ESC Congress Digital Experience 2021 Conference Review™

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In this review:

Abbreviations used in this review:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **BP** = blood pressure; **CV** = cardiovascular; **DAPT** = dual antiplatelet therapy; **EF** = ejection fraction; **HF** = heart failure; **HFpEF/HFrEF** = **HF** with preserved/reduced **EF**; **HR** = hazard ratio; **ILR** = implantable loop recorder; **LVEF** = left ventricular **EF**; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **TIA** = transient ischaemic attack.

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Welcome to this review of the ESC (European Society of Cardiology) Congress 2021 – The Digital Experience,

which I recently attended online. I have selected presentations that I found particularly interesting and relevant to local practice to include in this review, including some that have been simultaneously published in major journals – where possible the link to the published article has been provided. More information about the Congress itself can be found online at https://www.escardio.org/Congresses-&-Events/ESC-Congress.

We hope you find this Conference Review interesting, and we look forward to your feedback.

Kind Regards,

Professor John French
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MASTER DAPT: dual antiplatelet therapy after coronary stenting in high bleeding risk patients

Presenter: Prof M. Valgimigli (Lugano, CH)

Summary: The MASTER DAPT trial investigated the efficacy of DAPT in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent. Patients considered to be at high risk for bleeding (n=4434) received 1 month of DAPT after PCI before being randomised to single antiplatelet therapy or continued DAPT for ≥2 more months. A single third-generation sirolimus-eluting stent was used. PCI for ACS was performed in 48.3% of participants, and 36.4% were receiving concomitant anticoagulants. One month of DAPT was noninferior to 3 months of DAPT both for net adverse clinical events and major cardiac and cerebral events, and resulted in a lower incidence of major or clinically relevant nonmajor bleeding.

Session: Hot Line – MASTER DAPT

Abstract (N Engl J Med)

TWILIGHT-HBR: ticagrelor monotherapy in high bleeding risk patients

Presenter: Dr Davide Cao (New York, US)

Summary: This prespecified analysis of the TWILIGHT trial evaluated the treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin according to ARC-defined high bleeding risk status; TWILIGHT randomised patients who had undergone successful PCI with DESs to 12 months of ticagrelor with either aspirin or placebo after they had received 3 months of DAPT. Participants at high bleeding risk experienced significantly higher rates of bleeding as well as ischaemic events (HRs 1.70 [95% CI 1.27–2.26] for death, MI or stroke and 1.69 [1.26–2.28] for CV-related death, MI or ischaemic stroke). Moreover, participants with multiple ARC criteria for high bleeding risk were at higher risk than those meeting fewer ARC criteria. However, the most relevant finding was that the absolute reduction in BARC 3 or 5 bleeding events was significantly larger among participants with versus without high bleeding risk.

Session: Trial updates in ACS & PCI

STOPDAPT-2 ACS: one-month dual antiplatelet therapy followed by clopidogrel monotherapy in acute coronary syndrome

Presenter: Dr H. Watanabe (Kyoto, JP)

Summary: STOPDAPT-2 ACS randomised patients with ACS who had undergone everolimus-eluting cobalt-chromium stent implantation to receive 12 months of clopidogrel 75 mg/day plus aspirin, which was stopped either after 1 month (1 month of DAPT) or continued (12 months of DAPT). For the composite primary endpoint (CV-related death, MI, stent thrombosis, stroke, major/minor bleeding), stopping aspirin after 1 month did not meet noninferiority compared with 12 months of DAPT (HR 1.14 [0.80–1.62]; p=0.06 of noninferiority), with a trend for more CV events (1.50 [0.99–2.26]) despite a lower risk of major/minor bleeding (0.46 [0.23–0.94]).

Session: Hot Line – STOPDAPT-2 ACS

Comment: The contention that prolonged DAPT isn't required in patients treated with current (second-generation) drug-eluting stents, even in patients with high bleeding risk, was studied in three trials, **MASTER DAPT, TWILIGHT HBR and STOP DAPT-2.**

The Master DAPT trial presented in the late-breaking trials randomised patients, median age 76 years, considered at high bleeding risk with a precise DAPT score of 26.8, to strategies of abbreviated versus standard DAPT. There were no differences in major adverse CV events. Only stroke/transient ischaemic attack was different – interestingly higher in the standard DAPT arm. There was no increase in stent thrombosis – overall 0.5%, although CIs were wide.

The TWILIGHT HBR presentation was a secondary analysis of high bleeding risk patients among those randomised in the TWILIGHT trial (presented ESC 2019). This trial randomised patients at 3 months to discontinuation of aspirin and continuation of ticagrelor versus a further 12 months of therapy of ticagrelor and aspirin, and data were presented comparing the 1062 high bleeding risk patients in comparison with the remainder of randomised patients. Again, there were no significant differences in late ischaemic clinical events between the short and longer DAPT duration groups in those with high bleeding risk, although BARC 2, 3 and 5 bleeding was lower (6.3% vs. 11.4% [p=0.004]).

Finally the STOP DAPT-2 trial reported results from 4136 patients from this trial and STOP DAPT-2 ACS. The patients were randomised to 1 vs. 12 months of DAPT. Because it was a noninferiority trial for net clinical benefit, and the upper bound of the 95% CI was 1.50, noninferiority was not met as the CIs were 0.80 and 1.62. There was, however, a reduction in bleeding.

Taken together, these three trials suggest that in most patients with a higher bleeding risk , post-PCI with current drug-eluting stents, in whom it is desirable to stop the second antiplatelet agent early, either at 3 months or at 1 month, this strategy appears to be safe and reduces bleeding risk.

TOMAHAWK: immediate angiography after out-of-hospital cardiac arrest

Presenter: Prof S. Desch (Leipzig, DE)

Summary: Patients with successfully resuscitated out-of-hospital cardiac arrest of possible coronary origin were randomised to undergo immediate coronary angiography (n=265) or initial intensive care assessment with delayed or selective angiography (n=265) in the TOMAHAWK trial. The 30-day all-cause mortality rate (primary endpoint) did not differ significantly between the immediate versus delayed angiography groups (54.0% vs. 46.0%; HR 1.28 [95% CI 1.00–1.63]), but there was a greater rate for the composite of death or severe neurological deficit in the immediate angiography group (64.3% vs. 55.6%; 1.16 [1.00–1.34]). The two groups were also similar for peak troponin release and the incidences of moderate or severe bleeding, stroke and renal-replacement therapy requirement.

Comment: The TOMAHAWK trial is the second similarly designed randomised trial of patients with out-of-hospital cardiac arrest who have return of spontaneous circulation, to undergo emergency coronary angiography or standard care including potentially delayed angiography, among patients without ST-elevation on the following arrest ECG. Mortality was approximately 50% with no differences between each randomisation arm. Of note, in fact patients who had either died or had persistent severe neurological deficit were more common in the group randomised to emergency angiography. This trial together with the COACT trial reported in 2019, a similar-sized trial of between 500 and 600 patients with a similar design, suggest there is no evidence to support routine emergency angiography in the group of patients with return of spontaneous circulation but without ST-segment elevation following out-of-hospital cardiac arrest.

Session: Hot Line – TOMAHAWK
Abstract (N Engl J Med)

SSaSS: Salt Substitute and Stroke Study into the effect of salt substitutes on cardiovascular events and death

Presenter: Prof B. Neal (Sydney, AU)

Summary: This was a pragmatic trial in rural Chinese participants with a history of prior stroke (73%) or uncontrolled hypertension over the age of 60 years. Randomisation by village was to a salt substitute (25% KCl and 75% NaCl) or regular salt, and the 20,995 participants were followed up every 6 months over a mean of 4.7 years. Compared with the regular salt group, the salt substitute group had lower rates of stroke (primary endpoint; 29.14 vs. 33.65 events per 1000 person-years; rate ratio 0.86 [95% CI 0.77–0.96]), major CV events (49.09 vs. 56.29 per 1000 person-years; 0.87 [0.80–0.94]) and death (39.28 vs. 44.61 per 1000 person-years; 0.88 [0.82–0.95]), with no significant increase in serious adverse events attributable to hyperkalaemia (3.35 vs. 3.30 events per 1000 person-years; 1.04 [0.80–1.37]).

Comment: This trial presented by Prof Bruce Neal from the George Institute and UNSW shows that reduction in the salt content of routinely prepared food reduced both mortality (by 12%) and the stroke rate. This very important trial conducted in 400 villages in China randomised patients to receive standard salt versus a combination of KCl:NaCl ratio of 1:3. Prof Neal has had concerns regarding the salt content of commercially prepared food in 'Western countries', and although this trial was conducted in rural China, these results can most probably be extrapolated to other situations where salt is added to food.

Session: Hot Line – SSaSS
Abstract (N Engl J Med)

SYNTAX II trial: five year follow-up

Presenter: Prof A. Banning (Oxford, GB)

Summary: This was a presentation of 5-year data from the SYNTAX II trial, which recruited patients based on the original SYNTAX trial (PCI vs stenting); SYNTAX II has taken advantage of improved technologies since SYNTAX. A primary inter-trial comparison of the stent groups revealed significant improvements in SYNTAX II, with a lower 5-year rate of the composite outcome of CV-related death, death, MI or target-vessel revascularisation (21% vs. 36%; HR 0.54 [95% CI 0.41–0.71]), with lower rates of target-vessel revascularisation (13% vs. 24%), spontaneous MI (2% vs. 7%) and CV-related death (2.8% vs. 8.4%). Furthermore, the 5-year rate of the composite outcome for participants with stents (21%) was no longer dissimilar to the rate for surgical participants (25%).

Comment: This is a somewhat erroneously named study, as it is not a randomised trial but rather a matched comparison of outcomes of patients treated by PCI in the current era, compared with patients in the surgical arm of the SYNTAX-1 trial presented in 2009. The argument to perform such a comparison is that surgical techniques have not improved to the extent stent design and interventional techniques including 'routine' fractional flow reserve assessments have over the decade or so since SYNTAX-1 could be debated by cardiac surgeons. Nonetheless, the study found that in the patients with multivessel disease undergoing physiologically guided intervention, PCI had similar clinical outcomes at 5 years to CABG. Furthermore, the study showed that approximately 30% of lesions that were considered for intervention on angiographic grounds did not require this after physiological assessment, and deferring treatment of these appears safe.

EMPEROR-Preserved: effect of empagliflozin on cardiovascular death and heart failure hospitalisations in patients with heart failure with a preserved ejection fraction, with and without diabetes

Presenter: Prof S Anker (Berlin, DE)

Summary: In EMPEROR-Preserved, 5988 patients with New York Heart Association functional class II–IV HF, estimated glomerular filtration rate >20 mL/min/1.73m^2 and LVEF >40% were randomised to empagliflozin 10mg or placebo. Compared with placebo, empagliflozin reduced primary outcome events (CV death or hospitalisation for HF; HR 0.79 [95% CI 0.69–0.90]), with benefit seen as early as day 18 and most of the benefit attributable to reduced hospitalisations. Empagliflozin was also associated with improved quality of life, and no significant between-group difference was seen for all-cause mortality. Haematocrit rose in the empagliflozin group with a smaller fall in B-type natriuretic peptide level suggesting a probable mechanism for SGLT-2 inhibitor benefit.

Session: Hot Line – EMPEROR-Preserved/EMPEROR-Pooled
Abstract (N Engl J Med)

EMPEROR-Pooled: effect of empagliflozin on serious adverse renal outcomes in chronic heart failure – a prospective alpha-protected, individual patient-level pooled analysis

Presenter: Dr M Packer (Dallas, US)

Summary: This study evaluated renal outcome data from the EMPEROR-Reduced and EMPEROR-Preserved trials. Protocols were the same in the two trials but patients in EMPEROR-Reduced had LVEF ≤40% whilst those in EMPEROR-Preserved had LVEF >40%. There were 9718 patients included in the pooled analysis. A major adverse renal outcome was defined as a profound and sustained decrease in estimated glomerular filtration rate (≥50% reduction) or renal replacement therapy. Adverse renal outcomes were significantly lower for empagliflozin versus placebo in participants with HFrEF (HR 0.51 [95% CI 0.33–0.79]) but not in those with HFpEF (0.95 [0.73–1.24]).

Session: Hot Line – EMPEROR-Preserved/EMPEROR-Pooled

Comment: EMPEROR-Preserved examined randomisation to 10mg of empagliflozin compared with placebo in patients with HFpEF. The trial showed that if there was any drug-associated reduction in EF, there was likely to be a benefit of empagliflozin, although those with 'normal' EFs appeared not to benefit, the terminology could be slightly confused to the uninitiated and a further term HFmrEF, labelling an intermediate group between those with reduced and (truly) preserved EF, which has become evident; the absolute risk in this group is somewhat lower and the benefit appears to be of similar nature to those with reduced EF. However, evidence regarding treatment benefit in the group of patients with normal EF on echo, for which there is not a robust Lee accepted definition (?>55–60%), needs clarification. Thus **the ESC updated HF guidelines** released at this meeting add the SGLT-2 inhibitors to the HF therapeutic armamentarium. The therapeutic challenge is how all these evidence-based guideline-recommended agents are both introduced and optimised in terms of dosage, especially in patients with lowish BP who form a significant proportion of those with HF?

LOOP study: screening for AF with an implantable loop recorder to prevent stroke

Presenter: Prof J. Svendsen (Copenhagen, DK)

Summary: Individuals aged 70–90 years without AF but ≥1 risk factor for stroke were randomised to monitoring with an ILR (implantable loop recorder; n=1501) or usual care (n=4503) in the LOOP study. Compared with usual care, during median follow-up of 64.5 months greater proportions of the ILR group were diagnosed with AF (31.8% vs. 12.2%; HR 3.17 [95% CI 2.81–3.59]) and started on oral anticoagulants (29.7% vs. 13.1%; 2.72 [2.41–3.08]), with no significant difference in time to first stroke or systemic arterial embolism (primary outcome; 4.5% vs. 5.6%; 0.80 [0.61–1.05]) or major bleeding (4.3% vs. 3.5%; 1.26 [0.95–1.69]).

Comment: In this trial, 6004 Danes aged >70 years (average 74.7) with at least one risk factor for AF of hypertension, diabetes, HF or prior stroke were randomised 1:3 to an ILR, aiming to detect >6 minutes of AF, or usual care. The hypothesis was that AF would occur in 30% of the ILR group, and during follow-up (median 64.5 months), AF occurred in 32% in the ILR group; oral anticoagulant treatment rates in the ILR and usual care groups were 30% and 13%, respectively. The primary endpoint of stroke or systemic embolism occurred in 4.5% of the ILR group and 5.6% of the usual care group. Death rates were 11% in each group; bleeding was not significantly different; intracerebral haemorrhage was 0.8% in each group. Systolic BP >157mm Hg appeared to benefit as a subgroup. Although on sensitivity analysis among those with 3 years of screening, primary event rates were 3.9 vs. 5.6% (p=0.016), as per design this was a negative trial. Probably, the hypothesised rate of AF detection and thus of anticoagulant treatment in the usual care group was too low, and thus the 1:3 randomisation design did not allow for a sufficiently large absolute difference in event rates between the two randomised strategies for this to be a 'positive trial'.

Session: Hot Line – LOOP Study

Abstract (Lancet)

ACCOST-HH: Adrecizumab in cardiogenic shock

Presenter: Dr M. Karakas (Hamburg, DE)

Summary: The ACCOST-HH trial assessed the safety, tolerability and efficacy of a single dose of adrecizumab (a monoclonal antibody) 8 mg/kg versus placebo in all-comers with cardiogenic shock, with 30 days of follow-up for the safety primary endpoint (no requirement for CV organ support) and 3 months for secondary endpoints.

Comment: Attempts to modify the inflammatory milieu in patients with cardiogenic shock have been undertaken for over two decades. The ACCOST trial presented at this meeting randomised patients with cardiogenic shock to the biologic agent adrecizumab or matching placebo; this agent acts on the adrenal medulla and increases adrenomedullan levels, thus reducing vascular leakage. The trial's primary endpoint of days without mechanical support or vasopressors was no different between the treatment and placebo groups, and neither was mortality, which remained in the order of 40% through 90 days. While only 150 patients were randomised, there does not appear to be a signal for benefit, suggesting that the inflammatory response to cardiogenic shock is secondary and therapeutic interventions in various inflammatory pathways are unlikely to improve outcomes. The other trials in the cardiogenic shock space that may lead to improved outcomes including the DanGer trial, which will randomise 360 patients in Denmark and Germany to either routine Impella or 'standard care', were discussed by **Finn Gustafson** at another presentation. It is conceivable that newer mechanical approaches may impact mortality, although these trials will be presented at later meetings.

Session: Late Breaking Trials in ACS

Quadruple ultra-low-dose treatment for hypertension – QUARTET

Presenter: Prof C. Chow (Sydney, AU)

Summary: Australian adults with hypertension, untreated or treated with monotherapy, were randomised to treatment starting with a 'quadpill' containing irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg and bisoprolol 2.5mg (n=300) or irbesartan 150mg (control; n=291) in the phase 3 QUARTET trial. Additional medications were added as per protocol (target BP not met) for 15% of the quadpill arm and 40% of the control arm. Compared with the control group, the quadpill group had lower systolic BP by 6.9mm Hg by week 12 (primary outcome; p<0.0001) and a greater proportion had achieved BP control (76% vs. 58%; relative risk 1.30 [95% CI 1.15–1.47]), with no significant difference for adverse event-related treatment withdrawals (4.0% vs. 2.4% [p=0.27]). There were seven serious adverse events in the quadpill group and three in the control group. Among 417 participants who continued the study for 12 months, uptitration was significantly more frequent in the control group, but the intervention group continued to show a significantly lower mean unattended systolic BP (by 7.7mm Hg) and a significantly greater BP control rate at week 52 (81% vs. 62%; relative risk 1.32 [95% CI 1.16–1.50]).

Comment: This is another combination drug trial in a series of studies looking at the effect of a 'polypill'. A quartet of agents using one quarter of the standard dose in four different classes, a thiazide diuretic, a β-blocker, amlodipine and an ACE inhibitor, were compared with 150mg daily of irbesartan in a randomised trial. The combination therapy was quicker to achieve chart target BPs and shows promise, especially in environments where the individual agents may be expensive and/or are difficult to trial titrate. Whether this approach will be considered attractive in Australia remains to be seen.

Session: Late Breaking Trials in Hypertension

Abstract (Lancet)

Independent commentary by Professor John French.

Independent commentary by Professor John French, Director of Coronary Care and Cardiovascular Research at Liverpool Hospital, Sydney, and conjoint Professor at the University of New South Wales. After basic physician training he undertook a PhD at the University of Adelaide, further cardiology training at Greenlane Hospital, Auckland, New Zealand, and a Wellcome Trust Postdoctoral Fellowship at University College London, UK. Prior to his current position Professor French was appointed to Greenlane Hospital and the University of Auckland from 1992-2003. Professor French has been an investigator and co-investigator in numerous randomised controlled trials, and was on the steering committees of the SHOCK, OAT, HERO-2 and CRISP-AMI trials. Professor French has served on the clinical endpoints committees of several major trials. Professor French's current major research interests include the acute coronary syndromes especially ST elevation MI, and cardiac biomarkers, especially high-sensitivity troponins.

