Heart failure is the final common pathway of many cardiovascular risk factors and of most forms of heart disease. Myocardial ischaemia and reperfusion with evolving oxidative stress, either as repetitive episodes during increased demand or as a cause of myocardial infarction leading to scar formation and ventricular remodelling, is the most common form of this syndrome. Furthermore, different forms of myocardial disease either due to genetic causes or acquired in response to risk factors such as hypertension and/or diabetes are also of importance. Finally, congenital heart disease, either in the young or in adults, often leads to pump failure and death.

This issue begins with a Current Opinion article entitled ‘Should extensive myocardial ischaemia prompt revascularization in chronic coronary disease?’ by Raymond J. Gibbons from the Mayo Clinic in Rochester, MN, USA. Although stress-induced ischaemia was widely accepted in clinical decision-making for patients with coronary artery disease at the end of the 20th century, more recent trials on stress imaging and subanalysis thereof have raised concerns about the validity of this approach. The authors reviewed the three large clinical trials of coronary artery bypass surgery performed in the 1970s, as well as the landmark literature regarding stress imaging from the same era, to identify the best evidence supporting the utility of stress-induced ischaemia, as reflected in early clinical practice guidelines. They then examined the new evidence from contemporary trials in the 21st century, as well as the associated substudies focusing on stress imaging. Some of them have raised concerns about this dogma, and the impact of this new evidence on current clinical practice guidelines and appropriate use criteria. They identified multiple internal and external inconsistencies in current clinical practice guidelines and appropriate criteria with respect to the use of stress-induced ischaemia. Of note, it appears that contemporary clinical trials and their associated substudies of stress imaging do not provide definitive evidence about the value of stress-induced ischaemia to select patients for revascularization. Current evidence supports clinical equipoise, and provides a rationale for the ongoing ISCHEMIA trial.

Chronic exposure of the coronary arteries and myocardial cells to high glucose levels is a major cause of endothelial dysfunction, coronary artery disease, myocardial infarction, and eventually heart failure. Type 2 diabetes mellitus is characterized by multiple pathophysiological abnormalities. With time, an increasing number of glucose-lowering medications are commonly required to reduce and maintain plasma glucose concentrations within the normal range. Type 2 diabetics are also at a very high risk for microvascular complications, and the incidence of heart attack and stroke is increased two- to three-fold compared with non-diabetic individuals. Therefore, when selecting medications to normalize glucose levels in such patients, it is important that the agent does not aggravate, and ideally even improves, cardiovascular risk factors and reduces cardiovascular morbidity and mortality. In a Clinical Review article entitled ‘Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes’, Ele Ferrannini from the University of Pisa in Italy discusses the current evidence on this issue. The author examines the cardiovascular effects of oral antidiabetic drugs, such as metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-dependent glucose transporter 2 inhibitors, and α-glucosidase inhibitors, as well as injectable glucose-lowering agents such as glucagon-like peptide-1 receptor agonists or insulin, on established cardiovascular risk factors and long-term studies of cardiovascular outcomes. Firm evidence that in type 2 diabetics cardiovascular disease, in particular coronary artery disease, infarction, and heart failure, can be reversed or prevented by improving glycaemic control is unfortunately still missing. It is hoped that large, long-term clinical trials in patients at low risk using modern drug combinations designed to maximize haemoglobin A1c reduction while minimizing hypoglycaemia, which is a risk factor for sudden cardiac death and excessive weight gain, might show benefit.

In the first FAST TRACK paper entitled ‘A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure (AUGMENT-HF Trial)’, Stefan D. Anker from the Charité, Campus Virchow-Klinikum in Berlin, Germany evaluated the benefits and safety of a novel method of left ventricular augmentation with alginate-hydrogel. Alginate-hydrogel is an inert permanent implant that is directly injected into left ventricular myocardium and serves as a prosthetic scaffold to reduce wall stress, modify left ventricular shape and size, and prevent its further enlargement. AUGMENT-HF randomized 40 patients with advanced heart failure and an ejection fraction of 26% to alginate-hydrogel and 38 to standard medical therapy. The primary endpoint was the change in peak
VO_2_ from baseline to 6 months, while secondary endpoints included changes in 6-min walk test distance, symptoms, and echocardiographic parameters, as well as procedural safety. Thirty-five patients were successfully treated with alginate-hydrogel injections through a limited left thoracotomy approach without device-related complications. Thirty-day surgical mortality was 9%. At 6 months, alginate-hydrogel was associated with improved peak VO_2_ and an increase in the 6-min walk test distance and New York Heart Association (NYHA) functional class. The authors conclude that alginate-hydrogel on top of standard medical therapy is more effective than standard medical therapy alone in advanced heart failure and improves exercise capacity as well as symptoms. The results of AUGMENT-HF provide the rationale for a pivotal trial, an aspect that is discussed in an Editorial by G. Michael Felker from the Duke Clinical Research Institute in Durham, NC, USA.

Cardiovascular hospitalizations in patients with heart failure are associated with a high post-discharge rate of early re-admission and death. In the second research paper, ‘Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial’ by Nicolas Girerd and colleagues from the Heart and Vessels Institute of Lorraine in Vandoeuvre-lès Nancy, France hypothesized that the mineralocorticoid receptor antagonists eplerenone might be effective in reducing the incidence of such adverse events during this period. The EMPHASIS-HF trial compared eplerenone with placebo added to standard therapy in 2737 patients with heart failure in NYHA class II and with a left ventricular ejection fraction of ≤ 35%.

Girerd et al. conducted a post-hoc analysis in the 2338 patients randomized within 180 days of a cardiovascular hospitalization. The interaction between the time from the qualifying hospitalization to randomization and the primary outcome of cardiovascular death or hospitalization for heart failure, as well as other secondary outcomes, were assessed. Two-thirds of the qualifying hospitalizations were for heart failure, 17% due to acute coronary syndromes, and 7% for arrhythmias. The median time of study drug initiation from the qualifying hospitalization was 42 days. The relative reductions in death and heart failure hospitalizations were similar whether treatment was initiated before 42 days or thereafter. In the early group, 5.6 events per 100 patient-years were prevented and in the late group 3.6. Adverse effects of eplerenone were also unaffected by the time from the qualifying hospitalization. The authors conclude that eplerenone is safe, improves survival, and prevents readmission, both when initiated soon or when delayed after a hospitalization for heart failure or acute coronary syndromes in patients with systolic heart failure and mild symptoms.

In hypertensive heart disease and coronary artery disease with or without heart failure, renin–angiotensin system (RAS) enzyme inhibitors or RAS antagonists improve outcome. However, severe renal insufficiency to date has been an exclusion criterion in large clinical trials. In another FAST TRACK paper, ‘Association between renin–angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study’ by Lars H. Lund and colleagues from the Karolinska Institutet in Stockholm tested the hypothesis that RAS antagonists are also associated with reduced mortality in heart failure with severe renal insufficiency. To that end, they studied patients with an ejection fraction < 40%. In almost 25,000 patients of which ~ 10% had creatinine levels > 2.21 μmol/L or a creatinine clearance < 30 mL/min, propensity scores for RAS antagonist use were derived from 36 variables. In the matched cohort of 60 patients each, RAS antagonist use was associated with 55% vs. 45% 1-year survival with a hazard ratio of 0.76. In patients without severe renal insufficiency, the matched hazard ratio was 0.79. The authors therefore conclude that in heart failure with severe renal insufficiency, the use of RAS antagonists was associated with a lower all-cause mortality. These findings are critically discussed in an Editorial by Kenneth Dickstein from the Central Hospital in Rogaland in Stavanger, Norway.

Besides coronary artery disease and myocardial infarction, myocardial diseases, of which many are genetic in nature, are a common cause of heart failure. Despite an increased understanding of the genetic basis of dilated cardiomyopathy, the clinical utility of comprehensive next-generation sequencing-based genetic diagnostics in dilated cardiomyopathy remains uncertain. In the third paper, entitled ‘Genetics and genotype-phenotype correlations in Finnish patients with dilated cardiomyopathy’ by Juha W. Koskenvuo and colleagues from the Turku University Hospital in Finland utilized high quality oligonucleotide-selective sequencing (OS-Seq) to investigate the genetics of dilated cardiomyopathy. Using OS-Seq, the authors targeted and sequenced the coding regions and splice junctions of 101 genes associated with cardiomyopathies in 145 unrelated Finnish patients with dilated cardiomyopathy. The authors developed a bioinformatic variant filtering strategy and implemented a strict variant classification scheme to reveal diagnostic yield and genotype-phenotype correlations. Implemented OS-Seq technology provided high coverage of the target region. Diagnostic yield was 35% when both pathogenic and likely pathogenic variants were considered. Of these, 53% were titin truncations, affecting all titin transcripts in 20 cases. Titin truncations accounted for 21% and 15% of the familial and sporadic dilated cardiomyopathy cases, respectively. The authors conclude that panel-based high-quality next-generation sequencing enables high diagnostic yield especially in familial forms of dilated cardiomyopathies, and bioinformatic variant filtering is a reliable step in the process of interpretation of genomic data in a clinical setting.

The editors hope that the readers of the European Heart Journal will find this issue of interest.

References


