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Journal Scan: Updates from Important Trials in Cardiology of 2022 (3rd quarter of 2022)

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INTRODUCTION

In this edition of the Ibrahim Cardiac Medical Journal's "Journal Scan", we present an overview of important randomised controlled trials presented at the European Society of Cardiology (ESC) Congress and Transcatheter Therapeutics (TCT) Conference, with a brief critical appraisal.

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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TRIALS IN INTERVENTIONAL CARDIOLOGY & CORONARY ARTERY DISEASE

Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction (REVIVED BCIS-2 trial)

Presented at ESC Congress 2022

Background:

Ischaemic cardiomyopathy (ICM) is the most common cause (60%) of heart failure (HF) worldwide. The Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES) trial showed that surgical revascularisation improves long-term outcomes, with a 16% reduction in all-cause death.[1] The Percutaneous Revascularization for Ischaemic Left Ventricular Dysfunction (REVIVED-BCIS 2) trial aimed to investigate whether revascularization by percutaneous coronary intervention (PCI) on top of optimal medical therapy (OMT) can improve outcomes in patients with severe ischemic LV systolic dysfunction, as compared with OMT alone.[2]

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

REVIVED BCIS-2 was a multicenter prospective randomised open-label trial among patients with ICM (defined as LVEF < 35%), extensive coronary artery disease (CAD) (defined as BCIS jeopardy score > 6), and demonstrable viability in at least four dysfunctional myocardial segments.[2] Those with an acute myocardial infarction four weeks prior to randomization, decompensated HF and sustained ventricular arrhythmias within 72 hours were excluded. A total of 700 patients were randomised 1:1 ratio to PCI with OMT vs OMT alone. The primary endpoint was a composite of all-cause death and hospitalisation for heart failure (HHF). The secondary outcomes included LVEF at 6 and 12 months as well as quality of life measures.

Results:

The trial enrolled a cohort that was older than the typical HF cohort with a median age of 70 years and majority (88%) male. The mean LVEF was 28%. Over a median follow up of 3.4 years, a primary outcome event occurred in 37.2% of the PCI arm vs 38.0% of the OMT alone arm (HR: 0.99; 95% CI 0.78–1.27, p = 0.96). There were also no differences in the major secondary outcomes of LVEF at 6 and 12 months. Quality-of-life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, showed an initial improvement in favour of PCI,

however the OMT arm had caught up at 24 months resulting in no differences overall.[2]

Conclusion:

While this trial did not demonstrate a benefit for PCI over OMT in severe ischemic LV dysfunction, it is important to note that the incidence of mortality was still high (>1/3rd of patients) irrespective of treatment strategy.

Cerebral Embolic Protection during Transcatheter Aortic-Valve Replacement (PROTECTED TAVR) trial

Presented at TCT 2022

Background: There remains clinical equipoise on the utility of cerebral embolic protection (CEP) devices on the reduction of stroke risk among patients undergoing transcatheter aortic-valve replacement (TAVR) for the treatment of aortic stenosis. The TAVR procedure can lead to embolization of debris, which is captured by CEP devices, which could lead to reduced stroke risk.

PICO criteria:

PROTECTED TAVR randomised patients with severe aortic stenosis undergoing transfemoral TAVR in a 1:1 ratio to either CEP (CEP group) or no CEP (control group).[3] The trial was conducted in North America, Europe, and Australia. The primary end point, analyses as the intention-to-treat, was stroke within 72 hours after TAVR or before discharge (whichever came first). Patients were examined at baseline and after TAVR by a neurologist. A number of secondary endpoints for which the trial was not powered were also assessed, including disabling stroke, death, transient ischemic attack (TIA), delirium, major or minor vascular complications at the CEP access site, and acute kidney injury (AKI).

Results:

A total of 3000 patients were randomised, 1501 in the CEP group and 1499 in the control group. In 94.4%, in whom it was attempted, a CEP device was successfully deployed. There were no differences in the primary endpoint of stroke within 72 hours after TAVR or before discharge, between the two arms: (2.3% vs. 2.9% in CEP group vs control group respectively; difference,- 0.6 percentage points; 95% CI: −1.7 to 0.5; p = 0.30). There were also no intergroup differences for the secondary endpoint events of death, TIA, delirium, or AKI. Disabling stroke occurred in 0.5% of the patients in the CEP arm and in 1.3% of those in the control arm, however this was not an endpoint to which the trial was powered.[3]

Conclusion:

The use of a CEP did not significantly reduce periprocedural stroke among patients with aortic stenosis undergoing transfemoral TAVR. The results of the currently enrolling UK-TAVI trial could shed further light on this aspect, and pre-specified pooled analyses of PROTECTED TAVR & UK TAVI are planned.

Routine Ultrasonography Guidance for Femoral Vascular Access for Cardiac Procedures: The UNIVERSAL Randomized Clinical Trial

Presented at TCT 2022

Background: A significant limitation of femoral artery access for cardiac interventions is the increased risk of vascular complications and bleeding compared with radial access. Strategies to make femoral access safer are needed. Despite 60% reduced access site bleeding by TRA, TFA is still needed for procedures needing large bore access and among those with occluded radials. Femoral artery access is associated with increased risk of vascular complications and bleeding compared with TRA. Ultrasound-guided access of TFA might be safer, however, there are mixed results of RCTs pertaining to ultrasonography guidance. The Routine Ultrasound Guidance for Vascular Access for Cardiac Procedures (UNIVERSAL) randomised trial aimed to determine whether routinely using US guidance for TFA in coronary angiography/intervention reduces bleeding or vascular complications.[4]

PICO criteria:

UNIVERSAL was is a multicenter, prospective, open-label RCT which randomised patients with planned femoral access for coronary angiography or intervention procedures 1:1 to ultrasonography-

guided femoral access vs no ultrasonography (on a background of fluoroscopic landmarking). STEMI patients were excluded. The primary endpoint was a composite of 30-day major bleeding based on the Bleeding Academic Research Consortium (BARC) 2, 3, or 5 criteria or major vascular complications.[4]

Results:

A total of 621 patients were randomized at 2 centers in Canada; the mean age was 71 years and 25.4% were female. There was no difference in the primary composite endpoint of 30-day major bleeding or vascular complications between the two groups (12.9% in the ultrasonography arm vs 16.1% without ultrasonography (OR, 0.77 [95% CI, 0.49-1.20]; P = 0.25). Procedurally, ultrasonography improved first-pass success (86.6% vs 70.0%; OR, 2.76 [95% CI, 1.85-4.12]; p < 0.001) and reduced the number of arterial puncture attempts and venipuncture.[4] For the post randomization prespecified subgroup of those who received a closure device, however, there was a significant interaction with a benefit of ultrasonography-guided access observed in patients who received a closure device (primary endpoint event 11.8% vs 23.4% with and without ultrasonography respectively (OR, 0.44 [95% CI, 0.23-0.82]; interaction p = .004) with no benefit observed in those who received manual compression.

Conclusion:

In this relatively small trial, ultrasonography-guided TFA did not reduce bleeding or vascular complications. However, in an updated meta-analysis of 9 RCTs including a total of 4410 patients published alongside this trial, the authors reported reduced major bleeding or major vascular complications with ultrasound-guided TFA. Larger trials might potentially demonstrate additional benefits of ultrasonography-guided access.

A Randomised Controlled Trial assessing the value of Computed Tomography Coronary Angiography (CTCA) in Improving Patient-related Outcomes in Patients with prior CABG undergoing Invasive Coronary Angiography: The BYPASS-CTCA Study

Presented at TCT 2022

Background:

Increasingly more patients with prior Coronary Artery Bypass Grafting (CABG) are having to undergo invasive coronary angiography (ICA) for a variety of indications. The BYPASS-CTCA Study was designed to test whether adjunctive Computed Tomography Coronary Angiography (CTCA) can reduce procedure time, improve patient satisfaction and prevent procedural complications in patients with previous CABG undergoing planned ICA

PICO criteria:

This was a single-center UK trial which included patients with prior CABG undergoing ICA for stable angina and NSTE-ACS. Those presenting with STEMI, haemodynamic or clinical instability were excluded: A total 688 patients were randomised at St Bartholomew's Hospital, London, UK to receive CTCA+ICA vs ICA alone. The co-primary endpoints to which the trial was powered were procedural duration, patient satisfaction scores post ICA, and incidence of contrast-induced nephropathy (CIN) by KDIGO criteria.[5]

Results:

The mean age of the study subjects was 70 years; 15% were women, 45% presented with ACS, and 50% were diabetic. An adjunctive prior CTCA in patients with previous CABG undergoing ICA resulted in shortened procedure duration (adjusted difference-20.9 (98.3% CI: -23.50 to -18.35), p < 0.001), improved patient satisfaction (40% relative improvement) and lower rates of CIN (3.4% vs. 27.9% for CTCA vs. no-CTCA arms, p < 0.0001). CTCA use also reduced procedural complication rates, and reduced rates of 12-month MACE.[5]

Conclusion:

Given the reduced procedure times, CIN and patient satisfaction, a CTCA prior to ICA should be considered in stable patients with previous CABG undergoing ICA

Impact on Mortality and Major Bleeding of Radial Versus Femoral Artery Access for Coronary Angiography or Percutaneous

Coronary Intervention: a Meta-analysis of Individual Patient Data from Seven Multicenter Randomized Clinical Trials RTC: Radial Trialists' Collaboration

Presented at ESC Congress 2022

Background:

Radial access reduces bleeding and vascular access site complications, as evidenced by a number of randomized trials. The effect of radial access on mortality is less well-reconciled; the Radial Trialists' Collaboration (RTC) thus set out to perform an individual patient-level data (IPD) meta-analysis, which also allows to further conduct more granular secondary analyses to answer specific questions on outcomes pertaining to vascular access.[6]

PICO Criteria:

This RTC meta-analysis was the first large IPD meta-analysis, including multicentre RCTs of transradial access (TRA) versus transfemoral artery access (TFA) for coronary angiography or PCI reporting all-cause mortality and major bleeding at 30 days (primary outcomes). RCTS published between January 1st 2005 and July 22nd 2021, and which enrolled at least 100 PCI in each arm was included in the analysis.

Pooled data from seven RCTs were included, totaling 21,600 patients; of them 10,775 were randomized to TRA and 10,825 were randomized to TFA. The trials included were COLOR, MATRIX, RIFLE STEACS, RIVAL, SAFARI-STEMI, SAFE-PCI for Women and STEMI-RADIAL trials.[7-13] The primary endpoint was 30-day all-cause mortality, and the primary analysis was performed by one-stage mixed-effects models based on the intention-to-treat cohort.

Results:

The median age was 63.9 years; about one-third (31.9%) were women, 95% presented with ACS, 50% had multivessel disease, and 75.2% underwent PCI. 30-day all-cause mortality on ITT was lower in the TRA arm (1.6%) vs TFA (2.1%), [HR 0.77 (95% CI 0.63–0.95; p=0.012)]. These findings were consistent in sensitivity analyses, including PCI, ACS, women, per protocol and as-treated analyses. Major bleeding was also significantly reduced with TRA vs. TFA (1.5% & 2.7% respectively, OR 0.55 [95% CI 0.45–0.67; p<0.001]. In terms of secondary outcomes, TRA resulted in significantly less major adverse cardiac and cerebrovascular events (MACCE) and net adverse clinical events (NACE).[6]

Conclusion:

This IPD meta-analysis found that TRA was associated with reduced all-cause mortality and major bleeding, which translated into lower MACCE and NACE, further establishing the utility of TRA in reducing incidence of hard endpoints

TRIALS IN HEART FAILURE

Dapagliflozin in Heart Failure with Mildly Reduced and Preserved Ejection Fraction (DELIVER) trial

Presented at ESC Congress 2022

Background:

The efficacy of sodium–glucose cotransporter 2 (SGLT2) inhibitors in reducing the risk of cardiovascular death and hospitalization for heart failure (HHF) among patients with chronic heart failure and preserved ejection fraction (HFpEF) is not known.

PICO Criteria:

DELIVER was a randomised placebo-controlled multinational trial which recruited 6263 patients with HFpEF (defined as a left ventricular [LV] ejection fraction [EF] >40%). Patients were randomised to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, on top of usual medical therapy.[14] The primary endpoint, assessed in a time-to-event analysis, was a composite of cardiovascular death and worsening heart failure (defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure).

Results:

Dapagliflozin reduced the composite primary endpoint by 16% over a median follow-up of 2.3 years. (16.4% vs 19.5% for dapagliflozin vs placebo; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Results were

consistent across pre-specified subgroups including those with LVEF < 60% and ≥ 60%, as well as patients with or without diabetes. Among individual components of the primary endpoint, worsening heart failure occurred 11.8% vs 14.5% (HR, 0.79; 95% CI, 0.69 to 0.91) and CV death occurred in 7.4% vs 8.3% (hazard ratio, 0.88; 95% CI, 0.74 to 1.05) in dapagliflozin and placebo arms respectively.[14]

Conclusion:

The DELIVER trial extends the indications for his class of SGLT-2 inhibitors regardless of the LVEF, to include HFpEF.

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial

Presented at ESC Congress 2022

Background:

The ADVOR trial sought to investigate if the carbonic anhydrase inhibitor acetazolamide that acts by reducing proximal tubular sodium reabsorption, could improve the efficacy of loop diuretics, by faster and greater decongestion in acute decompensated heart failure (ADHF) patients with clinical volume overload (i.e., edema, pleural effusion, or ascites).[15]

PICO Criteria:

In the multicentre Belgian trial, 519 patients with ADHF, volume overload and elevated N-terminal pro–B-type natriuretic peptide > 1000 pg per milliliter or a B-type natriuretic peptide level > 250 pg per milliliter, were randomised 1:1 to receive intravenous acetazolamide (500 mg once daily) or placebo, on top of IV loop diuretics. The primary endpoint was successful decongestion, defined as the absence of signs of volume overload within 3 days and without an indication for escalation of decongestive therapy.[15]

Results:

Acetazolamide resulted in successful decongestion in 42.2% vs 30.5% in the placebo arm (risk ratio, 1.46; 95% CI, 1.17 to 1.82; P<0.001). The secondary endpoint composite of all-cause mortality or rehospitalization for heart failure at 3 months occurred in 29.7% in the acetazolamide group and in 27.8% in the placebo group (HR, 1.07; 95% CI, 0.78 to 1.48). Acetazolamide was also associated with higher cumulative urine output and natriuresis. In terms of safety, incidence of worsening kidney function, hypokalemia, hypotension, and adverse events were similar in the two groups.[15]

Conclusion:

Acetazolamide provides a novel therapeutic option for decongesting acute HF patients. Of note, the trial did not include patients on SGLT2-inhibitors, another drug class that exerts its effect in the proximal renal tubules. Thus, the safety of using both drugs in ADHF needs to be assessed further.

Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) trial

Presented at ESC Congress 2022

Background:

In patients with prior myocardial infarction (MI), a polypill comprising of key medications (aspirin, angiotensin-converting–enzyme [ACE] inhibitor, and statin) could potentially reduce downstream outcomes as a simple secondary prevention strategy, compared to multiple tablets. The SECURE trial was a phase 3 RCT investigating this concept of improved post-MI secondary prevention outcomes.[16]

PICO Criteria:

A total of 2,499 patients with prior MI in the preceding 6 months were randomised to receive the polypill (1,258 patients) versus usual care (1,241 patients). Fixed combinations in the form of the polypill comprised of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary endpoint was a composite of cardiovascular death, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization.[16]

Results:

At a median follow-up of 36 months, the primary composite endpoint occurred in fewer patients in the polypill arm (9.5%) compared to usual care (12.7%) (HR, 0.76; 95% CI 0.60 to 0.96; P=0.02). These results were consistent across prespecified subgroups. A key secondary-outcome event (composite of cardiovascular death, nonfatal type 1

MI, or nonfatal ischemic stroke) also occurred less frequently in the polypill arm (8.2%), as compared to usual care (11.7%) (HR, 0.70; 95% CI, 0.54 to 0.90; P=0.005). Medication adherence was better in the polypill arm, as expected. Both arms reported similar adverse events.[16]

Conclusion:

Overall, SECURE provides randomised evidence that treatment with a polypill containing aspirin, ramipril, and atorvastatin resulted in a significantly lower risk of major adverse cardiovascular events within 6 months of MI, as compared to usual care. Some limitations of the trial included the unblinded nature of the design (which could be argued as an important component of the polypill intervention itself), which was mitigated by a blinded outcomes adjudication. There were also reduced follow-up visits in this high-risk population, owing to the COVID19 pandemic.

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study)

Presented at ESC Congress 2022

Background:

The TIME trial was designed on the background of previous studies suggesting that an evening dosing of antihypertensive therapy leads to better outcomes than morning dosing. This study was a decentralized randomised controlled trial which aimed to investigate whether an improvement in major cardiovascular outcomes can be gained by evening dosing of usual antihypertensive medications as compared with morning dosing among hypertensive patients. Major trial processes including screening, consent, randomisation and follow-up were conducted via online portal or email.

PICO Criteria:

TIME was a prospective, pragmatic, decentralised, RCT in the UK, which recruited hypertensive patients aged ≥18 years and taking at least one antihypertensive medication. Hypertensive patients were randomized 1:1 to take their BP medications to evening dosing (8:00 pm to midnight) versus morning dosing (6:00 am to 10:00 am). The composite primary endpoint was vascular death or hospitalisation for non-fatal MI or non-fatal stroke.[17]

Results:

A total of 21,104 patients were randomised to evening (n = 10,503) or morning (n = 10 601) dosing. Mean age of participants was 65 years, 42.5% were women and 90.5% were White. At a median follow-up of 5.2 years, there were no differences in the primary endpoint for evening dosing vs. morning dosing (3.4% vs 3.7%; HR 0.95; 95% CI 0.83-1.1, p = 0.53), which was consistent across pre-specified subgroup analyses.

Conclusion:

As there are no differences in outcomes with either evening or morning dosing of antihypertensive drugs, patients can thus be advised to take their regular antihypertensive medications at a time that they find convenient.

TRIALS IN PHARMACOLOGY AND THERAPEUTICS

Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation (INVICTUS) trial

Presented at ESC Congress 2022

Background:

The burden of rheumatic heart disease (RHD)-associated atrial fibrillation (AF) is huge, especially in low-and-middle-income countries (LMIC). As these patients are at increased risk for embolic stroke, long-term anticoagulation is required with current guidelines recommending a vitamin K antagonist (VKA). The monitoring therapeutic international normalized ratio is a major issue pertaining to VKA, which is obviated by use of a NOAC. The INVICTUS trial aimed to compare the efficacy of oral anticoagulation with a vitamin K antagonist (VKA) versus novel oral anticoagulants (NOAC).

PICO criteria:

INVICTUS was an international randomised, open-label trial comparing VKA to the NOAC rivaroxaban.[18] The trial enrolled echocardiographically documented RHD patients with AF and an elevated risk of stroke, who had at least one of the following: mitral stenosis with valve area ≤ 2 cm2, CHA2DS2VASc score ≥ 2,

left atrial thrombus or spontaneous echo contrast. This was the largest trial in patients with RHD, enrolling 4,565 patients from 24 countries in Africa, Asia and South America, who were randomised 1:1 to rivaroxaban 20 mg once daily or adjusted dose VKA. The design was non-inferiority (or non-inferior?), based on a hypothesis that rivaroxaban would be non-inferior to VKA for a primary efficacy endpoint of a composite of stroke, systemic embolism, MI, or death from vascular (cardiac or noncardiac) or unknown causes. The primary safety endpoint was International Society on Thrombosis and Haemostasis (ISTH) major bleeding.[18]

Results:

The mean age of patients was 50.5 years; 72.3% were women, reflecting a typical LMIC RHD-associated AF cohort. At a median follow-up of 3.1 years, among 4,531 patients included in the final analysis, 8.26% per year of patients receiving rivaroxaban, versus 6.46% per year of patients receiving VKA had a primary efficacy outcome event. As proportional hazards assumption was not met, results were reported as restricted mean survival time (RMST), which was significantly lower for rivaroxaban (1,576 days) vs VKA (1,652 days); RMST difference -76 days; 95% CI -117 to 34; p<0.001). There was a higher risk of death (8% vs 6.4%, RMST -72; p=0.001) and ischaemic stroke (1.1% vs 0.7%, RMST -23; p=0.01) in the rivaroxaban arm. Notably, no differences were seen in the safety endpoint of major bleeding.[18]

Conclusion:

The results of INVICTUS reaffirm the current practice guidelines recommendations that adjusted dose VKA should remain the standard of care for RHD-associated AF. The signal of reduction in all-cause mortality with VKA, however, could not be readily explained by reduced strokes alone, and the authors suggest a possible direct effect on the disease process of RHD.

BOX-Oxygen Targets in Comatose Survivors of Cardiac Arrest and Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest

Presented at ESC Congress 2022

Background:

The Blood Pressure and Oxygenation Targets in Post-resuscitation Care (BOX) trial was a 2x2 factorial design trial intended to evaluate two therapeutic interventions in a critical care setting among comatose survivors of out-of-hospital cardiac arrest (OHCA). These were (a) appropriate oxygenation target for mechanical ventilation and (b) blood pressure (BP) targets, which were reported by separate publications.[19,20]

PICO Criteria:

In this 2x2 factorial design trial, comatose survivors of OHCA were randomised open-label in 1:1 ratio to either a restrictive oxygen target of a partial pressure of arterial oxygen (Pao2) of 9 to 10 kPa (68 to 75 mmHg) or a liberal oxygen target of a Pao2 of 13 to 14 kPa (98 to 105 mmHg) for the BOX-Oxygen therapy trial;[19] they were also randomly assigned 1:1 in a double-blind fashion to either of two blood-pressure targets (63 mmHg vs 77 mmHg) for the BOX-BP trial (20). The primary endpoint was a composite of death from any cause or hospital discharge with severe disability or coma (defined as Cerebral Performance Category [CPC] of 3 or 4), whichever occurred first within 90 days after randomization.

Results:

A total of 789 patients were randomised at two Danish tertiary cardiac arrest centers. Mean age of the patients was 62.5 years; majority (81%) was men; 86% received bystander cardiopulmonary resuscitation (CPR) and 85% had a shockable rhythm. The median interval from cardiac arrest to randomization was 146 minutes (interquartile range, 113 to 187).

Oxygen targets:

In the oxygen targets arm, no differences were seen in the primary composite endpoint between the restrictive oxygen target group and the liberal oxygen target group (32.0 vs 33.9%; HR 0.91; 95% CI 0.71–1.16; p=0.59). There were also no differences between these two arms in the modified Rankin Scale, CPC or Montreal Cognitive Assessment (MoCA) scores.[19] BP targets: In the BP targets arm

also, there were no differences in the primary endpoint (34% in the 77 mmHg arm versus 32% in the 63 mmHg arm; HR 1.08; 95% CI 0.84–1.37; p=0.56).[20]

Conclusion:

The results of BOX trials suggest that among comatose OHCA survivors, aiming for PaO_2 between 9 and 14 kPa balance the risks of low and high oxygenation in OHCA patients. Furthermore, the trial supports current guidelines on post resuscitation care, which suggest maintaining a mean arterial BP of at least 65 mmHg in these patients.[21]

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