Primary percutaneous coronary intervention (PCI) is the reperfusion therapy of choice for patients with acute myocardial infarction, provided that it is available and can be performed effectively and efficiently. Nine to 12 months of dual-antiplatelet therapy (DAPT) for patients presenting with acute coronary syndrome (ACS) is recommended regardless of whether revascularization is undertaken, although the use of a drug-eluting stent (DES) necessitates a plan for 1 year of uninterrupted DAPT, according to current guidelines. Whereas aspirin has been a mainstay of therapy, the second antiplatelet agent of a dual-antiplatelet regimen has evolved over the years from ticlopidine to clopidogrel, and now includes the options of prasugrel and ticagrelor.

THE CASE FOR DAPT AFTER CORONARY STENTING

In the Stent Anticoagulation Restenosis Study, DAPT in the form of aspirin plus ticlopidine was found to be superior to aspirin plus warfarin or aspirin alone in reducing the occurrence of stent thrombosis in elective PCI patients. In clinical practice, ticlopidine was found to be associated with neutropenia and/or thrombocytopenia, a finding that was infrequent but concerning enough to require periodic monitoring of blood counts while on therapy. When clopidogrel, which for practical purposes appeared to be better tolerated than and as effective as ticlopidine, became commercially available, it replaced ticlopidine.

Whether warfarin with single-antiplatelet therapy after coronary stenting is safe was readdressed from a slightly different perspective in the WOEST trial. The study demonstrated that in patients on chronic warfarin undergoing intracoronary stenting, concomitant treatment with clopidogrel rather than clopidogrel plus aspirin was, not surprisingly, associated with lower bleeding rates without an increase in ischemic events, although the study was not powered to detect differences in the latter in a sample size of 573 patients.

The CURE and PCI CURE studies established the role of prolonged (up to 12 months) DAPT in ACS patients, without and with PCI, respectively. The current PCI guidelines recommend 12 months of uninterrupted DAPT after stenting in ACS patients regardless of whether a bare-metal stent (BMS) or DES was utilized. DAPT for 1 year is mandated for DES patients; in BMS patients who may have a contraindication to prolonged DAPT (hence the reason for selection of BMS rather than DES in the first place), 30 days of therapy is recommended, with a minimum of 2 weeks, if 9 to 12 months cannot be completed. Notably, the clinical benefit of preloading with clopidogrel prior to arrival in the catheterization laboratory, although standard in clinical practice, remains somewhat uncertain. A 300-mg loading dose of clopidogrel demonstrates significant platelet inhibition at approximately 5 hours, whereas 600 mg achieves similar effects within 90 to 120 minutes.

With the availability of clopidogrel in generic formulation, drug cost has been largely eliminated as an obstacle to prescribing prolonged DAPT in ACS and DES patients. Nonetheless, the potential limitations of clopidogrel have included variable platelet inhibition, relatively slow onset of action, and possible drug interactions, notably with omeprazole. Reloading of patients with ST-segment elevation myocardial infarction (STEMI) with clopidogrel with or without short-term twice-daily dosing may potentially reduce adverse events, although the strength of the data has been insufficient to cause a major practice shift thus far. The addition of a third antiplatelet agent to the regimen, namely cilostazol, may improve...
measures of platelet aggression, and in a single-center trial of ACS patients improves outcomes compared to clopidogrel plus aspirin.12,13 These issues have opened the door for investigation and the use of other antiplatelet agents, namely prasugrel and ticagrelor.

**THE CASE FOR PRASUGREL**

Patients treated with clopidogrel with low on-treatment platelet inhibition are at increased risk for cardiovascular events.14 Variability in the bioavailability of clopidogrel may relate to several factors, including age, body mass index, and the presence of diabetes mellitus or dyslipidemia. There has been tremendous interest in genetic polymorphisms that alter clopidogrel metabolism, notably of CYP2C19, which have perhaps overshadowed these factors, and have garnered significant attention as the possible dominant etiology for observed reductions in clopidogrel bioavailability.15

Although a black box warning issued by the FDA recommends alternatives to clopidogrel when such polymorphisms exist, there is as of yet insufficient data to recommend routine genetic testing looking for these polymorphisms. Similar to clopidogrel, prasugrel is a thienopyridine P2Y12 ADP receptor antagonist; both are prodrugs that require intestinal absorption and metabolism to active metabolites by cytochrome P450 enzymes. Prasugrel, however, requires only a single cytochrome P-dependent step to transform into the active metabolite, in contrast to multiple steps for clopidogrel. In addition, prasugrel does not appear to be affected by reduced-function cytochrome P alleles.16,17

The TRITON TIMI 38 study randomized 13,608 ACS patients undergoing PCI between clopidogrel (300-mg loading dose and 75-mg daily dose) and prasugrel (60-mg loading dose and 10-mg daily dose) for 6 to 15 months. A significant relative risk reduction of 19% in the composite endpoint of cardiovascular death, myocardial infarction, and nonfatal myocardial infarction, and nonfatal stroke was observed in the prasugrel-treated patients; a reduction in urgent target vessel revascularization and stent thrombosis was also observed. Major bleeding, as well as life-threatening and fatal bleeding, however, was also more frequent in the prasugrel arm. Of particular note, patients with previous stroke or transient ischemic attack had excess hazard when treated with prasugrel; patients older than 75 years of age or < 60 kg in body weight did not benefit from prasugrel compared to clopidogrel.18

Bleeding in patients requiring coronary artery bypass grafting was substantially higher with prasugrel.

Patients presenting with STEMI in the TRITON TIMI 38 trial comprised 26% of the study cohort and constituted a prespecified subgroup analysis that was not powered to assess clinical endpoints in the STEMI cohort alone. The reductions in ischemic endpoints demonstrated in the main trial were again noted; however, bleeding rates were comparable between the two study arms, in contrast to the overall study findings.19

**THE CASE FOR TICAGRELOR**

Ticagrelor is a non-thienopyridine P2Y12 inhibitor; it is also unique in that it binds reversibly to the ADP receptor. This may be logistically advantageous insofar as if DAPT needs to be stopped for some reason, the offset of action may be on the order of approximately 3 days (although the packaging still recommends 5 days); however, this may also be a potential disadvantage with regard to patient compliance, because it requires twice-daily dosing.20

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was compared to clopidogrel in a broad population of non-ST elevation ACS patients (regardless of the intent to revascularize) and ST-elevation ACS patients with planned primary PCI. Accordingly, an invasive strategy was planned for 13,408 of 18,624 patients.21 Compared to clopidogrel in the PCI group, ticagrelor (180-mg loading dose, 90-mg twice-daily maintenance over 6 to 12 months) reduced the composite of cardiovascular death, myocardial infarction, or stroke by 16% (relative risk reduction); secondary endpoints of cardiovascular and all-cause death were also lower in the ticagrelor-treated arm, without increasing bleeding rates using multiple definitions. Stent thrombosis was also reduced.

In the 7,544 STEMI patients, a similar magnitude of benefit with use of ticagrelor was observed, without an increase in major bleeding; however, stroke and a combination of nonprocedural major and minor bleeding were more common with ticagrelor.22 Dyspnea was observed in follow-up more commonly with ticagrelor but was rarely a cause for drug discontinuation. Additionally, it should be noted that the primary endpoint occurred more commonly when aspirin dose was > 300 mg daily, such that ticagrelor appeared worse than clopidogrel when used with high-dose aspirin, an effect that was only observed in the North American patient cohort. Nonetheless, when ticagrelor is utilized as part of a DAPT regimen, high-dose aspirin should be avoided, and aspirin at less than 100 mg/d is the preferred dose.

**WHICH DRUG SHOULD WE USE?**

Each ADP receptor antagonist that is currently available has advantages and limitations that need to be individualized. Clopidogrel has been used for many years...
across a broad spectrum of patient and lesion types, is familiar to prescribers/interventionists, has convenient once-daily dosing, and, importantly, is now available as a generic formulation, which substantially reduces the cost of use. Concerns center around the relatively slow onset of effect relative to the need for rapid antiplatelet effect in STEMI as well as variability of bioavailability, which is perceived to be at least in part related to genetic polymorphisms affecting conversion to the active metabolite; however, the prevalence of such polymorphisms in the population is far more frequent than the occurrence of stent thrombosis.

Prasugrel and ticagrelor have only been tested and approved for use in ACS patients. In that context, both agents reduce ischemic endpoints, including stent thrombosis, compared to clopidogrel. While it is accepted that both of these agents have a rapid onset of potent antiplatelet effect, such pharmacodynamics have been previously reported only in healthy volunteers or patients with stable coronary disease. A recent small study in STEMI patients suggests less rapid onset of action and much more heterogeneity in antiplatelet effect than previously thought. These data, combined with the equivocal data regarding the clinical benefit of clopidogrel loading, may suggest that the benefit in ischemic event reduction with prasugrel and ticagrelor over clopidogrel may not necessarily relate to the perceived rapidity of effect of prasugrel and ticagrelor.

With prasugrel, bleeding rates are higher than with clopidogrel (although this was not shown in the STEMI subset of TRITON TIMI 38), and the hazard or lack of efficacy in patients with previous cerebrovascular events, in the elderly, and in those with low body weight makes it challenging to institute this agent in an algorithmic STEMI process pathway, where success depends heavily on a broadly applicable protocol and errors are more likely to occur when the process/regimen is varied based on individual patient characteristics.

Ticagrelor demonstrates reversible binding and has not been associated with excess bleeding compared to clopidogrel; the main logistic concerns would be the need for twice-daily dosing and whether patients may have greater difficulty with drug compliance compared to a once-daily drug. In that context, missing more than one dose may possibly have more serious consequences with regard to the risk of stent thrombosis because the shorter half-life results in a shorter-duration platelet inhibition effect. Clearly, a great responsibility exists, both on the part of interventionists and other care providers to underscore the critical importance of uninterrupted DAPT in DES patients in particular and on the part of the patient and family to understand and comply with this recommendation, whether it is a once-daily or twice-daily dosing regimen. Both prasugrel and ticagrelor will, for the foreseeable future, remain a more expensive course of therapy than generic clopidogrel.

The best of all worlds would be a composite of these features, which at present may require a combination approach or switching between agents. Our STEMI practice is currently evolving from using clopidogrel almost uniformly to an approach of loading upstream with ticagrelor. This can be used ubiquitously at the intake stage of our STEMI pathway, which includes a network of outlying hospitals that transfer their patients to our center for primary or rescue PCI and for elective angiography after successful pharmacologic reperfusion. Decisions regarding whether to continue maintenance dosing of ticagrelor or to switch to maintenance clopidogrel, while not evidence-based, can then be made depending on a variety of patient clinical factors and socioeconomic factors, including drug cost and the possibility of noncompliance with twice-daily dosing.

Genetic testing in our practice is individualized depending on the clinical context, although it should be reiterated that current guidelines do not recommend routine genetic testing for polymorphisms that may be associated with clopidogrel resistance. The value (or lack of value) of routine genetic testing remains a crucial question to answer and would have broad relevance to coronary interventional practice. For example, if it were demonstrated that choosing an ADP receptor antagonist for a specific patient guided by genetic testing could positively affect clinical outcomes, an individualized approach could become the standard approach to DAPT management.

CONCLUSION

The quest for the ideal antiplatelet regimen after PCI for STEMI has led to important insights and improvements in patient outcomes. Ideally, a regimen that is simple, is not cost-prohibitive, potently reduces ischemic events, and is associated with low bleeding rates is the goal. The solutions of the future may include novel agents yet in development, as well as the use of genetic and/or platelet function testing to tailor antiplatelet therapies for individual patients.

Verghe Mathew, MD, FACC, FSCAI, is Consultant, Department of Internal Medicine, Division of Cardiovascular Diseases and Department of Radiology; and Professor of Medicine, Mayo Clinic College of Medicine in Rochester, Minnesota. He has disclosed that he has no financial interest related to this article. Dr. Mathew may be reached at mathew.verghese@mayo.edu.


