



POLICY & PRACTICE

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'Just Say No' to Substitution

The terms "therapeutic substitution" and "therapeutic interchange" refer to two very different practices, and cardiologists should not accept the former but may be comfortable with the latter, according to a policy statement from the American College of Cardiology Foundation. Substitution occurs without a doctor's consent, whereas interchange is when a pharmacy dispenses a similarly acting drug with the physician's permission. If a payer is considering approving a certain interchange, it needs to take into account the strength of the evidence that the two drugs will work similarly, and it needs to consider the patient's specific medical condition. "Cost should be a consideration in this decision but not be the primary factor," according to the policy statement, which also recommends procedures for health care facilities and payers to follow when they are developing a therapeutic-interchange policy.

Heart Disease Is Most Costly

Heart disease in both women and men was the most expensive condition in the United States in 2008, while hypertension and hyperlipidemia also made the top-10 list, according to the Agency for Healthcare Research and Quality. The analysis found that the cost for inpatient and outpatient care, emergency department visits, home care, and prescriptions for men with heart disease reached \$47.3 billion, while payers spent \$43.6 billion to treat women for heart disease. Medicare paid more than half of those expenditures for women but only about 38% of the cost for men. In the same year, more men and women suffered from hypertension than from any of the other 10 most costly conditions: 29.5 million women and 25.6 million men were subject to expenditures that were related to hypertension, according to the agency.

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FDA Warns on Contrast Generator

The Food and Drug Administration is warning health care professionals to stop using CardioGen-82, a generator of rubidium-82 chloride, for cardiac positron emission tomography scans. The device's manufacturer, Bracco Diagnostics, announced that it will voluntarily recall the product. The FDA had re-

ceived reports of two patients who were getting more radiation than was expected from CardioGen-82, although the agency said that the individuals' risk of harm was minimal. However, the FDA determined that Bracco Diagnostics's manufacturing procedures are not sufficient to ensure reliable performance of the device. The agency said it also is investigating procedures that are used to detect radiation exposure from the CardioGen-82.

Senators: Stop the Imaging Cuts

A bipartisan group of seven senators has

called on President Obama to reject any further cuts to medical-imaging payments under Medicare, saying that the cuts already in place are harming both patients and the developers of these technologies. "As a result of these cuts, physicians are holding onto their old equipment longer, which means fewer patients have access to the newest technologies that are better at finding early-stage disease and guiding life-saving treatment," the senators wrote. Instead of cutting imaging payments, the group said, Medicare should implement clinical decision-support systems that will help doc-

BRILINTA™ (ticagrelor) Tablets

WARNING: BLEEDING RISK

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a P2Y₁₂ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [see Clinical Studies (14) in full Prescribing Information]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [see Warnings and Precautions (5.2) and Clinical Studies (14) in full Prescribing Information].

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS

History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see Clinical Studies (14) in full Prescribing Information].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see Warnings and Precautions (5.1) and Adverse Reactions (6.1) in full Prescribing Information].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see Clinical Pharmacology (12.3) in full Prescribing Information].

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see Adverse Reactions (6.1) in full Prescribing Information]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDs]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see Warnings and Precautions (5.5) and Adverse Reactions (6.1) in full Prescribing Information].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see Dosage and Administration (2) and Clinical Studies (14) in full Prescribing Information].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective

of whether they reported dyspnea. There was no significant difference between treatment groups for FEV₁. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in full Prescribing Information].

ADVERSE REACTIONS Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [see Warnings and Precautions (5.4) in full Prescribing Information]

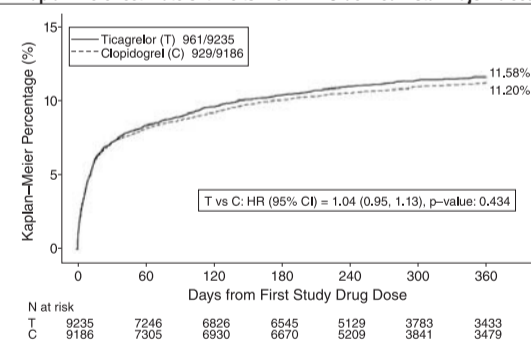
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:

- **Major bleed – fatal/life-threatening.** Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- **Major bleed – other.** Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- **Minor bleed.** Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- **Minimal bleed.** All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

tors determine when imaging is necessary. The senators signing the letter, many of whom come from states with strong biotech industries, are John Kerry (D-Mass.), David Vitter (R-La.), Scott Brown (R-Mass.), Ron Wyden (D-Ore.), Herb Kohl (D-Wis.), Lamar Alexander (R-Tenn.), and Maria Cantwell (D-Wash.).

Cardiologist Convicted of Fraud

A federal jury in Baltimore has convicted Salisbury, Md.-based cardiologist Dr. John McLean of six counts of fraud for implanting unnecessary car-

diovascular stents, ordering unnecessary tests, and making false entries in patients' medical records. According to evidence that was presented at his trial, Dr. McLean performed cardiac catheterizations and implanted unnecessary stents in more than 100 patients at the Peninsula Regional Medical Center in Salisbury. He also recorded false evidence or coronary artery blockages in patients' medical records to justify the stents that he implanted, the U.S. attorney's office alleged. Dr. McLean, who is scheduled to be sentenced on Nov. 10, faces a maximum sentence of 35 years

in prison and more than \$711,000 in forfeited profits.

Another Top Ranking for Harvard

The Harvard Clinical Research Institute received the highest payment from Eli Lilly of all physicians and physician groups in the United States in the first 3 months of 2011 – \$767,564 – for its work on the Dual Antiplatelet Therapy study, according to the drug manufacturer's new physician-payment registry. The antiplatelet therapy double-blind randomized controlled trial, which is sponsored by the Harvard Clinical Re-

search Institute and has multiple collaborators, including Eli Lilly, is designed to determine the appropriate combination of aspirin and a second anticoagulating therapy. Many of the top 10 payments on Eli Lilly's first quarter 2011 registry went to psychiatrists, neurologists, and rheumatologists. The company, which has started disclosing its payments to physicians under a corporate-integrity agreement with the federal government, indicated that 63% of its payments in the first quarter were related to research projects.

—Jane Anderson

BRILINTA™ (ticagrelor) Tablets

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Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding P2Y₁₂ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel. No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Dyspnea ^a	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
Non-cardiac 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

^a Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel. Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities Serum Uric Acid: Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group). Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

DRUG INTERACTIONS

Effects of other drugs Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

CYP3A inhibitors [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3) in full Prescribing Information].

CYP3A inducers [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3) in full Prescribing Information].

Aspirin Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [see Warnings and Precautions (5.2) and Clinical Studies (14) in full Prescribing Information].

Effect of BRILINTA on other drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin, lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see Clinical Pharmacology (12.3) in full Prescribing Information].

Digoxin *Digoxin*: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [see Clinical Pharmacology (12.3) in full Prescribing Information].

Other Concomitant Therapy BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m² basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m² basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternbrae, displaced articulation of pelvis, and misshapen/ misaligned sternbrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m² basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternbrae occurred. In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m² basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m² basis).

Nursing Mothers It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of BRILINTA in pediatric patients have not been established.

Geriatric Use In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3) in full Prescribing Information].

Renal Impairment No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [see Clinical Pharmacology (12.3) in full Prescribing Information].

OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

[see section (13.1) in full Prescribing Information]

PATIENT COUNSELING INFORMATION

[see section (17) in full Prescribing Information]

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Manufactured for: AstraZeneca LP, Wilmington, DE 19850

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Rev. 7/11 1320301 7/11