

Takotsubo syndrome or TTS is an acute cardiac syndrome with left ventricular dysfunction due to microvascular constriction[15] and myocardial dysfunction.[16] TTS is also associated with arrhythmias, stroke, and death.[17] In their manuscript '**Cardiac arrest in takotsubo syndrome: results from the InterTAK Registry**' Christian Templin and colleagues from the University Hospital Zurich in Switzerland determined the frequency, clinical features, and prognostic implications of cardiac arrest in TTS.[18] Of 2098 patients, 103 patients, or 5%, with cardiac arrest and known heart rhythm during cardiac arrest were evaluated. Compared with patients without cardiac arrest, those with cardiac arrest were more likely to be younger, of male gender, and to have apical-type TTS, atrial fibrillation, neurological comorbidities, physical triggers, and longer corrected QT-interval and lower LVEF on admission. Overall, 57% patients with cardiac arrest at admission had ventricular fibrillation/tachycardia, while 74% with cardiac arrest in the acute phase eventually had asystole or pulseless electrical activity. Patients with cardiac arrest showed a much higher 60-day mortality of 40.3% and a 5-year mortality of 68.9% than patients without cardiac arrest (4% and 16.7%, respectively; *Figure 2*). T-wave inversion and intracranial haemorrhage were independently associated with higher 60-day mortality after cardiac arrest, whereas female gender was associated with lower 60-day mortality. Thus, cardiac arrest occurs in 5% of TTS and is associated with higher short- and long-term mortality. These novel aspects of TTS are further discussed in an **Editorial** by Ilan Shor Wittstein from the Johns Hopkins Hospital in Baltimore, Maryland, USA.[19]

Currently, heart failure patients are mainly classified according to their LVEF.[1] Whether this is an oversimplification is discussed in a clinical review entitled '**The continuous heart failure spectrum: moving beyond an ejection fraction classification**' by Gilles W. De Keulenaer *et al.* from the University of Antwerp in Belgium.[20] Initially seminal randomized clinical trials used HFrEF patients to select high-risk populations to enhance statistical power. However, this may not be appropriate for such a complex syndrome. Connotations such as HFrEF, HFpEF, and, more recently, even HFmrEF, assigned based on arbitrary LVEF cut-off points, have arisen as separate disease entities, implying questionable distinct pathophysiologies. Thus, the paradigm of classifying heart failure according to LVEF may be misleading. Rather, heart failure is a heterogeneous syndrome in which disease progression is associated with a dynamic evolution of functional and structural changes leading to unique disease trajectories and creating a spectrum of phenotypes with overlapping as well as distinct characteristics. By recognizing the spectral nature of the disease, a novel stratification will arise from new technologies and scientific insights that will shape the design of future trials based on deeper understanding beyond the LVEF alone.

In cardiogenic shock due to myocardial infarction,[21] acute heart failure, or myocarditis,[22] the immense haemodynamic load induces cardiac remodelling via mechano-transduction pathways, which can further trigger inflammatory responses leading to a vicious cycle and eventually death. In a *Special Article* '**Mode-of-action of the PROPELLA concept in fulminant myocarditis**',[23] Carsten Tschöpe and colleagues from the Charité – University Medicine in Berlin in Germany hypothesized that particularly in an inflammatory disorder such as myocarditis, in addition to adequate circulatory support, a therapeutic strategy should unload the left ventricle, thereby decreasing cardiac wall stress and mitigating inflammatory responses as has been described in TTS.[24] Axial flow pumps such as the Impella systems comply with such requirements. Tschöpe *et al.* propose the use of prolonged Impella support[25] (PROPELLA-concept) in fulminant myocarditis based on a few intriguing case reports. A different approach has been reported in the older literature using percutaneous extracorporeal membrane oxygenation[26] which is obviously more invasive and does not provide comparable left ventricular unloading.

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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