

# AMERICAN COLLEGE OF CARDIOLOGY CONGRESS 2016



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## Introduction

The American College of Cardiology's 65th Annual Scientific Sessions were held in Chicago recently. Dr Anthony J Dalby attended the meeting and reports on the presentations that he considered to be of outstanding interest.

## KEY MESSAGES

- In a large group of patients with low-density lipoprotein cholesterol (LDL-C) above 5mmol/l, only 1.7% were positive for known genetic mutations of familial hypercholesterolaemia (FH)
- Rosuvastatin (10mg) in an intermediate-risk, ethnically diverse population without cardiovascular (CV) disease resulted in a 24% reduction in the primary endpoint of death from CV causes, non-fatal myocardial infarction (MI) and non-fatal stroke (HOPE-3 trial)
- Duration of dual antiplatelet therapy (DAPT) should be based on the balance between ischaemic and bleeding risks
- In patients with chronic heart failure, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit (ATMOSPHERE study)
- The prognosis of patients with peripartum cardiomyopathy in South Africa is worse than the international experience
- Positive results were shown from the IxCELL-DCM cell therapy study in patients with heart failure
- Cryoablation in atrial fibrillation (AF) is easier to perform than radiofrequency ablation and achieves similar efficacy results
- Transcatheter aortic valve replacement (TAVR) is non-inferior to surgical aortic valve replacement in intermediate-risk patients
- Stress and depression in heart disease deserve more clinical attention.

## Prevention

Many speakers in a number of sessions emphasised the need for lifestyle changes, the effects of which are estimated to provide greater protection against the development of atherosclerotic cardiovascular disease than pharmacotherapy. Several sessions were dedicated to the discussion of correct diet, regular moderate exercise, weight control and avoidance of smoking. The ACC strongly supports a diet low in

saturated fats, salt and refined carbohydrates. One web-based study demonstrated the benefits of a large international programme employing an inexpensive pedometer. With the support of their employers, participants were encouraged to download the records of their activity. The programme achieved a sustained increase in exercise, less time spent sitting down and a small but significant loss of weight.

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Another study included a large group of patients (26 000) whose LDL-C was 5.0mmol/l or greater and who underwent genetic screening for the presence of FH. Screening was positive in only 1.7% of this group.<sup>1</sup> The remainder were considered to have either a polygenic or environmental cause for their elevated LDL-C. Dr AV Khera, lead author, showed that at any given level of LDL-C the presence of the FH gene was associated with a marked increase in the risk of atherosclerotic CV disease. He quoted the example of two patients with a similar LDL-C around 5.4mmol/l. Whereas the risk for the patient not carrying the FH gene was estimated at 5%, the gene-positive patient had a risk of 17%. The difference may reside in the effect of lifelong exposure to a high LDL-C in the FH-positive patient.

HOPE-3<sup>2</sup> was a blinded, 2X2 factorial study of 12 705 patients at moderate risk of atherosclerotic CV disease (men aged 55 years or older, women 60 years or older, increased waist-hip ratio, smokers, low high-density lipoprotein cholesterol (HDL-C), dysglycaemia or mild chronic kidney injury) who were treated with candesartan 16mg plus hydrochlorothiazide 12.5mg daily, or atorvastatin 10mg daily, or both versus placebo for 5.6 years without reference to their baseline blood pressure or lipid profile. Forty-six percent of the study population were women. The average baseline blood pressure was 138/82mmHg and the LDL-C 3.3mmol/l. Candesartan reduced blood pressure by

6/3mmHg but had no effect on outcome overall. Those in the highest tertile of the blood pressure range had a mean baseline systolic pressure of 143.5mmHg and were shown to have an improved outcome whereas there was a trend towards harm in the lowest tertile of blood pressure. In the patients receiving rosuvastatin<sup>3</sup> alone, LDL-C fell around 1mmol/l and was accompanied by a reduction in the primary endpoint (death from CV causes, non-fatal MI and non-fatal stroke) from 4.8% with placebo treatment to 3.7% (a 24% reduction). The primary endpoint was reduced by 40% by the combination of rosuvastatin and candesartan in the subgroup with the highest tertile of baseline blood pressure.<sup>4</sup> Discontinuation occurred in 22% of patients. Muscle pain and weakness occurred in 6% of the treated group and 4% of those on placebo. No increase in new-onset diabetes was observed. A reviewer cautioned that HOPE-3 results should not be extrapolated to those of the SPRINT study.

Air pollution is a global problem which triggers 5% of MIs.<sup>5</sup> Prominent causes of air pollution are fossil fuel combustion and gaseous pollutants. Air pollution promotes inflammatory reactions but may also directly penetrate body surfaces and evoke vasomotor responses. Carotid intima medial thickness (IMT) has been shown to increase in relation to the individual's proximity to traffic. Life expectancy improves *pari passu* with reduction in air pollution.

## Secondary prevention

The ACCELERATE study evaluated the effect of the CETP inhibitor, anacetrapib, vs placebo in 12 092 patients with various manifestations of atherosclerotic CV disease (ASCVD). Follow-up was for a minimum of 18 months. The primary endpoint was CV death, MI, stroke, revascularisation and hospitalisation for unstable angina. The trial was terminated for futility. Despite a 130% increase in HDL-C and a 37% decrease in LDL-C, there was no difference in outcome. This trial result questions the value of raising HDL-C to prevent the complications of ASCVD, as well as raising concern as to

the reason why reducing LDL-C did not affect the outcome. In contrast to torcetrapib, blood pressure rose only 0.9mmHg in the anacetrapib-treated patients.

In GAUSS-3,<sup>6</sup> patients intolerant of statin therapy were randomised in a double-blind crossover trial design to 10 weeks of the PCSK9 inhibitor, evolocumab, or ezetimibe with a two-week wash-out period between the treatment phases. As anticipated, the reduction in LDL-C was greater with evolocumab (54.5%) vs ezetimibe (16.7%). Evolocumab was associated with a lower rate of muscle symptoms and of treatment discontinuation.

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## Acute MI (AMI)

The EARLY-BAMI study evaluated the effect of two 5mg intravenous (IV) bolus doses of metoprolol given in the ambulance during transport for ST segment elevation MI (STEMI). Reperfusion was established at an average of three hours and 15 minutes. Early IV metoprolol before primary PCI blockade had no effect on the outcome. Metoprolol reduced the incidence of malignant arrhythmias in the acute phase and was not associated with an increase in adverse events.<sup>7</sup>

A randomised trial of 1234 STEMI patients that examined the effect of post-conditioning in using four successive 30-second balloon inflations at intervals of 30 seconds was unable to demonstrate

a benefit at two-year follow-up despite the observation of a non-significant 25% reduction in mortality.

A trial comparing immediate vs deferred stenting of non-culprit vessels in AMI found no advantage in deferring revascularisation.

The LATITUDE trial studied the MAP kinase inhibitor, losmapimod, in MI as a means of reducing the inflammatory response and potentially improving outcome. Although the agent reduced CRP and NT-proBNP, there was no reduction in CV death, MI or severe ischaemia. Subgroup analysis suggested a marginal benefit in the 25% of patients presenting with STEMI.

## Antiplatelet therapy

An updated American guideline on DAPT was published shortly before the meeting opened. While it essentially restates the previous approaches, considerable debate has arisen as to which agent/s should be used and for how long. A meta-analysis by Udell *et al*, including 69 644 patients, has shown that prolonged DAPT is not associated with an increase in non-CV deaths.<sup>8</sup> Major bleeding is an independent predictor of mortality at one month and one year. Yeh *et al*<sup>9</sup> recently published a bleeding risk score in *JAMA*. They found that 70% of patients on DAPT are at low risk of bleeding. Proton pump inhibition has been shown to reduce gastrointestinal (GI) bleeding in patients on DAPT and its addition to treatment should be considered.

A symposium addressed various areas of uncertainty. There was no unanimity about which P<sub>2</sub>Y<sub>12</sub> inhibitor should be preferred, though clopidogrel would remain the mainstay of treatment. Prasugrel and ticagrelor should be selected when the future risk of an ischaemic event is high. Consideration was given to whether aspirin could be omitted from treatment. Shorter duration of DAPT (1-3

months) with bare metal stents was supported; shorter duration of DAPT with drug-eluting stents (six months) may be appropriate. Prolonged DAPT has a small overall effect, reducing stent thrombosis by 3/1000 cases and MI by 5/1000. In the PEGASUS study, ischaemic events were reduced by 0.4% per annum. Thus the clinician's decision regarding the duration of DAPT treatment must be based on the balance between ischaemic and bleeding risks, shortening the time on treatment when bleeding risk is high and extending the time on treatment when there is an ongoing risk of an ischaemic event. Regular reassessment of these competing factors is necessary during follow-up.

DAPT in the setting of oral anticoagulation is most often encountered in patients with AF. In this setting, a dose of 81mg of aspirin daily is preferred and clopidogrel is to be preferred. If warfarin is the preferred anticoagulant, the INR should be controlled between 2.0 and 2.5. It may be possible to omit aspirin from triple therapy at an early stage and shorten the duration of DAPT to three or six months, depending on the presenting problem.

## Heart failure

The ATMOSPHERE study, reported by Dr JJ McMurray, compared three groups: the renin inhibitor, aliskiren, as monotherapy, enalapril monotherapy and enalapril + aliskiren. There were

approximately 3200 patients in each arm of the study who were followed for 36 months. During the trial, patients with diabetes were excluded on the recommendation of the regulatory authority.

Aliskiren treatment failed to reach the non-inferiority boundary in comparison to enalapril. Aliskiren was associated with more hypotension, impairment of kidney function and hyperkalaemia.<sup>10</sup>

Recovery from peripartum cardiomyopathy relates to the degree of left ventricular dysfunction at presentation. Patients often recover, most often within two months, although recovery may take up to two years. The prognosis in South Africa is worse than in other countries. Supportive treatment is recommended. Atrial and ventricular arrhythmias may occur, even after apparent recovery and may be life-threatening. The presence of arrhythmia predicts a higher mortality risk.

Dr TD Henry reported the results of the IxCELL-DCM trial of Ixomyocel-T which was administered by transendocardial injection in 114 patients with a dilated cardiomyopathy (NYHA III to IV;

EF <35%) and who had an ICD in place. Ixomyocel-T stimulates an increase in mesenchymal cells and macrophages. The study found that CV events were reduced by 37%. Mortality was reduced from 13.7% to 3.4% and there was a reduction in hospitalisations. LV volumes and the ejection fraction were unchanged.<sup>11</sup>

IMPEDANCE-HF employed lung impedance-guided therapy for heart failure. Patients were evaluated weekly (more frequently if necessary) in the outpatient department to adjust their therapy according to their lung impedance measured by a novel electrode placement. Compared to controls, the investigators found a reduction in heart failure hospitalisations, a 62% reduction in worsening heart failure and a 43% reduction in mortality.

A trial of an implanted vagal stimulator in heart failure patients showed no benefits.

## AF and anticoagulation

Postoperative AF occurs in 20-50% of cardiac surgery patients. Postoperative AF is associated with a higher incidence of complications and death. A study was conducted in 2109 pre-consented patients undergoing cardiac surgery of whom 523 developed AF, defined as AF within seven days of surgery, which persisted for >60 minutes or was recurrent. Anticoagulation was commenced if AF persisted for >48 hours. Rhythm control with amiodarone followed by electrical cardioversion if sinus rhythm was not restored within 24 hours was compared to rate control with beta-blockade. There were no differences in the rate of mortality, readmissions or serious adverse effects. An equal number of patients were anticoagulated. Sinus rhythm was 4% more frequent with the rhythm control strategy.

Two methods of AF ablation for drug-refractory paroxysmal AF were compared in the FIRE & ICE trial. Radiofrequency ablation was compared to cryoablation in randomised fashion in 762 patients. Follow-up was for 1.5 years. The efficacy and safety of the two methods were the same. Dr Karl-Heinz Kuck, Germany, expressed the opinion that cryoablation was simpler and easier to perform. "In addition, there was, in general, a low risk of procedural complications in both groups."<sup>12</sup>

In a moderated poster presentation it was reported that octreotide stopped bleeding from the lower GI tract in a small group of patients with arteriovenous malformations who had been treated with anticoagulants for AF. This treatment allowed for anticoagulant treatment to be restarted without a recurrence of bleeding.

An expanded registry of the reversal of dabigatran's effect with idarucizumab was presented. The effect of dabigatran was immediately reversed. Bleeding ceased an average of 9.8 hours after administration.

Holmes (*Initials or first name required, plus title – i.e. Dr or Professor?*) presented data on the US 'real-world' experience with the Watchman device collected in the interim between its approval by the FDA and the commencement of the registry that the FDA has mandated. In many instances the operators involved were uninitiated. A high percentage of success was noted, equivalent to that seen in prior clinical trials.

An NCDR review of anticoagulant bleeds found similar rates of intracranial haemorrhage when comparing any of the non-vitamin K oral anticoagulants (NOACs) to warfarin. A numerically higher rate of gastrointestinal bleeding was noted with rivaroxaban and apixaban.

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## Cardiac arrest

Out-of-hospital cardiac arrest is estimated to occur in 326 000 persons in the USA annually and just 10% survive overall. In a study, 4667 patients with shock-refractory ventricular fibrillation/ventricular tachycardia were randomised to amiodarone (formulated to avoid hypotension), lignocaine or placebo after the administration of a vasopressor. Those receiving either antiarrhythmic drug (AAD)

required fewer subsequent shocks. AAD administration increased admission to hospital alive by 6-7%. Survival to hospital discharge was greater in those patients with witnessed arrest who received either AAD. Those patients receiving amiodarone required pacing more frequently. No benefit was discerned in patients with unwitnessed cardiac arrest.

## TAVR

The results of the PARTNER 2A randomised trial in 2032 intermediate-risk patients with critically tight aortic stenosis, which compared TAVR using the 2<sup>nd</sup> generation SAPIEN XT prosthesis to surgical aortic valve replacement, demonstrated that TAVR was non-inferior at two years. In the subgroup in which the transfemoral route was employed, TAVR was marginally superior to surgery. The post-procedure rate of moderate/severe aortic regurgitation (AR) was 8%. There was no impact on two-year mortality if only mild AR was present.

Combining the results of the SAPIEN-3 and PARTNER 2A and employing

propensity scoring,<sup>13</sup> TAVR was found to be statistically superior to surgical aortic valve replacement with reductions in mortality and stroke rates appearing early after the procedure. AR was more frequent after TAVR.

The TVT Registry (jointly maintained by the ACC and the Society of Thoracic Surgeons) examined the relationship between case volume and outcome in TAVR in 42 988 patients at 395 sites, finding that increased experience was associated with lower mortality, and less bleeding and vascular complications. Case volume did not influence the frequency of stroke.

## Stress and depression in heart disease

A moderated poster presentation reported that stress-induced increased activity in the amygdala detected by 18F FDG PET scanning represented a significant risk for subsequent CV events. A one unit increase in target to background ratio (TBR) was associated with a 14 to 41-fold increase in risk. Follow-up for 3.8 years showed a 77% survival in TBR-positive patients in comparison to 95% in those without these changes.

Twenty-two thousand, nine hundred and seventeen patients with stable coronary artery disease were followed for a minimum of one year after coronary angiography. The incidence of new-onset depression was 18.8% with a continuous

increment in incidence over the period of follow-up. The frequency of new-onset depression was related to the frequency of traditional risk factors and to peripheral arterial disease. Females and those with more severe cardiac symptoms were more likely to develop depression. Depression was associated with increases in MI and mortality.

Patients who are depressed after coronary bypass surgery have a 46% 10-year mortality compared to 29% in non-depressed patients. A nurse-led telephone-delivered intervention in depressed patients after coronary bypass surgery failed to show an effect upon 10-year mortality.

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