

EDITORIAL

I graduated in 1981. Thus, it is difficult not to feel a little bit sad when thinking about the extraordinary steps forward that cardiology witnessed in the previous decades. Current treatments of all major cardiovascular diseases still seem to be founded on those great achievements. However, cardiology is still moving forward and major changes have occurred, including in this last year, which may, in fact, be more than in the years before. Without any pretense of being comprehensive, I will just take this occasion to briefly present some of these impressive advances.

Prevention

Dyslipidemia. Major advances occurred in the treatment of dyslipidemia and diabetes. The REDUCE-IT trial showed that administration of a high-dose highly purified eicosapentaenoic acid ethyl ester to patients with established cardiovascular disease or diabetes, high triglycerides, and low LDL cholesterol levels reduced plasma triglycerides and, more importantly, major adverse cardiovascular events (MACE), cardiovascular death, stroke, or myocardial infarction (MI) by 25%. These results are in marked contrast with the neutral results of trials with n-3 fatty acids that had no effect on MACE in the ASCEND and VITAL trials in 2018, and they might be explained by the drug's anti-inflammatory and antiplatelet actions and by lowering triglyceride levels.

Hypercholesterolemia. In 2018, the second major trial of PCSK-9 inhibition with a human monoclonal antibody, the ODISEY trial, was concluded. The administration of alirocumab led to a 1.6% reduction in the rate of MACE in patients with a previous acute coronary syndrome and with LDL cholesterol levels ≥ 70 mg/dL, non-HDL cholesterol levels ≥ 100 mg/dL, or apolipoprotein B levels ≥ 80 mg/dL despite high-dose statin therapy. Practical recommendations for the use of PCSK-9 inhibitors were also published.

Diabetes. In 2018, confirmation of the favorable effects of SGLT2 inhibitors on cardiovascular outcomes was obtained. In previous trials in diabetic patients at high cardiovascular risk, both empagliflozin and canagliflozin reduced cardiovascular death and heart failure (HF) hospitalizations. These beneficial effects were confirmed this year with dapagliflozin in the DECLARE-TIMI 58 trial. SGLT2 inhibitors have neutral effects on nonfatal stroke or MI and their favorable effects are specific for cardiovascular death and, namely, HF events. There is the potential for favorable effects in patients with HF, independently of concomitant diabetes; this hypothesis is being tested in ongoing trials.

Antithrombotic strategies. When used in primary prevention, aspirin did not reduce cardiovascular events and increased the hemorrhagic risk, even in subjects at high risk, such as those with diabetes (ASCEND trial) or the elderly (ASPREE

trial). New avenues for antithrombotic treatment in secondary prevention were opened by the COMPASS trial, where the combination of low-dose rivaroxaban and aspirin led to a reduction in MACE (primary end point) and deaths, compared with aspirin alone, in patients with chronic atherosclerotic vascular disease.

Imaging

Major progress occurred with all imaging modalities, including (i) echocardiography, where global longitudinal strain established its role as an early measurement of left ventricular (LV) systolic dysfunction; (ii) cardiac magnetic resonance (CMR), with major studies about tissue characterization, T1 mapping, and extracellular volume assessment; (iii) coronary computed tomography (CT); (iv) nuclear imaging with quantitative coronary flow measurement and perfusion imaging with positron emission tomography (PET); and (v) fusion imaging with CMR/PET and CT/PET showing the relation between anatomical and functional abnormalities. In 2018, the results of the SCOT-HEART trial were presented and published, showing that patients who were referred to outpatient clinics for stable angina and received standard treatment, mainly based on exercise electrocardiography, plus coronary CT had a reduction in the primary end point of death or MI, mainly driven by a reduction in nonfatal MI, during a 5-year follow-up vs patients who received standard therapy alone. Interestingly, no difference in the revascularization procedures between treatment arms was observed at 5 years, suggesting that the beneficial effects of coronary CT were mainly caused by better secondary prevention.

Arrhythmias, valve disease, and heart failure

These three topics were tightly related in 2018 and, more than ever, results of major trials were extremely stimulating, although, to some extent, not conclusive. Atrial fibrillation (AF) and HF often coexist, but it is unproven whether AF treatment affects HF outcomes. This hypothesis was tested in CASTLE-AF where patients with paroxysmal or persistent AF, HF, and a LV ejection fraction (EF) $\leq 35\%$ who underwent AF ablation were almost 3-fold more likely to be in sinus rhythm during follow-up. AF ablation was associated with a reduction in the primary composite end point of all-cause death or worsening HF compared with conventional treatment during a median follow-up of 37.8 months; in addition, death and HF events alone were reduced in the AF ablation group. In addition to CASTLE-AF, the larger CABANA trial compared AF ablation with conventional treatment in patients with AF >65 years old or, if <65 years old, with ≥ 1 risk factor for stroke. There were no between-group differences in the primary end point, a composite of death, disabling stroke, serious bleeding, or cardiac arrest, and there was no difference in cardiovascular mortality. Limitations have been discussed for both of these trials and the effects of AF ablation on cardiovascular outcomes need to be shown in further trials, with quality of life as the main indication for AF ablation.

There is an even greater controversy regarding the results of two major outcome trials on the percutaneous treatment of secondary mitral regurgitation (MR) in HF patients with the MitraClip device. Secondary MR is associated with poorer outcomes in HF patients. Percutaneous treatment with the MitraClip device was effective in reducing MR, well tolerated, and associated with an improvement in quality of life measurements in observational studies. However, outcome data can only come from prospective, controlled, trials. Unfortunately, the results of two studies, concluded in 2018, could not be more different. In MITRA-FR, MR was reduced to ≤ 2 in 90% of the patients with HF, secondary MR, and reduced LVEF (15% to 40%) who were randomized to optimal treatment and MitraClip vs those randomized to ongoing optimal treatment with drugs and cardiac resynchronization therapy, if indicated. However, there was no difference in the primary end point of death or HF hospitalization at 12 months, death alone, and hospitalization alone. In addition, symptoms improved to a similar extent in both groups. In contrast, the COAPT trial showed that conventional treatment plus MitraClip reduced HF hospitalizations and all-cause mortality (primary end point), improved quality of life, functional capacity, and MR, and reduced LV volumes (prespecified secondary end points) in patients with HF and secondary MR at 2 years vs optimal conventional treatment with drugs. While it seems unlikely that the differences between the two trials regarding sample size, follow-up duration, and primary end points can explain the differences observed in the results, perhaps the differences in the inclusion criteria (ie, smaller effective regurgitant orifice area and larger LV volumes) and patient selection may explain the differences. Another randomized outcome trial, Reshape-HF-2, with a composite of cardiovascular death or HF rehospitalizations as the primary end point, is ongoing.

Heart failure

HF remains a major cause of morbidity and mortality; its impact was further shown by the 2018 publication of the National Audit of HF in England and Wales, a large epidemiological study with >500 000 patients. This study confirmed the increase in HF hospitalizations in the last decade with a persistently poor prognosis. The inpatient mortality and the 3-year mortality were about 5% and 30%, respectively, for patients <75 years old and they increased to 12% and 60%, respectively, for those >75 years old. The benefits of medical treatment with the association of ACE inhibitors/ARBs or ARNI and β -blockers and mineralocorticoid antagonists and ivabradine, when indicated, was confirmed in 2018 by meta-analyses and observational studies. Further indirect confirmation of the role of medical treatment came from the TRED-HF trial. In this study, 51 patients with recovered dilated cardiomyopathy and no symptoms, LVEF >50%, normal LV end-diastolic volume, and low BNP values were randomized to continuation of ongoing treatment or its withdrawal. Treatment withdrawal was associated with worsening LV function and an increase in heart rate and NT-proBNP values in 40% of the patients, showing that the disease is never fully “cured” and is ongoing in a significant proportion of our patients.

After the PIONEER trial, which studied sacubitril/valsartan vs enalapril initiated in patients hospitalized for HF, and other studies showing the importance of drug compliance and adherence to evidence-based treatment, neurohormonal antagonist treatment may undergo a potential widening of the indications of ARNI to hospitalized patients. Major advances in HF treatment may come from (i) the treatment of comorbidities, such as AF and MR (see above); (ii) the administration of SGLT2 inhibitors; or (iii) the treatment of iron deficiency (ongoing trials). The most positive results have come from treating transthyretin amyloidosis with tafamidis in the ATTR-ACT trial, which showed that patients with transthyretin amyloid cardiomyopathy who were treated with tafamidis (80 mg or 20 mg) had a lower rate of all-cause mortality and cardiovascular hospitalizations vs placebo. These favorable effects on outcomes were also accompanied by a lower rate of decline in the 6-minute walk test distance and quality of life.

Further results regarding devices, from simpler devices (eg, cardiac contractility modulation or an interatrial septal device to reduce left atrial pressure) to new LV assist devices, were presented in 2018. The 2-year outcomes of the MOMENTUM-3 trial showed that the new magnetically levitated centrifugal continuous-flow circulatory pump increase the survival free of disabling stroke and reduced the overall rate of stroke, and it also led to fewer reoperations for pump malfunctioning compared with the mechanical-bearing axial continuous-flow pump.

Conclusions

Major advances occurred in the diagnosis and treatment of cardiovascular disease in 2018 and this short editorial is not meant to summarize or even rank them at all. As a general consideration, we may note a gradual shift toward a more focused treatment, targeting the specific abnormalities in each single patient. At a simpler level, this concerns specific mechanisms of cardiovascular risk as well as of disease severity and progression, as is the case of cardiac and noncardiac comorbidities in HF patients. However, greater granularity may be foreseen in the future with the advances in imaging modalities and biomarkers, allowing greater accuracy and, hence, efficacy.

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