Conference highlights

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The leading cause of death in Australia, according to the Australian Bureau of Statistics, is ischaemic heart disease and the ninth ranked cause of death is cardiac failure; these conditions are managed every day by GPs, cardiologists and other clinicians.

Cardiology Today followed four Australian delegates (a GP, a cardiology nurse, a cardiology physician and an interventional cardiologist) attending the world's largest cardiology conference, ESC Congress 2017, in Barcelona. We present summaries of their highlighted sessions together with their commentaries on the implications of the findings. Video highlights can be viewed at: www.cardiologytoday.com.au/esc2017videos/day4.html.

Does reducing inflammation lower CV risk in high-risk population?

The inflammatory hypothesis of atherothrombosis has been debated for decades and has remained unproven. The randomised, double- blind, placebo-controlled Canakinumab ANti-inflammatory Thrombosis Outcomes Study (CANTOS), conducted in 39 countries, was specifically designed to test this hypothesis

Canakinumab is a human monoclonal antibody targeting interleukin-1, a pro-inflammatory cytokine that if overexpressed results in increased inflammation and increased levels of high sensitivity C-reactive protein (hsCRP).

In this industry-funded study, investigators randomised 10,061 patients who had a prior myocardial infarction (MI), had well-controlled conventional risk factors and had persistently elevated levels (2 mg/L or greater) of hsCRP to 50, 150 or 300 mg canakinumab or placebo, administered subcutaneously once every three months. The mean age of the patients at baseline was 61 years, most had undergone previous revascularisation procedures, and they had received aggressive secondary prevention strategies (median baseline LDL cholesterol level, 2.13 mmol/L). Patients were followed up for 48 months.

Compared with placebo, canakinumab reduced hsCRP from three months in a dose dependent manner and this was sustained during follow up while having no impact on LDL cholesterol levels.

At a median follow up of 3.7 years, there was a 15% relative reduction in the primary endpoint (composite of nonfatal MI, nonfatal stroke and cardiovascular [CV] death; p=0.007) and a 17% reduction in the secondary endpoint (all of the above plus unstable angina requiring urgent revascularisation; p=0.006) for the combined 150 mg and 300 mg canakinumab dose groups compared with placebo. Due to multiplicity testing, only the 150 mg dose formally met statistical significance for both the primary and secondary endpoints.

Professor Brieger

Exploratory analyses revealed that canakinumab reduced, in a dose dependent manner, the rates of total cancer death, especially death due to lung cancer, as well as the incidence of lung cancer. Compared with placebo, those taking 300 mg canakinumab had a 51% reduction in total cancer deaths (p=0.0009), a 67% reduction in incident lung cancer (p=0.00008) and a 77% reduction in fatal lung cancer (p=0.0002).

Although there was a reduction in cancer deaths with canakinumab, there was a significantly higher incidence of fatal infection in the pooled canakinumab groups compared with placebo, resulting in an overall neutral effect on mortality.

Describing the trial as 'ground breaking', lead investigator and presenter Dr Paul Ridker (Eugene Braunwald Professor of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA) said it provided for the first time proof that lowering inflammation independently of cholesterol reduces CV risk and potentially may alter the progression of some fatal cancers. 'It's a whole new way of looking at cardiovascular prevention,' he stressed.

Comment by Professor Brieger

Announced in one of the most exciting late breaking sessions at the ESC Congress in years, the findings of CANTOS have reaffirmed the inflammatory hypothesis of coronary disease. While the immediate application of this expensive therapy in patients with prior MI may be limited, these findings will likely stimulate evaluation of existing and new anti-inflammatory therapies in patients with vascular disease, as well as suggesting new avenues of endeavour in the prevention and treatment of cancer.

Ridker PM, et al, for the CANTOS Trial Group. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. Paper presented at: ESC Congress; August 27, 2017; Barcelona.
Ridker PM, et al, for the CANTOS Trial Group. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. NEJM: published online August 27, 2017.
Ridker PM, et al, on behalf of the CANTOS Trial Group. Effect of interleukin-1βinhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet: published online August 27, 2017.

Aspirin plus low-dose rivaroxaban improves secondary prevention of CV disease

In February 2017, the Data Safety Monitoring Board recommended the discontinuation of the Phase III Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial due to the demonstrated efficacy of the combination of rivaroxaban plus aspirin compared with aspirin alone in the secondary prevention of cardiovascular (CV) disease.

Primary results of the COMPASS study were from 602 sites in 33 countries, including Australia. Over 27,000 patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD) were followed for a mean of 23 months. Patients were being medically treated for hypertension, diabetes and dyslipidaemia.

In this double-blind, double dummy trial, patients were randomised to aspirin 10 mg daily, rivaroxaban 5 mg twice daily, or daily aspirin plus twice-daily rivaroxaban 2.5 mg. About 9,100 patients were in each treatment group and they had the following characteristics:

- mean age of 68 years
- mean blood pressure of 136/78 mmHg
- 90% had CAD and 27% had PAD
- 38% had diabetes
- 90% used a lipid-lowering medication
- 71% used an ACE-inhibitor or angiotensin-receptor blocking agent.

Exclusion criteria were a high bleeding risk, a recent stroke or previous haemorrhagic or lacunar stroke, severe heart failure and advanced stable kidney disease (estimated GFR <15 mL per minute).

There was a significantly reduced rate of the composite outcome of CV death, stroke or myocardial infarction (MI) in patients using aspirin plus rivaroxaban compared with aspirin alone (4.1% *vs* 5.4%). The risk was 4.9% in those on rivaroxaban alone but this was not statistically different from the other two groups.

There was an increased major bleeding risk associated with using aspirin plus rivaroxaban compared with aspirin alone (3.1% *vs* 1.9%). Nonetheless, there was an overall net benefit in using the combination of aspirin and low-dose rivaroxaban compared with aspirin alone – i.e. rate of composite CV outcome or severe bleeding, 4.7% *vs* 5.9%.

Presenting the findings of this industry funded study, Dr John William Eikelboom (Associate Professor in the Department of Medicine, McMaster University, and haematologist in the Thrombosis Service, Hamilton General Hospital, Ontario, Canada) concluded: 'COMPASS trial results demonstrate that the combination of rivaroxaban and aspirin compared with aspirin alone reduces the composite CV death, stroke or MI; increases major bleeding, but not significantly the most severe types of bleeds; and provides a net clinical benefit.'

Comment by Professor Brieger

The COMPASS study looked at a stable population of patients with either or both coronary and peripheral vascular disease and found an impressive reduction in CV events in patients being treated with a combination of low-dose rivaroxaban and aspirin compared with those using aspirin alone. Nonfatal bleeding was increased in the combination arm, but the net clinical benefit appears to favour addition of very low dose anticoagulant therapy to aspirin alone. Escalating therapy in a stable population



can be challenging in practice and future reports from this important study should provide guidance regarding the patient groups who have most to gain from this additional treatment.

Eikelboom JW, on behalf of the COMPASS Steering Committee and Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. Paper presented at: ESC Congress; August 29, 2017; Barcelona. Eikelboom JW, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med: Published online August 27, 2017.

Mortality benefit reported in triple vascular screening study

The only cardiovascular (CV) disease currently targeted by population screening is abdominal aortic aneurysm (AAA). The Viborg Vascular (VIVA) trial was established to investigate primarily the effect of triple vascular screening for AAA, peripheral arterial disease (PAD) and hypertension on mortality in a population of men living in central Denmark.

In total 50,156 men aged 65 to 74 years were randomised to be screened for AAA, PAD and hypertension or to no screening. Individuals who were subsequently found to have an AAA or PAD were recalled and if confirmed on repeated diagnostic testing, the total serum cholesterol was measured, and physical exercise, smoking cessation, a low-fat diet and appropriate pharmacological therapy were encouraged. A CT scan and referral to a vascular surgeon was arranged for individuals with an AAA >5 cm diameter. Individuals with possible hypertension were encouraged to see their GP. If the total serum cholesterol exceeded 4 mmol/L, a statin and aspirin were prescribed.

An AAA was detected in 3.3% (AAA >5 cm in 0.3%), PAD in 10.9% and previously unknown, possible hypertension in 10.5%. Repeat testing confirmed all the AAA cases detected on screening; however, 11.1% of the PAD cases detected on screening were false positives. 49.6% of the men diagnosed with an AAA had a repair within five years. The men allocated to screening who were not on therapy at baseline had a higher rate of initiation of antithrombotic therapy (hazard ratio [HR], 2.3; p<0.0001), lipid lowering therapy (HR, 2.1; p<0.0001) and antihypertensive therapy (HR, 1.6; p<0.0001). The rate of elective AAA repair was also 2.4-fold higher in the screening group.

There was a significant reduction in all-cause mortality after a median follow-up of 4.4 years with 2566 (10.2%) versus 2715 (10.8%) men dying in the groups allocated to screening and no screening respectively (HR, 0.93; p=0.01). The number needed to invite to prevent a death was 169.

Comment by Professor Atherton

Screening may be considered for conditions associated with substantial morbidity and mortality if a cohort of individuals can be reliably identified with a sufficiently high prevalence of that disease, there are effective treatments available that will lead to better outcomes compared with waiting for patients to present clinically, and there are affordable (preferably noninvasive) tests that allow these individuals to be identified.

The VIVA study is quite unusual, firstly as such large population-based, CV screening studies are rare, and secondly that this is the largest mortality benefit reported in any population-based, screening study conducted to date. The benefits appear likely to be largely related to additional appropriate pharmacological treatment.

Questions that remain include whether similar benefits could be achieved by a more focused approach to 'vascular' screening, whether it is cost-effective to introduce such screening programs in other jurisdictions, and whether similar screening programs should be considered in other cohorts, including women with associated high-risk features (e.g. diabetes mellitus). Finally, while overdiagnosis and overtreatment occur with any screening program, the adverse consequences of CV screening appear to be less than what is currently accepted by cancer screening programs.

Lindholt JS. The Viborg vascular (VIVA) randomised screening trial. Paper presented at: ESC Congress; August 28, 2017; Barcelona. Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. Lancet: published online August 28, 2017.

Benefits of risk factor management in patients with early persistent AF associated with heart failure

The Routine versus Aggressive upstream rhythm Control for prevention of Early persistent atrial fibrillation in heart failure (RACE 3) study was a randomised, open-labelled study conducted in the Netherlands and the UK that evaluated whether more aggressive cardiovascular (CV) risk factor management in patients with early, persistent atrial fibrillation (AF) associated with heart failure would increase the proportion of patients in sinus rhythm at 12 months (the primary endpoint).

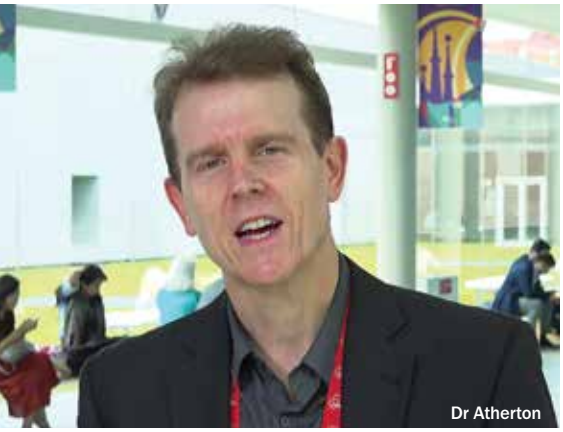
Patients enrolled in RACE 3 were in persistent AF for between seven days and six months with a history of at least one prior cardioversion associated with heart failure (with either a reduced or preserved LV ejection fraction [LVEF]) of less than one year duration. Patients with a left atrial dimension greater than 50 mm or a LVEF below 25% were excluded.

Patients were randomised to receive either conventional care or risk factor management, which included a mineralocorticoid receptor antagonist, statin, ACE inhibitor (and/or angiotensin receptor blocker) and cardiac rehabilitation (including physical activity, salt restriction, calorie reduction, fluid balance and counselling). Both groups had a cardioversion performed at three weeks.

A total of 245 patients were enrolled with an average age of 64 to 65 years; 79% were male and 29% had a LVEF <45%. The average CHA_2DS_2-VASc score was 2. A seven-day Holter monitor was performed at 12 months, which revealed that a higher proportion of patients were in sinus rhythm with risk factor management compared with usual care (75 *vs* 63%; p=0.021). There was no significant difference in CV events; however, the study was not powered to address this.

Comment by Professor Atherton

The RACE 3 trial demonstrates the benefit of


Dr Atherton

risk factor management in patients with early persistent AF associated with heart failure. This study builds on the impressive body of work from Professor Prash Sanders' group in Adelaide that upstream, risk-factor management decreases the risk of AF recurrence, which they have suggested should be considered the 'fourth pillar of AF care'. The RACE 3 trial extends this approach to patients with early persistent AF associated with heart failure, and that decreased AF recurrence was observed in the absence of a reduction in BMI. As with any multifactorial intervention, it is unclear which component(s) account(s) for the clinical benefit. It is also noted that addressing alcohol intake was not part of this intervention. Finally, is unclear whether this will translate to longer term clinical outcome benefits.

Van Gelder IC, for the RACE-3 Investigators. Routine versus aggressive upstream rhythm control for prevention of early atrial fibrillation in heart failure, the RACE 3 study. Paper presented at: ESC Congress; August 27, 2017; Barcelona.

Education and feedback improves anticoagulant use in patients with AF

Oral anticoagulation is underused in patients with atrial fibrillation (AF), with only about half of patients with AF and stroke risk factors being treated with these medications. The international, multicentre, clustered, randomised trial of multifaceted intervention to IMProve treatment with oral AntiCoagulants in Atrial Fibrillation (the IMPACT-AF trial) was designed to assess whether education of healthcare providers and patients with AF, with monitoring and feedback, could increase the use of oral anticoagulation compared with usual care.

The two-arm, prospective cluster-randomised controlled, industry-funded trial included 2281 patients from 48 centres in Argentina, Brazil, China, India and Romania. Centres in each country were randomised in a 1:1 ratio to receive a quality improvement educational intervention (intervention group; n=1187) or usual care (control group; n= 1094). The trial participants were 18 years or older, had AF that was not due to reversible causes and had an indication for oral anticoagulation (CHA_2DS_2-VASc score ≥2 or rheumatic valvular heart disease). Exclusion criteria included an absolute contraindication to anticoagulation.

The intervention involved education of healthcare providers and patients and their family, with regular monitoring and feedback and was customised to each country. Interventions included brochures, webinars, emails and social media, and involved monitoring and feedback on patients' adherence to oral anticoagulation. Every six and 12 months all patients enrolled had a 'clinical event assessment', and at one, three, six, nine and 12 months, patients in the intervention group were contacted by phone or in person to discuss their anticoagulation and its continuation.

The primary outcome was the change in the proportion of patients with AF treated with oral anticoagulation from baseline to one year. Secondary clinical outcomes were death, stroke and bleeding.

At 12 months, overall oral anticoagulant use had increased by 12% in the intervention group (from 68% at baseline to 80% at 12 months), and by 3% in the control group (64% at baseline to 67% at 12 months; p = 0.0002 for difference between the groups).

Similar number of patients in the intervention and control groups who were anticoagulated at baseline remained on treatment at 12 months (95% *vs* 94%, respectively). However, 48% of the patients in the intervention group who were not taking anticoagulants at baseline were on an anticoagulant at one year, compared with only 18% in the control group (p<0.0001). This finding shows how a relatively simple intervention can close the gap by almost half, principal investigator and presenter, Professor Christopher B. Granger (Professor of Medicine, Duke Clinical Research Institute, Durham, USA) told the delegates.

During the study there was nominally significant reduction, of 52%, in strokes in the intervention group (1% *vs* 2% in the controls; p=0.04), a finding that 'underscores the potential impact of such an intervention in improving the use of anticoagulants for stroke prevention around the world', Professor Granger concluded.

Comment by Professor Newton

With new developments in therapy there is the challenge of translating the evidence into routine practice. This use of anticoagulation in AF is no exception. This study, although not particularly novel or ground breaking, is important because it used multiple approaches and platforms in multiple countries to increase the appropriate use of anticoagulants by targeting both the prescriber and patient. Although this study was not powered to show improvements in clinical endpoints, we know the appropriate use of these therapies will prevent strokes. There need to be continued efforts to improve the use of these therapies in routine practice and this showed that a multipronged approach was effective. However, as each country was able to customise the intervention we don't know if some of the strategies used were more effective than others.

Vinereanu D, et al, on behalf of the IMPACT-AF investigators. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. Lancet: published online: August 28, 2017.

Granger CB, on behalf of the IMPACT-AF Steering Committee and Investigators. An international cluster randomized trial of a multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation: the IMPACT-AF trial. Paper presented at: ESC Congress; August 28, 2017; Barcelona.



Evolving concepts: lipids in atherosclerosis

There have been major advances relevant to GPs in lipid targets for the management of atherosclerosis. Research has suggested that serum LDL cholesterol levels are more important than serum HDL cholesterol levels in prevention of atherosclerosis. In fact, increasing serum HDL cholesterol does not translate into a reduction in cardiovascular disease (CVD), and very high levels may even indicate a genetically increased risk. Triglycerides and lipoproteins are another focus of research into CVD causation, especially regarding the genetics of heart disease.

HDL cholesterol is highly complex and protects against inflammation, is antioxidant and improves endothelial function. Serum levels of HDL cholesterol are no longer a target for treatment because increasing serum levels of this molecule is not associated with reduced CVD. However, low HDL levels are still undesirable. Low serum levels are associated with an increased risk of heart failure, independent of the presence of any CVD. There is also evidence that in patients who have kidney disease, a pro-inflammatory state, endothelial cell inflammatory activation is associated with dysfunctional HDL cholesterol activity. This indicates that it actually may be the quality of function of the HDL cholesterol that is important, as opposed to the serum levels.

Regarding atherosclerosis, hypertriglyeridaemia has been reaffirmed as a significant cardiovascular risk. However, the focus seems currently on medications that reduce LDL cholesterol. Statins favourably modify plaque stability via a reduction of the inflammatory effects associated with atherosclerosis. Research suggests that these benefits are especially obvious six weeks after myocardial infarction and before coronary artery bypass surgery.

Monoclonal antibodies are a hot topic in cardiology. Research into proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors is ongoing, but injections of this substance potently reduce LDL cholesterol, via degradation of hepatic LDL cholesterol receptors. Mutations in the PCSK9 gene are responsible for some types of familial hypercholesterolaemia.

Finally, genetic risk and the development of atherosclerosis has become increasingly important, given some patients have a strong family history of early CVD but few other risk factors. Lipoprotein A deficiency is under investigation as one genetic cause in this group; however, there are currently inadequate treatment options for this condition so investigating this condition is controversial. Research into this is ongoing.

Comment by Dr Miller

Thankfully, discussing cholesterol targets with our patients has now become simpler and clearer. Hypertriglyceridaemia and raised serum LDL cholesterol levels are the major treatable lipid risk factors for CVD and there is no debate about the importance of the use of statin medication when this is indicated. Also, importantly, though, GPs need to bear in mind the relevance of an early family history as an independent risk factor for CVD, even in the absence of other traditional risk factors, and refer such patients appropriately.

Libby P, Jukema JW (Chairpersons). Lipids in atherosclerosis - evolving concepts. Symposium presented at: ESC Congress; August 27, 2017; Barcelona.

Catheter ablation of AF in patients with heart failure compared with conventional care

Atrial fibrillation (AF) and heart failure are closely intertwined, but there are limited data regarding the clinical efficacy of catheter AF ablation in patients with both these conditions. The Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) trial was an international, multicentre, randomised, controlled study that compared the clinical efficacy of catheter ablation and conventional therapy in patients with coexisting heart failure and AF.

The 363 trial participants of this industry-funded trial had paroxysmal or persistent AF associated with heart failure (NYHA class 2-4) and a LV ejection fraction (LVEF) <35%, who had failed or were intolerant of at least one antiarrhythmic drug (AAD) or were not willing to take an AAD. All patients had an implantable cardioverter defibrillator with or without cardiac resynchronisation therapy. Patients were treated as per heart failure guidelines. It was recommended that there should be attempts to achieve sinus rhythm in patients randomised to conventional care, and a heart rate of 60 to 80 beats/min at rest and 9 to 115 beats/min during moderate exercise was recommended for rate control. Pulmonary vein isolation was performed in patients randomised to receive catheter ablation, with additional lesions at the discretion of the operator.

The average age of participants was 64 years, average LVEF 32%, and prescription rates for ACE inhibitors, beta blockers, diuretics and oral anticoagulants were over 90% for both treatment arms. Catheter ablation was associated with an acceptable adverse event profile, a lower proportion of patients in AF (which persisted to five years' follow up) and a greater increase in LVEF.

There was a 38% relative risk reduction in the primary endpoint (all-cause mortality or worsening heart failure hospitalisation) in the patients randomised to catheter ablation (p=0.007), which was driven by significant reductions in both all-cause mortality (hazard ratio [HR], 0.53; p=0.011) and worsening heart failure hospitalisation (HR, 0.56; p=0.004). The benefits were similar across most of the prespecified subgroups, although there was a nominally significant interaction with the baseline LVEF, with a greater benefit observed in patients with a LVEF 25 to 35%.

Comment by Professor Atherton

The CASTLE-AF study demonstrated a clinically and statistically significant reduction in death and worsening heart failure hospitalisation with catheter ablation in patients with paroxysmal or persistent AF associated with heart failure and a reduced LVEF (HFrEF). This study builds on previous studies demonstrating improvements in quality of life and surrogate endpoints such as LVEF and exercise capacity with catheter ablation. It also suggests that the failure of earlier studies to demonstrate a clinical benefit of rhythm versus rate control using pharmacological therapy may have been driven


Professor Newton

by the limited efficacy and side effect profile of the available drugs. As with any procedural intervention, an outstanding question is how this will translate more broadly with variable operator expertise. However, it clearly demonstrates that AF is not only a risk marker for poorer outcomes in patients with HFrEF, but also a modifiable risk factor.

Marrouche NF, on behalf the CASTLE AF Investigators. Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation: The CASTLE-AF trial. Paper presented at: ESC Congress; August 27, 2017; Barcelona.

Can exergaming improve exercise capacity of patients with heart failure?

Guidelines for patients who have heart failure recommend regular exercise, but adherence to exercise advice and physical activity levels remain low in these patients. An emerging tool in rehabilitation is exergaming – the playing of video games that require rigorous physical exercise and is intended to be performed as a work out. Heart Failure – Wii is a multicentre, randomised controlled trial designed to determine the effects of structured access to an exergame in patients with heart failure on their exercise capacity and physical activity level. The three-month follow-up data of this 12-month study were presented.

A total of 605 patients (mean age 67 +/- 11 years) with diagnosed heart failure in Sweden, the Netherlands, Germany, Italy, Israel and the USA were randomised to motivational support only (control) or structured access to an exergame (Nintendo Wii sports; Wii intervention). Patients in the intervention group received a game computer and an introductory group lesson to the exergame and were given personalised activity (gaming) advice. Those in the control group received personalised activity advice. All patients received motivational follow up calls at 2, 4, 8, and 12 weeks. The primary endpoint was blinded assessment of the 6-minute walk test (6MWT) at baseline and three months and secondary endpoints include the 6MWT at six and 12 months, muscle function, exercise motivation, health-related quality of life, mortality and costs.

At baseline there were no significant differences between the groups (mean 6MWT, 402 +/-141 metres), but at three months, follow up, there was a statistical and clinically significant difference in the 6MWT in the exergame group compared with the control group of 33 metres ($p = 0.004$). At three months, 62% of all patients had improved their 6MWT and 34% improved more than 30 metres, and there was no difference between the groups in the number of people whose 6MWT improved or decreased.

At three months, the median number of right shoulder abductions was significantly greater in the exergame group than controls ($p<0.05$), but no other significant differences in muscle function were recorded.

Subgroup analysis is planned to investigate who benefits most, and planned per protocol analysis will investigate adherence to and enjoyment of playing the Wii.

'This is the first large-scale, adequately powered study evaluating the effectiveness of exergaming on functional exercise capacity in patients with heart failure,' presenter and lead investigator Professor Tiny Jaarsma (Professor of Nursing at the Faculty of Medical and Health Sciences of the University of Linköping, Sweden), told delegates. Exergaming was shown at three months to have both a statistical and clinical significant difference in exercise capacity and was safe and feasible to introduce in this heart failure population, she said.

Comment by Professor Newton

In this relatively young but symptomatic heart failure population, the novel use of the Nintendo Wii was able to improve exercise capacity in the intervention group at three months. Whether these results will be sustained at 12 months is not yet known (results due 2018). We also await to see how well the participants adhered to the protocol over time which is also problematic for exercise-based interventions. But overall, the intervention was safe and improved exercise capacity.

Jaarsma T, et al. Improving exercise capacity of patients with heart failure through exergaming: the 3 months' results of an international multicenter randomised controlled trial. Paper presented at: ESC Congress; August 28, 2017; Barcelona.

Renal dysfunction and iron deficiency: facts, myths and solutions

Iron deficiency is extremely common in patients who have chronic renal dysfunction and especially if there is co-existent acute or chronic heart failure. This problem easily goes unrecognised, as doctors may be not be aware of the different definition of iron deficiency in patients who have chronic diseases that cause a rise in acute phase reactants (such as serum ferritin).

The usual definition of iron deficiency is a morning ferritin level of under 30 mcg/L, according to the Royal College of Pathologists of Australasia. However, the definition of iron deficiency in patients who have chronic disease or chronic inflammation is a morning ferritin level of under 100mcg/L, or a morning ferritin level of 100 to 199 mcg/L along with a transferrin level of less than 20%. The prevalence of iron deficiency by this second definition in patients who have acute or chronic cardiac failure is approximately 50%. Mitochondrial dysfunction of cardiomyocytes is thought to contribute to iron deficiency in this population.

Iron deficiency is associated with reduced life expectancy and increased morbidity. Symptoms and signs are broad, and include worsening dyspnoea, angina and cognitive function


and reduced energy levels.

There is currently research into future ways of diagnosing iron deficiency in patients with chronic disease. Hepcidin is a hepatic peptide hormone that acts as an acute phase reactant. High serum levels occur with chronic disease and systemic inflammation. Iron deficiency inhibits the production of hepcidin and this reduced hepcidin serum level then results in a release of iron stored in cells. Soluble transferrin factor receptor (sTfR) is a protein found in blood. The serum level of this protein is the most accurate biomarker of iron deficiency, but further research into its clinical use is required. It is not currently suggested that doctors use serum hepcidin or sTfR level measurement in general practice to assist in diagnosis of iron deficiency.

The identification of iron deficiency in patients who have chronic disease is difficult, as inflammation, chronic oxidative stress and dilution affect ferritin and transferrin levels. Transferrin saturation is more accurate than serum ferritin levels in oedematous patients. Currently, the above definitions remain the best diagnostic method for use in clinical practice.

Comment by Dr Miller

Traditionally, a reduced serum ferritin level has been the definition of iron deficiency. This is reflected in doctors being trained to be aware of the common risk factors, primarily blood loss and poor oral intake or absorption. The research presented at the 2017 ESC Congress is of great clinical relevance and when this additional definition of iron deficiency is applied to those who have chronic disease, many cases in practice are clearly going unrecognised. Quality of life, morbidity and mortality can all be improved by early identification and treatment of iron deficiency in this population. Both GPs and specialists need to be alert to the significant increase in the prevalence of iron deficiency in patients with chronic disease, especially those who have advanced renal dysfunction and co-existent acute or chronic heart failure.

Abdelhamid M, Packer M (Chairpersons). Renal dysfunction and iron deficiency: facts, myths, and solutions. Advances in Science session presented at: ESC Congress; August 26, 2017; Barcelona.

No role found for supplemental oxygen in patients with suspected MI who are not hypoxaemic

The practice of routine oxygen therapy in patients with suspected acute myocardial infarction (MI) has been questioned in the Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) trial. The trial was a registry-based, multicentre, open-label, randomised, controlled trial conducted in Sweden that compared routine supplemental oxygen therapy (6 L/min) with ambient air in 6629 patients with suspected acute MI who were not hypoxaemic (oxygen saturation >90%) when enrolled.

The median age was 68 years, the median oxygen saturation was 97% at the time of enrolment, and 76% of patients were subsequently confirmed to have a myocardial infarct. The median duration of oxygen therapy was 11.6 hours.

Supplemental oxygen compared with ambient air was associated with a lower proportion of patients requiring oxygen outside of the trial because they developed hypoxaemia (1.9% *vs* 7.7%), with no difference in the highest troponin level achieved. There was no difference in either the primary endpoint all-cause mortality (hazard ratio [HR], 0.97; p=0.80) or rehospitalisation for MI (HR, 1.13; p=0.33) at one year. The findings were consistent across the prespecified subgroups.

Comment by Professor Atherton

The role of supplemental oxygen in patients presenting with suspected acute MI has been long debated with limited evidence of efficacy, and concerns raised regarding toxicity, including the Australian Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction (AVOID) study that previously reported increased infarct size in patients who were randomised to receive supplemental oxygen (8L/min). The much larger DETO2X-AMI study puts to rest the debate and indicates that supplemental oxygen has no role in patients with suspected acute MI who are not hypoxaemic. This study also highlights the importance of pragmatic, registry-based studies to answer important clinical questions that are unlikely to be funded by industry.

Hofmann R. DETermination of the role of OXygen in suspected Acute Myocardial Infarction. Paper presented at: ESC Congress; August 28, 2017; Barcelona.
Hofmann R, et al, for the DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med: published online August 28, 2017.

Can renal denervation reduce blood pressure in patients with hypertension?

The SPYRAL HTN OFF-MED Study was a proof of concept study aiming to determine whether intensive renal denervation with the new SPYRAL catheter can reduce blood pressure (BP) in patients with uncontrolled (but not resistant) mild to moderate hypertension who are not using antihypertensive therapy. The previous SYMPLICITY HTN-3 trial failed to show a significant decrease in BP in patients with resistant hypertension.

In this industry-funded study that was conducted in the USA, the UK, Europe, Australia and Japan, 80 patients with mild to moderate hypertension (systolic BP 150 to 180 mmHg, diastolic BP ≥90 mmHg, systolic ambulatory BP ≥140 mmHg and <170 mmHg) were randomised to renal denervation or sham procedure. Patents were not using an antihypertensive medication (most often by choice); mean age was 52 and 58 years in the renal denervation and sham groups, respectively, and about 70% of patients were men. Excluded patients included those with diabetes and an HbA_{1c} >8%, secondary hypertension, eGFR <45 mL/min/1.7 m^2 or unsuitable renal artery anatomy. The procedure was quite intensive with a mean duration of about one hour and the use of 250 mL of contrast.

At three months, results showed significant improvements in BP in the patients who had undergone renal denervation compared with the sham group:

- decrease in ambulatory mean systolic BP of 5.5 mmHg *vs* no significant change in the sham group
- decrease in office systolic BP of 10 mmHg *vs* 2.3 mmHg in the sham group


Dr Miller

- decrease in office diastolic BP of 5.3mmHg *vs* no significant change in the sham group.

Professor Michael Böhm (Director, Department of Internal Medicine and Cardiology, University of the Saarland, Homburg/Saar, Germany) who presented the findings noted that there were no complications, specifically no death, no myocardial infarction, no new-onset renal disease and no major bleeding. He concluded that the study showed that 'renal denervation works to reduce BP', and that these results will inform a further larger pivotal study.

Comment by Professor Brieger

This study may have revived the hypothesis that renal denervation can reduce blood pressure in patients with hypertension, but as pointed out by Professor Bryan Williams, Chair of Medicine, University College London, UK, the discussant following the presentation, the mean fall in BP in these patients with mild to moderate hypertension was modest, inconsistent, often less than can be achieved with single agent therapy, and most patients didn't achieve BP targets. Further studies will be required to define in which patient populations this intervention may be of benefit.

Böhm M, on behalf of the SPYRAL HTN-OFF MED Trial Investigators. Investigation of catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications: Three-month results from the randomized, sham-controlled, proof of concept SPYRAL HTN-OFF MED Trial. Paper presented at: ESC Congress; August 28, 2017; Barcelona. Townsend, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medication (SPYRAL HTN-OFF MED): a randomise sham-controlled proof of concept trial. Lancet: published online August 28, 2017.

Community screening for AF using smartphone ECG to identify newly diagnosed AF

Community-based screening for newly diagnosed AF using smartphone ECG has been shown to be effective in two recently published large-scale studies. In this new study, the AFinder program, the effectiveness of a non-governmental organisation-led community-based AF screening program using a smartphone-based single-lead ECG and carried out by trained layperson volunteers was examined.

Eighty-four layperson volunteers aged over 50 years were trained to use the Kardia mobile device to perform smartphone-based single-lead ECG in a community-based AF screening program. All Hong Kong citizens aged over 50 years were eligible to participate in the program. ECGs were reviewed by a cardiologist, and participants found to have AF were contacted by phone to complete baseline and nine-month follow-up questionnaires. Those with AF were mailed their ECG reports and advised to seek medical attention.

Of the 11,574 participants screened, only 839 (7.2%) had uninterpretable ECGs. Of the 10,735 participants with interpretable ECGs, 244 (2.3%) were found to have AF, almost one-third of whom (74) had newly diagnosed AF (mean CHA_2DS_2-VASc score, 3.9). Notably, 36 (48%) of those with newly diagnosed with AF were asymptomatic. The number needed to screen (NNS) for one newly diagnosed AF was 145.

Oral anticoagulation was indicated in 72 of the 74 participants with newly diagnosed AF; however, only 47 (65%) sought medical attention, and of these, only 17 were prescribed oral anticoagulation. Once prescribed anticoagulation, however, patients were very adherent to treatment. The NNS for one patient with newly diagnosed AF who then received appropriate oral anticoagulation was 671, a 3.6-fold increase in the NNS for newly diagnosed AF.

The sensitivity of the ECGs performed by the Kardia mobile device was 75% and specificity 98.2%, with a positive predictive value of 64.9% and a negative predictive value of 99.5%.

Presenting the findings of this industry-funded trial, lead investigator Dr Ngai-Yin Chan (Associate Consultant in the Department of Medicine & Geriatrics, Director of Cardiac Pacing Services and Co-director of Cardiac Rehabilitation Services, Princess Margaret Hospital, Hong Kong) said this new approach to AF screening was feasible and capable of detecting members of the community with newly diagnosed AF with an NNS similar to that of other programs. However, he said, its effectiveness 'in subsequently leading participants with newly diagnosed AF or undertreated known AF to receive appropriate anticoagulation therapy is weakened by the lack of a structured downstream management pathway'. The sensitivity of the algorithm also needs to be further improved before it can be considered as a tool for 'autoscreening', he added.

Comment by Professor Newton

This study highlights that community-based screening programs using novel technologies are possible but in addition to screening there need to be appropriate pathways to manage the condition once it is identified. Cost effectiveness was not reported in this study but a recent Australian study screening for AF in pharmacies with an iPhone was cost effective when people over the age 65 years were screened.

Chan NY, et al. Effectiveness of community atrial fibrillation screening in over 10,000 citizens using smartphone electrocardiogram – The AFinder program. Paper presented at: ESC Congress; August 28, 2017; Barcelona.

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