

Antiplatelet Therapy: Role of Effient® (prasugrel)



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This publication provides an overview of the clinical efficacy and safety of Effient® (prasugrel). Effient is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows: 1) Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI), 2) Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

The prescribing information for Effient contains a Boxed Warning regarding Bleeding Risk (see this page). See also “Effient Important Safety Information” on next page, and the Effient Full Prescribing Information, including Boxed Warning, accompanying this supplement for additional information about Effient.

Introduction

Antiplatelet drugs represent the cornerstone of medical therapy for patients with ACS managed with PCI. The approval of Effient, a thienopyridine class inhibitor of platelet activation and aggregation mediated by the P2Y₁₂ADP receptor, offers another option. In TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction), Effient has been shown to reduce the rate of a composite endpoint of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to Plavix® (clopidogrel bisulfate).¹ The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death.

Clinical Pharmacology Pharmacodynamics

Following a 60-mg loading dose of Effient, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour.² Maximum platelet inhibition was about 80%. Mean steady state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10 mg daily after a 60-mg loading dose of Effient.²

Pharmacokinetics

Effient is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. The active metabolite has an elimination half-life of about 7 hours (range 2-15 hours).² Healthy subjects, patients with stable atherosclerosis, and patients undergoing PCI show similar pharmacokinetics.

Pharmacogenetics

There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.² In contrast, genetic variation in CYP2C19 has been shown to impact active metabolite formation and platelet aggregation of clopidogrel.³

WARNING: BLEEDING RISK

Effient® (prasugrel) can cause significant, sometimes fatal, bleeding.
 Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients ≥75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered. Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.
 Additional risk factors for bleeding include:

- body weight <60 kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs])

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 Effient. If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

TRITON-TIMI 38

The clinical evidence for the effectiveness and safety of Effient is derived from the TRITON-TIMI 38 study, a 13,608-patient, multicenter, international, randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin (ASA) and other standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI.¹ Randomization was stratified for UA/NSTEMI and STEMI.

Patients were randomized to receive Effient (60-mg loading dose followed by 10 mg once daily) or clopidogrel (300-mg loading dose followed by 75 mg once daily), with administration and follow-up for a minimum of 6 months (actual median 14.5 months).¹ It should be noted that in TRITON-TIMI 38, administration of the clopidogrel loading dose was delayed relative to the placebo-controlled trials that supported its approval for ACS.

The primary outcome of TRITON-TIMI 38 was the composite of CV death, nonfatal MI, or nonfatal stroke.

stroke.¹ The key safety endpoints were major or minor bleeding events based on TIMI criteria.

Efficacy

Effient plus ASA significantly reduced the total endpoint events compared to clopidogrel plus ASA (see Table 1).¹ The reduction of total endpoint events was driven primarily by a decrease in nonfatal MIs, both occurring early (through 3 days) and later (after 3 days). Approximately 40% of MIs occurred periprocedurally and were detected solely by creatine kinase muscle-brain (CK-MB) changes. Effient plus ASA, however, produced higher rates of clinically significant bleeding than clopidogrel plus ASA (see Bleeding).²

The efficacy of Effient plus ASA was generally consistent across various prespecified subgroups, including patients with diabetes mellitus.³ However, patients with a history of transient ischemic attack (TIA) or stroke had a higher rate of stroke on Effient plus ASA (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage [ICH]) than on clopidogrel plus ASA

TABLE 1. Patients With Outcome Events (Cardiovascular Death, Myocardial Infarction, Stroke) in TRITON-TIMI 38²

	Patients with events		From Kaplan-Meier analysis	
	Effient (%)	Clopidogrel (%)	Relative Risk Reduction (%) ^a (95% CI)	P-Value
UA/NSTEMI	N=5044	N=5030		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	0.002
CV death	1.8	1.8	2.1 (-30.9, 26.8)	0.885
Nonfatal MI	7.1	9.2	23.9 (12.7, 33.7)	<0.001
Nonfatal Stroke	0.8	0.8	2.1 (-51.3, 36.7)	0.922
STEMI	N=1769	N=1765		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	0.019
CV death	2.4	3.3	26.2 (-9.4, 50.3)	0.129
Nonfatal MI	6.7	8.8	25.4 (5.2, 41.2)	0.016
Nonfatal Stroke	1.2	1.1	-9.7 (-104.0, 41.0)	0.77

^aRRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

TRITON-TIMI 38=TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction; CV=cardiovascular; MI=myocardial infarction; CI=confidence interval; UA=unstable angina; NSTEMI= non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; RRR=relative risk reduction. Source: Effient® (prasugrel) prescribing information.²

(1.2%; all thrombotic).¹ The effect in patients ≥ 75 years of age was also somewhat smaller, and bleeding risk is higher in these individuals.¹

Stent Thrombosis

In TRITON-TIMI 38, there were 50% fewer stent thromboses (95% confidence interval 32%-64%; $P < 0.001$) reported among patients randomized to Effient plus ASA (0.9%) than among patients randomized to clopidogrel plus ASA (1.8%).² The difference manifested early and was maintained through 1 year of follow-up. Findings were similar with bare metal and drug-eluting stents.

Bleeding

General

Thienopyridines, including Effient, increase the risk of bleeding. With the dosing regimens used in TRITON-TIMI 38, TIMI Major and TIMI Minor bleeding were more common on Effient plus ASA than on clopidogrel plus ASA (Table 2).²

Bleeding Unrelated to CABG Surgery

In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient plus ASA than on clopidogrel plus ASA (Table 2).¹

Bleeding risk was highest in patients with the risk factors of age ≥ 75 years and weight < 60 kg.¹ In patients ≥ 75 years, the TIMI Major or Minor bleeding rate was 9% (1.0% fatal) for Effient plus ASA versus 6.9% (0.1% fatal) for clopidogrel plus ASA.² In patients < 60 kg, the TIMI Major or Minor bleeding rate was 10.1% (0.0% fatal) for Effient plus ASA versus 6.5% (0.3% fatal) for clopidogrel plus ASA.²

Bleeding Related to CABG

In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the course of the study.² The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient plus ASA group and 4.5% for the clopidogrel plus ASA group. The higher risk for bleeding adverse reactions in patients treated with Effient plus ASA persisted up to 7 days from the most recent dose of study drug.²

The choice of Effient in patients with ACS managed with PCI requires balancing the greater reductions in composite endpoint events versus clopidogrel against the higher rates of clinically significant bleeding.

Application of TRITON-TIMI 38 to Clinical Practice Appropriate Patient Selection

Based on TRITON-TIMI 38, Effient appears to be most appropriate for use in patients with ACS who are to be managed with PCI with no history of TIA/stroke, who are < 75 years of age, and who weigh ≥ 60 kg.² While TRITON-TIMI 38 was designed to evaluate reduction in the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI group before analyzing benefit in the overall ACS population and STEMI populations, the significant reduction in events noted in the STEMI cohort makes Effient an appropriate option for the spectrum of patients with ACS to be managed with PCI. Also of interest were the reductions in the primary endpoint noted in the subpopulation of patients with diabetes.⁴ Because these

TABLE 2. Non-CABG-Related Bleeding^a in TRITON-TIMI 38²

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)	P-Value
TIMI Major* or Minor [†] bleeding	4.5	3.4	$P=0.002$
TIMI Major bleeding ^b	2.2	1.7	$P=0.029$
Life-threatening	1.3	0.8	$P=0.015$
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥ 4 units)	0.7	0.5	
TIMI Minor bleeding ^b	2.4	1.9	$P=0.022$

^aPatients may be counted in more than one row.

*TIMI Major (intracranial hemorrhage or clinically overt bleeding associated with a fall in hemoglobin ≥ 5 g/dL)

[†]TIMI Minor (clinically overt bleeding associated with a fall in hemoglobin of ≥ 3 g/dL but < 5 g/dL)

^bSee 5.1 of full prescribing information for Effient for definition.

Source: Effient[®] (prasugrel) prescribing information.²

reductions were consistent with the reductions observed in the UA/NSTEMI and STEMI cohorts, Effient may be an especially attractive option for these high-risk patients. As noted, the benefits of Effient must be weighed against the increased risk of clinically significant bleeding events.

Timing of Administration

In TRITON-TIMI 38, investigators could administer assigned therapy at any time from randomization to 1 hour after leaving the catheterization lab.¹ Only 25% of the patients received assigned-antiplatelet therapy before guidewire placement.¹ Effient and clopidogrel were not administered to patients with UA/NSTEMI until coronary anatomy was established.^{1,2} For the small fraction of patients who required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial. Since the majority of patients are managed without CABG, treatment can be considered before determining coronary anatomy if the need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.²

Conclusion

The approval of Effient adds a new dimension to clinical decision making about antiplatelet therapy in patients with ACS managed with PCI. Given the recent Plavix label changes regarding the potential impact of genetic variation, it is of interest to note that the pharmacokinetics of the active metabolite of Effient is not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5.² In TRITON-TIMI 38, Effient reduced ischemic events (mainly nonfatal MIs) when compared with Plavix, but its choice as an oral antiplatelet agent in patients with ACS who are to be managed with PCI must be balanced against the increased risk of clinically significant bleeding relative to Plavix.^{1,2} In 2009, the American College of Cardiology Foundation and the American Heart Association Task Force on Practice Guidelines added Effient as a treatment option for STEMI and PCI.⁵

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Effient Important Safety Information

- Effient is contraindicated in patients with active pathological bleeding, such as from a peptic ulcer or intracranial hemorrhage (ICH), or a history of transient ischemic attack (TIA) or stroke
- Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued. Effient should also be discontinued for active bleeding and elective surgery
- Premature discontinuation of Effient increases risk of stent thrombosis, myocardial infarction (MI), and death
- Thrombotic thrombocytopenic purpura (TTP), a rare but serious condition that can be fatal, has been reported with the use of other thienopyridines, sometimes after a brief exposure (< 2 weeks), and requires urgent treatment, including plasmapheresis

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