

# Unpredictability of Ventricular Arrhythmias in Takotsubo Syndrome: Echocardiography to the Rescue!



Ventricular arrhythmias (VA), that is, frequent ventricular premature complexes, monomorphic ventricular tachycardia, both nonsustained and sustained, torsades de pointes, ventricular fibrillation, and sudden cardiac death (SCD), are known to be frequent in patients with takotsubo syndrome (TTS), and are characterized by their unpredictability in regards to the timing of their occurrence during hospitalization.<sup>1–6</sup> Also, well known is the association of such VA with alterations of repolarization (negative T waves) and prolonged corrected QT-interval by the Bazett formula (QTc), although VA are seen in patients with or without prolongation of the QTc. Since mortality is ‘higher in patients with TTS, than without VA, electrocardiographic (ECG) telemetry monitoring for early detection of QTc prolongation and VA throughout hospitalization, and ECG recordings at follow-up has been recommended.<sup>1–6</sup> In addition better characterization of ECG and other correlates of the VA needs to be instituted for unraveling the mechanisms underlying VA in TTS.<sup>7</sup>

Congenital and acquired long QTc is also associated with VA and SCD, and a recent validation study of patients with the long QTc syndrome (LQTS)<sup>8</sup> found that the electromechanical window (EMW), calculated as the difference between the interval from the onset of the ECG QRS complexes to the aortic valve closure midline, as derived by the continuous wave Doppler echocardiogram, and the ECG-derived QT for the same beat, was *negative*, while it was *positive* in control subjects of similar age and gender distribution. Furthermore, the EMW was *more negative* in symptomatic than asymptomatic patients with the LQTS. In a ROC analysis, EMW *outperformed the QTc*, as an identifier of patients with previous life-threatening VA and SCD in the patients with LQTS.<sup>8</sup> In addition, the authors showed the feasibility/reproducibility of routine calculation of EMW by sonographers, after training. Consequently, the authors’

institution adopted the routine reporting of EMW for their patients with LQTS, and the authors expressed the opinion that “future studies should examine the value of EMW in patients with other types of inherited arrhythmias and cardiomyopathies.”<sup>8</sup>

EMW has been considered in the study/management of patients with coronary artery disease, mitral valve prolapse, and other cardiac diseases.<sup>8</sup> TTS shares the profile of LQTS as an “electrical disease” in association with cardiomyopathic features.<sup>1–8</sup> Accordingly, it is worth considering the adoption of the EMW in the management of patients with TTS during hospitalization. To this effect, clinicians and workers in the TTS field, should look carefully on the feasibility and usefulness of the echocardiography-derived EMW calculation for their patients and research subjects; it is conceivable that EMW may be a *better prognosticator* of VA in patients with TTS, than the currently exclusive focusing on a prolonged QT.

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16 December 2020

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## Meta-Analysis Comparing Ticagrelor or Prasugrel Versus Clopidogrel in Patients Undergoing Elective Percutaneous Coronary Intervention



Ticagrelor and Prasugrel are more potent antiplatelet agents via their inhibition of P2Y12 receptors compared to clopidogrel, and they have become the mainstay of antiplatelet therapy in patients with acute coronary syndrome since Platelet Inhibition and Patient Outcomes (PLATO)<sup>1</sup> and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel –Thrombolysis in Myocardial Infarction (TRITON–TIMI 38 TRITON–TIMI 38)<sup>2</sup> trials, respectively. However, their use has not been well established in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention (PCI). The recently published ALPHEUS trial (Assessment of Loading With the P2Y12 Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting)<sup>3</sup> failed to demonstrate Ticagrelor’s superiority over Clopidogrel in reducing periprocedural myocardial infarction or major bleeding after elective PCI, with an increase in the rate of minor bleeding at 30 days.

The current meta-analysis aimed to compare the safety and efficacy of potent P2Y12 inhibitors (pP2Y12-I) versus clopidogrel in patients with coronary artery disease undergoing elective PCI. We searched electronic databases for randomized clinical trials

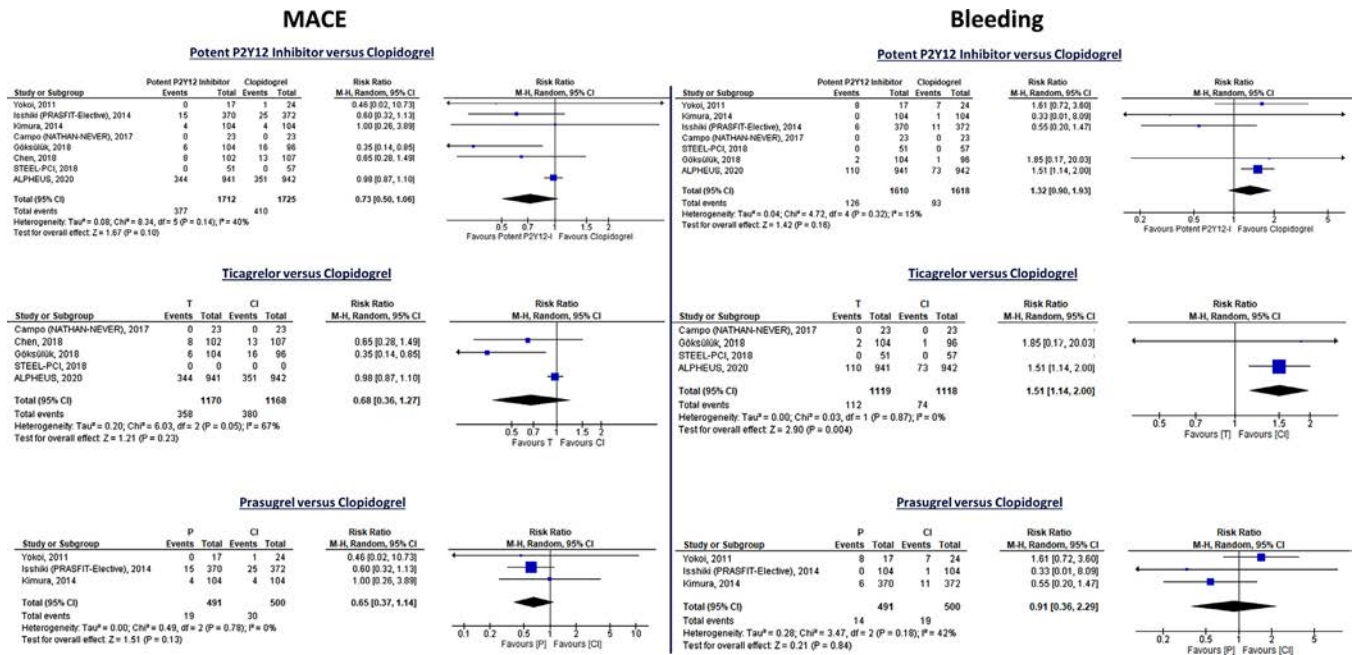


Figure 1. Comparison of the outcomes between potent P2Y12 inhibitors and Clopidogrel, and subgroup analysis of the outcomes between Ticagrelor and Clopidogrel, and Prasugrel and Clopidogrel. MACE; major adverse cardiovascular events.

reporting the outcomes of clopidogrel use compared to pP2Y12-I in patients undergoing elective PCI. The primary outcome of interest was major adverse cardiovascular events, a composite of all-cause mortality, myocardial infarction, and thromboembolic events. The safety outcome was a composite of major and minor bleeding. Two investigators (MS and SK) screened the trials and extracted the data independently. Results were pooled using the random effect model. All statistical analyses were conducted with RevMan version 5.3 Windows.

A total of 8 RCTs<sup>3–10</sup> involving 2,338 patients (1,712 in pP2Y12-I arm and 1,725 in clopidogrel arm, 76.9% male and mean age  $65.6 \pm 9.1$  years) were included. Outcomes were recorded during a median follow up of one month. Results are reported as risk ratio (RR) and 95% confidence interval (CI).

There was no difference between pP2Y12-I and clopidogrel in major adverse cardiovascular events (RR 0.73, 95% CI 0.5 to 1.06,  $p = 0.14$ ) or bleeding events (RR 1.32, 95% CI 0.9 to 1.93,  $p = 0.32$ ). Subgroup analysis of outcomes between ticagrelor and clopidogrel, and prasugrel and clopidogrel failed to demonstrate any significant difference except for bleeding events, which were

more common with ticagrelor compared with clopidogrel (RR 1.51, 95%CI 1.14 to 2.00,  $p = 0.004$ ) (Figure 1).

Our results demonstrate that in patients undergoing elective PCI, pP2Y12-I and Clopidogrel resulted in comparable outcomes. The limitations of this meta-analysis include inter-study variability, lack of patient-level data, differences between drug loading and maintenance doses, and a short median follow-up time. Unlike acute coronary syndrome, existing evidence does not support the preferential use of a more potent agent like Ticagrelor or Prasugrel over Clopidogrel for elective PCI patients.

## Disclosures

The authors have no conflicts of interest to disclose.

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13 December 2020

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## Prevalence of In-Hospital Stroke Comparing MitraClip and Transcatheter Aortic Valve Implantation



Transcatheter aortic valve implantation (TAVI) and mitralclip (MC) are increasingly utilized for the treatment of aortic stenosis and mitral regurgitation, respectively. Perioperative stroke is one of the most serious complications following TAVI given the valve calcification and possible embolization during valve implantation, and thus ongoing trials are assessing the use of embolic protection device following TAVI. On the other hand, no such trials are being

conducted on MC as the evidence of stroke following MC is lacking and MC does not share the same etiology with TAVI.<sup>1</sup>

We studied the risk of stroke after TAVI and MC procedures from the Nationwide Readmission Database between January 2014 and December 2017.<sup>2</sup> Patients who underwent either TAVI or MC were selected using the appropriate ICD-9 or ICD-10 procedure codes. Among included patients, the occurrence of in-hospital stroke and the occurrence of in-hospital stroke within any readmission within 30 days were assessed. We performed chi-square and multivariable logistic regression to compare baseline characteristics and the rate of stroke after TAVI and MC procedures. Odds ratios and the 95% confidence intervals were used to report the risk of in-hospital stroke. All statistical analyses were performed by using the weighted values, hospital clusters, and strata of observations as provided by the Nationwide Readmission Database to measure national estimates. All statistical analyses were conducted using SPSS version 23. A 2-sided value of  $p < 0.05$  was set for statistical significance.

A total of 148,645 and 15,570 patients underwent TAVI and MC, respectively. Most procedures were performed in high volume hospitals and teaching hospitals. Compared with MC patients, those who underwent TAVI were more likely to have hypertension, diabetes mellitus, dyslipidemia, and a history of a stroke/TIA. However, patients who underwent MC were significantly more likely to have congestive heart failure, and atrial fibrillation. During the study period, 2,974 (2%) TAVI patients and 169 (1.1%) MC patients developed in-hospital stroke ( $p < 0.001$ ). Rates of in-hospital stroke following TAVI and MC did not differ based on the hospital procedural volume. A total of 843 (0.6%) TAVI patients and 92 (0.7%) MC patients developed stroke within 30-days following discharge ( $p = 0.658$ ). Table 1 summarizes the baseline characteristics and outcomes. After adjusting for age and the presence of atrial fibrillation, congestive heart failure, hypertension, CHA2DS2-VASc score, and a history of stroke and/or TIA, TAVI was still

associated with a higher risk of in-hospital stroke when compared with MC (OR = 1.866, 95% CI [1.595 to 2.184],  $p < 0.001$ ).

This study demonstrates that in-hospital stroke rates are significantly higher among patients undergoing TAVI than those undergoing MC. Previous studies using the American College of Cardiology and/or Society of Thoracic Surgery Transcatheter Valve Therapies registry have reported similar rates of after-procedural stroke rates for TAVI (2.3%) and MC (0.7%) as our analysis.<sup>3,4</sup> We cannot accurately specify the cause of relatively lower stroke rates in MC but we hypothesize that this may be because of the different underlying etiologies and thus mechanism of stroke. MC patients, specifically those with atrial fibrillation where strokes are more likely to be related to thrombus formation, may benefit more from anticoagulation than protection devices, decreasing the incentive to experiment these devices with MC procedures.

Another significant result of our analysis is that the penetration of MC was similar to TAVI in different hospital settings such as low vs. high procedural volume hospitals with no difference in stroke rates among hospitals based on their procedural volume. It is essential to recognize that procedural volume was not associated with any differences in stroke rate for TAVI or MC, a finding noted by other investigators.<sup>5</sup>

Limitations of this study include its retrospective nature as well as the limitations of the database itself that does not include the physical examination, imaging, procedural details, antithrombotic treatment, or long term follow up data.

Our study demonstrates that the MC procedure has a low but not negligible stroke rate.

## Disclosure

The authors declare no conflict of interest.

## Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could