THE ANNUAL MEETING OF THE EUROPEAN SOCIETY OF CARDIOLOGY (ESC)

Fira, Barcelona, Spain – 26-30 August 2017

The European Society of Cardiology’s annual meeting took place from 26 to 30 August in Barcelona and was attended by 32 000 cardiologists and other health care professionals from 147 countries. This meeting took place a week after the terror attack on the Ramblas. Although there was increased security at the meeting venue, it did not detract from the proceedings.

KEY MESSAGES

- Technology used by patients, e.g. personalised hand-held mobile devices, will alter the relationship between physician and patient as the latter become better informed about their disease
- Lower total mortality in the PURE study was associated with moderate intake of vegetables and fruit, moderately increased proportions of fat and lower intake of carbohydrates
- Celecoxib is associated with less elevation of blood pressure and the lowest incidence of developing hypertension, as compared to ibuprofen and naproxen
- Incliseran, a PCSK9 inhibitor given in thrice-yearly injections, maintains a 50% reduction in LDL cholesterol
- Dynamic changes in hs-troponin levels are the most sensitive means of detecting myocardial ischaemia, as opposed to the use of cut-off values only
- In post-acute coronary syndrome (ACS), the de-escalated use of clopidogrel after one month of prasugrel, showed no increment in ischaemic events in clopidogrel responders and a non-significant lesser bleeding risk
- The result of the COMPASS secondary prevention trial that added low-dose rivaroxaban to aspirin vs aspirin alone supports the concept that atherothrombotic events do not depend solely on platelet activation but also result from thrombin generation
- The CANTOS study of canakinumab, an interleukin 1 (IL-1) beta antibody, proves the concept that complications of atherosclerotic cardiovascular disease can be reduced by suppressing inflammation.

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Changing professional/patient relationships

Dr Eric Topol’s (USA, Scripps Health) opening address examined the developments in personalised and digitised medicine. He foresees that with the ability to perform genetic testing at relatively low cost coupled with the increasing capacity of hand-held mobile devices to monitor a variety of vital functions and perform ultrasound with ever greater clarity, the knowledge that patients can and will acquire about their own disease will impact upon the traditional doctor-patient relationship. This will soon change the current situation where the doctor maintains exclusive knowledge of the diagnosis and treatment plan, information that is not always communicated to the patient.

New ESC guidelines

New guidelines unveiled at the ESC this year covered acute myocardial infarction (MI) and ST-elevation myocardial infarction (STEMI), peripheral arterial disease and valvular heart disease, and included a focused update on dual antiplatelet therapy (DAPT) in coronary artery disease. The full text of these documents can be found at escardio.org/guidelines. In particular, the focused update on DAPT merits careful reading as it sets out recommended practice in a number of situations in which the indication, specific agent, duration of treatment, and the assessment of whether to combine DAPT with oral anticoagulation have required clarification.

Late-breaking clinical trials

The major presentations at the congress concerned:

1. The safety and efficacy of adding rivaroxaban to aspirin as secondary prevention in patients with established coronary or peripheral artery disease (COMPASS).

2. The safety and efficacy of adding the IL-1 beta antibody, canakinumab, to excellent secondary prevention in stable coronary artery disease patients with an hs-CRP >2mg/l (CANTOS).

Prevention and lifestyle

The PURE study is a large multinational study including 135 335 individuals. It covers most areas of the world, including South Africa and Zimbabwe. Two presentations from this study dealt with diet. Diet composition was assessed from a single questionnaire at the outset of the study. Subjects were followed up to assess their total mortality and the development of major cardiovascular disease. Neither the first presentation on fruit and vegetable content nor the second on fat and carbohydrate content found any relationship with cardiovascular disease whereas total mortality was less with a moderate intake of (especially raw) vegetables and fruit, less with increasing proportions of fat (polyunsaturated and mono-unsaturated fats having a greater effect than saturated fat) and greater with increasing proportions of carbohydrates. Dietary legumes were shown to affect both total mortality and cardiovascular disease. The commentary on these intriguing results was that they should be interpreted with caution as PURE is an observational study and the proportions of fat in the diet, although greater than recommended amounts, were not excessive.

Hypertension

Determination of the ideal diastolic blood pressure from the HOPE 3 study suggests that the best on-treatment results are obtained when a systolic blood pressure of 130-140mmHg and diastolic of 75-80mmHg are reached. The J-curve was important only in the presence of cardiovascular disease. Similar results were found in a study from Taiwan. On treatment, blood pressure <120mmHg systolic and <70mmHg diastolic in patients with coronary artery disease was associated
with an increased risk of morbidity and mortality of 40-50%.

Spironolactone may be superior to other agents in reducing blood pressure in patients with resistant hypertension. A similar effect on office blood pressure has been observed with amiloride 10-20mg daily.

SPYRAL HTN-OFF MED\textsuperscript{2} was a proof-of-concept trial. Forty hypertensive patients with blood pressure 150-180mmHg systolic and >90mmHg diastolic were submitted to renal denervation with a spiral catheter while off treatment and compared to a sham-operated group. Both main renal arteries and their accessible branches were treated. Follow-up was for three months. Systolic and diastolic office blood pressure were reduced 7.7mmHg and 4.9mmHg, respectively, compared to sham-operated controls.

**Arthritis medication and hypertension**

In the PRECISION trial,\textsuperscript{3} changes in 24-hour ambulatory blood pressure over four months in 450 of the 24 000 patients with arthritis randomised to celecoxib 100-200mg bd, ibuprofen 600-800mg tds or naproxen 375-500mg bd, show that celecoxib is associated with the least elevation in blood pressure and the lowest incidence of developing hypertension. In the main trial, pain relief was equivalent in the three groups. Adverse events were lowest with celecoxib, including gastrointestinal side-effects and iron deficiency.

**Lipid-lowering therapy**

There were a number of discussions on the application of PCSK9 inhibitor treatment with evolocumab as shown in the FOURIER study. Dr RP Giugliano (Boston, US) presented a subgroup analysis of the trial which shows the efficacy and safety of treating LDL cholesterol to very low levels (<0.5mmol/l) which suggests that LDL treatment targets should be considerably below current values.

In the GLAGOV study, there was no change in the plaque composition with evolocumab, despite the reduction in plaque volume that was demonstrated.

Dr K Ray (London, UK) reported that inclisiran, an alternative and potentially much less expensive PCSK9 inhibitor, injected thrice-yearly (at onset, 90 days and 270 days) maintains a 50% reduction in LDL cholesterol.

Dr BA Ferrence (Plymouth, USA) investigated an untreated population in which subjects could be randomised according to their genetic propensity to
the presence or absence of cholesteryl ester transfer protein (CETP) inhibition and similarly to HMG-CoA inhibition. In those with dual inhibition, although HDL cholesterol was higher and LDL cholesterol was lower, the effect on apolipoprotein A was attenuated; this suggests that there may be a discord in the effects when lowering LDL cholesterol with a statin concurrently with CETP inhibition. The altered response in lipid particles might account for the previous lack of success of CETP inhibitor trials.

REVEAL\textsuperscript{5} was a trial to investigate the effects of the CETP inhibitor, anacetrapib (100mg once daily) in 30 000 patients over 50 years of age with atherosclerotic cardiovascular disease on treatment with atorvastatin 20-80mg daily and an average baseline LDL cholesterol of 1.6mmol/l. HDL cholesterol was raised 104\% in the treated group. LDL cholesterol fell only 0.3mmol/l. Patients were followed for four years. There was a 9\% reduction in the primary endpoint (coronary death, MI or coronary revascularisation) with no reduction in coronary deaths. A small decrease in new-onset diabetes was noted, as well as a minor increment in blood pressure and minor decrease in kidney function. The doubling of HDL was not considered to have affected the endpoint. Dr J Chapman (Paris, Frans) commented that anacetrapib (and potentially other CETP inhibitors) might raise the ‘wrong’ HDL particles, large particles rich in cholesterol along with the creation of very small LDL particles that are atherogenic.

EMPATHY was a Japanese study of some 5 000 patients with diabetic retinopathy but no history of coronary artery disease or stroke who were treated with statins to one of two targets: LDL cholesterol <1.8mmol/l or the Japanese guideline standard of <3mmol/l. On-treatment LDL cholesterol was 2mmol/l and 2.5mmol/l, respectively. Follow-up over 37 months yielded a non-significant 16\% reduction in events with a 46\% reduction in stroke. There was an almost 50\% reduction in events when the groups reaching the preset LDL targets were compared to those not reaching these targets.

Myocardial infarction

Interpretation of hs-troponin

A symposium dealt with the interpretation of high-sensitivity (hs) troponin in various clinical settings. The test performs best in ruling out acute MI in patients with chest pain. An hs-troponin T <5ng/l in this setting is associated with only 0.4\% ischaemic events in the ensuing year. However, there is a progressive increase in events as the hs-troponin T rises beyond this value. Speakers emphasised that there is no ‘cut-off’ value and that dynamic changes in the value provide the most sensitive means of detecting myocardial ischaemia. If the hs-troponin T is <12ng/l and changes less than 3ng/l over the succeeding hour, the negative predictive value for MI is very close to 100\%. Frequently a raised hs-troponin T may be the result of type 2 MI arising from supply-demand imbalance; yet, especially in postoperative patients, it may also be associated with obstructive coronary artery disease. Type 2 MI carries a poorer prognosis. Elevations in hs-troponins in asymptomatic individuals have been shown to be associated with a higher risk of future cardiovascular events. In situations such as impaired kidney function, heart failure and the postoperative state, hs-troponins pose a problem in interpretation as to the presence of acute MI while also predicting a worse longer-term prognosis. In these settings, it is important to consider the absolute value and the magnitude of change over time. In high-risk patients who are to undergo surgery it is valuable to obtain a baseline hs-troponin T reading preoperatively and repeat the test daily postoperatively. The maximal value is generally seen on the second postoperative day.
Patterns of MI outcomes over time

FAST-MI is a French registry that has recorded the incidence of STEMI and non-STEMI at five-yearly intervals since 1995. Each cohort has included between 2,000 and 4,000 patients. Dr N Danchin (Paris, France) reported that the percentage of non-STEMI patients increased after the introduction of hs-troponin measurement. There was a trend towards STEMI occurring more frequently in younger patients (under age 60) and especially in women. There was no observable change in the age at presentation in non-STEMI patients. Percutaneous coronary intervention (PCI) has increased in frequency along with less recurrent MI, heart failure and peripheral arterial disease. Thrombolysis and patients not getting reperfusion treatment have diminished. Ticagrelor use has increased, with a concurrent decrease in clopidogrel use. The prognosis in non-STEMI improved over the observation period but is better in reperfused compared to non-reperfused patients. Over the period of observation STEMI mortality fell from 17.2% to 5.3% and non-STEMI from 17.2% to 6.3%, but both show no further improvement in comparison to the penultimate study five years earlier.

In Sweden, a countrywide survey of 105,000 patients treated for STEMI over the last 20 years showed a fall in average age by two years, a fall in the percentage of women and a rise in the percentage of patients with hypertension from 32% to 54%. Currently 85-90% of patients receive guideline-recommended treatment. In-hospital mortality and recurrent MI have fallen from 14% to 8% and from 3% to 1%, respectively. One-year mortality has decreased from 21% to 14%, with reductions also noted in recurrent MI, heart failure and stroke, improvements that are ascribed to the application of new therapies.

Oxygen therapy in MI

The SWEDHEART DETOX study included 6,629 patients admitted for exclusion of MI who were randomised either to oxygen by face mask at 6l/min or to room air and then followed for one year. Hypoxaemia was recorded in 62 patients on oxygen and 254 on room air. There was no beneficial effect of routine oxygen therapy. Both groups had identical troponin levels and a similar one-year mortality rate.
Anticoagulation after ACS

TROPICAL-ACS investigated whether patients on prasugrel one month after an ACS could have their P2Y12 inhibitor de-escalated to clopidogrel if they exhibited adequate platelet inhibition on clopidogrel. Those that did not (40%) reverted to prasugrel. There was a non-significant 19% lower bleeding risk and no increment in ischaemic events in the clopidogrel responders. Subgroup analysis showed greater benefit in STEMI patients and those <70 years.

Coronary intervention

In a series of presentations relating to the results of coronary intervention, it was reported *inter alia* that in SWEDHEART registry patients with type 1 diabetes with multivessel disease, there had been a swing away from coronary bypass surgery to PCI over time. Although the two groups were not completely contemporaneous, PCI was associated with a greater incidence of MI and the need for revascularisation. The authors found that coronary bypass remains the preferred strategy.

Another presentation from SWEDHEART, ‘ALIDATE’ compared the effects of bivalirudin with unfractionated heparin in STEMI and non-STEMI patients and found no difference in outcome at 180 days.

Dr M Holzmann (Stockholm, Sweden) reported that there was no difference in outcome between bare metal and drug-eluting stent use in patients undergoing PCI for stenosed saphenous vein grafts.

Dr J Escaned (Madrid, Spain) reported on the SYNTAX II trial results, in which contemporary PCI in 450 patients with de novo triple-vessel disease was compared to historical controls that had undergone coronary bypass in the original SYNTAX trial. In contrast to SYNTAX I, these patients had measurement of fractional flow rate (FFR or iFR), intracoronary ultrasound, and treatment of chronic occlusions using second-generation drug-eluting stents as well as guideline-recommended secondary prevention. This combination resulted in reduced major adverse cardiac and cerebrovascular events (MACCE), MI, repeat revascularisation and stent thrombosis, yielding a result equivalent to coronary bypass in SYNTAX. Whether the clinical and anatomical SYNTAX score was below or above 22 had no influence on the outcome.

The Bioflow V trial, using the Orsiro ultrathin strut stent with biodegradable polymer, resulted in a 30% reduction in target lesion failure compared to an everolimus-eluting stent.

RE-DUAL7 explored a strategy for combining anticoagulation with anti-platelet therapy in patients with non-valvular atrial fibrillation (AF). Patients were randomised 1-5 days after PCI to either dabigatran 150mg or 110mg bd plus a P2Y12 inhibitor (clopidogrel or ticagrelor) vs warfarin plus a P2Y12 inhibitor and (for the first 1-3 months only) aspirin. Two thousand seven hundred and twenty-five patients were included. Patients on warfarin had a time-in-therapeutic range (TTR) of 64%. The clinical endpoint per the International Society on Thrombosis and Haemostasis (ISTH) was major bleeding plus clinically relevant non-major bleeding. Sixteen percent

### Conclusions

- In patients with 3VD the use of the SYNTAX-II strategy was associated with improved clinical outcomes at one year, compared to matched patients treated percutaneously in the original SYNTAX-I trial
- The one-year exploratory comparison between SYNTAX II and matched CABG patients from the original SYNTAX-I trial suggests non-inferiority of PCI when the SYNTAX-II strategy is followed
- Compared to SYNTAX I, contemporary state-of-art PCI in SYNTAX II led to significantly fewer lesions treated with PCI, and significantly higher success rates in CTO revascularisation
- One-year outcomes of patients with SYNTAX score >22, treated with PCI using the SYNTAX II risk stratification, were similar to those observed in patients with low anatomical risk (SYNTAX score ≤22).
of the patients discontinued treatment. Compared to warfarin the dabigatran 110mg dose was associated with an 11.5% absolute and 46% relative risk reduction in the endpoint (a major or clinically relevant non-major bleeding event during 14 months of follow-up), while the 150mg dose reduced the bleeding rate by 5.5%. No increase in ischaemic or thrombotic events was observed with dabigatran, although cases of stent thrombosis were numerically higher.

Secondary prevention

Vascular screening

Routine triple vascular screening (blood pressure, peripheral arterial ultrasound and abdominal ultrasound) in men aged 65-74 years was shown to be cost effective. Detection rates for the three components were 10%, 11% and 3.3%, respectively. Positive results in patients resulted in increased use of aspirin, statins and antihypertensive treatment. There was a 7% reduction in all-cause mortality when screened subjects were compared to those not screened.

Figure 2: Amended from ESC presentation, 2017 ESC Congress
The COMPASS study randomised patients with stable coronary artery disease or stable peripheral arterial disease to secondary preventive treatment with aspirin 100mg daily alone, aspirin 100mg plus rivaroxaban 2.5mg bd, or rivaroxaban 5mg bd alone as secondary preventive treatment. Patients were followed for 23 months. The trial was terminated early because of greater efficacy in the rivaroxaban-plus-aspirin group. The primary endpoint of cardiovascular death, MI and stroke was reduced by 24% (Figure 2). The benefit was evident early on and increased with time. All components of the endpoint were reduced. Total mortality was reduced by 18%. Both coronary artery disease and peripheral arterial disease patients benefited equally. There was a low incidence of major bleeding, which was greater in the rivaroxaban-treated patients. There were fewer amputations in the rivaroxaban groups (0.2% vs 0.7%; relative risk reduction 70%). The results of COMPASS indicate that atherothrombotic events do not depend solely on platelet activation and that thrombin generation via the coagulation pathway also plays an important role.

CANTOS was the second major secondary prevention study presented. Ten thousand and sixty-one patients with stable coronary artery disease and an hs-CRP >2mg/l were randomised to placebo or the IL-1 beta human antibody, canakinumab, in doses of 50mg, 150mg or 300mg given parenterally at three-month intervals. At baseline patients had an average LDL cholesterol of 2.1mmol/l and an hs-CRP of 4mg/l. HDL and LDL cholesterol and triglycerides were not altered by canakinumab during the trial, whereas CRP was reduced by 39-40%. Reductions were noted also in fibrinogen and interleukin-6. The primary endpoint of non-fatal MI, non-fatal stroke and cardiovascular death was reduced by 15%. Dr Paul Ridker (Boston, USA) noted that the composite endpoint was reduced by 27% in those patients whose on-treatment hs-CRP fell below the median. Treated patients had a reduced incidence of fatal malignancy (51% in the group on the 300mg dose), new lung cancer, gout, osteoarthritis and rheumatoid arthritis. CANTOS proves the concept that the complications of atherosclerotic cardiovascular disease can be reduced by suppressing inflammation and that this effect is achieved independently of lipid lowering. It is unlikely that this therapy will become available as the estimated annual cost is $200 000!

Atrial fibrillation

Dr CB Granger (Durham, US) presented results from IMPACT AF, a multinational educational intervention to promote the appropriate use of anticoagulant treatment in patients with AF. Adherence to treatment improved (82% vs 66%) and anticoagulant use in treatment-naïve patients increased (48% vs 18%).

The diagnosis of previously undetected AF in an aging population using an intermittent monitoring device showed a four-fold increase in a positive diagnosis. The best predictor of AF was a CHA2DS2-VaSC score of four or more. There were more cerebrovascular events in the unmonitored comparator group.

The RACE III study examined a risk factor-driven approach to the prevention of AF in patients with paroxysmal or early persistent AF who were not on an antiarrhythmic drug and had had no more than one previous electrical cardioversion. The actively treated group received information on lifestyle change and cardiac rehabilitation and treatment with renin-angiotensin-aldosterone inhibition, mineralocorticoid antagonists and statins. Obstructive sleep apnea was not addressed. Patients were electrically cardioverted after three weeks. ‘Upstream’ management resulted in lower blood pressure, lower LDL cholesterol, improved LV ejection fraction and a lower incidence of AF (63% vs 75%), but with no difference in BMI or mortality.

Compliance with the prescription of anticoagulants for the prevention of stroke and systemic embolism in AF is often poor and may be influenced by physician opinion.

Dr MD Ezekowitz (Villanova, US) reported on EMANATE, a randomised trial of early, image-guided cardioversion for AF which compared apixaban to heparin plus warfarin. No stroke or embolic event was encountered in the apixaban group. Three major bleeds occurred with heparin-warfarin. Clinically relevant
non-major bleeding was equivalent in the two groups. Of note, when intracardiac thrombus was identified by non-invasive imaging, only 50% of thrombi had resolved by three months.

The CASTLE-AF trial (catheter ablation versus standard conventional treatment in patients with LV dysfunction and AF) evaluated the effects of AF ablation in patients with reduced ejection fraction <0.35 in NYHA class 2 or greater who already had a cardiac resynchronisation therapy defibrillator (CRT-D) or implantable cardioverter defibrillator (ICD) implanted and who had failed treatment with at least one antiarrhythmic drug.

 Patients had paroxysmal or persistent AF. They were followed for 60 months. At five years, 80% of treated patients were in sinus rhythm and overall there was a 22% reduction in AF burden. Left ventricular ejection fraction was improved. There was a 38% reduction in all-cause mortality (decreased 47%) and worsening heart failure.

The CAPTAF study compared the quality of life and AF burden in patients on anti-arrhythmic drugs to patients after pulmonary vein isolation (PVI) using an implanted continuous monitor for between 12 and 48 months. The PVI group had better quality of life with a non-significant reduction in AF burden.

Heart failure

The sodium-glucose co-transporter 2 (SGLT-2) inhibitors, developed for the treatment of diabetes, have been shown to have important ‘off-target’ effects, which may influence the future treatment of cardiovascular disease. The randomised EMPA-REG OUTCOME and CANVAS studies and evidence accumulated from ‘real-world’ surveys confirm that despite relatively small changes in HbA1C, blood pressure and body weight, hospitalisation for heart failure in patients with diabetes is reduced by 33% using these agents.

Empagliflozin was shown to reduce cardiovascular death by 38% and protect against progression of kidney injury. The results with canagliflozin went in a similar direction, although in the CANVAS trial there was an as yet unexplained increase in the incidence of limb amputation. The mechanism/s of these cardioprotective effects are being explored. Preliminary data indicate that SGLT-2 inhibition is associated with progressive reduction in proBNP and troponin levels.

Cardiogenic shock

Mortality from cardiogenic shock remains around 50%. Critical reduction in microvascular perfusion initiates cytokine release which creates a vicious circle of continued lactate production and acidosis. Circulatory failure may be aggravated by therapy such as inotropes, vasodilators and fluid loading. When present, the immediate relief of myocardial ischaemia is beneficial. There is no evidence to indicate that inotropic support and vasodilation are beneficial; indeed the use of adrenaline and/or dopamine is associated with worse outcome. Early mechanical circulatory support is recommended despite a lack of proven benefit. Elevation of both proBNP and ST2 (a biomarker of cardiac stress) predicts an 80% mortality.

Venous thromboembolism (VTE)

The diagnosis of VTE and its severity are best assessed by using the simplified Pulmonary Embolism Severity Index (sPESI) score (age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate >110/min, systolic blood pressure <100mmHg, oxygen saturation <90%) combined with proBNP, hs-tropanin and the detection of venous thrombosis on ultrasound. Although non-VKA oral anticoagulants (NOACs) have been shown to be as effective as treatment with standard heparin and warfarin with a lower risk of bleeding, patients treated with NOACs are inappropriately dosed in 20% of cases, resulting in an increase in mortality. In addition, lytic therapy and inferior vena cava (IVC) filters are frequently used inappropriately. The duration of anticoagulant therapy...
Aortic disease

One session dealt with the surgical management of aortic disease. One in six patients presenting with an aortic aneurysm have a family history of the condition. Multimodality imaging is generally employed to assess aortic size. However, the various imaging techniques produce results that differ from one another. MRI is the preferred investigation, especially in those patients with an aortic root diameter <45mm who then require six-monthly reassessment. Dr R De Paulis (Rome, Italy) emphasised the importance of recreating the aortic sinuses when replacing the ascending aorta. The sinuses should be of sufficient width and length not to impede full opening of the aortic valve. The annulus size, leaflet length as well as the height and diameter of the sinotubular junction must be taken into account. The diameter of the sinuses of the Valsalva graft should be 20% greater than the graft diameter. Dr M Shrestha (Hannover, Germany) spoke about aortic arch repair. Better results are obtained with a beating heart. A ‘frozen elephant trunk’ is employed, which stents the distal anastomosis. The success of surgery relates to the annual case volume of the particular centre. In certain cases medical therapy or endovascular repair may therefore be more appropriate.

References