An update on heart failure and peripheral arterial disease

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With cardiovascular disease still the most important cause of morbidity and mortality in Western countries, in particular in Europe, heart failure with preserved (HFrEF) or reduced ejection fraction (HFrEF) remain at the centre of interest. Overall, there are many causes which can lead to a failing heart, such as genetic disposition, nutrition, age, hypertension, diabetes, coronary artery disease, and infarction, among others.

An important dietary factor is alcohol, which is consumed in large amounts in various beverages all over the world. Initially considered a health hazard mainly due to its addictive potential and as a cause of liver cirrhosis and pancreatitis, it has recently been recognized that moderate alcohol consumption can actually protect against heart attacks. The protective effects of a low intake of certain alcoholic beverages against myocardial infarction have been documented in large registries, and more recently also in Mendelian randomization studies. This supported the concept of the French paradox in cardiovascular prevention. However, heart failure to date was considered a contraindication even for moderate alcohol consumption. Alcohol is a cardiac toxin and potentially a cause of dilated cardiomyopathy in addicts. Hence, many doctors have recommended abstinence for such patients.

All the more surprising are the results of the first paper of this issue entitled 'Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study' by Scott Solomon from the Brigham and Women’s Hospital in Boston. This is also pointed out by the comprehensive Editorial by David Conen from the University Hospital in Basel, Switzerland which has also been recorded as a podcast for our readers’ convenience. The authors examined 14,629 participants of the Atherosclerosis Risk in Communities (ARIC) study without heart failure at baseline, followed-up for 20 years. Self-reported alcohol consumption was assessed as the number of drinks per week at baseline, and updated cumulative alcohol intake was calculated over almost 9 years. Overall, almost half of the participants were abstainers and a fifth were former drinkers, while a quarter reported consumption of up to seven drinks per week, 8% ≥7–14 drinks per week, and 3% each ≥14–21 and ≥21 drinks per week, respectively. Men consuming up to seven drinks per week had a reduced risk of heart failure compared with abstainers, while this was less prominent in women. Even in the higher drinking categories, the risk of heart failure was not different from that of abstainers of both genders. The authors therefore conclude that alcohol consumption of up to seven drinks per week at early to middle age is associated with lower risk for future heart failure, with a similar, but less robust association in women than in men. Therefore, although heavy drinking is certainly a health hazard, these findings suggest that modest alcohol consumption in early to middle age confers protection against future development of heart failure.

The second paper, 'Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure using olmesartan (SUPPORT) trial' by Hiroaki Shimokawa from the Tohoku University Graduate School of Medicine in Sendai, Japan, which is accompanied by an Editorial by Michael Böhm from the Uniklinikum des Saarlandes in Germany, examined whether an additive treatment with the angiotensin receptor blocker olmesartan reduces mortality and morbidity in hypertensive patients with chronic heart failure already treated with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or both. In a prospective, randomized, open-label, blinded endpoint study, the authors enrolled 1147 hypertensives with symptomatic heart failure and randomized them to the addition of olmesartan or control treatment. The primary endpoint was a composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospitalization for worsening heart failure. During a median follow-up of 4.4 years, the primary endpoint occurred in 192 patients (33.2%) in the olmesartan group and in 166 patients (29.2%) in the control group, while renal dysfunction developed more frequently in the olmesartan group (16.8% vs. 10.7%). A subgroup analysis revealed that addition of olmesartan to the combination of ACE inhibitors and beta-blockers was associated with an increased incidence of the primary endpoint (38.1% vs. 28.2%), of all-cause death (19.4% vs.13.5%), and of renal dysfunction (21.1% vs. 12.5%). The authors therefore conclude that the additive use of olmesartan did not improve clinical outcomes, but worsened renal function in hypertensive patients with symptomatic heart failure treated with evidence-based medication. In particular, the triple combination of olmesartan, ACE inhibitors, and beta-blockers was associated with increased adverse cardiac events. The SUPPORT trial in Japanese patients is
therefore in line with previous trials and current recommendations for the management of hypertensive patients; too much is indeed also too much in hypertensive patients with heart failure.

In the third manuscript ‘Presentation blood glucose and death, hospitalization, and future diabetes risk in patients with acute heart failure syndromes’ by Douglas Lee and colleagues from the University of Toronto in Canada, the authors investigated the prognostic implications of blood glucose on outcomes such as early mortality, hospitalizations, and incident diabetes in acute heart failure. In a population-based cohort of 16 524 acute heart failure patients presenting to the emergency department, the authors analyzed 30-day mortality, new diabetes, and hospitalization. Blood glucose at presentation was divided into five categories, i.e. 3.9–6.1, >6.1–7.8, >7.8–9.4, >9.4–11.1, and >11.1 mmol/L. Among the 9275 acute heart failure patients without diabetes, blood glucose levels >6.1 mmol/L provided an increased risk of total and cardiovascular death. Similarly, diabetics with acute heart failure presenting with glucose >11.1 mmol/L were at increased risk of all-cause death and diabetes-related hospitalizations. Presentation blood glucose >9.4 mmol/L was associated with increased risks of hospitalization for heart failure or cardiovascular causes in all patients. With increasing blood glucose levels at presentation, the risk of incident diabetes also increased. The authors conclude that in patients with acute heart failure, mildly elevated blood glucose levels at presentation in the emergency department are associated with early death, future diabetes, and hospitalizations for diabetes, heart failure, and cardiovascular causes. Thus, blood glucose in acute heart failure should be used for risk stratification and management in the future.

In the fourth paper, ‘Peripheral arterial disease and critical limb ischemia: still poor outcomes and lack of guideline adherence’, Holger Reinecke and colleagues from the University Hospital of Münster in Germany focus on a neglected disease in cardiovascular medicine. As also outlined in a comprehensive Editorial by Iris Baumgartner from the University of Berne in Switzerland, the management and outcome of critical limb ischemia remains an unresolved health issue in spite of the availability of evidence-based guidelines in peripheral arterial disease. All patient diagnosis and procedural data were retrospectively obtained from a cohort of 41 882 patients hospitalized due to peripheral arterial disease during 2009–2011 with a follow-up until 2013. Patients were classified in Rutherford categories 1–3, 4, 5, and 6. Of note, the prevalence of hypertension, dyslipidemia, and smoking declined with the higher Rutherford categories, while that of diabetes, chronic kidney disease, and chronic heart failure increased. Angiographies and revascularizations were performed less often in advanced peripheral arterial disease. In-hospital amputations increased continuously from 0.5% in Rutherford 1–3 to 42% in Rutherford 6, as did myocardial infarction, stroke, and death. Among 4298 amputated patients with critical limb ischemia, 37% had not received any angiography or revascularization either during the index hospitalization or in the 24 months before. During a follow-up of >3 years, 7825 patients underwent amputation surgery and 10 880 died. The 4-year mortality risks in the Rutherford categories were 18.9, 37.7, 52.2, and 63.5%, and for amputation were 4.6, 12.1, 35.3, and 67.3%, respectively. Altogether, peripheral arterial disease severity was a strong predictor of death, amputation, myocardial infarction, and stroke. Similarly, the length of hospital stay and mean case costs increased continuously from low to high Rutherford categories. While only half of the patients suffered from critical limb ischemia, these generated two-thirds of hospital costs. Thus, the authors conclude that regardless of recent advances in the treatment of peripheral arterial disease, outcomes remain poor, especially in critical limb ischemia. Specifically, there is a major underuse of angiographic evaluation and revascularizations.

The first three papers on heart failure are complemented by a Current Opinion entitled ‘Neprilysin, cardiovascular, and Alzheimer’s diseases: the therapeutic split?’ by Alain Cohen Solal from the Hopital Beaujon in Clichy, France. This is a timely topic given the recent publication of the PARADIGM trial in which a combined inhibitor of the angiotensin receptor and of neprilysin [also known as the neutral endopeptidase (EC 3.4.24.11)], a so-called ARNI, is used. Of note, neprilysin is a ubiquitous transmembrane and circulating protease with many substrates such as natriuretic and vasoactive peptides (e.g. endothelin-1, bradykinins), neuropeptides (e.g. substance P, enkephalins), and importantly also the β-amylloid peptide. Given the central role played by neprilysin in the metabolism of cardiovascular peptides and the β-amyloid, neprilysin has emerged as a pharmaceutical target of interest, in the fields of both cardiovascular disease and Alzheimer’s disease. However, the therapeutic strategies in these two fields are opposite. Thus the authors of this Current Opinion piece discuss the safety of neprilysin as a pharmaceutical target in the long term, as the populations suffering from heart failure and Alzheimer’s are overlapping. Similar concerns are raised for the use of ANRIs in hypertensives with HFpEF for which these novel drugs are currently developed.

The issue concludes with a Clinical Review on ‘Cardiac computed tomography in patients with acute chest pain’ by Koen Nieman from the Erasmus Medical Center in Rotterdam, The Netherlands. The efficient and reliable evaluation of patients with acute chest pain in the emergency department remains challenging. Coronary computed tomography (CT) angiography may play a major role in this setting, since it permits fast ruling out of coronary artery disease, if performed properly. Several randomized trials have established cardiac CT as a safe and efficient alternative to functional testing in the evaluation of acute chest pain. Ongoing investigations exploring advanced anatomic and functional assessments, such as high risk coronary plaque, resting myocardial perfusion and left ventricular function, or the simulation of the fractional coronary flow reserve, will add clinically relevant information which would allow expansion of the benefits of cardiac CT from triage to treatment decisions. In particular, the combination of high-sensitive troponins and coronary CT angiography may be a promising approach in the future for the management of patients presenting with acute chest pain.

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

References