What Can We Learn from ESC 2013?

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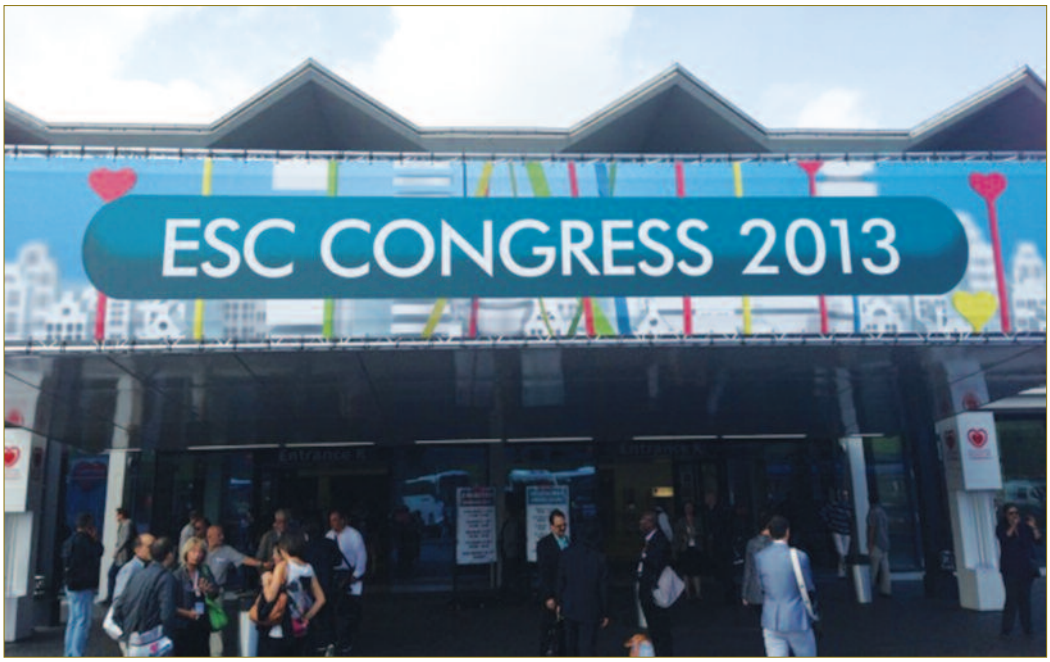
The European Society of Cardiology (ESC) Congress 2013 has become the world's largest cardiology meeting. This year saw more than 30,000 participants and record-breaking numbers of hotline trials and scientific abstracts submitted for presentation in Amsterdam from 31 August to 4 September, 2013. This article will review some of the highlights from the conference.

Hypertension

This year saw the release of the latest update on the ESC guidelines for the management of arterial hypertension [1]. Hypertension has been described as "the leading global risk for mortality in the world" [2]. It continues to affect 30-45% of the European population. The authors of the guidelines expressed disappointment that this figure has remained high since the 2003 edition with presentation at the ESC of the **EUROASPIRE IV** [3] survey showing that 50% of patients on treatment for hypertension remain outside the recommended targets. According to the report, "lifestyle changes are the cornerstone for the prevention of hypertension", including reduction of salt (to roughly half present levels) and alcohol, as well as maintaining a healthy body weight, regular exercise, and the elimination of smoking. The guidelines highlight the lack of awareness of the potential problems of hypertension amongst patients, with poor long-term adherence to treatment, and the 'inertia' of doctors, who don't take appropriate action when confronted with patients with uncontrolled blood pressure. The 2013 Task Force reviewed all relevant data since the last revision (in 2007), with 18 specific diagnostic and therapeutic areas identified as containing significant change. A major development is the decision to recommend a single systolic blood pressure target of 140mmHg for almost all patients. This contrasts with the 2007 version which recommended a 140/90mmHg target for moderate to low-risk patients, and 130/80mmHg target for high-risk patients. "There was not enough evidence to justify two targets," said Prof Robert Fagard, from Leuven, Belgium. Other changes include: an increasing role for home blood pressure monitoring, alongside ambulatory blood pressure monitoring; a greater emphasis on assessing the totality of risk factors for cardiovascular and other diseases; special emphasis on specific groups, e.g. diabetics, the young, the elderly, pregnancy, and drug treatment of the over



80s; special consideration is given to new treatments such as renal denervation for resistant hypertension – which is described as "promising", although more trials are called for. New guidance on how and when to take anti-hypertensive drugs is given: no treatment for high normal blood pressure; no specific preference for single drug therapy; and an updated protocol for drugs taken in combination, emphasising an individualised treatment approach rather than a more dogmatic hierarchy of recommended drugs. The many side-effects of beta-blockers, including new-onset diabetes in predisposed patients, are acknowledged.

There continued to be interest in catheter-based therapies for treatment of resistant hypertension and the three-year follow-up data from **SYMPLICITY-HTN 1** were presented. This is a prospective trial investigating the safety and efficacy of renal denervation using the Medtronic® (Minneapolis, USA) Symplicity™ system. The 88 patients included in the study demonstrated sustained reductions in blood pressure year-over-year with an average reduction of -32/-14mmHg ($p<0.01$). Of these 88 patients, approximately half achieved the goal of a systolic blood pressure <140mmHg despite having a mean systolic blood pressure of 169.8mmHg pre-denervation. Clinically significant late adverse events reported through three years of follow-up were very low. These results have been accepted for publication in *The Lancet*. Data from the **Global SYMPLICITY Registry** were also presented. This is a multicentre, prospective, observational registry (n=1558) designed to collect comprehensive 'real-world' data evaluating procedural and long-term safety of the Symplicity system, and showed a low incidence of adverse events (<0.1%) and sustained blood pressure reductions at 6 and 12-months in the follow-up population.

The effect of the renin inhibitor aliskiren on progression of coronary atherosclerosis in patients with pre-hypertension was investigated by the **AQUARIUS** (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study) study (n=613). Although there was a trend to slowing of atheroma progression in the study group compared to placebo these differences were not statistically significant.

Cardiac pacing and resynchronisation therapy

This year also saw the release of the ESC cardiac pacing and resynchronisation guidelines [4], providing an overview of the indications for antibradycardia pacing, with recent evidence for its use in different syncope populations, revised indications for biventricular pacing and discussions on its additive value with internal defibrillation, optimal lead placements and device programming. The **ECHO-CRT** study demonstrated that in patients with systolic heart failure and a QRS duration of less than 130msec, cardiac resynchronisation therapy (CRT) does not reduce the rate of death or hospitalisation for heart failure and may increase mortality [5]. The results of the **MADIT-CRT LIFR** (MADIT-CRT Long-term International Follow-up Registry) were also presented showing CRT with a defibrillator (CRT-D), as compared to implantable cardiac defibrillation (ICD) alone, is associated with significant reductions in the long-term risk of heart failure or death. These findings are based on a six-year follow-up in 549 mild heart failure patients enrolled in the MADIT-CRT study. In the original 1,820-patient trial, CRT-D was associated with a significant 34% reduction in the risk of heart failure or death over 2.4 years of follow-up compared to ICD alone. This benefit was sustained at long-term follow-up with rates of heart failure or death in 29% of patients in the CRT-D arm of the study versus 47% of patients who received ICD-only therapy ($p<0.001$). The **DECAAF** (Delayed enhancement-MRI determinant of successful catheter ablation of atrial fibrillation) trial was designed to assess the predictive value of left atrial fibrosis diagnosed by high resolution delayed enhancement cardiac magnetic resonance (CMR) imaging on the success of atrial fibrillation (AF) ablation. Two hundred and sixty patients were included, 65% with paroxysmal AF and the results suggested that the evaluation of atrial fibrosis might help to identify the best candidates for AF ablation.

Other highlights included a study from Maastricht, Netherlands, showing that a systematic approach to the investigation of idiopathic ventricular fibrillation (VF) can reveal an underlying aetiology in 75% of cases. In addition, a longitudinal study investigating the death of every deceased French cyclist to take part in the Tour de France since 1947 showed that riders had a 41% lower mortality compared to an age matched population in France [6]. There was also a tantalising view into the future with presentations on leadless pacing and interventional cardiac MRI suites to help guide ablation procedures and pacemaker lead placement.

Ischaemic heart disease and PCI

It has been an important year for coronary intervention with the presentation of several large studies and the latest ESC guidelines on the management of stable coronary disease [7]. The **TASTE** (Thrombus Aspiration during ST-segment Elevation myocardial infarction) was a multicentre, prospective, registry based, randomised clinical trial that enrolled 7244 patients with STEMI undergoing percutaneous coronary intervention (PCI). Aspiration of the thrombus prior to re-opening the artery with a balloon catheter in STEMI patients does not improve survival any more than balloon dilation and stenting [8]. Results at 30 days showed that mortality was low in both groups: 3.0% in the PCI group and 2.8% in the PCI + thrombus aspiration group (HR 0.94; CI 0.72-1.22, P=0.63). Even high-risk groups, such as smokers, patients with diabetes or patients with large clots, had similar survivals with either approach. In an accompanying editorial in the *New England Journal of Medicine* it was commented that an updated analysis of outcomes at 12 months of follow-up was imperative, suggesting that the potential benefits of thrombus aspiration may not be captured at 30 days but may be expected to emerge during the first year after

infarction through enhanced myocardial salvage and favourable remodelling. This study also attracted attention for its unprecedented design, a so-called "registry-based randomized clinical trial" (RRCT), enrolling STEMI patients as they entered the long-standing, pan–Sweden and Iceland **SWEDEHEART** (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry. This method increased capture of the available population (allowing 60% of those presenting with STEMI during the

duration of the study to be recruited), improved completeness of follow-up and drastically reduced costs and provides an exciting and innovative prospect for future studies.

The **PRAMI** (Preventive Angioplasty in Myocardial Infarction) trial was presented by David Wald, London [9]. In this study, patients undergoing emergency PCI for acute ST elevation (n=462) or left bundle branch block (n=3) MI and multivessel coronary artery disease were randomised while in the catheterisation laboratory to either preventive PCI (n=234), or culprit-only PCI (n=231). Patients were eligible for the preventive procedure if their culprit artery had been treated successfully and they had a >50% stenosis that was treatable by PCI in another or several other coronary arteries. The results were considered conclusive and the trial stopped early by the data and safety monitoring committee. After a mean follow-up of 23 months a total of 21 patients in the preventive PCI group and 53 in the culprit-only group had experienced a primary outcome event (cardiac death, non-fatal MI or refractory angina) showing an absolute risk reduction of 14 per hundred patients in the preventive PCI group [hazard ratio 0.35 (95% CI 0.21-0.58), p<0.001], and a relative risk reduction of 65%. Procedure related complications were similar in both groups. Lead investigator David Wald said, "The results of this trial show that in this situation preventive PCI reduces the risk of cardiac death, a subsequent myocardial infarction or angina resistant to medical therapy, by about two-thirds." Current ESC and American College of Cardiology / American Heart Association (ACC/AHA) guidelines suggest only revascularisation of the infarct related vessel during primary PCI in patients with multi-vessel disease because of a lack of evidence in favour of preventative PCI. With this new evidence, "consideration can be given to revising current guidelines," he added.

The **TAO** (Treatment of Acute Coronary Syndromes with Otamixaban) trial was a multicentre, phase 3 trial that randomised 13,229 patients to either standard treatment consisting of unfractionated heparin (UFH) plus downstream eptifibatide or otamixaban, an injectable factor Xa inhibitor [10]. All patients received both aspirin and an oral adenosine diphosphate receptor antagonist. Rates for the primary outcome, a composite of all-cause death or new MI from randomisation to day seven, were not significantly different between the two groups. However, the primary safety outcome, the rate of major or minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria was more than doubled with otamixaban (3.1% vs. 1.5%, relative risk 2.13, P<0.001). The incidence and impact of dual antiplatelet therapy (DAPT) cessation on adverse cardiac events following PCI were investigated through the two-year results from the **PARIS** (Patterns of Non-Adherence to Anti-Platelet Regimens In Stented Patients) study [11]. In this investigator-initiated registry of 5,018 patients undergoing PCI the investigators prospectively defined DAPT cessation according to three types: physician-recommended discontinuation; interruption related to surgical procedures with resumption of DAPT within 14 days; and disruption due to bleeding or non-compliance and investigated its impact on two-year cardiac adverse event rates. After stenting most ischaemic events occurred while on DAPT. Timely physician-initiated discontinuation or short interruption of DAPT seemed relatively safe, but disruption, e.g. due to bleeding, was associated with a substantial risk. Sustained DAPT throughout two years was not associated with additional benefit compared to physician-guided discontinuation. The optimum duration of DAPT after PCI remains to be established and we await further results from **ISAR-SAFE** (six months vs. twelve months of DAPT), **ISAR-CAUTION** (six months abrupt cessation vs. six months gradual), and **DAPT** (12 vs. 30 months).

The **ACCOAST** (A Comparison of prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction) trial was presented showing that in patients with non-ST-elevation ACS pre-treatment with the P2Y12 antagonist prasugrel prior to catheterisation, significantly increases the risk of life-threatening bleeding without reducing the risk of major ischemic events [12]. Current ESC and ACC/AHA guidelines recommend that pre-treatment with P2Y12 inhibitors should be added to aspirin as soon as possible before catheterisation and maintained over 12 months based on the results of observational, subgroup and non-randomised analyses performed with the older drug clopidogrel, explained the lead investigator, Gilles Montalescot, Paris. But newer P2Y12 receptor antagonists such as prasugrel are more potent and have a faster onset of action, and the modern era of short delays between hospital admission and catheterisation, the risk of an ischaemic complication before catheterisation is extremely low, suggesting that there is no longer a need for pre-treatment in NSTE-ACS patients to prevent ischaemic complications while

waiting for catheterisation. He went on to say, "Moreover, there is also no benefit of pre-treatment on peri-PCI complications. Together, our findings suggest use of prasugrel should be considered only after the coronary anatomy has been defined."

The use of comprehensive non-invasive imaging protocols for the diagnosis and work-up of patients with suspected IHD, as presented in the latest ESC guidelines [7], were extensively discussed at presentations throughout the meeting, with an emphasis of the use of local expertise, avoidance of multi-layering of tests, internal validation and reproducibility, and "choosing the right test for the right patient". Computed tomography (CT) angiography incorporating coronary plaque morphology and perfusion (CT-FFR) to improve diagnostic accuracy, ultra fast high-resolution CMR perfusion imaging and image-fusion CT with 3D echo stress offer exciting insights into the future.

Valves

It was revealed by Danish investigators that people with first degree relatives with aortic stenosis have twice the risk of developing the condition. In a retrospective cohort study presented by Mattis Ranthe, Copenhagen, 3.3 million people aged over 35 between 1977 and 2012 were followed up to see if they developed aortic stenosis. The Danish system of assigning residents with unique personal identification numbers allowed linkage of individual patient information from multiple registers and the Danish Family Relations Database. Overall, 13,499 people developed aortic stenosis during the follow-up period, and of these 148 had a first degree relative also diagnosed with aortic stenosis. When people with a first degree relative with aortic stenosis were compared to those without a family history, their risk of aortic stenosis increased 2.2-fold. This corroborates evidence also presented by a group from Montreal that aortic stenosis, a disease known to be caused by calcification and hardening of the aortic valves, may carry a genetic component. They reported that those carrying a single nucleotide polymorphism at the lipoprotein (a) locus had double the risk of valve calcification on CT [13].

The impact of gender on outcome following transcatheter aortic valve intervention (TAVI) is unclear. Investigators from Coburg Hospital, Germany, examined outcome differences according to gender in 1432 patients who had been enrolled in the German TAVI registry between January 2009 and June 2010. This study, undertaken in 30 centres, represents the largest study yet of gender differences in TAVI. Women comprised 57.8% of the cohort, with an average age at baseline of 83 years (vs. 80 years for men). Mortality rate at 30 days was 7.6% for women vs. 8.6% for men; however, by one year all-cause mortality was 17.3% for women vs. 23.6% for men ($p<0.01$). In the discussion the authors suggest that lower levels of fibrosis in women might explain their more rapid reversal of myocardial hypertrophy after correction of aortic stenosis. Other studies showed that resting

and peak exercise B-type natriuretic peptide (BNP) levels could predict outcome in patients with asymptomatic AS. The **France-2 TAVI Registry** found that transfemoral vascular access and self-expanding devices were associated with increased para-valvular aortic regurgitation post procedure.

Advances in valve imaging were also highlighted and a wide range of presentations included the use of CMR in patients with aortic stenosis for evaluation of myocardial fibrosis to help guide therapeutic intervention and predict outcome, and the potential usefulness of positron emission tomography – computed tomography (PET-CT) in assessment of aortic stenosis and infective endocarditis.

One of the main trials presented at this year's congress was **RE-ALIGN** comparing dabigatran, an oral direct thrombin inhibitor, with warfarin in patients with mechanical heart valves [14]. Dabigitran has been shown to be an effective alternative to warfarin in patients with atrial fibrillation, but in this case the trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischaemic or unspecified stroke occurred in nine patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in seven patients (4%) and two patients (2%), respectively. In conclusion, the authors write that dabigitran should not be used in patients with mechanical heart valves. The principal investigator, Van de Werf, Belgium, said that the most likely explanation for the negative result was the inability of dabigatran to suppress the activation of coagulation that occurs when blood is exposed to the artificial surface of prosthetic valves. "We believe that dabigatran only works on thrombin activity, while warfarin is also effective via factor IX. If this hypothesis is correct it will also be valid for other factor Xa inhibitors such as rivaroxaban or apixaban. Patients with mechanical heart valves will have to take warfarin or other vitamin K antagonists for the next 5 to 10 years."

Heart failure

In the **ATOMIC-AHF** (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) phase II study Omecamtiv, a cardiac myosin-activator, did not achieve its primary efficacy endpoint in reducing dyspnoea (shortness of breath) in patients with acute heart failure. However, the cohort which received the highest dose of the drug showed greater dyspnoea relief compared with placebo, and there were also other favourable dose and concentration-related trends. Lead investigator, John Teerlink, USA, commented that the main objective of ATOMIC-AHF was to investigate the pharmacokinetics and tolerability of intravenous omecamtiv mecarbil in the acute heart failure population as a dose-finding, safety and tolerability study. "In these terms the study was a real success," he said, "and, like most Phase II studies, it was not powered or designed around the efficacy endpoint. We are pleased to see as much efficacy signal as was apparent, and the study provides essential data to inform the dosing regimen for future Phase 3 trials of the intravenous formulation."

Some other interesting insights into the treatment of acute heart failure were presented. Prof P Ponikowski, Wroclaw, discussed the potential role of lung

impedance and lung ultrasound in the early diagnosis of acute pulmonary oedema to identify those at most risk of decompensation and who require hospitalisation. In addition, he suggested procalcitonin as a potential marker to identify pneumonia in these patients with pulmonary infiltrates of uncertain origin. Strategies and novel options of positive pressure ventilation (CPAP and non-invasive positive pressure ventilation (NIPPV)) in acute heart failure with pulmonary oedema were presented by Prof J Masip, Barcelona, emphasising the careful initiation of the therapy with fairly low positive end-expiratory pressure (PEEP) of 4-5cmH20 and low inspiratory positive airway pressure in NIPPV. Some new modalities like high flow nasal cannula may be a novel option for patients with subacute symptoms of dyspnoea.

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone which mediates the physiological cardiovascular (CV) and renal adaptations of pregnancy. In the **RELAX-AHF** trial (n=1161), a phase III randomised, double-blind trial comparing a 48-hour intravenous infusion of serelaxin with placebo in patients hospitalised for AHF, serelaxin was associated with dyspnea relief (primary objective) but no effect on readmission to hospital for heart or renal failure or on cardiovascular death through day 60 was observed [15]. The authors then presented the results of an extensive subgroup analysis across multiple pre-specified and other subgroups of interest which confirmed the beneficial effects of serelaxin vs. placebo with benefits with respect to the primary endpoint of dyspnoea relief, but no difference in the secondary endpoint of outcomes at day 60, and CV death and all-cause death at day 180. Nominally significant treatment-by-subgroup interactions were observed with the better mortality rate at day 180 in patients older than 75 years, in those with HF hospitalisation in the previous year, with lack of beta-blocker treatment at baseline, and low estimated glomerular filtration rate. However, due to lack of statistical power these results should be considered hypothesis generating rather than conclusive and we await results from the forthcoming RELAX-AHF-2 trial comprising more than 6,000 patients and having mortality as primary endpoint.

Post hoc analysis from **RAFT** (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) [16] was presented, examining the dosing of beta-blocker therapy against a background of optimal, contemporary treatment, from 1800 patients with heart failure treated with cardiac resynchronisation therapy. The purpose of this analysis was to ask if beta-blockers at full dosages are still better than not using a full-dose beta-blocker despite all the other treatments that patients received while in the study during 2003-2009. The analysis showed that those receiving full-dosage or nearly full-dosage beta-blocker regimens had a one-third cut in all-cause death or heart failure hospitalisation, compared with patients receiving less than half the recommended dosage, after adjustment for many baseline differences between these two subgroups. The patients in the group who were undertreated with beta-blockers were significantly older and had a significantly greater prevalence of New York Heart Association (NYHA) class III heart failure and heart failure with an ischaemic aetiology compared with those who received at least 50% of the target dosage and this most be considered as a potential confounder commented Karl Swedeberg, Gothenburg, but the study does emphasise the need to optimise drug dosing in patients with heart failure.

Heart failure patients have significant survival benefits when their implanted cardioverter-defibrillators (ICD) or cardiac resynchronisation therapy defibrillators (CRT-D) are fitted with telemonitoring technology that alerts medical experts to potential problems, results of the **IN-TIME** trial reveal. New technology that allows transmission of diagnostic data from implanted devices to a monitoring physician or clinic, as opposed to patients being followed via hospital visits, allows early detection of atrial or ventricular arrhythmias or specific trends in certain clinical parameters. The IN-TIME trial showed that at one-year, significantly more patients randomised to telemonitoring scored better on a composite endpoint that included all-cause mortality and specific cardiac measures. The prospective, randomised, controlled, multicentre trial analysed 664 chronic heart failure patients with class II/III NYHA symptoms, and a reduced left ventricular ejection fraction (LVEF) of ≤35%.

See you in Barcelona in 2014!

Further information

The ESC Congress 2014 will take place in Barcelona, Spain from 30 August to 3 September. Visit www.escardio.org for further information.

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