Oral DAPT After PCI for STEMI

An assessment of the current role of dual-antiplatelet therapy after primary percutaneous coronary intervention.

BY VERGHESE MATHEW, MD, FACC, FSCAI

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.[1] 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.[2] 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.[3]

Whether warfarin with single-antiplatelet therapy after coronary stenting is safe was readdressed from a slightly different perspective in the WOEST trial.[4] 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.[1,5] 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.[6] Notably, the clinical benefit of preloading with clopidogrel prior to arrival in the catheterization laboratory, although standard in clinical practice, remains somewhat uncertain.[7-9] 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.[10,11] 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 $P2Y_{12}$ 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, 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 $P2Y_{12}$ 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.[23-25] A recent small study in STEMI patients suggests less rapid onset of action and much more heterogeneity in antiplatelet effect than previously thought.[26] 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),[19] 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.[27] 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.[21] 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. ■

Verghese 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.

1. Yusuf S, Zhao F, Mehta SR, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494-502.
2. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339:1665-1771.
3. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS).. Circulation 2000;102:624-9
4. Dewilde WJ, Oirbans T, Verheugt FWA, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381:1107-1115.
5. Mehta SR, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527-533.
6. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:e574-e651.
7. Steinhubl SR, Berger PB, Mann JT 3rd, et al; CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288:2411-2420.
8. Di Sciascio G, Patti G, Pasceri V, et al; ARMYDA-5 PRELOAD investigators. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. J Am Coll Cardiol. 2010;56:550-557.
9. Widimsky P, Motovská Z, Simek S, et al; PRAGUE-8 Trial Investigators. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. Eur Heart J. 2008;29:1495-1503.
10. Dangas G, Mehran R, Guagliumi G, et al; HORIZONS-AMI Trial Investigators. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. J Am Coll Cardiol. 2009;54:1438-1446.
11. Mehta SR. CURRENT OASIS 7 Trial Results: A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes. Presented at the Hotline Session European Society of Cardiology; Barcelona, Spain; August 2009.
12. Jeong YH, Hwang JY, Kim IS, et al. Adding cilostazol to dual antiplatelet therapy achieves greater platelet inhibition than high maintenance dose clopidogrel in patients with acute myocardial infarction: results of the adjunctive cilostazol versus high maintenance dose clopidogrel in patients with AMI (ACCEL-AMI) study. Circ Cardiovasc Interv. 2010;3:17-26.
13. Han Y, Li Y, Wang S, et al. Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes: a randomized, controlled study. Am Heart J. 2009;157:733-739.
14. Hochholzer W, Trenk D, Bestehorn HP, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol. 2006;48:1742-1750.
15. Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2010;56:321-341.
16. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation. 2009;119:2553-2560.
17. Varenhorst C, James S, Erlinge D, et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J. 2009;30:1744-1752.
18. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001-2015.
19. Montalescot G, Wiviott SD, Braunwald E, et al; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009;373:723-731.
20. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120:2577-2585.
21. Cannon CP, Harrington RA, James S, et al; PLATelet inhibition and patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010;375:283-293.
22. Steg PG, James S, Harrington RA, et al; PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010;122:2131-2141.
23. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J. 2006;27:1166-1173.
24. Matsushima N, Jakubowski JA, Asai F, et al. Platelet inhibitory activity and pharmacokinetics of prasugrel (CS-747) a novel thienopyridine P2Y12 inhibitor: a multiple-dose study in healthy humans. Platelets. 2006;17:218-226.
25. Bliden KP, Tantry US, Storey RF, et al. The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: combined analysis of the ONSET/OFFSET and RESPOND studies. Am Heart J. 2011;162:160-165.
26. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol. 2013;61:1601-1606.
27. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol. 2007;50:1844-1851.