Introduction
The American College of Cardiology’s 64th Annual Scientific Sessions were held in San Diego from 13 to 16 March 2015. During my stay in San Diego, I was able to attend the ACC sessions as well as several International Steering Committee meetings of the phase 3 clinical trials for which I am the national lead investigator in South Africa.

ACC15 provided a large number of valuable insights into the immediate and longer-term management of patients with acute coronary syndromes, providing new information on thrombus aspiration, anticoagulant strategies, the management of non-culprit lesions in STEMI and dual antiplatelet therapy. In addition there were important reports of trials in TAVR, AF and PCSK9 inhibition. I trust that what follows will share my experience with you, the reader.

KEY MESSAGES

- Whereas traditional risk factors predict cardiovascular (CV) events in the long-term, carotid plaque plus coronary calcification is highly predictive of near-term events
- Coronary CT angiography is not better than functional testing in the evaluation of patients with recent-onset chest pain.
- Type 2 myocardial infarction (MI) (due to haemodynamic stress rather than coronary thrombosis) is associated with a worse outcome
- Prolonged treatment with the P2Y12 inhibitor, ticagrelor, was shown to improve CV outcomes in patients who had had an MI more than a year earlier, albeit at the cost of increased bleeding
- Radial artery access is the preferred procedure in acute coronary intervention
- A randomised trial of thrombus aspiration in STEMI failed to show any benefit of clot removal
- An invasive strategy in over-80-year-olds with NSTEMI/unstable angina, already on optimal medical therapy, resulted in fewer events and less MI than using a non-invasive approach
- PCSK9 inhibitors show further positive results consequent on lower LDL-cholesterol levels

I wish to express my gratitude to Boehringer Ingelheim for sponsoring my economy class return airfare.
Stable coronary artery disease

Dr Valentine Fuster, New York, discussed the question of whether a vulnerable plaque could be detected before the onset of an atherothrombotic event. Investigations reveal that there are multiple ‘vulnerable’ plaques, most of which develop by enlarging and which do not progress to rupture and thrombosis. It is more important to recognise that the disease is systemic; wherever it is detected, it represents systemic involvement.

Whereas traditional risk factors predict the likelihood of events in the longer term, the identification of carotid plaque plus coronary calcification is highly predictive of near-term events. Iliofemoral disease develops earlier than carotid disease and aids the assessment of near-term risk. He does not consider intima media thickness (IMT) measurements to be useful. He has observed that even when adults are made aware of the arterial changes, they do not alter their behaviour. However, influencing children has a knock-on effect on the parents. Lacunar lesions in the brain arise in association with the traditional risk factors (predominantly hypertension and diabetes but not dyslipidaemia) and correlate with the development of cognitive dysfunction. Similarly atrial fibrillation (AF) and prosthetic valve replacement are associated with silent cerebral infarction and cognitive dysfunction. Oxidative stresses promoted by smoking, obesity and lack of exercise result in degradation of the telomere which promotes aging.

Evaluation of chest pain

Little is known about the correct approach to evaluating patients presenting with recent-onset stable chest pain. The pitfalls of traditional ECG stress testing are well recognised. Dr Pamela Douglas led the Prospective Multicentre Imaging Study for Evaluation of Chest Pain trial (PROMISE) and reported on the results. The study compared the management strategy and outcomes after functional stress testing (ECG, stress echo or radioisotope myocardial perfusion imaging) to those after anatomical evaluation with 64-slice computed tomographic angiography (CTA). The study included 10 003 patients in North America. The patients were aged >55 years or >45 years with at least one risk factor. Ninety-four percent of patients were tested as planned. In the functional testing group, stress nuclear or stress echo was performed in almost all patients. Only 10% had ECG stress testing. Follow-up was for 12 months. PROMISE could not show a benefit of CTA over functional testing. CTA was associated with higher radiation exposure and a greater cost. Notwithstanding, CTA may be a viable alternative form of testing.

In a similar study, SCOT HEART employed CTA in patients presenting with angina pectoris in the emergency room (ER). Patients aged 18-75 years presenting with suspected angina were selected. Of the 9 849 patients who presented to the ER, half were recruited into the study. Obstructive coronary disease was detected in 25%. CTA clarified diagnosis, increased diagnosis of coronary artery disease (CAD) and possibly led to improvement in outcome in patients who underwent intervention. However, this was a low-risk population with an overall event rate around 2% per annum. The authors claimed that CTA benefits might relate not only to outcomes, but also to appropriate increases or decreases in preventive treatment.

The Prevention of Cardiovascular Events in patients with a Prior Heart Attack using Ticagrelor compared to Placebo on a Background of Aspirin - TIMI54 trial (PEGASUS) randomised 21 162 stable patients 1-3 years post-myocardial infarction (MI). They were all on background aspirin treatment and treated on ticagrelor 60 mg bd, 90 mg bd or placebo for between 16 and 48 months. The rate of premature discontinuation was 12% per year. By the end of the trial, 25% of patients had had their MI half a decade earlier. The two dosage regimens of ticagrelor reduced the primary endpoint (PEP) (CV death, MI and stroke) by 15 and 16%, respectively. All the individual components of the primary endpoint (PEP) were significantly reduced. Ticagrelor did not decrease all-cause mortality. Bleeding increased with ticagrelor (to a lesser extent with 60 mg
bd) but neither fatal bleeding nor intracranial haemorrhage was impacted. Dr Marc Sabatine, Harvard Medical School, USA, who presented the results, favours using the 60 mg bd dose, suggesting that the ticagrelor dose could be titrated down from 90 mg bd (as was used in the PLATO study) around a year after an MI.

Acute coronary syndromes (ACSs)

Although the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation MI to open the Coronary Artery study (ATLANTIC) showed no benefit of pre-loading ticagrelor in ST segment elevation MI (STEMI), a subgroup analysis demonstrated a benefit in the patients who had not received morphine. Morphine delays the onset of ticagrelor’s action. However, the pre-treatment of STEMI patients was not beneficial. Rather patients were harmed because of increased bleeding. Dr Giles Montelescot, Paris, recommended ticagrelor pre-treatment for STEMI once the diagnosis is confirmed but that treatment be reserved in non-ST segment elevation MI (NSTEMI) until immediately after diagnostic angiography. Whether using clopidogrel, prasugrel or ticagrelor it takes 4–6 hours to achieve platelet inhibition after oral administration, even at higher doses. Switching between ticagrelor and either of the thienopyridines is not recommended.

Dr D Aradi, Hungary, defined the cut-off criteria for high- and low on-treatment platelet reactivity for clopidogrel and prasugrel from previous trials. He considered the VerifyNow, Multiplate and VASP methods to have been validated to determine their cut-off values. He pooled results from 15 studies in over 18 000 patients. High on-treatment platelet reactivity (HPR) increased stent thrombosis (ST) (2.64X) but low on-treatment platelet reactivity (LPR) did not reduce ST. LPR was associated with increased bleeding; HPR slightly reduced bleeding. HPR was associated with a 1.65-fold increase in mortality.

Platelet function after STEMI in patients with human immune deficiency virus (HIV) was reported in a moderated abstract. Eighty HIV patients vs 160 non-HIV patients were studied on dual anti-platelet therapy (DAPT) a month after their first ACS. HPR was more prevalent in the HIV group.

Bacteraemia increases the risk of MI and stroke 20-fold. In the PLATO study, ticagrelor reduced the incidence of infection-related events. Ticagrelor reduces platelet-leucocyte interactions and pro-inflammatory cytokines. A trial compared ticagrelor, clopidogrel and placebo in response to a mimic of bacterial endotoxaemia. The marked rise in D-dimer after stimulation with endotoxin was reduced by 50% by ticagrelor and less so by clopidogrel. The study demonstrated how ticagrelor might reduce thrombotic events and inflammatory responses to pulmonary infection and sepsis.

Although we do not use bivalirudin in South Africa, the current debate regarding whether unfractionated heparin (UFH) or bivalirudin should be preferred for percutaneous coronary intervention (PCI) in ACS is instructive. The superiority of bivalirudin has come into question recently. Reviewers noted a lower major adverse CV event (MACE) rate and less stent thrombosis (ST) with heparin at a reduced cost. After the introduction of $P_{2Y_12}$ inhibition, the reduction in glycoprotein (GP) IIb/IIIa inhibitor use, the use of new generations of less thrombogenic drug-eluting stents (DESs) and radial artery access, the perceived lower bleeding risk with bivalirudin (which in any event was probably driven by the GPIIb/IIIa inhibitors given along with heparin in the trials) is no longer considered important.

The Minimising Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation on AngioX trial (MATRIX) compared bivalirudin to UFH with optional use of GPIIb/IIIa inhibition (GPI) in both arms of the study. Seven thousand patients were recruited. A small minority of bivalirudin-treated patients received GPI whereas 25% got the combination in the UFH arm. There was no difference in the primary outcome. Mortality was reduced by 29% in the bivalirudin arm and bleeding was less, especially at non-access sites. However ST was increased with bivalirudin.

A second part of the MATRIX trial
examined radial access vs the transfemoral route in NSTEMI and STEMI. Eight thousand four hundred and four patients were included and treated by experienced ‘radialists’. With radial access there was a 1.5% absolute reduction in PEPs and 17% relative reduction in bleeding. Bleeding at non-access sites was not affected. There was no difference in overall mortality. No differences were detected between the UFH- and bivalirudin-treated subgroups. The authors recommended radial access as the default procedure for acute intervention.

Dr Roxana Mehran, Mount Sinai, New York, presented REG-17. This trial employed a novel antithrombin, pegnivacogin, to inhibit Factor IXa. Pegnivacogin can be reversed by anivamersen. The system was compared to bivalirudin. The pegnivacogin was reversed at the end of PCI. The study was discontinued due to an excess of allergic reactions to pegnivacogin. There were otherwise similar outcomes for pegnivacogin and bivalirudin.

Dr David Holmes, Mayo Clinic, USA, argued in favour of culprit-only primary PCI with staged multivessel PCI thereafter. The available data point to adverse outcomes with primary multivessel treatment. However, not all lesions are similar. The data from recent small trials are insufficient to change the current guidelines. Although they may indicate otherwise, the general rule is that their implausibly large treatment effects have to be treated with reserve.

Dr Cindy Grines, Detroit, USA, pointed to the fact that there are no data on fractional flow reserve (FFR) to guide non-culprit lesion treatment. FFR is not helpful in the acute phase of STEMI as the distal flow and area of supply are unpredictable. FFR in NSTEMI (FAMOUS FFR) showed that the result can change the treatment decision. However FFR becomes a valid test only after the acute phase.

DANAMI3-PRIMULTI8 enrolled patients after successful culprit-vessel primary PCI, randomising them to staged non-culprit FFR-guided PCI within days vs no PCI. The 44% reduction in PEPs in the FFR-PCI group was entirely due to the reduction in ischaemia-driven revascularisation. Forty percent of subsequent revascularisations in the no-PCI group were urgent procedures. There was no difference in mortality between the two groups.

The BEST trial9 compared an everolimus-eluting stent to coronary artery bypass grafting (CABG) in 880 patients with multivessel disease. This trial was discontinued before full enrolment. Five-year follow-up was available in 170 patients in both groups. BEST demonstrated that the stent strategy was not non-inferior to CABG. Patients were worse off in the stent group (although not always significantly so). The stent results were clearly worse in diabetics.

Remote ischaemic preconditioning can be applied by inflating a blood pressure cuff on the arm. In a clinical trial involving 1 612 high-risk STEMI patients with an average age of 76 years, four inflations of five minutes each at five-minute intervals was the method used. The trial found no difference in outcome.

Dr Mike Gibson, Boston, USA, presented the EMBRACE study10 with benadavia, an agent that targets mitochondria to preserve the integrity of their electrolyte transport function and improves myocardial energetics. One hundred and eighteen patients with their first MI, with a proximal or mid-LAD lesion, arriving at the cath lab <4 hours were enrolled before reperfusion. Treatment was started 15 minutes before reperfusion. The success rates of primary PCI were equal. The study found no difference between groups for benadavia and bivalirudin.

Thrombus aspiration reduces the subsequent rise in inflammatory markers after STEMI.

The TOTAL trial evaluated thrombus aspiration in STEMI in a randomised trial of 10 732 patients. Bail-out was allowed in the PCI-only group (crossover occurred in 1.4%). Although aspiration reduced the incidence of no-reflow, there was no difference in eventual outcome. More strokes occurred in the aspiration group. Aspiration had no effect on ST.
patients in the two arms of the trial; 25% of patients had no significant coronary stenosis at angiography. There was a 52% reduction in the PEP in the invasive arm with less MI. There were no significant differences in bleeding.

**Dyslipidaemia: PCSK9 inhibitors and other novel agents**

Dr Marc Sabatine, Boston, presented the OSLER study, an extension of a number of Phase 2 & 3 studies conducted with evolucumab (a PCSK9 inhibitor) in patients who had been followed for one year. Seven percent discontinued treatment. Both 140 mg and 340 mg doses were included. The average age of patients was 58 years; 51% were male and 25% were known to have CV disease. Most were also on moderate- or high-dose statin therapy. The mean on-treatment LDL cholesterol level was 1.2 mmol. A consistent 50% reduction in events was observed without heterogeneity between subgroups. Neurocognitive events increased slightly in the PSCK9 group (0.9% vs 0.3%). There was no gradient for those with a lower LDL cholesterol level. This study reinforces the cholesterol hypothesis, demonstrating a reduction in CV events with both statin and non-statin agents.

An overview of 14 trials of alirocumab found no increase in the incidence of side-effects in large subgroups of patients whose LDL cholesterol levels fell to <0.6 and <0.4 mmol.

The primary result in IMPROVE-IT showed 6% reduction in PEPs by adding ezetimibe 10 mg daily to simvastatin treatment after an ACS. When considering the sum total of events (9 545 first and subsequent events) over the entire trial period of 6-8.6 years, total events were reduced by 9%; CVD, MI and stroke by 12%.

ETC 1002 is a novel agent that has been shown to lower LDL cholesterol to a greater extent than ezetimibe, effecting a greater than 50% reduction in LDL cholesterol in combination with ezetimibe in both statin-tolerant and statin-intolerant patients, with a low incidence of side-effects.

**AF**

The AATAC-AF in Heart Failure study compared amiodarone to AF ablation in patients with persistent AF and HF with an implanted CRT Device. It showed a 50% reduction in recurrence of AF in the ablation group, along with reduced hospitalisation and improved all-cause mortality.

The LEGACY study found that weight loss but not fluctuation in weight in obese or overweight patients reduces the frequency of AF. Participants were directed by a dedicated weight loss clinic prescribing diet and an exercise programme.

The risk of systemic embolism rises in the presence of any AF. Arbitrarily, a cut-off of six minutes of device-detected AF has been selected as an indicator of the need for oral anticoagulation. Silent AF may become more frequent after AF ablation. Although successfully ablated patients may not require long term oral anticoagulation, the decision must be individualised. The onset of stroke has a variable temporal relationship with the occurrence of paroxysms of AF. Factors relating to the risk of systemic embolism may operate either directly through AF or AF may be simply another risk marker for systemic embolism.

**Transcutaneous aortic valve replacement (TAVR) for aortic stenosis**

The PARTNER 1A trial five-year outcome was reported. Six hundred and ninety-nine high-risk patients were randomised to receive either the Edwards Sapien valve or be treated surgically. The mean age of patients was 83-84 years. An STS of 11.8 indicated very high risk. There was no significant difference in outcome at five years with identical survival rates for the transfemoral route. There was no difference in stroke. Left ventricular mass index improved for two years; 85%
vs 81% of patients were in NYHA Class 1-2 at five years. Low body mass index (BMI), liver disease and peripheral vascular disease predicted a worse outcome with TAVR. No structural deterioration in the valve was observed in either arm. However, the question of structural deterioration is not yet resolved completely. Aortic regurgitation (AR) of more than mild degree was a predictor of mortality. The intolerance of AR may relate to the hypertrophied left ventricle (LV) being unprepared to accept the new additional volume.

The CoreValve was shown to have superior survival by 5% over one year. This superiority over surgical valve replacement is sustained at two years with a slight increase in the differences, with less stroke and stroke mortality. MACE differed by 8.9%. However the incidence of AR is greater. No heterogeneity could be demonstrated in various groups. The benefit applied also to the lower-risk patients.

PARTNER II high- and intermediate-risk patients receiving the Sapien 3 valve had a very low early mortality (1.1%) and stroke risk (1%) and a low incidence of AR. Permanent pacing was required in 10-13%.

The TriGuard protection device, which shields the aortic arch vessels during TAVR, reduced stroke rate by 10% and reduced the incidence of ischaemic brain lesions.

Cardiomyopathy

The definition of cardiomyopathy should not include ischaemic, valvular or hypertensive diseases. Cardiomyopathy may be divided into genetic, acquired and mixed forms. They may be primary or secondary, familial or non-familial. The clinician is advised to look for the ‘diagnostic red flags’ in the clinical examination, ECG, laboratory tests (first level: creatine kinase, liver function, urea, electrolytes and creatinine and endomyocardial biopsy) before progressing to genetic testing.

Amyloid heart disease is best diagnosed directly from myocardial biopsy rather than biopsy of other tissues (which offer good specificity but poor sensitivity). However myocardial biopsy may not always diagnose cardiac amyloid or sarcoid due to the focal nature of the myocardial involvement.

Dr CY Liu, Taiwan, reviewed the use of biomarkers in cardiomyopathy. HF markers (CRP, proBNP and hs-troponin T) are prognostic and disease-specific markers that characterise the phenotype. In stress cardiomyopathy proBNP is often high without a marked elevation in hs-troponin T. Proteomic approaches are being used to recognise severe forms of myocarditis.

Dr DA Bluemke, NIH, USA, discussed the use of cardiovascular magnetic resonance (CMR) in cardiomyopathy which is good for structural aspects (right ventricle, myocardium) and tissue characterisation. Reaching the specific diagnosis often depends on knowing the patient’s background. Typical CMR changes are found in endomyocardial fibrosis, Duchenne muscular dystrophy, ventricular non-compaction, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Probably 3-5% of patients diagnosed with hypertrophic cardiomyopathy (HCM) have Fabry disease, which has a distinct appearance on CMR. Although it is not always diagnostic, CMR is also useful in identifying the patterns of amyloid and sarcoid involvement of the heart.

FDG-PET is useful for the diagnosis of sarcoid but the changes are non-specific as they may reflect changes of ischaemic, inflammatory, infiltrative or tumorous conditions. 2-[fluorine 18] fluoro-2-deoxy-d-glucose (FDG) may be combined with perfusion imaging. Tc-pyrophosphate aids in diagnosing amyloid but a negative study does not exclude it. Amyloid light chains may be myotoxic. Amyloid infiltration may impair microvascular flow and result in perfusion defects. Specialised imaging may be able to differentiate the type of amyloid which clarifies the prognosis. Isotopic studies are being investigated for the early identification of cardiotoxicity resulting from chemotherapy.

Dr EA Ashley from Stanford, USA spoke on genetic testing in cardiomyopathy. He highlighted the high frequency of familial involvement in idiopathic dilated cardiomyopathy (IDCM). Twenty-nine percent of relatives of patients with cardiomyopathy have a genetic defect. It is a disadvantage of CMR that it is not diagnostic but it is useful for identifying patterns of amyloid and sarcoid involvement.

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IDCM have an abnormal echo. He recommended that genetic evaluations be conducted by a licensed counsellor because genetic testing forms only one part of this. As an example, he noted that in HCM, genetic testing may be helpful in only 35-60% of cases. Frequently the abnormality detected is rare and may not have been seen previously. Panel testing is expensive and costs US$1500 - 6000.

**HF**

Depression relates in a dose-dependent fashion to mortality and morbidity in HF patients. MOOD-HF trial\(^{16}\) randomised 376 patients to evaluate the effect of escitalopram vs placebo. There was no difference in outcome between escitalopram and placebo despite a marked improvement in depression. Escitalopram may have attenuated the improvement in HF parameters compared to placebo.

Baroreflex stimulation (baroreceptor activation therapy) for treatment of HF with reduced ejection fraction improved NYHA functional class, quality of life and the six-minute walk test. The magnitude of the changes observed was greater than that for guideline-recommended pharmacotherapy. Hospitalisations were decreased. Although ejection fraction improved and proBNP came down, there was no change in LV dimension.

Transfemoral pulmonary artery denervation for pulmonary hypertension improved the six-minute walk test by 20% and reduced mean pulmonary artery pressure.

**Cardiology in emerging countries**

This international symposium was addressed by a variety of speakers from Brazil, Mexico, Africa, India and China. A common thread in these presentations was the disproportion between the number of cardiologists and the population that they are required to serve. Added to this, there is a regional and economic maldistribution within countries, with the rural areas and the poor being underserved. In this situation the contribution of primary care providers has to assume much greater importance and places the responsibility on specialists to disseminate information to other providers to influence their treatment patterns.

No ‘one size fits all’ in relation to guidelines. Priorities vary between countries and those undergoing the epidemiological transition experience a lesser incidence of atherosclerotic vascular disease but a greater incidence and impact of the risk factors leading up to it. In Nigeria, two-thirds of CV admissions are for the treatment of hypertension and its complications. Though guideline-based care has been shown to improve patient outcomes, the implementation thereof remains problematic. Confusion is created when various bodies within a country generate guidelines on a given topic which are not harmonised with those of other local recommendations. National societies, government departments and health care insurers have independently set out recommendations without necessarily making reference to one another. Successful guideline implementation depends on quality, dissemination, incentivising the role-players and the integration of the recommendations into health policy. On the positive side, when governments do become involved in implementing guidelines, such as in Mexico, both primary prevention and the treatment of disease improve. The Mexican Health Ministry supports risk factor detection, the implementation of preventive care and periodic risk re-evaluation. They lend support to stopping smoking, anti-obesity programmes, the promotion of exercise, the early detection and treatment of hypertension, and the removal of salt from foods and restaurants.

The care of the elderly was discussed in the second session of this meeting. The elderly comprise a heterogeneous group. Roughly 55% are healthy and active, 20% have chronic disease with frailty, 20% are depressed and immobile, and 5% are totally dependent. In dealing with their situation, their individual wishes, beliefs and cultural values must be respected.

The significance of managing both depression and dementia is emphasised by their impact on morbidity/mortality and the monetary burden they impose. The physician must recognise the need to
curtail disease-modifying care in favour of providing palliative treatment. At the end of life it is important to see that the patient ‘dies well’.

It is apparent that there are few, if any, facilities to care for the burgeoning elderly population in developing countries. Demographic changes have led to a reduction in family support for elderly parents and pensions are small or non-existent. Many patients must pay for medical care out of their own pockets, in some instances in amounts that are equivalent to many years of their annual income. In Mexico there is a law to ensure protection against catastrophic health care costs; a measure which should be considered by other central governments to assist patients, particularly the elderly, to avoid financial ruin.

The future of CV medicine

The third in a series of presentations examined the future of CV medicine. Diverse topics such as computer-aided design, the use of mobile technology to improve efficiency, and using social media were discussed. By using social media it is possible to reach the most people in the shortest time to provide critical information. However, there is a risk that by using social media in patient interactions, protected health information may be broadcast to the public. The United States Food and Drug Administration regards this in the same light as direct-to-consumer advertising.

Social media may be used to ‘spread the word’ for patient education but only already published, reliable information should be divulged. The information provided should be accurate, clear and easily digestible. For their part, patients may use a symptom checker to begin to decipher their condition, which in turn may facilitate contact with their health care provider. Patients also may seek group support through communication with fellow sufferers. One patient had allayed her fears by discussing her problem over the internet with other patients. She found that the group support was helpful and improved her compliance with treatment. Social media can facilitate collaboration between doctor, patient, colleague and industry. Social media sites can also be curators of information. They may be useful in recruitment for clinical trials and interaction during trials. However, caution is advised when using social media as the physician remains liable for the effects of any information transmitted by her/him.

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