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The Complexities of Dual Antiplatelet Therapy

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Dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) is becoming more complex, making it difficult to select the optimal therapy, said Matthew J. Price MD, FACC, Scripps Clinic, La Jolla, California, USA. With several $P2Y_{12}$ ADP receptor antagonists that have been approved at varying doses, as well as three different doses of aspirin that are commonly used, there are multiple different combinations of oral DAPT. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines note the options for DAPT as clopidogrel, prasugrel, and ticagrelor but provide no guidance on the selection of a particular agent [Levine GN et al. *Circulation* 2011]. The optimal regimen; the potential risk for adverse events, bleeding in particular; and the role of genotyping are among the most important questions that remain unanswered.

Drug Options for DAPT

Clopidogrel, when combined with aspirin, leads to improved outcomes (compared with aspirin alone) for patients with ACS, regardless of whether they are undergoing percutaneous coronary intervention (PCI) or not. Despite better results, studies showed that inhibition of platelet aggregation with clopidogrel was "variable, unpredictable, and insufficient," said Paul Gurbel, MD, FACC, Sinai Center for Thrombosis Research, Baltimore, Maryland, USA [Gurbel PA et al. *Circulation* 2003].

DAPT with prasugrel achieved more rapid, potent, and consistent inhibition of platelet function than clopidogrel + aspirin. In the TRITON-TIMI 38 trial, prasugrel substantially reduced rates of ischemic events (9.9% vs 12.1%; HR, 0.81; 95% CI, 0.73 to 0.90; p<0.001), including stent thrombosis (1.1% vs 2.4%; HR, 0.48; 95% CI, 0.36 to 0.64; p<0.001), compared with clopidogrel in patients with ACS treated with coronary stenting [Wiviott SD et al. *N Engl J Med* 2007]. However, prasugrel increased the rate of major bleeding (2.4% vs 1.8%; HR, 1.32; 95% CI, 1.03 to 1.68; p=0.03), including fatal bleeding (0.4% vs 0.1%; HR, 4.19; 95% CI, 1.58 to 11.11; p=0.002). Overall mortality was similar for the two drugs.

The most recently approved $P2Y_{12}$ antagonist, ticagrelor, has a rapid onset, consistent antiplatelet effect, and is reversible [Gurbel PA et al. *Circulation* 2009]. Ticagrelor was compared with clopidogrel in the PLATO trial and significantly reduced the rate of the primary composite endpoint (cardiovascular [CV]-related death, myocardial infarction [MI], and stroke) by 1.9% absolute (p=0.0003), including a significant reduction in CV mortality (4.0% vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91; p=0.001) [Wallentin L et al. *N Engl J Med* 2009]. The results were consistent in many subgroups including patients who were planned for an invasive strategy; those with ST-elevation myocardial infarction (STEMI), renal dysfunction and, previous stroke; and those having coronary artery bypass grafting within 5 days of treatment. Ticagrelor was of benefit independently of the loading dose of clopidogrel (300 or 600 mg) [Cannon CP et al. *Lancet* 2010], and also regardless of the genetic *CYP2C19* polymorphism that identifies low responders to clopidogrel [Wallentin L et al. *Lancet* 2010]. Ticagrelor achieves a greater pharmacodynamic effect than clopidogrel, irrespective of *CYP2C19* genotype [Tantry US et al. *Circ Cardiovasc Genet* 2010], which likely explains the higher rate of bleeding with ticagrelor compared with clopidogrel that is seen outside of the operating room.

Comparisons across the trials of $P2Y_{12}$ antagonists are difficult due to differences in the study designs in which the efficacy and safety of the drugs are evaluated (Table 1). Dr. Price suggested that physicians look at the study designs to see where their patients "fit" in terms of the type of MI (NSTEMI or STEMI), management strategy, pretreatment with clopidogrel, start of treatment before coronary angiography, potential need for CABG, and clinical characteristics (eg, advanced age, low body weight, previous stroke – each of which increases the risk of major bleeding).

Risk of Bleeding

The risk of bleeding is the greatest safety concern with DAPT. "It's been difficult, if not impossible, to disassociate a reduction in things like, stent thrombosis, from increases in bleeding," said Deepak L. Bhatt MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA. The potential for increased risk of bleeding must be an important factor in selecting an antiplatelet regimen. It is wise to factor gastrointestinal (GI) bleeding risk in particular, whether the patient is older, has a history of ulcers, has *H. pylori,* or is on an anticoagulant, corticosteroids, or an NSAID, advised Dr Bhatt.

Proton pump inhibitors (PPIs) have been used widely to reduce the risk of upper GI bleeding that is associated with clopidogrel, but studies have shown a pharmacodynamic interaction between PPIs and clopidogrel, potentially reducing its clinical effectiveness. However, the clinical significance of this interaction has not been substantiated in more recent data. An analysis from TRITON-TIMI 38 indicated no influence of PPIs on outcomes in patients who are treated with clopidogrel [O'Donoghue ML et al. *Lancet* 2009]. Likewise, recent analyses from PLATO showed no interaction of clopidogrel with PPI, with a consistent benefit of ticagrelor, regardless of PPI treatment [Goodman S et al. *Circulation* 2012].

The best clinical data that have evaluated the interaction of PPIs and clopidogrel are from the prospectively designed, randomized, double-blinded COGENT trial, in which prophylactic use of omeprazole reduced the rate of upper GI bleeding compared with placebo (HR, 0.13; 95% CI, 0.03 to 0.56; p=0.001) [Bhatt DL et al. *N Engl J Med* 2010]. There was no apparent CV interaction between clopidogrel and omeprazole (HR in patients who were randomized to omeprazole, 0.99; 95% CI, 0.68 to 1.44; p=0.96), but the study could not rule out a potentially clinically meaningful difference in CV events due to use of a PPI.

To help provide insight on the issue, the ACC and AHA worked with the American College of Gastroenterology to develop an Expert Consensus Document on the use of PPIs and thienopyridines [Abraham NS et al. *Circulation* 2010]. The consensus document, recommends using a PPI to reduce GI bleeding among patients with a history of upper GI bleeding, stating that PPIs are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy. The document also indicates that the routine use of a PPI is not recommended for patients who are at lower risk of upper GI bleeding.

Table 1. Comparative Study Designs Testing the Safety and Efficacy of the $P2Y_{12}$ Antagonists in ACS.

	CURE	TRITON- TIMI 38	PLATO	OASIS
Study drug	Clopidogrel	Prasugrel	Ticagrelor	Clopidogrel 600/150 mg
Comparator	Placebo	Clopidogrel 300 mg	Clopidogrel 300/600 mg	Clopidogrel 300/75 mg
Size (n)	12,562	13,608	18,624	25,807
Clinical Presentation	NSTE-ACS	NSTE-ACS 74% STEMI 26%	NSTE-ACS 60% STEMI 38%	NSTE-ACS 71% STEMI 29%
Drug timing	Presentation	After angiography (75%)	Presentation	Presentation
Pre-Tx with non-study drug?	No	No	Yes in 46%	No
PCI performed	21%	99%	65%	38%
Median Rx	9 months	14.5 months	9.3 months	7 days
1° Endpoint	CVD, MI, CVA	CVD, MI, CVA	V. Death, MI, CVA	Death, MI, CVA
ARR	2.1%	2.2%	1.9%	0.6%

Pre-Tx=pre-therapeutics; PCI=percutaneous coronary intervention; CVD=cardiovascular disease; MI=myocardial infarction; CVA=cerebrovascular accident; V. Death=vascualr death; ARR=absolute risk reduction.

The risk of bleeding with prasugrel is higher than it is with clopidogrel. In particular, prasugrel should not be used in patients who have had a prior stroke or transient ischemic attack, and is not recommended for patients aged >75 years, except in high-risk situations. "This recommendation is derived from the data evaluating the net clinical benefit. [If] patients have high ischemic risk, they will benefit overall from prasugrel because the ischemic benefit outweighs the risk of bleeding, and that was seen in elderly patients with diabetes or prior MI," said Dr. Price. He also added that dose adjustment in lightweight patients should be considered.

Concerns were initially raised about using ticagrelor for patients who had prior stroke as there was nearly a doubling of intracranial hemorrhage (ICH; HR, 1.87; 95% CI, 0.98 to 3.58; p=0.06) that was associated with ticagrelor compared with clopidogrel among all patients in the PLATO trial. However, further analysis showed that patients who had a prior stroke actually fared substantially better with ticagrelor than with clopidogrel in terms of the primary endpoint (HR, 0.62; 95% CI, 0.42 to 0.91). This suggests any increased risk of ICH in patients who were treated with ticagrelor (compared with clopidogrel) was counterbalanced by a larger benefit in the reduction of ischemic events.

A higher rate of non-CABG bleeding was also more common with ticagrelor than clopidogrel (2.8% vs 2.2%; HR, 1.25; 95% CI, 1.03 to 1.53; p=0.03), similar to the excess that was seen with prasugrel versus clopidogrel. However there was no difference in perioperative CABG bleeding between ticagrelor and clopidogrel, and a study by Held et al. found that the mortality rate after CABG was significantly lower for patients who were treated with ticagrelor versus clopidogrel (4.7% vs 9.7%; p<0.01) [Held et al. *JACC* 2011]. Because ticagrelor *reversibly* binds the $P2Y_{12}$ receptor, the rate of recovery of platelet function is faster after ticagrelor than clopidogrel [Gurbel PA et al. *Circulation* 2009]. However, since ticagrelor achieves a higher steady-state level of platelet inhibition than clopidogrel, it is recommended that both be stopped for 5 days before CABG, compared with 7 days prior to CABG for prasugrel.

Genotyping

Some of the variability in platelet inhibition with clopidogrel can be explained by the presence of *CYP2C19* polymorphisms [Shuldiner AR et al. *JAMA* 2009]. Loss-of-function alleles are common, occurring in ~30% of white individuals, ~35% of African-Americans, and 55% of East Asians, said Malcolm R. Bell, MBBS, FRACP, FACC, Mayo Clinic, Rochester, Minnesota, USA. However, patients with these polymorphisms make up less than 20% of patients with a low response to clopidogrel, and other factors also contribute to the variability in platelet inhibition [Hochholzer et al. *J Am Coll Cardiol* 2010].

In 2011, the ACCF/AHA published an update to its unstable angina/NSTEMI guidelines, with two new class IIb recommendations, noting that platelet function testing or genotyping for *CYP2C19* loss-of-function variants may be considered if the testing may alter management [Wright RS et al. *JACC* 2011]. However, a benefit of altering management based on platelet function or genetic testing has never been demonstrated in a large-scale prospective trial.

European Society of Cardiology 2011 ACS Guideline

Unlike the ACCF/AHA guidelines, the European Society of Cardiology guidelines now recommend the newer $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) over clopidogrel in patients with NSTE-ACS. Ticagrelor has a Class I, level B recommendation, with the guidelines stating that a 180-mg loading dose, followed by 90 mg given twice daily, is recommended for "all patients at moderate-to-high risk of ischemic events, regardless of initial treatment strategy, and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced)" [Hamm CW et al. *Eur Heart J* 2011]. Ticagrelor is of benefit regardless of type of ACS, a noninvasive or invasive strategy (including CABG), renal function and diabetes, use of PPIs, or *CYP2C19* polymorphism. Prasugrel also has a Class I, level B recommendation; a 60-mg loading dose, followed by a 10-mg daily dose, is recommended for "$P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications." In contrast, clopidogrel is recommended only if patients are not candidates for ticagrelor or prasugrel (Class I, level A). Prof. Wallentin concluded that compared with clopidogrel, one life would be saved for every 54 ACS patients who are treated with ticagrelor for one year.

Science Advisor's Note:

Whether the benefits of ticagrelor and prasugrel over clopidogrel that were observed in a rigorous randomized trials will hold up in routine practice, the side effect profile, and anticipated use in patients who would not have qualified for a clinical trial remains to be seen.