Late Breaking Clinical Trials in Cardiology - Update from the American College of Cardiology Annual Scientific Meeting 2021

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This year's meeting of the American College of Cardiology took place from 15th to 17th May 2021 and was an all virtual meeting. The meeting was highly successful, and a host of high-quality late breaking clinical trials were presented along with simultaneous publication of a large number of accompanying manuscripts in high impact journals including *New England Journal of Medicine* and *Lancet*.

The trials discussed in this article the subject of an online lecture as part of the Dublin Cardiovascular Research Forum (DCRF). DCRF is a weekly meeting hosted by the Cardiovascular Research Institute at Mater Private Network in association with RCSI University of Medicine and Health Sciences. A recording of the lecture is available at the following link: https://www.cvridublin.ie/education-and-publication/dublin-cardiovascular-research-forum/past-events/. To register for notification of upcoming lectures please visit www.cvridublin.ie or send an e-mail to cvri@materprivate.ie.

ADAPTABLE (Aspirin Dosing: A Patient-Centric trial Assessing Benefits and Long-term Effectiveness)[1] compared the effectiveness of two doses of aspirin in patients with known atherosclerotic cardiovascular disease and at least one other risk factor or *enrichment factor*. The study was remarkable for its large-scale design, screening more than 400,000 and enrolling more than 15,000 patients, and also for using an innovative approach to patient enrolment, largely bypassing study centres and communicating with potential candidates via a participant portal, which included facility for electronic consent and self-randomization. Treatment was randomly allocated with either aspirin 81 milligrams once a day or aspirin 325 milligrams once a day. Follow up was done electronically by direct contact with the patient as well as via electronic health records and health plans. The primary endpoint was a composite of all-cause mortality, hospitalisation for myocardial infarction or stroke. The primary safety endpoint was hospitalization for major bleeding. The main finding was that there was no difference between the groups, hazard ratio (HR) = 1.02 (95% CI 0.91 - 1.14, P = 0.75). The main safety endpoint also showed a similar rate between the groups. Tolerability was better and rates of discontinuation were lower in patients receiving low dose aspirin. These findings are limited by the open label design of the trial.

The results are of interest to the community, particularly in the United States, where two different doses of aspirin are frequently prescribed, suggesting that low dose is the best option for patients taking aspirin for secondary prevention. The other main learning from the trial is that it is feasible to do large scale trials with direct patient screening, consenting and enrolment. This design might be used for other studies in the future.

The **LAAOS III (Left Atrial Appendage Occlusion Study III)**[2] was an important study examining the efficacy and safety of routine left atrial appendage exclusion at the time of surgery in patients with atrial fibrillation undergoing cardiac surgery for another indication. Patients were randomly allocated to routine LAA exclusion versus usual care. All patients received anticoagulation during follow up. This study was stopped early at the time of the planned interim analysis by the Data Safety Monitoring Board after enrolment of 4811 patients and at a median follow-up of 3.8 years. There was a clear efficacy advantage for LAA exclusion with a 33% reduction in the primary endpoint of stroke or systemic embolism (HR= 0.67, 95% CI 0.53 - 0.85, P = 0.001). The benefit appears additive to oral anticoagulation. There was no difference in the primary safety endpoint of hospitalization for heart failure, which might theoretically have been different in the presence of relevant neurohormonal influence of the left atrial appendage. Unfortunately, the study doesn't inform us as to whether, if this strategy is adopted going forward, there continues to be a requirement for oral anticoagulation. Currently, perhaps somewhat counterintuitively, ESC clinical practice guidelines suggest against discontinuation of oral anticoagulant in patients who have surgical LAA exclusion (due in part to unconvincing results from earlier studies and varying completeness of exclusion depending on the surgical method used). In contrast, patients who received percutaneous LAA exclusion, usually discontinue oral anticoagulation.

The **FLOWER-MI (FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction)**[3] investigated patients undergoing primary angioplasty for ST-elevation myocardial infarction who turn out to have multivessel disease rather than disease restricted to the culprit lesion. Earlier studies, done predominantly in patients with stable chronic coronary syndrome, suggests that in multivessel disease, pressure wire guided intervention is superior to and results in fewer stents implanted compared with intervention based on stenting of all high-grade lesions. The generalizability of this data to patients with catheterization and intervention in the settings of an acute myocardial infarction is open to question, making the study of high clinical relevance. The primary endpoint was a composite of all-cause mortality, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year. The main finding was that there was no difference between the groups in terms of the primary endpoint, hazard ratio= 1.32 (95% CI 0.78-2.23, P = 0.31). The main conclusion that can be drawn from the trial is that in patients presenting with ST-elevation myocardial infarction,

pressure wire guided intervention is comparable to intervention of all angiographically high-grade lesions in terms of major clinical adverse events at 1-year follow-up timepoint.

REHAB-HF (An Innovative Physical Function Intervention for Older Patients Hospitalised for Acute Decompensated Heart Failure)[4] examined the effects of a rehabilitation intervention that included multiple physical-function domains in frail, older patients who were hospitalised for acute decompensated heart failure. The primary outcome was the score on the Short Physical Performance Battery (total scores range from 0 to 12, with lower scores indicating more severe physical dysfunction) at 3 months. The secondary outcome was the 6-month rate of rehospitalisation for any cause.

A total of 349 patients underwent randomisation; 175 were assigned to the rehabilitation intervention and 174 to usual care (control). The Short Physical Performance Battery at 3 months was 8.3±0.2 in the intervention group and 6.9±0.2 in the control group (mean between-group difference, 1.5; 95% confidence interval [CI], 0.9 to 2.0; P<0.001). At 6 months, the rates of rehospitalisation for any cause were 1.18 in the intervention group and 1.28 in the control group (rate ratio, 0.93; 95% CI, 0.66 to 1.19).

This study demonstrated that in a diverse population of older patients who were hospitalised for acute decompensated heart failure, an early, tailored, rehabilitation intervention resulted in greater improvement in physical function than usual care.

In recent years there has been renewed debate regarding the optimal antiplatelet agent in the chronic maintenance period in patients who undergo coronary stenting with drug eluting stents. The **HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy) trial**[5] aimed to compare the efficacy and safety of aspirin and clopidogrel monotherapy. This prospective, randomised, open-label, multicentre trial enrolled 5,530 patients at 37 study sites in South Korea. Patients were randomly assigned (1:1) to receive a monotherapy agent of clopidogrel 75 mg once daily or aspirin 100 mg once daily for 24 months. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium (BARC) bleeding type 3 or greater, in the intention-to-treat population. During follow-up, the primary outcome occurred in 152 (5·7%) patients in the clopidogrel group and 207 (7·7%) in the aspirin group (hazard ratio 0·73 [95% CI 0·59–0·90]; p=0·0035).

This trial showed that among patients who were event free for 6–18 months post-PCI and successfully received the intended duration of DAPT, clopidogrel monotherapy compared with aspirin monotherapy significantly reduced the risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC type bleeding of 3 or more. This trial has important clinical implications for patients requiring indefinite antiplatelet monotherapy after percutaneous coronary intervention though must be interpreted against the background of prior studies, which failed to demonstrate an advantage of P2Y12 inhibitors over aspirin.[6]

Enthusiasm for renal denervation faded with the observation of lack of efficacy in the first large sham-controlled clinical trial in the field some years ago. Recent trials incorporating sham control, however, have showed encouraging results. The **RADIANCE-HTN TRIO trial (A Study of the ReCor Medical Paradise System in Clinical Hypertension: TRIO cohort)**[7] investigated efficacy and safety of endovascular ultrasound renal denervation in patients with office blood pressure of at least 140/90 mm Hg despite on three or more antihypertensive medications. Earlier published evidence from several meta-analyses, suggested efficacy of renal denervation in reducing 24-h ambulatory systolic blood pressure as compared to the sham procedure. A total of 136 participants were randomly assigned to either renal denervation (n=69) or a sham procedure (n=67) and were compared for a primary endpoint of change in daytime ambulatory systolic blood pressure at 2 months post procedure.

The main finding was that renal denervation reduced daytime ambulatory systolic blood pressure

more than the sham procedure (–8·0 mmHg [IQR –16·4 to 0·0] vs –3·0 mmHg [–10·3 to 1·8]; median between-group difference –4·5 mm Hg [95% CI –8·5 to –0·3]; adjusted p=0·022). The results can be of interest for patients with resistant hypertension, as this study showed renal denervation induced blood pressure reduction at 2-month follow-up timepoint. Evidence of long-term reduction in blood pressure after ultrasound renal denervation is still awaited.

The next major international cardiology meeting is the annual meeting of the European Society of Cardiology which will take place between 27th and 31st of August 2021. Next year the American College of Cardiology meeting is scheduled to take place between 2nd and 4th April 2022.

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