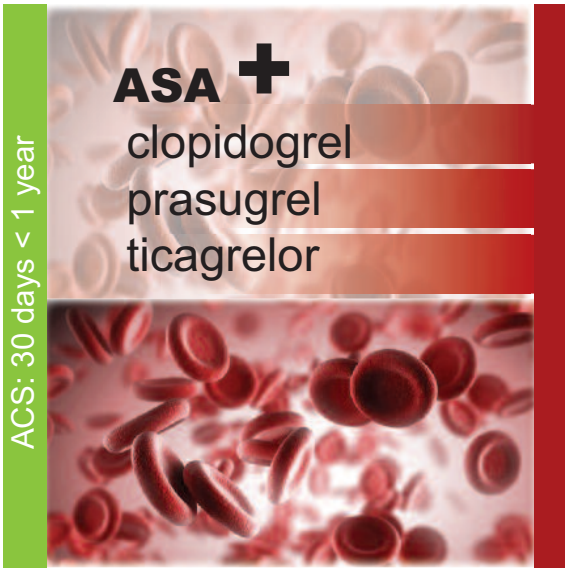
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Dual antiplatelet therapy: net health benefit or harm?



The antiplatelet drugs acetylsalicylic acid (ASA), clopidogrel (Plavix) and ticlopidine (Ticlid) were reviewed in TL #37.[1] Ticlopidine is no longer available in Canada. ASA has a unique action, irreversibly inhibiting platelet cyclooxygenase. Clopidogrel and two new drugs, prasugrel (Effient) and ticagrelor (Brilinta), reduce platelet activation and aggregation by inhibiting $P2Y_{12}$ adenosine diphosphate receptors. Prasugrel and ticagrelor have been suggested as alternatives to clopidogrel for patients presenting with acute coronary syndrome. This letter analyses published RCTs comparing these two new platelet inhibitors with clopidogrel, and includes additional information available from the US FDA's medical reviews of these RCTs.

Background

The SPS3 trial[2] showed in 2012 that harms of long-term dual antiplatelet therapy (DAPT) outweigh benefits after lacunar stroke; 3020 people with recent lacunar infarcts were followed for 3.4 years after randomization to ASA 325 mg/d plus clopidogrel 75 mg/d, or to ASA 325 mg/d plus placebo. DAPT increased mortality as compared to ASA alone: RR 1.45 [1.10-1.93], ARI = 2.3%, NNTH = 44 in 3.4 years. A meta-analysis of all trials of DAPT versus ASA alone (N = 69,644) found numerically higher mortality with this strategy, HR 1.04 [0.96-1.18].[3] A recently published study[4] comparing ticagrelor 60 or 90 mg twice/d plus low dose ASA 75-150 mg/d vs ASA alone did not affect mortality and when added to the meta-analysis will not change the conclusions. A 2015 meta-analysis limited to patients who had received drug-eluting stents demonstrated increased total mortality from DAPT > 1 year duration as compared to DAPT≤ 1 year duration, HR 1.22 [1.02-1.45].[5]

DAPT is indicated for early treatment of patients presenting with acute coronary syndrome (ACS), including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), with or without revascularization with percutaneous coronary intervention (PCI).[6-10]

Clopidogrel (Plavix)

Our understanding of clopidogrel in this setting is based primarily on the CURE RCT.[11] In this trial, adding clopidogrel to ASA did not reduce all-cause mortality, and information on total serious adverse events was not reported. DAPT reduced myocardial infarction, RR 0.77 [0.67-0.89], ARR = 1.5%, but increased major bleeds, RR 1.38 [1.13-1.67], ARI = 1%. Our assessment of this trial concluded that half of the cardiovascular benefit occurred within the first 24 hours after a loading dose of clopidogrel, and almost all within the first 30 days of therapy.

Prasugrel (Effient)

Prasugrel was approved by Health Canada in 2010 for co-administration with ASA for ACS. It is not recommended for people >75 years, due to increased bleeding risk. Approval was based primarily on the multicenter, randomized controlled trial TRITON-TIMI 38, comparing prasugrel/ASA vs clopidogrel/ASA in 13,608 patients with ACS and scheduled PCI.[12] The investigators concluded that prasugrel 10 mg/d reduced ischemic events as compared with clopidogrel, but increased major bleeding events. Benefit of prasugrel was driven by a decrease in nonfatal myocardial infarctions (NFMI). 60% of NFMI occurred <24 hours after PCI ("periprocedural") and represented asymptomatic elevations in cardiac enzymes. These are of uncertain clinical impact, but clearly less dangerous than symptomatic myocardial infarction. Prasugrel (vs clopidogrel) did not reduce cardiovascular death or stroke. Prasugrel increased major bleeds by 0.6% (including life-threatening and fatal bleeds). More patients discontinued prasugrel than clopidogrel due to adverse effects, including haemorrhagic adverse events.

The US FDA review cautioned that methodological concerns about ascertainment of clinical outcomes should temper conclusions about this

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study, noting that loss to follow-up occurred in 4.9% of patients (clopidogrel) and 5.1% (prasugrel).[13]

The overall clinical impact of prasugrel vs clopidogrel can be assessed by all-cause mortality and total serious adverse events (SAEs). TRITON-TIMI 38 found no significant difference in all cause mortality, RR = 0.95 [0.78-1.16], nor for total serious adverse events, RR = 1.02 [0.96-1.08]. Similarly, 5 years after the publication of TRITON-TIMI 38, the TRILOGY ACS trial of prasugrel vs clopidogrel in UA/NSTEMI patients without planned revascularization reported no difference for the primary outcome of cardiac death, nonfatal MI or stroke.[14] All-cause mortality did not differ and total serious adverse events were not reported.

Ticagrelor (Brilinta)

Ticagrelor was approved by Health Canada in 2011 for co-administration with ASA for ACS. Approval was based primarily on the PLATO trial comparing ticagrelor/ASA vs clopidogrel/ASA in 18,624 patients with ACS (UA/NSTEMI/STEMI) managed by PCI, CABG or medical therapy alone.[15] The published report indicates that ticagrelor 90 mg bid decreased the primary outcome of death from vascular causes, MI or stroke at 12 months: 9.8% for ticagrelor vs 11.7% for clopidogrel, HR 0.84 [0.77-0.92], ARR 1.9%, NNT = 53. All-cause mortality was reported as ticagrelor 4.5% vs clopidogrel 5.9%, HR 0.78 [0.69-0.89], ARR = 1.4%, NNT = 71.

However, the FDA medical review documents a number of irregularities in reporting of serious adverse events (including deaths) that brings these findings into question.[16] Mortality was numerically higher with ticagrelor at North American sites, and was reduced only in countries outside of North America. Unblinding was declared in at least 452 patients, much higher than the numerical difference of 107 people for all-cause mortality or 150 for the primary end point. There were also important losses to follow-up in this trial: 19.7% of patients receiving ticagrelor and 18.1% for clopidogrel.

In contrast with the published report of PLATO, the FDA concluded that ticagrelor increased major or minor bleeding events vs clopidogrel (ARI = 1.5%, NNH = 66).[16] Ticagrelor also increased withdrawals due to adverse effects, ARI 2% mostly due to dyspnea or epistaxis. The overall net impact of ticagrelor could not be assessed, as there was inadequate reporting of total serious adverse events. To prepare this Letter, we contacted the PLATO study authors and the manufacturer of ticagrelor requesting details on total SAEs, but have received no reply by the date of publication. We remain uncertain about the net benefit/harm of ticagrelor vs clopidogrel. Independently conducted trials could resolve this uncertainty.

Conclusions

- In assessing and interpreting the findings of clinical trials, important additional information and insight can be found on the FDA website: www.fda.gov
- **Long-term dual antiplatelet therapy (vs ASA alone) does not decrease all-cause mortality and increases it in some settings.**
- All antiplatelet agents cause increased bleeding, which reduces their net benefits.
- **Dual antiplatelet therapy is indicated after acute coronary syndrome. It should be started immediately and continued for a maximum duration of 1 year. Most of the benefit occurs in the first 30 days.**
- It is uncertain whether prasugrel or ticagrelor have any therapeutic advantages or disadvantages, compared with clopidogrel.

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94 The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

The Therapeutics Initiative is funded by the BC Ministry of Health through a grant to the University of BC. The Therapeutics Initiative provides evidence-based advice about drug therapy, and is not responsible for formulating or adjudicating provincial drug policies.