Conference highlights

ESC CONGRESS PARIS 2019

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Held recently in Paris and attended by almost 33,000 delegates from 146 countries, the European Society of Cardiology (ESC) Congress, together with the World Congress of Cardiology, focused on global cardiovascular (CV) health. Its sessions highlighted differences in prevalence, clinical manifestations, prevention strategies, diagnostic modalities and management of CV diseases around the world.

Cardiology Today followed five Australian delegates (a cardiology physician, an interventional cardiologist, a cardiology nurse, an endocrinologist/general medicine physician and a GP) attending the congress. We present summaries of some of the late breaking science sessions, attended by three of the delegates, together with their comments on the implications of the findings. Video highlights from all five delegates can be viewed on the *Cardiology Today* website (https://cardiologytoday.com.au/esc2019videos/day1.html).

HEART FAILURE

PARAGON-HF highlights heterogeneity of heart failure with preserved ejection fraction

Although evidence-based therapies exist for patients with heart failure with reduced ejection fraction (HFrEF), no therapy has been clearly shown to be beneficial in those with heart failure and a preserved ejection fraction (HFpEF). The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction trial (PARAGON-HF) was a randomised, controlled, industry-funded trial evaluating the clinical efficacy of sacubitril-valsartan compared with valsartan in 4822 patients with HFpEF (left ventricular ejection fraction [LVEF] 45% or higher) associated with elevated natriuretic peptides and evidence of structural heart disease (LV hypertrophy and/or left atrial dilatation). The trial narrowly missed its primary endpoint, which was a composite of cardiovascular (CV) death and all heart failure hospitalisations (rate ratio, 0.87; 95% confidence interval [CI], 0.75-1.01; p=0.056), which was largely driven by a nonsignificant reduction in total heart failure hospitalisations in the sacubitril-valsartan group (rate ratio, 0.85; 95% CI, 0.72-1.00).

In a multivariable model that accounted for interactions, there was significant heterogeneity for the primary endpoint, with greater benefit observed in women (hazard ratio [HR], 0.73; 95% CI, 0.59–0.90) and patients with lower LVEF. Findings in subsequent exploratory analyses included a larger proportion of patients randomised to receive sacubitril-valsartan experiencing improved symptoms and clinically relevant improvements in quality of life compared with patients randomised to receive valsartan.

Comment by Professor Atherton

This study follows on from the Prospective Comparison of ARNI with ACEI to determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), which reported significant reductions in CV mortality and heart failure hospitalisation with sacubitril-valsartan compared with enalapril in patients with heart failure with reduced ejection fraction (HFrEF). The Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction Trial (PARAMOUNT) subsequently reported favourable effects of sacubitril-valsartan compared with valsartan on N-terminal proB-type natriuretic peptide (NT-proBNP) and left atrial volume in patients with HFpEF. Unfortunately, this did not translate into a significant benefit for the primary endpoint in PARAGON-HF. We should keep in mind that sacubitril-valsartan was being compared with an active comparator. However, while favourable trends were observed, the effect in the overall trial population was modest.

The larger benefit reported in patients with a mildly reduced LVEF is biologically plausible, with similar interactions observed for candesartan (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity [CHARM] Programme), spironolactone (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial [TOPCAT]) and beta blockers (individual patient data meta-analysis).

The significant interaction according to sex is intriguing, and although this could represent the play of chance, the subgroup analysis was based on large numbers (923 primary endpoint events in women). It is possible that male HFpEF is more heterogeneous with a higher proportion of subjects having underlying undiagnosed ischaemic heart disease or infiltrative cardiomyopathies.

This study highlights the heterogeneity of HFpEF, where it appears that a 'one-size-fits-all' approach is unlikely to apply. Better phenotyping is required to identify patients unlikely to respond to neurohormonal modulation.

Solomon SD, McMurray JJV, for the PARAGON-HF Committees, National Leaders and Investigators. PARAGON-HF - angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction. Hot Line Session 1 presented at: ESC Congress; September 1, 2019; Paris.

Solomon SD, et al, for the PARAGON-HF Investigators and Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019; doi: 10.1056/NEJMoa1908655.

Dapagliflozin improves outcomes in patients with HFrEF with or without diabetes

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to prevent the development of heart failure in patients with type 2 diabetes, but their effects in patients with established heart failure and a reduced left ventricular ejection fraction (HFrEF), regardless of the presence or absence of type 2 diabetes, is unclear.

The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure Trial (DAPA-HF) was a placebo-controlled, randomised, industry-funded trial evaluating the clinical efficacy of the SGLT2 inhibitor, dapagliflozin in 4744 patients with HFrEF (left ventricular ejection fraction [LVEF] 40% or lower) associated with elevated natriuretic peptides. The study achieved its primary endpoint with a highly statistically significant reduction in CV mortality or worsening heart failure in the dapagliflozin group (HR, 0.74; 95% CI, 0.65-0.85; p=0.00001), which was seen on top of standard heart failure therapy, including baseline prescription rates of 93 to 94% for renin angiotensin system blockers, 96% for beta blockers and 71% for mineralocorticoid receptor antagonists. Similar and statistically significant benefits were observed in patients with and without diabetes mellitus. There were also statistically significant reductions in CV mortality (HR, 0.82; 95% CI, 0.69-0.98; p=0.029), worsening heart failure (HR, 0.70; 95% CI, 0.59-0.83; p=0.00003) and all-cause mortality (HR, 0.83; 95% CI, 0.71-0.97; p=0.02) in the dapagliflozin group. A larger proportion of patients in the dapagliflozin group demonstrated a clinically important improvement in quality of life.

Dapagliflozin was well tolerated with no excess in adverse events.

Comment by Professor Atherton

This study builds on the favourable evidence to date in trials enrolling patients with type 2 diabetes mellitus that SGLT2 inhibitors decrease CV death in patients with CV disease and decrease heart failure and renal adverse events in patients at high risk. However, prior studies were neither primarily designed nor powered to evaluate the clinical efficacy of SGLT2 inhibitors in patients with heart failure.

DAPA-HF has clearly demonstrated the benefits of a novel pharmacological approach to improve clinical outcomes in HFrEF that does not involve modulation of the neurohormonal system. Furthermore, the benefits of dapagliflozin were similar in patients with and without diabetes. This clearly establishes SGLT2 inhibitors as primarily CV drugs, with benefits that are likely to be mediated by mechanisms independent of glucose lowering. Ongoing studies are also underway in heart failure with preserved ejection fraction (HFpEF).

McMurray JJV. DAPA HF - the Dapagliflozin And Prevention of Adverse-outcomes in


Heart Failure Trial. Hot Line Session 1 presented at: ESC Congress; September 1, 2019; Paris.
McMurray JJV, et al, for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; doi: 10.1056/NEJMoa1911303.

Sacubitril-valsartan in HFrEF: mechanisms of benefit explored

The Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction (EVALUATE-HF) was a randomised controlled, double-blind, industry-funded study that compared the effect of sacubitril-valsartan with enalapril on aortic characteristic impedance, a measure of central aortic stiffness (primary endpoint) in 464 patients with heart failure associated with a LVEF of 40% or lower over 12 weeks. Despite greater reductions in blood pressure, there was no significant difference between the groups in the primary endpoint. However, there were greater reductions in some prespecified secondary endpoints with sacubitril-valsartan, including LV end-diastolic volume, LV end-systolic volume, left atrial volume, mitral E/e' ratio, N-terminal proB-type natriuretic peptide (NT-proBNP), soluble ST2 and high sensitivity troponin T. Post-hoc analyses identified that the changes in NT-proBNP correlated with both changes in LV volumes and quality of life.

The Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodelling During Entresto Therapy for Heart Failure (PROVE-HF) was a prospective, single-arm, open-label, industry-funded study evaluating the effect of sacubitril-valsartan on reverse remodelling in 794 patients with HFrEF. The change in log2-NT-proBNP was weakly, but significantly, correlated with LV ejection fraction ($r = -0.381$; $p < 0.001$), indexed LV end-diastolic volume ($r = 0.320$; $p < 0.001$), indexed LV end-systolic volume ($r = 0.405$; $p < 0.001$), indexed left atrial volume ($r = 0.263$; $p < 0.001$) and mitral E/e' ($r = 0.269$; $p < 0.001$).

Comment by Professor Atherton

EVALUATE-HF and PROVE-HF both explored the mechanism of benefit of sacubitril-valsartan in HFrEF. Neprilysin inhibition has been shown to decrease aortic stiffness in patients with hypertension. However, EVALUATE-HF demonstrated no significant difference in aortic stiffness comparing sacubitril-valsartan with enalapril at 12 weeks in patients with HFrEF. Although it is possible that differences may have been observed with longer follow up, the improvements in quality of life seen in EVALUATE-HF suggest that changes in aortic stiffness are unlikely to explain the early benefits observed in PARADIGM-HF.

Both EVALAUTE-HF and PROVE-HF suggest that LV reverse remodelling at least partly explains the beneficial effect of neprilysin inhibition on top of renin angiotensin system inhibition in HFrEF. This is consistent with other analyses that have identified that short-term effects of drugs and devices on LV remodelling in HFrEF are associated with longer term benefits in survival.

Desai AS, et al, for the EVALUATE-HF Investigators. Effects of sacubitril-valsartan compared with enalapril on arterial hemodynamics and cardiac remodeling in patients with heart failure and reduced ejection fraction. Late Breaking Science in Heart Failure 1 presented at: ESC Congress; September 2, 2019; Paris.
Desai S, et al, for the EVALUATE-HF Investigators. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction.A randomized clinical trial. JAMA 2019; 322: 1077-1084.
Januzzi JL Jr, et al, on behalf of the PROVE-HF Investigators. Effects of angiotensin receptor/neprilysin inhibitor therapy on NT-proBNP and cardiac remodeling in heart failure with reduced ejection fraction: primary results of the PROVE-HF study. Late Breaking Science in Heart Failure 1 presented at: ESC Congress; September 2, 2019; Paris.
Januzzi JL Jr, et al, for the PROVE-HF Investigators. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 2019; 322: 1085-1095.

No improvement in acute heart failure outcomes with early intensive vasodilation

Acute heart failure is one of the most common diagnoses in the emergency department leading to hospitalisation. In contrast to improvements in the management of patients with chronic heart failure, morbidity and mortality remain unacceptably high in patients with acute heart failure.

The Goal-Directed Afterload Reduction in Acute Congestive Cardiac Decompensation Study (GALACTIC) was an investigator-initiated, randomised controlled trial evaluating an early, intensive and sustained vasodilation strategy compared with standard care in 788 patients presenting to the emergency department with acute heart failure associated with elevated natriuretic peptide levels. The vasodilation strategy was based on sublingual and transdermal nitrates combined with oral hydralazine, followed by commencement of renin angiotensin system blockers on day two, with uptitration aiming for target dose (or near target dose) during that admission.

There was no significant difference between the groups in the primary endpoint of all-cause mortality or acute heart failure rehospitalisation within 180 days (adjusted HR, 1.07; 95% CI, 0.83-1.39; p=0.59). In a prespecified subgroup analysis, there was a significant difference according to sex, with apparent harm in women in the intervention group compared with the standard-care group (HR, 1.67; 95% CI, 1.08-2.59; p=0.022). Dyspnoea improvement and hospital length of stay were also similar in the intervention and standard-care groups. Although the intensive vasodilation strategy was generally well tolerated, there were more serious adverse events recorded for the intervention arm, driven by more headaches and more systolic arterial hypotension.

Comment by Professor Atherton

This is the largest investigator-initiated

acute heart failure randomised controlled trial conducted to date. These are very difficult studies to conduct, and randomising patients to the different arms in the same centre may have been problematic. Although a previous study reported superior clinical outcomes with high-dose nitrates plus low-dose loop diuretics compared with low-dose nitrates plus high-dose loop diuretics in patients with acute pulmonary oedema, this was a small study (104 patients) and involved a composite clinical endpoint that included mechanical ventilation. GALACTIC aimed to extend these findings in a larger study involving a broader population of patients with acute heart failure.

Coupled with the recent results of the Relaxin in Acute Heart Failure-2 (RELAX-AHF2) study where serelaxin failed to improve long-term clinical outcomes following acute heart failure, the neutral outcome in GALACTIC suggests that aggressive vasodilation should not be routinely applied in acute heart failure; however, it does not exclude a role in selected cases. The significant interaction according to sex should be interpreted with caution, given there were only 87 primary endpoint events recorded in women.

Mueller CE. Goal-directed afterload reduction in acute congestive cardiac decompensation: a randomized controlled trial. Hot Line Session 3 presented at: ESC Congress; September 3, 2019.

CORONARY ARTERY DISEASE, ACUTE CORONARY SYNDROMES AND ACUTE CARDIAC CARE

Long-term DAPT investigated in patients with stable CAD and diabetes

Dual antiplatelet therapy (DAPT) with aspirin and ticagrelor is very effective in preventing recurrent ischaemic events in the 12 months following an acute coronary syndrome (ACS); however, studies investigating longer duration DAPT treatment after an ACS have shown more modest results with benefits outweighed by an increased risk of bleeding in most patients.

The Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) focused on a particular group of patients with stable coronary disease: those with diabetes. This was a carefully selected population; those with prior myocardial infarction (MI) and stroke were excluded as previous studies had not shown convincing benefit in these subpopulations.

In this industry-funded trial, over 19,000 patients were randomised to aspirin alone or aspirin plus ticagrelor. Most patients received 60 mg of ticagrelor twice daily. The primary endpoint was a composite of CV death, MI or stroke, and the primary safety outcome was TIMI (thrombolysis in MI) major bleeding.

Although ticagrelor resulted in a modest reduction in the primary endpoint of 10% (6.9% *vs* 7.6% in the aspirin-only group over three years), this was accompanied by an increased bleeding hazard; TIMI major bleeding was increased 2.3-fold (2.2% in the ticagrelor group *vs* 1.0% in the aspirin-only group), resulting in no net clinical benefit.

In a second presentation, in the same setting, results in the subgroup with prior percutaneous coronary intervention (PCI) were presented. This group comprised about half of the primary population and the median time from prior PCI was three years. Although there was no statistical evidence that these patients responded any differently from the nonPCI population to DAPT (i.e. no evidence of heterogeneity between the PCI and nonPCI cohort), this analysis was prespecified and was biologically plausible. Patients with a history of prior PCI had tolerated DAPT for at least 12 months after their original procedure and were therefore likely to better tolerate long-term ticagrelor. Consistent with this, the benefit appeared marginally greater with a 15% relative risk reduction in the primary endpoint in patients treated with ticagrelor (6.5% *vs* 7.7% in the aspirin-only group over three years). Bleeding was still increased twofold in the ticagrelor group (2.0% *vs* 1.1% in the aspirin- only group), and although there was a suggestion of net clinical benefit, this was modest and dependent on how bleeding was defined.

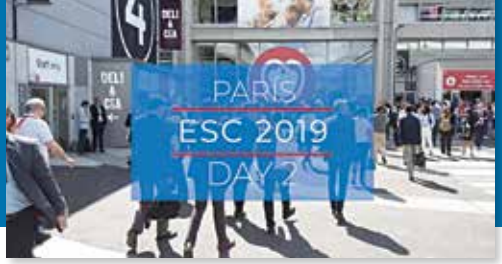
Comment by Professor Brieger

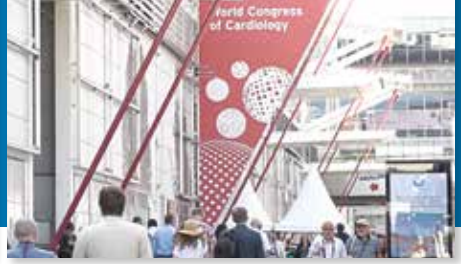
This is the final instalment in a series of mega-atrials investigating the use of longer term ticagrelor, a valiant attempt to find the population in which prevention of recurrent ischaemic events is achieved without causing an unacceptable increase in bleeding. This study is unlikely to change practice; the population was highly selected, outcomes were modest, and, even in the PCI subgroup, the benefit was underwhelming. Furthermore, the applicability is limited in Australia as the 60-mg dose of ticagrelor has not been approved for use in this country.

Bhatt DL, et al, on behalf of the THEMIS Steering Committee and Investigators, co-Chairs and co-Principal Investigators of THEMIS. THEMIS-main results of The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study. Hot Line Session 1 presented at: ESC Congress; September 1, 2019; Paris.

Steg PG, et al, for the THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019; doi: 10.1056/NEJMoa1908077.

Bhatt DL, et al, on behalf of the THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. Lancet 2019; 394: P1169-1180; doi: https://doi.org/10.1016/S0140-6736(19)31887-2.





Steg PG et al, on behalf of the THEMIS Steering Committee and Investigators, co-Chairs and co-Principal Investigators of THEMI. THEMIS-PCI: ticagrelor in patients with diabetes and stable coronary artery disease with a history of prior percutaneous coronary intervention. Hot Line Session 1 presented at: ESC Congress; September 1, 2019; Paris.

Consider prasugrel for patients with ACS with planned invasive strategy

The two landmark acute ACS studies – the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON TIMI 38) and the Platelet Inhibition and Patient Outcomes (PLATO) trial – that established the superior efficacy of prasugrel and ticagrelor, respectively, over clopidogrel in the acute treatment of ACS, were conducted over a decade ago. Both of these potent adeonosine diphosphate (ADP)-receptor antagonist drugs now play a role in the acute treatment of patients with ACS, with ticagrelor more often used than prasugrel, but until now there has been no substantial sized study directly comparing the two.

At this meeting, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) group presented an open-label, head-to-head comparison of ticagrelor with prasugrel in patients with an ACS and a planned invasive strategy. Patients with prior stroke/transient ischaemic attack (TIA) were excluded; ticagrelor was given immediately after randomisation whereas prasugrel was deferred in most patients until coronary anatomy was known. Other differences between the two strategies included that the prasugrel dose was reduced from the standard 10 mg to 5 mg daily in patients aged 75 years or over or those weighing less than 60 kg whereas a single dose of ticagrelor (90 mg twice daily) was used for all.

The primary endpoint was a composite of death, MI or stroke at 12 months. The study enrolled over 4000 patients; about 45% of the patients had ST-segment elevation MI (STEMI), all had angiograms and 85% underwent percutaneous coronary intervention. After 12 months of follow up, there was a 36% increased event rate in patients randomised to ticagrelor (9.3% *vs* 6.9% in the prasugrel group), driven primarily by an increase in (re)MI (4.8% *vs* 3.0% for prasugrel). There was no bleeding penalty; in fact, major bleeding was numerically greater in the ticagrelor arm (5.4% *vs* 4.8% for prasugrel).

Comment by Professor Brieger

As this study was unblinded, both patients and investigators knew the treatment allocation, exposing the study to the risk of bias. However, the investigators had powered this study for a 22.5% relative-risk reduction in the primary endpoint for treatment with ticagrelor, suggesting that any investigator bias would have favoured this drug. This study suggests that in patients with ACS undergoing a planned invasive strategy, prasugrel could be considered a first-line option, which is contrary to current common practice.

Schüpke ST, for the ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. Hot Line Session 2 presented at: ESC Congress; September 1, 2019; Paris.

Schüpke S, et al, for the ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019; doi: 10.1056/NEJMoa1908973.

Benefits for complete revascularisation in patients with STEMI and multivessel CAD

One of the more positive studies to emerge from ESC 2019 Congress was the Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial. Several previous smaller studies have suggested the benefit of complete revascularisation, performed either at the time of the primary PCI or during the same hospital admission, over medical management of the remaining disease. Outcomes in these trials have mostly been driven by repeat revascularisation, which is a subjective endpoint of questionable value in nonblinded studies. This is because both conservatively randomised patients and their treating doctors are aware that they have residual untreated disease, resulting in a bias to repeat intervention in these patients.

At over 4000 patients, the partially industry-funded COMPLETE trial was almost twice as large as all the previous studies combined and was therefore able to look at the objective endpoints of CV death or repeat MI. And indeed, complete revascularisation did result in a 26% relative reduction in this coprimary endpoint (7.8% in the complete revascularisation group *vs* 10.5% in the culprit-lesion-only PCI group) over three years of follow up. This was driven by reduction in MI, both STEMI and nonSTEMI. The difference in the second coprimary outcome, which included CV death, new MI and ischaemia-driven revascularisation was even greater (49%; absolute reduction 3.1% in the complete revascularisation group *vs* 6.2% in the culprit-lesion-only PCI group). There was no difference in bleeding, stroke or kidney injury, indicating that the additional procedure was safe. A prespecified subgroup analysis showed that the benefit was apparent regardless of whether the second intervention was performed in hospital or within 45 days of discharge.

Comment by Professor Brieger

This is an important trial in patients with STEMI and multivessel disease, who comprise about half of all patients with STEMI. The timing of this second procedure appears to be less critical than previously thought, because most of the events accrued during the three years of follow up, not in the early post-MI phase.

Most nonculprit lesions were angiographically severe (greater than 70% by visual estimate) and all the benefit was found in patients with these lesions. Fractional flow reserve measurement was not performed in these angiographically severe lesions, and it may be that some interventions may not have been necessary in the complete revascularisation arm. Equally importantly, noninvasive functional testing to evaluate ischaemia in

nonculprit territories was strongly discouraged in the conservative group. This may have introduced a bias in favour of patients randomised to complete revascularisation.

Mehta SR, on behalf of the COMPLETE Trial Executive & Steering Committees and Investigators. COMPLETE revascularization with multivessel percutaneous coronary intervention in ST-segment elevation myocardial infarction. Hot Line Session 1 presented at: ESC Congress; September 1, 2019; Paris.

Mehta SR, et al, for the COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med 2019; doi: 10.1056/NEJMoa1907775.

Anticoagulant therapy alone for patients with AF and stable CAD

Patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) constitute an increasing population for whom antithrombotic management is challenging. Until relatively recently, these patients had been managed with combined antiplatelet and anticoagulant therapy to prevent arterial thrombotic events and AF-related embolic events, respectively. However, most recent guidelines, including those produced in Australia, have recommended anticoagulation alone, on the basis of observational data suggesting that combination therapy results in unacceptable increase in bleeding with little impact on atherothrombotic events. The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial was the first substantive study to address this issue. This Japanese study enrolled over 2200 patients who had either been revascularised more than 12 months earlier or had stable CAD not requiring revascularisation. Patients were randomised to rivaroxaban alone (dose 10 or 15 mg/day, approved for the Japanese population) or rivaroxaban plus low-dose antiplatelet agents (aspirin 81 or 100 mg/day, clopidogrel 50 or 75 mg/day or prasugrel 2.5 or 3.75 mg/day). The primary endpoint was the composite of all-cause death, stroke, systemic embolism, MI and unstable angina with revascularisation; the primary safety endpoint was major bleeding.

The study was terminated early (after a median follow up of 23 months) because of increased mortality in the dual therapy arm. By this time, the primary endpoint was significantly reduced by 28% in the monotherapy arm (4.14% *vs* 5.75% with dual therapy), driven by a reduction in total mortality and stroke due to intracranial haemorrhage. There was also a 41% relative reduction in major bleeding events in the monotherapy arm (1.62% *vs* 2.76% with dual therapy).

Comment by Professor Brieger

There are some methodological limitations to this study: the open-label nature could have biased the outcomes, early termination may have overestimated the benefit of rivaroxaban alone and there was some loss to follow up (10% in the monotherapy and 14% in the dual therapy arms). Noncardiovascular mortality was substantially lower in the rivaroxaban-alone arm, a likely chance finding that did contribute to the primary outcome. Finally, the doses of all medications were adjusted for the Japanese population and lower than those approved for use in Australia. However, given the dearth of data in this area, these findings are welcome and provide some justification for guideline recommendations of anticoagulant therapy alone for patients with stable CAD and AF at risk of stroke.

Yasuda S, on behalf of the AFIRE Investigators. AFIRE - rivaroxaban monotherapy versus combination therapy in patients with atrial fibrillation and stable coronary artery disease. Hot Line Session 3 presented at: ESC Congress; September 2, 2019; Paris.

Yasuda S, et al, for the AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019; 381: 1103-1113.

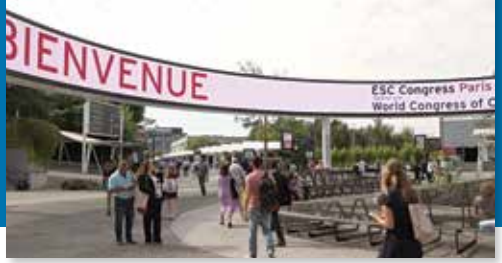
Oxygen therapy in ACS: no benefit in most patients, may benefit those with low SpO_2

Oxygen therapy has been used in the management of patients with ACS for over 50 years despite no study showing it improves outcomes and some suggesting it could be harmful. Current European Society of Cardiology guidelines recommend oxygen be used only when a patient's oxygen saturation (SpO_2) is less than 90%.

The New Zealand Oxygen Therapy in Acute Coronary Syndromes (NZOTACS) trial aimed to compare the 30-day mortality for two oxygen protocols as part of routine care in almost 41,000 patients with suspected ACS in New Zealand. The high-oxygen protocol recommended oxygen (6 to 8 L/minute) for ischaemic chest pain or ECG changes irrespective of the patient's SpO_2. Oxygen was stopped when clinical evidence of myocardial ischaemia resolved. The low-oxygen protocol recommended oxygen only if the SpO_2 was less than 90%, with a target SpO_2 of 90 to 94%.

The protocols were used as routine care in ambulances, emergency department, cardiac catheterisation labs and acute cardiac care units throughout New Zealand's four healthcare regions. Each region used the two protocols separately for about one year, in a randomised crossover design.

No differences were found between the two protocols in the primary outcome of 30-day mortality for all patients with suspected ACS (3.02% *vs* 3.12% in the high- and low-oxygen protocols, respectively). However, in patients whose final diagnosis was STEMI, there was a suggested, but nonsignificant, benefit with the high-oxygen protocol in 30-day mortality



(8.8% *vs* 10.6% for the high- and low-oxygen protocol, respectively). There were no significant differences between the protocols in patients whose final diagnosis was nonSTEMI or no ACS.

In an analysis of SpO_2 at presentation, using the first measurement taken on ambulance arrival, mortality was no different with either protocol for the majority of the population who had an SpO_2 of 95% or greater. However, for the 12% of patients with an SpO_2 of less than 95% at presentation, mortality was lower with the high-oxygen protocol (10.1% *vs* 11.1% for high and low protocols, respectively).

Patients with suspected ACS who have a normal oxygen saturation level are therefore unlikely to benefit from high-flow oxygen. It is possible, however, that high-flow oxygen improves outcomes for patients with SpO_2 less than 95%, and with STEMI, but further confirmation is needed.

Comment by Professor Brieger

This is the largest trial yet evaluating the use of oxygen in patients with suspected MI and confirms the findings of the Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) trial reported in 2017 that there does not appear to be a role for oxygen in patients with an SpO_2 greater than 90% and non-ST segment elevation ACS. In contrast to the earlier Swedish study, however, in NZOTACS there was a suggestion of benefit in the more than 4000 patients with STEMI (odds ratio, 0.81; 95% CI, 0.66-1.00). The picture becomes more confusing when we consider the Australian Air Versus Oxygen in Myocardial Infarction (AVOID) study, which showed increased infarct size in patients with STEMI and normoxaemia randomised to supplemental oxygen. This smaller study was not powered for clinical endpoints. The role of oxygen in the important population of patients with STEMI and normoxaemia remains unanswered.

Steward R. NZOTACS - The New Zealand Oxygen Therapy in Acute Coronary Syndromes trial. Hot Line Session 2 presented at: ESC Congress; September 1, 2019; Paris.

Rapid troponin protocol in patients with suspected ACS appears to be safe

The availability of the new high-sensitivity troponin assays has increased the sensitivity but decreased the specificity of diagnosing MI in patients with chest pain. It also provides opportunities to rule out MI earlier following presentation to hospital, therefore shortening hospital stay. The goals of the National Health and Medical Research Council-funded Rapid Assessment of Possible ACS in the Emergency Department with High Sensitivity Troponin T (RAPID-TnT) trial were to determine whether the high-sensitivity troponin assay coupled with a rapid 0/1-hour protocol was noninferior in terms of patient outcomes and/or resulted in greater emergency department efficiency.

This study was conducted in four Adelaide hospitals that randomised patients to the standard protocol, using the non-high-sensitivity troponin assay with blood collection at 0 and 3 hours, or the RAPID protocol, which used the high-sensitivity assay with blood collection at 0 and 1 hour. This study randomised almost 1700 patients into each arm. Patients randomised to the RAPID-TnT arm were more likely than those in the standard protocol arm to be directly discharged from the emergency department (45.1% in the RAPID arm and 32.3% in the standard arm), with no difference in the primary endpoint of 30-day death or MI between the two arms. There was a small increase in rehospitalisation for cardiovascular diagnoses within 30 days in the RAPID arm (1.41% *vs* 0.92% in the standard protocol arm).

Comment by Professor Brieger

This important local study prospectively validates recommendations made in the European and Australian guidelines regarding the rapid performance of troponin measurements in patients presenting to emergency departments with suspected acute coronary syndrome. The RAPID strategy improved emergency department and hospital efficiency with more patients directly discharged from the emergency department. Although there was a small increase in readmissions at 30 days, there was no difference in the important primary endpoint of death or MI at 30 days, suggesting the strategy to be safe. Outcomes at 12 months are awaited and will confirm the safety and cost-effectiveness of this approach.

Chew D. RAPID-TnT - a randomised trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the rapid assessment of possible ACS in the emergency department with high sensitivity troponin T. Hot Line Session 6 presented at: ESC Congress; September 3, 2019; Paris.

Chew DP, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the rapid assessment of possible ACS in the emergency department with high sensitivity troponin T (RAPID-TnT) study. Circulation 2019; doi: 10.1161/CIRCULATIONAHA.119.042891.

Objective risk scores in treating high-risk ACS: benefits assessed

Assessing risks and weighing the benefits of treatments is an essential component of the acute management of ACS, and guidelines recommend the use of objective risk tools like the Global Registry of Acute Coronary Events (GRACE) risk score to aid in these decisions. Although these tools are effective at stratifying a patient's risk retrospectively, their value in improving care when applied prospectively has not been assessed. The Australian GRACE Risk Intervention Study (AGRIS) was an Australian cluster-randomised, industry-funded trial involving 24 hospitals that evaluated whether prospective application of the GRACE risk score improved adherence to evidence-based treatments among patients with high-risk ACS. The primary endpoint was the achieved 'treatment performance score', incorporating inpatient angiography, receipt of evidence-based medications and referral to cardiac rehabilitation services.

Over 1400 patients with high-risk ACS were enrolled, 716 in the intervention arm and 687 in the control arm. Although patients in the

intervention arm were significantly more likely to undergo angiography (91% *vs* 85% in the control arm; p=0.01), there was no difference in receipt of evidence-based treatment or referral to cardiac rehabilitation resulting in no difference in the primary endpoint (mean performance score 2.42 *vs* 2.36 in the intervention and control arms, respectively; p=0.75). The authors commented that this was largely explained by better than expected performance in control hospitals.

Comment by Professor Brieger

As one of the investigators, I can say that these results did surprise and disappoint us. However, the fact that hospital performance was better than expected reflects positively on the standard of ACS care delivered in many hospitals in Australia. In AGRIS, recruitment was biased towards better resourced hospitals with ready access to cardiology expertise. Future effort to address this question (and there are ongoing international studies which have been developed in collaboration with our own) should focus on hospitals with known challenges in the provision of evidence-based care.

Brieger DB, on behalf of the Australian GRACE Risk Intervention Study (AGRIS) investigators. A cluster randomized trial of objective risk assessment versus standard care for acute coronary syndromes: the Australian GRACE Risk score Intervention Study. Late Breaking Science in Acute Coronary Syndromes 1 presented at: ESC Congress; August 31, 2019; Paris.

ATRIAL FIBRILLATION: POST-DISCHARGE MANAGEMENT

A personalised home-based education program to reduce hospitalisation in patients with AF

The number of people worldwide living with AF has grown exponentially over the past few decades, and AF is now a more common cause of hospital presentation than heart failure or heart attacks. As healthcare costs increase, development of programs that reduce hospitalisations is essential.

The Australian Home-based Education and Learning Program for Atrial Fibrillation (HELP-AF) study was designed to examine whether involving patients in their care, helping them understand their condition and providing tools to manage their AF might avoid hospitalisation.

The study, led by Professor Prashanthan Sanders, Director of the University of Adelaide's Centre for Heart Rhythm Disorders, enrolled 627 patients with a primary diagnosis of AF presenting to the emergency department of six hospitals in Adelaide. Patients were randomised to the HELP-AF intervention or to usual care from their GP and/or cardiologist.

Patients in the intervention group received two educational home visits by the same nurse or pharmacist – the first one about two weeks after enrolment, the second six weeks later. The education, delivered in a structured and personalised manner, focused on four messages: management of future AF episodes; importance of medicines to manage symptoms and stroke risk; appropriate use of stroke preventative medications; and the role of lifestyle modification.

Patients in the intervention group were also given an educational booklet providing an ongoing reminder of the four key messages and outlining the 'REST plan' for them to follow during and AF episode (Relax, Estimate pulse, See your action plan, Telephone the help line). Management was carried out as usual by the patient's cardiologist or GP.

After two-years' follow up, researchers assessed the primary endpoint of total all-cause unplanned hospitalisation and health-related quality of life using the Short-Form Health Survey (SF-36) and the AF Effect on QualiTy of life (AFEQT).

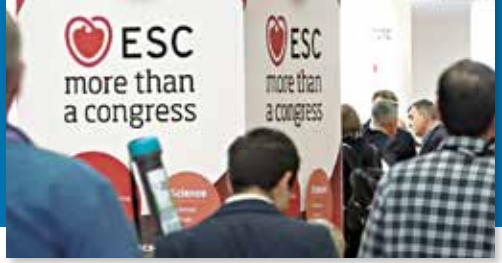
Overall, there were 233 unplanned hospitalisations in the intervention group and 323 in the usual-care group. After multivariate adjustments, the researchers found that the intervention reduced total unplanned hospitalisations by 26%. It also reduced AF-related hospitalisation by 31% and other cardiovascular hospitalisations by 49%.

Although there were no differences between the intervention and usual care in health-related quality of life as measured by the SF-36 survey, use of the more specific AFEQT questionnaire showed significant benefit at 24 months in favour of the intervention in two subcategories of the 'Symptoms' and 'Treatment Concern' domains.

Comment by Professor Newton

This is an important Australian study that demonstrated the benefit of providing good post-discharge management and support to patients following an admission for primary AF. There were significant reductions in all-cause hospitalisations, AF-related hospitalisation and cardiovascular hospitalisations. Based on the results of this study, as well as other AF postdischarge management programs, I am sure we will start to see post-discharge management programs becoming more common. One of the challenges of a multicomponent intervention such as this is knowing what part of the intervention drove the outcome. I also see some challenges trying to introduce these programs into routine care. Not all patients with AF will be able to take part in these programs, so understanding which patients will benefit the most is going to be an important question that will need to be answered. We also have several different models of post-discharge interventions for AF that have shown improvement but we do not know if one of these models is superior to another.

Sanders P. A home-based education and learning program for atrial fibrillation: the HELP-AF study. Late Breaking Science in Atrial Fibrillation 2 presented at ESC Congress; September 1, 2019; Paris.




Nurse-led postdischarge AF management compared with usual care

Current guidelines recommend integrated chronic care for patients with AF; however, supporting data are lacking. Previous studies have suggested that nurse-led integrated care of patients with AF may be beneficial compared with usual care. On this background, the Integrated Chronic Care at Specialized AF Clinic Versus Usual Care in Patients with AF (RACE4) trial was designed to examine whether nurse-led care was superior to usual care provided by a cardiologist in terms of CV mortality and unplanned CV hospitalisation. It was a prospective, superiority, open-label trial conducted in eight cardiology departments in the Netherlands.

Patients with newly detected AF who were stable and had been referred for specialist outpatient management were randomised to specialised nurse-led care (671 patients) or regular outpatient management (683 patients). Nurse-led care was conducted at a specialised AF clinic and guided by ESC guidelines-based decision-support software. Preset follow-up pathways were followed on CV risk factor management, stroke and heart failure risk management, and rate and rhythm control therapy. Education on AF and psychosocial support were also provided. Usual care was conducted at the regular outpatient clinic by a cardiologist without a specified clinical pathway.

After a median follow up of 3.1 years, the primary endpoint of CV mortality and unplanned CV hospitalisation occurred less often in the nurse-led care group than in the usual care group; however, superiority was not met. The composite primary endpoint occurred in 24% of patients with nurse-led care and 28% of patients with usual care (event rate, 9.7% and 11.6% per year, respectively).

Guideline recommendations for CV risk management were found to be better implemented under nurse-led care, and subgroup analysis suggested that nurse-led care by an experienced team was clinically beneficial. However, there were no differences in quality of life, patients' knowledge on AF or patients' self-management scores between nurse-led or usual management.

Comment by Professor Newton

In this study, nurse-led care resulted in better adherence to guideline-recommended therapy. This was likely due to more visits being made by patients to the nurse-led clinic. The finding that nurse-led care in advanced centres was more beneficial than in less advanced centres may reflect patients having easier access to more experienced advice. The primary endpoint was driven by admission for AF, which occurred less often with nurse-led care.

Wijtvliet E, Crunis H. Randomised clinical trial of nurse-led integrated care for atrial fibrillation, a comparison with care as usual provided by the cardiologist. Late Breaking Science in Atrial Fibrillation 2 presented at: ESC Congress; September 1, 2019; Paris. Wijtvliet EPJP, et al, for the RACE 4 Investigators. Nurse-led vs. usual-care for atrial fibrillation. Eur Heart J 2019 0, 1–8 doi:10.1093/eurheartj/ehz666.