ACC.15 Report

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The American College of Cardiology’s 64th Annual Scientific Sessions were held in San Diego from 13 – 16 March 2015. I wish to express my gratitude to Boehringer-Ingelheim for sponsoring my economy class return airfare. 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.

Stable coronary artery disease

Fuster 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 will 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. Ilio-femoral disease develops earlier than carotid disease and aids the assessment of the near-term risk. Fuster does not consider IMT measurements to be useful. He has observed that even when they are made aware of the arterial changes, adults do not alter their behavior. 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 cognitive dysfunction. Similarly atrial fibrillation (AF) and prosthetic valve replacement associate with silent cerebral infarction and cognitive dysfunction. Oxidative stresses promoted by smoking, obesity and lack of exercise result in degradation of the telomere that promotes aging.

Little is known about the correct approach to evaluating patients presenting with recent onset stable chest pain. The pitfalls with traditional ECG stress testing are well recognized. Dr Pamela Douglas led the PROMISE trial and reported on the results which compared the management strategy and outcomes after functional stress testing (ECG, stress echo or radioisotope myocardial perfusion imaging) to those after anatomic evaluation with 64-slice computed tomographic angiography (CTA). 10 003 patients in North America were included. The patients were aged >55 years or >45 years with at least 1 risk factor. 94% 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). They selected patients with suspected angina aged 18-75 years. Of the 9849 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 CAD and possibly lead to improvement in outcome in patients who underwent intervention. However this was a low risk population with an overall risk event rate around 2% p.a. The authors claimed that CTA benefits might relate not only to outcomes but appropriate increases or decreases in preventive treatment.

The PEGASUS trial randomised 21 162 patients 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% /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 (cardiovascular [CV] death, MI and stroke) by 15 and 16% respectively. All the components of the primary end point (PEP) were individually 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 or intracranial haemorrhage was impacted. Dr Marc Sabatine 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 (ACS)*

Type 2 MI (MI due to haemodynamic stress rather than coronary thrombosis) is associated with a worse outcome.

Stress is associated with telomere shortening and results in a greater risk of MI.

MI is associated with higher risk of subsequent cancer – lung and bladder.

Although the ATLANTIC study showed no benefit of pre-loading ticagrelor in ST segment elevation MI (STEMI), a subgroup analysis demonstrates 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 did not benefit but rather were harmed due to increased bleeding. Montelestoc recommended ticagrelor pretreatment for STEMI once the diagnosis is confirmed but reserving treatment 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.

Aradi defined the cut-off criteria for high- and low-on-treatment platelet activity 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 1.65X increase in mortality.
Platelet function after STEMI in patients with human immune deficiency virus (HIV) was reported in a moderated abstract. 80 HIV patients vs. 160 non-HIV patients were studied on dual antiplatelet therapy (DAPT) a month after their 1\textsuperscript{st} ACS. HPR was more prevalent in HIV group.

Bacteraemia increases the risk of MI and stroke 20 fold. In PLATO 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 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 cardiovascular event (MACE) risk and less stent thrombosis (ST) with heparin and a reduced cost. After the introduction of P2Y\textsubscript{12} inhibition, the reduction in glycoprotein (GP) IIb/IIIa inhibitor use, the use of new generations of less thrombogenic drug eluting stents (DES) 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 MATRIX study compared bivalirudin to UFH with optional use of GPIIb/IIIa inhibition (GPI) in both arms of the study. 7000 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.

Dr Roxana Mehran presented REG-1. This trial employed a novel system of the antithrombin pegnivacogin to inhibit Factor IXa. Peginivacogin can be reversed by anivamersen. The system was compared to bivalirudin. The pegnivacogin was reversed at the end of PCI. The study was discontinued for an excess of allergic reactions to pegnivacogin. There were otherwise similar outcomes for pegnivacogin and bivalirudin.

A second part of the MATRIX trial examined radial access vs transfemoral route in NSTEMI and STEMI. 8404 patients were included and treated by operators experienced in radial access. With radial access there was a 1.5\% absolute reduction in PEP 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.

Holmes argued in favour of culprit only primary PCI with staged multivessel PCI thereafter. The available data points to adverse outcomes with primary multivessel treatment.
However not all lesions are similar. The data from recent small trials is 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. Grines pointed to the fact that there is no data on FFR to guide non-culprit lesion treatment. FFR is not helpful in acute phase of STEMI as the distal flow and area of supply 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.

The BEST trial compared an evorolimus-eluting stent (EES) to CABG in 880 patients with multivessel disease. This trial was discontinued before full enrollment. 5 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 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 in of 1 612 high risk STEMI patients with an average age of 76 years, 4 inflations of 5 minutes each at 5 minute intervals was the method used. The trial found no difference in outcome.

Dr Mike Gibson presented the EMBRACE study with bendavia, an agent that targets mitochondria to preserve the integrity of their electrolyte transport function and improves myocardial energetics. 118 patients with their first MI with a proximal or mid-LAD lesion arriving in 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 cardiac markers, cardiac magnetic resonance imagain (CMRI), or ST-segment resolution. There was a trend towards reduction in new-onset heart failure <24 hours with bendavia.

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

TOTAL 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.

DANAMI3-PRIMULTI 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 PEP in the FFR-PCI group was entirely due to the reduction in ischaemia-driven revascularisation. 40% of subsequent revascularisations in the no-PCI group were urgent procedures. There was no difference in mortality between the 2 groups.

A conservative vs invasive strategy was compared in patients with NSTEMI or unstable angina who were over age 80 years of age. All patients were on optimal medical therapy. The trial included 229 and 228 patients in the two arms. 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 Sabatine presented the OSLER Study, an extension of a number of Phase 2 & 3 studies with 1 year follow-up conducted with evolucumab (a PCSK9 inhibitor). 7% discontinued treatment. Both 140 mg and 340 mg doses were included. The average age of patients was 58 years. 51% were male. 25% were known to have CV disease. Most were on moderate- or high-dose statin therapy. The mean on-treatment LDLc 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 LDLc. This study reinforces the cholesterol hypothesis by 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 sub-groups of patients whose LDLc fell to <0.6 and <0.4 mmol.

The primary result in IMPROVE-IT showed 6% reduction in PEP by adding ezetimibe 10 mg daily to simvastatin treatment after an ACS. By 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 were reduced 12%.

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

Atrial fibrillation

The AATAC-AF in Heart Failure study comparing amiodarone to atrial fibrillation ablation in patients with persistent AF and heart failure with an implanted CRT-D or CRT device. It showed a 50% reduction in recurrence of AF in the ablation group, reduced hospitalisation and improved all-cause mortality.

The LEGACY study showed 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 exercise programme.

The risk of systemic embolism rises in the presence of any AF. Arbitrarily, a cut-off of 6 min 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 5-year outcome was reported. 699 high risk patients were randomized to receive either the Edwards Sapien valve or be treated surgically. The mean
age of patients was 83 to 84 years. An STS of 11.8 indicated very high risk. There was no significant difference in outcome at 5 years with identical survival for trans femoral route. There was no difference in stroke. Left ventricular mass index improved for 2 years. 85% vs 81% of patients were in NYHA Class 1-2 at 5 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 1 year. This superiority is sustained at 2 years with a slight increase in the differences, with less stroke and stroke mortality. MACCE 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.

Liu reviewed the use of biomarkers in cardiomyopathy. Heart failure markers (CRP, proBNP and hs-troponin T are prognostic) and disease specific markers 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.

Bluemke discussed the use of CMR in cardiomyopathy which is good for structural aspects (RV, 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 it may reflect changes of ischaemic, inflammatory, infiltrative or tumourous conditions. FDG may be combined with perfusion imaging. Tc-pyrophosphate aids in diagnosing amyloid but a negative study does not exclude amyloid. 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.

Ashley from Stanford spoke on genetic testing in cardiomyopathy. He highlighted the high frequency of familial involvement in idiopathic dilated cardiomyopathy (IDCM). 29% of relatives of patients with 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 the 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.

Heart failure (HF)

Alfisol's implanted inert material at various sites into the myocardium via mini-thoracotomy which improved peak VO₂ at 6 months.

Depression relates in a dose-dependent fashion to mortality and morbidity in HF patients. MOOD HF 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 heart failure parameters compared to placebo.

Baroreflex stimulation (baroreceptor activation therapy) for treatment of heart failure with reduced ejection fraction improved NYHA functional class, quality of life and the 6 min 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 6-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 healthcare 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.

In a second session at this meeting, the care of the elderly was discussed. 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 both morbidity-mortality and the monetary burden they impose. The physician needs to recognise the necessity to diminish 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 for the Protection against Catastrophic Health Care Costs, a measure should be considered by central governments to assist patients and particularly the elderly to avoid financial ruin.

Notwithstanding advancing age, the application of standard of care preventive measures (non-smoking, a healthy diet and regular physical activity) has been shown in the SENECA study to add a decade to the lifespan.

A third part of this symposium dealt with the problem of training cardiologists in the developing world. Mayosi from Cape Town made the most significant contribution in this
respect, outlining an innovative modular training programme which in step-wise fashion prepares the trainee to become a fully-fledged cardiologist while also ensuring that the skills acquired are used in his/her country of origin and not lost through emigration to more developed countries.

The future of cardiovascular medicine

I attended the third in a series of presentations examining the future of CV medicine. Diverse topics such as computer aided design, the use of mobile technology to improve efficiency, and using social media had been 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, industry. Social media sites can also be curators of information. They may be useful in recruitment for clinical trials and interaction during trials. Caution is advisable when using social media – the physician’s liability constitutes a risk.