European Society of Cardiology (ESC) Congress 2020

The digital experience

Learning objectives
You will learn:

• Updated ESC guidelines on the management and treatment of atrial fibrillation, as well as ACS in non-STEMI; most recent clinical trial findings on treatment of these conditions in subpopulations
• Current trial data on the role of SGLT-2 inhibitor therapy in reducing cardiovascular events
• Newest findings on the treatment of valvular heart disease, cardiomyopathies, acute pulmonary embolism and patent foramen ovale.

Introduction
The 2020 ESC congress was presented as a four-day online programme with no registration fee required; it was hosted on ten concurrent channels and attracted 115 000 attendees. Many presentations were pre-recorded while others were live. As is the tradition, new guidelines were issued during the meeting: these related to atrial fibrillation (AF), acute coronary syndrome (ACS) due to non-ST segment elevation myocardial infarction (non-STEMI), sports cardiology and exercise, and adult congenital heart disease. The full texts of these guidelines are available at https://programme.escardio.org/ESC2020/Full-Programme

Hypertension

The Blood Pressure Trialists’ Collaboration performed a meta-analysis of 48 trials including 348 854 participants, who were treated for hypertension for either primary or secondary prevention. It was concluded that for each 5mmHg reduction in systolic blood pressure (SBP), the same degree of benefit was achieved in those with and without established cardiovascular disease. A 5mmHg reduction in SBP resulted in reductions of fatal and non-fatal stroke (13%), myocardial infarction (MI) (7%), heart failure (HF) hospitalisation (14%) and cardiovascular death (5%). The relative benefit was similar at all levels of blood pressure from <120mmHg to ≥170mmHg. Dr Rahimi suggested that the decision to prescribe blood pressure lowering medication should not be based simply on a prior diagnosis of cardiovascular disease or an individual’s current blood pressure, but rather be used as risk-modifying treatment for the prevention of incident or recurrent cardiovascular events regardless of the blood pressure at baseline. He also noted that despite the relative benefit being similar for all patients, it did not imply that everyone should receive treatment.
Atrial fibrillation

The 2020 ESC guideline on AF focuses largely on practical matters relating to the detection of the arrhythmia and a comprehensive approach to its management. The guideline defines AF as an arrhythmia which lasts at least 30 seconds or is recorded throughout the 12-lead ECG. Screening for AF should be conducted particularly in those with suggestive symptoms and the elderly. The detection of atrial high-rate episodes on a pacemaker does not necessarily imply the presence of AF. Currently, there is no clear indication for treatment of these episodes.

The AF guideline advocates a CC–ABC mnemonic:
- **C**onfirm the arrhythmia
- **C**haracterise the problem in relation to 4 S’s – *Stroke risk* – *Severity of symptoms* – *Severity of the AF burden* – *Identification of the Substrate*

Planning the clinical approaches to:
- **A**nticoagulation
- **B**etter rhythm control
- **M**anagement of Cardiovascular risk factors and **C**omorbidities.

The dynamic nature of AF requires regular re-evaluation of the management plan. The default approach is to anticoagulate all patients unless they are shown to be at low risk. When a high bleeding risk is identified, an attempt should be made to eliminate the modifiable factors in addition to enabling more frequent review of the patient’s case. There was strong emphasis on the necessity for lifestyle change, particularly weight reduction, exercise and moderation of alcohol intake. Physical rehabilitation should be considered. Additional medication may include angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockade and statin treatment. There are no new additions to antiarrhythmic drugs in the guideline. Class II agents are recommended in the absence of structural heart disease. Digoxin or beta-blockade is recommended in patients with HF. Amiodarone was accorded a lower priority. The use of antiarrhythmic drugs is inappropriate when reversion to sinus rhythm cannot be anticipated.

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The ELDERCARE-AF trial showed that very low-dose edoxaban was superior to placebo in reducing stroke and systemic embolism among Japanese patients older than 80 years and with very low weight (median 50.6kg). Treated patients received 15mg edoxaban per day (25% of standard dose). Stroke and systemic embolism occurred in 2.3% of the treated group versus 6.7% on placebo. Both ischaemic stroke and haemorrhagic stroke were reduced by treatment. Major bleeding occurred in 3.3% of treated patients versus 1.8% in those on placebo, with no excess in intracranial bleeding; gastrointestinal bleeding occurred in 2.3% versus 0.8%, respectively. It is unclear whether similar elderly patients with a higher body weight would respond in similar fashion.

The RATE-AF study included an aged population of whom 50% were in permanent AF; half of those had HF. The study included 160 patients with an NT-proBNP >1 000 who were followed for six months. Treatment with a beta-blocker, as compared to digoxin, showed similar heart rate control and no differences were noted in quality of life. At 12 months there was >50% improvement on digoxin in comparison to beta-blockade, with a greater reduction in HF, a larger fall in NT-proBNP, a lesser incidence of adverse events and no increase in mortality.

The IMPACT-AF study was of elderly patients (average age 77 years) with AF who received a single educational intervention instructing them about AF and the need for oral anticoagulation. These patients, identified through their pharmacy claims, had a baseline oral anticoagulant use of 67%. After one year there was no significant difference in those who received the information and those who did not. The reviewers proposed that a greater benefit might have been achieved by increasing the number of interventions during the year.

In the EAST-AFNET 4 trial a strategy of rhythm control was compared to usual care in 2 789 patients older than 70 years who had experienced a stroke or transient ischaemic attack (TIA) and who had had AF for less than a year. The median time of enrolment after AF detection was 36 days. HF was present in 29% of patients and 11% had previously had a stroke or TIA; 90% received oral anticoagulants and 80% were on a beta-blocker. The initial rhythm control strategy was flecainide in 36% of the patients, amiodarone in 20%, and AF ablation in 8%. The
The rhythm control strategy was associated with a 28% reduction in cardiovascular death and a 35% reduction in stroke. Reductions in HF hospitalisation, ACS, nights in hospital, improvements in ejection fraction, and all-cause mortality were noted. Of patients in the rhythm control arm, 82.1% were in sinus rhythm versus 60.5% in the usual care group. Adverse event rates were 4.9% with rhythm control versus 1.4% with usual care.

In the CASA-AF6 trial, 120 patients with long-standing (>2 years) persistent AF were submitted to either thoracoscopic surgical ablation or transvenous catheter ablation of their AF. The average age of patients was 61 years, 75% were males. There was no difference in freedom from AF between the two techniques, although the surgical ablation required a longer hospital stay. It was concluded that catheter ablation should be recommended as the initial intervention.

Cryoballoon ablation in patients with symptomatic paroxysmal AF was compared to antiarrhythmic drug therapy in about 200 drug-naïve patients in the STOP AF7 study. At 12 months, the freedom from atrial arrhythmia in the ablation group was 75% versus 45% on an antiarrhythmic. There was a low incidence of adverse events.

Heart failure

SGLT-2 inhibitors

Last year the DAPA-HF8 trial of dapagliflozin reported reductions in cardiovascular events in patients with HF, both with and without diabetes. One year on, substudies have shown the effectiveness of SGLT-2 inhibitors across the entire range. The effect is independent of the level of HbA1c and there is no effect on HbA1c in patients without diabetes. Dapagliflozin benefit was seen whether given with or without concomitant sacubitril-valsartan. There is a rapid onset of benefit with a 27% reduction in the incidence of worsening HF. Whereas there was a progressive rise in NT-proBNP on placebo, NT-proBNP was reduced with dapagliflozin. Although dapagliflozin initially decreased the eGFR, the reduction was transient and a 44% reduction in the rate of doubling of the serum creatinine was recorded. The treatment was safe. Hypoglycaemia and normoglycaemic diabetic ketoacidosis were rare in patients without diabetes. There was a low incidence of volume depletion. There were no interactions between dapagliflozin and the range of drugs used to treat HF.

The EMPEROR-REDUCED9 trial of empagliflozin included 3 730 patients with and without diabetes with an ejection fraction <30% and/or a raised proBNP, of whom 20% were treated with sacubitril-valsartan. Between 8% and 9% of patients discontinued medication. There was a 99% follow-up. Cardiovascular death and hospitalisation for HF were reduced by 25%. There was an 8% reduction in cardiovascular death. The incidence of sudden death declined even in those who had an implantable cardioverter defibrillator (ICD). The rate of decline in kidney function was reduced and quality of life was improved. This trial did not show a reduction in all-cause mortality.

The VERTIS CV10 trial enrolled about 8 000 patients. Ertugliflozin 5mg and 15mg were compared to placebo. On treatment, body weight was reduced by 2.2kg, SBP by 2.3mmHg and HbA1c by 0.5%. There was no difference in major adverse cardiovascular events (MACE). A 17% lower incidence of cardiovascular death and hospitalisation for HF was noted; the latter was reduced by 30%.

Yet another study involving an SGLT-2 inhibitor was the DAPA-CKD11 study, which included 4 304 patients with chronic kidney disease whose eGFR was 25-75ml/min/1.73m² and who had a urinary albumin-creatinine ratio of 300-500mg/g. Follow-up was terminated after 2.4 years. In comparison to placebo, dapagliflozin 10mg daily resulted in a 33% reduction in the combined endpoint of the rate of decline of the eGFR, renal death and cardiovascular death. The number needed to treat was 19. There was a 44% reduction in end-stage kidney disease. Cardiovascular death was not significantly reduced. Despite this, all-cause mortality declined by 31%.

SGLT-2 therapy is now shown to be effective in diabetes, in HF and in chronic kidney disease.
It was proposed that SGLT-2 inhibition should henceforth be incorporated as one of the four pillars of HF treatment along with neprilysin (NEP) inhibition, which has been shown to be superior to renin-angiotensin-aldosterone system (RAAS) inhibition, as well as treatment with mineralocorticoid antagonists and beta-blockers. There is little doubt that SGLT-2 inhibition will shortly be included in the HF guidelines.

**NEP inhibition**

The search for effective treatment for patients with HF with preserved ejection fraction continues. In the PARALLAX study, 2,566 patients with HF with an ejection fraction >40% were treated with sacubitril-valsartan or placebo. Although NT-proBNP was reduced, there was no effect on quality of life or any significant effect on cardiovascular outcomes.

**Atherosclerotic cardiovascular disease**

The REDUCE-IT trial of eicosapent ethyl treatment in patients with atherosclerotic disease, an LDL cholesterol of 1.0-2.0mmol/l, and persistently raised serum triglycerides on statin treatment, showed an absolute 5% reduction in cardiovascular death, MI and stroke. There was a 13% nonsignificant reduction in all-cause mortality. Coronary revascularisation was reduced by 34%. The effect of treatment was observed across the entire range of triglyceride elevation. The changes observed in LDL cholesterol and C-reactive protein did not influence the outcome. The improved outcome was proportional to the change in serum eicosapentanoic acid and could not be accounted for entirely by the reduction in triglyceride levels. The treatment was shown to be highly cost-effective. The subsequent EVAPORATE study demonstrated a reduction in plaque volume with the treatment. It was noted that over-the-counter fish oil supplements do not have a similar effect as they have a high saturated fat content.

**Chronic coronary syndromes**

The CLARIFY study evaluated the evolution of angina. It was found that 40% of patients had no symptoms at one year, 15% developed angina between one and two years and 46% of patients had no symptoms at five years. While many patients may lose their symptoms, persistent symptoms are associated with a higher incidence of MI and death.

The Australian LoDoCo trial in 5,522 patients with chronic coronary artery disease evaluated colchicine 0.5mg daily versus placebo. Over two-and-a-half years the incidence of MI was reduced from 4.2% to 3.0%, ischaemia-driven revascularisation from 6.4% to 4.9% and cardiovascular mortality from 0.9% to 0.7%. Despite these findings, all-cause mortality increased from 2.2% to 2.6% with a 51% increase in non-cardiovascular deaths. A similar increase in non-cardiovascular death has been noted in previous trials of colchicine.

Trimetazidine is an antianginal medication approved in Europe. The agent is devoid of haemodynamic effects and favours the production of free fatty acids from glucose. In the ATPCI study in patients with stable angina or after non-STEMI, trimetazidine 35mg BD was compared to placebo in 6,059 patients who had angina class 2-4 following percutaneous coronary intervention (PCI) who were treated intensively with secondary preventive medications, including RAAS inhibitors, beta-blockers and statins. There was no effect upon the combined endpoint of cardiac death, hospitalisation for a cardiac event or recurrent angina after five years of follow-up.

**Acute coronary syndromes**

The ACS in non-STEMI ESC 2020 guideline recognises a predictive value of high-sensitivity troponin >20ng/l. The positive predictive value is 50-60% when the troponin level is three times above normal, and very high when five times above normal. The
The current guideline recommends prasugrel in preference to ticagrelor in patients undergoing percutaneous revascularisation. This follows the results of the ISAR-REACT 5 publication demonstrating that prasugrel reduced combined ischaemic events with an equivalent frequency of bleeding. P2Y12 inhibition should not be given prior to coronary intervention. The current guideline recommends prasugrel in preference to ticagrelor in patients undergoing percutaneous revascularisation. This follows the results of the ISAR-REACT 5 publication demonstrating that prasugrel reduced combined ischaemic events with an equivalent frequency of bleeding. Extended dual antiplatelet therapy (DAPT) may be considered in high-risk individuals who do not have a high risk of bleeding. In patients with AF with an indication for long-term oral anticoagulation, triple therapy should be given for a short period. After seven days, aspirin may be withdrawn and, if the patient is treated with a non-vitamin K antagonist oral anticoagulant (NOAC), dual therapy in combination with clopidogrel is recommended. Antiplatelet therapy may be withdrawn 12 months after intervention if the patient is receiving a NOAC.

Peripheral arterial disease

The THEMIS trial randomised patients with diabetes and stable coronary artery disease to treatment with aspirin or aspirin and ticagrelor. Although the overall trial showed no net benefit due to an increase in bleeding, those patients who underwent PCI benefited.

Valvular heart disease

The POPULAR TAVI trial in 665 patients with an average age of 80 years compared aspirin alone to aspirin plus clopidogrel following valve implantation. There was a marked increase in bleeding with DAPT. All bleeding increased from 26% to 55% and major bleeding from 5% to 11%. There were no differences in stroke or MI. Between 10-13% of all patients were receiving concomitant oral anticoagulation. The trial supports the use of single antiplatelet therapy with aspirin following transcatheter aortic valve implantation.
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The gradient was completely relieved in 27% of patients and accompanied by an 80% fall in NT-proBNP and a 42% reduction in troponin-T. Of the treated patients, 27% were in NYHA class I at the end of the study. The treatment effect appears to be independent of the hypertrophic cardiomyopathy genotype.

Amyloidosis occurs in two forms: the so-called AL amyloidosis that is associated with plasma cell dyscrasia, and transthyretin or TTR amyloidosis which is separated into wild-type and mutant amyloidosis. A familial form occurs in 3-4% of persons of West African origin. The transthyretin forms are distinguished by TTR genetic testing. Differentiating between AL and TTR amyloidosis is important as there is specific treatment for each type. The echocardiogram shows symmetrical and often severe LV hypertrophy. MRI scanning may be useful, but technetium pyrophosphate bone scintigraphy showing an increased myocardial uptake is highly specific. Patients suspected of having amyloidosis should have their serum and urine tested for gammopathy. There is a very limited requirement for cardiac biopsy to confirm the diagnosis, although salivary gland biopsy should be considered. Genetic testing for transthyretin usually entails significant delay in obtaining a result. While genetic testing should not be overlooked, the diagnosis can be reached sooner using other non-invasive tests. AL amyloidosis constitutes a medical emergency requiring definite confirmation before commencement of chemotherapy. In these patients a cardiac biopsy may be necessary; however, interpretation of the cardiac biopsy requires specific expertise and specialised technology.

Patients with cardiac amyloid have frequently received treatment for HF prior to diagnosis. These patients will not respond to standard anti-failure therapy. It is recommended that beta-blockers and ACE inhibitors be discontinued, recognising that the amyloid heart has a reduced stroke volume and increased stiffness rendering the cardiac output heart-rate dependent. As these patients are at risk of complete heart block and ventricular arrhythmia, cardiac resynchronisation therapy (CRT)-ICD implantation should be considered. Tafamidis 80mg daily is the specific treatment for TTR cardiac amyloid. In certain patients the hepatic production of transthyretin can be inhibited by the so-called ‘silencers’ inotersen or patisiran. Given the multiple manifestations of amyloidosis, these patients are best dealt with by a multidisciplinary team.

Acute pulmonary embolism

By applying two risk stratification scores (HESTIA or PESI) to patients with acute pulmonary embolism, it was shown that those at low risk who were discharged home for outpatient care constituted 40-50% of the entire group. The HESTIA rule was non-inferior to the PESI score. All-cause death and recurrent venous thromboembolism or major bleeding at 30 days occurred, respectively, in 3.8% and 3.6% of those patients treated at
Patent foramen ovale

Controversies around the closure of patent foramen ovale (PFO) were discussed. Following a patient’s presentation with TIA or stroke, the detection of a PFO should not eliminate the search for an alternative cause. Although closure is a low-risk procedure, it may precipitate AF in around 5% of patients. It was agreed that defects >5mm should be closed although the estimation of size is problematic. The amount of bubbles passing from right to left across the interatrial septum is used to estimate size of the PFO, but this may be highly dependent upon the technique used. Women seem to benefit less from closure. PFO closure in patients older than 60 years may be considered if all other possible precipitating factors for the TIA or stroke can be excluded. There remains uncertainty around the value of antiplatelet therapy or anticoagulation as an alternative to closure.

RAAS inhibition in COVID-19

The BRACE CORONA study involved 659 patients with mild-to-moderate COVID-19 infection who had hypertension and were on treatment with either an ACE inhibitor or an angiotensin receptor blocker. At baseline, 35% of patients were obese and 30% had diabetes. These patients were randomised to continued RAAS inhibition or withdrawal of those agents. The endpoint was the number of patients alive and out-of-hospital at 30 days. There were no differences in mortality. Reviewers concluded that there is no indication to withdraw RAAS inhibitors in patients presenting with mild-to-moderate COVID-19 infection.

Key learnings

- The ESC has updated their guidelines for the treatment and management of AF, ACS in non-STEMI, sports cardiology and exercise, and adult congenital heart disease
- Current findings of numerous trials on the treatment of AF
- Data from numerous trials further elucidating the cardiorenal protective effects of SGLT-2 inhibitor therapy
- Current trial data on the management and treatment of chronic coronary syndromes, ACS, valvular heart disease, cardiomyopathies, acute pulmonary embolism and PFO
- There is no indication to withdraw RAAS inhibitors in patients present with mild-to-moderate COVID-19 infection.
References
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2. Okumura K. ELDERCARE-AF: Edoxaban 15 mg for elderly Japanese AF patients ineligible for standard anticoagulants.
3. Kotecha D. RATE-AF: Rate control therapy evaluation in permanent atrial fibrillation.
6. Haldar S. CASA-AF RCT - Catheter ablation versus thoracoscopic surgical ablation in LSPAF.
7. Wazni O. STOP AF First: Cryoballoon catheter ablation as a first line treatment for paroxysmal atrial fibrillation.
8. Docherty K. The effect of dapagliflozin across the spectrum of baseline risk: a post-hoc analysis of DAPA-HF.
10. Cosentino F. VERTIS CV Heart failure failure results.
12. Pieske B. PARALLAX: Sacubitril/valsartan versus individualized RAAS blockade in patients with HFrEF.
17. Ferrari R. ATPCI - Trimetazidine in angina patients with recent successful percutaneous coronary intervention: a randomized, double-blind, placebo-controlled trial.
22. Bonaca M. THEMIS-PAD ticagrelor in patients with and without peripheral artery disease.
23. Brouwer J. POPULAR TAVI - Aspirin with or without clopidogrel after transcatheter aortic valve implantation.
25. RELAX-PE study: real-life validation of the age-adjusted D-dimer cutoff to exclude PE.