Dr Anthony Dalby attended the recent European Society of Cardiology (ESC) Congress, held at the Excel Conference Centre, Canary Wharf, London. This report is based on his impressions of the various sessions he attended and includes notes from three symposia on valvular heart disease.

Five updated ESC guidelines were launched during the meeting: non-ST segment elevation (NSTEMI) acute coronary syndrome (ACS), pulmonary hypertension, ventricular arrhythmias and sudden cardiac death, pericardial diseases, (to separate pericardial diseases from infective endocarditis which is covered in a separate guideline) and infective endocarditis. The full texts of all of these are available at escardio.org/guidelines. Year-long access to the presentations at ESC is available at escardio.org/ESC365.

Hypertension

**KEY MESSAGES**

- Adding spironolactone as the fourth antihypertensive agent in drug-resistant hypertension enables 60% of patients to achieve blood pressure control
- Half doses of hydrochlorothiazide (HTCZ) and amiloride control blood pressure without increasing serum potassium levels
- The angiotensin receptor-neprilysin inhibitor LCZ696 (valsartan/sacubitril) targets both blood pressure and arterial stiffness

The PATHWAY hypertension studies were undertaken by the British Hypertension Society. PATHWAY-2 investigated the optimal treatment for drug-resistant hypertension adding an α-blocker, β-blocker, spironolactone and placebo in four consecutive 12-week cycles to an angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) + calcium channel blocker + thiazide diuretic in patients with uncontrolled hypertension. Sixty percent of patients treated with spironolactone achieved blood pressure control. The response when spironolactone (25mg daily) was added was superior to that achieved when adding a β-blocker or α-blocker. The blood pressure response was inversely related to the renin level.

PATHWAY-3 examined the differences between HCTZ (25-50mg), amiloride (10-20mg) and their combination at half-dose...
levels (HCTZ 12.5-25mg + amiloride 5-10mg) on blood pressure, serum potassium, plasma glucose and uric acid in patients with hypertension and at least one characteristic of the metabolic syndrome (99% were obese). The greatest fall in blood pressure occurred with the lower-dose combination while the serum potassium level was unchanged. Plasma glucose rose in the HCTZ-only group, but was lower with amiloride alone or in combination. Uric acid rose on HCTZ.

Professor Bryan Williams, University College, London, presented the findings of the PARAMETER trial, which compared the angiotensin receptor-neprilysin inhibitor LCZ696 (valsartan/sacubitril) to ACE inhibition over 12 weeks in elderly patients with an elevated systolic pressure and a wide pulse pressure. LCZ696 achieved a 4mmHg greater reduction in central systolic pressure with a greater fall in night time blood pressure and in NT proBNP. A greater percentage of patients on ACE inhibition required additional medications to achieve control.

ATTEMPT-CVD compared the ARB, telmisartan, with alternative antihypertensive therapy over a three-year period. The endpoints were cardiovascular (CV) events, urinary albumin creatinine ratio (UACR), and brain natriuretic peptide (BNP). Identical blood pressure control was achieved with little difference in UACR and BNP. There was a non-significant reduction in CV events with the ARB.

Not part of the ESC presentations but nonetheless a ‘top-line’ result from the EMPA-REG OUTCOMES trial of the SGLT2 inhibitor, empagliflozin, reported cardioprotective effects. The complete results were released at the EASD meeting on 17 September. It was noted that SGLT2 inhibitors are also active in pancreatic α-cells, increasing glucagon secretion and stimulating gluconeogenesis.

The IMPROVE-IT study which evaluated simvastatin 40mg + ezetimibe 10mg vs simvastatin 40mg in post-ACS patients demonstrated a small benefit in favour of the combination. Dr RP Guigliano, Brigham and Women’s Hospital, USA, presented a subgroup analysis of patients with and without diabetes. The effect in the diabetes sub-group was markedly greater than in those without diabetes; there was a significantly greater reduction in the primary endpoint driven by a 24% reduction in myocardial infarction (MI) and a 39% reduction in ischaemic stroke.

Another sub-group analysis from the IMPROVE-IT study found no increase in new-onset diabetes over six years in those treated with the combination. Dr D Kotecha, Birmingham University, United Kingdom, reported that his meta-analysis of the individual data of 13 000 patients from various trials could not show a difference in the effect of β-blockers in respect of either age or gender.

The results of the PLATFORM study were presented by Dr Pamela Douglas, Duke University, USA. The investigators assessed the effect of fractional flow reserve by computed tomographic angiography (CTA-FFR) versus the standard practice of invasive angiography; the intention was to rule out obstructive coronary artery disease (OCAD) in moderate-risk patients. The trial was fairly small and was not randomised. Of note was that CTA-FFRCT could not be completed in 12% of patients. Follow-up was for 90 days only. In the CTA-FFR CT group, only 39% eventually underwent invasive angiography. The rates of detection of OCAD were similar (27% and 30%) whereas the primary endpoint, viz. no OCAD, was reached in 73% of the planned invasive group vs 12% in those who first had CTA-FFRCT.
The FREEDOM trial evaluated revascularisation by coronary bypass surgery vs percutaneous coronary intervention (PCI) in patients with diabetes. An analysis presented at the congress considered the effect of baseline blood pressure upon outcome. There was a dichotomy between coronary artery bypass grafting (CABG) and PCI patients. A lower blood pressure before CABG was associated with worse outcome whereas this relationship was not present in the PCI group. A previously reported adverse effect of ACE inhibition immediately pre-operatively, which might complicate the management of intra-operative hypotensive events, should be considered.

The five-year results of the FAME trial, which was not powered for this length of follow-up, nonetheless showed a non-significant benefit for FFR-guided PCI extending through the entire period. A 1.3% reduction in mortality and 27% reduction in CV events were observed in the FFR group.

Celecoxib was compared to diclofenac or ibuprofen in arthritic patients who were free from known CVD to assess whether the cardiovascular event rate differed; 7 297 low-risk arthritic patients from the UK, Denmark and the Netherlands were studied in the Standard Care versus Celecoxib Outcome Trial (SCOT). The observed primary event rate was low at 0.9 events/100 patient years, and was no different with celecoxib in comparison to the other NSAIDs. Serious adverse events were encountered in 30% of patients in both groups. The withdrawal rate was higher on celecoxib therapy.

Acute MI

**KEY MESSAGES**

- A one-hour rule-out strategy for NSTEMI using hs-troponin T was safe and effective
- The healing of Absorb bioreabsorbable stents compared favourably to that of metallic stents
- Second-generation drug-eluting stents (DESs) show superiority at five years
- There is no benefit in prolonging bivalirudin infusion after PCI

The BACC study investigated the value of a one-hour rule-out strategy for NSTEMI using hs-troponin I; 1045 patients with acute chest pain presenting to the emergency room (ER) were included. A cut-off of 6ng/l (rather than the 99th percentile) was used. Determination of hs-troponin I was performed at the time of presentation and after one hour. It was shown that those with values below the cut-off or with a differential of <12mg/l could be discharged safely. Caution was, however, advised in applying these findings as the type of test used and local laboratory norms determine the absolute values and cut-offs which should be used.

The healing of everolimus-eluting Absorb bioreabsorbable scaffolds was compared to that of everolimus-eluting metallic stents in 191 patients with STEMI and found to be non-inferior. The five-year follow-up of the EXAMINATION study, which used Xience V DESs in all comers with STEMI found a 4% reduction in the primary end-point with a reduction in mortality but no change in the incidence of MI and a trend towards reduced revascularisation. Most of the benefit of DESs was derived within the first year.

The MATRIX Duration study, which compared stopping bivalirudin at the conclusion of PCI vs continuing the infusion for four hours in STEMI and NSTEMI patients with high-risk characteristics could show no benefit of prolonging the infusion.
Antiplatelet therapy

**KEY MESSAGES**

- Extending dual antiplatelet therapy (DAPT) beyond one year after coronary stenting has advantages
- Fatal bleeding is rare with extended DAPT
- DAPT is not related to an increased cancer risk

The ATLANTIC study evaluated the benefit of immediate (pre-hospital) versus delayed (in the catheterisation laboratory) ticagrelor administration in patients with STEMI and could not demonstrate an early benefit. Pre-hospital administration was associated with more bleeding. Analysis of the trial results at a later time point showed a slight improvement in ST segment resolution and a reduction in new MI and stent thrombosis in the early treatment group.

The BASKET-PROVE II trial found no difference in non-CABG major bleeding after PCI between prasugrel 10mg daily (reduced to 5mg daily in patients >75 years or <60kg) and clopidogrel. Bleeding was more frequent in patients with ACS. Bleeding was not reduced in the group which received 5 mg prasugrel.

The OPTIDUAL trial examined whether there was a benefit in prolonging DAPT with aspirin and clopidogrel from 12 to 48 months after DES placement. Two-thirds of the almost 1400 patients underwent an elective PCI. The trial was terminated early. Although not reaching its combined endpoint of death, MI, stroke and major bleeding, there was a strong trend towards reduced ischaemic events in the 48-month group without an increase in bleeding (2% in both groups).

The PEGASUS trial compared aspirin with aspirin and ticagrelor initiated 1-3 years after an MI. In a sub-group analysis, though there were variations in their baseline characteristics, the benefit of DAPT was greatest in the group commencing the combined treatment within 30 days of stopping prior DAPT. There was less benefit in the group starting treatment after a gap of 30 days to one year and no benefit in those who had stopped DAPT for more than a year.

Dr J Udell surveyed the effects of prolonged DAPT (L-DAPT) after PCI (findings now published in the *European Heart Journal*). He found no increase in total deaths, non-CV deaths, fatal bleeding or intracranial haemorrhage. While there are no guidelines to assist in the decision whether to prolong DAPT, the decision should be individualised according to the assessed risk of future ischaemic events and bleeding risk (e.g. need for oral anti-coagulation, recent bleeding, recent surgery or prior intracranial haemorrhage).

The DAPT trial reported a higher rate of cancer in those on ticagrelor. However, the site of neoplasm was inconsistent and numbers were small, suggesting the play of chance.

Heart failure

**KEY MESSAGES**

- Normal hs-troponin T in acute heart failure signals lower risk
- Survival in low-body-weight diabetics with heart failure is better than in obese diabetics
- There was no increase in the risk of heart failure with sitagliptin in the TECOS trial

The AHEAD score, drawn from the Czech National Registry of Heart Failure, considered the influence on prognosis of a wide variety of co-morbidities. By simply adding one point each for atrial fibrillation (A), haemoglobin <12g/dl in women or <13g/dl in men (H), age >70 years (elderly = E), abnormal kidney function (A) and
the presence of diabetes (D), a score was derived that correlated accurately with the five-year prognosis, whether assessed at the time of admission for acute heart failure or at discharge. Those with a zero score had an excellent prognosis, whereas those with higher scores probably merit more intensive observation and treatment.

**Biomarkers in heart failure**

Ten percent of patients presenting with acute heart failure had an hs-troponin T <14 ng/L in the RELAX-HF trial. Their 180-day mortality rate was zero even though their BNP levels were >3000, suggesting that such patients may not require hospital admission.

The concentration of micro-RNA miR-22-3p is inversely related to the occurrence of worsening heart failure independent of recognised biomarkers such as CRP, hs-troponin T and BNP. Elevation of serum ST2, which is associated with interleukin-33 signalling when membrane bound, relates to heart failure mortality. Fibroblast growth factor 23, which regulates phosphate metabolism, was also shown to be predictive of mortality in heart failure with reduced ejection fraction (HeF-REF) but not with preserved ejection fraction (HeF-PEF). Prediction was improved by combining FRF23 with BNP.

The obesity paradox, which suggests that obese patients with heart failure have an improved survival, was studied in ambulatory diabetic and non-diabetic patients with heart failure. Patients with diabetes were more obese, were more often male, had more hypertension and were in a worse NYHA class with more chronic kidney injury. Survival was worse among the group with diabetes. Obese non-diabetic patients had better survival whereas those with the lowest weight in this group did worse. However, survival was best among the very small group of diabetes patients with low body weight. This study suggests that the obesity paradox does not seem to hold in the diabetic population.

Persistent or worsening dyssynchrony over six months in patients with a narrow QRS complex predicted a higher risk of worsening heart failure.

Although depression could not be shown to be an independent predictor of outcome in heart failure, the hospital admission rate (80% vs 64%) and mortality (30% vs 16%) were higher in depressed patients over two years.

The Swedish Heart Failure Registry found that kidney failure in association with heart failure exerts an adverse effect on outcome, independent of age, NYHA class, haemoglobin values and diabetes.

The commonly used measure of sleep-disordered breathing, the apnoea-hypopnoea index (AHI), turns out to be a weak predictor of prognosis in HeF-REF. The absolute time that oxygen saturation falls below 90% is a more robust measure. The risk of death rises 16% for each additional hour that the ‘hypoxaemic burden’ increases.

The SERVE-HF trial evaluated adaptive servoventilation in 1300 patients with chronic systolic heart failure (NYHA class III/IV) with predominant central sleep apnoea; 60% of patients used the intervention for an average of 3-4 hours/night. Treated patients had a 28% increase in all-cause deaths and a 34% increase in CV deaths, without improvement in quality of life and a greater reduction in the six-minute walk test distance.

The OPTILINK study failed to demonstrate a beneficial effect on outcome using remote monitoring of pulmonary fluid to modify treatment in implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy – defibrillator (CRT-D) patients with recently worsening heart failure.

An increased risk of heart failure had previously been found with saxagliptin (significant) and alogliptin (borderline effect). No evidence of increased risk was found with sitagliptin in the TECOS trial. However, patients with diabetes and prior heart failure remain at high risk of recurrence.

A meta-analysis of 41 trials of digoxin, seven of which were randomised, included 100 000 patients. Though the unadjusted observational studies suggested a 76% increase in mortality, the effect was neutral in the randomised trials. Hospitalisation for heart failure was slightly reduced in the digoxin group. The authors concluded that digoxin is safe while simultaneously favouring a low dose.

An Australian group investigated the benefit of a comprehensive CV nurse-led, home-based education and management
programme encompassing ACS, heart failure and atrial fibrillation (AF). Their interesting finding was that the intervention was effective in situations of high clinical complexity, but deleterious in those of lower complexity.

**Atrial fibrillation**

**KEY MESSAGES**

- Anti-arrhythmic agents given post-AF ablation do not improve outcomes
- Isolation of the left atrial appendage in addition to AF ablation is associated with thrombus development and stroke

AEGEAN compared an intensive educational programme to promote adherence to and persistence with anticoagulant treatment vs usual care and could not demonstrate an improved outcome. In this study, usual care was associated with a high rate of compliance.

EAST AF evaluated the use of anti-arrhythmic drug (AAD) therapy for 90 days after AF ablation vs no AAD. Although early arrhythmias were suppressed, the strategy did not influence outcome.

The five-year follow-up of the MANTRA-AF trial comparing AAD therapy to AF ablation was reported. Follow-up was 80% in the AAD group and 86% with AF ablation. The results were in favour of AF ablation with more patients being asymptomatic (94 vs 85%), having a lower AF burden and being in sinus rhythm (86 vs 71%). AADs were being used in almost half of the patients who had ablation.

Isolation of the left atrial appendage in addition to standard AF ablation reduced the risk of recurrent AF but was associated with thrombus development and stroke in a few patients. The procedure is not recommended.

**Pacing**

**KEY MESSAGES**

- Catheter-delivered leadless pacemakers offer high success rates and reduced device-related adverse events

The LEADLESS II study reported on the Nanostim LP leadless pacemaker implanted in 526 patients with a 96% success rate and freedom from device-related serious adverse effects in 93%. The unit provides rate-responsive VVI pacing. It was projected to be applicable in approximately 15% of patients needing pacing. Vascular complications and pericardial tamponade were noted as potential hazards. The generator life of these pacemakers is estimated at 15 years.

The frequency of sudden cardiac death was identical for CRT-D and CRT-P patients.

The 12-month mortality rate after pacemaker lead extraction is 6.7%. Fully 20% of patients undergoing lead extraction have not required re-implantation.

**Athlete’s heart**

Whereas the T-wave inversion in hypertrophic cardiomyopathy (HCM) occurs in the lateral chest leads, the most common findings in athletes’ heart are T-wave inversion in V1-V4 (71%), with J-point elevation (83%) and ST segment elevation (80%) in the same leads. This T-wave inversion is encountered in 1-4% of white athletes and 25% of black athletes. The changes are more pronounced in endurance athletes and less pronounced in women and children. Individuals
suspected of athletes’ heart should be intensively investigated to exclude HCM, arrhythmogenic right ventricular dysplasia and other forms of cardiomyopathy.

Valvular heart disease

**KEY MESSAGES**

**Bicuspid aortic valves (BAVs)**
- Intervening in BAV disease requires careful individual assessment
- Clinical notes on BAV disease are presented from a focused-symposium at ESC

**Aortic stenosis (AS)**
- A focused report on changing disease concepts in aortic stenosis with linked review

**Tricuspid regurgitation (TR)**
- A focused symposium on tricuspid regurgitation discussed new percutaneous device

**Bicuspid Aortic Valves (BAVs)**

BAV disease is congenital, associated with a variety of conditions and present in 1-2% of patients, with a 2:1 male to female predominance. There is no uniform phenotype. Eighty percent of cases are due to fusion of the leaflets between the left and right coronary arteries. A raphe is not inevitably present although it may be difficult to identify. BAV disease is associated with large aortic sinuses, an increase in aortic stiffness, a dilated ascending aorta and an increased incidence of aortic dissection. By determining the direction of the jet, the specific deformity of the valve influences the form the aortic dilatation will take. The increase in aortic size is influenced by family history, gender, patient age and body size. BAV disease is more frequently encountered in aortic coarctation (50%), Turner’s syndrome (30%) and supravalvular AS (30%). Both the valvular disease and the aortic dilatation have variable rates of progression. Follow-up studies have demonstrated that the aortic root size did not progress in 43% patients. Degeneration of the BAV constitutes 50% of cases requiring aortic valve replacement (60% under age 70 years and 40% above 70 years). The risk of aortic dissection is low. Ten percent of cases may require replacement of the ascending aorta. Elective surgery is recommended if the aortic diameter exceeds 5.5 cm or is 4.5 cm or greater at the time of other cardiac surgery.

There is difficulty establishing the natural history of BAV disease. Aortic regurgitation (AR), infective endocarditis (IE) and aortic valve replacement occur more frequently in males. Severe AR and a higher NYHA class predict a worse prognosis in women. The outcome of surgery for BAV disease is worse than that for other pathologies needing aortic valve replacement.

**Aortic Stenosis (AS)**

Dr CM Otto, University of Washington, USA, discussed the role of echocardiography in diagnosing the severity of AS in asymptomatic patients. The aortic velocity is a better predictor of the onset of symptoms than the aortic valve area. In low-flow situations the stroke volume index should be calculated. Dobutamine stress echo is useful in this setting; an aortic velocity >4 m/second indicates severe stenosis. A less common presentation of severe AS is that with severe left ventricular hypertrophy and a low stroke volume.10

Dr B Iung, Bichat Hospital, Paris, addressed the question of whether it is appropriate to intervene in the asymptomatic patient. Current studies have found that the risk of sudden death in severe AS is <1 in 100 per annum. However, there are difficulties in watchful waiting in severe AS, particularly in the elderly who may require, *inter alia*, urgent non-cardiac surgery at which time their AS confers a higher, potentially avoidable risk.
Extensive valvular calcification and high aortic velocity present a higher degree of risk. Symptoms may be unmasked by exercise testing in 37% of ‘asymptomatic’ patients. An inadequate rise in systolic blood pressure in exercise (<20mmHg) is also significant. If exercise echocardiography is employed, an increase in the gradient >18mmHg is significant. BNP is also useful in determining the severity of the problem. However, there is as yet no proof that survival is improved by intervention in the truly asymptomatic patient.

Regarding alternative forms of imaging in AS, valvular calcium scoring on CT is independently predictive of both the severity of stenosis and prognosis. Critical levels of calcium score are 1300 in women and 2000 in men. Imaging with Na-FI positron emission tomography (PET) can demonstrate the presence of active calcification, which also relates to prognosis. The demonstration of fibrosis on cardiac magnetic resonance imaging (CMR) correlates with left ventricular hypertrophy in the ECG. Myocardial fibrosis on MRI is associated with higher mortality and poorer response to surgery. Biomarkers such as hs-troponin T also relate to outcomes in AS.

The mortality rate in aortic stenosis is reduced by RAAS inhibition, to a greater degree with ARBs than with ACEs. Given the demonstrated low risk of stroke and the reduction in the frequency of significant aortic regurgitation (NOTION valve) in recent studies, transcatheter aortic valve replacement (TAVR) may soon become an alternative strategy for intermediate-risk patients with severe AS. One study reported success with the performance of TAVR under local anaesthesia. Only 0.7% of patients required conversion to general anaesthesia and 37% needed deep sedation. Another TAVR study found that the best results were obtained by employing subclavian artery access when femoral access was not possible.

Tricuspid Regurgitation (TR)

A Cleveland Clinic symposium discussed TR. It was emphasised that the observed frequency varies in accordance with the population studied. However, there is a high frequency of TR in heart failure, which exerts profound effects on morbidity and mortality. TR is more frequently observed in HeF-PEF. Surgical morbidity and mortality remain high, in the region of 20%. Appreciating that the annular dilatation that drives the TR is the result of expansion in the region of the commissure between the anterior and posterior leaflets and the posterior leaflet itself, a percutaneous device is being pioneered that allows the placement of a pledged stitch from the atrial surface of the anterior leaflet to the posterior aspect of the posterior leaflet under transoesophageal echo guidance. By drawing in this stitch, the tricuspid valve effectively becomes bicuspid. Only nine cases have been attempted to date. In eight of these cases the TR disappeared after the procedure. A patient with pulmonary hypertension succumbed.

Infective Endocarditis (IE)

The risk of IE associated with dental surgery is reduced from one in 500 000 cases without to around one in 150 000 with antibiotic prophylaxis. This understanding has led to a downscaling of the guideline recommendations to confining antibiotic prophylaxis to the highest-risk patients undergoing the highest-risk procedures. As the risk of tooth brushing approximates that of dental surgery, meticulous oral and cutaneous hygiene is recommended.

The new guidelines place strong emphasis on the performance of transoesophageal echocardiography (TEE) in the diagnosis of IE, particularly in the presence of a valve prosthesis. TEE should be repeated in 5-7 days if there is continuing uncertainty about the diagnosis. Additional information may be gained from CT, MRI and FDP PET scanning.

The stroke risk in IE is highest in the first week after initiating treatment.

References


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