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Updates from Important Trials in Cardiology of 2021 (January – June)

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Critical appraisal of scientific publications is an important skill that must be acquired by the contemporary cardiologists. The preliminary step to a good critical appraisal is a sound understanding of the important aspects of a trial. In this issue of the Ibrahim Cardiac Medical Journal's "Journal Scan", we are first providing a brief summary of late-breaking randomised controlled trials published and presented at American College of Cardiology (ACC) Scientific Sessions 2021, and EuroPCR 2021, both of which were held virtually. We look at the important points to be derived from both potentially practice-changing trials, as well as key neutral trials of relevance in the above-mentioned meetings. In keeping with a critical appraisal format, each trial is introduced with its background and aims, PICO (Population, Intervention, Comparator, Outcomes) Criteria, main results and concluding remarks.

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JOURNAL SCAN

TRIALS IN INTERVENTIONAL CARDIOLOGY AND ANTIPLATELET THERAPIES

The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBCMAIN)

Hildick-Smith, et al., published in European Heart Journal (2021) 00, 1–11

Presented at Euro PCR 2021

Background:

The debate over the optimum stenting strategy for true left main (LM) bifurcation lesions remains. While the European Bifurcation Club (EBC) consensus is that the majority of true bifurcation anatomies can be approached using a stepwise provisional technique,[1] European Society of Cardiology (ESC) myocardial revascularisation guidelines mention a Class IIb (Level of Evidence B) recommendation for the Double-kissing (DK) crush technique in preference over provisional T-stenting in true left main bifurcations.[2] This was based on the landmark DK Crush V trial,[3] which was the only randomised trial of LM bifurcations prior to EBC MAIN[4] that showed better outcomes with an upfront two-stent strategy by DK crush technique over a provisional stenting strategy.[3] The EBC MAIN trial, designed and run by the EBC in 11 European countries, investigated clinical outcomes in patients with true distal LM bifurcation lesions randomised to receive either a stepwise layered provisional stenting strategy, or a systematic dual stenting strategy.[4] This was an investigator-led prospective randomized multicentre trial, which recruited.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 467 patients with true left main bifurcation lesions (Medina 1,1,1 or 0,1,1, with > 50% narrowing of both the main branch and side branch and in which both vessel reference diameters were ≥ 2.75mm) were randomised 1:1 to a stepwise layered provisional strategy (n=230) or a systematic two-stent strategy (n=237). The primary endpoint was a composite of death, myocardial infarction (MI), and target

lesion revascularization (TLR) at 12 months. Secondary endpoints were death, MI, TLR and stent thrombosis.

Main results:

No significant differences were observed in the primary endpoint between the two groups. The composite of death, MI and TLR at one year was 14.7% vs 17.7% in the provisional and dual stent groups respectively (hazard ratio [HR] 0.8, 95% confidence interval [CI] 0.5 – 1.3, p=0.34), with numerically fewer major adverse cardiac events (MACE) occurring with a stepwise layered provisional approach. There was a 22% cross-over to a two-stent strategy from provisional approach. The use of intravascular ultrasound (IVUS) was not mandated by protocol, and used in only 36% of provisional stenting cases and 31% of systematic dual stent strategy cases (p = 0.3).

In EBC MAIN, the two-stent strategy of choice was left to operator discretion: the upfront two-stent strategy adopted the greatest frequency was Culotte (53%), followed by T or TAP (33%), and only a small minority undergoing DK Crush (5%). Among the 22% who were randomised to provisional and who required a bail-out 2nd stent, the use of Culotte and TAP was observed in equal proportions (11% each).

Conclusions:

This trial found no significant differences in MACE between a stepwise provisional approach and a planned dual stenting strategy in true LM bifurcation lesions requiring stenting. These results need to be interpreted taking into consideration nuances such as lesion complexities, especially in comparison with the lesion subsets of the DK Crush V trial.

Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease: ADAPTABLE trial (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits & Long-Term Effectiveness)

Jones SW, et al. Published in N Engl J Med. 2021;384(21):1981-1990

Presented at ACC Scientific Sessions 2021

Background:

Novel P_2Y_{12} inhibitor antiplatelet therapies and the focus on the mortality and morbidity caused by bleeding among patients defined as high bleeding risk (HBR) has raised the important issue of striking an appropriate balance between ischemic and bleeding risk when prescribing antiplatelet drugs. There remains some controversy on the appropriate dosing of the aspirin in lowering the risk of death, MI and stroke and minimise bleeding in patients with established atherosclerotic cardiovascular disease (ASCVD).

The ADAPTABLE trial[5] is a multicentre, randomized, open-label trial that sought to evaluate the efficacy of two separate doses of aspirin (325 mg vs 81 mg) in patients with ASCVD with a unique pragmatic design. The trial employed methods and quality-by-design guiding principles, and was the first clinical trial to use PCORnet, the National Patient-Centred Clinical Research Network, a "network of networks" to conduct comparative-effectiveness research.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 15,076 patients with established ASCVD were enrolled following identification by means of electronic health record data; 96% of them were already on aspirin. Patients were randomised 1:1 through the patient portal to take either aspirin 81 mg (n = 7,540) or aspirin 325 mg, the active comparator (n = 7,536), which was purchased over the counter. The primary efficacy endpoint was the time to a first occurrence of any event in the composite of all-cause death, hospitalization for MI or stroke. The primary safety outcome was hospitalization for major bleeding with an associated blood-product transfusion. They were followed up for a median duration of 26.2 months.

Main results: The primary efficacy endpoint was met in 7.28% of patients in the aspirin 81 mg arm

as compared with 7.51% of the aspirin 325 mg arm (HR, 1.02; 95% CI, 0.91 to 1.14; p = 0.75). The primary safety outcome, hospitalisation for major bleeding was also non-significant between both groups, occurring in 0.63% and 0.60% in the aspirin 81mg and 325 mg arms respectively (HR, 1.18; 95% CI, 0.79 to 1.7; p=0.41). Importantly, patients assigned to 325 mg had a much higher incidence of dose switching than those assigned to 81 mg (41.6% vs. 7.1%) and fewer median days of exposure to the assigned dose.

Conclusions:

A strategy of 81 mg of daily aspirin had similar effectiveness as that of 325 mg in patients with established ASCVD, as evidenced by the absence of significant differences in cardiovascular events or major bleeding, and substantial dose switching to 81mg of daily aspirin from the 325 mg arm. Better long-term adherence was observed with the 81-mg dosing strategy.

JOURNAL SCAN

TALOS-AMI: TicAgrelor Versus CLOpidogrel in Stabilized Patients with Acute Myocardial Infarction

Park MW, et al. Protocol published in EuroIntervention. 2021;16(14):1170-1176

Presented at ACC Scientific Sessions 2021

Background:

De-escalation of dual antiplatelet therapy (DAPT) entails switching from the more potent P_2Y_{12} inhibitor Ticagrelor to the lesser potent Clopidogrel. There is limited data on preferred de-escalation strategies in patients with acute myocardial infarction (AMI) undergoing Percutaneous coronary intervention (PCI). More potent DAPT is prescribed during the first 30 days post-MI as the risk of ischaemic complications is highest during this period. On the contrary, most bleeding events occur predominantly during the maintenance phase of treatment, thus justifying a de-escalation of antiplatelet therapies, particularly P_2Y_{12} inhibitors. The TALOS-AMI study, a multicentre, randomised, open-label study originating from South Korea aimed to study the efficacy and safety of switching from ticagrelor to clopidogrel in post-AMI patients who underwent PCI, and who experienced no adverse clinical events during one month post PCI.[6]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The study enrolled 2,697 AMI patients who underwent index PCI with a newer-generation drug-eluting stents (DES) following an AMI and who did not experience adverse clinical events during the first month after the index PCI. They were randomised 1:1 to the de-escalation arm (i.e., aspirin 100 mg plus clopidogrel 75 mg daily; n = 1,349), or the active control arm (i.e., aspirin 100 mg plus ticagrelor 90 mg twice daily; n=1,348). The de-escalation was not guided by platelet function tests. The primary outcome was a composite of cardiovascular death, MI, stroke, and Bleeding Academic Research Consortium (BARC) bleeding type 2, 3 or 5 from 1 to 12 months after the index PCI.

Main results:

The composite primary endpoint was observed in 4.6% of the de-escalation arm (i.e., aspirin and clopidogrel) and 8.2% of the active control arm (i.e., aspirin and ticagrelor), (p for noninferiority <0.001, p for superiority < 0.001). There were no significant differences in the secondary outcome of composite cardiovascular death, MI, stroke between the de-escalation and active control arms (2.1% vs 3.1% respectively, p = 0.148). Notably, BARC 2,3, or 5 bleeding was significantly lower in the de-escalation arm (3.0% vs 5.6%, p = 0.001).

Conclusion:

In acute MI patients who have remained event-free for one-month post-index PCI, a DAPT regimen comprising of a uniform un-guided de-escalation strategy from aspirin plus ticagrelor to aspirin plus clopidogrel is superior to in terms of

net clinical benefit, with significantly lower bleeding and no increase in ischaemic events. Given the well-recognized "East Asian paradox" of antiplatelet therapy, these findings probably need to be interpreted in this context, and their applicability to other ethnicities across the globe remain to be seen. Notwithstanding, these data are encouraging for low-income countries where most patients are unable to afford novel P_2Y_{12} inhibitors such as ticagrelor in the long-term.

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial

Koo BK, et al. Published in Lancet 2021 ;397(10293):2487-2496.

Presented at ACC Scientific Sessions 2021

Background:

The HOST-EXAM trial was an investigator-initiated, prospective, randomised, open-label, multicentre trial in South Korea, which aimed to compare the efficacy and safety of aspirin versus clopidogrel, among patients who have undergone coronary stenting and are in the chronic maintenance phase.[7] The optimal antiplatelet monotherapy of choice in this subset of chronic patients post-PCI is not known.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The population included 5,438 patients who maintained DAPT without any clinical events (i.e., ischaemic and major bleeding complications) for a 6-18 months period after PCI with DES. They were randomly assigned (1:1) to receive antiplatelet monotherapy of either once-daily clopidogrel 75 mg (n=2710) or once-daily aspirin 100 mg (n=2728) for 2 years. The primary endpoint was a composite of all-cause death, non-fatal MI, stroke, readmission due to acute coronary syndrome, and BARC bleeding type 3 or greater.

Main results:

During 24-month follow-up, the primary outcome occurred in significantly fewer patients in the clopidogrel arm (5.7%), as compared with the aspirin arm (7.7%) [HR, 0.73; 95% CI 0.59-0.90; p=0.0035], with no significant interactions observed between the treatment effect and subgroups. Indications for PCI included stable angina (25.5%), unstable angina (35.5%), non-ST segment elevation myocardial infarction [NSTEMI] (19.4%) and ST-segment elevation myocardial infarction [STEMI] (17.2%). Clopidogrel monotherapy also fared significantly better in terms of secondary outcomes including thrombotic composite outcome (3.7% vs. 5.5% for clopidogrel vs. aspirin respectively, p = 0.003) and any bleeding (2.3% vs. 3.3% for clopidogrel vs. aspirin respectively, p = 0.003).

Conclusions:

In post-PCI patients stented with DES, who remained event-free from ischaemic and bleeding events on DAPT for 6-18 months, a clopidogrel monotherapy strategy was superior to an aspirin monotherapy strategy in terms of net clinical benefit of a composite of ischaemic and bleeding outcomes. Longer-term follow-up of these patients are likely to yield more definitive results of prolonged single antiplatelet therapy. Even here, the extent of the applicability of these findings globally might be limited by the "East Asian paradox" of antiplatelet therapy.

Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial

Puymirat E, et al. Published in N Engl J Med. 2021 Jul 22;385(4):297-308. Presented at ACC Scientific Sessions 2021

Background:

Multiple trials have demonstrated that complete revascularization (CR), involving PCI of both

culprit and non-culprit lesions, is associated with better clinical outcomes that treatment of the culprit lesion alone among patients with STEMI and multivessel disease (MVD), irrespective of whether this was carried out during index procedure, index admission or subsequent admission, no later than 45 days.[8-13] STEMI patients often have MVD. Whether CR that is guided by physiology, i.e. fractional flow reserve (FFR) is superior to an angiography-guided approach remains uncertain. The Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial, a prospective, multicenter, randomized, open-label study was designed to answer this.[14]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 1,171 patients with STEMI and MVD (defined as at least one non-culprit lesion of >50% stenosis judged amenable to PCI) who had undergone successful primary PCI of the infarct-related artery were randomised 1:1 to receive complete revascularization guided by either FFR (the intervention arm, n = 590) or angiography (control arm, n = 581). The primary outcome was a composite of all-cause death, nonfatal MI, or unplanned hospitalization leading to urgent revascularization at 1 year. Non-culprit lesions were revascularized as staged PCI procedures in the vast majority of patients (97%).

Main Results:

PCI of non-culprit lesions was performed in 66% of the patients with the FFR-guided strategy and in 97% with the angiography-guided strategy. No significant differences were observed in the primary outcome between the FFR-guided arm versus the angiography-guided arm (5.5 vs. 4.2% respectively, HR, 1.32; 95% CI, 0.78 to 2.23; p = 0.31). There were no significant differences observed between the two arms in terms of individual components of the composite primary outcome as well: death (1.5% vs 1.7%), non-fatal MI (3.1% vs 1.7 %) and unplanned hospitalization for urgent revascularization (2.6% vs 1.9%) for FFR-guided versus angiography-guided groups respectively. Cost-effectiveness and cost-utility favoured non-culprit vessel revascularization via an angiography-guided approach, as compared with FFR-guidance (€ 8,322 vs € 8,832 respectively; P < 0.01), a matter of pertinence to low-income countries.

Conclusions:

The FLOWER MI trial showed no benefit to an FFR-guided strategy over an angiography-guided strategy in case of complete revascularization in STEMI patients with MVD, with respect to the composite ischaemic outcome of death, MI, or urgent revascularization at 1 year. However, the wide confidence intervals for the estimate of effect do not allow for a conclusive interpretation of the data.

Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis-ATLANTIS trial

Presented by Jean-Philippe Collet and Gilles Montalescot at ACC Scientific Sessions 2021

Background:

The ATLANTIS trial is a randomized, open-label trial designed to assess the efficacy and safety of apixaban 5 mg BID compared with standard of care (comprising of either antiplatelet therapy (APT) or vitamin K antagonist (VKA) where oral anticoagulation is indicated), among patients undergoing Trans-Aortic Valve Implantation (TAVI).[15] Thrombotic events (Especially the formation of thrombus on the implanted bioprosthesis) and bleeding events post-TAVI are frequent and negatively affect short-term survival. The GALILEO trial demonstrated more harm than benefit with low-dose rivaroxaban compared with APT. As such, there is no current evidence that a newer oral anticoagulant (NOAC)

could replace antiplatelet therapy or a Vitamin K antagonist (VKA) following TAVI.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 1,500 eligible patients who underwent successful TAVI (either a native or valve-in-valve procedure) were stratified according to having an indication for OAC or not. Stratum 1 (n = 451) comprised of patients with an indication for oral anticoagulation (OAC), and they were randomly assigned to either apixaban 5 mg BID or standard of care (SOC), the VKA (21%). Stratum 2 consisted of patients without an indication for OAC (n = 1,049); these patients were randomised to apixaban 5 mg BID vs. SOC, where SOC was either single antiplatelet therapy [SAPT] (14.9%) or DAPT (56.9%). Overall, 749 patients were randomised to Apixaban and 751 to relevant SOC. The primary end-point was a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, or major bleedings over one year follow-up.

Main results:

The composite primary endpoint was observed in 18.4% of the apixaban group, and 20.1% of the SOC group (HR 0.92; 95% CI 0.73–1.16, p for interaction = 0.57). There were no significant differences in the primary outcome for apixaban vs SOC in stratum 1 (apixaban vs VKA: 21.9% vs 21.9%) or stratum 2 (apixaban vs APT: 16.9% vs 19.3%). Bioprosthetic valve thrombosis was significantly higher in the standard of care group (4.7% vs 1.1% for apixaban vs. SOC respectively, $p < 0.05$); this was primarily driven by stratum 2, i.e., the antiplatelet stratum of SOC (apixaban vs. APT: 1.1% vs. 6.1%; $p < 0.05$).

Post-hoc sensitivity analysis of the composite primary endpoint after exclusion of bioprosthetic valve thrombosis found greater rates of the composite of time to death, stroke, MI, systemic emboli, DVT/PE and major bleedings in the apixaban group (17.8 % vs 16.1 % for apixaban vs SOC, HR 1.12; 95% CI 0.88–1.44). No between-group differences were seen for the primary safety endpoint of life-threatening (including fatal) or disabling or major bleeding (BARC4, 3a,b and 3c), as defined by Valve Academic Research Consortium-2 (8.5% vs 8.5%; HR 1.02, 95% CI 0.72–1.44). Looking specifically at the patients with no indication for oral anticoagulation, a higher rate of non-cardiovascular death was observed in the apixaban-treated patients (2.66% vs 0.96%; HR 2.99; 95% CI 1.07-8.35).

Conclusions:

There is no benefit of apixaban over the standard of care (VKA if an indication for OAC; APT if no indication for OAC) in post-TAVI patients, in terms of net clinical benefit. Safety endpoints were also similar. Albeit not statistically significant, subclinical valve thrombosis is decreased with apixaban driven mainly by the stratum with no indication for OAC.

Trials in arrhythmia and cardiac surgery

Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke Whitlock RP, et al. Published in N Engl J Med. 2021;384(22):2081-2091

Presented at ACC Scientific Sessions 2021

Background:

This multicenter, randomized double-blind trial recruited patients with atrial fibrillation undergoing cardiac surgery, based on the hypothesis that the concomitant surgical occlusion of the left atrial appendage (LAA) as an adjunctive procedure during other cardiac surgery would prevent ischaemic stroke in patients with atrial fibrillation receiving routine standard of care, including anticoagulation.[16]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The patient population were those with atrial fibrillation and a CHA2DS2-VASc score of at least

2, and were scheduled to undergo cardiac surgery for another indication. They were randomised 1:1 to either receive the LAA occlusion procedure (intervention arm) or not during surgery; all participants also received usual care, including oral anticoagulation. The primary endpoint was the occurrence of ischemic stroke (including transient ischemic attack) or systemic embolism. The primary safety outcome was hospitalization for heart failure.

Main results:

A total of 4811 patients in 105 centres in 27 countries were recruited. The primary analysis population included 2379 participants in the occlusion group and 2391 in the no-occlusion group, with a mean follow-up of 3.8 years. Their mean age was 71 years, with a mean CHA2DS2-VASc score of 4.2. On January 28, 2021, following the second interim analysis of efficacy, the data and safety monitoring board recommended that the trial be stopped and the results reported. The primary outcome of stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168(7.0%) in the no-occlusion group (HR 0.67; 95% CI 0.53 to 0.85; p=0.001), an effect that was consistent across sub-groups. After 30 days, a primary-outcome event occurred in 61 participants (2.7%) in the occlusion group and in 103 (4.6%) in the no-occlusion group (hazard ratio, 0.58; 95% CI, 0.42 to 0.80). Furthermore, a larger difference was noted between groups after 30 days of surgery, as compared with during the first 30 days post-surgery. At 3 years, 76.8% of the participants continued to receive oral anticoagulation. No significant differences were seen for perioperative bleeding, heart failure, or death.

Conclusions:

LAA occlusion at the time of other cardiac surgery significantly reduces the incidence of stroke and systemic embolism among patients with atrial fibrillation, most of whom continued to receive anticoagulation. However, as this trial did not compare LAA occlusion head-to-head with anticoagulation, the procedure is not a replacement for anticoagulation in stroke prevention of atrial fibrillation patients.

Trials in heart failure

Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI)

Presented by Pfeffer MA at ACC Scientific Sessions 2021

Protocol published in Eur J Heart Fail. 2021;23(6):1040-1048

Background:

The angiotensin-receptor neprolysin inhibitor (ARBI) sacubitril/valsartan, has proven efficacy in chronic heart failure. The PARADISE-MI double-blind active-controlled trial aimed to compare the efficacy of ARNI against ramipril, in preventing the development of symptomatic heart failure and premature death in patients surviving an AMI.[17]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 5,669 patients from 495 Sites in 41 Countries were recruited. The population included patients within 0.5–7 days of presentation with an index AMI, with transient pulmonary congestion and/or left ventricular ejection fraction (LVEF) ≤ 40%, with at least one additional factor augmenting risk of HF or death (age ≥70 years, estimated glomerular filtration rate <60 mL/min/1.73 m^2, diabetes, prior myocardial infarction, atrial fibrillation, LVEF <30%, Killip class ≥III, STEMI without reperfusion). They were assigned 1:1 to receive either the active intervention: sacubitril/valsartan (target dose 97/103 mg BID) (n = 2,830) or active control: ramipril (target 5 mg BID) (n = 2,831). The primary endpoint of this event-driven trial was of

cardiovascular (CV) death, first heart failure (HF) hospitalization, or outpatient development of HF.

Main results:

The mean age was 64±12 years, and 24% were women. The majority of patient's index MI was a STEMI (76%), of whom 6% were thrombolysed, and 88% underwent acute percutaneous coronary. Mean left ventricular ejection fraction was 37±9% and 58% were in Killip class ≥II. There were no significant differences in the primary outcome for sacubitril/valsartan vs. ramipril (11.9% vs. 13.2% respectively, HR 0.90; 95% CI, 0.78-1.04; p = 0.17). No differences were observed between groups for individual components of the primary outcome as well.

Conclusions:

Compared to ramipril, Sacubitril/valsartan did not reduce CV death, heart failure hospitalization or outpatient heart failure requiring treatment in a contemporary enriched AMI population, compared with ramipril.

Sacubitril/Valsartan in Patients with Advanced Heart Failure with Reduced Ejection Fraction (LIFE Trial)

Presented by Mann DL at ACC Scientific Sessions 2021 Protocol published in JACC Heart Fail. 2020 Oct;8(10):789-799.

Background:

The landmark PARADIGM HF trial demonstrated the efficacy of Sacubitril/Valsartan in improving morbidity and mortality in patients with chronic heart failure with reduced ejection fraction (HFrEF). However, < 1% of these patients had NYHA class IV, i.e., advanced HF. The LIFE trial was designed to assess the efficacy and safety of sacubitril/valsartan compared with valsartan in patients with advanced heart failure with HFrEF.[18]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The population included patients of NYHA class IV symptomatology in the previous 3 months receiving guideline directed medical therapy (GDMT) for HF for >3 months and/or intolerant to GDMT, with LVEF ≤ 35%, BNP levels ≥ 250 pg/mL or NT-proBNP ≥ 800 pg/mL and systolic BP >90 mmHg with at least 1 additional objective finding of advanced HF. They were randomised 1:1 to either sacubitril/valsartan (starting dose 24/26 mg or 49/51 mg BID, uptitrated to 97/103 mg BID if tolerated after 4 weeks) (intervention arm; n = 167), or valsartan (starting dose 40 or 80 mg BID, uptitrated to 160 mg BID if tolerated) (control arm; n = 168). The primary endpoint was the area under the curve (AUC) for the proportional change in NT proBNP levels from baseline through 24 weeks.

Main results:

The primary outcome, area under the curve (AUC) for the proportional change in the ratio of NT-proBNP to baseline, for sacubitril/valsartan vs. valsartan, was p = 0.45. There were no between-group differences for the clinical composite of days alive, out of hospital, or freedom from HF events. Of note, a COVID-19 mitigation strategy was applied in this trial wherein a revised statistical analysis plan specified a decrease from 400 to 335 randomized patients, which nominally reduced the statistical power, which was not powered to see changes in clinical endpoints.

Conclusion: In this small trial which included patients that were sicker than the PARADIGM HF cohort (lower BP and LVEF, worse renal function, more atrial fibrillation and higher baseline NT-proBNP), sacubitril/valsartan did not reduce NT-proBNP or clinical outcomes among patients with advanced HFrEF and comorbidities.

Trials in hypertension

Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill: The Randomized Sham Controlled RADIANCE HTN TRIO Trial

Azizi M, et al; RADIANCE-HTN investigators.

Published in Lancet.;397(10293):2476-2486.

Presented by Ajay Kirtane at ACC Scientific Sessions 2021

Background:

The RADIANCE HTN TRIO trial was a international, multicentre, single-blind, sham-controlled trial to investigate the efficacy and safety of endovascular renal denervation in reducing blood pressure in daytime ambulatory systolic blood pressure (BP) in patients with hypertension resistant to three or more antihypertensive medications.[19]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The population included 18–75-year-old patients with office BP of at least 140/90 mm Hg despite three or more antihypertensive medications including a diuretic. They were then all switched to a once daily, fixed-dose combination pill comprising of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic for 4 weeks. Those with a baseline daytime ABP ≥135/85 mmHg were randomly assigned (1:1) to ultrasound renal denervation (intervention arm) or a sham procedure (control arm). The primary endpoint was the change in daytime ambulatory systolic BP at 2 months in the intention-to-treat population. Safety was also assessed in the intention-to-treat population.

Main results:

A total of 989 participants were enrolled. Among those who met inclusion criteria, and 136 were randomly assigned to renal denervation (n=69) or a sham procedure (n=67).

After 2 months follow-up, those assigned to renal denervation with ultrasound energy showed a significant median 4.5–mm Hg reduction in daytime ambulatory systolic BP more than the sham procedure (-8.0 mm Hg [IQR -16.4 to 0.0] vs -3.0 mm Hg [-10.3 to 1.8]; median between-group difference -4.5 mm Hg [95% CI-8.5 to -0.3]; adjusted p=0.022) in drug-resistant hypertension maintained on a triple-drug regimen during the study. 75% of subjects were fully adherent at both baseline and 2 months

Conclusion:

In comparison with sham procedures, renal denervation was found to safely reduce BP at 2 months in resistant hypertensive patients maintained on triple-drug combination antihypertensive medications. While additional follow-up is needed to determine the durability of this effect over time, this study indicates that renal denervation might be making a comeback, and may be complimentary to multidrug antihypertensive medications in patients with resistant hypertension.

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