REPORT ON ESC 2012

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The 60th European Society of Cardiology Annual Meeting was held in Munich, Germany from 25-29 August 2012. My travel costs and accommodation were generously sponsored by Sanofi. The meeting was of a very high standard and all the South African participants to whom I spoke found it very enjoyable. What follows are some of the impressions that I obtained from the meeting.

New ESC Guidelines:

During the meeting significant emphasis was placed upon the six ESC Guidelines published during the year. They concern:

- Cardiovascular disease prevention,
- Valvular heart disease,
- ST elevation myocardial infarction,
- The 3rd universal definition of myocardial infarction,
- A focussed update on atrial fibrillation, and
- Heart failure.

The full text of all these Guidelines is freely accessibly to all at escardio.org/guidelines . These Guidelines are important as they are adopted by the SA Heart Association.

Population studies, registries and preventive therapy:

The PURE study was presented by Prof Salim Yusuf which surveyed 154 000 subjects in 17 countries evaluating the relationships between the life style factors smoking, diet and physical activity, and national GDP and individual wealth. South Africa and Zimbabwe were included. Poorer countries were characterised by less calorie intake with a major contribution from carbohydrates and less fruit and vegetable, a greater amount of non-recreational activity and more ever having smoked. By contrast wealthier countries and particularly individual wealth correlated with higher calorie intake (by about 10%) with more meat, a greater saturated fat intake and more fruit and vegetables. Recreational physical activity was more frequent in wealthier society, but the energy expenditure did not equal the non-recreational energy expenditure in the poorer communities. Increased wealth was associated with a higher incidence of having quit smoking in both men and women. Follow-up is planned to assess the effects of these differences on outcome.

A study mentioned during the highlights session found that the incidence of cardiovascular (CV) risk factors rose sharply in children aged 3 - 1 8 years in proportion to their degree of obesity. Non-obese children had a frequency of risk factors of 2% whereas the most obese had an incidence of 88%.

In a survey of 7 000 adults over 60 years at risk of CV disease, there was a low percentage who received statin treatment and a low number of the treated patients who achieved their target LDL cholesterol level.

Lonn reported the atherosclerosis sub-study of the ORIGIN trial which observed the effects of glargine and polyunsaturated fatty acid (PUFA) on carotid intima-media thickness. PUFA's had no

effect in these high risk patients (>50 years with dysglycaemia and additional CHD risk) over 4.9 years. There was possibly a marginal benefit with glargine.

The effects of major stress were illustrated by the experience during the Great East Japan Earthquake Disaster. 16 000 people were killed and 3 000 are still missing. In survivors the incidences of heart failure (HF), acute coronary syndrome (ACS), stroke, cardiopulmonary arrest (CPA) and pneumonia all increased immediately thereafter. HF and stroke (ischaemic rather than haemorrhagic) increased earliest, followed by brief upsurges in ACS and CPA. Environmental conditions were adverse and pneumonia increased from early on and continued for some weeks.

FAST-MI registry of ST segment elevation myocardial infarction (STEMI) has been conducted 4 times at regular intervals over the past 14 years in France. 6707 patients were included. During this series of observations there has been a reduction in age at presentation (especially in women) with less comorbidity, less prior myocardial infarction (MI) and a lower risk factor profile. Younger women were observed to be smoking more frequently and to be more obese. The time to first medical contact has diminished from 2 hours to 74 minutes. Less patients now get no reperfusion and whereas fibrinolysis has declined, percutaneous intervention (PCI) has increased. Evidence-based preventive therapy has increased and mortality has decreased from 13.7% in the first survey to 4.4% in the latest, a fall of 61%.

Hypertension and diabetes:

In a study comparing office vs. ambulatory BP recording it was shown that 2/3 hypertensive patients who record normal office BP have an elevated BP on 24 hour monitoring. In another it was concluded that nocturnal elevation in BP correlated with atrial fibrillation (AF), stroke and CV events.

The ALTITUDE study compared the effect of the renin inhibitor aliskiren to usual therapy with an ACE inhibitor or ARB in patients with Type 2 diabetes and proteinuria or reduced kidney function over a 32 month period. The trial was stopped due to futility. In the aliskiren group there was a 1.3/0.6 mm Hg difference in BP and albuminuria was reduced by 14%. Hyperkalaemia was encountered, related to the impairment of the eGFR and albuminuria.

A speaker in the highlights session drew attention to the fact that there are no new anti-hypertensive agents in development at present.

The 18 month follow-up of the SIMPLICITY-2 trial showed a persistent reduction in BP associated with variable change (decrement or increment) in anti-hypertensive therapy. No rebound has been observed. The original control group had delayed renal denervation (RDN) and although their BP fell by a similar amount, that group did not achieve the same BP as the originally treated group. In other studies, no postural hypotension was observed post-RDN. In RDN one study reported an increase in sodium excretion (persisting for 6 months?), another showing that the ultrasound measured renal resistive index was reduced unrelated to the response in BP with no effect on renal function and a reduction in proteinuria. Patients after RDN exhibited less depression, anxiety and headache and an improved quality of life score.

Sleep apnoea:

Sleep disordered breathing (SDB) is associated with hypertension, pulmonary hypertension, stroke, coronary artery disease (CAD), heart failure (HF) and AF. The relationship of obstructive sleep apnoea (OSA) to the risk of developing HT is documented (Peppard, NEJM 2000; Marin 2012). OSA is associated with a higher incidence of CV events (Marin, Lancet 2005). ICD discharges are more frequent in OSA and the relapse rate of AF is 50% higher (including post-ablation cases). There is a 2.5X higher mortality in untreated OSA. Successful treatment (CPAP >4 hours /night) of OSA modifies outcomes. Central sleep apnoea may also be treated successfully by alternatives to CPAP.

Heart failure:

The assertion continues to be made that heart failure with preserved ejection fraction (HeFpEF) constitutes the majority of HF and carries the same prognosis as HF with a reduced ejection fraction. The pathophysiology of HeFpEF is multifactorial and best identified by its "fingerprints": female sex, age, obesity and hypertension. Common comorbidity such as COPD (30-40%), chronic kidney disease and anaemia each increase the risk of HeFpEF by 20%. HeFpEF may occur due to alterations in myocytes, the interstitial tissue or the microcirculation. Diagnosis remains difficult and there is no specific echocardiographic parameter that has proved its value in establishing the diagnosis. The echo substudy of I-PRESERVE demonstrated that 50% of patients in the trial had no little or no evidence of remodelling. There are no new treatment recommendations.

Two trials in HeFpEF were reported. PARAMOUNT compared the neprilysin inhibitor (which is in effect the angiotension receptor blocker valsartan and a neutral endopeptidase (NEP) inhibitor in combination) with valsartan 160 mg bd. NEP-inhibition blocks degradation of BNP, promoting the effect of the natural vasodilator. NT proBNP at 12 weeks was the endpoint. At 12 weeks NT proBNP was reduced by 33% but the difference was insignificant at 36 weeks. The trial drug lowered BP and reduced LA size. No change in diastolic function was detectable and the NYHA class was not altered.

ALDO DHF enrolled 420 patients with HeFpEF comparing spironolactone to placebo. Although diastolic function, systolic and diastolic BP, LV mass and NTproBNP altered in the right direction, exercise capacity was not affected.

Atrial fibrillation:

The GARFIELD registry is an on-going international study of patients with AF at risk of stroke. A report on 7 630 patients revealed that 37% of these patients had either mild or moderate renal dysfunction with only 2% with severe dysfunction or renal failure. Factors associated with an increased risk of renal dysfunction were increasing age, PAD, carotid disease, a history of stroke and history of bleeding. VKA was prescribed in 57%, with 15% getting aspirin as well. Aspirin alone was given in 25-30% and neither in 12%.

There was a paradigm shift in AAD therapy for AF after AFFIRM was published about a decade ago. While uncertain that rhythm control may confer benefit, there are indications that this may be a long-term effect (>4 years). Because of progressive electrical, structural and contractile changes in the atria, the success of cardioversion is dependent upon the duration of AF. In a discussion on IV vernakalant for the cardioversion of recent-onset AF, it was reported that sinus rhythm is usually restored within 11 minutes after injection with few side-effects and apparent safety when structural heart disease, left ventricular dysfunction and appropriate anticoagulation are taken into account.

A symposium was held on anticoagulation in AF. In patients with AF, hospitalisation has constituted 52% of the cost with drugs making up only 23%. Trials have shown that warfarin reduces stroke rates by 60%. The new ESC guideline mandates anticoagulation in all patients with lone AF >65 years and those with a $CHADS_2$-VaSC score of >1. In those with a score of 1, the bleeding risk should be evaluated to guide the decision about anticoagulant use. Despite the (upcoming) availability of novel oral anticoagulants (NOAC), VKA antagonists (warfarin) remains indicated in valvar AF, prosthetic heart valves, renal failure, other indications not yet defined for NOAC's and possibly those on warfarin with a stable INR who see no reason to change. The Hemoclot test can measure the effect of dabigatran and anti-Factor Xa measurements are appropriate with the oral anti-Xa agents (rivaroxaban, apixaban and the trial agent edoxaban). The lack of an antidote to any of the NOAC's is a relative contraindication. However all the speakers in this symposium felt that NOAC therapy was to be preferred to VKA in non-valvar AF. NOAC agents have been included in the 2012 focussed update of the ESC AF Guideline.

Wallentin reviewed the relative effects of the NOAC's, concluding that there are more similarities than differences between the various agents. Hohnloser concurred. In the trials, all showed a similarity of outcome, all were associated with less intracranial haemorrhage and a lower mortality. Ezekowitz, who spoke on bleeding risk, pointed out that in AF many clinicians are more prone to avoid (what are perceived as) errors of commission (giving a drug associated with increased bleeding) than errors of omission (not prescribing an anticoagulant to avoid stroke). Although supporting the use of NOAC's, he advised caution in patients with declining renal function and taking care to adjust the dose appropriately. Pre-surgical protocols, missed dose protocols, patient understanding and cooperation to ensure compliance will improve outcomes with NOAC's.

In ROCKET-AF the lack of a transition strategy at trial end lead to an excess of stroke (22 vs. 6) in the rivaroxaban treated group within the first 30 days. Although fully 92% were transitioned to warfarin, INR control above 2.0 by the end of the 30 days was only 51.9%. The median time to successful transition was 13 days. Following the detection of this problem, the protocols of ARISTOTLE and ENGAGE-AF were modified to overcome this effect. Also in ROCKET-AF, when TTR was evaluated by site, the event rate on warfarin was lower the higher the INR, but there was a parallel fall-off in event rate in the rivaroxaban group, suggesting overall better care at those sites. Throughout the range of TTR, rivaroxaban performed better than warfarin.

Platelet function inhibition was examined in two small groups of patients with AF, one on warfarin and the other on dabigatran. There was little effect in responsiveness to ADP but a distinct effect with TRAP with dabigatran and to a lesser extent with warfarin, raising the possibility that thrombin receptors downregulate when thrombin is inhibited by dabigatran or its production is reduced by warfarin.

Arbelo reported on the European registry on AF ablation in 1 300 patients followed for 1 year. 67% had paroxysmal AF; 25% persistent AF. Average age was 60 years. 90% were symptomatic. 50% had $CHADS_2$ score 0. 78% were treated with open irrigation RF. Complications occurred in 2.6%. 30% required readmission. There were 4 deaths. Repeat procedures were needed in 18%. By one year there was a 74% success rate. Palpitations, fatigue and dyspnoea were less frequent. 50-60% were still on AAD and disappointingly 20-25% were not receiving guideline-mandated OAC.

PRAGUE-12 is a randomised trial of cryomaze (98%) in all forms of cardiac surgery in 224 patients (mean age 70 years) with pre-operative AF. 1 year follow-up showed maintenance of SR in 60% vs. 35.5% with less surgical complications but no difference in clinical outcome. Greater benefit was observed in long-standing persistent AF. Follow-up will continue for 5 years.

Coronary imaging:

CORE 320 compared computed tomographic angiography (CTA) + CT perfusion with adenosine to coronary angiography and positron emission tomography (PET). A 320 slice scanner was used. The procedure entailed additional contrast and radiation. The authors claimed improved discrimination of significant lesions with distal ischaemia with about 80% sensitivity and specificity. It may be prove to be a better rule out test as the negative predictive value was 92%.

The DE FACTO trial evaluated CT fractional flow rate (FFR) with the outcomes of conventional CTA. The evaluation was derived from standard CTA without requiring additional contrast medium. FFR-CT was superior to CTA. However, when commenting on the results, Bassand showed data from the same study indicating a poor correlation with conventional FFR.

Percutaneous intervention (PCI):

FAME-2 randomised patients post-angiography who had stable angina or asymptomatic ischaemia, and all of whom had the FFR measured, to either optimal medical therapy (OMT) or OMT + intervention if at least 1 vessel had an FFR <0.80. 60% had a significant proximal or mid-LAD lesion. Patients with FFR >0.80 were followed in a registry. The baseline characteristics of all 3 groups were similar. 73% of patients were entered into the trial; 27% into the registry. Around 1.5 lesions were treated in the intervention group. Registry patients (those with an FFR >0.80) had a very low incidence of events. OMT alone was associated with a high incidence of an adverse outcome (15%) by 12 months, driven by the need for urgent target vessel revascularisation for MI (21%), unstable angina (UA) with ECG changes (27%) or UA alone. Although there was a small early hazard with PCI, overall PCI controlled symptoms better.

The PROTECT study was a randomised study of 4 400 patients comparing the drug-eluting zatrolimus (Endeavour®) vs. sirolimus (Cypher®) stents showing no effective difference in stent thrombosis (ST) at 3 years although the early ST rate was higher with zatrolimus and the very late ST higher with sirolimus.

Hamm reported the results of the German survey of aortic valve procedures which includes 13 860 patients. Transcatheter aortic valve implantation (TAVI) patients were sicker and more than 50% had CAD. Their risk score was <20 in 50% of cases. TAVI was more frequent in females and 85% were >75 years. Aortic regurgitation was not a significant problem after TAVI. Mortality rates were 2.2% for AVR only, 4.6% for AVR + CABG, 5.5% for transvascular TAVI and 7.8% for transapical TAVI. Stroke rates were similar for TAVI and AVR + CABG. Transvascular cases had a greater incidence of vascular complications. 24% required PPM. The observed mortality was lower than that predicted from the risk score.

Experience with the Mitraclip® at 1 year suggests that it is a safe treatment option, improving MR by 80% and associated with a 70% symptomatic and functional improvement.

Acute coronary syndromes:

TRILOGY is the largest trial in post-ACS patients <75 years of age who did not undergo revascularisation. Patients were followed for a median of 17 months. TRILOGY compared clopidogrel with prasugrel. The patients constituted at least a moderate risk group and above average event rates were recorded in the trial. There were no differences in CV outcome nor a significant increase in bleeding between the 2 groups, although a significant, time-dependent benefit of prasugrel was observed, commencing at 1 year. This difference was present in all three components of the primary endpoint (death, MI and stroke). The protocol provided for separate analysis of patients >75 years of age and who received ½ dose of prasugrel only if there was a detectable difference in the younger group. The older group will be the subject of a subsequent sub-study.

The WOEST trial compared dual anti-platelet therapy (DAPT) vs. clopidogrel alone in patients on oral anticoagulation who required stenting for ACS. 573 patients were randomised. 65% received a drug eluting stent. 25% had radial access. In the clopidogrel alone arm bleeding was reduced 64% when compared to DAPT. The secondary endpoint (death, stroke, MI, revascularisation and stent thrombosis) was reduced by 40% and mortality from 6.4% to 2.6%. This preliminary study has important implications for the future treatment of patients on warfarin who then require stent implantation.

An important symposium addressed anaemia and bleeding in ACS. Pre-existing anaemia, bleeding and transfusion have all been independently associated with an adverse outcome in ACS. First, Kelm discussed the function of red blood cells in vascular disease. He emphasised that rbc function dpends not only on their quantity (number) but also their morphology, integrity and function. Free haemoglobin in plasma acts as a nitric oxide (NO) scavenger and affects vascular reactivity. Red blood cells (and not only vascular endothelium) is involved in NO production with a bidirectional production-uptake of NO dependent on the pO_2. Red cell nitric oxide synthase (NOS) affects the deformability of rbc's, inhibits platelet function and causes vessel dilation. The destruction of rbc's (erythroptosis) is mediated by caspase 3 prior their removal by the spleen.

Bassand then discussed the influence of anaemia (both pre-existing and hospital-acquired) on the outcome of ACS. Various reports indicate an incidence of pre-existing anaemia of between 15% (Sabatine) and 25% (Nikolsky). It is more frequent in the elderly. The major causes of pre-admission anaemia are anaemia of chronic disorder and CKD. ACS outcome is adversely affected by too low and too high haemoglobin. The "sweet spot" is an HB around 14 gm/dl. Anaemia has effects on prognosis beyond atherothrombotic events. Although having little impact on CV complications post-CABG, anaemia is associated with a higher incidence of both renal and cerebral events. In ACS an admission Hb <13 gm/dl is associated with an excess of bleeding complications. Moderate or severe hospital acquired anaemia is associated with increased mortality. Correction of anaemia above an Hb of 8 gm/dl (Hct 25%) is associated with poorer outcome.

Vrints pointed out the large variety of bleeding definitions and the discordance between them. He recommended using the BARC definition of bleeding (Circulation 2011) and the CRUSADE risk score to assess the risk.

Regarding treatment, Anker highlighted the inability of oral iron (absorbed at 6-8 mg/day) to effectively counter iron deficiency which when present ranges between 800 and 1 600 mg. He recommended parenteral iron carboxymaltose as an alternative to dextran containing preparations which are responsible for anaphylaxis. Eryhthropoeitin (EPO) is of no value in CHF as it does not improve effort tolerance of quality of life. Furthermore EPO treatment may deplete iron stores during treatment. He discussed functional iron deficiency when the ferritin level is below 100 or when the TSAT is <20% in association with a ferritin in the range 100-300, whether or not associated with anaemia. In this setting parenteral supplementation has been shown to improve exercise tolerance briskly. Supplementation should not be continued if Hb >16 gm/dl or ferritin > 800.

Miscellaneous:

BNP measured 3 minutes after peak exercise is predictive of future events in valvular heart disease.

The incidence of kidney dysfunction in S. faecalis infective endocarditis was reduced safely by restricting gentamicin use to 2 weeks.

There is a significant increase in the incidence of deep venous thrombosis and pulmonary embolism in the first trimester in women after in-vitro fertilisation.

In the REVERSE study of CRT in mild HF the effect of treatment was sustained at 5 years.