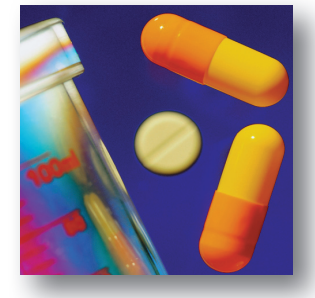

Ticagrelor (Brilinta), an Antiplatelet Drug for Acute Coronary Syndrome

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INTRODUCTION

Acute coronary syndrome (ACS) comprises myocardial infarction (MI) and unstable angina (UA). UA, non–ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI) share the pathophysiological characteristics of erosion, fissure, or rupture of atherosclerotic plaque, followed by platelet adherence and aggregation along with activation of the clotting cascade.[1] Consequently, patients with ACS require treatment with antiplatelet drugs.

In the U.S., an estimated 7.9 million people have experienced an MI, and 9 million people have experienced angina pectoris. Each year, approximately 785,000 people experience a new MI; approximately 470,000 have a recurrent MI; and 195,000 people have a silent MI. In 2009, approximately 605,000 patients underwent a percutaneous coronary intervention (PCI) and 242,000 patients underwent cardiac revascularization, consisting of coronary artery bypass graft (CABG) surgery.[2]

On July 20, 2011, the FDA approved AstraZeneca's oral antiplatelet agent ticagrelor (Brilinta), based on results from the pivotal phase 3 PLATelet inhibition and patient Outcomes (PLATO) study.[3,4]

The current American Heart Association/American College of Cardiology treatment guidelines recommend a P_2Y_{12} receptor antagonist in combination with aspirin for patients with ACS (class 1 recommendation) and for patients undergoing PCI with stent placement (level of evidence: A). Treatment options include clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi) 75 mg once daily, prasugrel (Effient, Eli Lilly) 10 mg once daily, and ticagrelor 90 mg twice daily.[5]

Table 1 presents a comparison of these three medications.

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Disclosure: The authors report no commercial or financial relationships in regard to this article.

INDICATION

Ticagrelor is indicated for reducing the rate of thrombotic cardiovascular events in patients with ACS (i.e., UA, NSTEMI, or STEMI).[6]

PHARMACOLOGY

Ticagrelor is a cyclopentyltriazolopyrimidine. The drug's empirical formula is $C_{23}H_{28}F_2N_6O_4S$, and its molecular weight is 522.57. The chemical structure is shown in Figure 1.

Mechanism of Action

Ticagrelor inhibits platelet activation and aggregation by reversibly interacting with the platelet P_2Y_{12} adenosine diphosphate (ADP) receptor to prevent signal transduction.[6]

Pharmacodynamics

A 6-week study compared the inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel in response to 20 micromolar (μM) of ADP as a platelet-aggregation agonist.[6] The onset of IPA was evaluated on day 1 of the study after loading doses of 180 mg ticagrelor and 600 mg clopidogrel were administered. At all time points, IPA was higher in the ticagrelor group. The maximum IPA effect of ticagrelor was reached at about 2 hours and was maintained for at least 8 hours.[6]

The offset of IPA was examined after 6 weeks of therapy with ticagrelor 90 mg twice daily or with clopidogrel 75 mg daily, again in response to 20 μm of ADP.[6]

The mean maximum IPAs following the last dose of ticagrelor and clopidogrel were 88% and 62%, respectively. After 24 hours, IPA in the ticagrelor group (58%) was similar to that in the clopidogrel group (52%), indicating that patients who missed a dose of ticagrelor would still maintain an IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to that in the placebo group. It is not known how bleeding risk and thrombotic risk correspond to IPA for either ticagrelor or clopidogrel.[6]

Switching patients from clopidogrel to ticagrelor resulted in an absolute IPA increase of 26.4%, and switching from ticagrelor to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without interrupting the antiplatelet effect.[6]

Pharmacokinetics

Ticagrelor demonstrates dose–proportional pharmacokinetic characteristics. These features are similar in both patients and healthy volunteers.[6]

Absorption. Oral ticagrelor may be taken with or without food. The drug's mean absolute bioavailability is approximately 36%, and the median time to maximum plasma concentration (t_{max}) is 1.5 hours (range, 1–4 hours).[6]

Distribution. The steady-state volume of distribution of ticagrelor is 88 L. Ticagrelor and its active metabolite are extensively (more than 99%) bound to human plasma proteins.[6]

Metabolism. Ticagrelor is metabolized by cytochrome P450 (CYP) isoenzymes, primarily by CYP3A4. This results in the formation of the major active metabolite. Ticagrelor and its active metabolite are weak P-glycoprotein substrates and inhibitors.[6]

Excretion. The primary route of elimination for ticagrelor is hepatic, whereas the primary route of elimination for the major metabolite is most likely biliary

Table 1 Comparison of Medications Used in the Treatment of Acute Coronary Syndromes

	Clopidogrel (Plavix)	Prasugrel (Effient)	Ticagrelor (Brilinta)
Class	Thienopyridines	Thienopyridines	Cyclopentyltriazolopyrimidine
Dosing	Once daily	Once daily	Twice daily
Onset	Slow (prodrug)	Slow (prodrug)	Faster
Offset	Irreversible	Irreversible	Reversible; wears off faster
Stop before surgery	5 days	7 days	5 days
Drug interactions	CYP2C19 omeprazole	—	CYP3A4 inhibitors
Pharmacogenetics	Genetic variation	Does not seem to be affected	Does not seem to be affected
Effectiveness	Delayed onset and variable response	More effective than clopidogrel but causes more bleeding	Ticagrelor seems more effective than clopidogrel for acute coronary syndromes; in most cases, has a similar risk of major bleeding but also higher spontaneous bleeding

CYP = cytochrome P450.

excretion. The mean half-life of ticagrelor is approximately 7 hours. The active metabolite has a mean half-life of about 9 hours.[6]

CLINICAL EFFICACY

Clinical evidence for the effectiveness of ticagrelor was provided by the phase 3, randomized, double-blind PLATO trial, in which ticagrelor (n = 9,333) was compared with clopidogrel in patients with ACS (n = 9,291). Both medications were given in combination with aspirin and other standard therapy.[4,6]

In the clopidogrel arm, patients received an initial loading dose of clopidogrel 300 mg if previous clopidogrel therapy had not been given before randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at the investigator's discretion.

In the ticagrelor arm, patients received a loading dose of 180 mg, followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at loading doses of 160 to 500 mg. A low daily maintenance dose of aspirin (75–100 mg) was recommended, but higher maintenance doses were allowed. The patients were treated for 6 to 12 months.[4,6]

The study's primary endpoint was a composite of first occurrence of cardiovascular death, nonfatal MI (excluding silent MI), and nonfatal stroke. The individual components were also assessed as secondary endpoints.[4,6] Patients were predominantly male (72%) and Caucasian (92%). About 43% of the patients were older than 65 years, and 15% were older than 75 years.[4,6]

The key findings are summarized in Table 2.

Efficacy Results

The primary composite endpoint—cardiovascular death, nonfatal MI (excluding silent MI), or stroke—occurred in 9.8% of the ticagrelor group and in 11.7% of the clopidogrel group after 12 months of treatment (hazard ratio, 0.84; $P = 0.0003$).[4,6]

Figure 2 shows the time to the first occurrence of the primary composite endpoint in the overall study. In the figure, the ticagrelor and clopidogrel curves separate within 30 days from randomization and continue to diverge throughout the 12-month treatment period.[4,6]

Other key efficacy outcomes in the PLATO study included the following:[4]

- Ticagrelor patients had a significantly reduced rate of the secondary composite endpoint of death from any cause, MI, or stroke compared with clopidogrel patients (10.2% vs. 12.3%, respectively; $P < 0.001$).
- Ticagrelor resulted in a significantly reduced rate of the secondary composite endpoint of death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic events versus clopidogrel (14.6% vs. 16.7%, respectively; $P < 0.001$). Ticagrelor patients had a

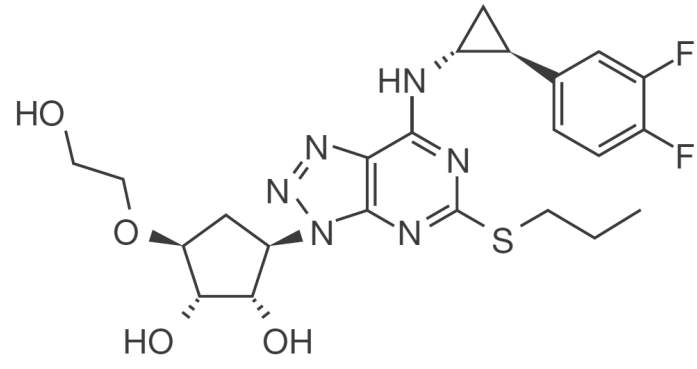

Figure 1 Chemical structure of ticagrelor. (From Brilinta prescribing information.[6])

Table 2 Summary of Key Outcomes of the PLATO Trial: Benefits and Limitations of Ticagrelor (Brilinta)

Benefits of Ticagrelor Compared With Clopidogrel
• At 12 months, lower rates of the first occurrence of primary composite endpoint—death from vascular causes, nonfatal MI (excluding silent MI), or stroke. • Lower rates of the primary composite endpoint. • Decreased rates of the composite endpoint of death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic events. • Reduced rates of MI alone. • Reduced rates of death from vascular causes and from any cause. • Fewer episodes of fatal bleeding (other than fatal intracranial bleeding). • Fewer adverse events in patients undergoing invasive treatment. • Lower rates of definite stent thrombosis.
Limitations of Ticagrelor
• A greater number of hemorrhagic strokes compared with clopidogrel. • An attenuated benefit in patients weighing less than the median weight for their sex, in those not taking lipid-lowering drugs at randomization, and in those enrolled in North America. • Higher rates of non–CABG-related major bleeding, according to TIMI criteria, compared with clopidogrel. • More episodes of intracranial bleeding and fatal intracranial bleeding compared with clopidogrel. • Higher rates of premature discontinuations than with clopidogrel. • Higher rates of discontinuations resulting from adverse events versus clopidogrel. • More cases of dyspnea than with clopidogrel.
Outcomes Showing No Differences Between Ticagrelor and Clopidogrel
• No differences in rates of stroke; major bleeding (per TIMI criteria); fatal or life-threatening bleeding; CABG-related major bleeding; bleeding requiring transfusion of red blood cells; syncope, pre-syncope, or loss of consciousness; or pacemaker implantation.

CABG = coronary artery bypass graft; TIMI = Thrombolysis in Myocardial Infarction.
Data compiled from Wallentin et al.[4] and from Brilinta (ticagrelor) prescribing information.[6]

significantly reduced rate of MI compared with clopidogrel patients (5.8% vs. 6.9%, respectively; $P = 0.005$).

- Ticagrelor therapy led to a significantly reduced rate of death resulting from vascular causes versus clopidogrel (4.0% vs. 5.1%, respectively; $P = 0.001$).
- Ticagrelor resulted in a significantly reduced rate of death from any cause when compared with clopidogrel (4.5%, vs. 5.9%, respectively; $P < 0.001$).

Influence of Aspirin Maintenance

In the PLATO protocol, the choice of the aspirin maintenance dose was left up to the investigators. Consequently, the patterns of aspirin use differed greatly in the U.S. and elsewhere. About 8% of non-U.S. investigators used aspirin doses above 100 mg, and about 2% used doses above 300 mg. In contrast, 57% of patients in the U.S. received aspirin doses above 100 mg, and 54% received doses exceeding 300 mg.

Overall, the efficacy results favored ticagrelor when the drug was used with lower maintenance doses of aspirin (100 mg or less). Higher doses of aspirin appear to reduce the effectiveness of ticagrelor. Therefore, the ticagrelor labeling recommends that aspirin maintenance dosing be restricted to 100 mg with concomitant ticagrelor administration.[6]

SAFETY PROFILE

Bleeding Events

Figure 3 shows the estimated time to a major bleeding event in the PLATO trial. Ticagrelor was associated with significantly higher rates of major or minor bleeding compared with clopidogrel (16.1% vs. 14.6%, respectively; $P = 0.008$). Non–CABG-related major bleeding also occurred more often with ticagrelor than with clopidogrel (4.5% vs. 3.8%, respectively; $P = 0.03$).[6,7] Other important bleeding-related outcomes were as follows:[4]

- Ticagrelor was associated with significantly fewer episodes of fatal bleeding (other than fatal intracranial bleeding) compared with clopidogrel (9 [0.1%] vs. 21 [0.3%], respectively; $P = 0.03$).

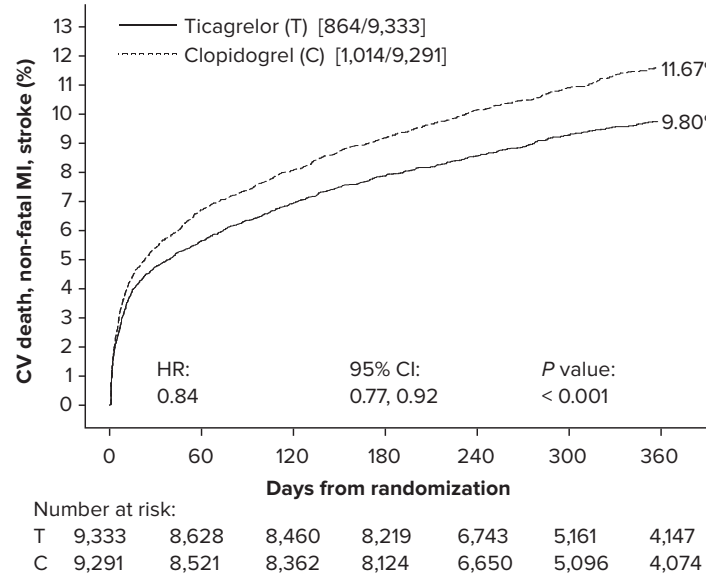

Figure 2 Time to first occurrence of cardiovascular death, MI, or stroke in the PLATO trial. CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction. (From Brilinta prescribing information.[6])

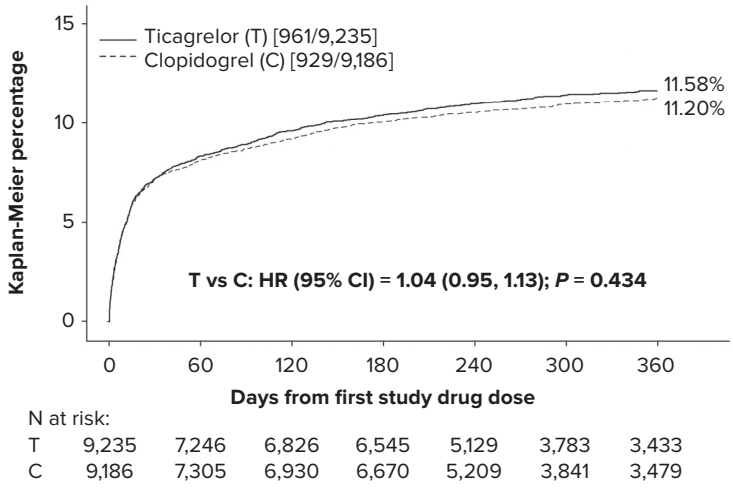

Figure 3 Kaplan–Meier estimate of the time to first "total major" bleeding event in the PLATO trial. CI = confidence interval; HR = hazard ratio. (From Brilinta prescribing information.[6])

- The rate of definite stent thrombosis was significantly lower with ticagrelor than with clopidogrel (1.3% vs. 1.9%, respectively; $P = 0.009$).
- A greater number of hemorrhagic strokes occurred with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], respectively; $P = 0.10$).
- The ticagrelor group had significantly higher rates of non–CABG-related major bleeding, according to TIMI criteria, compared with the clopidogrel group (2.8% vs. 2.2%, respectively; $P = 0.03$).
- Ticagrelor was associated with more episodes of intracranial bleeding compared with clopidogrel (26 [0.3%] vs. 14 [0.2%], respectively; $P = 0.06$).
- Ticagrelor was associated with significantly more episodes of fatal intracranial bleeding versus clopidogrel (11 [0.1%] vs. 1 [0.01%], respectively; $P = 0.02$).
- There was no significant difference between ticagrelor and clopidogrel in rates of stroke (1.5% vs. 1.3%, respectively; $P = 0.22$); major bleeding according to TIMI criteria (7.9% vs. 7.7%, respectively; $P = 0.57$); fatal or life-threatening bleeding (5.8% in both groups; $P = 0.70$); and bleeding requiring transfusion of red blood cells (8.9% in both groups; $P = 0.96$).

Dyspnea

Dyspnea was the most common adverse event in the PLATO trial, with rates of 13.8% for ticagrelor and 7.8% for clopidogrel (Table 3). Dyspnea was usually mild or moderate in severity and often resolved during continued therapy.[6]

ONSET/OFFSET was a trial that investigated dyspnea associated with ticagrelor. In this study, 123 stable aspirin-treated patients with coronary artery disease were randomly assigned to receive ticagrelor (a loading dose of 180 mg, then 90 mg twice daily; n = 57); clopidogrel (a 600-mg loading dose, then 75 mg daily; n = 54); or placebo (n = 12) for 6 weeks.

Dyspnea was reported by 39%, 9%, and 8% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively ($P < 0.001$). Most cases were mild or lasted less than 24 hours, although three patients discontinued ticagrelor because of dyspnea. In all treatment groups, including the subgroup of ticagrelor-treated patients with dyspnea, no significant changes were observed between baseline and 6 weeks in any cardiac or pulmonary function parameters.[8]

Drug Discontinuation

Adverse events included gastrointestinal bleeding, epistaxis, contusions, cutaneous bleeding, and hematuria.[6,7] The rates of drug discontinuation resulting from adverse events were 7.4% for ticagrelor and 5.4% for clopidogrel.[6] Ticagrelor therapy was discontinued more often than

Table 3 Percentage of Patients Reporting Nonhemorrhagic Adverse Events (At Least 3% or More in Either Group)

	Ticagrelor (%) (n = 9,235)	Clopidogrel (%) (n = 9,186)
Dyspnea*	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Noncardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

*Includes dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, and paroxysmal nocturnal dyspnea.

From Brilinta (ticagrelor) prescribing information.[6]

clopidogrel because of bleeding (2.3% vs. 1.0%, respectively). Dyspnea led to drug discontinuation in 0.9% of the ticagrelor group and in 0.1% of the clopidogrel group.[6]

Bradycardia

The PLATO investigators excluded patients who were at increased risk of bradycardic events. In PLATO, syncope, presyncope, and loss of consciousness were reported by 1.7% and 1.5% of ticagrelor and clopidogrel patients, respectively.[6]

Gynecomastia

In PLATO, gynecomastia was more common in men who received ticagrelor than in those who received clopidogrel (0.23% vs. 0.05%, respectively).[6]

Laboratory Abnormalities

During the PLATO study, serum uric acid levels increased approximately 0.6 mg/dL from baseline during ticagrelor treatment compared with an increase of 0.2 mg/dL during clopidogrel treatment. However, this difference disappeared within 30 days after the drugs were discontinued. Gout was reported in 0.6% of each treatment group.[6]

Serum creatinine levels increased by more than 50% in 7.4% of the ticagrelor group compared with 5.9% of the clopidogrel group. These increases did not usually progress with ongoing treatment and often decreased with continued therapy. Serious renal adverse events (e.g., acute or chronic renal failure, toxic nephropathy, and oliguria) did not differ between treatment groups.[6]

Pregnancy

Ticagrelor is a Pregnancy Category C drug. No adequate or well-controlled studies of ticagrelor have been conducted in pregnant women. Ticagrelor should be used in pregnant patients only if the potential benefits of treatment outweigh the risks to the fetus.[6]

Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Health care practitioners and patients, therefore, should decide whether to stop nursing or to discontinue ticagrelor, taking into account the importance of the drug to the mother.[6]

Pediatric Use

The safety and efficacy of ticagrelor have not been established in pediatric patients.[6]

Geriatric Use

In the PLATO trial, no overall differences in efficacy or safety were observed between patients 65 years of age or older versus younger patients. However, the greater sensitivity of some older patients cannot be ruled out.[6]

Hepatic Impairment

According to the labeling for ticagrelor, no dosage adjustments are needed in patients with mild hepatic impairment. Because the liver metabolizes ticagrelor, impaired hepatic function can increase the risk of adverse events, such as bleeding. Therefore, ticagrelor is contraindicated in patients with severe hepatic impairment, and the drug should be prescribed with caution in patients with moderate impairment.[6]

Renal Impairment

Dose adjustments of ticagrelor are not needed for patients with renal impairment. Patients receiving dialysis have not been studied.[6]

Smoking

Although habitual smoking increased the mean clearance of ticagrelor by 22% in smokers compared with that in nonsmokers, no dosage adjustments are necessary based on smoking status.[6]

DOSAGE AND ADMINISTRATION

Oral ticagrelor is initiated as a one-time loading dose of 180 mg (two 90-mg tablets), followed by continued treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg) is given, ticagrelor should be administered with a daily maintenance dose of aspirin 75 to 100 mg. ACS patients who have received a loading dose of clopidogrel may be started on ticagrelor.[6]

Ticagrelor may be taken with or without food.[6] If a dose is missed, patients should take their next dose (one 90-mg tablet) at the scheduled time.[6]

WARNINGS

The ticagrelor labeling includes boxed warnings regarding the risk of bleeding during ticagrelor therapy and the potential for high maintenance doses of aspirin to interfere with the effectiveness of ticagrelor.[6]

Bleeding Risk

Ticagrelor, like other antiplatelet drugs, can cause significant, sometimes fatal, bleeding. Ticagrelor should not be used in patients with active pathological bleeding or a history of intracranial hemorrhage. Clinicians should not prescribe ticagrelor for patients who are expected to undergo urgent CABG surgery. If possible, ticagrelor should be discontinued for at least 5 days before any surgery.[6]

Clinicians should suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures during ticagrelor therapy.[6] If possible, clinicians should manage bleeding without discontinuing ticagrelor, because stopping therapy increases the risk of subsequent cardiovascular events.[6]

Aspirin and Ticagrelor Effectiveness

Maintenance doses of aspirin above 100 mg daily reduce the effectiveness of ticagrelor and should be avoided. After any initial aspirin dose, ticagrelor should be used with an aspirin dose of 75 to 100 mg/day.[6]

DRUG INTERACTIONS

Because ticagrelor is metabolized predominantly by the CYP3A4 isoenzyme, medications that are CYP3A inducers or inhibitors may affect ticagrelor levels and should be avoided. CYP3A inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital) may increase ticagrelor serum levels, whereas CYP3A inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) may reduce ticagrelor levels.[6]

Because the statin medications simvastatin (Zocor, Merck) and lovastatin (Mevacor, Merck) are metabolized by CYP3A4, ticagrelor therapy may result in increased serum concentrations of these drugs. Simvastatin and lovastatin should not be used with ticagrelor at doses exceeding 40 mg.[6]

As a result of its ability to weakly inhibit the P-glycoprotein transporter, ticagrelor may increase serum levels of digoxin.

Digoxin serum levels should be monitored with the initiation of or any change in ticagrelor therapy.[6]

P&T COMMITTEE CONSIDERATIONS

Ticagrelor is the first reversibly binding oral P_2Y_{12} ADP-receptor antagonist for the treatment of ACS.[9] Reversible inhibition with ticagrelor may allow more rapid surgical intervention after discontinuation, suggesting greater flexibility in the treatment of ACS.[10] Moreover, ticagrelor is not a prodrug, and metabolic activation is not required to inhibit the P_2Y_{12} ADP receptor.[9] As a result, a loading dose of 180 mg achieves effective IPA within 30 minutes.[11]

However, certain factors may limit the use of ticagrelor. For example, ticagrelor must be taken twice daily because of its rapid reversibility.[6,11] By contrast, both of ticagrelor's key competitors (clopidogrel and prasugrel) are taken once daily,[12,13] thus offering a potential advantage over ticagrelor in terms of convenience and compliance (see Table 1).

Cost is another limiting factor. AstraZeneca set the wholesale acquisition price of ticagrelor at $7.24 per day (approximately $220 per month), which represented a 20% increase over clopidogrel and a 25% increase over prasugrel.[14,15] Further complicating the matter, clopidogrel recently went off-patent, making ticagrelor's higher price even more important in coverage decisions.[14,15]

Ticagrelor's safety profile is another consideration. Although ticagrelor provided a 16% relative risk reduction in the primary endpoint—a composite of death from vascular causes, nonfatal MI (excluding silent MI), and stroke—and a 22% relative risk reduction in all-cause mortality versus clopidogrel in the PLATO trial, it also was associated with a greater risk of non-CABG bleeding compared with clopidogrel, and more patients discontinued treatment with ticagrelor than with clopidogrel because of adverse events in general.[4,6] In particular, ticagrelor is associated with dyspnea and bradyarrhythmia, which may lead to the need for discontinuation.[6,11]

CONCLUSION

Ticagrelor offers a treatment option for patients with ACS and is included in the American Heart Association/American College of Cardiology 2011 guidelines for secondary prevention and risk-reduction therapy for patients with coronary and other atherosclerotic vascular diseases.[5] In the pivotal PLATO trial, ticagrelor treatment significantly reduced mortality rates from vascular causes, nonfatal MI, and stroke compared with clopidogrel, but it was associated with a significant increase in the rate of non–procedure-related bleeding.[4,6] Ticagrelor also showed higher rates of dyspnea, intracranial bleeding, and premature discontinuations resulting from adverse events.[4,6]

The increased cost of ticagrelor, compared with that of competitor drugs, as well as the need for twice-daily dosing (compared with once-daily for competitors), are also important considerations in formulary decision-making.[6,11–15]

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