De-Escalation of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndromes

J Am Coll Cardiol. 2021 Aug 24;78(8):763-777. PMID: 34275697; https://doi.org/10.1016/j.jacc.2021.06.012
Satoshi Shoji, Toshiki Kuno, and Tomohiro Fujisaki

Abstract

Background: Balancing the effects of dual antiplatelet therapy (DAPT) in the era of potent P2Y12 inhibitors has become a cornerstone of acute coronary syndrome (ACS) management. Recent randomized controlled trials (RCTs) have investigated DAPT de-escalation to decrease the risk of bleeding outcomes.

Objectives: The aim of this study was to compare the efficacy and safety outcomes of various DAPT strategies in patients with ACS, including de-escalation from a potent P2Y12 inhibitor to clopidogrel or low-dose prasugrel.

Methods: MEDLINE and EMBASE were searched through January 2021 for RCTs investigating the efficacy and safety of DAPT in patients with ACS, and a network meta-analysis was conducted. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, and stroke. The primary bleeding outcome was trial-defined major or minor bleeding.

Results: Our search identified 15 eligible RCTs, including 55,798 patients with ACS. De-escalation therapy was associated with reduced risk of primary bleeding outcomes (hazard ratio [HR]: 0.48 [95% confidence interval [CI]: 0.30-0.77] vs clopidogrel; HR: 0.32 [95% CI: 0.20-0.52] vs ticagrelor; HR: 0.36 [95% CI: 0.24-0.55] vs standard-dose prasugrel and HR: 0.40 [95% CI: 0.22-0.75] vs low-dose prasugrel) without negatively affecting primary efficacy outcomes. There were no significant differences in ischemic or bleeding outcomes between de-escalation to clopidogrel or low-dose prasugrel.

Conclusions: Compared with other established uses of DAPT, de-escalation was the most effective strategy for ACS treatment, resulting in fewer bleeding events without increasing ischemic events.

Comments: The use of dual antiplatelet therapy is titrated based on the balance of bleeding risk vs thrombosis risk. The latest guidelines prefer the use of potent P2Y12 inhibitors such as ticagrelor and prasugrel over clopidogrel in ACS; as they have shown pronounced platelet inhibition and have demonstrated reduced ischemic events in various randomized controlled trial. We also know that improving stent technology has reduced stent thrombosis events drastically. So are we justified to continue these powerful antiplatelets for prolonged periods is a pertinent question. This meta-analysis attempts to answer precisely this. Here, the authors have taken 4 strategies for de-escalation. First, cessation of aspirin and continuation of P2Y12 monotherapy, second is aspirin monotherapy, third DAPT with low-dose P2Y12 therapy, and the last is DAPT with de-escalation of high-potent P2Y12 inhibitor to clopidogrel. Of interest, there was no difference in the all-cause mortality among the 4 strategies, but there was substantial reduction in cardiovascular death. De-escalation should be the new mantra in majority of the patients who under-go PCI, except for a small group of special cases where there is use of very long stents/use of multiple stents/complex PCI or in-born metabolic disorders. This was also highlighted in a review article published in the IJCC Journal on DAPT usage recently titled “Evolving Concepts in Post-PCI Antiplatelets Therapy”. [https://doi.org/10.1177/2632463620953677]
A Biomarker Model to Distinguish Types of Myocardial Infarction and Injury

J Am Coll Cardiol. 2021 Aug 24;78(8):791-793. https://doi.org/10.1016/j.jacc.2021.06.027
Johannes T. Neumann, Jessica Weimann, and Nil A. Sorensen

Abstract

Background: Discrimination among patients with type 1 myocardial infarction (T1MI), type 2 myocardial infarction (T2MI), and myocardial injury is difficult.

Objectives: The aim of this study was to investigate the discriminative value of a 29-biomarker panel in an emergency department setting.

Methods: Patients presenting with suspected myocardial infarction (MI) were recruited. The final diagnosis in all patients was adjudicated on the basis of the fourth universal definition of MI. A panel of 29 biomarkers was measured, and multivariable logistic regression analysis was used to evaluate the associations of these biomarkers with the diagnosis of MI or myocardial injury. Biomarkers were chosen using backward selection. The model was internally validated using bootstrapping.

Results: Overall, 748 patients were recruited (median age: 64 years), of whom 138 had MI (107 T1MI and 31 T2MI) and 221 had myocardial injury. In the multivariable model, 4 biomarkers (apolipoprotein A-II, N-terminal prohormone of brain natriuretic peptide, copeptin, and high-sensitivity cardiac troponin I) remained significant discriminators between T1MI and T2MI. Internal validation of the model showed an area under the curve of 0.82. For discrimination between MI and myocardial injury, 6 biomarkers (adiponectin, N-terminal prohormone of brain natriuretic peptide, pulmonary and activation-regulated chemokine, transthyretin, copeptin, and high-sensitivity troponin I) were selected. Internal validation showed an area under the curve of 0.84.

Conclusions: Among 29 biomarkers, 7 were identified to be the most relevant discriminators between subtypes of MI or myocardial injury. Regression models based on these biomarkers allowed good discrimination. (Biomarkers in Acute Cardiac Care [BACC]; NCT02355457)

Comments: The concept of use of biomarkers in the field of cardiology is evolving. With the discovery of new biomarkers and/or combination of old biomarkers have refined our diagnosis when combined with clinical judgement. In our day-to-day practice, we tend to use clinical judgement, objective evidence of ischemia or not, and highly sensitive troponin to differentiate between different types of myocardial infarction (type 1 and type 2) and myocardial injury. But these methods are not entirely helpful. The authors of this article tried to analyze 29 biomarkers to judge the best model, where a set of biomarkers were helpful to discriminate between subtypes of myocardial infarction or injury. In one of the multivariate models, 4 biomarkers were found to discriminate between MI subtypes type-1 and type-2. These biomarkers were highly sensitive troponin I, NT-Pro BNP, Copeptin and Apolipoprotein A-II. To discriminate between infarction vs injury, 6 biomarkers were helpful which included hs-troponin I, NT-Pro BNP, Co-peptin, Adiponecint, transthyretin, and pulmonary- and activation-regulated chemokine. So, the authors conclude that 7 out of 29 biomarkers helped to distinguish between infarction subtypes and injury. But I feel this theory requires further studies to know the sensitivity and specificity of these 7 biomarkers when compared to clinical judgement and experience.

Effects of Lignocaine vs. Opioids on Antiplatelet Activity of Ticagrelor: The LOCAL Trial

Eur Heart J. 2021 Aug 23. https://doi.org/10.1093/eurheartj/ehab557
Himawan Fernando, Thy Duong, and Kevin Huynh

Abstract

Aims: We assessed the impact of intravenous fentanyl and lignocaine on the pharmacokinetics and pharmacodynamics of ticagrelor in patients with unstable angina and non-ST-elevation myocardial infarction and their procedural analgesic efficacy and safety.

Methods and Results: Seventy patients undergoing coronary angiography with ticagrelor loading were included in the pharmacokinetic and pharmacodynamic analyses of this randomized trial. Plasma ticagrelor levels 2 h post-loading dose were significantly lower in the fentanyl arm than in the lignocaine treatment arm (598 vs. 1,008 ng/mL, P = .014). The area under the plasma-time curves for ticagrelor (1,228 vs. 2,753 ng h/mL, P < .001) and its active metabolite (201 vs. 447 ng h/mL, P = .001) were both significantly lower in the fentanyl arm. Expression of activated platelet glycoprotein IIb/IIa receptor (2,829 vs. 1,426 mean fluorescence intensity, P = .006) and P-selectin (439 vs. 211 mean fluorescence intensity, P = .001) was significantly higher at 60 min in the fentanyl arm. A higher proportion of patients had high on-treatment platelet reactivity in the fentanyl arm at 60 min using the Multiplate Analyzer (41% vs. 9%, P = .002) and 120 min using the VerifyNow (30% vs. 3%, P = .003) and VASP (37% vs. 6%, P = .002) assays. Both drugs were well-tolerated with a high level of patient satisfaction.

Conclusions: Unlike fentanyl, lignocaine does not impair the bioavailability or delay the antiplatelet effect of ticagrelor. Both drugs were well-tolerated and effective with a high level of patient satisfaction for procedural analgesia. Routine
procedural analgesia during percutaneous coronary intervention should be reconsidered and if performed, lignocaine is a beneficial alternative to fentanyl.

**Comments** Intravenous fentanyl is the most commonly used drug for routine sedation and analgesia in the Cath Lab. According to an international survey, 92% of the Cath Labs routinely use opioid analgesics during PCI procedures. There were many anecdotal studies in the past hinting at delayed platelet inhibition after antiplatelet loading dose when coadministered with fentanyl. To address the same question, this study [LOCAL trial] analyzed data on 70 patients. Here, the study population was divided into fentanyl arm and lignocaine arm. The main observations were that the fentanyl arm had significantly lower plasma ticagrelor levels/active metabolite levels 2 h post-loading dose. Activated GP IIb/IIIa receptor and P-selectin were higher in fentanyl arm when compared to lignocaine arm. As concluded, lignocaine is safer alternative to fentanyl for analgesia in Cath Lab.

### Ten-Year All-Cause Death After Percutaneous or Surgical Revascularization in Diabetic Patients with Complex Coronary Artery Disease

Eur Heart J. 2021 Aug 18. https://doi.org/10.1093/eurheartj/ehab441
Rutao Wang, Patrick W. Serruys, and Chao Gao

**Abstract**

**Aims:** The aim of this article was to compare rates of all-cause death at 10 years following coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) in patients with or without diabetes.

**Methods and Results:** The SYNTAXES study evaluated up to 10-year survival of 1,800 patients with three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) randomized to receive either PCI or CABG in the SYNTAX trial. Ten-year all-cause death according to diabetic status and revascularization strategy was examined. In diabetics (n=452), the risk of mortality was numerically higher with PCI compared with CABG at 5 years (19.6% vs. 13.3%, hazard ratio [HR]: 1.53, 95% confidence interval [CI]: 0.96, 2.43, P=.075), with the opposite seen between 5 and 10 years (PCI vs. CABG: 20.8% vs. 24.4%, HR: 0.82, 95% CI: 0.52, 1.27, P=.366). Irrespective of diabetic status, there was no significant difference in all-cause death at 10 years between patients receiving PCI or CABG, the absolute treatment difference was 1.9% in diabetics (PCI vs. CABG: 34.6% vs. 36.4%, difference: 1.9%, 95% CI: −7.6%, 11.1%, P=.551). Among insulin-treated patients (n=182), all-cause death at 10 years was numerically higher with PCI (47.9% vs. 39.6%, difference: 8.2%, 95% CI: −6.5%, 22.5%, P=.227).

**Conclusions:** The treatment effects of PCI vs. CABG on all-cause death at 10 years in patients with 3VD and/or LMCAD were similar irrespective of the presence of diabetes. There may, however, be a survival benefit with CABG in patients with insulin-treated diabetes. The association between revascularization strategy and very long-term ischemic and safety outcomes for patients with diabetes needs further investigation in dedicated trials.

**Comments:** The first topic which I will be commenting will be on age-old debate regarding CABG vs PCI. Multiple guidelines have given preference to CABG over PCI for revascularization of complex coronary lesions. Multiple studies were unable to establish superiority of CABG or PCI for multivessel CAD. Both SYNTAX trial and FREEDOM trial showed marginal benefit of CABG over PCI over 5-year follow-up. Similarly, BARI trial with 10-year follow-up too showed survival benefit with CABG over PCI for multivessel CAD. Diabetic patients were at higher risk than nondiabetic patients, for all-cause mortality in both CABG and PCI arms. Also, diabetic patients were shown to get benefit from CABG over PCI over 5 years follow-up in various studies. But this important study partially blunts the arguments being presented in favor of CABG. Here in this study, the all-cause mortality between CABG and PCI arms showed no statistically significant difference. CABG did not provide survival to diabetic patients on oral pharmacotherapy over PCI in complex CAD. Insulin-dependent diabetic patients did derive survival benefit from CABG. This study may not have statistical power to conclusively prove the difference in CABG and PCI outcomes over long-term follow-up, but it reveals some interesting outcomes. One of them is that PCI is noninferior to CABG on long-term follow-up and even though CABG might show initial benefit at the end of 5-year follow-up, but eventually 10-year follow-up data shows no significant difference in the outcomes. This study encourages us to take up bigger and longer studies to compare these 2 revascularization techniques. Still jury is out and we don’t have a clear winner. Therefore, it is left to the wisdom, judgement of treating physician based on experience and availability of the surgical backup at the tertiary care center in deciding the mode of treatment.

### Aspirin Versus Clopidogrel for Chronic Maintenance Monotherapy After Percutaneous Coronary Intervention (HOST-EXAM): An Investigator-Initiated, Prospective, Randomized, Open-Label, Multicenter Trial

Lancet. 2021 Jun 26;397(10293):2487-2496. https://doi.org/10.1016/S0140-6736(21)01063-1
Prof Bon-Kwon Koo, Jeehoon Kang, and Kyung Woo Park
Abstract

Background: Optimal antiplatelet monotherapy during the chronic maintenance period in patients who undergo coronary stenting is unknown. We aimed to compare the head-to-head efficacy and safety of aspirin and clopidogrel monotherapy in this population.

Methods: We did an investigator-initiated, prospective, randomized, open-label, multicenter trial at 37 study sites in South Korea. We enrolled patients aged at least 20 years who maintained dual antiplatelet therapy without clinical events for 6 to 18 months after percutaneous coronary intervention with drug-eluting stents (DES). We excluded patients with any ischemic and major bleeding complications. 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, nonfatal 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. This trial is registered with ClinicalTrials.gov, NCT02044250.

Findings: Between March 26, 2014 and May 29, 2018, we enrolled 5,530 patients. A total of 5,438 (98.3%) patients were randomly assigned to either the clopidogrel group (2,710 [49.8%]) or to the aspirin group (2,728 [50.2%]). Ascertainment of the primary endpoint was completed in 5,338 (98.2%) patients. During 24-month 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 = .0035).

Interpretation: Clopidogrel monotherapy, compared with aspirin monotherapy during the chronic maintenance period after percutaneous coronary intervention with DES, significantly reduced the risk of the composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC bleeding type 3 or greater. In patients requiring indefinite antiplatelet monotherapy after percutaneous coronary intervention, clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events.

Comment: Another interesting study published by Koo et al, compared aspirin monotherapy vs clopidogrel monotherapy as maintenance therapy in post-PCI patients. Over a period of 24 months, the primary endpoint like all-cause mortality, MI, Stroke, and major bleeding were 5.7% in clopidogrel group and 7.7% aspirin group with hazard ratio 0.73. This study challenges how we treat our patients following PCI. This also proves long-term efficacy of clopidogrel as monotherapy.

While there was no significant difference between the clopidogrel and aspirin groups in terms of all-cause death (1.9% vs 1.3%; P = .10), the number of events—cardiac or noncardiac—was greater, with 51 for clopidogrel and 36 for aspirin. This result was quite strange. Another interesting finding in this study was higher incidence of malignancies among clopidogrel group vs aspirin group. One of the reasons for this could be aspirin’s protective role especially in colorectal carcinomas. Another issue was that the study population were all Korean patients. The last issue is that the dose of aspirin used in this study, that is, 100 mg once daily. The usual dose used in India for post-PCI is 75 mg; therefore, the incidence of bleeding in the aspirin group of this study could have been higher than clopidogrel group.

In spite of multiple issues, this study is quite interesting and needs larger and longer studies for better understanding of the efficacy of aspirin vs clopidogrel in post-PCI patients.

Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases: JACC State-of-the-Art Review

J Am Coll Cardiol. 2021 Sep;78(13):1352-1371. PMID: 34556322, PMCID: PMC8528638, DOI: 10.1016/j.jacc.2021.07.042.
Marco Giuseppe Del Buono, Rocco A. Montone, and Massimiliano Camilli

Abstract

Coronary microvascular dysfunction (CMD) encompasses several pathogenetic mechanisms involving coronary microcirculation and plays a major role in determining myocardial ischemia in patients with angina without obstructive coronary artery disease, as well as in several other conditions, including obstructive coronary artery disease, nonischemic cardiomyopathies, takotsubo syndrome, and heart failure, especially the phenotype associated with preserved ejection fraction. Unfortunately, despite the identified pathophysiological and prognostic role of CMD in several conditions, to date, there is no specific treatment for CMD. Due to the emerging role of CMD as common denominator in different clinical phenotypes, additional research in this area is warranted to provide personalized treatments in this “garden variety” of patients. The purpose of this review is to describe the pathophysiologival mechanisms of CMD and its mechanistic and prognostic role across different cardiovascular diseases. We will also discuss diagnostic modalities and the potential therapeutic strategies resulting from recent clinical studies.

Comments: Angina in nonobstructive coronary artery disease (NOCAD) constitutes 40% of patients presenting with history of angina. The main mechanisms involved in the NOCAD angina are epicardial vasospasm and coronary microvascular dysfunction (impaired vasodilator reserve and minimal increase in microvascular resistance). These subsets...
of patients are known to have high cardiac morbidity and mortality. Individualized therapy directed at patient gives good results. But the lack of better diagnostics tools for identifying microvascular dysfunction creates ambiguity with regard to the diagnosis and affects proper treatment. This article encapsulates the basics of the disease and the modalities of diagnosis of CMD.

Smoking, hypertension, hyperlipidemia, and insulin resistance are the risk for the CMD along with atherosclerosis, left ventricular hypertrophy, and primary/secondary cardiomyopathies. These risk factors lead to microvascular remodeling (wall:lumen ratio) along with changes in physiology (imbalance of vasodilator v/s vasoconstrictors). A coronary flow reserve (CFR) can only be measured directly by invasive technique but noninvasive technique can detect CFR only indirectly. The techniques include PET imaging with tracer concentration (gold standard for noninvasive), MRI imaging with gadolinium detecting T1c intensity increase (requires further study), stress doppler echocardiography (requires highly trained user), and last one is computed tomography (still evolving). All these techniques measure CFR but not microvascular resistance. These tests are expensive, nonconclusive, and have questionable sensitivity/specificity. Invasive CFR measurement can be done by doppler crystal phasic flow velocity (not accurate) and other is bolus thermodilution technique (inter-user variability and use of adenosine). Adenosine can lead to hyperemia but it has multiple side-effects. There is lot of research on continuous thermodilution technique where the accuracy improves and it doesn’t require hyperemic agent. There is randomized controlled trial involving calcium channel blocker.

I personally feel this field of the cardiology is barely touched and has huge scope for further research in pathophysiology, diagnostics, and therapy.

Healthy Sleep Patterns and Risk of Incident Arrhythmias

*J Am Coll Cardiol.* 2021 Sep;78(12):1197-1207. PMID: 34531019, PMCID: PMC8454031, DOI: 10.1016/j.jacc.2021.07.023.

Xiang Li, Tao Zhou, Hao Ma, and Tao Huang

**Abstract**

**Background:** Emerging evidence has linked sleep behaviors with the risk of cardiac arrhythmias. The various sleep behaviors are typically correlated; however, most of the previous studies only focused on the individual sleep behavior, without considering the overall sleep patterns.

**Objectives:** The purpose of this study was to prospectively investigate the associations between a healthy sleep pattern with the risks of cardiac arrhythmias.

**Methods:** A total of 4,03,187 participants from UK Biobank were included. A healthy sleep pattern was defined by chronotype, sleep duration, insomnia, snoring, and daytime sleepiness. Weighted genetic risk score for atrial fibrillation was calculated.

**Results:** The healthy sleep pattern was significantly associated with lower risks of atrial fibrillation/flutter (AF) (hazard ratio [HR] comparing extreme categories: 0.71; 95% confidence interval [CI]: 0.64-0.80) and bradyarrhythmia (HR: 0.65; 95% CI: 0.54-0.77), but not ventricular arrhythmias, after adjustment for demographic, lifestyle, and genetic risk factors. Compared with individuals with a healthy sleep score of 0 to 1 (poor sleep group), those with a healthy sleep score of 5 had a 29% and 35% lower risk of developing AF and bradyarrhythmia, respectively. Additionally, the genetic predisposition to AF significantly modified the association of the healthy sleep pattern with the risk of AF ($P$ interaction = .017). The inverse association of the healthy sleep pattern with the risk of AF was stronger among those with a lower genetic risk of AF.

**Conclusions:** Our results indicate that a healthy sleep pattern is associated with lower risks of AF and bradyarrhythmia, independent of traditional risk factors, and the association with AF is modified by genetic susceptibility.

**Comments:** This particular article is important from the point of view of lifestyle changes which are beginning to affect the general population. The change in the sleep patterns among the Indians is a cause of worry. It has not only affected the well-known vulnerable groups such as software engineers who work according to Western time shifts or personnel from medical profession involved in patient care but also affected the younger generations who spend sleepless nights either for academic reasons or for recreational purposes.

This article prospectively looked into the relation between sleep pattern and occurrence of cardiac arrhythmias (atrial fibrillation/flutter/bradyarrhythmias). A sleep score was used here for the study which included factors such as sleep chronotype, sleep duration, lack of insomnia, snoring, and day-time sleepiness. Ideal score is 5, healthy score is 4 to 5, intermediate score is 2 to 3, and poor sleep score in 1 or less. The participants with healthy sleep score of 5 had lower incidence (29%) of AF when compared to poor sleep score; similarly, bradyarrhythmias were 35% lesser in healthy as compared to poor sleep score.

This article does pose interesting hypothesis which needs further validation. Some of the limitations of such large population-based studies are lack of details. There is no rigorous monitoring of the participants in such study. Therefore, let us not lose sleep over this study for now. But it is better to advise the patients to have good night’s sleep.
Empagliflozin in Heart Failure With a Preserved Ejection Fraction

*N Engl J Med.* 2021 Oct 14;385(16):1451-1461. August 27, 2021; DOI: 10.1056/NEJMoa2107038.
Stefan D. Anker, Javed Butler, Gerasimos Filippatos, et al., for the EMPEROR-Preserved Trial Investigators

**Abstract**

**Background:** Sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

**Methods:** In this double-blind trial, we randomly assigned 5,988 patients with class II-IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

**Results:** Over a median of 26.2 months, a primary outcome event occurred in 415 of 2,997 patients (13.8%) in the empagliflozin group and in 511 of 2,991 patients (17.1%) in the placebo group (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.69 to 0.90; *P* < .001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; HR, 0.73; 95% CI, 0.61 to 0.88; *P* < .001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

**Conclusions:** Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951. opens in new tab.)

**Comments:** HFpEF is a global health problem. HFpEF has high mortality and morbidity. There was no proven therapy till now for HFpEF. But with this trial now there will be a therapy for HFpEF with robust data. These set of molecules (SGLT2i) have consistently shown benefit in all types of heart failure.

One of the major determinants for mortality is number of hospitalizations due to heart failure. In this study, we see that primary endpoint like cardiovascular death, heart failure hospitalization, and total failure hospitalization reduced with 20% to 28-29% relative risk reduction. But the bottom line was that there was no significant improvement in mortality. One of the reasons which I see contributing to this result is presence of elderly population mostly in their 7th and 8th decade. Another explanation would be inadequate follow-up (2 years). Probably a longer study would have revealed a significant mortality benefit. After this study, the SGLT2i have fortified their position as a major cardiovascular risk modifying agents.

**ORCID iD**
Kartik Pandurang Jadhav [https://orcid.org/0000-0002-1253-1912](https://orcid.org/0000-0002-1253-1912)
Pankaj Jariwala [https://orcid.org/0000-0003-1747-9276](https://orcid.org/0000-0003-1747-9276)