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Drug Class Literature Scan: Antiplatelets

Date of Review: September 2017

Date of Last Review: July 2015
Literature Search: July 2015-June 2017

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- A Cochrane systematic review evaluated the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis on the outcome of graft patency.[3] The overall applicability of this systematic review to clinical practice is low and results cannot be used to make policy changes at this time. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) could not be calculated.
- There are significant new data from multiple trials, systematic reviews, and guidelines addressing the most appropriate duration of dual antiplatelet therapy (DAPT) with aspirin and other antiplatelet agent following acute coronary syndrome (ACS). Overall, the data suggests that DAPT beyond 12 months decreases ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk.
- Previous large randomized controlled trials (RCTs) have demonstrated a reduction in ischemic events with the more potent P2Y12 inhibitors (prasugrel and ticagrelor) compared to clopidogrel with an absolute risk reduction (ARR) of approximately 2%.[1,2] A recent network meta-analysis[7] and a large RCT[20] have conflicting results. The meta-analysis with many limitations found no difference in mortality, cardiovascular (CV) death, myocardial infarction (MI) or stent thrombosis with either prasugrel or ticagrelor compared to clopidogrel. Additionally, a large RCT in patients with symptomatic peripheral arterial disease found no difference in a composite CV outcome or major bleeding with ticagrelor versus clopidogrel (10.8% vs. 10.6%).
- A fixed-dose combination of aspirin and omeprazole (Yosprala®) was FDA approved in September 2016 for those patients at high risk of developing aspirin associated gastric ulcers. Approval studies demonstrated a significant reduction at 6 months in the incidence of gastric or duodenal ulcer formation compared to aspirin alone (ARR 3.8%-4.9%).[6] However, these studies remain unpublished and cannot be assessed for quality. Additionally, only patients with a history of gastric or duodenal ulcer were included in trials and comparison to aspirin alone in these high risk patients is not a clinically relevant comparison.

Recommendations:

- No changes to the PDL recommended at this time.
- After evaluation of comparative drug costs in executive session, no PDL changes were recommended.

Previous Conclusions:

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- 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).
- 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). 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. 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.
- 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.

Previous 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

Methods:

A DERP scan searched Ovid MEDLINE from December 2015 through January 2017 using terms for included drugs. An additional Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted from January 2017 through June 2017. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Lower Limb Atherosclerosis

A Cochrane systematic review was done to determine the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis undergoing bypass grafting.[3] A total of 16 studies (n=5683) were included in the analysis. The quality of evidence was low to moderate. Many of the treatment comparisons had few data to contribute, treatment dosages varied between studies, and the majority of studies did not describe their methods of randomization, allocation concealment or blinding of outcome assessors. The primary efficacy outcome was success of therapy, measured by graft patency. Six of the studies compared aspirin (ASA) or ASA plus dipyridamole (ASA/DIP) versus placebo or no treatment. There was improved graft patency in the ASA or ASA/DIP treatment group (OR 0.42; 95% CI 0.22 to 0.83; p=0.01). However, there was no improvement in those who received venous grafts. Additionally, studies included in the comparison were very old, and ASA doses ranged from 300mg to 325 mg given two to three times daily which is not consistent with doses used in clinical practice today. There was no difference in CV events (OR 1.27; 95% CI 0.43 to 3.80; 4 trials). The data was too scarce to combine and make definitive conclusions for all other comparisons of antiplatelet agents or other comparisons were not applicable to clinical practice standards. There was one large study (n=851) that evaluated clopidogrel and ASA versus ASA alone, and there was no difference of primary patency at 24 months (OR 0.95; 95% CI 0.69 to 1.31). There were fewer cases of total bleeding in the ASA alone group compared to ASA + clopidogrel (OR 2.65; 95% CI 1.69 to 4.15), but there was no difference in severe bleeding or fatal bleeding with few events in either group. There was no difference in all-cause mortality (OR 1.44; 95% CI 0.76 to 2.72). The overall applicability of this systematic review to practice is low and results cannot be used to make policy changes at this time. Further high-quality studies evaluating clinically meaningful outcomes are necessary. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) were not able to be calculated.

Dual Antiplatelet Therapy

Three systematic reviews were published evaluating the duration of dual antiplatelet therapy (DAPT).[7–9] One review included studies with patients after acute myocardial infarction (MI), one included trials with patients after a drug-eluting stent (DES) implantation, and the third review included all secondary prevention populations. The results are consistent with previous data and guidelines suggesting that DAPT beyond 1 year decreased ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk. Since these trials only compared duration of treatment and did not compare individual antiplatelet agents, they will not impact the current preferred drug list (PDL) or prior authorization policy and will not be explored further.

Comparison of platelet adenosine diphosphate (ADP) $P2Y_{12}$ Inhibitors

A network meta-analysis to compare clinical outcomes of patients receiving clopidogrel, prasugrel, ticagrelor and cangrelor prior to or during percutaneous coronary intervention (PCI) was performed.[7] A literature search identified RCTs comparing at least 2 of the P2Y12 inhibitors in those who had a PCI. The Cochrane Collaboration tool for assessing risk of bias was used to evaluate included trials. The meta-analysis used indirect comparisons to compare each agent to clopidogrel. A total of 15 RCTs (n=54,025) were included in the meta-analysis.[7] Of the patients included in these trials, 29.4% of patients had a STEMI, 87.2% with ACS, and 92.4% underwent PCI. Compared to clopidogrel, there was no significant difference between either prasugrel or ticagrelor in all-cause mortality, CV death, MI, stent thrombosis, stroke, or major bleeding. There was an increased risk of minor bleeding with ticagrelor compared to clopidogrel (OR 1.59; 95% CI 1.10 to 5.03). Previous literature has suggested that prasugrel and ticagrelor achieve faster and greater inhibition of platelet binding compared to clopidogrel and individual RCTs have demonstrated a reduction in ischemic events after PCI for these agents compared to placebo.[7] Results of this analysis conflict with those findings. However, there are limitations of a network meta-analysis, a loss of statistical power for direct comparison, and follow-up times which varied greatly among the studies. This systematic review was not funded.

Aspirin in Peripheral Vascular Disease:

A systematic review registered in PROSPERO International prospective register of systematic reviews evaluated aspirin in patients with peripheral vascular disease.[10] A literature search limited to RCTs through January 2017 identified 11 studies that were included (n=6560). The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary efficacy outcome was all-cause mortality, and the primary safety outcome was major bleeding. The majority of trials had an unclear risk of bias due to lack of reporting of detailed methods. Two trials had a low risk of bias. Using the GRADE assessment tool, the level of evidence was considered low to moderate. Results from 9 trials found no difference in the incidence in all-cause mortality with aspirin versus control (7.7% vs. 8.5%; RR -0.93; 95% CI 0.8 to 1.1).[10] The incidence of MI and stroke were also similar between both groups. There was no difference incidence of major bleeding with aspirin compared to control (1.3% vs. 1.1%; RR 1.59; 95% CI 0.96 to 2.62).[10] These results conflict with recent guideline recommendations for aspirin in symptomatic peripheral vascular disease. The authors point out that the guideline recommendations were made based on 3 studies only with a high risk of bias in combination with older evidence using antiplatelet agents other than aspirin.[10]

New Guidelines:

Aspirin for Primary Prevention of Cardiovascular Disease

The U.S. Preventive Services Task Force (USPSTF) updated their recommendations to prevent cardiovascular disease (CVD) in June 2016.[11] The USPSTF is an independent, voluntary body and authors had no conflicts of interest. The USPSTF commissioned 3 systematic reviews and a decision-analysis model to develop its recommendation. The following recommendations were made:

Population	Recommendation	Evidence Grade
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	the USPTF recommends initiating low-dose aspirin for the primary prevention of CVD and colorectal cancer (CRC) in those who are not at increased risk of bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin for at least 10 years	B (high certainty that the net benefit is moderate)
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate aspirin should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C (recommend selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small)
Adults younger than 50 years	Evidence is insufficient	I
Adults aged 70 years or older	Evidence is insufficient	I

Management of Patients with Lower Extremity Peripheral Artery Disease (PAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published guidelines in 2016.[12]

The guidelines were sponsored by ACC/AHA and without commercial support. Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry.

Approximately half of the other members disclosed some sort of relationship with industry within 12 months prior. There was one lay volunteer/patient representative on the guideline committee; however, the majority of other members were cardiovascular specialists and the committee was missing representation from primary care or other non-specialty practitioners. A contracted methodologist and external evidence review committee addressed systematic review questions and appraised the evidence.

The following recommendations for medical therapy with antiplatelets for the patient with PAD were provided. There were no strong recommendations for one agent over another, but aspirin is the favored medication for symptomatic PAD. Clopidogrel remains an alternative.

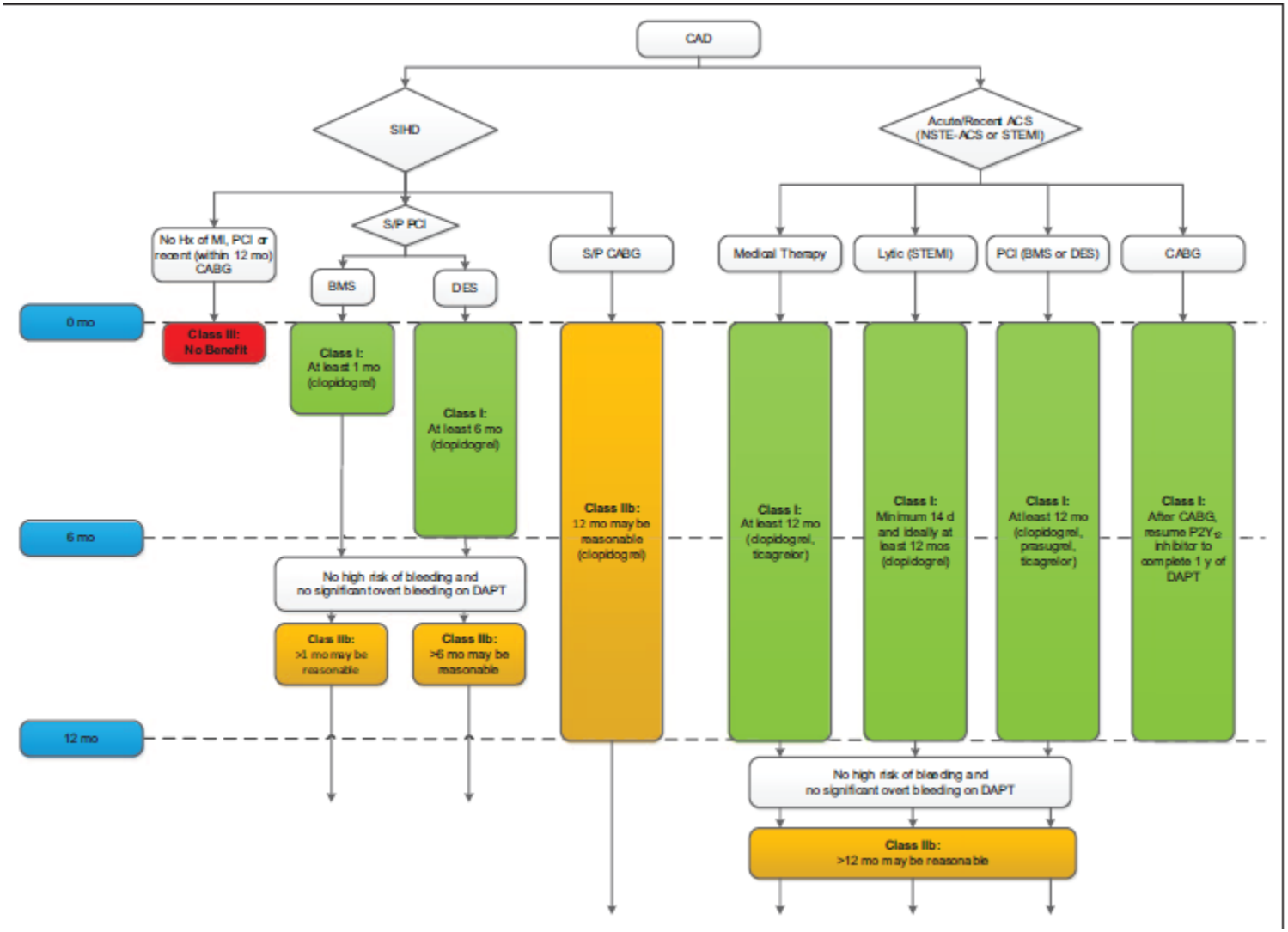
- Antiplatelet therapy with aspirin alone (75-325 mg) or clopidogrel alone is recommended to reduce myocardial infarction (MI), stroke and vascular death in patients with symptomatic PAD. Symptomatic PAD includes those with claudication and those with prior lower extremity revascularization.
    - Class of Recommendation I (Strong)
    - Level of Evidence A (high quality)
- In asymptomatic patients with PAD, antiplatelet therapy is reasonable to reduce the risk of MI, stroke or vascular death.
    - Class of Recommendation IIa (Moderate)
    - Level of Evidence C-EO (Expert Opinion)
- The effectiveness of dual antiplatelet therapy (DAPT) to reduce the risk of CV ischemic events in patients with symptomatic PAD is not well established.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)
- The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)

Duration of Dual Antiplatelet Therapy (DAPT) in Coronary Artery Disease (CAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published a focused update on DAPT in CAD in 2016.[13] This update was necessary due to 11 studies of patients with stent implantation assessing shorter-duration or longer-duration of DAPT and one large RCT assessing DAPT versus aspirin monotherapy. This guideline focused on duration of DAPT and aspirin dosing and not if one particular $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is preferred over another. Recommendations were made based on a systematic review conducted by an external evidence review committee.[14] Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry.

Overall, the new evidence supports the concept that duration of DAPT should be individualized based on risk of bleeding and ischemic risk. Longer duration compared with shorter duration of DAPT generally results in decreased ischemic risk at the expensive of an increased bleeding risk. Additionally, use of more potent $P2Y_{12}$ inhibitors in place of clopidogrel may result in decreased ischemic risk and increased bleeding risk. For patients with acute coronary syndrome (ACS), there is a strong recommendation that DAPT should be given for a minimum period of time (usually 6 to 12 months) and a weak recommendation for continuation of DAPT beyond that period of time. Additionally, shorter duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk. This is outlined in **Figure 1**.

Figure 1: Treatment algorithm for duration of DAPT therapy in patients with CAD[13]



In regards to choosing an antiplatelet, the guidelines state that "*it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel in patients with ACS treated with DAPT after coronary stent implantation and to use ticagrelor in those treated with medical therapy alone".* These are both moderate recommendations based on moderate quality evidence from 1 RCT.

New Formulations:

Yosprala® is a combination of aspirin and omeprazole approved September 2016 for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.[6] This is the only prescription fixed-dose combination of aspirin and a proton pump inhibitor and is available with both 81 and 325 mg of aspirin in combination of 40 mg of omeprazole. Approval was based on 2 unpublished, randomized, double-blind studies (n=524) over 6 months evaluating incidence of gastric ulcer formations with Yosprala compared to aspirin 325 mg alone in those at risk for developing gastric ulcers.[6] Patients had a cerebro- or cardiovascular diagnosis, were on aspirin for at least 3 months, and had a history of gastric or duodenal ulcer within the past 5 years. At month 6, the incidence of gastric or duodenal ulcer formation was lower in the Yosprala group compared to aspirin in study 1 and study 2 (3.8% vs. 8.7%; ARR 4.9%; NNT 21 and 8.5% vs. 2.7%; ARR 5.8%; NNT 18, respectively).[6] One study reported a higher rate of serious adverse events in the study group compared to aspirin alone (8.95% vs. 6.56%). Conversely, in the second study, rate of serious adverse events was higher in the aspirin group (9.06% vs. 6.06%). P-values were not reported. These studies remain unpublished and could not be assessed for quality. Results were collected from the prescribing information[6] and clinicaltrials.gov. Additionally, the comparison to aspirin alone in those with a history of an ulcer is not a clinically relevant comparison.

Long term CV and gastrointestinal (GI) safety were evaluated in a 12-month, open-label, phase 3 study in adults requiring aspirin for secondary prevention of cardiovascular or cerebrovascular events with history of a gastric or duodenal ulcer (n=380).[14] Only 290 subjects completed the 12 month study. The most common GI events were diarrhea, dyspepsia, and nausea which were reported in 4-5% of the overall population. The overall incidence of treatment emergent adverse events was 75%. Adverse events leading to study withdrawal occurred in 13.5% of subjects, with the most common reason being gastroesophageal reflux disease (1.1%).[14]

New FDA Safety Alerts:

A safety alert was released in November 2015 after an FDA review on long-term treatment with clopidogrel.[15] The FDA concluded that the long term use of clopidogrel does not increase or decrease overall risk of death in patients with heart disease and there does not appear to be an increase in the risk of cancer related deaths or cancer related adverse events.

New FDA Approved Medications:

Cangrelor (Kengreal™) is a $P2Y_{12}$ inhibitor approved on 6/22/2015 as an adjunct to PCI for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.[16] It is administered as an intravenous bolus prior to PCI followed by an infusion during the procedure. Because it is not used in outpatients, the evidence will not be evaluated further.

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Author: M. Herink Date: September 2017

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CPMP 12HR	AGGRENOX	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	CPMP 12HR	ASPIRIN-DIPYRIDAMOLE ER	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	TABLET	CILOSTAZOL	CILOSTAZOL	Y
ORAL	TABLET	CLOPIDOGREL	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	PLAVIX	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	DIPYRIDAMOLE	DIPYRIDAMOLE	Y
ORAL	TAB CHEW	ASPIRIN	ASPIRIN	Y
ORAL	TAB CHEW	CHILDREN'S ASPIRIN	ASPIRIN	Y
ORAL	TABLET	ASPIRIN	ASPIRIN	Y
ORAL	TABLET DR	ASPIR 81	ASPIRIN	Y
ORAL	TABLET DR	ASPIRIN EC	ASPIRIN	Y
ORAL	TABLET DR	ASPIR-LOW	ASPIRIN	Y
ORAL	TABLET DR	ECPIRIN	ASPIRIN	Y
ORAL	TABLET DR	LOW DOSE ASPIRIN EC	ASPIRIN	Y
ORAL	CAP ER 24H	DURLAZA	ASPIRIN	N
ORAL	TABLET	BRILINTA	TICAGRELOR	N
ORAL	TABLET	EFFIENT	PRASUGREL HCL	N
ORAL	TABLET	TICLOPIDINE HCL	TICLOPIDINE HCL	N
ORAL	TABLET	ZONTIVITY	VORAPAXAR SULFATE	N

Appendix 2: New Comparative Clinical Trials

A total of 13 citations were manually reviewed from the initial literature search and an additional 5 were reviewed from the DERP scan. After further review, 15 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (platelet reactivity, platelet aggregation rates, mean platelet volume). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
PHILO[17] RCT, DB	Clopidogrel vs. ticagrelor	ACS in patients in Asia treated with PCI on background aspirin	Time to occurrence of myocardial infarction, stroke or death from vascular causes	Composite CV outcome: Clo: 25 (6.3%) Tic: 36 (9.0%) HR 1.47; 95% CI 0.88 to 2.44 Major Bleeding: Clo: 26 (6.8%) Tic: 40 (10.3%) HR 1.54; 95% CI 0.94 to 2.53
He at al.[18] RCT, open-label	Clopidogrel + ASA vs. ASA	Minor stroke or TIA	Neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days after admission	Deterioration of stroke: Clo+ASA: 9 ASA: 19 *Statistics not provided
Johnston et al.[19] RCT, DB	Ticagrelor vs. ASA	Non-severe ischemic stroke or high-risk TIA	Time to occurrence of stroke, myocardial infarction, or death within 90 days	Composite of stroke, myocardial infarction, or death Tic: 442/6589 (6.7%) ASA: 497/6610 (7.5%) HR 0.89; 95% CI 0.78 to 1.01 Major Bleeding: Tic: 31(0.5%) ASA: 38 (0.6%) HR 0.83; 95% CI 0.52 to 1.34
Hiatt et al.[20] RCT, DB	Ticagrelor vs. Clopidogrel	Symptomatic peripheral arterial disease	Composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke	Composite CV outcome: Clo: 740 (10.6%) Tic: 751 (10.8%) HR 1.02; 05% CI 0.92 to 1.13 P=NS Major Bleeding: Clo: 109 (1.6%) Tic: 113 (1.6%) HR 1.10; 95% CI

Abbreviations: ASA = aspirin; DB = double blind; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; TIA = transient ischemic attack

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Appendix 3: Abstracts of Comparative Clinical Trials

1. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. *Circ J*. 2015;79(11):2452-60. doi: 10.1253/circj.CJ-15-0112. Epub 2015 Sep 16.

BACKGROUND:
Few data on the relative efficacy and safety of new P2Y12inhibitors such as prasugrel and ticagrelor in Japanese, Taiwanese and South Korean patients with acute coronary syndromes (ACS) exist.

METHODS AND RESULTS:
The multicenter, double-blind, randomized PHILO trial compared the safety and efficacy of ticagrelor vs. clopidogrel in 801 patients with ACS (Japanese, n=721; Taiwanese, n=35; South Korean, n=44; unknown ethnicity, n=1). All were planned to undergo percutaneous coronary intervention and randomized within 24 h of symptom onset. Primary safety and efficacy endpoints were time to first occurrence of any major bleeding event and to any event from the composite of myocardial infarction, stroke or death from vascular causes, respectively.At 12 months, overall major bleeding occurred in 10.3% of ticagrelor-treated patients and in 6.8% of clopidogrel-treated patients (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94-2.53); the composite primary efficacy endpoint occurred in 9.0% and in 6.3% of ticagrelor- and clopidogrel-treated patients, respectively (HR, 1.47; 95% CI: 0.88-2.44). For both analyses, the difference between groups was not statistically significant.

CONCLUSIONS:
In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population.

2. He F, Xia C, Zhang JH, Li XQ, Zhou ZH, Li FP, Li W, Lv Y, Chen HS. Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. *J Clin Neurosci.* 2015 Jan;22(1):83-6. doi: 10.1016/j.jocn.2014.05.038. Epub 2014 Sep 10.

Abstract
Recent studies have suggested that combination antiplatelet therapy may be superior to monotherapy in the treatment of acute stroke. However, additional prospective studies are needed to confirm this finding. The present trial compared the efficacy and safety of clopidogrel plus aspirin versus aspirin alone in the treatment of non-cardioembolic ischemic stroke within 72 hours of onset. Six hundred and ninety patients aged $\geqslant$ 40 years with minor stroke or transient ischemic attack (TIA) were identified for enrollment. Experienced physicians determined baseline National Institutes of Health Stroke Scale scores at the time of admission. All patients were randomly allocated (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100mg/day). The main endpoints were neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days of admission. After 43 patients were excluded, 321 patients in the dual therapy group and 326 patients in the monotherapy group completed the treatment. Baseline characteristics were similar between groups. During the 2 week period, stroke deterioration occurred in nine patients in the dual therapy group and 19 patients in the monotherapy group. Stroke occurred after TIA in one patient in the dual therapy group and three patients in the monotherapy group. Similar

numbers of adverse events occurred in both groups. This study showed that early dual antiplatelet treatment reduced early neurological deterioration in patients with acute ischemic stroke, compared with antiplatelet monotherapy. These results imply that dual antiplatelet therapy is superior to monotherapy in the early treatment of acute ischemic stroke.

3. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med.* 2016 Jul 7;375(1):35-43. doi: 10.1056/NEJMoa1603060. Epub 2016 May 10.

BACKGROUND:
Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischemia.

METHODS:
We conducted an international double-blind, controlled trial in 674 centers in 33 countries, in which 13,199 patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2 through 90). The primary end point was the time to the occurrence of stroke, myocardial infarction, or death within 90 days.

RESULTS:
During the 90 days of treatment, a primary end-point event occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio, 0.87; 95% CI, 0.76 to 1.00). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.

CONCLUSIONS:
In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.).

4. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med*. 2017 Jan 5;376(1):32-40. doi: 10.1056/NEJMoa1611688. Epub 2016 Nov 13.

BACKGROUND:
Peripheral artery disease is considered to be a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. Data from previous trials have suggested that patients receiving clopidogrel monotherapy had a lower risk of cardiovascular events than those receiving aspirin. We wanted to compare clopidogrel with ticagrelor, a potent antiplatelet agent, in patients with peripheral artery disease.

METHODS:
In this double-blind, event-driven trial, we randomly assigned 13,885 patients with symptomatic peripheral artery disease to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patients were eligible if they had an ankle-brachial index (ABI) of 0.80 or less or had undergone previous revascularization of the lower limbs. The primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety end point was major bleeding. The median follow-up was 30 months.

RESULTS:
The median age of the patients was 66 years, and 72% were men; 43% were enrolled on the basis of the ABI and 57% on the basis of previous revascularization. The mean baseline ABI in all patients was 0.71, 76.6% of the patients had claudication, and 4.6% had critical limb ischemia. The primary efficacy end point occurred in 751 of 6930 patients (10.8%) receiving ticagrelor and in 740 of 6955 (10.6%) receiving clopidogrel (hazard ratio, 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65). In each group, acute limb ischemia occurred in 1.7% of the patients (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85) and major bleeding in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49).

CONCLUSIONS:
In patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups. (Funded by AstraZeneca; EUCLID ClinicalTrials.gov number, NCT01732822 .).

Author: M. Herink

Date: September 2017

Appendix 4: Medline Search Strategy

1	Platelet Aggregation Inhibitors/ or antiplatelets.mp.	27809
2	aspirin.mp. or Aspirin/	33795
3	Aspirin/	22000
4	Dipyridamole/ or Aspirin, Dipyridamole Drug Combination/	2499
5	clopidogrel.mp.	10526
6	ticagrelor.mp.	1229
7	prasugrel.mp. or Prasugrel Hydrochloride/	1540
8	Ticlopidine/ or ticlodipine.mp.	8530
9	vorapaxar.mp.	191
10	acute coronary syndrome.mp. or Acute Coronary Syndrome/	17978
11	Coronary Artery Bypass/ or Myocardial Revascularization/ or Angioplasty, Balloon, Coronary/ or coronary revascularization.mp.	62248
12	Stents/ or drug eluding stent.mp.	53562
13	Arterial Occlusive Diseases/ or Cerebral Infarction/ or Stroke/ or ischemic stroke.mp. or Ischemic Attack, Transient/	107484
14	peripheral vascular disease.mp. or Peripheral Vascular Diseases/	11432
15	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9	54413
16	10 or 11 or 12 or 13 or 14	229804
17	15 and 16	15201
18	limit 17 to (english language and humans and yr="2017 -Current" and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or systematic reviews))	13

Author: M. Herink

Date: September 2017

Appendix 5: Prior Authorization Criteria

Antiplatelets

Goal:

- Approve antiplatelet drugs for funded diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is this continuation of hospital treatment?	**Yes:** Approve for 30 days only and inform provider of preferred products.	**No:** Go to #5

Approval Criteria		
5. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

FDA Approved Indications (July 2017)

	2º Stroke	2º PAD	2º 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: 2º = secondary prevention; ACS=Acute Coronary Syndrome; ASA/DP ER = aspirin/dipyridamole; CI=contraindication; PCI=Percutaneous Intervention; X = FDA-approved indication.

P&T / DUR Review: *9/17; (MH) 7/15 (KK); 11/11*
Implementation: *10/15, 8/15; 7/31/14; 4/9/12*