Current treatment of acute myocardial infarction complicated by cardiogenic shock (CS) or resuscitated cardiac arrest (CA) (whether in hospital or out of hospital) almost always includes percutaneous coronary intervention (PCI) as studies have shown improved in-hospital and long-term outcomes with PCI compared with medical therapy alone.\(^1\)\(^-\)\(^3\) Use of dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor is considered standard of care with PCI regardless of the circumstance, unless the patient is at a very high risk of bleeding, although the post-PCI duration of therapy is often debated.\(^3\) There are 4 oral P2Y12 receptor inhibitors currently in use in the United States, with clopidogrel dominating the market at approximately 60%, ticagrelor accounting for approximately 24% of the market, and prasugrel having approximately 17% of the market, with ticlopidine rarely used at less than 5% of the market.\(^4\) For the decade from 1999 to 2009, only clopidogrel and ticlopidine were available, and clopidogrel was almost exclusively used because of fewer life-threatening adverse effects and better gastrointestinal tolerability than ticlopidine.

Clopidogrel has mild to moderate potency in inhibiting the ADP pathway of platelet aggregation with 30% to 40% incidence of not achieving adequate platelet inhibition.\(^5\) Thus, more potent compounds, ticagrelor and prasugrel, were developed, with pharmacodynamic trials demonstrating more potent inhibition of ADP-induced platelet aggregation and large clinical trials showing improved efficacy with ticagrelor and prasugrel over clopidogrel, albeit at a cost of increased non–coronary artery bypass grafting bleeding in acute coronary syndrome (ACS) patients, most of whom underwent PCI.\(^6\)\(^-\)\(^7\) However, the most severe ACS patients, those who had CS or survived CA, were not included in these studies.

In this issue of *Mayo Clinic Proceedings*, Patlolla et al\(^\text{8}\) attempt to determine if more potent antiplatelet inhibition with prasugrel or ticagrelor is more effective at improving outcomes than clopidogrel in patients with CS or CA. These investigators did an exhaustive search of the literature to perform a meta-analysis of these agents in this patient population using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors found only 8 studies that fit their criteria of having a cohort of adult patients with acute myocardial infarction complicated by CS or CA, treated with dual antiplatelet therapy comparing clopidogrel to prasugrel or ticagrelor, and reporting mortality (early or late), bleeding events, or stent thrombosis. In their analysis, treatment with prasugrel or ticagrelor (405 patients [36.8%]) resulted in lower rates of in-hospital or 30-day mortality (odds ratio [OR], 0.60; 95% CI, 0.45 to 0.81) as well as lower rates of 1-year mortality (OR, 0.51; 95% CI, 0.36 to 0.71) compared with treatment with clopidogrel (605 patients [63.2%]). Interestingly, there was no significant increase in bleeding events between clopidogrel and the more potent P2Y12 receptor inhibitors (OR, 1.2; 95% CI, 0.71 to 2.06), although there were numerically more bleeding events in the patients treated with prasugrel or ticagrelor. There was no significant difference in stent thrombosis between the 2 cohorts. There are limitations to their study that limit the interpretation of their results. First, all but 1 study was observational. Therefore, many confounders exist in patient selection that may account for the results, particularly...
operator bias in selection of patients that the operators believe would benefit from the more potent P2Y\textsubscript{12} receptor inhibitors. Second, there are major differences between patients with CS and CA. Frequently, patients who attain return of spontaneous circulation after CA will have normal perfusion of their organs, particularly after successful revascularization, such that the metabolic anomalies caused by the hypoperfusion seen in CS are not present. This can result in better metabolism of clopidogrel and decrease the difference in platelet inhibition from the more potent agents. This hypothetical argument is supported by data presented in Figure 1 in the article by Patlolla, where there is clear reduction of events by the more potent P2Y\textsubscript{12} receptor inhibitors in the studies of patients with CS, for whom prasugrel or ticagrelor may have an advantage, but no observable difference between clopidogrel and the more potent P2Y\textsubscript{12} receptor inhibitors in the studies of CA.

We should not be surprised by the results. The clopidogrel molecule is a parent compound that must undergo metabolic steps in the liver using cytochrome P450 enzymes, predominantly CYP2C19. Under normal conditions, there is significant competition for the parent clopidogrel compound by esterases in the gut wall that create an inactive intermediate molecule, leaving only 15% of the parent compound available to be converted to the active metabolite.\textsuperscript{9,10} Anything that would alter this balance, such as liver dysfunction from hypoperfusion in CA or CS, will result in less active metabolite available for inhibiting the P2Y\textsubscript{12} receptor. Prasugrel, although also needing a 2-step conversion from the parent compound to the active metabolite, has the first step conversion in the gut by esterases in the intestinal wall and the second step in the liver by multiple cytochrome P450 enzymes.\textsuperscript{10} Ticagrelor's parent compound is active without needing to be metabolized but also has an active metabolite from a 1-step process.\textsuperscript{11} Therefore, both ticagrelor and prasugrel have a more efficient process leading to platelet inhibition, which may not be as severely affected by hepatic hypoperfusion.

Recent studies have demonstrated that platelet aggregation may be enhanced in low-flow states and hypothermia, now routine in treatment of resuscitated CA.\textsuperscript{12} In addition, gastric motility is decreased in these CS and CA patients, which slows down the absorption of oral therapeutics.\textsuperscript{12} When this enhanced platelet reactivity is combined with the low-flow state in all patients in CS and most patients with resuscitated CA, the environment is right for enhanced thrombus formation. However, a study by Ibrahim et al\textsuperscript{13} showed increased platelet inhibition and less high on-treatment platelet reactivity with prasugrel or ticagrelor in patients after CA treated with hypothermia, giving biological plausibility to the findings by Patlolla et al. The unknown factor in reducing early events in the CS/CA patient population is whether an intravenous drug such as cangrelor early in treatment followed by a transition to an oral agent would provide better results as cangrelor does not rely on gastrointestinal absorption or hepatic metabolism to inhibit platelets.

The take-home message from this paper is that within limits discussed, prasugrel or ticagrelor should be preferred to clopidogrel in this very high-risk population. Currently, the major impediments in choosing 1 of these agents over clopidogrel are cost and inertia. Ticagrelor and prasugrel were approved for market use more than 10 years ago and so are not really new (therefore, the word “new” in relation to these drugs was not used in this editorial), but they are more potent than clopidogrel. Now that prasugrel is generic and ticagrelor will soon be generic, the price differential should no longer play a role in the decision-making of which agent to use in these very high-risk patients. Overcoming inertia will be more challenging. It has been more than a decade since prasugrel and ticagrelor received market approval, yet despite all the data demonstrating better outcomes with these agents and guidelines recommending their use over clopidogrel,\textsuperscript{3} most ACS patients undergoing PCI are still treated with clopidogrel. It is extremely unlikely that randomized trials of these agents in CA or CS...
patients will be performed in the future because of difficulty in enrollment, as we have seen in other shock trials, and the large expense for what would be very little gain in knowledge to what we already know to justify the expense of such a clinical trial. Studies such as the one by Patlolla et al are useful in guiding clinicians in the direction of the best medical care for their patients.

POTENTIAL COMPETING INTERESTS
Dr Effron has equity in and receives a pension from Eli Lilly and Company.

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