AMERICAN COLLEGE OF CARDIOLOGY CONGRESS 2017

Washington, DC, 17–19 March 2017

Introduction

The meeting was held in Washington again after a break of three years. An unusual experience was that I did not run into any South African colleagues during the entire conference. This probably reflects the fact that pharmaceutical companies have withdrawn virtually all sponsorship for attendance at international meetings. Although companies may see this as a marketing code necessity, the longer-term impact upon the continuing professional development of, especially, our younger colleagues is surely yet to be felt.

Advances in lipid-lowering treatment

Undoubtedly, one of the most significant reports at ACC was the FOURIER study, the first to report on cardiovascular outcomes with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition using evolocumab.¹ There were also reports on the effects of bococizumab, another PCSK9 inhibitor, and inclisiran, a synthetic small interfering RNA (siRNA) molecule, which inhibits PCSK9 synthesis in the liver.

PCSK9 is of interest as it chaperones LDL cholesterol bound to its receptor into the liver cell where both LDL cholesterol and the receptor are destroyed, thus making the receptor unavailable to return to the cell wall and consequently depleting LDL cholesterol receptor numbers that could remove further LDL cholesterol from the circulation. By inhibiting PCSK9, the LDL cholesterol receptor population is preserved and the circulating LDL cholesterol concentration reduced by as much as 60%. This effect is attenuated to around 30% reduction in patients with homozygous familial hypercholesterolaemia in proportion to their residual LDL cholesterol receptor density and function. Dr EA Stein (Ohio, USA) noted that 75mg of the human antibody is sufficient to obtain complete inhibition of PCSK9. Larger doses do not increase the LDL cholesterol-lowering any further, though they do prolong the duration of action. Of interest, is the observation that the concentration of (inactivated) PCSK9 may rise as much as fivefold during treatment. Several preliminary studies have demonstrated the safety of combining PCSK9 inhibition with statin treatment, frequently achieving LDL cholesterol levels of 1mmol or lower.

Dr Paul Ridker (Boston, USA) reported on SPIRE-1 and SPIRE-2, which examined the effect of bococizumab* in 27 000 patients who were either high risk or statin intolerant. Baseline LDL was >1.8mmol/l in the high-risk group (SPIRE 1) and >2.6mmol/l in the statin-intolerant group (SPIRE 2).² Although LDL cholesterol was reduced initially by 55-60%, there was an unexpected loss of effect in 10-15% of patients, in part due to the development of antibodies to the humanised antibody in 50% of patients and in part due to unexplained individual variations in response. Bococizumab has been withdrawn from further development and the SPIRE trials were halted prematurely. Although no conclusion could be drawn...
in relation to cardiovascular event rates, there was a trend to reduced events with the active agent dependent upon the magnitude of LDL cholesterol reduction and the length of exposure. A high rate of injection site reactions was noted.

Dr Kausik Ray (London, UK) presented the ORION-1 phase 2 trial with inclisiran, which achieved a sustained average reduction in LDL cholesterol of 53% over six months after two injections 90 days apart. As this agent would then be given as a single injection every six months, the potential for adherence to therapy is expected to be much greater. No severe side-effects were observed in the trial. A phase 3 trial is planned.

Evolocumab is a fully human monoclonal antibody inhibitor of PCSK9 that reduces LDL cholesterol by around 60%. The agent does not provoke an antibody reaction and there is no attenuation of its effect over time. The FOURIER trial enrolled 27 564 high-risk patients with established atherosclerotic cardiovascular disease on statin therapy (if tolerated) with an LDL cholesterol level >1.8mmol/l. They were randomised to fortnightly or monthly injections of evolocumab or placebo and followed for 26 months. The primary endpoint was cardiovascular death, myocardial infarction (MI), stroke, hospitalisation for unstable angina, or coronary revascularisation. LDL cholesterol was reduced by 59% with 25% of actively treated patients having an LDL cholesterol level <0.5mmol/l. The frequency of the composite primary endpoint was reduced from 14.6% to 12.6% with a 20% reduction in cardiovascular death, MI and stroke, and a 27% reduction in the need for revascularisation. As has been observed in previous lipid-lowering trials, the effect increased over time. MI and stroke were reduced by 19% in the first year and by 33% in the second.

Although commentators were enthusiastic about the outcome of FOURIER because it fully supports the lipid hypothesis and shows that ‘even lower is better’, there were concerns that the absolute reduction of only 2% in the primary endpoint suggests that the cost-effectiveness of the agent will be impaired. When compared to placebo in the FOURIER trial, evolocumab was not associated with any increase in the adverse events often attributed to statin therapy. No excess in myalgia, cataract formation, new-onset diabetes or neurocognitive disorders was observed. The EBBINGHAUS substudy specifically evaluated 1974 patients for the development of memory impairment and neurocognitive deficits and found none.4

Investigations are ongoing into the use of other antisense therapies that will influence lipid metabolism by interfering with messenger RNA translation, as well as into whether suppression of the inflammatory response associated with atherosclerosis will influence future cardiovascular events. Dr Paul Ridker (Boston, USA) will shortly report on a study using low-dose methotrexate and another which targets suppression of interleukin-6.

The role of HDL cholesterol continues to be explored, despite the failure of the cholesterol ester transfer protein (CETP) inhibitors to show any effect upon outcome in cardiovascular trials, even though large increases in HDL cholesterol were observed. Dr JJ Kastelein (Amsterdam, Netherlands) pointed out that fewer cardiovascular events occur in persons with genetically mediated low CETP activity and that although CETP inhibition has impressive effects on lowering LDL cholesterol and raising HDL cholesterol when given alone, these unsuccessful trials used CETP inhibition in combination with statins. The combined therapy is associated with failure to reduce atherogenic particles and attenuation of the response in apolipoprotein B, which is possibly the reason why CETP inhibition had no effect on outcomes.

The CARAT study randomised 301 patients to the HDL cholesterol mimetic CER001 or placebo to evaluate the effect upon the change in atheroma volume over nine weeks seen on IVUS in post-acute coronary syndrome patients with carotid plaque. All patients were on statin treatment. Similar degrees of plaque regression were observed in both groups.

No convincing evidence for adverse effects on neurocognitive function and neural activity of high-dose atorvastatin was found in a study which assessed patients on treatment and then two months after discontinuation.
Angina pectoris

A session was devoted to the investigation and management of patients with anginal symptoms, ST segment changes in the ECG and the absence of coronary obstruction on angiogram. A variety of syndromes may be operating in this situation, including microvascular disease, coronary vasospasm, myocardial bridging, endothelial dysfunction and/or increased cardiac nociception. Rather than dismissing many of these patients as having non-cardiac chest pain, a number of units now undertake extensive investigations to tease out the cause/s before prescribing specific treatment. Coronary reactivity testing using acetylcholine, adenosine and nitroglycerine, stress echocardiography, myocardial perfusion imaging, MRI and coronary flow reserve form part of the investigative armamentarium.

Coronary vasospasm does not occur solely at night or at rest; 14-28% of spasm episodes are precipitated by exertion. Calcium channel blockade is the favoured treatment. In certain cases more than one calcium channel blocker may be required to control the symptoms.

Not all muscle bridges are significant, but they are twice as common in patients with angina as in those without. Myocardial bridging may not become symptomatic until the third decade of life. The commonest site for bridging is over the left anterior descending. Arterial compression by the bridge is not limited to systole, so coronary diastolic flow may be impaired. Dobutamine stress echo may be employed to diagnose bridging; the precipitation of septal buckling seen in the apical four-chamber view on echocardiogram may indicate the diagnosis. Stenting and bypass surgery are ineffective. In proven cases when medical therapy fails to relieve symptoms, unroofing the artery has been effective.

Endothelial dysfunction should be suspected in patients complaining of persistent chest pain with ST segment changes and no obstructive coronary artery disease. These patients have an adverse outcome. Endothelial dysfunction is demonstrated by a paradoxical vasoconstriction after low-dose intracoronary acetylcarnitine. Increased cardiac nociception is likely when a patient develops her/his usual chest pain during adenosine injection in the setting of normal endothelial function. These patients respond to treatment with tricyclics.

In general, many of these conditions are unusual manifestations of atherosclerotic disease and patients should receive treatment with ACE inhibition, third-generation beta blockade (e.g. carvedilol), and a statin, all of which improve endothelial function. Coronary ectasia was mentioned. Dr P Beltrane (Barcelona, Spain) recommended managing symptomatic patients with antiplatelet agents and vasodilators. He acknowledged that some clinicians choose to anticoagulate these patients.

Acute coronary syndromes (ACSs)

The GEMINI-ACS phase 2 trial examined the safety of replacing aspirin with low-dose rivaroxaban 2.5mg bd in combination with either clopidogrel or ticagrelor 2-10 days after an ACS. Whereas a previous trial that added rivaroxaban to dual antiplatelet therapy showed an excess of bleeding, GEMINI-ACS found equivalent rates of bleeding in the two groups. A phase 3 outcome trial is planned.

Coronary intervention

Radial artery access is now widely recognised as the preferred method for both routine angiography and intervention. Speakers addressing the preferred methods of performing radial access stressed that there is no correlation between tests for the adequacy of radial artery perfusion and the precipitation of ischaemia. Counterpuncture, meaning puncturing both the front and back walls of the artery, is more successful for obtaining access. Hydrophilic sheaths cause less pain and are associated with a lower incidence of spasm. One experienced operator recommended using the ‘baby J’ wire for navigating tortuous arteries. Similarly, a pigtail catheter is useful in traversing a tortuous subclavian.
Complications of the procedure include coronary spasm, which may be overcome with 5mg verapamil in 10ml 0.9% NaCl or 60ml of the patient’s blood. Radial artery occlusion is avoided using hydrophilic sheaths along with the mandatory use of heparin, enoxaparin or bivalirudin. Forearm pain following the procedure may suggest non-occlusive radial artery injury or compartment syndrome. A treatment paradox exists in that patients most likely to benefit from radial artery access remain the least likely to receive it, especially those who are haemodynamically unstable or have comorbid conditions. Studies have shown that there is no difference in door-to-balloon and reperfusion times using radial access.

Fifty percent of patients with ST segment elevation myocardial infarction (STEMI) have multivessel coronary disease. COMPARE ACUTE was a randomised trial comparing intracoronary fractional flow rate-guided (FFR) immediate complete multivessel revascularisation with single-vessel culprit lesion revascularisation with 12 months of follow-up.6 Approximately 50% of non-culprit lesions were shown to have an FFR <0.80. The FFR-guided strategy was associated with a 65% reduction in all-cause death, recurrent MI, stroke and revascularisation (7.8% vs 20.5%). Recurrent MI and the combination of re-MI and death were numerically fewer in the FRR-guided group.

Two trials (DEFINE FLARE and iFR SWEDHEART)7 with 2492 and 2037 patients, respectively, compared FFR to the instantaneous wave free ratio (iFR) technique. The two were shown to have a similar power to detect ischaemia. iFR was non-inferior to FFR. Both studies found that there was no difference in outcome between FFR and iFR.

DECISION-CTO compared the outcomes in 398 patients on optimal medical therapy who underwent revascularisation without intervention upon their single chronic total occlusion (CTO) with 417 patients on optimal medical therapy who underwent revascularisation that included the CTO. The CTO vessel had to be a proximal vessel >2.5mm in diameter. The CTO procedure was successful in 91%. CTO revascularisation was not associated with any improvement in outcome.

ABSORB III is following the outcomes after the implantation of a biodegradable coronary vascular scaffold. As resorption is now known to occur over three years, the period of observation has been extended. Prior results have shown increased target lesion failure, MI and stent thrombosis in vessels 2.5mm or less in diameter, although even when omitting those cases from analysis, numerical increases in these complications persist when compared to the use of a drug-eluting stent.

Heart failure

Following the demonstration of a reduction in heart failure hospitalisation in the EMPA-REG study of the sodium-glucose cotransporter 2 (SGLT2), empagliflozin, there is considerable research currently underway exploring the effects of SGLT2 inhibitors in heart failure, both in patients with diabetes and those without. A meta-analysis of reports from national registries of real-world use of SGLT2 inhibitors compared to other oral hypoglycaemic treatments included 364 828 patients. Dr M Kosibrod (Kansas, USA) found a 48% reduction in the incidence of new heart failure, a 39% reduction in hospitalisation for heart failure and a 46% reduction for the combination of hospitalisation for heart failure and all-cause death. These benefits are seen as a class effect of the SGLT2 inhibitors.

A Japanese group investigated the effects of another of these inhibitors, ipragliflozin, on the renin-angiotensin-aldosterone and sympathetic nervous systems (RAAS and SNS) and urine output in type 2 diabetes patients with stable heart failure.8 They found minimal influences on the RAAS and SNS, a reduction in proBNP and increments in urine volume due to natriuresis rather than osmotic diuresis, despite recording an increment in urine glucose output of 23g/day.

Levosimendan is a calcium sensitisser with inotropic, vasodilatory and cardioprotective actions. In the LEVO-CTS randomised trial it was evaluated in 882 high-risk patients with a left ventricular ejection fraction <35% who were undergoing cardiac surgery with cardiopulmonary bypass. The composite outcome
Arrhythmia and electrophysiology

The PARADIGM and ATMOSPHERE trials included 15,415 patients with heart failure and preserved ejection fraction; 5,500 patients had atrial fibrillation (AF). Investigators found a worse outcome among the third of patients with paroxysmal AF vs the two-thirds with permanent AF (2/3). Those with paroxysmal AF were anticoagulated less frequently. Their risk of cardiovascular death, systemic embolism and stroke were higher. New-onset AF carried a substantially higher risk and these patients had a higher baseline proBNP.

Electrical cardioversion in patients with AF of less than 48 hours duration is usually regarded as a low-risk procedure. A study reported that there is risk associated with this approach as systemic embolism does occur. It was suggested that the risk may be lower in patients with a CHADS-VaSC score <2.

A study including 10,524 patients undergoing cardiac surgery (1/3 mitral valve replacement (MVR) with coronary bypass grafting (CABG), 1/3 aortic valve replacement (SAVR) + CABG and 1/3 CABG alone) compared the outcomes in those patients who underwent surgical closure of the left atrial appendage (37%) with those who did not. The median age was 76 years, 39% were women and the CHADS-VaSC score was 4. Those in the closure group were slightly younger, had a lower CHADS-VaSC score and lower surgical risk. In the closure group, thromboembolism was reduced by 38% and death by 15% with no difference in haemorrhagic stroke. The risk of thromboembolism was reduced 71% in those not anticoagulated (three patients) but there was no difference between the groups when receiving anticoagulation (6676 patients).

Uninterrupted dabigatran treatment was compared to warfarin in patients undergoing catheter ablation for AF. There was a notable reduction in the rate of major bleeding with dabigatran (1.6% vs 6.9%) while minor bleeds were no different between the groups. No thromboembolism was encountered.

The ARISTOTLE trial compared apixaban to warfarin in patients with non-valvular AF. A subgroup analysis of the trial assessed the outcomes in patients on digoxin. The investigators found digoxin levels >1.2ng/ml increased the risk of death by 56% with a 19% increase in risk for each 0.5ng/ml increment in serum concentration. They found that new users of digoxin were at particularly high risk, with an increased risk of 78% and a four-fold increase in the risk of sudden death within the first six months of starting treatment. The risk was higher in those with heart failure than those without.

The following abstract presentations were of interest:

1. A Johns Hopkins study of arrhythmogenic right ventricular cardiomyopathy/dysplasia among probands and family members followed over 8½ years found that while male sex and a positive electrophysiological study predict ventricular arrhythmia and the need for defibrillator implantation (ICD) in probands, an ICD is appropriate among their relatives when a high burden of premature ventricular contractions and evidence of structural heart disease on MRI are present.

2. The commonly used anti diarrhoeal agent, loperamide, is a hERG channel blocker that may precipitate torsades de pointes.
3. A meta-analysis including 2573 patients from trials of ICD implantation for non-ischaemic cardiomyopathy showed a 17% reduction in mortality with an ICD plus optimal medical therapy compared to optimal medical therapy alone. The analysis included the DANISH study published last year that reported no benefit from ICD implantation.

4. A 13-year follow-up in 469 patients with an implanted ventricular assist device showed that ventricular tachycardia (VT) within the first 30 days after implantation predicts higher mortality when compared to patients without VT or those with VT occurring after the first 30 days.

Valvular heart disease

The SURTAVI trial was undertaken in 1746 patients comparing surgical aortic valve replacement (SAVR) to transfemoral aortic valve replacement (TAVR) with a self-expanding prosthesis (84% CoreValve®; 16% EvolutR®) in intermediate-risk patients. Patients with bicuspid valves were excluded. Although the surgical results were outstanding (mortality at one month 1.7% and 11.5% at two years), TAVR was ‘robustly’ non-inferior in outcome. Twenty-six percent of TAVR patients required permanent pacemaker implantation. Five percent of TAVR patients had aortic regurgitation at two years.

Twenty-five to thirty-three percent of patients who require SAVR exhibit cognitive impairment preoperatively. Patients undergoing SAVR have a radiographic cerebral infarction rate of 61%; 17% have a clinical stroke and 4% of all strokes are severe. Dr MJ Mack (Texas, USA) reported the results using two cerebral embolic protection devices, the Cardiogard® suction system (133 patients) and the EmbolX® filter (118 patients) during SAVR with or without coronary bypass surgery compared to a common control. The endpoint was freedom from radiographic or clinical stroke seven (+/− three) days postoperatively. A high percentage of emboli were collected by the filters, including fragments of myocardium, vessel wall, plaque, calcium and thrombus. Less delirium was noted in the treated groups. The trial was halted prematurely for lack of benefit. One-third of strokes were found to occur after day three.

Dr E Van Belle (Netherlands) reported on the incidence of silent cerebral microbleeds during TAVR with the Edwards Sapien® prosthesis. Eighty-four patients with an average age of 80.6 years underwent MRI before and after the procedure; 26% had microbleeds prior to intervention and 22% thereafter (the majority with a single bleed). Greater neurological impairment was noted in those with microbleeds, though no correlation was found between the microbleeds and cerebral embolism. A higher incidence of microbleeds was associated with longer fluoroscopy times (probably a surrogate for longer procedures).

Subclinical leaflet thrombosis is observed in 10-15% of patients after TAVR as well as after bioprosthetic SAVR. A study of 890 patients who underwent CT scanning at variable times after their procedure looked for the presence of reduced leaflet motion. Patients with AF (because they were anticoagulated), and more frequent in the older patients. Non-vitamin K oral anticoagulants and warfarin were found to be equally effective in resolving the thrombosis in all patients receiving an anticoagulant. Thrombosis persisted in those who were not anticoagulated. Thrombosis recurred in 50% of those whose anticoagulant was withdrawn later. Subclinical leaflet thrombosis was associated with a higher incidence of transient ischaemic attack but not of stroke.

The US guideline on mitral regurgitation no longer recognises a difference between the effective regurgitant orifice area (EROA) for primary and secondary mitral regurgitation. An EROA >0.4 is an indication for surgery in both cases. Speakers emphasised the importance of not ‘just going with the numbers’ and of taking factors such as leaflet morphology and the presence of a flail leaflet into account when considering the need for surgery.
Mitral annular calcification in the presence of degenerative mitral stenosis in the elderly poses a significant surgical challenge. A novel approach has been the excision of the mitral anterior leaflet and the insertion of a Sapien® valve under direct vision. Left ventricular outflow tract obstruction may occur.

**Venous thromboembolism (VTE)**

The EINSTEIN CHOICE trial evaluated rivaroxaban 10 or 20mg daily vs aspirin 100mg daily for one year in patients with prior VTE who had completed 6-12 months of anticoagulant therapy. Over 1000 patients completed the trial. Fifty percent had had deep-vein thrombosis (DVT), 34% pulmonary embolism and the remainder both; 40% were unprovoked. Recurrent VTE occurred in 4.4% of the aspirin-treated patients compared to 1.5% and 1.2% in the 20mg and 10mg rivaroxaban groups (66% and 74% reductions vs aspirin) respectively. Bleeding rates were low, in the region of 0.3-0.5% in the three groups.

**Assessing the risk of non-cardiac surgery**

The average mortality rate is 1.3% among the five million Americans older than 45 years who undergo non-cardiac surgery annually. The leading cause of death in this group is cardiac. The predictive value of hs-troponin T estimations was assessed in 21 842 patients with a mean age of 63 years. Troponin was measured 6-12 hours after surgery and daily thereafter for three days; 13.8% of patients had a raised level before surgery. Myocardial injury occurred most frequently on day two. Ninety-three percent of those with MI did not develop symptoms of cardiac ischaemia and 93% would have escaped detection had hs-troponin T not been measured. There was a stepwise relationship between peak postoperative hs-troponin T levels and 30-day mortality (Table 1). Myocardial injury was found to account for 24% of postoperative deaths.

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*Source: PJ Devereaux (410-16 Late-Breaking Clinical Trials Sunday 09.00 to 09.10)*
References


