European Society of Cardiology (ESC) Congress 2015

CONFERENCE REVIEW

Making Education Easy

29 Aug – 2 Sep 2015, London, England

In this review:

Abbreviations used in this review
ACS = acute coronary syndromes
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
LDL = low-density lipoprotein
LVEF = left ventricular ejection fraction
MI = myocardial infarction
SBP = systolic blood pressure
STEMI = ST elevation MI

Welcome to our review of the recent ESC Congress, held in London for the first time in 63 years.

The Excel Centre in Docklands provides adequate space for the usual ESC requirements even if it is a bit out of the way for most other London attractions. Nevertheless, the Docklands area has undergone a huge transformation in the last couple of decades changing from a dour industrial area to one full of major office buildings and a few worthwhile restaurants, hotels and other attractions. These include the "Emirates Air Line", a gondola trip across the Thames (from which we observed the fleet of Tall Ships on their way to the Atlantic) and the O_2 Arena, formerly the Millennium Dome. We bring you a small selection of papers at the meeting which interested us, both non-interventional (Stewart Mann) and interventional (John Elliott). As with last year, where publications have ensued, the hyperlink to these is included. Otherwise abstracts or presentations can be reached via the ESC365 application on the ESC website (www.escardio.org).
Kind regards,

Associate Professor Stewart Mann
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Assisted servo-ventilation in central sleep apnoea SERVES a double fault

Presenter: M Cowie, London

Summary: This study investigated the effects of adaptive servo-ventilation in patients with heart failure and predominantly central sleep apnoea. 1325 patients with LVEF ≤45%, an apnoea-hypopnoea index ≥15 events/hour, and a predominance of central events were randomised to receive guideline-based medical treatment with adaptive servo-ventilation or guideline-based medical treatment alone (control). The incidence of the primary end-point (death from any cause, lifesaving cardiovascular intervention or unplanned hospitalisation for worsening heart failure) did not differ significantly between groups (54.1% vs 50.8%, respectively). Rates of all-cause mortality (hazard ratio 1.28) and cardiovascular mortality (hazard ratio 1.34) were significantly higher in the adaptive servo-ventilation group than in the control group.

Comment (SM): The use of assisted servo-ventilation for patients with heart failure and consequent central sleep apnoea (essentially Cheyne-Stokes respiration) has been noted for improvement in frequency of apnoea events, oxygen saturation and other parameters including anecdotal improvements in quality of life. The only remaining question was how big the consequent improvement in mortality and morbidity might be. This randomised controlled trial surprised everyone with a negative result showing increased mortality in users and no improvement in quality of life overall. Consequently, the manufacturers have recalled the equipment when being used for this purpose and recommended that it not be used. With a personal sample size of two, both of whom have had clear improvements in quality of life, there is understandable reluctance from some patients to part with the gear even with the knowledge that remaining life expectancy might be shortened.

Reference: Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373:1095-1105
Abstract

Ezetimibe IMPROVES IT only in diabetics

Presenter: R Giugliano, Boston

Summary and comment (SM): The IMPROVE-IT trial published last year showed benefit for the addition of ezetimibe to simvastatin in patients who had suffered a coronary event. The positive result was trumpeted loudly, claimed as a proof of the LDL hypothesis and laid ground work for purveyors of even more powerful LDL cholesterol-lowering agents such as PCSK9 inhibitors. However, even the overall result raised questions given the huge numbers needed to treat (NNTs) – 50 patients needing to be treated for 7 years (=350 patient-years of treatment) to prevent one cardiovascular event. Buried in page 41 of the online supplementary material was an analysis of subgroups including the substantial one of diabetes versus non-diabetes. This analysis was presented more specifically in London and is certainly thought-provoking. In diabetics the hazard ratio for the primary end-point was 0.86, in non-diabetics 0.98. Although subgroup analyses are always difficult to interpret and some commentators (particularly the trialists) have said that the overall result should be taken as guidance, others have said that it would now be hard to justify the use of supplementary ezetimibe in non-diabetics.

Reference: Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with vs without diabetes: the IMPROVE-IT trial. ESC 2015. Session: Clinical Trial Update I – Cardiovascular diseases: prevention, outcomes, quality. FP#1947

Plotting the right PATHWAYS for difficult hypertension

Presenter: B Williams, London

Summary: The PATHWAY-2 study compared the effects of spironolactone with those of non-diuretic drugs when used as add-on therapy in patients with resistant hypertension. 335 patients with seated clinic SBP ≥140mmHg (or ≥135mmHg for diabetics) despite treatment for at least 3 months with 3 antihypertensives were randomised in a crossover design to receive add-on therapy with spironolactone (25–50mg), bisoprolol (5–10mg), doxazosin modified release (4–8mg) or placebo, once daily for 12 weeks each in addition to their baseline antihypertensive regimen. 230 patients completed all treatment cycles. Add-on spironolactone caused significantly greater reductions in SBP than placebo, doxazosin and bisoprolol after 12 weeks.

Comment (SM): When your patient's blood pressure is still uncontrolled despite a combination of diuretic, ACE inhibitor and calcium channel blocker where do you go next? In the UK, beta-blockade has been largely relegated to a 4th or 5th line treatment although it is commonly indicated in any case for subgroups, especially those with concomitant coronary disease. By contrast, there has been growing awareness of the effectiveness of spironolactone in resistant hypertension, use of which earlier drastically reduced the number of potential recruits to a local trial of renal nerve ablation. Both of these assumptions were given support in this "PATHWAY-2" crossover trial where patients randomly took spironolactone, bisoprolol, doxazosin or placebo for periods of 12 weeks each. Spironolactone produced about double (–8.7mmHg) the reduction of the other two active agents (<–4.5mmHg) when measured on clinic and home measurements.

Reference: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2). Lancet 2015; published online Sep 20
Abstract

Back to the future for Amizide®/ Moduretic®

Presenter: M Brown, Cambridge

Summary and comment (SM): Also presented in London for the first time were the results of PATHWAY-3 which again looked at old freely available drugs which have fallen a bit out of fashion. Trialists recruited patients with hypertension and at least one other component of the metabolic syndrome (nearly all obesity) and not currently on diuretics. Patients were randomised to amiloride 10 mg/day, hydrochlorothiazide 25 mg/day or a combination (amiloride 5mg + hydrochlorothiazide 12.5mg). Each treatment was doubled after 12 weeks and assessments made at 12 and 24 weeks. Amiloride achieved similar reduction of BP to hydrochlorothiazide but improved glucose tolerance and raised potassium (although no patient exceeded 5.8 mmol/L). Combination treatment achieved better BP reduction than either drug alone (and reduces it more than single beta-blockers or calcium channel blockers) with more neutral metabolic effects. There was no support for an initial hypothesis that adverse effects on glucose metabolism were correlated with or caused by changes in potassium.

Reference: Principal results from prevention and treatment of hypertension with algorithm based therapy (PATHWAY): comparison of single and combination diuretics in essential hypertension - PATHWAY-3. ESC 2015. Session: Hot Line IV – Hypertension. FP#4140

RNZCGP Endorsed CPD Activity

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**

The Ancient Mariner's curse strikes again

Presenter: J McMurray, Glasgow

Summary: The ALBATROSS trial randomised 1,622 patients with acute MI to receive standard therapy alone or with aldosterone blockade (200mg IV potassium canrenoate followed by oral spironolactone 25 mg/day for 6 months). At 6 months, the incidence of the composite end-point (death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, and new/worsening heart failure) did not differ significantly between groups. Secondary end-points were also similar between groups, but hyperkalaemia was more common in the group receiving spironolactone.

Comment (SM): Coleridge's poem describes the opprobrium heaped by his crew mates on a sailor who shot an albatross and ended up having to wear it around his neck. These French trialists spent several years examining the acute use of an aldosterone antagonist, potassium canrenoate, followed by 6 months of oral spironolactone in ACS without heart failure. The acronym of "ALBATROSS" for the trial may have been portentous as they must now wonder what they have around their necks given negative outcomes. Some consolation might come from one of the several end-points (mortality among STEMI patients) that showed positive results albeit in a very small subgroup in a trial that was probably considerably underpowered. On the other hand there was a 3% incidence of significant hyperkalaemia (potassium >5.5 mmol/L). Other trialists reporting positive results are often "condemned" (like the aforesaid mariner) to wander the world telling their tale but there may be less such demand for the further narration of this study. This must be a rare trial that showed negative results for an ancient drug group that is continually finding new uses.

Reference: ALBATROSS: discussant review. ESC 2015. Session: Hot Line I – Acute Myocardial Infarction. FP#1168

DAPT – how long is long enough after DES?

Presenter: G Helft, Paris

Summary: The open-label OPTIDUAL trial investigated whether continuing with clopidogrel would be better than stopping it 12 months after DES implantation. 1385 patients who had undergone placement of ≥1 DES for stable coronary artery disease or ACS were included. They were randomised to continue taking clopidogrel 75mg daily plus aspirin (extended DAPT group) or to stop taking clopidogrel after 12 months (aspirin group). Median follow-up after stenting was 33.4 months. The primary composite outcome (death, MI, stroke, or major bleeding) occurred in 5.8% of patients in the extended-DAPT group and 7.5% of patients in the aspirin group (hazard ratio 0.75; p=NS). Rates of death were 2.3% and 3.5% in the respective groups (p=NS). Major bleeding rates did not differ between groups.

Comment (JE): The DAPT study suggested that cardiovascular end-points were reduced if DAPT was continued for 30 months compared with 12 months. The OPTIDUAL trial presented at ESC was of similar design to the DAPT study but open-label, smaller and it was stopped prematurely due to slow recruitment. Median follow-up was 33 months. Cardiovascular end-points were reduced by 20–25% but, although consistent with those in the DAPT study, were not statistically significant. There was no difference in stent thrombosis or bleeding. The OPTIDUAL trial adds to accumulating evidence that DAPT for longer is better with an acceptable increased risk of bleeding. However all these trials have only randomised patients who are doing well 6 or 12 months after receiving a DES. None of the patients in these studies have had major bleeds, an MI or required repeat percutaneous coronary intervention. So we still don't have reliable data on how to treat all comers after DES, and in particular those who are at higher risk for bleeding.

Reference: Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J 2015; published online Sep 12
Abstract

Independent commentary by Associate Professor Stewart Mann

Associate Professor Stewart Mann trained at Oxford University and Kings College Medical School, London. He undertook research at Northwick Park Hospital, Harrow especially in 24-hour ambulatory blood pressure monitoring leading to a doctorate. He trained in cardiology in Bristol, London and Sydney. He was a cardiologist at Wellington and Hutt Hospitals from 1986 until 2003 and then moved to his present post of Associate Professor of Cardiovascular Medicine at the University of Otago, Wellington, becoming Head of the Department of Medicine from 2009 until 2014. He continues clinical activity in the cardiology department, Wellington Hospital and in private practice at Wakefield Hospital and Ropata Village Medical Centre. His interests include preventive cardiology (especially hypertension), vascular biology and clinical information science. He has no current ties to any pharmaceutical or equipment supplier although has attended and spoken at sponsored meetings. He serves on the Board of the Heart Foundation.

DAPT – how long is long enough after previous MI?

Presenter: J Udell, Toronto

Summary: This meta-analysis investigated the long-term (>1 year) use of DAPT compared with aspirin alone in high-risk patients with previous MI. Data from 6 trials (n=33,435) were pooled. Extended DAPT decreased the risk of major adverse cardiovascular events compared with aspirin alone (risk ratio [RR] 0.78; p=0.001) and reduced cardiovascular deaths (RR 0.85; p=0.03), with no increase in non-cardiovascular deaths. The resultant effect on all-cause mortality was an RR of 0.92 (p=NS). Extended DAPT also reduced MI (RR 0.70; p=0.003), stroke (RR 0.81; p=0.02), and stent thrombosis (RR 0.50; p=0.02). Extended DAPT was associated with an increased risk of major bleeding (RR 1.73; p=0.004) but not fatal bleeding.

Comment (JE): Current guidelines recommend continuing DAPT for up to 1 year after acute MI whether treatment has included stenting, bypass surgery or medical therapy only. But should we be using DAPT for longer than that? Jacob Udell presented a meta-analysis of patients who had a history of MI and who were randomised to short (<1 year) or long duration (>1 year) DAPT in previously published trials. Absolute incidence of the combined end-point of cardiovascular death, non-fatal MI and non-fatal stroke was reduced by 1.1%, compared with a 0.7% increase in the incidence of major bleeding. Although the number of patients included is impressive, separate data were not presented for patients receiving clopidogrel, prasugrel or ticagrelor in addition to aspirin. There was no subanalysis identifying a group who may benefit the most, and the average delay between MI and enrollment in the randomised studies was 18 months. So the conclusions from this meta-analysis cannot be used to plan care immediately after an acute MI. Patients would need to re-evaluated 1 or 2 years after MI, which is not usual clinical practice in New Zealand.

Reference: Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction. Eur Heart J 2015; published online Aug 31
Abstract

More exercise is not necessarily better

Presenter: A Merghani, London

Summary: This study assessed the dose relationship between endurance exercise and coronary artery calcification (CAC) in 112 veteran athletes (aged >40 years). The lowest incidence of significant CAC was observed in athletes running <20 miles per week and finishing marathons in 2:45–3:15h for males, and running 20–30 miles per week and finishing marathons in 3–3:30h for females. Running more or less than these mileages and running slower or faster than these marathon times conferred unfavourable CAC.

Comment (JE): This is an interesting study for those of us who dream of retirement while enjoying aerobic exercise. CAC scores were compared with usual exercise patterns in a relatively small number of "veteran athletes" with a mean age of 56 years. A U-shaped curve was demonstrated with the highest CAC scores in men who ran >20 miles a week and women who ran >30 miles a week. A CAC score of >70th centile was detected in 39% of those who ran more than these distances. Obviously some variables were not controlled for but this study does support the concept that more is not necessarily better. Another excuse to rest.

Reference: The relationship between the dose of exercise and coronary artery calcification in veteran athletes. ESC 2015. Session: Sports Cardiology in Development. FP#2968

Independent commentary by Associate Professor John Elliott

Associate Professor John Elliott trained in New Zealand and Australia and was Chief Interventional Fellow at The Cleveland Clinic in Ohio before returning to Christchurch in 1995. He continues to enjoy interventional and general cardiology, research, audit and teaching. John previously served as NZ Chairman and Board Member of CSANZ and was on the Board of the Heart Foundation. He is a currently a member of the Scientific Committee of CSANZ and a member of the Cardiovascular Sub-Committee of PTAC. He received support for accommodation at ESC from Sanofi.

Reassuring news from Spain: 5-year EXAMINATION data

Presenter: M Sabaté, Barcelona

Summary: The EXAMINATION trial compared the performance of everolimus-eluting stents (EES) and bare-metal stents (BMS) in an all-comer STEMI population. 1,498 patients with STEMI requiring primary PCI were randomised 1:1 to receive EES or BMS. The primary end-point was the patient-oriented combination of all-cause death, any recurrent MI and any revascularisation. During the 5-year follow-up, the primary end-point occurred in 21% and 26% of patients in the EES and BMS groups, respectively (p=0.033). The difference was mainly driven by a reduction in all-cause mortality (9% vs 12%; p=0.047).

Comment (JE): This analysis demonstrates a significant reduction in the primary end-point of all cause death, any recurrent MI and any revascularisation in those who were randomised to an everolimus stent at the time of STEMI compared with those who received a BMS. There was no evidence of late hazards such as probable or definite stent thrombosis. However the primary end-point still occurred in 21.6% of the everolimus stent group, so we still need to improve secondary prevention efforts. And it is still important to assess the likely compliance and bleeding risks of STEMI patients prior to inserting a drug eluting stent, thus minimising early adverse outcomes.

Reference: Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. Lancet 2015; published online 28 Oct
Abstract

Time trends in MI survival – the Danish National Patient Registry

Presenter: M Schmidt, Aarhus

Summary: This interesting population-based cohort study was presented by Morten Schmidt from Aarhus University Hospital. He used the Danish National Patient Registry to compare 30-year outcomes in 21,693 patients aged <50 years (84% were aged 40–49) at the time of acute MI, with those in a comparison cohort for the Danish population (n=216,930). Short and long term mortality was much higher in the 1980–1989 cohort than in the 2000–2009 cohort, for example 10-year mortality was 24.2% compared with 8.9%. If both MI groups were compared with the general population, the adjusted mortality ratio at 10 years fell from 4.77 in the 1980–89 cohort to 1.89 in the 2000–2009 cohort. Thus, prognosis has improved remarkably. But the absolute mortality rate remains twice that of the general population, is mainly due to deaths from ischaemic heart disease and smoking related diseases, and is predicted by the usual co-morbidities including diabetes, obesity, hypertension and atrial fibrillation.

Comment (JE): This is yet another valuable study made possible by the extensive patient and population registries that have been efficiently collecting data in several Scandinavian countries for many years. The results confirm that major decreases in 30-day and 1-year mortality after treatment of acute MI in patients aged <50 years translate into improved 10- and 30-year survival. Survival has improved as each decade passes, but mortality remains about twice that of the general population. There is persisting improvement in outcomes long after discharge from hospital. These reductions in early and late mortality after treatment of acute MI contribute to the reduction in coronary heart disease mortality observed in Denmark and other countries including New Zealand.

Reference: 30-year survival among patients with myocardial infarction before 50 years of age compared with the general population: a nationwide cohort study. ESC 2015. Session: Young Investigators Awards Session Population Sciences. FP#1842