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Is prasugrel or ticagrelor a better choice than the new generic clopidogrel?

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Antiplatelet drugs are used to prevent cardiovascular events and premature death in patients with multiple risk factors and in patients who have experienced Acute Coronary Syndrome (ACS) which includes unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), or ST segment elevation myocardial infarction (STEMI). Other potential indications for antiplatelet drugs include history of transient ischemic attack or thromboembolic stroke, or symptomatic peripheral arterial disease. Aspirin has been considered the gold standard antiplatelet agent. Aspirin is effective in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Several practice guidelines have been published that provide recommendations regarding the role of aspirin.[1 2 3 4 5 6]

Clopidogrel is used as an aspirin substitute for patients who are intolerant or contraindicated and as an adjunct to aspirin in patients who have received stents. Prasugrel and ticagrelor are indicated only for patients with stents. Their role relative to each other and clopidogrel is still evolving. There is reported variability in patient platelet aggregation response to clopidogrel, though the risk of adverse outcomes due to these variations has yet to be fully elucidated.[7 8 9] This article reviews the evidence and role for the newest antiplatelet drugs, ticagrelor (Brilinta™) and prasugrel (Effient™).

PRASUGREL

Prasugrel inhibits platelet activation and aggregation by irreversibly binding its active metabolite to the P2Y12 class of adenosine diphosphate (ADP) platelet receptors.[10] It is dosed with a 60 mg load, followed by 10 mg daily to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in the following groups of patients with ACS who are to be managed with percutaneous coronary intervention (PCI):

- Patients with unstable angina or NSTEMI
- Patients with STEMI when managed with primary or delayed PCI

It is not indicated for ACS in the absence of PCI. Safety and effectiveness in patients more than 75 years old is uncertain and generally not recommended.[10]

A recent Drug Effectiveness Review Project (DERP) systematic, comparative effectiveness review found high-strength evidence that prasugrel reduced target-vessel revascularization more than clopidogrel at 15 months in patients with ACS undergoing coronary revascularization.[11] There was moderate- to high-strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes including: all-cause mortality and cardiovascular mortality outcomes. Moderate-strength evidence indicated that more major bleeding occurred with prasugrel use. There was no evidence meeting inclusion criteria for prasugrel used for other indications (ACS managed medically, secondary stroke prophylaxis, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

Prasugrel was compared to clopidogrel in the phase 3 trial, TRITON-TIMI 38.[12] It included 13,608 patients with moderate- to high-risk acute coronary syndromes (74% unstable angina or NSTEMI, 26% STEMI) who underwent PCI. It was a good-quality, multi-site, head-to-head trial. The primary efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. All outcomes were assessed at 15 months.

The primary efficacy endpoint occurred in 12.1% of patients receiving prasugrel compared to 9.9% of patients receiving clopidogrel (hazard ratio, 0.81; 95% CI, 0.73 to 0.90; P<0.001).[12] There were no significant differences between prasugrel and clopidogrel in the most important effectiveness component outcomes of all-cause mortality (hazard ratio, 0.95; 95% CI, 0.78 to 1.16) and CV mortality (hazard ratio, 0.89; 95% CI, 0.70 to 1.12).[12] The study was not powered or designed to detect differences in these secondary outcomes. However despite the lack of power, it provided high-strength evidence of superiority of prasugrel over clopidogrel for prevention of target vessel revascularization post-percutaneous coronary intervention (2.5% compared with 3.7%; hazard ratio, 0.66; 95% CI, 0.54 to 0.81; P<0.001; absolute risk reduction, 1.2%; number needed to treat, 83).[12]

The DERP review[11] did not find studies that met inclusion criteria and evaluated differences in all cause mortality, CV mortality, or target-vessel revascularization rates between clopidogrel and prasugrel when used concomitantly with proton pump inhibitors or based upon patient genotype. There continues to be controversy about the clinical impact of both concomitant use of clopidogrel with proton pump inhibitors and in certain genotypes.

Major bleeding was experienced with prasugrel in 2.4% of patients compared to 1.8% of patients on clopidogrel (RR 1.32 95% CI 1.03 to 1.68, p=0.03, NNH 167).[12] The product labeling recommends prasugrel not be used in patients with active pathological bleeding or those with a history of transient ischemic attack or stroke. It is not recommended in patients more than 75 years old due to increased risk of fatal and intracranial bleeding coupled with uncertain benefit. However, based on sub-group analyses, prasugrel may be considered in this age group in certain high-risk patients (diabetes or prior MI) where the antiplatelet effect appears to be greater. Additional risk factors for bleeding include: body weight less than 60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding.[10] Prasugrel has a pregnancy rating of B indicating there are no adequate and well-controlled studies of use in pregnant women.[10]

In TRITON-TIMI 38, dropout rates for prasugrel (7.2%) compared to clopidogrel (6.4%) were not significantly different. [12] There was an increased rate of colonic neoplasm in the phase III study, but it is unclear if these observations are causally-related or are random occurrences. Colonic neoplasms occurred in 13 (0.2%) prasugrel patients compared to 4 (0.1%) clopidogrel patients, p=0.03.[10]

Unanswered safety questions revolve around whether the significant efficacy benefit associated with prasugrel outweighs the risk of increased bleeding for general clinical use or only high risk patients.[11]

TICAGRELOR

Ticagrelor inhibits platelet activation and aggregation through the reversible binding to the P2Y12 class of ADP platelet receptors.[15] It belongs to a new class of antiplatelet agents called cyclopentyl-triazolo-pyrimidines. In contrast to clopidogrel and prasugrel, ticagrelor is not a prodrug and thus binds and inhibits the P2Y12 receptor directly with no need for metabolic activation which limits any potential impact of genetic variations in CYP enzymes on its pharmacological profile. The metabolite of ticagrelor is equally potent.[15] It is dosed with a 180 mg load, then 90 mg twice daily.

Ticagrelor was compared to clopidogrel in the phase 3 trial, PLATO.[16 17] It included 18,624 patients admitted to 862 centers in 43 countries from October 2006 through July 2008. Patients were admitted to the hospital with ACS (62% NSTEMI or unstable angina, 38% STEMI) and 64% of patients underwent PCI during the study. It was a fair-quality, multi-site, head-to-head trial. The primary efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at 12 months.

The primary efficacy endpoint occurred in 9.8% of patients receiving ticagrelor compared to 11.7% of patients receiving clopidogrel (hazard ratio, 0.84; 95% CI, 0.77 to 0.92; P<0.001). Based on the PLATO study[16], there is moderate strength evidence of a benefit of ticagrelor over clopidogrel in the most important component outcomes of all-cause mortality (hazard ratio,

0.78; 95% CI, 0.69 to 0.89), CV mortality (HR 0.79; 95% CI, 0.69 to 0.91), and for prevention of stent thrombosis post-PCI (HR 0.77; 95% CI, 0.62 to 0.95). The study was not powered or designed to detect differences in these secondary outcomes but the statistical analysis did plan for and confirm statistical significance. Moderate strength evidence also indicated that there was no more major bleeding with ticagrelor (HR 1.04; 95% CI 0.95 to1.13). There was moderate strength evidence of more withdrawals due to adverse events with ticagrelor (7.4% vs. 6.0%, RR 1.24; 95% CI 1.11 to 1.33).

Despite the published positive findings the Food and Drug Administration (FDA) delayed approval of ticagrelor for more than 6 months. A FDA report[18] identifies several issues. One critical point is the regional difference noted. The discussion on that point is pasted below:

"As shown in the table below (Table 1 in the statistical review of 31 August), in the US, ticagrelor fared worse with respect to each of the components of the primary end point.:

	Characteristic	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Hazard ratio (95% CI)
Non-US	Composite of CV Death/MI (excl. silent MI)/Stroke	780	947	0.82 (0.74,0.90)
	CV death	329	423	0.77 (0.67, 0.89)
	MI (excl. silent MI)	440	546	0.80 (0.70, 0.90)
	Stroke	118	102	1.15 (0.88, 1.50)
US	Composite of CV Death/MI (excl. silent MI)/Stroke	84	67	1.27 (0.92,1.75)
	CV death	24	19	1.26 (0.69, 2.30)
	MI (excl. silent MI)	64	47	1.38 (0.94, 2.01)
	Stroke	7	4	1.73 (0.51, 5.92)

In the US the point estimate of the hazard ratio was about 1.27. The point estimates for the hazard ratios in placebo-controlled studies of clopidogrel are in the ballpark of 1/1.27, so, by the most generous of non-inferiority calculations, based solely on point estimates, the US results are entirely consistent with there being no effect whatsoever of ticagrelor in the US.

No single or combination of baseline covariates was found to explain the US-foreign differences in outcome. However, post-randomization dose of aspirin does appear to account for regional differences, at least in the statistical sense."

Because of this regional difference, concomitant doses of aspirin above 100mg should be avoided with ticagrelor.[15] Ticagrelor carries a black box warning of serious, sometimes fatal bleeding. Contraindications for use include active pathological bleeding, a history of intracranial hemorrhage, and patients with a need for urgent coronary artery bypass graft surgery (CABG). When possible, discontinue ticagrelor at least 5 days prior to any surgery. For hypotensive patients on ticagrelor who have undergone recent coronary angiography, PCI, CABG or other surgical procedures, bleeding may have occurred. If possible, bleeding should be managed without discontinuing ticagrelor to avoid risk of subsequent CV event.[15]

Ticagrelor has a pregnancy rating of C indicating there are no adequate, well controlled studies in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5-7 times the maximum recommended human dose based on surface area.[15] There is a potential risk of bradyarrhythmia with ticagrelor, however the clinical significance of this risk is unknown. PLATO excluded patients at increased risk of bradycardic events.[16]

LENGTH OF TREATMENT POST PCI

The DERP report also reviewed evidence for length of treatment post PCI. No head-to-head trials that directly compared newer antiplatelet agents based on duration of therapy were found.[11] Compared with 1 month of treatment with clopidogrel plus aspirin, there was moderate-strength evidence of a significant reduction in risk of revascularization with 6 months of treatment, with no significant increase in bleeding risk.[11] The benefit appeared to decrease in a step-wise manner and lose statistical significance at 8 months (PCI-CURE, low strength) and 12 months (CREDO, moderate strength).[11] TRITON-TIMI 38[12] treated patients for a median of 14.5 months. PLATO[16] treated patients for a median of 9 months.

CONCLUSION

The Oregon Health Authority Pharmacy and Therapeutics Committee met on November 17, 2011 to review antiplatelet drugs.[19] [20] [21] Prasugrel and ticagrelor were recommended as second line agents behind clopidogrel for prevention of cardiovascular events post-PCI for ACS. Comparative evidence for the recommended length of treatment post PCI is limited to clopidogrel. Risks of bleeding begin appear to outweigh the benefit beyond 6-8 months of treatment.

Reviewed by:

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