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Abbreviated Class Update: Antiplatelet Drugs

Month/Year of Review: July 2014 **End date of literature search:** April 2014
New drug(s): vorapaxar (Zonitivity™) **Manufacturer:** Merck

Current Status of PDL Class:

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

Research Questions:

- Is there new comparative evidence that antiplatelet drugs differ in effectiveness for adult patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack (TIA), or symptomatic peripheral arterial disease (PAD)?
- Is there any new evidence that antiplatelet drugs differ in harms for adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease?

Conclusions:

- 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).

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).
- Add vorapoxar to antiplatelet PA Criteria.

Reason for Review:
Two new drugs have been reviewed by the FDA (vorapaxar in January 2014 and cangrelor in February 2014) and a new Drug Effectiveness Review Project (DERP) scan of the literature was published.[1]

Previous P&T Conclusions (November 2011[2,3]):

- There was high strength evidence prasugrel reduced target-vessel revascularization more than clopidogrel at 15 months in patients with acute coronary syndrome (ACS) undergoing revacularization (HR 0.66 95% CI 0.54 – 0.81). There was moderate-high strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes of all-cause mortality (HR 0.95 95% CI 0.78 – 1.16) and cardiovascular mortality (HR 0.89 95% CI 0.70 – 1.12). There was moderate evidence of ticagrelor superiority over clopidogrel for all-cause mortality (HR 0.78 95% CI 0.69-0.89) and cardiovascular mortality (HR 0.79 95% CI 0.69 – 0.91) but concerns regarding a lack of benefit in the United States arm of the study.
- There was moderate strength evidence of more major bleeding with prasugrel than clopidogrel (RR 1.32 95% CI 1.03 – 1.68). There was moderate evidence of no difference in major bleeding with the use of ticagrelor versus clopidogrel (RR 1.04 95% CI 0.94-1.13).
- There was no evidence of effectiveness for prasugrel or ticagrelor for other indications (i.e. secondary stroke prevention, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

Background:
Antiplatelet drugs are recommended to prevent cardiovascular events and premature death in patients who have experienced Acute Coronary Syndrome (ACS), transient ischemic attacks (TIA), thromboembolic stroke, MI or symptomatic peripheral arterial disease (PAD).[4] 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		

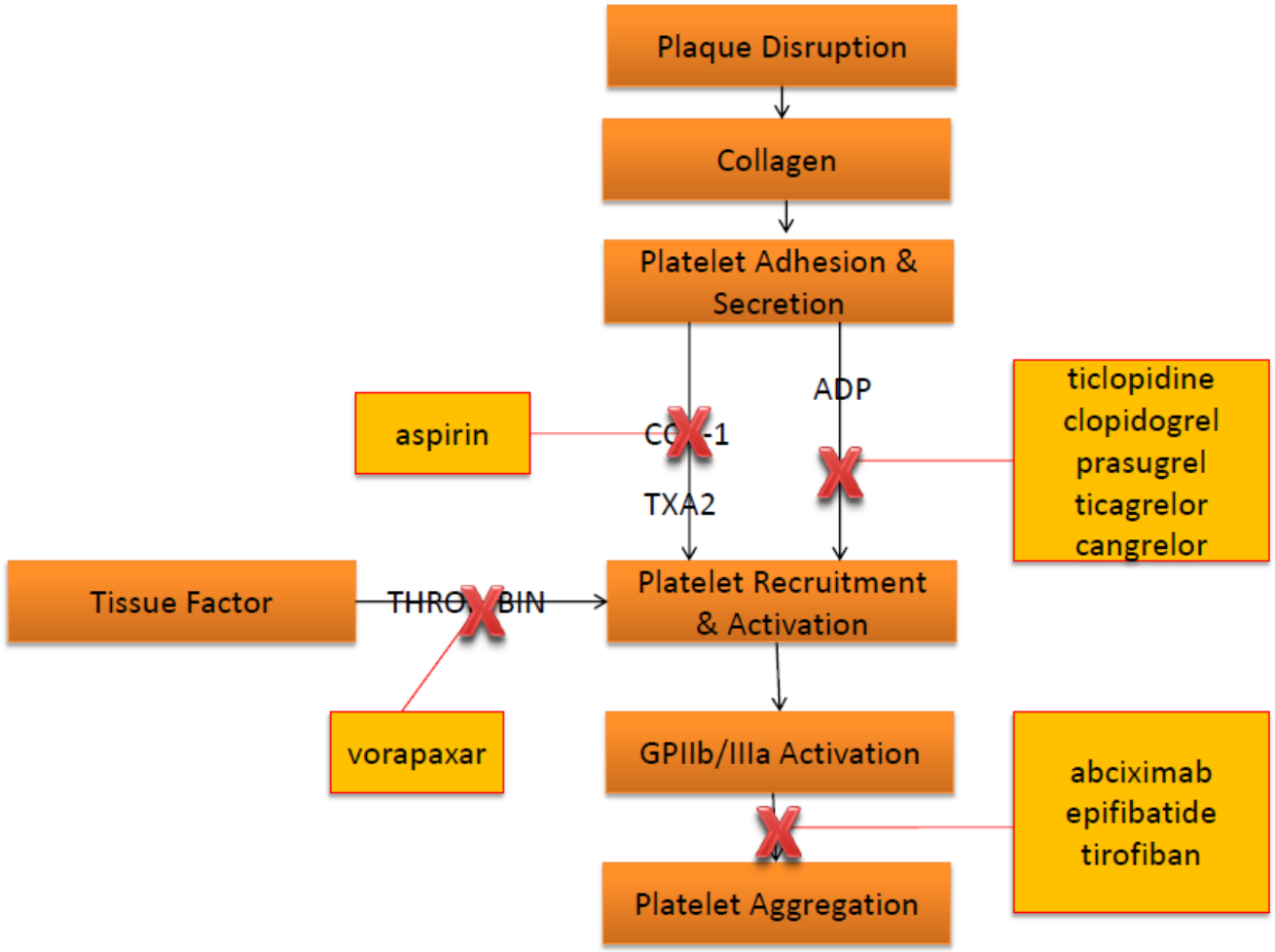
X = FDA indicated; CI=contraindication; ACS=Acute Coronary Syndrome; PCI=Percutaneous Intervention

Figure 1 below is adapted from Goodman and Gilman and identifies the site of action of the various antiplatelet drugs.[5] 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. 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. Cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Cangrelor is a new rapid acting injectable intended for percutaneous interventional (PCI) use and will not be covered in this review. Vorapaxar is a new selective antagonist of the protease-activated receptor-1 (PAR-1), the primary thrombin receptor and, a novel site of action.

The multiple guidelines for treatment of CAD recommend aspirin 75-162mg daily for all patients[6,7,8] and clopidogrel 75mg daily as an alternative for patients intolerant to aspirin.[7,8] Dual antiplatelet therapy ($P2Y_{12}$ inhibitor plus aspirin) is recommended for ACS.[6,9] The recommendation of which $P2Y_{12}$ inhibitor to use in various ACS patient types is evolving and varies depending on the guideline source interpretation of the PLATO trial.[10]

Either aspirin (50-325mg) or D-ER/ASA is recommended over anticoagulants for secondary non-cardioembolic stroke prevention.[6,11] Clopidogrel is an option for aspirin intolerant patients. Aspirin 75-325mg daily or clopidogrel 75mg daily is recommended for symptomatic PAD patients to reduce the risk of myocardial infarction, stroke or vascular death.[6,12] Neither prasugrel or ticagrelor have evidence to support their use for PAD or stroke patients.[2,3]

Figure 1: Sites of action of antiplatelet drugs adapted from Goodman & Gilman[5]



Methods:
The DERP scan searched Ovid MEDLINE from September 2012 to January 2014 for new systematic reviews and randomized controlled trials (RCTs) comparing any of the antiplatelet agents.[1] An additional search through April 2014 was done. Agency for Healthcare Research and Quality (AHRQ),[13] Cochrane Collection, National Institute for Health and Clinical Excellence (NICE),[14] Department of Veterans Affairs, Clinical Evidence, Up To Date,[15,16] Dynamed,[4] and the Canadian Agency for Drugs and Technologies in Health (CADTH)[17] 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[1] tabulated the potentially relevant new RCTs by drug comparison and population. Important RCTs identified and not included in other systematic reviews were the TRILOGY ACS trial comparing prasugrel to clopidogrel for ACS without revascularization and the TRACER[18]and TRA 2P[19] placebo controlled Phase III trials for vorapaxar. They will be reviewed in detail below. The other trials are summarized in Appendix 2.

<u>Acute Coronary Syndrome</u>
UpToDate recommends ticagrelor or prasugrel over clopidogrel for NSTEMI or STEMI ACS patients who have had PCI and ticagrelor in patients without PCI except when patients are at high risk for bleeding or concurrent fibrinolytic therapy is used and then clopidogrel is recommended.[15,16]

AHRQ published a comparative effectiveness review of antiplatelet and anticoagulant treatments for UA/NSTEMI.[13] It included an extensive literature search through July 2012 and all publications were subject to quality assessments. Both prasugrel and ticagrelor were superior to clopidogrel after 1 year in terms of reduction of composite ischemic endpoints based upon moderate strength of evidence from the TRITON-TIMI 38[20] and PLATO[10] trials. Only prasugrel showed an increase in major bleeding events and it was only studied in patients who had PCI. High strength evidence supports the use of dual antiplatelet therapy for 6 months to one year reduces rates of composite ischemic outcomes but there is insufficient evidence to recommend short-term over long-term therapy. The findings are mixed for composite ischemic events for proton-pump inhibitor use with antiplatelet therapies based on low strength evidence.

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 thru 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 clinically managed or revascularized. Prasugrel (TRITON-TIMI 38[20]) and ticagrelor (PLATO[10]) were more effective than standard clopidogrel doses but with a higher risk of bleeding. It was noted that the PLATO[10] trial had no difference for the composite primary outcome in the North American subpopulation and was theorized this was due to higher aspirin doses but that this hypothesis has yet to be proven. 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 you have not received antiplatelet therapy prior to arrival in catheterization lab or high risk NSTEMI patients where quick onset of action is a concern.

Stroke

A recent meta-analysis investigating the effectiveness of combination clopidogrel and aspirin therapy compared to aspirin alone for stroke prevention concluded it reduced the risk of total stroke without increasing the risk of intracranial hemorrhage.[21] In the overall population, those with CV disease with or without previous CV events, 2.2% of aspirin patients and 1.8% of combination therapy patients experienced a stroke at a median of 12 months of follow-up (RR 0.80; 95% CI 0.73-0.88; I^2=28% for 10 RCTs, n=93405).[21] For the secondary stroke prevention cohort, data from 7 RCTs, 13237 patients and 12 months of follow-up found 9.2% of aspirin patients and 7.0% of combination therapy patients experienced a stroke (RR 0.76; 95% CI 0.68-0.86, I^2=0%).[21] However, the result of this review need to be interpreted cautiously as explicit RCT quality assessment was not reported. Intracranial bleeding was evaluated but other safety outcomes such as all-cause mortality and other bleeding outcomes were not. Intracranial bleeding was also sometimes included in the composite total stroke outcome of included studies.

New Guidelines:

Acute Coronary Syndrome

NICE recommends ticagrelor as a treatment alternative to clopidogrel post MI for up to 12 months.[14] This was based upon a technology assessment of ticagrelor that estimated a cost less than £10,000 per Quality Adjusted Life Year gained over clopidogrel for the treatment of ACS.[22]

The American College of Chest Physicians published their 9th edition of antithrombotic therapy which incorporated prasugrel and ticagrelor recommendations.[6] They recommend 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 60kg, over 75 years old or with a previous stroke history. Patients undergoing elective PCI and stent placement are recommended clopidogrel plus aspirin for 6-12 months.

The American Heart Association/ American College of Cardiology Foundation (AHA/ACCF) gives all three $P2Y_{12}$ inhibitors equal weight for ACS with or without stent placement but recommends avoiding prasugrel in patients with a history of stroke or TIA (IIIB recommendation –harmful treatment based upon a single randomized controlled trial).[7]

The European Cardiology Society recommends ticagrelor for all ACS NSTEMI patients at moderate to high risk of ischemic events (Level B – single RCT).[23] Prasugrel is recommended for patients who are naïve to $P2Y_{12}$ inhibitors and known to be progressing to PCI (Level B – single RCT). Clopidogrel is recommended for patients not able to receive either ticagrelor or prasugrel (Level A).

Noncardioembolic Ischemic Stroke or Transient Ischemic Attack

The AHA/ACCF published updated guidelines for secondary prevention of stroke on May 1, 2014.[11] The update includes a new recommendation to consider a dual antiplatelet therapy with aspirin and clopidogrel within 24 hours of a minor ischemic stroke or transient ischemic attack (TIA) (Level B). This recommendation is based upon 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 primary outcomes of ischemic or hemorrhagic stroke in the combination group (8.6%) compared to the aspirin group (11.7%) [HR 0.68; 95% CI 0.57 - 0.81].[24] Rates of bleeding were similar.[24] Additionally, Level C evidence highlights the uncertainty of adding antiplatelet therapy to vitamin K antagonist for patients with a history of ischemic stroke, transient ischemic attack, atrial fibrillation or CAD.[11]

Peripheral Artery Disease

The AHA/ACCF recommends aspirin or clopidogrel daily for symptomatic PAD.[7,12] Combination aspirin and clopidogrel may be considered for patients with symptomatic lower extremity PAD who are at perceived high CV risk (Level B evidence).[12] Antiplatelet therapy in asymptomatic PAD is not supported in patients with ankle-brachial indexes 0.91-0.99 (Level A evidence) and potentially beneficial in ankle-brachial indexes ≤ 0.90 (Level C evidence).

Randomized Controlled Trials:

The TRILOGY ACS[25] was a fair quality, randomized, double-dummy active control trial that evaluated whether prasugrel 10mg daily was superior to clopidogrel 75mg daily for UA/NSTEMI patients 75 years old or younger and selected for medical management. The median duration of exposure to a study drug was 14.8 months (interquartile range, 8.2 to 23.6). All patients were on concurrent daily aspirin. Median follow-up time was 17 months. The Kaplan-Meir (K-M) hazard ratio (HR) at 30 months for the composite outcome of CV death, MI or stroke was 0.91 95% CI (0.79–1.05). Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening (not CABG related) K-M HR at 30 months was 0.94 95% CI (0.44 – 1.99). Prasugrel did not significantly reduce the primary endpoint compared to clopidogrel and the bleeding rates were similar.

New FDA Safety Alerts:

Aspirin

May 2, 2014[26]: Use of Aspirin for Primary Prevention of Heart Attack and Stroke

"The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke."

Clopidogrel:

December 2013[27]: Thienopyridine Cross - Reactivity

"Hypersensitivity including rash, angioedema or hematologic reaction has been reported in patients receiving Plavix, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines"

December 2011[28]: Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

"Proton Pump Inhibitors - Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix"

Prasugrel:

September 2011[29]:

"WARNINGS AND PRECAUTIONS

Hypersensitivity including angioedema has been reported in patients receiving Effient, including patients with a history of hypersensitivity reaction to other thienopyridines."

Vorapaxar New Drug Evaluation:

Vorapaxar (Zontivity™) was reviewed by the FDA Cardiovascular and Renal Drugs Advisory Committee on January 15, 2014.[30] It was approved May 8, 2014 "for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)."[31]

The TRACER[18,32,33] trial was a good quality Phase III, placebo controlled, randomized, superiority trial that evaluated vorapaxar efficacy and safety when added to standard antiplatelet therapy to prevent cardiovascular complications in patients with UA/NSTEMI. It reported no difference between vorapaxar and placebo for the primary outcome, a composite of cardiovascular deaths, MI, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization using K-M time to event analysis at 2 years (HR 0.92 95% CI 0.85 - 1.01). Only the MI component showed a significant reduction (HR 0.88 95% CI 0.79 – 0.98, ARD 1.2%, NNT 83). GUSTO moderate to severe bleeding rates using K-M time to event analysis at 2 years were significantly higher for vorapaxar (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). TRACER was internally valid with significant power (95%) which reduces the likelihood of β-error and strengthens the negative finding. There remains a risk of attrition bias due to the early discontinuation of the trial (69% of follow-up achieved) which means late developing differences between groups may have gone undetected. The GUSTO bleeding risk (NNH 63) was higher than the reduction in MI (NNT 83). The most generous interpretation of results suggests the benefit does not outweigh the risk. The study was limited to a subset of ACS patients and excluded those at higher risk of bleeding.

TRA2P-TIMI50[19,34,35] was a good quality Phase III, placebo controlled, randomized, superiority trial that evaluated vorapaxar efficacy and safety added to standard antiplatelet therapy for secondary prevention after stroke, PAD or in MI patients who have not undergone percutaneous coronary intervention (PCI). It reported significantly lower rates of the primary outcome, a composite of CV deaths, MI or stroke using K-M time to event analysis at 3 years for vorapaxar versus placebo (HR 0.87 95% CI 0.80 - 0.94, ARD 1.1%, NNT 91). This was driven primarily by the MI component (HR 0.83 95% CI 0.74 – 0.90, ARD 0.8%, NNT 125). GUSTO moderate to severe bleeding rates using K-M time to event analysis at 3 years were significantly higher for vorapaxar (HR 1.66 95% CI 1.43 - 1.93, ARD 1.3%, NNH 76). The trial was stopped after 2 years in patients with history of stroke due to an excess of intracranial bleeding for vorapaxar (HR 1.94 95% CI 1.39 – 2.70, ARD 0.3%, NNH 333). There was low and balanced attrition (2.1%) but high and balanced non-adherence (40%) due to the discontinuation of stroke patients. There was a median of 30 months (83%) of follow-up. The GUSTO bleeding risk (NNH=76) was higher than the reduction in the composite outcome (NNT=91). The study applicability was broadened by inclusion of several qualifying diagnoses, but notably excluded ACS patients undergoing PCI and patients at higher risk of bleeding. It reliably predicts the addition of vorapaxar to the standard antiplatelet regimens does reduce clinically relevant CV events, especially MI, but increases risk of serious bleeding, especially for those with history of stroke.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CV-related deaths
2) MI
3) Stroke
4) Major bleeding

Primary Study Endpoints:

1) Composite of CV-related deaths, MI, Stroke
2) GUSTO moderate to severe bleeding

Study	Population	Intervention	Analysis	Results	Safety	Comments
TRACER[18,32,33] RCT, PC, PG, DB To determine whether the addition of vorapaxar to standard therapy would be superior to placebo in reducing recurrent ischemic cardiovascular events and to determine its safety profile in patients with acute coronary syndromes without ST-segment elevation.	Target Population: Patients with acute coronary syndromes within 24 hours of hospital presentation, without ST-segment elevation. Setting: - Multinational, 818 sites in 37 countries Region of enrollment: North America (26.3%), South America (6.6%), Western Europe (45.1%), Eastern Europe (11.5%), Asia (7.2%), Australia or New Zealand (3.3%) - presumably hospitals settings Inclusion criteria: >18 yo -current clinical manifestation of NSTE ACS confirmed by biomarker or EKG + 1 or more CV risk factors (>55yo; DM, previous MI, PCI or CABG, or PAD) Exclusion criteria: -PG or breast feeding -Concurrent or anticipated treatment with warfarin, oral factor Xa inhibitor, or oral direct thrombin inhibitor. -Concurrent or anticipated treatment with a potent CYP3A4 inducer or inhibitor. -an unusual susceptibility to bleeding w/in 30 days -Hx of intracranial hemorrhage, intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm.	Experimental Intervention Description: V: 40mg @ randomization & at least 1 hour prior to procedure, then 2.5 mg x 1 year Control Intervention Description: P: Matching loading dose and matching daily tablets x 1 year Other Care Provided: -Investigators were encouraged to follow current practice guidelines of professional societies (i.e. ASA & clopidogrel) – add-on therapy. - stratified by intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and the intention to use a parenteral direct thrombin inhibitor (vs. other antithrombin agents). Follow-up Time: - Patients were followed until the final visit or the last assessment of end points. -Median follow-up period was 502 days (interquartile range, 349 to 667).	ITT V: 6473 P: 6471 Total: 12944 PP (Safety): V: 4628 P: 4715 Attrition: V: 336 (5.2%) P: 396 (6.1%) Total: 732 (5.7%) Non-Adherence: V: 1818 (28.1%) P: 1726 (26.7%) Total: 3544 (27%) Power: Calculated a minimum of 1900 primary events would provide a power of more than 95% to detect a 15% hazard reduction in the vorapaxar vs placebo. Power goals met with 2133 events. Trial stopped 6 months early with unplanned safety review and terminated study drug in patients with a history of stroke. Statistical Tests:	Primary Outcome: Composite of r. K-M HR @ 2 years: 0.92 95% CI (0.85–1.01) p-value: 0.07 V: 1031 (15.9%) P: 1102 (17.0%) RR: 0.94 RD: 1.1% NNT: NS Component Outcomes: Cardiovascular deaths: K-M HR @ 2 years: 1.00 95% CI (0.83–1.22) p-value:0.96 V: 208 (3.2%) P: 207 (3.2%) RR: 1.00 RD: 0% NNT: NS Myocardial infarction K-M HR @ 2 years: 0.88 95% CI (0.79–0.98) p-value: 0.02 V: 621 (9.6%) P: 698 (10.8%) RR: 0.89 RD: 1.2% NNT: 83 Stroke K-M HR @ 2 years: 0.93 95% CI (0.70–1.23) p-value: 0.61 V: 96 (1.5%) P: 103 (1.6%) RR: 0.94 RD: 0.1% NNT:NS	Withdrawals d/t ADE: V: 649 (10.0%) or (14% PP) P: 489 (7.6%) or (10.4% PP) RR 1.31 p-value: NR RD: 2.4% NNH: p NR GUSTO mod/sev bleeding: K-M HR @ 2 years: 1.35 95% CI (1.16–1.58) p-value: <0.001 V: 391 (6.1%) or (8.4% PP) P: 290 (4.5%) or (6.2% PP) RR 1.36 RD: 1.6% NNH: 63 TIMI clinically significant bleeding: K-M HR @ 2 years: 1.43 95% CI (1.31-1.57) p-value: <0.001 V: 1065 (16.5%) or (23% PP) P: 755 (11.7%) or (16% PP) RR 1.41 RD: 4.8% NNH: 21 Hemorrhagic Stroke: K-M HR @ 2 years: 2.73 95% CI (1.22 – 6.14) p-value: 0.02 V: 22 (0.3%) or (0.5% PP) P: 8 (0.1%) or (0.2% PP) RR: 3.00 RD: 0.2% NNH: 500	Overall Study Quality: **GOOD** Risk of Bias: Selection: Low- assumed computer generated randomization; allocation concealment via IVR; groups well matched at baseline. Performance: Low- described as double-blind with noted "matched placebo" Detection: Low- central committee blinded with adjudication protocols; objective outcome Attrition: Mod- Attrition was low (5.7%) and even between groups. But, non-adherence was high (27%) and median f/u was 502/650 days (77%). Used time to event analysis at 2 years to impute missing data for ITT. RR and HR are similar indicating imputed data did not significantly change results. Trial stopped 6 months early for safety. External Validity: Recruitment:. Details not provided; Recruitment from December 18, 2007, and ended on June 4, 2010. Patient Characteristics: Confirmed NSTE ACE without significant comorbidities, a likely population to be treated with vorapaxar. Excluded patients at higher risk of bleeding and those concurrent anticoagulants which exclude likely patients to be treated. Setting: multi-center, multi-national hospitals doing heart procedures. Unclear how other country demographics and treatment standards apply to US population.

	-sustained severe hypertension w/in 10days - Severe valvular heart disease - Hx of major surgery other than mentioned above or of ischemic (presumed thrombotic) stroke w/in 2 weeks - Hx thrombocytopenia w/in 30 days - active hepatobiliary disease w/in 30 days - serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated -the subject's life expectancy is <24 months. - current substance abuse <u>Baseline Comparison:</u> Groups were compared on significant factors (e.g. age, race, gender, weight, CV risk factors and disease history). No factor differed by more than 0.7%.		Cox proportional-hazards model used to calculate HR and 95% CIs for event rates of time to the first occurrence of any component of the composite end points and presented as 2-year Kaplan–Meier HR.	<u>Recurrent ischemia with rehospitalization</u> <u>K-M HR @ 2 years:</u> 1.14 95% CI (0.83–1.58) p-value: 0.42 V: 79 (1.2%) P: 69 (1.1%) RR: 1.09 RD: 0.1% NNT: NS <u>Urgent coronary revascularization</u> <u>K-M HR @ 2 years:</u> 1.07 95% CI (0.88–1.31) p-value: 0.49 V: 203 (3.1%) P: 189 (2.9%) RR: 1.07 RD: 0.2% NNT:NS		<u>Intervention:</u> Patients managed with local practice standards. Unclear how other country treatment standards apply to US population. <u>Outcomes:</u> Primary composite outcome driven by MI component. Rehospitalization and revascularization components less severe than others. Multiplicity of outcomes planned for. Hemorrhagic stroke obscured by composite bleeding outcomes but composite bleeding outcomes appropriate and validated in previous studies.

Study	Population	Intervention	Analysis	Results	Safety	Comments
TRA2P-TIMI50[19,34,35] RCT, PC, DB Does vorapaxar reduce atherothrombotic events in patients with established atherosclerosis who were receiving standard therapy.	Target Population: Patients with a known history of atherosclerotic disease receiving standard therapy Setting: -1032 sites in 32 countries Inclusion: 1. At least 18 years old 2. Evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems: a. CAD: presumed spontaneous MI ≥ 2 wk but ≤ 12 m prior, or b. CVD: ischemic (presumed thrombotic) stroke ≥ 2 wk but ≤ 12 m prior, or c. PAD: history of intermittent claudication and i. An ABI of b0.85, or ii. Amputation or revascularization of the extremities secondary to ischemia 3. Able and willing to give appropriate informed consent 4. A woman of child-bearing potential who is sexually active must agree to use contraception -stopped enrolling patients with stroke or PAD when reached 15% Exclusion: 1. Clinically unstable at the	Experimental Intervention Description: Patients received Vorapaxar (2.5 mg po qd) in a blinded fashion until the end of follow-up Control Intervention Description: Patients received matched placebo po qd in a blinded fashion until the end of follow-up. -Therapy DC'd in both groups if patient needed a potent CYP3A4 inhibitor or warfarin concurrent with a thienopyridine Follow-up Time: -Primary and secondary outcomes assessed at 3 years. -Median follow up time was 30 months. Average follow up time was 18-24 months. Other Care Provided: -All concomitant medical therapy, including the use of other antiplatelet agents, was managed by the clinicians at the study sites who were responsible for the care of the patients, according to local standards of care. Stratified by qualifying diagnosis and physician's intent to administer thienopyridine.	ITT: V: 13,225 P: 13,224 Total: 26,479 PP (Safety): V: 7,818 P: 8,028 Attrition Total: 549 (2.1%) V: 272 (2.1%) P: 292 (2.2%) Non-Adherence: Total: 10603 (40%) V: 5407 (40.9%) P: 5196 (39.3%) Power Analysis: -1400 events needed 85% power to detect 15% RR difference in primary endpoint. -protocol amended and primary endpoint changed after review of TRACER study results. Multiplicity hierarchy reversed. -DSMB stopped trial at a median of 24 months of follow-up d/t excess of intracranial hemorrhage in patients with stroke Hx in the	Primary Outcome: Composite of CV death, MI or stroke K-M HR @ 3 years: 0.87 95% CI (0.80–0.94) p: < 0.001 V: 1028 (7.8%) P: 1176 (8.9%) RR: 0.88 ARR: 1.1% NNT: 91 CV Death: K-M HR @ 3 years: 0.89 95% CI (0.76–1.04) p: 0.15 V: 285 (2.2%) P: 319 (2.4%) RR: 0.92 ARR: 0.2% NNT: NS MI: K-M HR @ 3 years: 0.83 95% CI (0.74–0.93) p: 0.001 V: 564 (4.3%) P: 673 (5.1%) RR: 0.84 ARR: 0.8% NNT: 125 Stroke: K-M HR @ 3 years: 0.97 95% CI (0.83–1.14) p: 0.73 V: 315 (2.4%) P: 324 (2.5%) RR: 0.96 ARR: 0.1%	Withdrawals d/t ADEs: V: 1381 (10.4%) or (17.7% PP) P: 1299 (9.8%) or (16.2% PP) RR: 1.06 ARR: 0.6% p: NR NNH: NA GUSTO moderate or severe: K-M HR @ 3 years: 1.66 95% CI (1.43–1.93) p: <0.001 V: 438 (3.3%) P: 267 (2.0%) RR: 1.65 ARR: 1.3% NNH: 76 TIMI Clinically significant bleeding: K-M HR @ 3 years: 1.46 95% CI (1.36–1.57) p: <0.001 V: 1759 (13.3%) P: 1241 (9.4%) RR: 1.41 ARR: 3.9% NNH: 26 Intracranial bleeding: K-M HR @ 3 years: 1.94 95% CI (1.39–2.70) p: <0.001 V: 102 (0.7%) P: 53 (0.4%) RR: 1.75 ARR: 0.3% NNH: 333	Overall Study Quality: **GOOD** Risk of Bias: Selection: Low- good randomization but unclear allocation concealment; groups well matched at baseline. Performance: Low-blinding by "matched placebo". Detection: Low- central committee blinded and objective outcome. Attrition: Mod- Low attrition (2.1%) and even but very high non-adherence (40%) d/t mid-study protocol change for safety. Used time to event analysis at 3 years to impute missing outcome data. RR and HR are similar indicating imputed data did not significantly change results. Low power (85%) for primary outcome. External Validity: Recruitment:. Not described Patient Characteristics: Diverse population including positive history for atherosclerosis except those with planned PCI (a likely group to use). Patients with common co-morbidities excluded, especially those on anticoagulants & at higher risk of bleeds (common risks with treatment population). Setting: multi-center, multi-national. Unclear how foreign demographics apply to US population. Intervention: Locat treatment standards used. Unclear if standard of care similar in other countries. Outcomes:. Primary composite outcome appropriately conceived of

	time of enrollment 2. Planned coronary revascularization or peripheral intervention 3. Concurrent or anticipated treatment with warfarin, oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrollment 4. Concurrent or anticipated treatment with a potent inducer or potent inhibitor of CYP3A4 isoenzymes 5. History of a bleeding diathesis, or evidence of active abnormal bleeding within 30 d before enrollment 6. History at any time of intracranial hemorrhage, intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm 7. Documented sustained severe hypertension (systolic blood pressure N200 mm Hg or diastolic blood pressure N110 mm Hg) at enrollment or within the previous 10 d 8. Severe valvular heart disease 9. History within 2 wk prior to enrollment of major surgery or ischemic stroke 10. Known platelet count b100 000/mm3 within 30 d before enrollment 11. Known active hepatobiliary disease, or unexplained persistent increase in ALT or AST activity ≥2× ULN 12. Any serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated or (b) would limit the prognosis		vorapaxar group and recommended discontinuation of the drug in all patients with stroke. <u>Statistical Test for primary outcome:</u> Cox proportional-hazards model used with the study group and stratification factors at randomization as covariates. Cumulative event rates calculated with Kaplan–Meier method at 3 years.	NNT: NS		equal severity and driven by MI component. Bleeding composites validated in previous studies.

	of the subject, regardless of investigational therapy 13. Any serious medical comorbidity (eg, active malignancy) such that the subject's life expectancy is b24 m <u>Baseline Group Comparison:</u> Similar in all known demographic and prognostic factors					

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Appendix 1: Specific Drug Information[31]

CLINICAL PHARMACOLOGY

Vorapaxar is a reversible antagonist of the PAR-1 receptor. This is a novel site of antiplatelet action and thus, theoretically, a rational add-on therapy for patients needing additional antiplatelet activity. There are many other cell types that express PAR-1 receptors, including endothelial cells, neurons, and smooth muscle cells, but the vorapaxar effects in these cell types have not been evaluated.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	>99%
Elimination	58% of metabolized dose recovered in feces; 25% in urine
Half-Life	Multi-exponential disposition; steady-state achieved in 21 days; terminal half-life is ~8 days.
Metabolism	Metabolized by CYP3A4 and CYP2J2

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
2.08mg (equivalent to 2.5mg vorapaxar sulfate)	Oral tablets	Daily	No adjustment needed	Not recommended for patients with severe hepatic impairment due to bleeding risk.	Use not established	No Adjustment needed	B	-Use with aspirin and/or clopidogrel. There is limited experience with other antiplatelet drugs or as monotherapy. -Give without regard to food.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

BBW: Do not use in patients with a history of stroke, TIA, intracranial hemorrhage (ICH) or active pathological bleeding. Antiplatelet drugs increase the risk of bleeding, including ICH and fatal bleeding.

Contraindications:

History of Stroke, Transient Ischemic Attack (TIA), or Intracranial Hemorrhage (ICH)
Active Pathologic Bleeding

Warnings and Precautions:

Antiplatelet agents, including vorapaxar, increase the risk of bleeding, including ICH and fatal bleeding.
Strong CYP3A inhibitors increase and inducers decrease vorapaxar exposure. Avoid use with either.

Look-alike / Sound-alike (LA/SA) Error Risk Potential: NA

Appendix 2: RCTs identified by DERP Scan[1]

Table 1. New Trials of Antiplatelet Drugs in Previous Report

Study	Population	Comparison
ACS		
Wallentin 2009 (PLATO)	ACS	Ticagrelor vs Clopidogrel
Cannon, 2007 (DISPERSE-2)	non-ST-segment elevation ACS	Ticagrelor vs Clopidogrel
Roe, 2012 (TRILOGY ACS)	ACS without revascularization	Prasugrel vs clopidogrel
Coronary Revascularization		
Isshiki, 2012 (CLEAN) Japan	PCI in patients with stable angina or recent MI	Clopidogrel vs Ticlopidine
Mannacio, 2012 (CRYSSA)	Off-pump CABG patients	Clopidogrel+ASA vs ASA
Patti, 2013	Reloading clopidogrel prior to PCI	Clopidogrel vs Placebo
Stroke/TIA		
Benavente, 2012	Lacunar Infarct	Clopidogrel +ASA vs ASA
Wang, 2013	Minor stroke or TIA	Clopidogrel +ASA vs ASA
Peripheral Artery Disease		
Tepe, 2012	PAD with endovascular therapy	Clopidogrel+ASA vs ASA

Secondary publications of trials listed above or included in report previously

Study	Subgroup or Secondary Outcome	Comparison
JASAP	**Stroke**	
Uchiyama, 2011	full publication of results	ER Dipyridamole + ASA vs ASA
CHARISMA	**High risk patients**	Clopidogrel + ASA vs ASA
Berger, 2011	Bleeding and cause of mortality	
Hankey, 2011	Stroke or TIA patients	
PLATO	**ACS**	Ticagrelor vs Clopidogrel
Goodman, 2012	PPI and CV outcomes	
Becker, 2011	Bleeding risk	
James, 2010	Diabetes	
James, 2010	Renal disease	
James, 2011	Non-invasive management	
James, 2012	Stroke or TIA patients	
Mahaffey, 2011	Geographic variation	
Scirica, 2011	bradyarrhythmias	
Steg, 2010	ACS with ST-elevation	
Storey, 2011	Dyspnea events	
Storey, 2011	Pulmonary function	
Varenhorst, 2012	Factors associated with mortality	
Husted, 2012	Patients > 75 years	
Cornel, 2012	Smoking status	
Steg, 2013	Stent thrombosis	
Levin, 2013	Quality of life	
Kohli, 2013	Combined primary endpoint analysis	
Brilakis, 2013	Prior CABG	
TRITON-TIMI-38	**ACS**	Prasugrel vs Clopidogrel
Ruff, 2012	Geographic regions	
Wiviott, 2011	Standard dose vs dose by age/weight,	
Smith, 2012	Effect of timing of drug withdrawal	
TRILOGY ACS		Prasugrel vs Clopidogrel
Wiviott, 2013	Unstable angina, non-ST elevation MI with/without angiography	

Table 2. Trials of Vorapaxar

Author, Year	Indication	Outcomes
TRA 2° P-TIMI 50 Trial; N = 26,449; Follow-up 3 years		
Morrow, 2012	History of myocardial infarction, ischemic stroke, or peripheral arterial disease	Composite of cardiovascular death, myocardial infarction, or any stroke
Bonaca, 2013	PAD (subgroup)	
Morrow, 2013	Prior Ischemic Stroke (subgroup)	
Scirica, 2012	Previous myocardial infarction (subgroup)	
TRACER Trial; N = 12 944; Follow-up 16 months (mean)		
Tricoci, 2012	Non-ST-segment elevation Acute coronary syndromes	Cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization
Leonardi, 2013	Non-ST-segment elevation MI (subgroup)	
Phase II studies; 60 days duration with Primary outcomes = adverse events, Major and minor bleeding		
Becker, 2009	PCI	Clinically significant major or minor bleeding
Hinohara, 2012	Previous ischemic stroke	Overall incidence of adverse events
Goto, 2010	Non-urgent PCI	TIMI major and minor bleeding

Appendix 3: Suggested PA Criteria

Platelet Inhibitors

Goal(s):

- Approve platelet inhibitors for covered 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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3	No: pass to RPh, Deny for OHP coverage.
3. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class.	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
5. Is the patient unable to take clopidogrel due to one of the following: • clopidogrel allergy • contraindications to clopidogrel therapy e.g. poor metabolizers of CYP2C19 (document) • drug-drug interactions e.g. omeprazole (document) • intolerable side effects (document)	Yes: Go to #6	No: Pass to RPh. Deny Recommend clopidogrel trial

Approval Criteria		
6. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	Yes: Deny (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 antiplatelet drugs or as monotherapy.

FDA Approved Indications (May 2014)

	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		

X = FDA indicated; CI=contraindication; ACS=Acute Coronary Syndrome; PCI=Percutaneous Intervention

P&T / DUR Action: *7/31/2014 (KK); 11/17/11(KS)*
Revision(s): _____
Initiated: *4/9/12 (KS)*