Heart failure, be it with preserved or reduced left ventricular function, is the cardiovascular epidemic of the 21st century,\textsuperscript{1–4} and it thus appropriate to devote a whole issue of the European Heart Journal to this problem. It is of note that this is at least in part a consequence of the success of our discipline. In the 1950s when Eisenhower had his famous heart attack,\textsuperscript{5} the treating physician did not have many options; accordingly, the mortality rate averaged \( \sim 50\% \) for those reaching hospital. Heart attack survivors of the time were prone to developing heart failure or sudden death. Today we are much more successful in treating patients with acute myocardial infarction. Thanks to the implementation of current guidelines,\textsuperscript{6,7} the mortality rate today is \( \sim 5\% \) for those getting to hospital and receiving appropriate treatment in a hospital with the capability to perform primary percutaneous coronary intervention.\textsuperscript{8} Another reason for the increase in heart failure hospitalizations is the prevention of sudden death in patients with impaired left ventricular function by the use of devices and antiarrhythmic drugs.\textsuperscript{9,10} Finally, the introduction of drugs and interventions for the treatment of high blood pressure\textsuperscript{11,12} has reduced the occurrence of stroke and myocardial infarction, but has led to an increase in heart failure with preserved and reduced ejection fraction.\textsuperscript{3,4}

In this issue, several major developments in the treatment of heart failure at large, as well as in the field of cardiac synchronization therapy, novel drugs interfering with several neurohumoral mediators, catheter-based valvular interventions, and novel developments such as vagal stimulation are discussed.

The first paper, a FAST TRACK manuscript entitled 'Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial',\textsuperscript{13} by Faiez Zannad et al. from Nancy, France presents a completely novel approach for the treatment of heart failure. The paper, that is accompanied by an Editorial by John Camm from St. George’s, University of London\textsuperscript{14} as well as a video interview (http://eurheartj.oxfordjournals.org/esc_bar_2014.html), is a randomized, sham-controlled trial designed to evaluate whether a single dose of vagal nerve stimulation would attenuate cardiac remodelling, improve cardiac function, and increase exercise capacity in symptomatic heart failure patients with severe left ventricular systolic dysfunction despite guideline-recommended medical therapy. Patients were randomized in a 2:1 ratio to receive therapy vagal nerve stimulation or not for 6 months. The primary endpoint was the change in left ventricular end-systolic diameter, with secondary endpoints of other echocardiography measurements, exercise capacity, quality of life assessments, 24-h Holter monitoring, and circulating biomarkers. Of the 96 implanted patients, 87 had paired data sets for the primary endpoint. The left ventricular end-systolic diameter from baseline to 6 months remained unchanged in both groups, as did other echocardiographic parameters of ventricular function as well as peak VO\textsubscript{2} and N-terminal pro brain natriuretic peptide (NT-proBNP). However, there were statistically significant improvements in quality of life and New York Heart Association (NYHA) class. The authors therefore conclude that vagal nerve stimulation failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic HF patients, but improved quality of life.

A second FAST TRACK article, 'An imputed placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure'\textsuperscript{15} by John J.J.V. McMurray from the Western Infirmary in Glasgow, provides further evidence on the effects of combined AT\textsubscript{1}-receptor and nephrresin antagonist in heart failure with reduced ejection fraction (HFrEF). The paper, which is accompanied by an insightful Editorial by Robert Califf from Duke University Medical Center,\textsuperscript{16} reports a subanalysis of the PARADIGM-HF trial available to the readers of the European Heart Journal. In this study, the authors made indirect comparisons of the effects of LCZ696 with putative placebos. They used the treatment arm of the Studies of Left Ventricular Dysfunction (SOLVD-T) as the reference trial for comparison of an angiotensin-converting enzyme (ACE) inhibitor with placebo and the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Alternative trial (CHARM-Alternative) as the reference trial for comparison of an angiotensin receptor blocker (ARB) with placebo. The hazard ratio of LCZ696 vs. a putative placebo was estimated through the product of the hazard ratio of LCZ696 vs. enalapril (active control) and that of the historical active control (enalapril or candesartan) vs. placebo. For the primary composite outcome of cardiovascular death or heart failure hospitalization, the relative risk reduction with LCZ696 vs. a putative placebo was 43% (with similarly large effects) and was significant for cardiovascular (CV) death (34%) and heart failure hospitalization (49%). For all-cause mortality, the reduction compared with a putative placebo was 28%. Putative placebo analyses based on CHARM-Alternative gave relative risk reductions of 39% for CV death or heart failure hospitalization, 32% for CV death, 46% for heart failure hospitalization, and 26% for all-cause mortality.
mortality. Thus, the authors conclude that the strategy of combined angiotensin receptor blockade and nephrin inhibition led to striking reductions in CV and all-cause mortality, as well as heart failure hospitalization. These benefits were obtained even though LCZ696 was added to beta-blockers and mineralocorticoid antagonists.

In the third paper, ‘The association between biventricular pacing and cardiac resynchronization therapy-defibrillator defibrillator on outcomes and reverse remodelling’ was investigated by Anne-Christine Ruwald from the University of Rochester Medical Center. The manuscript is accompanied by an excellent Editorial by Jagmeet P. Singh from Massachusetts General Hospital. In the study the authors compared biventricular (BIV) pacing and cardiac resynchronization therapy-defibrillator (CRT-D) with implantable cardioverter defibrillator (ICD) patients as a control group. Using Kaplan–Meier plots, they estimated the threshold of the BIV pacing percentage needed for CRT-D to be superior to ICD to prevent heart failure or death in 1219 patients with left bundle branch block in the MADIT-CRT trial. No difference was noted as regards the risk of heart failure and death between ICD and CRT-D patients. However, with increasing BIV pacing, the risk of heart failure or death was decreased. Further, the risk of death alone was reduced by 52% in CRT-D patients with BIV ≥ 97%. Within the CRT-D group, for every 1 percentage point increase in BIV pacing, the risk of heart failure and/or death and death alone decreased by 6% and 10%, respectively. Increasing BIV pacing led to marked reductions in left ventricular volume. As a result, the authors concluded that in patients with left bundle branch block in sinus rhythm, BIV pacing exceeding 90% was associated with a reduction in heart failure and death.

In the fourth paper, entitled ‘Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes’, by Susheel K. Kodali from Columbia University Medical Center and New York Presbyterian Hospital, accompanied by a well-balanced Editorial by Francesco Maisano from University Hospital Zurich, the authors investigated the impact of paravalvarul regurgitation following transcatheter aortic valve replacement (TAVR). Clinical and echocardiographic outcomes of patients who underwent TAVR were analysed after stratifying by severity of post-implant paravalvarul regurgitation graded as none or trace and moderate or severe. After TAVR, left ventricular function increased and left ventricular mass decreased. Thirty-day mortality was similar in all groups. However, at 1 year, increased all-cause mortality, cardiac mortality, and re-hospitalizations were noted in patients with worsening paravalvarul regurgitation. Thus, it appears that both mild and moderate and/or severe paravalvarul regurgitation predicted higher 1-year mortality.

The issue is complemented by two Papers summarizing the most important developments in 2014 in heart failure and valvular heart disease. The year in Cardiology: heart failure 2014 has been provided by the team from the University Hospital Groningen, The Netherlands led by Adriaan Alexander Voors. The authors feel that 2014 was remarkable for heart failure. The year did start on a bad note caused by the publication of TOPCAT which was unable to prove that spironolactone is beneficial in heart failure with preserved ejection fraction. Nevertheless, further insights in the study yielded a few bright spots when patients recruited in the USA and Europe were considered. In acute heart failure, subanalyses on the effects of serelaxin in acute heart failure became available. Of note, serelaxin reduces wedge pressures, and has similar effects in acute heart failure patients with and without HFrEF. The most exciting news was the results of PARADIGM, where LCZ696, the first-in-class angiotensin receptor nephrisin inhibitor, proved to be superior to enalapril in reducing mortality and morbidity in patients with HFrEF and—as reported in this issue—also compared with placebo.

Last but not least, Luc A. Pierard et al. from the University Hospital of Liège summarized ‘The year in cardiology 2014: valvular heart disease’ for our readers. Indeed, numerous articles related to valvular heart disease were published last year. Many focused on percutaneous interventions, i.e. transcatheter aortic valve implantation, and percutaneous mitral valve repair. Pierard and co-workers present the most relevant articles published in 2014 in this important clinical setting.

The editors of the European Heart Journal sincerely hope that this issue will update readers on these important topics of cardiology and help them to better manage this increasingly frequent patient population.

References


