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Abbreviations used in this issue:

ACS = acute coronary syndrome; CV = cardiovascular;
DAPT = dual antiplatelet therapy; EF = ejection fraction;
HDL/LDL = high/low-density lipoprotein; MI = myocardial infarction;
ST = stable therapy; TIMI = thrombolysis in MI;
MINS = myocardial injury after noncardiac surgery;
NSTEMI/STEMI = non-ST-segment elevation; NSTEMI/STEMI = non-ST-segment elevation;
PCI = percutaneous coronary intervention; MI = myocardial infarction;

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Cardiovascular outcomes with alirocumab after acute coronary syndrome

**Authors:** Steg P et al., for the ODYSSEY Outcomes Investigators

**Summary:** CV outcome results of the ODYSSEY Outcomes trial of alirocumab in ACS were presented in this special late-breaking clinical trial presentation. The trial randomised 18,924 patients with recent ACS receiving statin therapy up to the maximum tolerated dose and with a residual LDL cholesterol level ≥70 mg/dL (1.8 mmol/L), a non-HDL cholesterol level of ≥100 mg/dL (2.6 mmol/L) or an apolipoprotein B level of ≤80 mg/dL to receive SC alirocumab 75mg every 2 weeks or matching placebo. The alirocumab dosage was doubled in participants with an LDL cholesterol level ≥50 mg/dL on alirocumab 75mg, and those with two consecutive LDL cholesterol level measurements of <50 mg/dL on alirocumab 75mg were switched to placebo. The trial’s primary outcome was time to first occurrence of coronary heart disease death, nonfatal MI, unstable angina requiring hospitalisation or ischaemic stroke. At the time of reporting, it was anticipated that follow-up would be a median of 33 months, with ≥40% of participants followed for ≥36 months. The results were reported at the conference.

**Comment:** The ODYSSEY trial represents the second outcomes trial of PCSK9 inhibitors, using alirocumab from Sanofi. This was a large multinational trial including sites in Australia, which achieved its primary endpoint and in an exploratory analysis reduced total mortality. There were some differences from the Fourier trial including a more recent history of an ACS (average 2.6 months), a run-in period of statin usage, enrolment of patients who were truly statin intolerant (0.9%) and a protocol that allowed down titration or cessation of the active drug if LDL cholesterol levels were extremely low (2 × <15mg/dL – 7.7%). The results are exciting but we need to work out how we are going to afford these newer agents, although the investigators highlighted that the greatest absolute benefits were in patients whose baseline LDL cholesterol level was ≥100 mg/dL despite a maximal tolerated dose of statin.

**Session 401**

Efficacy of a wearable cardioverter-defibrillator after myocardial infarction

**Authors:** Olgin JE et al.

**Summary:** VEST (Vest Prevention of Early Sudden Death Trial) randomised patients with acute MI and an EF of ≤35% to receive medical therapy with (n=1524) or without (n=778) a wearable cardioverter-defibrillator vest from hospital discharge. Sudden death at 3 months was the primary outcome, with total and cause-specific mortality, nonfatal ventricular arrhythmias and hospitalisations evaluated as secondary outcomes; both intent-to-treat and on-therapy analyses were planned. Follow-up concluded in August 2017, and findings were reported at the conference.

**Comment:** This long-awaited trial failed to reach its primary endpoint (sudden cardiac death and death from ventricular arrhythmia), although tantalisingly showed a reduction in total mortality from 4.9% to 3.1% (p=0.04) in the vest group. This may have been related to miscategorisation of sudden cardiac death or other benefits of wearing the vest, including detecting and treating non-sustained ventricular tachycardias or atrial arrhythmias. Notably due to slow recruitment, the primary endpoint was changed, and patients only wore the vest for an average of 14.1 hours a day, and up to 20% of patients assigned to the vest group did not wear it at all. There were 20 appropriate shocks delivered in the vest group, and of these, 14 survived. We await further analysis of what number of subjects died whilst not wearing the vest, but at this point in time the usage of the device should remain as a class IIb indication.

**Session 401**
A pragmatic randomized trial of CYP2C19 genotyping implementation following percutaneous coronary intervention (PCI)

Authors: Tuteja S et al.

Summary: Patients scheduled for PCI were randomised to point-of-care CYP2C19 genotyping (n=249) or usual care (n=255) in this trial; 27% of the genotype group were loss-of-function carriers. Recommendations for antiplatelet therapy were provided with the genotype results, and the choice was left to the 15 treating interventional cardiologists. The interventional cardiologists followed the genotype-guided recommendations (primary outcome) for 70% of the participants. In the genotype group, prasugrel/ticagrelor was used by a significantly greater proportion of loss-of-function allele carriers than noncarriers (53% vs. 21% [p<0.0001]). The major adverse CV event rate was 12% and the major bleeding event rate was 4%, with no significant differences between the randomised groups. A post hoc analysis revealed that loss-of-function carriers who received clopidogrel had an increased adjusted incidence of a composite of major adverse CV events, major bleeding and death than those without loss-of-function alleles (1.84 [95% CI 1.06–2.26]).

Comment: Clopidogrel is a prodrug that requires metabolism in the liver. Loss-of-function alleles of CYP2C19 result in reduced effectiveness of clopidogrel, and this study used a point-of-care genotyping device (SpartanRx) with results and advice given to the treating cardiologists to see if it changed practice. Up to 30% of operators did not follow suggested therapeutic strategies. This may be because the results took 1 hour, so patients were loaded with the operator’s drug of choice prior to the results being known, resulting in possible therapeutic inertia to change. There are also issues with indications for the use of drugs other than clopidogrel for patients with stable coronary syndromes. Whilst not powered for clinical results, there was a higher incidence of major adverse CV events in patients with loss-of-function alleles (15.6% vs. 10.1%). Further research is needed, powered for clinical events, to see if we should up- or downtitrate antiplatelet agents using point-of-care devices such as these.

Session 402

One-year clinical outcomes of the bio-engineered COMBO stent

Authors: de Winter R et al.

Summary: This presentation reported 1-year outcomes for 3614 all-comer participants in the COMBO collaboration study of the bio-engineered COMBO stent placement following PCI; 16.4% of participants underwent multivessel PCI, and a total of 4445 lesions were treated. DAPT was prescribed according to local recommendations and guidelines, and follow-up assessments were conducted at 1, 6 and 12 months. One-year target lesion failure, a composite of cardiac-related death, target-vessel MI and clinically driven target-lesion revascularisation, was assessed in a pooled patient-level analysis, with the individual components and definite/probable stent thrombosis evaluated as secondary endpoints. Primary and secondary endpoint data were reported at the conference.

Comment: The COMBO stent (Orbus Neich Medical) is a stainless steel stent that elutes sirolimus from a biodegradable polymer on the abluminal side and has a luminal prohealing layer that attracts circulating endothelial progenitor cells. These results represent a combination of two large-scale registries of a largely all-comer population (including 21.8% STEMI patients and >50% B2/C lesions). The use of DAPT was not mandated and was based on local preference. Although not a randomised trial, the results are impressive, with a target lesion failure rate of 3.9% and a definite/probable stent thrombosis rate of only 0.8%. This suggests a role for this stent, although cost and clinical effectiveness in comparison with current third-generation drug-eluting stents should be made.

Session 402
A phase III, randomized, international, multicenter, open label, with blinded adjudication of outcomes, noninferiority clinical trial to explore the safety and efficacy of ticagrelor compared with clopidogrel in patients with acute coronary syndrome with ST elevation treated with thrombolysis

Authors: Berwanger O et al.

Summary: This international (including Australian sites) randomised, multicentre noninferiority trial assessed the safety of ticagrelor versus clopidogrel in patients treated with fibrinolytic therapy within 24 hours (median 2.6 hours). The primary endpoint was TIMI major bleeding at 30 days and, whilst assessed, the trial was not powered for early major adverse CV events. Whilst there was more total bleeding in the ticagrelor group (5.4% vs. 3.8%), TIMI major bleeding was similar (0.73% ticagrelor vs. 0.69% clopidogrel) and the trial demonstrated noninferiority of ticagrelor. Notably the study did not assess ticagrelor given with fibrinolysis, as 87% of patients had received clopidogrel before randomisation. It will be interesting to see if there will be longer term benefits of ticagrelor, and further analysis is awaited of the subpopulation (56%) who underwent PCI.

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Session 404
Reference: JAMA Cardiol; Published online March 11, 2018; Abstract

The effect of dabigatran in patients suffering myocardial injury after noncardiac surgery

Authors: Devereaux PJ et al.

Summary: The MANAGE trial randomised 1754 patients who experienced MINS (myocardial injury after noncardiac surgery) to receive dabigatran 110mg twice daily or placebo for ≥2 years, and using a partial 2 × 2 factorial design, those not receiving a proton-pump inhibitor were also randomised to omeprazole 20mg daily or placebo; aspirin plus statin use was encouraged. The primary efficacy outcome was vascular-related mortality, MI, nonhaemorrhagic stroke, peripheral arterial thrombosis, amputation or symptomatic venous thromboembolism, and the primary safety outcome was life-threatening, major or critical organ bleeding. Patient follow-up was completed in November 2017. The results for dabigatran were reported at the conference, with the omeprazole results to be reported at a later date.

Comment: This study introduces a new term, MINS, and was a partial 2×2 factorial design assessing the benefits of dabigatran (presented here) and omeprazole (to be presented in the future). This was originally planned as a larger study but due to slow enrolment and loss of funding was reduced. The trial included patients ≥45 years of age who met the universal definition of MI or had isolated ischaemic troponin level elevation. Despite nearly 50% of patients stopping the trial drug, the results are impressive with a significant reduction in major vascular events in the dabigatran group (11% vs. 15% [p=0.012]) with no increase in major bleeding. More than 90% of patients were asymptomatic and were only detected by a rise in troponin level, which perhaps should be the focus of future studies. We know giving statins long term in ACS is good, and there appears to be no harm in starting this as soon as possible in this population.

Session 405
Reference: N Engl J Med; Published online March 11, 2018; Abstract

Loading doses of atorvastatin versus placebo in patients with acute coronary syndromes and planned revascularization

Authors: Berwanger O et al.

Summary: Patients with ACS suitable for PCI were randomised to receive two loading doses of atorvastatin 80mg (n=2087) or matching placebo (n=2104), administered before and 24 hours after the procedure, and all participants received atorvastatin 40mg for 30 days starting 24 hours later in the SECURE-PCI trial conducted by Brazil-based researchers; 99.3% of participants completed the 30-day follow-up, with 64.7% undergoing PCI, 8% undergoing coronary artery bypass graft surgery and 27.3% receiving medical management only. No significant difference was seen between the atorvastatin and placebo recipients for the 30-day major adverse CV event rate (6.2% vs. 7.1%; hazard ratio 0.88 [95% CI 0.69–1.11]). There were no cases of hepatic failure and there were three cases of rhabdomyolysis, all in the placebo arm.

Comment: There are no large studies assessing the benefits of high-dose statin loading prior to planned coronary intervention in an ACS population. This 4191-patient study addressed this gap, in a multicentre, double-blind, placebo-controlled trial from Brazil. Up to 25% of patients had STEMI, and overall 64% of patients underwent PCI. The overall results of the trial did not suggest a reduction in 30-day major adverse CV events by high-dose atorvastatin given between 7 and 9 hours before angiography, but there was a suggestion of benefit in the group who actually underwent PCI (7.0% vs. 8.5%), which perhaps should be the focus of future studies. We know giving statins long term in ACS is good, and there appears to be no harm in starting this as soon as possible in this population.

Session 404
Reference: JAMA; Published online March 11, 2018; Abstract

Multicenter study of MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3)

Author: Mehra MR

Summary: Patients requiring circulatory support for advanced HF were randomised to a magnetically levitated centrifugal (n=190) or a mechanical-bearing axial (n=176) continuous-flow pump in this trial; long-term outcomes were reported in this presentation from the Brigham and Women’s Hospital Heart and Vascular Center in Boston, USA. Compared with the axial-flow pump, the centrifugal-flow pump was associated with a significantly better 2-year disabling stroke-free or reoperation-free survival rate (composite primary endpoint: 79.5% vs. 60.2% [p<0.001 for both noninferiority and superiority]), with lower rates of reoperations for pump malfunction (1.6% vs. 17.0% [p<0.001]) and overall stroke (10.1% vs. 19.2% [p=0.02]), and similar rates of death and disabling stroke.

Comment: The HeartMate 3 LV assist system is a novel centrifugal, fully magnetically levitated continuous-flow pump with an intrinsic pulse that is designed to improve biocompatibility in patients with severe HF. Results at 6 months comparing this device with the HeartMate 2 were published last year, and the current study presents longer term results out to 2 years. Overall survival was not significantly better with the HeartMate 3 device (82.8% vs. 76.2% [p=0.16]), but there was a significant difference in the need to replace the pump (10 times less likely). There were only two cases of pump thrombosis in the HeartMate 3 group, neither of which required surgery. There was also a reduction in stroke, suggesting this device should now become the standard of care for these difficult patients.

Session 405
Reference: N Engl J Med; Published online March 11, 2018; Abstract

Independent commentary by Associate Professor Craig Juergens

Associate Professor Craig Juergens is an Interventional Cardiologist at Liverpool Hospital where he is Director of the Cardiac Catheterisation Laboratories. He established the coronary interventional service at Liverpool hospital which has subsequently become a centre of training for Interventional Cardiologists. Apart from his interest in Interventional Cardiology, he has a major interest in acute coronary syndromes and has been involved in a large number of multicentre, multinational clinical trials. He has been author of over 40 peer reviewed papers and he continues as an active clinician in the Department of Cardiology at Liverpool Hospital, as well as providing support for the Interventional Cardiology programme at Orange Base Hospital.

Session 404
Carvedilol for prevention of chemotherapy-induced cardiotoxicity

Authors: Avila M et al.

Summary: Patients with HER2-negative breast cancer tumour status and normal LVEF referred for anthracyline therapy were randomised to treatment with carvedilol or placebo until completion of chemotherapy in the Cecchi trial from Brazil. There was no significant difference between the carvedilol and placebo arms for preventing a ≥10% reduction in LVEF at 6 months (primary endpoint; 14.5% vs. 13.5% [p=1.0]) or for change in LVEF or BNP (brain natriuretic peptide) level, although carvedilol recipients did have a significantly lower troponin I level over time (p=0.003), a significantly lower incidence of diastolic dysfunction (p=0.039) and a trend for a lesser increase in LV end-diastolic diameter (p=0.057).

Comment: Anthracycline chemotherapy is associated with cardiotoxicity and it is important to find ways to minimise this. This study from Brazil compared carvedilol with placebo in patients with a baseline normal resting EF receiving doxorubicin. Whilst carvedilol did not prevent the incidence of a decrease in EF by ≥10% (15% vs. 14%), there was a reduction in biomarker elevation, the significance of which remains to be seen. Interestingly, there were large numbers of patients excluded due to baseline usage of β-blockers and ACE (angiotensin-converting enzyme) inhibitors/ARBs (angiotensin receptor blockers), which made the study difficult to do, and there was no mention of subter measures of LV function such as global longitudinal strain. The authors hope to follow patients out to 2 years, which will be of interest.

Session 405
Reference: J Am Coll Cardiol; Published online March 11, 2018; Abstract

SMART-DATE: safety of 6-month duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndromes

Authors: Gwon HC et al.

Summary: Patients with unstable angina and NSTEMI or STEMI scheduled for PCI were randomised to receive 6 months (n=1357) or ≥12 months (n=1355) of DAPT in this trial from South Korea; DAPT included clopidogrel in 79.7% and 81.8% of the respective 6- and ≥12-month DAPT arms. Six months of DAPT was found to be noninferior to ≥12 months for the cumulative composite primary endpoint event rate (death from any cause, MI or stroke at 18 months; 4.7% vs. 4.2% [p=0.03 for noninferiority]); of the component endpoints, neither the all-cause mortality rate (2.6% vs. 2.9% [p=0.90]) nor the stroke rate (0.8% vs. 0.9% [p=0.84]) differed significantly between the two groups, but the MI rate was significantly greater in the 6-month DAPT group (1.8% vs. 0.8% [p=0.02]). No significant difference was seen between the 6- and 12-month DAPT groups for the stent thrombosis rate (1.1% vs. 0.7% [p=0.32]) or the Bleeding Academic Research Consortium type 2–5 bleeding rate (2.7% vs. 3.9% [p=0.09]). Per-protocol analysis results were similar to these intent-to-treat analysis results.

Comment: Current guidelines suggest the use of DAPT for at least 12 months after ACS, but there is interest in reducing this duration in the current era of newer generation drug-eluting stents. This multicentre, randomised, open-label, noninferiority trial from South Korea sought to compare 6 months with 12 months of therapy. Whilst the trial met noninferiority, there was a concerning higher rate of MI after 6 months (1.8% vs. 0.8% [p=0.02]) in the 6-month therapy group, and consistent with other data, close to half of these were in the nonculprit vessel (0.5%). As expected, there was more total bleeding in the 12-month group, but no significant difference in major bleeds. Overall the recommendation of minimum 12-month therapy should remain, particularly in patients at low bleeding risk.

Session 409
Reference: Lancet; Published online March 12, 2018; Abstract