

Journal Scan: Updates from Important Trials in Cardiology of 2022 (4th quarter of 2022)

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INTRODUCTION

In this issue of the Ibrahim Cardiac Medical Journal's "Journal Scan", we present an overview of important randomised controlled trials presented at the American College of Cardiology Scientific Sessions 2022, 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

Bivalirudin plus a high-dose infusion versus heparin monotherapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (BRIGHT-4): a randomized trial

Presented at AHA Scientific Sessions 2022

Background:

BRIGHT-4 was an investigator-initiated, randomized controlled trial designed to examine the efficacy of a higher dose of bivalirudin vs. heparin among patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).¹ The study aimed to reconcile prior conflicting evidence across six widely varying RCTs of these two anticoagulants, by testing a different dose of bivalirudin in a predominantly radial access pPCI population.

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

In this open-label trial, patients were randomized 1:1 to receive bivalirudin with an additional post-primary PCI high-dose infusion for 2–4 hours (which has not

been previously used in RCTs) vs. unfractionated heparin (UFH) monotherapy. A composite of 30-day all-cause mortality or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding was the primary endpoint.

Results:

The patient population included 6016 STEMI patients who underwent predominantly trans-radial (93.1%) primary PCI within 48 hours of symptom onset, with no prior fibrinolytic, anticoagulants, or glycoprotein IIb/IIIa inhibitors use. The regimen of a bivalirudin bolus followed by a 2-to 4-hour high-dose infusion reduced the primary endpoint of 30-day all-cause mortality and major bleeding by 31% relative risk reduction, as compared with UFH monotherapy (3.1% from 4.4%, hazard ratio [HR], 0.69; P=.007), primarily driven by a reduction in mortality (HR 0.75; 95% CI 0.57–0.99; p=0.0420). While overall bleeding was low across the trial, bivalirudin was also associated with fewer major bleeds (0.8% vs 0.17%; HR 0.21; 95% CI 0.08–0.54; p=0.0014). While there were no differences in 30-day rates of reinfarction, stroke, or ischemia-driven target vessel revascularisation, stent thrombosis occurred in fewer patients receiving bivalirudin (0.37% vs 1.10%; p=0.0015).

Conclusion:

While the trial had an open-label design and exclusive Chinese population limiting its generalizability, BRIGHT-4 showed that in a contemporary pPCI population with predominant radial access, an additional post-PCI infusion of bivalirudin reduced both all-cause mortality and major bleeding, as compared with heparin monotherapy.

Survival After Invasive or Conservative Management of Stable Coronary Disease (ISCHEMIA-EXTEND)

Presented at AHA Scientific Sessions 2022

Background:

ISCHEMIA-EXTEND is an interim snapshot of extended follow-up to the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical And Invasive Approaches) trial, which compared an initial invasive (INV) versus an initial conservative (CON) strategy of optimal medical therapy for patients with stable, moderate-to-severe CAD and ischemia based on stress testing.² In the initial publication, at a median of 3.2 years, there was no difference in the primary endpoint of cardiovascular death, MI, hospitalization for unstable angina or heart failure, or resuscitation due to cardiac arrest.

PICO Criteria:

ISCHEMIA-EXTEND reported all-cause, cardiovascular, and non-cardiovascular mortality by randomized strategy, at an extended median follow-up of 5 years. Nonparametric cumulative incidence estimators, Cox regression models, and Bayesian methods were used. Follow-up was conducted by sites or through a central death index search. Data on all 2,588 patients randomized to the INV arm and 2,591 patients randomized to the CON arm through December 2021 were included in this interim report, with varying lengths of follow-up. There were 65 patients lost to follow-up due to withdrawal or declining to participate.

Results:

Over a median follow-up of 5.7 years, there were no differences in all-cause mortality between randomized INV and CON treatment groups [7-year rate 12.7% vs. 13.4%; adjusted hazard ratio (HR)=1.00, 95% CI: 0.85-1.18]. However, a lower 7-year rate of cardiovascular mortality was noted in the invasive arm (6.4% vs. 8.6%, adjusted HR=0.78, 95% CI: 0.63-0.96) and a higher 7-year rate of non-cardiovascular mortality in the conservative arm (5.6% vs. 4.4%, adjusted HR=1.44, 95% CI: 1.08-1.91). Treatment effects were consistent across prespecified subgroups.

Conclusion:

Over an extended follow-up of a median of 5.7 years, compared with an initial conservative strategy, an initial invasive strategy showed no difference in all-cause mortality but there was a lower risk of cardiovascular mortality and higher risk of non-cardiovascular mortality.

TRIALS IN HEART FAILURE

Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF Trial)

Presented at AHA Scientific Sessions 2022

Background:

TRANSFORM HF was a pragmatic, comparative effectiveness trial of torsemide versus furosemide in heart failure.^{3,4} Loop diuretic agents are key to a successful treatment strategy for heart failure, as recommended by clinical practice guidelines. However, there is insufficient evidence as to which loop diuretic is superior, and indeed, insufficient evidence to conclude that torsemide should be routinely recommended over furosemide.

PICO Criteria:

This was a prospective, randomized, event-driven, parallel-arm (1:1), comparative-effectiveness trial designed to compare the effect of torsemide versus furosemide among patients hospitalized for HF (regardless of ejection fraction) at 60 sites in the United States. For equivalence purposes, 1 mg of

torseamide corresponded to 2-4 mg of furosemide. The primary endpoint was all-cause mortality in a time-to-event analysis, as measured by follow-up phone calls. All-cause mortality or all-cause hospitalization, and health-related quality of life, also measured by a follow-up phone call, were among the 5 secondary endpoints.

Results:

Among 2859 participants randomised, at a median of 17.4 months, there was no difference in all-cause mortality, between torseamide vs furosemide (26.1% vs 26.2%; HR 1.02; 95% CI 0.89-1.18). There were also no differences in the secondary endpoint of all-cause mortality or all-cause hospitalization over 12 months (47.3% vs 49.3% for torseamide vs furosemide, HR, 0.92 [95% CI, 0.83-1.02]).

Conclusion:

The study concluded that torseamide is not superior to furosemide for admitted HF patients. The interpretation of these findings is limited by loss to follow-up, participant crossover, and nonadherence.

STRONG-HF - Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure.

Presented at AHA Scientific Sessions 2022

Background:

STRONG-HF Trial was designed on the background of lack of evidence for dose and pace of up-titration of guideline-directed medical therapies (GDMT) for patients following admission to hospital for acute HF.⁵

PICO Criteria:

This was an open-label, randomised, parallel-group randomised controlled trial. The patient population included participants aged 18 and 85 years admitted to hospitals with acute HF at 87 centres in 14 countries, which were not treated with full doses of GDMT, with randomisation occurring just prior to discharge. Eligible patients were randomised 1:1, stratified by left ventricular ejection fraction ($\leq 40\%$ vs $> 40\%$). The intervention group, i.e. high-intensity care involved the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge, and scheduled outpatient follow-up with monitoring

of clinical status & lab investigations. The comparator group received usual care as per usual local practice

Results:

The trial randomised 1078 patients, and was terminated early as per recommendation of the data and safety monitoring board, owing to greater than expected between-group differences. A significantly higher proportion of high-intensity care group patients had been up-titrated to full doses of prescribed GDMT drugs, leading to reduced HF readmission or all-cause death up to day 180 (15.2% in the high-intensity care group vs. 23.3% in the usual care group (adjusted risk difference 8.1% [95% CI = 2.9-13.2]; $p=0.0021$; risk ratio 0.66 [95% CI 0.50-0.86]). Both groups had similar incidences of serious adverse events, although more adverse events overall occurred in the high-intensity care group (41% vs 29%).

Conclusion:

In acute HF patients at discharge, an intensive treatment strategy of rapid up-titration of GDMT and close follow-up reduced symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care.

EMPA-KIDNEY - Empagliflozin and Cardiovascular Outcomes in Patients with Chronic Kidney Disease.

Presented at AHA Scientific Sessions 2022

Background:

The EMPA-KIDNEY trial was designed to assess the effects of empagliflozin in patients with chronic kidney disease (CKD) who are at risk for disease progression.⁶

PICO Criteria:

A broad range of CKD patients were included: the trial enrolled those with an estimated glomerular filtration rate (eGFR) of 20-45 ml per minute per 1.73 m² of body-surface area and patients who had an eGFR of 45-90 ml per minute per 1.73 m² with a urinary albumin-to-creatinine ratio (UCR) of at least 200 mg/g. They were randomised to receive the sodium-glucose cotransporter 2 (SGLT2) inhibitor

empagliflozin 10 mg once daily versus placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decline in eGFR to < 10 ml per minute per 1.73 m², a sustained decline in eGFR of ≥ 40% from baseline, or mortality from renal causes) or mortality from cardiovascular causes.

Results:

In this large trial, which randomised 6609 patients, at a median of 2 years of follow-up, the primary endpoint of progression of kidney disease or death from cardiovascular causes occurred in significantly fewer patients in the empagliflozin arm, as compared to placebo (13.1% vs. 16.9 HR, 0.72; [95% CI: 0.64 to 0.82]; $p < 0.001$). Empagliflozin also resulted in a reduced rate of hospitalization from any cause, but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes.

Conclusion:

The study expanded on the indications for empagliflozin, by demonstrating a lower risk of progression of kidney disease or death from cardiovascular causes among CKD patients over a wide range of eGFR.

TRIALS IN ARRHYTHMIA

Early AF - Progression of Atrial Fibrillation after Cryoablation or Drug Therapy.

Presented at AHA Scientific Sessions 2022

Background:

The Early AF trial was designed to investigate whether catheter ablation as initial therapy modifies the pathogenesis of paroxysmal, untreated atrial fibrillation, thereby altering the progression to persistent atrial fibrillation.⁷

PICO Criteria:

The trial included 303 patients with paroxysmal, untreated atrial fibrillation, randomised 1:1 to undergo an initial rhythm-control strategy with cryoballoon ablation vs. antiarrhythmic drug therapy.

The primary endpoint was the incidence of persistent atrial fibrillation.

Results:

Over 3 years of follow-up, significantly fewer patients in the ablation group had episodes of persistent atrial fibrillation, as compared with the antiarrhythmic drug group (1.9% vs. 7.4%, HR, 0.25; [95% CI: 0.09 to 0.70]). Recurrent atrial tachyarrhythmia (56.5% vs. 77.2%, HR, 0.51; [95% CI: 0.38 to 0.67]), hospitalization (5.2% vs. 16.8%, RR, 0.31; [95% CI: 0.14 to 0.66]) and serious adverse events (4.5% vs. 10.1%) were also fewer in the ablation group.

Conclusion:

At 3 years, the initial treatment of paroxysmal atrial fibrillation with catheter cryoablation appears superior to drug therapy with respect to reduced persistent atrial fibrillation or recurrent atrial tachyarrhythmia than antiarrhythmic drugs.

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