Ticagrelor (BRILINTA)
National Drug Monograph Addendum
October 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum to the original drug monograph provides information on the evidence for the use of ticagrelor in patients with a history of myocardial infarction (MI). The original drug monograph can be found at: **PBM MAP VPE National Drug Monographs** .

Introduction

Ticagrelor is a reversible $P2Y_{12}$ platelet inhibitor that was originally approved in the U.S. in 2011 for the reduction in the risk of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS). FDA approval was based on results of the PLATO study which showed that ticagrelor was superior to clopidogrel in reducing the risk of vascular death, MI, or stroke with similar to higher rates of bleeding. When effects were examined by region, the subanalysis of PLATO patients from the U.S. showed a trend of worse outcomes on ticagrelor compared to clopidogrel. After exploratory investigations were conducted to evaluate potential reasons for the geographic differences in outcomes, the only explanation identified for the difference was the higher aspirin dose primarily used in the U.S. As a result, FDA approved ticagrelor with the recommendation to avoid maintenance doses of aspirin greater than 100 mg daily.

In September 2015, FDA expanded the indication for ticagrelor to include patients with a history of myocardial infarction (MI) based on results of the PEGASUS TIMI-54 study.[1] The approved dose for the new indication is 60 mg twice daily (along with daily aspirin), which is lower than the 90 mg twice daily dose indicated for the treatment of patients with acute coronary syndrome (ACS).

Efficacy (Long-term treatment in patients with a history of MI)[2]

- The PEGASUS-TIMI 54 study (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) was a randomized, double-blind, placebo-controlled, multinational, industry sponsored trial that evaluated the efficacy and safety of two doses of ticagrelor in patients with a spontaneous MI one to three years previously and a predefined high risk feature. Key exclusion criteria were: bleeding disorder, history of stroke or intracranial bleeding, recent gastrointestinal bleed or major surgery, or planned use of a $P2Y_{12}$ receptor antagonist, dipyridamole, cilostazol, or anticoagulant.
- A total of 21,162 patients were randomized to treatment to one of three arms: ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo. This review will focus on the 60 mg dose that was approved by FDA for the expanded indication. All patients were on background, low dose aspirin therapy. The mean age of the study population was 65 years, and the qualifying event occurred at a median of 1.7 years previously. Most patients had undergone percutaneous coronary intervention (PCI), and ST segment elevation MI (STEMI) was the qualifying event for about half of the population. The median duration of follow-up was 33 months.
- For the primary composite efficacy endpoint of cardiovascular death, MI, or stroke, ticagrelor 60 mg was superior to placebo based on 3 year Kaplan Meier estimates (NNT=79). There was a trend favoring ticagrelor in the reduction of cardiovascular death, but statistical significance was not reached. Due to the hierarchical testing

design, other efficacy endpoints were considered exploratory. Effects appeared to be consistent among several subgroups tested including examination by age, geographic region, and aspirin dose.

- Overall, there is moderate quality of evidence for the use of ticagrelor with aspirin in patients with a history of MI (Refer to Appendix A).

Selected Efficacy Endpoints PEGASUS TIMI-54[2]

Endpoint	Ticag 60 BID n=7,045 n (%)	Placebo n=7,067 n (%)	HR (95% CI)	P value
Primary Endpoint: CV death, MI, stroke	487 (7.77)	578 (9.04)	0.84 (0.74 – 0.95)	0.004
CV death	174 (2.86)	210 (3.39)	0.83 (0.68 – 1.01)	0.07
MI	285 (4.53)	338 (5.25)	0.84 (0.72 – 0.98)	0.03
Stroke	91 (1.47)	122 (1.94)	0.75 (0.57 – 0.98)	0.03
All cause death	289 (4.69)	326 (5.16)	0.89 (0.76 – 1.04)	0.14

Efficacy as 3-year Kaplan-Meier Estimates; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; 3 yr Kaplan-Meier Estimates.

Safety[2]

- Bleeding: Ticagrelor 60 mg was associated with significantly more TIMI major bleeding (NNH=81), TIMI minor bleeding, and bleeding leading to transfusion or study discontinuation compared to placebo. There was not a significantly increased risk of fatal bleeding or intracranial hemorrhage with ticagrelor. Safety among several subgroups tested appeared to be consistent, including examination by age, geographic region, and aspirin dose.
- Other adverse events: Dyspnea occurred significantly more often in patients receiving ticagrelor vs. placebo and more frequently led to study drug discontinuation (4.6% vs. 0.8%; p <0.001). Most events were classified as mild to moderate in severity. There was a higher rate of gout-related adverse events with ticagrelor vs. placebo (2% vs. 1.5%; p=0.01). A nonsignificant excess of bradyarrhythmia and renal adverse events were reported with ticagrelor.
- Tolerability: Discontinuation due to adverse events was higher with ticagrelor 60 mg vs. placebo (16.4% vs. 8.9%), with most adverse events related to bleeding.

Selected Safety Endpoints PEGASUS TIMI-54[2]

Endpoint	Ticag 60 BID n=6,958 n (%)	Placebo n=6,996 n (%)	HR (95% CI)	P value
Primary Endpoint: TIMI major bleed	115 (2.30)	54 (1.06)	2.32 (1.68 – 3.21)	<0.001
TIMI minor bleed	55 (1.18)	18 (0.36)	3.31 (1.94 – 5.63)	<0.001
Bleed requiring transfusion	105 (2.09)	37 (0.72)	3.08 (2.12 – 4.48)	<0.001
Bleed leading to study drug DC	354 (6.15)	86 (1.50)	4.40 (3.48 – 5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	33 (0.71)	30 (0.60)	1.20 (0.73 – 1.97)	0.47
Fatal bleeding	11 (0.25)	12 (0.26)	1.00 (0.44 – 2.27)	1.00
Dyspnea	987 (15.84)	383 (6.38)	2.81 (2.50 – 3.17)	<0.001

Safety as 3-year Kaplan-Meier Estimates; CI=confidence interval; DC=discontinuation; HR=hazard ratio; TIMI=Thrombolysis in Myocardial Infarction major bleeding=clinically overt bleeding with drop in Hemoglobin (Hgb) ≥5 g/dL, fatal bleeding, or any intracranial bleeding. TIMI minor bleed=clinically overt bleeding with drop in Hgb of 3 to <5 g/dL.

Other Considerations[3]

A recent meta-analysis was conducted by Udell and colleagues to evaluate long-term DAPT (beyond one year) vs. aspirin alone in patients with a previous MI. The study included a total of 33,435 patients from 6 studies followed for a mean duration of 31 months. The PEGASUS study was included and comprised 63% of the total population. When results were pooled together, long term DAPT was found to reduce the rate of major adverse cardiovascular events (MACE) compared to aspirin alone (6.37% vs. 7.46%; RR 0.78; 95% CI 0.67-0.90; p-0.001; NNT = 91). Individual endpoints including cardiovascular death, MI, stroke, and very late stent thrombosis were also significantly lower with DAPT vs. aspirin alone. The benefit of DAPT was offset by an increased risk of major bleeding vs. aspirin alone (1.85% vs. 1.09%; RR 1.73; 95% CI 1.19-2.50; p=0.004; NNH = 132). However, fatal and intracranial bleeds were infrequent and not significantly increased with DAPT. Non-cardiovascular death was also statistically similar between DAPT and aspirin only groups.

Projected Place in Therapy

Dual antiplatelet therapy (DAPT) is guideline-recommended standard of care in patients with ACS; however, the optimal duration of dual antiplatelet therapy (DAPT) is unclear. Several recent studies have examined shorter and longer durations of DAPT in different patient populations (e.g., ACS, drug eluting stents, PCI, etc.) and with different drug regimens (clopidogrel, prasugrel, ticagrelor). Stabilized patients with prior MI are at risk for subsequent cardiovascular events.

American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the management of Non-ST elevation MI ACS and STEMI were published before PEGASUS and other more recent studies and meta-analyses examining different DAPT durations. The 2014 AHA/ACC Guidelines for Non-ST elevation ACS recommend DAPT for up to 12 months for patients managed with an ischemia guided strategy and at least 12 months in patients who receive a stent during PCI. Longer durations may be considered in patients with stents.[4] Conversely, shorter durations of DAPT may be reasonable in patients where the bleeding risk outweighs anticipated benefit. The 2013 AHA/ACC Guidelines for STEMI recommend DAPT for 12 months in patients who receive stents and up to 12 months in patients managed with fibrinolytic therapy.[5]

In patients with a history of MI maintained on low-dose aspirin, the addition of ticagrelor was superior to placebo in reducing the risk of cardiovascular death, MI, or stroke. The benefit of ticagrelor was offset by an increased risk of major and minor bleeding, though fatal bleeding and intracranial bleeding were infrequent and not significantly higher with ticagrelor. Similarly, a meta-analysis of a broader patient population with prior MI also found that long-term DAPT (beyond one year) was more effective than aspirin alone in reducing MACE as well as the individual components of cardiovascular death, MI, and stroke with an increased risk of major bleeding (but not fatal or intracranial bleeding).

Careful selection of patients at high risk of subsequent cardiovascular events and low risk of bleeding, similar to patients enrolled in clinical trials, should be done to help maximize the benefit-to-risk ratio of long-term DAPT. Reassessment of risk and benefit of DAPT in individual patients should occur regularly. In both the PEGASUS trial and meta-analysis by Udell and colleagues, the NNT to prevent one event was only slightly higher than the NNH for a major bleeding event. Considering characteristics of patients in the PEGASUS study, results may not be generalizable to a more broad ACS population. Patients enrolled in PEGASUS had at least one high risk feature (e.g., hypertension, diabetes, hypercholesterolemia, multi-vessel disease) and had tolerated prior DAPT treatment for their initial ACS. Patients with recent bleeding, bleeding disorder, or who were on concomitant medications that increase the risk of bleeding were excluded.

References

[1]BRILINTA (ticagrelor) [prescribing information]. AstraZeneca LP, Wilmington DE. September 2015.

[2] Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction (PEGASUS-TIMI 54). N Engl J Med. 2015; 372:1791-1800.

[3] Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2015;doi:10.1093/eurheartj/ehv443.

[4] Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344-e426.

[5] O-Gara PT, Kushner G, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the management of 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(4):e78-140.

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.