This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

DERP VI Targeted Update Scan #1: Newer Antiplatelet Drugs

July 2018

Table of Contents

Objectives

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on newer antiplatelet drugs. The literature search for this scan focuses on new randomized controlled trials (RCTs) and systematic reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participating organizations agreed to proceed with a full report update or other research product.

Topic History

Targeted Update Report: August 2017, searches through March 31, 2017

Scan #5: February 2017

Scan #4: February 2016

Expanded Scan Report: January 2016, searches through December 31, 2015

Scan #3: February 2015

Scan #2: January 2014

Scan #1: October 2012

Update #2: June 2011, searches through December 31, 2010

Update #1: January 2007

Original Report: November 2005

Background and Context

In 2017, more than 90 million Americans had at least 1 type of cardiovascular disease, including ischemic coronary heart disease, stroke, and/or peripheral artery disease.[1] Although there are various approaches to secondary prevention of vascular disease, a principal component is the use of antiplatelet agents.[2-6] Aspirin has been considered the standard agent for many years, but in the past 2 decades newer antiplatelet agents have come to the forefront as adjuncts to or substitutes for aspirin in many clinical situations.[2-6] The role of individual antiplatelet agents relative to each other is still evolving.[2-6]

Key Questions

For adults with acute coronary syndrome (ACS), coronary revascularization via stenting or coronary artery bypass graft (CABG), previous ischemic stroke or transient ischemic attack (TIA), or symptomatic peripheral artery disease (PAD):

1. Do antiplatelet agents differ in efficacy or effectiveness?

2. Do antiplatelet agents differ in harms?

3. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?

4. Do antiplatelet agents differ in effects when therapy duration varies?

Inclusion Criteria

Using the PICO outlined below, we screened our search results for eligible systematic reviews and RCTs published since the implementation of the search strategy in the most recent update report, which occurred on March 31, 2017.

Populations

- Adults (age 18 years and older) with one of the following:
    - ACS
    - Recent or ongoing coronary revascularization by stenting or CABG
    - Prior ischemic stroke or TIA
    - Symptomatic PAD

Interventions

Table 1. Included Interventions

Active Ingredient	Brand Name	Form, Route of Administration
Clopidogrel[1]	Plavix	Tablet, oral
Dipyridamole[2]	Persantine, generic brands	Tablet, oral
Dipyridamole extended release/aspirin	Aggrenox	Extended release capsule, oral
Prasugrel	Effient	Tablet, oral
Ticagrelor	Brilinta, generic brands with tentative approval	Tablet, oral
Vorapaxar	Zontivity	Tablet, oral

Notes. [1] Alone or in combination with aspirin; [2] In combination with aspirin.

Table 2. Excluded Interventions

Active Ingredient	Brand Name	Form, Route of Administration
Ticlopidine	Generic brands	Tablet, oral
Cangrelor	Kengreal	Powder, IV (infusion)

Comparators

- Antiplatelet drugs compared with each other (head-to-head)
- Placebo or aspirin (for included drugs with no head-to-head evidence)

Outcomes

Efficacy and Effectiveness

- All-cause mortality
- Cardiovascular mortality
- Myocardial infarction
- Stroke
- Failure of an invasive vascular procedure

Safety

- Overall adverse effects
- Withdrawals due to adverse effects
- Serious adverse events, such as neutropenia or major hemorrhage
- Specific adverse events, such as diarrhea or rash
- Withdrawals due to specific adverse events

Methods

We searched the FDA website to identify newly approved drugs and indications and new serious harms (i.e., boxed warnings) for included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information, and conducted an internet search using Google. To identify relevant RCTs and systematic reviews, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2017 to June 22, 2018, using terms for included drugs and limits for English language and humans. We also conducted an internet search using Google and Google Scholar using key words for included drugs.

Findings

New Drugs or Formulations

No new drugs or formulations were identified since the search strategy was conducted in the last targeted update report on March 31, 2017.

New Indications

No new indications were identified since the search strategy was conducted in the last targeted update report on March 31, 2017.

New Serious Harms

No new serious harms were identified since the since the search strategy was conducted in the last targeted update report on March 31, 2017.

Systematic Review

In this scan, we identified 1 systematic review of ticagrelor compared to other antiplatelet agents or placebos for stroke prevention, with searches conducted through February 24, 2018.[7] The reviewers included 13 RCTs with a total of 64,360 patients and a follow-up duration ranging from 1 month to 3 years (median 6 months).[7]

Randomized Controlled Trials

Subgroup Analyses of RCTs Previously Included

Since the last targeted update report on this topic, we have identified 4 new publications from trials previously included (Table 3).[8-11]

- A subgroup analysis comparing patients with or without diabetes mellitus from the TRILOGY ACS trial, which compared aspirin plus prasugrel to aspirin plus clopidogrel in patients with ACS[8]
- A subgroup analysis of patients with previous CABG or undergoing CABG during the trial from the TRA 2°P-TIMI 50 study, which compared vorapaxar to a placebo in patients with myocardial infarction or PAD[9]
- A subgroup analysis of patients with critical limb ischemia from the EUCLID trial, which compared ticagrelor to clopidogrel in patients with CAD[10]
- A post hoc subgroup analysis comparing outcomes for patients with early (< 3 hours) or late (≥ 3 hours) angiography from PLATO, a head-to-head trial of ticagrelor and clopidogrel in patients with ACS[11]

Head-to-Head Trials

Since the last targeted update report on this topic, we have identified 4 comparative trials with biochemical or other intermediate primary outcomes that reported short-term (10 days to 30 days) harms as secondary outcomes (Table 4).[12-15] These trials compared ticagrelor to clopidogrel or prasugrel in patients with CAD who were undergoing PCI or other therapeutic interventions. [12-15]

Table 3. Characteristics of New Publications from RCTs of Newer Antiplatelet Drugs

Author, Year Study Name NCT Number	Analysis Sample Size	Population	Intervention	Comparator	Outcomes
Dalby et al., 2017[8] TRILOGY ACS NCT00699998	Subgroup analysis comparing patients with or without diabetes mellitus N = 9,306	Patients with ACS who did not undergo coronary revascularization	Prasugrel plus aspirin	Clopidogrel plus aspirin	Primary: composite of cardiovascular death, myocardial infarction, or stroke Secondary: individual components of the composite endpoint and all-cause death Safety: severe, life-threatening, or moderate bleeding unrelated to CABG, major and/or minor bleeding unrelated to CABG
Kosova et al., 2017[9] TRA 2°P-TIMI 50 NCT00526474	Subgroup analysis comparing patients with prior CABG to patients undergoing CABG during the trial N = 3,309	Patients with myocardial infarction or PAD, no history of stroke and a history of CABG	Vorapaxar	Placebo	Primary: composite of cardiovascular death, myocardial infarction, or stroke Secondary: exploratory composite endpoints of net clinical outcome that integrated efficacy and safety outcomes Safety: major bleeding
Norgren et al., 2018[10] EUCLID NCT01732822	Subgroup of patients with critical limb ischemia, defined clinically by ischemic rest pain, ischemic ulcers, or gangrene N = 643	Patients with PAD	Ticagrelor	Clopidogrel	Primary: time to first occurrence of any event in the composite of cardiovascular death, myocardial infarction, or ischemic stroke and thrombolysis in myocardial infarction major bleeding Secondary: all-cause mortality, cardiovascular and non-cardiovascular death, hospitalization for acute limb ischemia (ALI), lower limb revascularization, any

Author, Year Study Name NCT Number	Analysis Sample Size	Population	Intervention	Comparator	Outcomes
					revascularization, and major and minor amputation
Pollack et al., 2017[11] PLATO NCT00391872	Post hoc subgroup analysis comparing "early" (< 3 hours) to "late" (≥ 3 hours) time to angiography N = 6,792	Patients with ACS	Ticagrelor	Clopidogrel	Primary: composite of death from vascular causes, myocardial infarction, and stroke Secondary: individual components of the composite endpoint Safety: major bleeding

Abbreviations. ACS: acute coronary syndrome; CABG: coronary artery bypass graft, PAD: peripheral artery disease.

Table 4. Characteristics of New Head-to-Head Trials of Newer Antiplatelet Drugs

Author, Year Study Name NCT Number	Population Sample Size	Intervention	Comparator	Primary Outcome	Clinical or Harms Outcomes
Campo et al., 2017[12] NCT02519608	Patients with stable CAD and COPD undergoing PCI N = 46	Ticagrelor	Clopidogrel	Rate of apoptosis in human umbilical vein endothelial cells at 30 days	Ischemic and bleeding adverse events at 30 days
Dehghani et al., 2017[13] NCT01930591	Patients undergoing PCI within 24 hours of receiving fibrinolysis for STEMI N = 140	Ticagrelor	Clopidogrel	Platelet reactivity units at 4 hours post-PCI	Major bleeding, minor bleeding, major adverse cardiac events, death, reinfarction, revascularization, and stroke at 30 days
Guimaraes et al., 2017[14] SAMPA NCT02215993	Patients with STEMI previously treated with clopidogrel and undergoing a pharmacoinvasive strategy N = 50	Ticagrelor	Prasugrel	Platelet reactivity units at 2, 6, and 24 hours after initial dose	Bleeding at 30 days
Pelletier-Galarneau et al., 2017[15] NCT01894789	Patients with CAD who received therapeutic interventions N = 22	Ticagrelor	Clopidogrel	Myocardial blood flow and myocardial flow reserve at 10 days, measured with PET	Not specified, but reported that there were no adverse events during the study

Abbreviations. CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; PET: positron emission tomography.

Summary

In this scan, we identified no new drugs, indications, or serious harms since the searches for the last update report were conducted on March 31, 2017. We identified 1 systematic review of RCTs of ticagrelor compared to other antiplatelet agents or placebos. We identified 4 subgroup analyses from trials previously included and 4 head-to-head trials of ticagrelor compared to clopidogrel or prasugrel that reported short-term clinical outcomes or harms as secondary outcome measures.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation.* 2017;135(10):e146-e603. doi: 10.1161/cir.0000000000000485.

2. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 Suppl):e669S-e690S. doi: 10.1378/chest.11-2307.

3. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 Suppl):e601S-e636S. doi: 10.1378/chest.11-2302.

4. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61(23):e179-347. doi: 10.1016/j.jacc.2013.01.014.

5. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(7):2160-2236. doi: 10.1161/str.0000000000000024.

6. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg.* 2016;152(5):1243-1275. doi: 10.1016/j.jtcvs.2016.07.044.

7. Malhotra K, Goyal N, Kasunich AS, et al. Ticagrelor for stroke prevention in patients with vascular risk factors: a systematic review and meta-analysis. *J Neurol Sci.* 2018;390:212-218. doi: 10.1016/j.jns.2018.05.001.

8. Dalby AJ, Gottlieb S, Cyr DD, et al. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. *Am Heart J.* 2017;188:156-166. doi: https://dx.doi.org/10.1016/j.ahj.2017.03.015.

9. Kosova EC, Bonaca MP, Dellborg M, et al. Vorapaxar in patients with coronary artery bypass grafting: findings from the TRA 2°P-TIMI 50 trial. *Europ Heart J Acute Cardiovasc Care.* 2017;6(2):164-172. doi: https://dx.doi.org/10.1177/2048872616644910.

10. Norgren L, Patel MR, Hiatt WR, et al. Outcomes of patients with critical limb ischaemia in the EUCLID trial. *Eur J Vasc Endovasc Surg.* 2018;55(1):109-117. doi: https://dx.doi.org/10.1016/j.ejvs.2017.11.006.

11. Pollack CV, Jr., Davoudi F, Diercks DB, et al. Relative efficacy and safety of ticagelor vs clopidogrel as a function of time to invasive management in non-ST-segment elevation acute coronary syndrome in the PLATO trial. *Clin Cardiol.* 2017;40(6):390-398. doi: https://dx.doi.org/10.1002/clc.22733.

12. Campo G, Vieceli Dalla Sega F, Pavasini R, et al. Biological effects of ticagrelor over clopidogrel in patients with stable coronary artery disease and chronic obstructive pulmonary disease. *Thromb Haemost.* 2017;117(6):1208-1216. doi: https://dx.doi.org/10.1160/TH16-12-0973.

13. Dehghani P, Lavoie A, Lavi S, et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. *Am Heart J.* 2017;192:105-112. doi: https://dx.doi.org/10.1016/j.ahj.2017.07.013.

14. Guimaraes LdFC, Genereux P, Silveira D, et al. $P2Y_{12}$ receptor inhibition with prasugrel and ticagrelor in STEMI patients after fibrinolytic therapy: analysis from the SAMPA randomized trial. *Int J Cardiol.* 2017;230:204-208. doi: https://dx.doi.org/10.1016/j.ijcard.2016.12.173.

15. Pelletier-Galarneau M, Hunter CRRN, Ascah KJ, et al. Randomized trial comparing the effects of ticagrelor versus clopidogrel on myocardial perfusion in patients with coronary artery disease. *J Am Heart Assoc.* 2017;6(5):02. doi: https://dx.doi.org/10.1161/JAHA.117.005894.

Appendix A. Abstracts of Relevant Studies

Campo G, Vieceli Dalla Sega F, Pavasini R, et al. Biological effects of ticagrelor over clopidogrel in patients with stable coronary artery disease and chronic obstructive pulmonary disease. *Thromb Haemost.* 2017;117(6):1208-1216.

Patients with SCAD and concomitant COPD are at high risk of cardiovascular adverse events, due to chronic inflammation, responsible of endothelial dysfunction, oxidative stress and heightened platelet reactivity (PR). The objective of this randomised clinical trial was to test if ticagrelor is superior to clopidogrel in improving endothelial function in patients with stable coronary artery disease (SCAD) and concomitant chronic obstructive pulmonary disease (COPD). Forty-six patients with SCAD and COPD undergoing percutaneous coronary intervention (PCI) were randomly assigned to receive clopidogrel (n=23) or ticagrelor (n=23) on top of standard therapy with aspirin. The following parameters were assessed at baseline and after 1 month: i) rate of apoptosis and ii) nitric oxide (NO) levels in human umbilical vein endothelial cells (HUVECs), iii) levels of reactive oxygen species (ROS) in peripheral blood mononuclear cell, iv) 29 cytokines/chemokines, v) on-treatment PR. The primary endpoint of the study was the 1-month rate of HUVECs apoptosis. The rate of apoptosis after 1 month was significantly lower in patients treated with ticagrelor (7.4 +/- 1.3% vs 9.3 +/- 1.5%, p<0.001), satisfying the pre-specified primary endpoint. In the ticagrelor arm, levels of NO were higher (10.1 +/- 2.2 AU vs 8.5 +/- 2.6 AU, p=0.03) while those of ROS (4 +/- 1.8 AU vs 5.7 +/- 2.8 AU, p=0.02) and P2Y₁₂ reactivity units (52 +/- 70 PRU vs 155 +/- 62 PRU, p<0.001) were lower. There were no differences in cytokines/chemokines levels and aspirin reactivity units between groups. In patients with SCAD and COPD undergoing PCI, ticagrelor, as compared to clopidogrel is superior in improving surrogate markers of endothelial function and on-treatment PR.

Dalby AJ, Gottlieb S, Cyr DD, et al. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. *Am Heart J.* 2017;188:156-166.

OBJECTIVE: Patients with diabetes mellitus (DM) presenting with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI) derived enhanced benefit with dual antiplatelet therapy (DAPT) with prasugrel vs. clopidogrel. The risk profile and treatment response to DAPT for medically managed ACS patients with DM remains uncertain.

METHODS: The TRILOGY ACS trial compared aspirin + prasugrel vs. aspirin + clopidogrel for up to 30months in non-ST-segment elevation (NSTE) ACS patients managed medically without revascularization. We compared treatment-related outcomes among 3539 patients with DM vs. 5767 patients without DM. The primary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke.

RESULTS: Patients with vs. without DM were younger, more commonly female, heavier, and more often had revascularization prior to the index ACS event. The frequency of the primary

endpoint through 30 months was higher among patients with vs. without DM (24.8% vs. 16.3%), with a higher risk for those patients with DM treated with insulin vs. those treated without insulin (35.3% vs. 19.9%). There was no significant difference in the frequency of the primary endpoint by treatment with prasugrel vs. clopidogrel in those with or without DM (P_{int}=0.82) and with or without insulin treatment among those with DM (P_{int}=0.304).

CONCLUSIONS: Among NSTE ACS patients managed medically without revascularization, patients with DM had a higher risk of ischemic events that was amplified among those treated with insulin. There was no differential treatment effect with a more potent DAPT regimen of aspirin + prasugrel vs. aspirin + clopidogrel.

Dehghani P, Lavoie A, Lavi S, et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. *Am Heart J*. 2017;192:105-112.

OBJECTIVES: Patients undergoing PCI early after fibrinolytic therapy are at high risk for both thrombotic and bleeding complications. We sought to assess the pharmacodynamic effects of ticagrelor versus clopidogrel in the fibrinolytic-treated STEMI patients undergoing early PCI.

METHODS AND RESULTS: Patients undergoing PCI within 24 hours of tenecteplase (TNK), aspirin, and clopidogrel for STEMI were randomized to receive additional clopidogrel 300 mg followed by 75 mg daily or ticagrelor 180 mg followed by 90 mg twice daily. The platelet reactivity units (PRU) were measured with the VerifyNow Assay before study drug administration (baseline) at 4 and 24 hours post-PCI. The primary end point was PRU <=208 at 4 hours. A total of 140 patients (74 in ticagrelor and 66 in clopidogrel group) were enrolled. The mean PRU values at baseline were similar for the 2 groups (257.8+/-52.9 vs 259.5+/-56.7, P=.85, respectively). Post-PCI, patients on ticagrelor, compared to those on clopidogrel, had significantly lower PRU at 4 hours (78.7+/-88 vs 193.6+/-86.5, respectively, P<.001) and at 24 hours (34.5+/-35.0 and 153.5+/-75.5, respectively, P<.001). The primary end point was observed in 87.8% (n=65) in the ticagrelor-treated patients compared to 57.6% (n=38) of clopidogrel-treated patients, P<.001.

CONCLUSION: Fibrinolysis-treated STEMI patients who received clopidogrel and aspirin at the time of fibrinolysis and were undergoing early PCI frequently had PRU >208. In this high-risk population, ticagrelor provides more prompt and potent platelet inhibition compared with clopidogrel

Guimaraes, LdFC, et al. $P2Y_{12}$ receptor inhibition with prasugrel and ticagrelor in STEMI patients after fibrinolytic therapy: analysis from the SAMPA randomized trial. *Int J Cardiol*. 2017;230: 204-208.

BACKGROUND: A pharmacodynamic comparison between ticagrelor and prasugrel after fibrinolytic therapy has not yet been performed.

METHODS: In the single-center SAMPA trial, 50 consecutive STEMI patients previously treated with clopidogrel and undergoing a pharmacoinvasive strategy were randomized to either a ticagrelor (n=25) 180mg loading dose followed by 90mg bid, or a prasugrel (n=25) 60mg loading dose followed by 10mg/day, initiated after fibrinolytic therapy but before angiography. Platelet reactivity was assessed with the VerifyNow $P2Y_{12}$ assay at 0, 2, 6, and 24h after randomization.

RESULTS: Mean times from fibrinolysis to prasugrel or ticagrelor administration were 11.1+/-6.9 and 13.3+/-6.3h, respectively (p=0.24). The values of PRU decreased significantly from baseline to 2h (all p<0.001) and from 2h to 6h (all p<0.001) in both groups. There was no difference in PRU values between 6h and 24h. The mean PRU values at 0, 2, 6, and 24h were 234.9, 127.8, 45.4, and 48.0 in the prasugrel group and 233.1, 135.1, 67.7, and 56.9 in the ticagrelor group, respectively. PRU values did not significantly differ between groups at any time period of the study.

CONCLUSIONS: In patients with STEMI treated with fibrinolytic therapy, platelet inhibition after clopidogrel is suboptimal and can be further increased with more potent agents. Ticagrelor and prasugrel demonstrated a similar extent of P2Y₁₂ receptor inhibition within 24h, although maximal platelet inhibition after these potent agents was not achieved for 6h.

Kosova EC, Bonaca MP, Dellborg M, et al. Vorapaxar in patients with coronary artery bypass grafting: findings from the TRA 2°P-TIMI 50 trial. *Europ Heart J Acute Cardiovasc Care.* 2017;6(2):164-172.

BACKGROUND: Vorapaxar is a first-in-class protease-activated receptor-1 antagonist indicated for the reduction of cardiovascular death, myocardial infarction, and stroke in stable patients with prior atherothrombosis, who have not had a prior stroke or transient ischemic attack. The aims of this study were to investigate: 1) the role of vorapaxar in patients with severe coronary artery disease treated previously with coronary artery bypass grafting (CABG); and 2) safety in patients undergoing CABG while receiving vorapaxar.

METHODS: TRA 2degreeP-TIMI 50 was a randomized, double-blinded, placebo-controlled trial of vorapaxar in 26,449 stable patients with prior atherothrombosis followed for a median of 30 months. We 1) investigated the efficacy of vorapaxar among patients with a history of CABG prior to randomization (n=2942); and 2) assessed the safety among 367 patients who underwent a new CABG during the trial.

RESULTS: Patients with a prior CABG were at higher risk for cardiovascular death, myocardial infarction, or stroke at three years compared with patients without a prior CABG (13.7% vs. 7.8%, p<0.001). Among patients with a prior CABG, vorapaxar significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke (11.9% vs. 15.6%, hazard ratio 0.71, 95% confidence interval 0.58-0.88, p=0.001; number-needed-to-treat = 27). In patients undergoing CABG while receiving vorapaxar, the rate of Thrombolysis in Myocardial Infarction CABG major

bleeding was 6.3% vs. 4.1% with placebo (hazard ratio 1.53, 95% confidence interval 0.58-4.01, p=0.39).

CONCLUSIONS: In patients with a prior CABG, vorapaxar significantly reduced the risk of recurrent major cardiovascular events. In patients undergoing CABG while receiving vorapaxar, bleeding risk appeared similar to that seen in the overall trial population.

Malhotra K, Goyal N, Kasunich AS, et al. Ticagrelor for stroke prevention in patients with vascular risk factors: a systematic review and meta-analysis. *J Neurol Sci.* 2018;390:212-218.

BACKGROUND: Even though ticagrelor was beneficial in prior cardiovascular trials, its efficacy in stroke prevention was inconclusive in recent randomized-controlled clinical trials (RCTs). We sought to consolidate the evidence for efficacy and safety of ticagrelor for stroke prevention. METHODS: We conducted a systematic review and meta-analysis of RCTs in major databases reporting following efficacy and safety outcomes among patients with cerebral or cardiovascular risk factors treated with ticagrelor (vs. control): ischemic stroke (IS), combined ischemic and hemorrhagic stroke, myocardial infarction (MI), cardiovascular death (CVD), all-cause mortality, and major bleeding events. We pooled risk ratios (RR) and adjusted hazard ratios (HR adjusted) from each trial using random-effect models, and assessed the heterogeneity using Cochran Q and I^2 statistics.

RESULTS: We identified 13 RCTs, comprising 64,360 patients. In comparison to control group, ticagrelor reduced the risk of IS (RR=0.86; 95%CI=0.78-0.95, p=.003; I(2)=0%), combined ischemic and hemorrhagic strokes (risk ratio: 0.90; 95%CI: 0.81-1.00, p=.05; I(2)=0%), and composite stroke/MI/CVD (RR=0.90; 95%CI=0.81-0.99, p=.03; I(2)=47%). Ticagrelor was not associated with increased risk of mortality (RR: 0.95; 95%CI: 0.84-1.07; p=.40) or major bleeding events (RR: 1.18; 95%CI: 0.92-1.50; p=.19). Additional analyses demonstrated that ticagrelor reduced the risk of incident strokes (HR adjusted=0.87; 95%CI=0.76-0.98; p=.03) and composite stroke/MI/CVD (HR adjusted=0.88; 95%CI=0.78-0.98; p=.02) among patients with prior history of IS or transient ischemic attack.

CONCLUSIONS: Ticagrelor seems to be a beneficial option for primary and secondary stroke prevention in patients with cerebral or cardiovascular risk factors. Further RCTs are needed to evaluate the role of ticagrelor in secondary stroke prevention.

Norgren L, Patel MR, Hiatt WR, et al. Outcomes of patients with critical limb ischaemia in the EUCLID trial. *Eur J Vasc Endovasc Surg.* 2018;55(1):109-117.

OBJECTIVES: Critical limb ischaemia (CLI) implies an increased risk of cardiovascular morbidity and mortality, and the optimal antithrombotic treatment is not established.

DESIGN, MATERIALS, METHODS: The EUCLID trial investigated the effect of monotherapy with ticagrelor versus clopidogrel in 13,885 patients with peripheral artery disease (PAD); the primary

endpoint was cardiovascular death, myocardial infarction, or ischaemic stroke. Patients planned for revascularisation or amputation within 3 months, were excluded. This analysis focuses on the subgroup with CLI, defined by rest pain (58.8%), major (9.0%) or minor (32.2%) tissue loss.

RESULTS: In EUCLID, 643 patients (4.6%) had CLI at baseline. Diabetes mellitus was more common in the CLI group, while coronary disease, carotid disease, and hypertension were more common in the non-CLI group. A majority of CLI patients (62.1%) had only lower extremity PAD. In patients enrolled on the ankle brachial index (ABI) criteria, ABI was 0.55 +/- 0.21 (mean +/- SD) for those with CLI versus 0.63 +/- 0.15 for those without CLI. The primary efficacy endpoint significantly increased among patients with CLI compared with those without CLI with a rate of 8.85 versus 4.28/100 patient years (adjusted for baseline characteristics hazard ratio [HR] 1.43 [95% CI 1.16-1.76]; p = 0.0009). When acute limb ischaemia requiring hospitalisation was added to the model, significant differences remained (adjusted HR 1.38, [95% CI 1.13-1.69]; p = 0.0016). The 1 year mortality was 8.9%. A trend towards increased lower limb revascularisation among those with CLI was observed. Bleeding (TIMI major, fatal, intracranial) did not differ between those with and without CLI.

CONCLUSIONS: Nearly 5% of patients enrolled in EUCLID had CLI at baseline. Milder forms of CLI dominated, a result of the trial design. Patients with CLI had a significantly higher rate of cardiovascular mortality and morbidity versus those without CLI. Further efforts are required to reduce the risk of cardiovascular events in PAD, especially in patients with CLI.

Pelletier-Galarneau M, Hunter CRRN, Ascah KJ, et al. Randomized trial comparing the effects of ticagrelor versus clopidogrel on myocardial perfusion in patients with coronary artery disease. *J Am Heart Assoc.* 2017;6(5):02.

BACKGROUND: Ticagrelor is a P2Y₁₂ receptor inhibitor used in acute coronary syndromes to reduce platelet activity and to decrease thrombus formation. Ticagrelor is associated with a reduction in mortality incremental to that observed with clopidogrel, potentially related to its non-antiplatelet effects. Evidence from animal models indicates that ticagrelor potentiates adenosine-induced myocardial blood flow (MBF) increases. We investigated MBF at rest and during adenosine-induced hyperemia in patients with stable coronary artery disease treated with ticagrelor versus clopidogrel.

METHODS AND RESULTS: This randomized double-blinded crossover study included 22 patients who received therapeutic interventions of ticagrelor 90 mg orally twice a day for 10 days and clopidogrel 75 mg orally once a day for 10 days, with a washout period of at least 10 days between the treatments. Global and regional MBF and myocardial flow reserve were measured using rubidium 82 positron emission tomography/computed tomography at baseline and during intermediate- and high-dose adenosine. Global MBF was significantly greater with ticagrelor versus clopidogrel (1.28+/-0.55 versus 1.13+/-0.47 mL/min per gram, P=0.002) at intermediate-dose adenosine and not different at baseline (0.65+/-0.19 versus 0.60+/-0.15

mL/min per gram, P=0.084) and at high-dose adenosine (1.64+/-0.40 versus 1.61+/-0.19 mL/min per gram, P=0.53). In regions with impaired myocardial flow reserve (<2.5), MBF was greater with ticagrelor compared with clopidogrel during intermediate and high doses of adenosine (P<0.0001), whereas the differences were not significant at baseline.

CONCLUSIONS: Ticagrelor potentiates global and regional adenosine-induced MBF increases in patients with stable coronary artery disease. This effect may contribute to the incremental mortality benefit compared with clopidogrel.

Pollack CV, Jr., Davoudi F, Diercks DB, et al. Relative efficacy and safety of ticagelor vs clopidogrel as a function of time to invasive management in non-ST-segment elevation acute coronary syndrome in the PLATO trial. *Clin Cardiol.* 2017;40(6):390-398.

BACKGROUND: Guidelines suggest that "upstream" $P2Y_{12}$ receptor antagonists should be considered in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS).

HYPOTHESIS: Early use of ticagrelor in patients managed with an invasive strategy would be more effective than clopidogrel because of its more rapid onset of action and greater potency.

METHODS: In the PLATO trial, 6792 NSTE-ACS patients were randomized to ticagrelor or clopidogrel (started prior to angiography) and underwent angiography within 72 hours of randomization. We compared efficacy and safety outcomes of ticagrelor vs clopidogrel as a function of "early" (<3h) vs "late" (>=3h) time to angiography. Adjusted Cox proportional hazards models evaluated interaction between randomized treatment and time from randomization to angiography on subsequent outcomes.

RESULTS: Overall, a benefit of ticagrelor vs clopidogrel for cardiovascular death/myocardial infarction/stroke was seen at day 7 (hazard ratio [HR]: 0.67, P = 0.002), day 30 (HR: 0.81, P = 0.042), and 1 year (HR: 0.80, P = 0.0045). There were no significant interactions in the <3h vs >=3h groups at any timepoint. For major bleeding, overall there was no significant increase (HR: 1.04, 95% confidence interval: 0.85-1.27); but there was a significant interaction with no difference between ticagrelor and clopidogrel in the early group (HR: 0.79), but higher bleeding risk with ticagrelor in the late angiography group, at 7 days (HR: 1.51, P_{int} = 0.002). Patterns were similar at 30 days and 1 year.

CONCLUSIONS: The benefit of ticagrelor over clopidogrel was consistent in those undergoing early and late angiography, supporting upstream use of ticagrelor.