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Class Update: Antiplatelet Drugs

Month/Year of Review: July 2015 **Last Review:** July 2014

Current Status of PDL Class:

- See Appendix 1

Research Questions:

- Is there new comparative evidence that antiplatelet drugs differ in effectiveness or safety for adult patients with acute coronary syndromes (ACS) or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack (TIA), or symptomatic peripheral arterial disease (PAD)?
- Is there evidence of a difference in effectiveness or harms for the length of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ receptor antagonist) after drug-eluting stent (DES) implantation?

Conclusions:

- There is moderate quality evidence that prasugrel is associated with a lower rate of major adverse cardiovascular events (MACEs) compared to clopidogrel in patients with coronary artery disease (CAD) (OR 0.86; 95% CI 0.78 to 0.94), but also a high risk of major bleeding (OR 1.33; 95% CI 1.09 to 1.61). However, a recent meta-analysis demonstrated that the risk of MACEs far outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009).[5]
- There is no other new comparative effectiveness evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or dipyridamole ER/aspirin (D-ER/ASA) other indications.
- Dual antiplatelet therapy (DAPT) consisting of aspirin plus a $P2Y_{12}$ receptor antagonist is recommended after drug-eluting stent (DES) implantation for at least 12 months by the American College of Cardiology/American Heart Association (ACC/AHA) and for six to 12 months by European guidelines, followed by aspirin monotherapy.
- There is low quality evidence that short-term DAPT (less than 12 months) compared to-12 month therapy is associated with a similar rate of stent thrombosis and MI, with a reduced risk of major bleeding, while extended therapy (>12 months) compared with 12-month therapy is associated with reduction in stent thrombosis (NNT 100-250) and MI (NNT 50-125), but increased risk of major bleeding (NNH 111-325).[1–3] Studies have also demonstrated an increase in all-cause mortality with extended DAPT beyond one year (2.0% vs. 1.5%; OR 1.36; 95% CI 1.00-1.85; NNH 200), driven by non-cardiovascular events.[1] Further studies are needed to evaluate this risk and define the optimal duration of therapy. At this time, DAPT should be recommended for a year in most patients receiving a DES with high risk patients considering longer term use (up to 30 months) and patients at high risk of bleeding considering therapy for less than 6 months.
- There is moderate quality evidence that long term use (> 1 year) of ticagrelor may reduce risk of myocardial infarction (MI) (NNT 118) and stroke (NNT 303), but increase risk of major bleeding (NNH 65) in patients with prior MI (more than 1 year previously) taking aspirin, based on the PEGASUS-TIMI 54 trial.[4]

- New recommendations from the AHA for the primary prevention of stroke do not recommend antiplatelet regimens other than aspirin (and cilostazol for patients with PAD) be used for prevention of stroke due to a lack of evidence from relevant clinical trials. Primary prevention of stroke with aspirin is recommended for high risk individuals (10-year risk >10%), for persons with chronic kidney disease, and as a reasonable treatment option for patients with heart failure who do not have Atrial Fibrillation (AF) or a previous thromboembolic event.

Recommendations:

- Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).
- Make cilostazol a preferred drug on the PDL; no other changes to the PMPDP recommended.
- Continue the prior authorization policy with minor modifications consistent with updated treatment guidelines

PA Criteria:

Current PA criteria is in place for platelet inhibitors (Appendix 3) to approve platelet inhibitors for covered diagnoses which are supported by medical literature

Reason for Review:

Routine update of class and evaluation of new comparative evidence.

Previous P&T Conclusions (July 2014[6]):

- There is no new comparative effectiveness evidence for clopidogrel, prasugrel, ticagrelor, ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar produces lower rates of a composite of cardiovascular (CV) deaths, myocardial infarction (MI) or stroke at 3 years versus placebo when added to standard antiplatelet therapy for secondary prevention in patients experiencing a stroke, PAD or MI patients who have not undergone percutaneous coronary intervention (PCI) (HR 0.87 95% CI 0.80 - 0.94, ARD 1.1%, NNT 91). Significance was driven primarily by the MI component (HR 0.83 95% CI 0.74 – 0.90, ARD 0.8%, NNT 125). There is moderate quality evidence that vorapaxar does not prevent cardiovascular complications in patients with unstable angina or non-ST elevated MI (UA/NSTEMI).
- There is no new comparative safety evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar increases moderate to severe bleeding rates at 3 years compared to placebo (HR 1.35 95% CI 1.16 -1.58, ARD 1.6%, NNH 63). The trial was stopped 6 months early because of more hemorrhagic stroke for vorapaxar (HR 2.73 95% CI 1.22 – 6.14, ARD 0.2%, NNH 500).

Background:

Antiplatelet drugs are recommended to prevent cardiovascular (CV) events and premature death in patients who have experienced Acute Coronary Syndrome (ACS), transient ischemic attacks (TIA), noncardioembolic stroke, MI or symptomatic peripheral arterial disease (PAD).[7] Prasugrel and vorapaxar are contraindicated in patients with prior TIA or stroke. The FDA approved indications are represented in Table 1 below.

Table 1: FDA Approved Indications.

	2° Stroke	2° PAD	2° MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

Abbreviations: 2° = secondary prevention; x = FDA-indicated; CI=contraindication; PCI= percutaneous coronary intervention

Ticlopidine, clopidogrel, and prasugrel irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Ticlopidine causes rare, but serious, neutropenia and is rarely prescribed. [6] Clopidogrel is the only generically available $P2Y_{12}$ inhibitor but is limited by a slower onset of action, incomplete platelet inhibition and poor response in some patients. Variability in responsiveness to clopidogrel has been documented, but there are no guideline recommendations for testing or how to manage this unknown risk. Cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Cangrelor is a rapid acting injectable drug intended for percutaneous coronary interventions (PCI) and will not be covered in this review. Vorapaxar is unique because it is a selective antagonist of the protease-activated receptor-1 (PAR-1), the primary thrombin receptor. Vorapaxar has not been studied alone and should only be used with aspirin and/or clopidogrel according to their indications or standard of care.[8]

The multiple guidelines for treatment of CAD recommend aspirin 75-162 mg daily for all patients[9–11] and clopidogrel 75 mg daily as an alternative for patients intolerant to aspirin. Recently, the U.S. Food and Drug Administration recommended against routine use of aspirin for primary prevention but stated it may still be appropriate when prescribed by a healthcare provider to higher-risk patients.[12,13] Conversely, various clinical guidelines, including the American Diabetes Association guidelines do recommend aspirin for primary prevention in certain high risk individuals (those with a 10-year risk > 10%).[14]

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor plus aspirin is recommended for ACS, following PCI, for certain high risk patients with stable ischemic heart disease or peripheral artery disease, and for minor ischemic stroke or transient ischemic attack.[9,15] The recommendation of which $P2Y_{12}$ inhibitor to use concomitantly with ASA in various ACS patient types is evolving and varies depending on the guideline source.[15] The duration of DAPT has also been debated in the literature. Finding the duration that appropriately balances the risk of ischemic complications and bleeding risk has remained a challenge and guidelines have differing recommendations for use.[15,16] The ACCF/AHA/SCAI guideline recommends DAPT for at least 12 months for patients with ACS receiving a stent, with a consideration for greater than 12 months with a drug-eluting stent. However, the recent ESC/EACTS guideline recommends DAPT for 12 months only for patients at high-risk of thrombosis with ACS, with a consideration for less than 6 months if the patient is at high risk for bleeding. While guidelines have recommended 12 months with DAPT following ACS (with or without stent placement), some evidence has shown shorter durations (3-6 months) may be sufficient. None of these trials, however, were powered for ischemic endpoints; all were open-label and the time from stenting to randomization varied. The first large RCT powered to detect differences in ischemic outcomes was the DAPT study,[17] which demonstrated decreased rates of stent thrombosis and major CV events with extending DAPT up to 30 months, with an unexplainable increase in overall mortality, primarily driven by non-cardiovascular mortality. This has been editorialized as due to cancer, bleeding, and trauma-related deaths.[18] In addition, results seemed to be more significant in the subgroup of 'older generation' stents which may not be as effective in preventing thrombosis as the newer generation drug-eluting stents. A cohort of patients from the DAPT trial

with bare metal stents (BMS) showed insufficient evidence to evaluate DAPT for 30 months compared to 12 months as the trial was not powered to assess differences in this group.[19]

Either aspirin (50-325 mg daily) or D-ER/ASA is recommended over anticoagulants for secondary prevention of non-cardioembolic ischemic stroke.[9,20] Clopidogrel is an option for aspirin-intolerant patients. [9,20]

Aspirin 75-325 mg daily or clopidogrel 75 mg daily is recommended for symptomatic PAD patients to reduce the risk of myocardial infarction, stroke or vascular death.[9,21] Neither prasugrel or ticagrelor have evidence to support their use for PAD or stroke patients. [6]

Methods:
The DERP scan searched Ovid MEDLINE from January 2014 through January 2015 for new systematic reviews and randomized controlled trials (RCTs) comparing any of the antiplatelet agents.[22] An additional search through June 2015 was done. Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The DERP Scan identified no new potentially relevant comparative effectiveness reviews. Since the literature search done by the DERP scan, the following systematic reviews were identified. They are tabulated by indication and population.

<u>Acute Coronary Syndrome</u>

Extended duration dual antiplatelet therapy

Since the release of the DAPT study, systematic reviews and meta-analyses have further evaluated extended duration DAPT after coronary stenting, particularly its effect on overall mortality due to the difference in all-cause mortality seen in the DAPT trial.[23] The first systematic review included a literature search identifying 14 relevant articles, including the DAPT trial. While this review did not limit studies to patients with ACS, the majority of the trials (10) evaluated DAPT following ACS. All studies included DAPT with aspirin and a thienopyridine, the majority being clopidogrel. Thirty two percent of patients in the DAPT study received prasugrel with aspirin. Meta-analysis using a random-effects model of study results found no difference in all-cause mortality (HR 1.04; 95% CI 0.96 – 1.14) or cardiovascular mortality (HR 1.01; 95% CI 0.93 – 1.12) with extended duration DAPT (at least 6 months) compared with a short duration (less than 6 months) or aspirin alone. While this review did not show an overall difference in mortality, it included a heterogeneous population including patients with PAD, Atrial Fibrillation, and CAD managed medically and those undergoing PCI. Thus, it is unknown whether the effects of DAPT on cardiac mortality might be disease-specific.

A similar systematic review was conducted but only included trials in patients post-PCI with a DES.[2] Ten trials (n=31,666) were included in the meta-analysis comparing different durations of DAPT; shorter duration being 6 months or less and longer duration being longer than 1 year. As the DAPT trial resulted in an

unexpected increase in all-cause mortality, the goal of this review was to further evaluate the risk of mortality with longer duration of DAPT. Overall, shorter DAPT (1 year) was associated with significantly lower rates of mortality compared with longer DAPT (≥1 year) (HR 0.82; 95% CI 0.69-0.98). The results were primarily driven by a reduction in non-cardiac mortality as there was no difference in cardiac mortality. There was no significant difference in all-cause death comparing ≤6 months vs. ≥1 year duration of DAPT (HR 0.87; 95% CI 0.64 to 1.19). Similar to the DAPT study, there was a significantly lower rate of stent thrombosis with 1 year and longer of DAPT compared to shorter durations. However, shorter DAPT duration was associated with significantly lower rates of major bleeding and any bleeding compared with longer DAPT.

Lastly, a meta-analysis of RCTs assessed the benefits and risks of short term (< 12 months) or extended (> 12 months) DAPT versus standard 12 month therapy following PCI with DES.[3] A total of 10 RCTs (n=32,287) were included in the meta-analysis, including the DAPT trial. Clopidogrel and aspirin was the most frequent drug combination; prasugrel or ticagrelor were available in three and two studies, respectively. The majority of patients in the trials had either stable angina or non-ST elevation MI (NSTEMI) ACS. Cardiovascular mortality between short-term and 12-month DAPT did not differ significantly (OR 0.95; 95% CI 0.68 to 1.33). Similarly, CV mortality did not significantly differ between extended DAPT and 12-month therapy (OR 1.09; 95% CI 0.79 to 1.50). There was a significant reduction in the odds of a MI with extended DAPT compared with 12-month therapy (OR 0.53; 95% CI 0.42 to 0.66), as well as in stent thrombosis (OR 0.33; 95% CI 0.21 to 0.51). There was no difference in MI or stent thrombosis between shorter duration of DAPT and 12-month therapy. As expected, the risk of bleeding increased as the duration of therapy increased with the highest risk in the extended DAPT therapy and a reduction in risk in the short term therapy. There was no difference seen in all-cause mortality between short-term and 12-month DAPT; with a higher risk of all-cause death in extended therapy versus 12-month therapy (OR 1.30; 95% CI 1.02 to 1.66; NNH 238).

CADTH summarized the evidence for clinical effectiveness, cost effectiveness and recent guidelines for clopidogrel, prasugrel and ticagrelor in adults with ACS.[17] The literature search extended from January 2007 through May 2012 and was limited to RCTs, systematic reviews, technology assessments, meta-analyses, economic evaluations and guidelines that were appraised for quality. Aspirin plus clopidogrel was found to reduce the risk of CV events and was cost-effective compared to aspirin alone in ACS patients with UA/NSTEMI or STEMI whether patients were medically managed or revascularized. Prasugrel (TRITON-TIMI 38[24]) and ticagrelor (PLATO[25]) were more effective than standard clopidogrel doses but with a higher risk of bleeding. It was noted that the PLATO[25] trial had no difference for the composite primary outcome in the North American subpopulation, though it is unknown whether this was due to higher aspirin doses observed in this population. CADTH authors concluded that clopidogrel and aspirin remain the recommended therapy for ACS patients but that ticagrelor or prasugrel may be considered in STEMI patients that have not received antiplatelet therapy prior to arrival to the catheterization lab, or in high risk NSTEMI patients where quick onset of action is a priority.

Current guidelines recommend the use of proton pump inhibitors (PPIs) with DAPT in individuals at high risk for gastrointestinal ulceration or bleed. However, studies have noted a drug-drug interaction between PPIs and clopidogrel, which may reduce activation of clopidogrel when used concomitantly. A recent systematic review evaluated the comparative effectiveness and safety of concomitant use of PPIs and DAPT among patients with unstable angina and NSTEMI. [26] Results from this review conflicted with the original observational studies that demonstrated an association between concomitant administration of PPIs and poor clinical outcomes. Four RCTs included in this review demonstrated use of omeprazole resulted in no differences in ischemic events versus the control group but led to a greater reduction in upper GI bleeds. Evidence from RCTs should be weighted heavier compare to observational data.

A high quality meta-analysis of RCTs compared major adverse cardiac events (MACEs) and bleeding in patients with prasugrel versus clopidogrel to help determine if the increased risk of bleeding associated with prasugrel is outweighed the decreased risk of MACEs compared to clopidogrel.[5] All studies in patients

with CAD were included through a literature search up to December 15, 2014. Nine studies (n=25,214) were included in the meta-analysis and MACEs were defined as a composite outcome of CV deaths, MI, and ischemic stroke. As expected, the incidence of MACEs was lower in the prasugrel group than in the clopidogrel group (OR 0.86; 95% CI 0.78 to 0.94; p<0.0001) and the incidence of major bleeding was higher in the prasugrel group (OR 1.33; 95% CI 1.09 to 1.61; p=0.004). The risk of MACEs outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009). Results using a fixed effect model were of the same conclusion. In double-dose clopidogrel trials, there was no difference in the incidence of MACEs, major bleeding, and minor bleeding between prasugrel group and clopidogrel group. Sensitivity analysis suggested the presence of publication bias for the outcome of major bleeding only. [5]

Stroke

A review by the Cochrane Collaboration assessed the efficacy and safety of immediate oral antiplatelet therapy in people with acute ischemic stroke, including RCTs comparing oral antiplatelet therapy started within 14 days of stroke, with control (placebo or no treatment) in people with definite or presumed ischemic stroke.[27] A total of 8 trials with a low risk of bias were identified, but two trials evaluating aspirin 160-300 mg daily accounted for 98% of the data. The review found treatment with aspirin led to a significant decrease in death or dependent on help from other people for their activities of daily living (OR 0.95; 95% CI 0.91 to 0.99)and a nominally significant reduction in death (OR 0.92; 95% CI 0.85 to 1.00; p=0.05), with a small increased risk of intracranial hemorrhage (OR 1.23; 95% CI 1.00 to 1.50). The authors concluded that this small risk was outnumbered by the benefit, including a reduction in recurrent stroke (OR 0.77; 95% CI 0.69 to 0.87) and pulmonary embolism (OR 0.71; 95% CI 0.53 to 0.96). In addition, the indirect comparisons of different agents showed no evidence of significant heterogeneity of effect between the different agents tested (aspirin alone, ticlopidine alone, the combination of aspirin and dipyridamole). However, the data from the non-aspirin regimens were extremely limited.

New Guidelines:

Acute Coronary Syndrome

NICE recommends ticagrelor as a treatment alternative to clopidogrel post-MI for up to 12 months. The recommendation is based on a technology assessment of ticagrelor that estimated a decreased cost per Quality Adjusted Life Year gained over clopidogrel for the treatment of ACS in Great Britain.[28] A separate technology assessment from NICE also provided guidance for prasugrel for ACS and recommends prasugrel in combination with aspirin as a possible option for preventing atherothrombotic events in adults with ACS having PCI.[29]

The American College of Chest Physicians recommends ticagrelor over clopidogrel for patients the first year after ACS (2B recommendation, based upon unclear or close risk/benefit balance and moderate quality evidence) and recommend against prasugrel for patients less than 60 kg, over 75 years of age or with a previous history of stroke. Clopidogrel plus aspirin are recommended for 6-12 months in patients undergoing elective PCI and stent placement.[9]

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of patients with NSTEMI ACS recommends aspirin 162-325 mg be given as soon as possible after presentation with a maintenance dose of 81 to 325 mg per day continued indefinitely.[30] Clopidogrel is recommended for those who cannot tolerate aspirin. For those undergoing early invasive therapy, the guidelines recommend a P2Y12 inhibitor (clopidogrel or ticagrelor) with aspirin for up to 12 months of therapy, but ticagrelor is preferred over clopidogrel (Class IIa). Ticagrelor and prasugrel are preferred over clopidogrel in post-PCI patients (Class IIa), but prasugrel should be avoided in patients who are at a high risk of bleeding.

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) also released 2014 guidelines on myocardial revasculrization.[31] In patients with NSTE-ACS or STEMI undergoing PCI, the guideline recommends prasugrel or ticagrelor in combination with aspirin for 12 months if there is no excessive risk of bleeding (Class 1; Level B). Clopidogrel is recommended only when prasugrel or ticagrelor are not available or are contraindicated. In those with stable CAD undergoing PCI, the guidelines recommend clopodgrel for elective stenting with DAPT for at least 1 month after BMS and at least 6 months after DES implantation (Class I; Level B), with shorter DAPT considered (< 6 months) in patients at high bleeding risk (Class IIB; Level A) and longer therapy in patients at high ischemic risk and low bleeding risk.

Noncardioembolic Ischemic Stroke or Transient Ischemic Attack

The AHA/ACCF published updated guidelines for secondary prevention of stroke in 2014.[11] The guidelines state that aspirin 50 to 325 mg daily monotherapy or D-ER/ASA twice daily are indicated as initial therapy for TIA or ischemic stroke for prevention of future stroke. Clopidogrel 75 mg daily as monotherapy is a reasonable option for secondary prevention, especially for patients allergic to aspirin. The update includes a new recommendation to consider DAPT with aspirin and clopidogrel within 24 hours of a minor ischemic stroke or TIA for 90 days (Level B). This recommendation is based on the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which enrolled patients within 24 hours of a minor ischemic stroke or TIA.[24] Patients were assigned aspirin plus clopidogrel or aspirin plus placebo for 90 days. There were fewer ischemic or hemorrhagic stroke events in the combination group (8.6%) compared to the aspirin group (11.7%) [HR 0.68; 95% CI 0.57 -0.81] and rates of bleeding were similar. Initiation of aspirin and clopidogrel days to years after a stroke increases the risk of hemorrhage compared to either agent alone and is not routinely recommended. Additionally, Level C evidence highlights the uncertainty of adding antiplatelet therapy to a vitamin K antagonist (i.e., warfarin) in patients with a history of ischemic stroke, TIA, AF or CAD.[11] For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit.

The guidelines for the primary prevention of stroke were also updated in 2014.[32] The majority of the recommendations regard controlling modifiable risk factors to prevent stroke and for antithrombotic therapy for the prevention of stroke in AF, with aspirin as a consideration for patients with nonvalvular AF and a CHA_2DS_2-VAS_c score of 1. A new recommendation lists anticoagulants or antiplatelet agents as reasonable treatment options for patients with heart failure who do not have AF or a previous thromboembolic event (CLASS IIa; Level of Evidence A). This recommendation comes from the WARCEF trial which showed no difference in the primary outcome of ischemic stroke, intracranial hemorrhage (ICH), or death between warfarin and aspirin, but found a significant reduction in the rate of ischemic stroke with warfarin compared to aspirin and an increased rate of major hemorrhage with warfarin. Other recommendations for the use of antiplatelet agents, including aspirin, for primary prophylaxis are as follows:

- Antiplatelet agents and aspirin are recommended for primary prophylaxis for people whose risk is sufficiently high (10-year risk >10%) when the benefits outweigh the risks of bleeding (CLASS IIA; Level of Evidence A).
- Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (Class IIB; Level of Evidence C). This does not apply to severe kidney disease (stage 4 or 5; Glomerular Filtration Rate <30 mL/min).
- Cilostazol may be reasonable for primary prevention of stroke in people with PAD (Class IIb; Level of Evidence B).
- As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for primary prevention (Class III; Level of evidence C).

Peripheral Artery Disease

Guidelines for PAD have not been recently updated. The 2011 AHA/ACCF guidelines recommend aspirin or clopidogrel daily for symptomatic PAD.[21] Combination aspirin and clopidogrel may be considered for patients with symptomatic lower extremity PAD at perceived high CV risk (Level B evidence).

Antiplatelet therapy in asymptomatic PAD is not supported in patients with ankle-brachial indexes 0.91-0.99 (Level A evidence) but may be beneficial in ankle-brachial indexes ≤ 0.90 (Level C evidence).

Randomized Controlled Trials: A recent DERP literature scan[1] tabulated the potentially relevant new RCTs by drug comparison and population. Overall, 2 new head-to-head trials, 5 post-hoc or secondary analyses of published trials (Appendix 2), and 2 placebo-controlled trials were considered potentially relevant. One head to head trial was not designed to evaluate a clinically important outcome. [34] The head to head trials are summarized in Table 1 below. Full abstracts are included in Appendix 2.

In addition, 3 relevant RCTs were identified; of these, the DAPT trial[1] and the ISAR-SAFE trial[33] were included in systematic reviews assessed above, exploring the optimal duration of DAPT following ACS and will not be evaluated further. The remaining study is summarized in Table 1 below. Full abstracts are included in Appendix 2.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results		Quality*
PEGASUS-TIMI 54[4] RCT, DB	Ticagrelor 90 mg BID vs. ticagrelor 60 mg BID vs. placebo (all with background aspirin therapy)	Patients with a MI 1-3 years previously (median time 1.7 years)(n=21,162)	Composite of CV death, MI, or stroke	Composite Endpoint: Ticagrelor 90: 7.85% Ticagrelor 60: 7.77% Placebo: 9.04% Tic90 vs. placebo: HR 0.85; 95% CI 0.75 to 0.96; p=0.008 Tic60 vs. placebo: HR 0.84; 95% CI 0.74 to 0.95; p=0.004	TIMI major bleeding: Ticagrelor 90: 2.6% Ticagrelor 60: 2.3% Placebo: 1.06% Tic90 vs. placebo: HR 02.69; 95% CI 1.96 to 3.70; p<0.001 Tic60 vs. placebo: HR 2.32; 95% CI 1.68 to 3.21; p<0.001	Good
Gasparovic[35]	Clopidogrel + ASA vs. ASA	Aspirin-resistant patients following CABG	Composite of all-cause death, nonfatal MI, stroke, or CV hospitalization at 6 months postoperatively	Composite Endpoint: DAPT: 6% ASA: 10% RR 0.61; 95% CI 0.25 to 1.51; p=0.33 DAPT did lower the incidence of the primary endpoint in obese patients and those < 65 y/o	Bleeding events DAPT: 25% ASA: 19% RR 1.34; 95% CI 0.8 to 2.23; p=0.33	Fair

Abbreviations: BID = twice daily; CV = cardiovascular; DB = double-blind; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis in Myocardial Infarction.
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

New FDA Safety Alerts:
None identified.

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Appendix 1: Current Status on Preferred Drug List

Current Status of PDL Class:

- Preferred Agents: ASPIRIN, CLOPIDOGREL, DIPYRIDAMOLE, DIPYRIDAMOLE ER 200MG/ASPIRIN 25MG (D-ER/ASA)
- Non Preferred Agents: TICAGRELOR (BRILINTA), PRASUGREL (EFFIENT), TICLOPIDINE, VORAPAXAR (ZONTIVITY)

Appendix 2: RCTs identified by DERP Literature Scan[1]

Table 2. Secondary publications of trials listed above or included in report previously (N=32)*

Study	Subgroup or Secondary Outcome	Comparison
PLATO	**ACS**	Ticagrelor vs. Clopidogrel
Kotsia, 2014	Clinical events and safety in relation to extent of CAD	
Mahaffey, 2014	MI and impact of event adjudication	
Varenhorst, 2014	Factors associated with mortality	
TRITON-TIMI-38	**ACS**	Prasugrel vs Clopidogrel
Kohli, 2014	Discharge aspirin dose and clinical outcomes	
TRILOGY ACS	**ACS**	Prasugrel vs Clopidogrel
Cornel, 2014	Impact of smoking status on clinical outcomes in ACS patients without revascularization	

1. Dasbiswas A[1], Rao MS[2], Babu PR[3], Vijayvergiya R[4], Nayak R[5], Dani S[6], Tyagi S[7], Hiremath S[8], Patel T[9], Alexander T[10], Prakash VS[11], Singh DP[8], Yadav MK[4], Pathak K[12], Srivastava A[12]. A comparative evaluation of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *J Assoc Physicians India.* 2013 Feb;61(2):114-6, 126.

OBJECTIVE: Primary objective of this study was to compare the efficacy of Prasugrel vs. Clopidogrel in the patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) by measuring inhibition of platelet aggregation after loading and maintenance dose of both the drugs. The patients were also assessed for safety of the drugs.

METHODS: This was a randomised, double-blind, double-dummy, comparative, multicentric clinical trial in patients with acute coronary syndrome (unstable angina, non-ST elevation MI and ST elevation MI) undergoing PCI. The patients were randomly assigned to receive prasugrel (loading dose of 60 mg followed by maintenance dose of 10-mg once daily) or clopidogrel (loading dose of 300 mg followed by maintenance dose of 75 mg once daily) for a period of 12 weeks. All the patients were co-prescribed aspirin 325 mg with both the drugs. The primary efficacy end point in this study was percentage inhibition of ADP induced platelet aggregation (IPA) at 4 +/- 1 hours after the loading dose and at 30 +/- 3 days during maintenance treatment. The platelet aggregation of both the drugs was measured by whole blood aggregometer using 10 mmol of ADP as an aggregant. Though this study was not powered to see the difference in clinical efficacy parameters, the patients were observed for the incidence of nonfatal MI, nonfatal stroke, re-hospitalization, death, or need for urgent revascularization due to a cardiac ischemic event at days 30 and 90 during the study. The safety of study drugs were evaluated by incidence of major bleeding, reported adverse drug reaction and alterations of any laboratory parameters.

RESULT: A total of 220 patients were enrolled at 11 centres across India. Ten patients were given the loading dose of prasugrel or clopidogrel but did not underwent PCI due to change in investigator's decision to go for PCI. Out of 210 eligible patients, 21 patients were discontinued during the study. 157 patients were evaluated for platelet inhibition after loading dose at 4 hours and 150 patients at day 30 during maintenance phase of antiplalelet therapy. The investigators could not perform this test in remaining patients due to urgency and criticality of the patients. 189 patients were observed for the incidence of nonfatal MI, nonfatal stroke, rehospitalisation, urgent revascularisation or death due to a cardiac ischemic event. All eligible patients who received at least a loading dose were evalauted for safety. In prasugrel group, 85 and 77 patients were evaluated for IPA at 4 hours and day 30 respectively whereas in clopdogrel group 72 and 73 patients were tested for IPA at 4 hours and at 30 days. Patients in prasugrel group have demonstrated significantly higher inhibition of platelets as compared to clopidogrel group (82.5% vs 71.1%) at 4 hours and at 30 days (84.1% vs 67.4%). The difference in inhibition of platelets between prasugrel and clopidogrel after loading dose and maintenenace dose was statistically significant ($p <$ or $= 0.01$). The patients were also evaluated for drug hyporesponsiveness to antiplatelet therapy if IPA was < 20% at day 30 from the baseline. More patients on prasugrel have shown response to antiplatlet therapy than on clopidogrel (97.4% vs 87.6%). The difference between the two groups was statistically significant ($p < 0.05$). There was no difference observed during the study in the incidence of nonfatal MI, nonfatal stroke, death, rehospitalisation or need for urgent revascularisation due to a cardiac event between prasugrel and clopidogrel. Both the drugs were found to be to be well tolerated and have comparable safety profile.

CONCLUSION: This study suggests that prasugrel is more effective than clopidogrel as an anti platelet drug as evident by inhibition of platelet aggregation. More patients on clopidogrel are likely to have poor response to therapy as compared to prasugrel. Both the drugs were well tolerated and have comparable safety profile.

2. Gasparovic H[1], Petricevic M[2], Kopjar T[2], Djuric Z[2], Svetina L[2], Biocina B[2]. Impact of dual antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. Am J Cardiol. 2014 May 15;113(10):1660-7. doi: 10.1016/j.amjcard.2014.02.024. Epub 2014 Mar 1.

Coronary artery bypass grafting is pivotal in the contemporary management of complex coronary artery disease. Interpatient variability to antiplatelet agents, however, harbors the potential to compromise the revascularization benefit by increasing the incidence of adverse events. This study was designed to define the impact of dual antiplatelet therapy (dAPT) on clinical outcomes among aspirin-resistant patients who underwent coronary artery surgery. We randomly assigned 219 aspirin-resistant patients according to multiple electrode aggregometry to receive clopidogrel (75 mg) plus aspirin (300 mg) or

aspirin-monotherapy (300 mg). The primary end point was a composite outcome of all-cause death, nonfatal myocardial infarction, stroke, or cardiovascular hospitalization assessed at 6 months postoperatively. The primary end point occurred in 6% of patients assigned to dAPT and 10% of patients randomized to aspirin-monotherapy (relative risk 0.61, 95% confidence interval 0.25 to 1.51, p = 0.33). No significant treatment effect was noted in the occurrence of the safety end point. The total incidence of bleeding events was 25% and 19% in the dAPT and aspirin-monotherapy groups, respectively (relative risk 1.34, 95% confidence interval 0.80 to 2.23, p = 0.33). In the subgroup analysis, dAPT led to lower rates of adverse events in patients with a body mass index >30 kg/m(2) (0% vs 18%, p <0.01) and those <65 years (0% vs 10%, p = 0.02). In conclusion, the addition of clopidogrel in patients found to be aspirin resistant after coronary artery bypass grafting did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events. dAPT did, however, lower the incidence of the primary end point in obese patients and those <65 years.