

BRIEF COMMUNICATION

# Platelet Quiescence in Patients With Acute Coronary Syndrome Undergoing Coronary Artery Bypass Graft Surgery

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**BACKGROUND:** The optimal antiplatelet strategy for patients with acute coronary syndromes who require coronary artery bypass surgery remains unclear. While a more potent antiplatelet regimen will predispose to perioperative bleeding, it is hypothesized that through “platelet quiescence,” ischemic protection conferred by such therapy may provide a net clinical benefit.

**METHODS AND RESULTS:** We compared patients undergoing coronary artery bypass surgery who were treated with a more potent antiplatelet inhibition strategy with those with a less potent inhibition through a meta-analysis. The primary outcome was all-cause mortality after bypass surgery. The analysis identified 4 studies in which the antiplatelet regimen was randomized and 6 studies that were nonrandomized. Combining all studies, there was an overall higher mortality with weaker strategies compared with more potent strategies (odds ratio, 1.38; 95% CI, 1.03–1.85;  $P=0.03$ ).

**CONCLUSIONS:** Our findings support the concept of platelet quiescence, in reducing mortality for patients with acute coronary syndrome requiring coronary artery bypass surgery. This suggests the routine up-front use of potent antiplatelet regimens in acute coronary syndrome, irrespective of likelihood of coronary artery bypass graft.

**Key Words:** acute coronary syndrome ■ antiplatelet ■ coronary artery bypass graft surgery

Patients with acute coronary syndrome (ACS) benefit from antiplatelet therapy, including platelet P2Y<sub>12</sub> receptor inhibitors and glycoprotein IIb/IIIa inhibitors; however, in subgroups requiring coronary artery bypass graft (CABG) surgery, no dedicated randomized study exists. The concept of “platelet quiescence,” the hypothesis of the benefit of residual platelet inhibition extending to the time of CABG and conferring ischemic protection, is long-standing.<sup>1</sup> Clinically, this possible benefit must be balanced against the risk of antiplatelet drugs predisposing to perioperative bleeding and its sequelae. To explore the hypothesis of more potent platelet inhibition providing net clinical benefit, we conducted a systematic review and meta-analysis of studies of all antiplatelet agents involving patients admitted with ACS who underwent CABG. To

establish overall balance of ischemic versus bleeding risk, we compared those treated with a more potent platelet inhibition strategy with those with a less potent inhibition to determine effects on all-cause mortality.

## METHODS

A search strategy, using Ovid MEDLINE, EMBASE, Cochrane, Google Scholar, and PubMed databases, included the following search terms: *platelet inhibitor, ADP antagonist, P2Y<sub>12</sub> inhibitor, ticagrelor, clopidogrel, aspirin, prasugrel, glycoprotein IIb/IIIa inhibitor, mortality, death, major adverse cardiovascular events, coronary artery bypass, and acute coronary syndrome*. No limit to the start date was applied, with the search conducted up to April 1, 2019. Studies were included

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if there was documentation of all-cause mortality rate. We included comparative studies of case-control design (randomized control trials and observational studies). Only studies with  $\geq 10$  patients were considered eligible. Inclusion was restricted to publications in the English language or when translation of the foreign language publications was provided. When data were reported from overlapping study samples (eg, multiple publications from the same group), the most recent study or the one with the highest number of patients was included in the analysis. Single case reports and previous systematic reviews were not included. Studies that included multiple antiplatelet agents in 1 arm and compared them with a single antiplatelet strategy were excluded. We hand searched the references cited in the previous reviews and important articles. Two authors (K.S. and D.S.) screened titles and abstracts independently, followed by full-text review and data extraction from selected studies using a standardized, pilot-tested extraction template. The following data were extracted: study characteristics (author, country, study design, study population, number of participants, and objective of the study), participant characteristics (age and sex), clinical characteristics (acute coronary syndrome, type of antiplatelet use, type of glycoprotein IIb/IIIa inhibitor use, and whether it was a substudy of randomized trial or not), 30-day mortality, and major adverse cardiovascular end points. The primary outcome of the study was all-cause mortality. Risk estimates are presented using odds ratios (ORs; calculated using raw frequency data), with 95% CI. Heterogeneity between studies was assessed by a combination of the  $I^2$  point estimate, Cochran's Q test, and observation of the data for each outcome. To obtain meta-analytic ORs and 95% CIs, a random-effects model using number of events and total sample size was used, which provides more conservative results than a fixed-effects model and assumes that each sample comes from a different population and that the effects in these populations may also differ. In cases of heterogeneity (defined as  $I^2 > 40\%$ ), random-effects models were used. The reported  $P$  values are 2-tailed, with continuity correction. Significant interaction between variables was considered when  $P$  value was  $< 0.05$ . All calculations were performed using Review Manager software, version 5.2. The authors declare that all supporting data are publicly available or within the article. No patient-level data were used, and all original studies included in the meta-analysis had local ethics approval.

## RESULTS

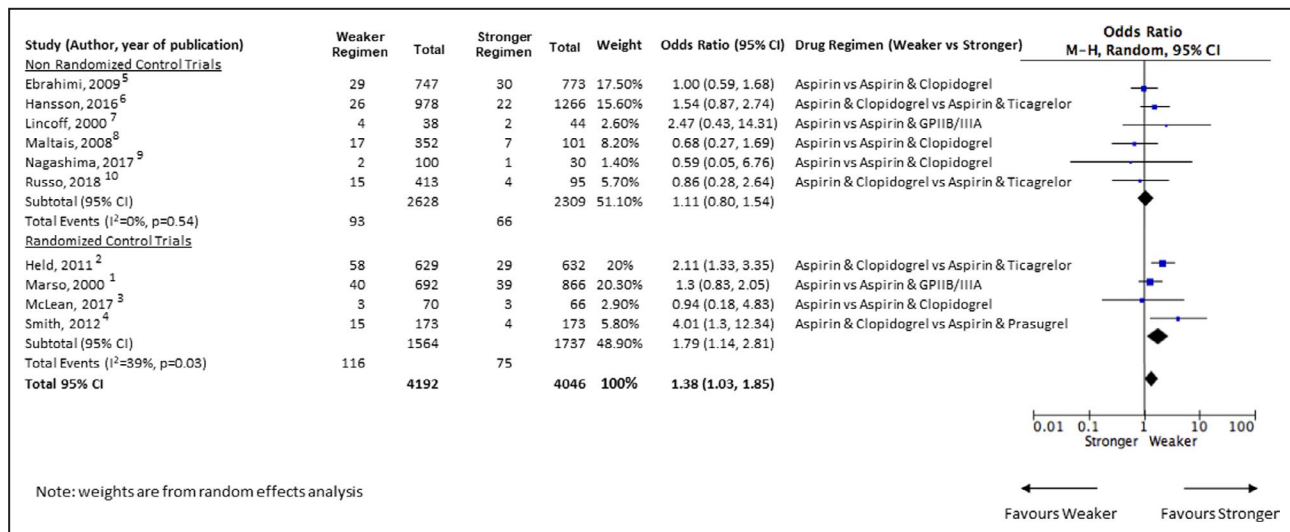
There was good interrater agreement with a Cohen's kappa of 0.811 (95% CI, 0.46–1.00). Although not unexpected, there were no studies in which the antiplatelet

regimen was randomized after patients were found to require CABG. The analysis identified 4 studies<sup>1–4</sup> in which the antiplatelet regimen was randomized and 6 studies<sup>5–10</sup> in which they were nonrandomized (Figure). Notably, for the 4 randomized controlled trials, the groups being compared for the present study are subgroups of the patients in the randomized controlled trial and not randomized within themselves across the 2 subgroups. Consequentially, all the identified studies were essentially observational studies. Grouped by a more potent antiplatelet strategy as the intervention arm, there were 2 studies using glycoprotein IIb/IIIa inhibitors versus aspirin,<sup>1,7</sup> 4 studies using clopidogrel versus aspirin,<sup>3,5,8,9</sup> and 4 using novel P2Y12 inhibitors (ticagrelor or prasugrel) versus clopidogrel.<sup>2,4,6,10</sup> Analysis of the nonrandomized studies showed a directional trend toward increased mortality with weaker antiplatelet strategies (OR, 1.11; 95% CI, 0.8–1.54;  $P=0.54$ ); analysis of the randomized trials showed that strategies with weaker antiplatelet effects were associated with an increase in mortality (OR, 1.79; 95% CI, 1.14–2.81;  $P=0.01$ ). Combining all studies (Figure), there was an overall higher mortality with weaker strategies compared with more potent strategies (OR, 1.38; 95% CI, 1.03–1.85;  $P=0.03$ ).

## DISCUSSION

Our meta-analysis demonstrates that more potent antiplatelet inhibition when compared with a weaker antiplatelet strategy before CABG reduces mortality in patients with ACS. Conceptually, this supports the notion that inducing platelet quiescence results in overall clinical benefit. Mechanistic explanations include early pacification of plaque rupture in preventing thrombotic sequelae, increased graft patency, and decreased platelet activation during cardiopulmonary bypass.<sup>11</sup> For ticagrelor, its fast offset and reversibility may increase platelet availability postoperatively to minimize bleeding. With respect to glycoprotein IIb/IIIa inhibitors, fibrinogen binding also preserves platelet function postoperatively.<sup>12</sup>

Importantly, antiplatelet therapies (except aspirin) in these studies were stopped before CABG. Current guidelines recommend ideal withdrawal of clopidogrel or ticagrelor for 5 days and prasugrel for 7 days before CABG, predicated upon the stated intervals in randomized studies in which the drugs were studied, which in turn were based on drug pharmacokinetics. It is notable that in the PLATO (Platelet Inhibition and Patient Outcomes) trial's surgical cohort, there appears to be a mortality benefit for ticagrelor over clopidogrel among patients with discontinuation between 1 and 4 days before CABG, when ticagrelor-mediated platelet inhibition is still strong; no difference was observed



**Figure** Forest plot of all-cause perioperative mortality among patients with acute coronary syndrome undergoing coronary artery bypass graft surgery assigned to stronger vs weaker antiplatelet regimens.

The blue marker represents the hazard ratio estimate for the study. The box around the marker corresponds to the weight of study in the random-effects model. The diamond-shaped box is the summary estimate from the random-effects model. The horizontal black lines denote 95% CIs of hazard ratios of each study. The black vertical line is the line of no effect difference. M-H indicates Mantel-Haenszel analysis.

for those with CABG beyond 4 days, but only 20% of patients underwent surgery within 48 hours after the last dose of ticagrelor.<sup>2</sup> This observation is further evidence in support of the benefits of early platelet quiescence and brings forth the clinical dilemma of the optimal timing between antiplatelet cessation and CABG. Indeed, the ability to perform earlier revascularization and avoidance of a guideline suggested that a 5- to 7-day delay in ACS may be a significant factor in mortality reduction. The ongoing RAPID CABG (Timing of Coronary Artery Bypass Surgery Among Patients With Acute Coronary Syndromes Initially on Ticagrelor) randomized trial where patients with ACS are randomized to early (2–3 days) versus delayed (5–7 days) CABG after ticagrelor discontinuation (ClinicalTrials.gov, NCT02668562) will further elucidate the safety and potential benefits of antiplatelet therapy in this setting.

A limitation of our study is that the antiplatelet regimens from the studies were not randomized uniquely on the basis of patients requiring CABG. Not surprisingly, however, there are no studies in which patients were randomized when the need for surgery was known. Finally, ORs were calculated from raw frequency data for mortality, as adjusted mortality data were not available for all studies.

## CONCLUSIONS

Taken collectively, our meta-analysis supports the concept of platelet quiescence in reducing mortality for patients with ACS requiring CABG. Hence, these data

support the routine up-front use of potent antiplatelet regimens in ACS, irrespective of likelihood of CABG. Future data may further provide guidance on optimal timing of CABG in these scenarios.

## ARTICLE INFORMATION

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