croscarmellose sodium, microcrystalline cellulose, and vegetable magnesium stearate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10 mg tablet).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Prasugrel produces inhibition of platelet aggregation to 20 μM or 5 μM ADP, as measured by light transmission aggregometry. Following a 60-mg loading dose of Effient, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour. Maximum platelet inhibition was about 80% (Figure 2). 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.

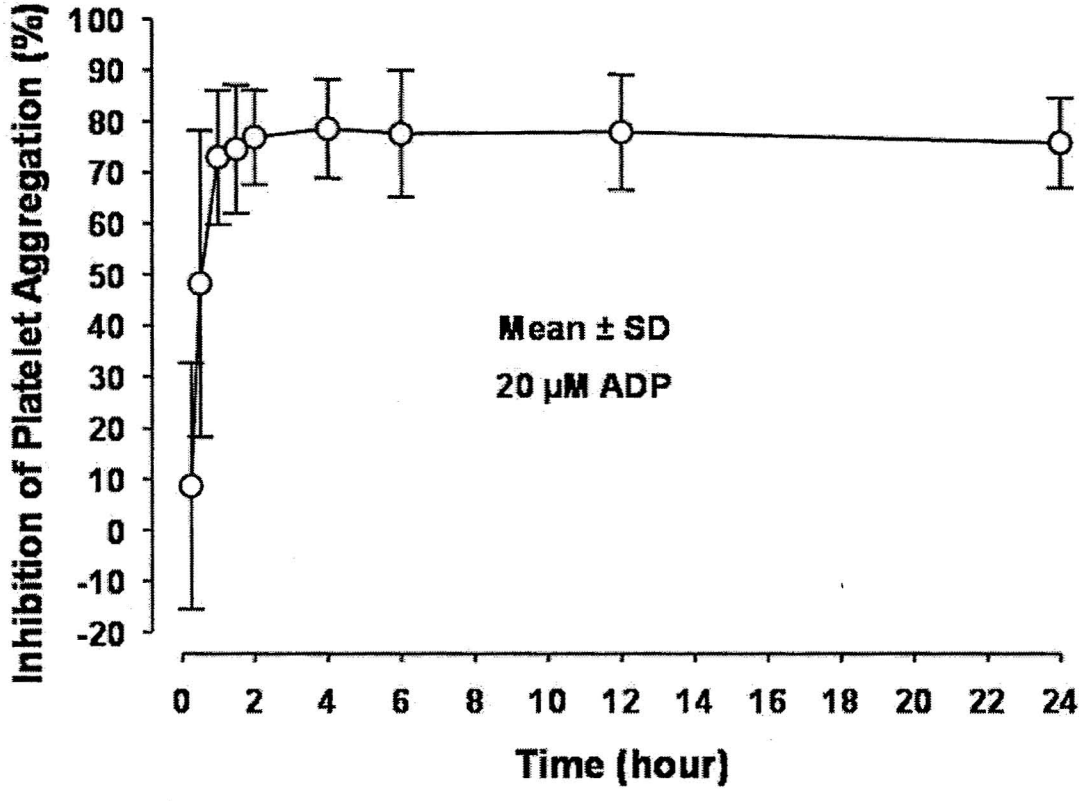


Figure 2: Inhibition (Mean±SD) of 20 μM ADP-induced Platelet Aggregation (IPA) Measured by Light Transmission Aggregometry after Prasugrel 60 mg

Platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation of prasugrel, this time course being a reflection of new platelet production rather than pharmacokinetics of prasugrel. Discontinuing clopidogrel 75 mg and initiating prasugrel 10 mg with the next dose resulted in increased inhibition of platelet aggregation, but not greater than that typically produced by a 10 mg maintenance dose of prasugrel alone. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

12.3 Pharmacokinetics

Prasugrel 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). Healthy subjects, patients with stable atherosclerosis, and patients undergoing PCI show similar pharmacokinetics.

Absorption and Binding - Following oral administration, ≥ 79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly more than proportionally over the dose range of 5 to 60 mg. Repeated daily doses of 10 mg do not lead to accumulation of the active metabolite. In a study of healthy subjects given a single 15 mg dose, the AUC of the

active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and T_{max} was increased from 0.5 to 1.5 hours. Effient can be administered without regard to food. The active metabolite is bound about 98% to human serum albumin.

Metabolism and Elimination - Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The estimates of apparent volume of distribution of prasugrel's active metabolite ranged from 44 to 68 L and the estimates of apparent clearance ranged from 112 to 166 L/hr in healthy subjects and patients with stable atherosclerosis. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. The major inactive metabolites are highly bound to human plasma proteins. Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites.

Specific Populations

Pediatric - Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a pediatric population *[see Use in Specific Populations (8.4)]*.

Geriatric - In a study of 32 healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. In TRITON-TIMI 38, the mean exposure (AUC) of the active metabolite was 19% higher in patients ≥75 years of age than in patients <75 years of age *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Use in Specific Populations (8.5)]*.

Body Weight - The mean exposure (AUC) to the active metabolite is approximately 30 to 40% higher in subjects with a body weight of <60 kg than in those weighing ≥60 kg *[see Dosage and Administration (2), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

Gender - Pharmacokinetics of prasugrel's active metabolite are similar in men and women.

Ethnicity - Exposure in subjects of African and Hispanic descent is similar to that in Caucasians. In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects than in Caucasian subjects.

Smoking - Pharmacokinetics of prasugrel's active metabolite are similar in smokers and nonsmokers.

Renal Impairment - Pharmacokinetics of prasugrel's active metabolite and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. In patients with end stage renal disease, exposure to the active metabolite (both C_{max} and AUC(0-t_{last})) was about half that in healthy controls and patients with moderate renal impairment *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment - Pharmacokinetics of prasugrel's active metabolite and inhibition of platelet aggregation were similar in patients with mild to moderate hepatic impairment compared to healthy subjects. The pharmacokinetics and pharmacodynamics of prasugrel's active metabolite in patients with severe hepatic disease have not been studied *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.8)]*.

Drug Interactions

Potential for Other Drugs to Affect Prasugrel

Inhibitors of CYP3A - Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as verapamil, diltiazem, indinavir, ciprofloxacin, clarithromycin, and grapefruit juice are not expected to have a significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Inducers of Cytochromes P450 - Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not expected to have significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Drugs that Elevate Gastric pH - Daily coadministration of ranitidine (an H_2 blocker) or lansoprazole (a proton pump inhibitor) decreased the C_{max} of the prasugrel active metabolite by 14% and 29%, respectively, but did not change the active metabolite's AUC and T_{max}. In TRITON-TIMI 38, Effient was administered without regard to coadministration of a proton pump inhibitor or H_2 blocker *[see Drug Interactions (7.3)]*.

Statins - Atorvastatin (80 mg daily), a drug metabolized by CYP450 3A4, did not alter the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation *[see Drug Interactions (7.3)]*.

Heparin - A single intravenous dose of unfractionated heparin (100 U/kg) did not significantly alter coagulation or the prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Aspirin - Aspirin 150 mg daily did not alter prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Warfarin - A significant prolongation of the bleeding time was observed when prasugrel was coadministered with 15 mg of warfarin *[see Drug Interactions (7.1)]*.

Potential for Prasugrel to Affect Other Drugs

In vitro metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A.

Drugs Metabolized by CYP2B6 — Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%, an amount not considered clinically

significant. Prasugrel is not anticipated to have significant effect on the pharmacokinetics of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine.

Effect on Digoxin - The potential role of prasugrel as a Pgp substrate was not evaluated. Prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration *[see Drug Interactions (7.3)]*.

12.5 Pharmacogenomics

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (>250 times the human metabolite exposure).

Mutagenesis - Prasugrel was not genotoxic in two *in vitro* tests (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one *in vivo* test (micronucleus test by intraperitoneal route in mice).

Impairment of Fertility - Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (80 times the human major metabolite exposure at daily dose of 10 mg prasugrel).

14 CLINICAL STUDIES

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

Patients with UA/NSTEMI presenting within 72 hours of symptom onset were to be randomized after undergoing coronary angiography. Patients with STEMI presenting within 12 hours of symptom onset could be randomized prior to coronary angiography. Patients with STEMI presenting between 12 hours and 14 days of symptom onset were to be randomized after undergoing coronary angiography. Patients underwent PCI, and for both UA/NSTEMI and STEMI patients, the loading dose was to be administered anytime between randomization and 1 hour after the patient left the catheterization lab. If patients with STEMI were treated with thrombolytic therapy, randomization could not occur until at least 24 hours (for tenecteplase, reteplase or alteplase) or 48 hours (for streptokinase) after the thrombolytic was given.

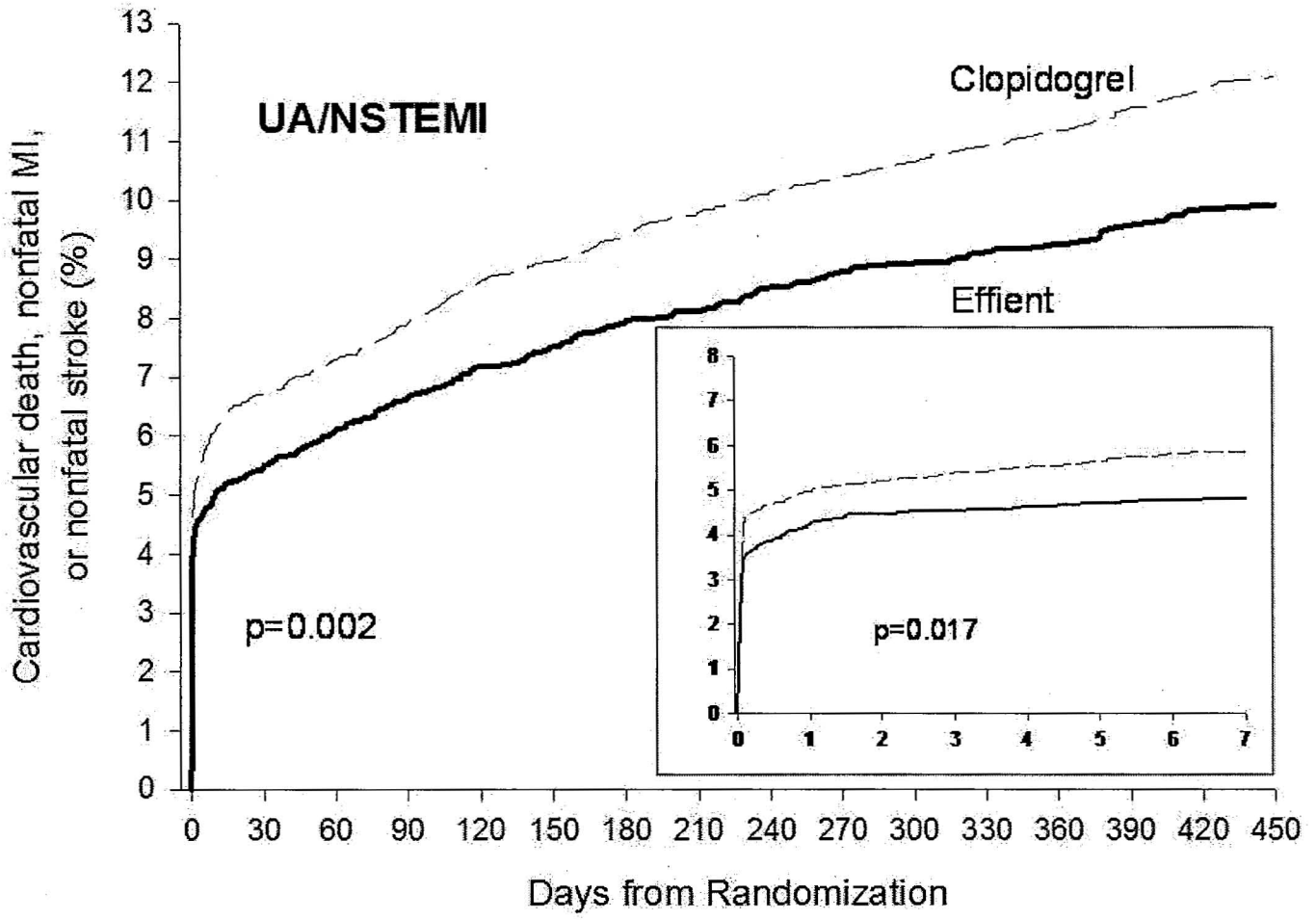
Patients were randomized to receive Effient (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily), with administration and follow-up for a minimum of 6 months (actual median 14.5 months). Patients also received aspirin (75 mg to 325 mg once daily). Other therapies, such as heparin and intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, were administered at the discretion of the treating physician. Oral anticoagulants, other platelet inhibitors, and chronic NSAIDs were not allowed.

The primary outcome measure was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI population. Success in this group allowed analysis of the same endpoint in the overall ACS and STEMI populations. Nonfatal MIs included both MIs detected solely through analysis of creatine kinase muscle-brain (CK-MB) changes and clinically apparent (investigator-reported) MIs.

The patient population was 92% Caucasian, 26% female, and 39% ≥65 years of age. The median time from symptom onset to study drug administration was 7 hours for patients with STEMI and 30 hours for patients with UA/NSTEMI. Approximately 99% of patients underwent PCI. The study drug was administered after the first coronary guidewire was placed in approximately 75% of patients.

Effient significantly reduced total endpoint events compared to clopidogrel (*see* Table 5 and Figure 3). The reduction of total endpoint events was driven primarily by a decrease in nonfatal MIs, both those occurring early (through 3 days) and later (after 3 days). Approximately 40% of MIs occurred peri-procedurally and were detected solely by changes in CK-MB. Administration of the clopidogrel loading dose in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS. Effient produced higher rates of clinically significant bleeding than clopidogrel in TRITON-TIMI 38 *[see Adverse Reactions (6.1)]*. Choice of therapy requires balancing these differences in outcome.

The treatment effect of Effient was apparent within the first few days, and persisted to the end of the study (Figure 3). The inset shows results over the first 7 days.


UA/NSTEMI
Clopidogrel
Effient
p=0.002
p=0.017
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)
Days from Randomization
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
0
1
2
3
4
5
6
7
8
9
10
11
12
13

398
399

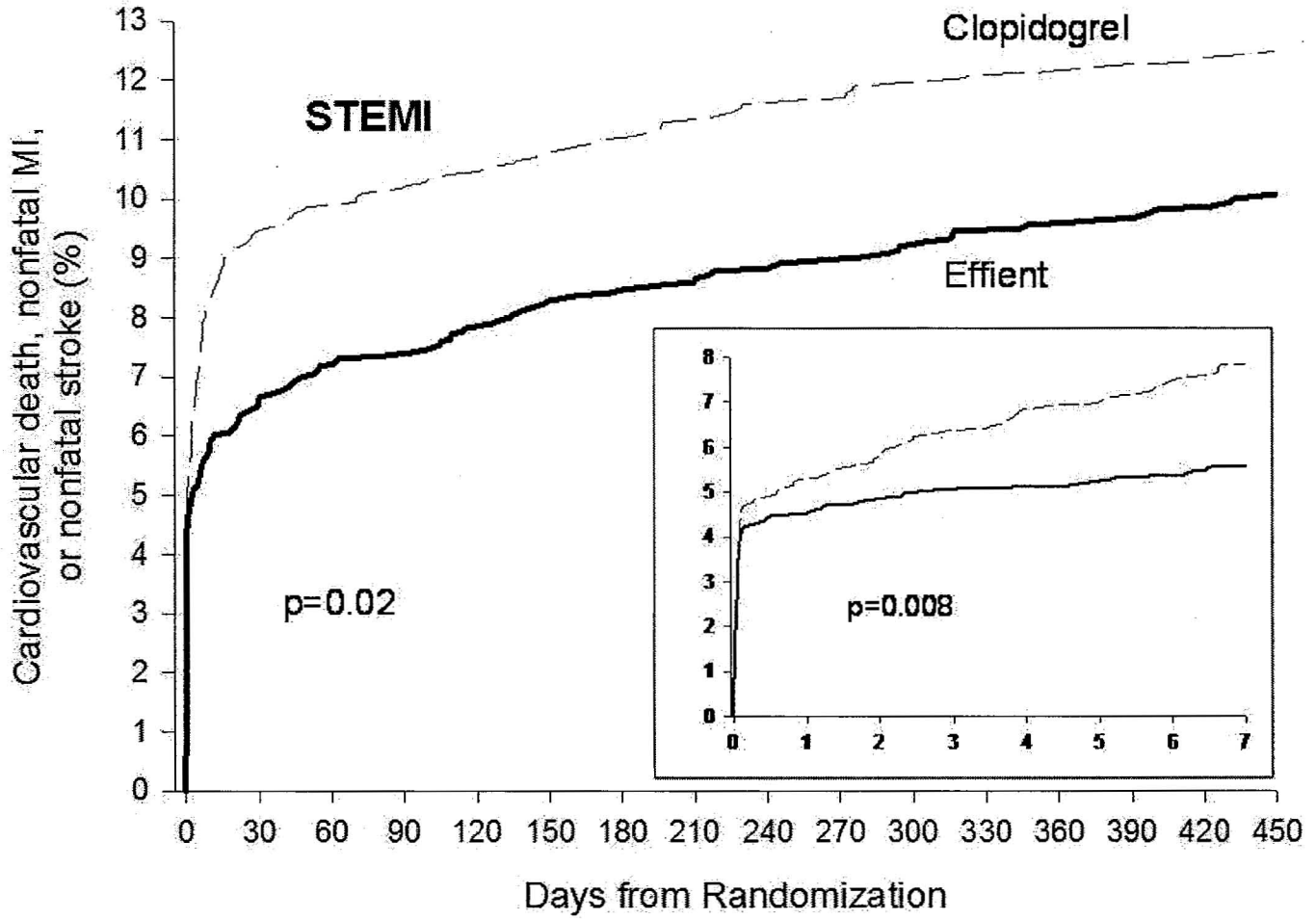


Figure 3: Time to first event of CV death, MI, or stroke (TRITON-TIMI 38)

The Kaplan-Meier curves (Figure 3) show the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations. In both populations, the curves separate within the first few hours. In the UA/NSTEMI population, the curves continue to diverge throughout the 15 month follow-up period. In the STEMI population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

Effient reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI populations (*see* Table 5). In patients who survived an on-study myocardial infarction, the incidence of subsequent events was also lower in the Effient group.

Table 5: Patients with Outcome Events (CV Death, MI, Stroke) in TRITON-TIMI 38

	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

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

The effect of Effient in various subgroups is shown in Figures 4 and 5. Results are generally consistent across pre-specified subgroups, with the exception of patients with a history of TIA or stroke *[see Contraindications (4.2)]*. The treatment effect was driven primarily by a reduction in nonfatal MI. The effect in patients ≥75 years of age was also somewhat smaller, and bleeding risk is higher in these individuals *[see Adverse Reactions (6.1)]*. See below for analyses of patients ≥75 years of age with risk factors.

Baseline Characteristics		N	Percent Events	
			Effient	Clopidogrel
OVERALL-UA/NSTEMI		10074	9.9	12.1
Age	<65 y	5987	7.5	10.0
	≥65 y	4087	11.9	13.1
	<75 y	8672	8.2	10.5
	≥75 y	1402	15.8	16.2
Gender	Female	2724	10.3	11.4
	Male	7350	8.9	11.2
Body Weight	<60 kg	503	9.2	9.8
	≥60 kg	9458	9.2	11.1
Region	North America	3538	9.6	11.9
	United States	3382	9.7	12.2
	South America	534	13.3	15.2
	Western Europe	2527	8.8	9.8
	Eastern Europe	2300	8.5	10.0
	Rest of World	1175	9.1	13.1
Diabetes Mellitus	Yes	2472	10.8	15.0
	No	7602	8.8	10.0
Metabolic Syndrome	Yes	4511	9.1	11.5
	No	5563	9.5	11.1
Previous MI	Yes	2075	12.9	15.8
	No	7999	8.3	10.1
Previous PCI	Yes	1597	12.0	14.8
	No	8477	8.8	10.6
Previous CABG	Yes	957	16.0	18.2
	No	9117	8.6	10.5
Previous TIA/Stroke	Yes	405	18.3	12.5
	No	9669	8.9	11.2
Time From Symptom Onset	≤24 h	3902	8.3	10.8
	>24 h	5976	10.1	11.5
Stent Type	Drug-eluting ≥1	5225	9.2	10.9
	Bare Metal Only	4362	9.2	11.6
	None	401	11.7	14.9
GP IIb/IIIa Inhibitor Use	Yes	5183	9.9	11.9
	No	4891	8.7	10.5

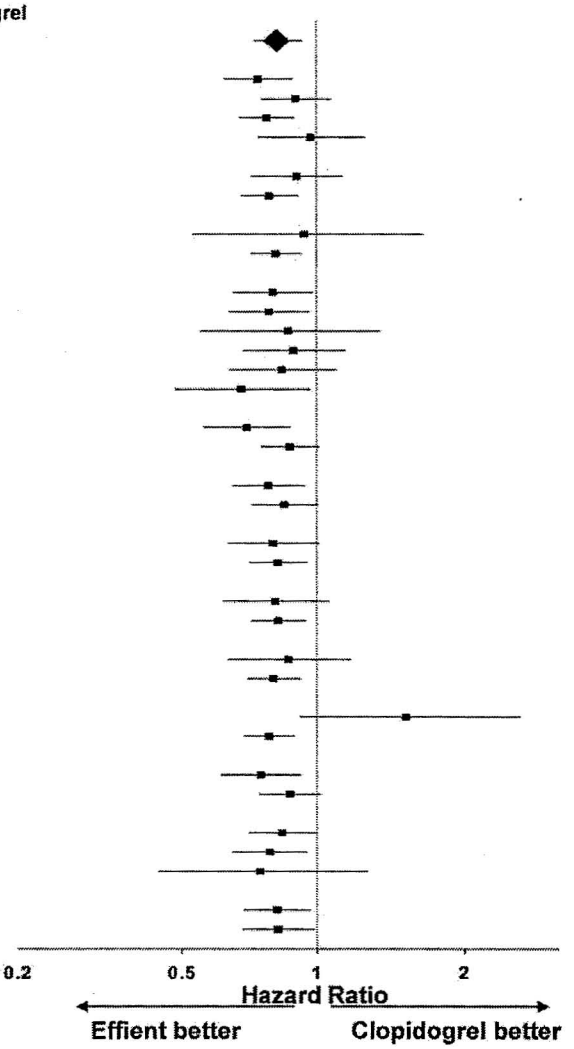


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

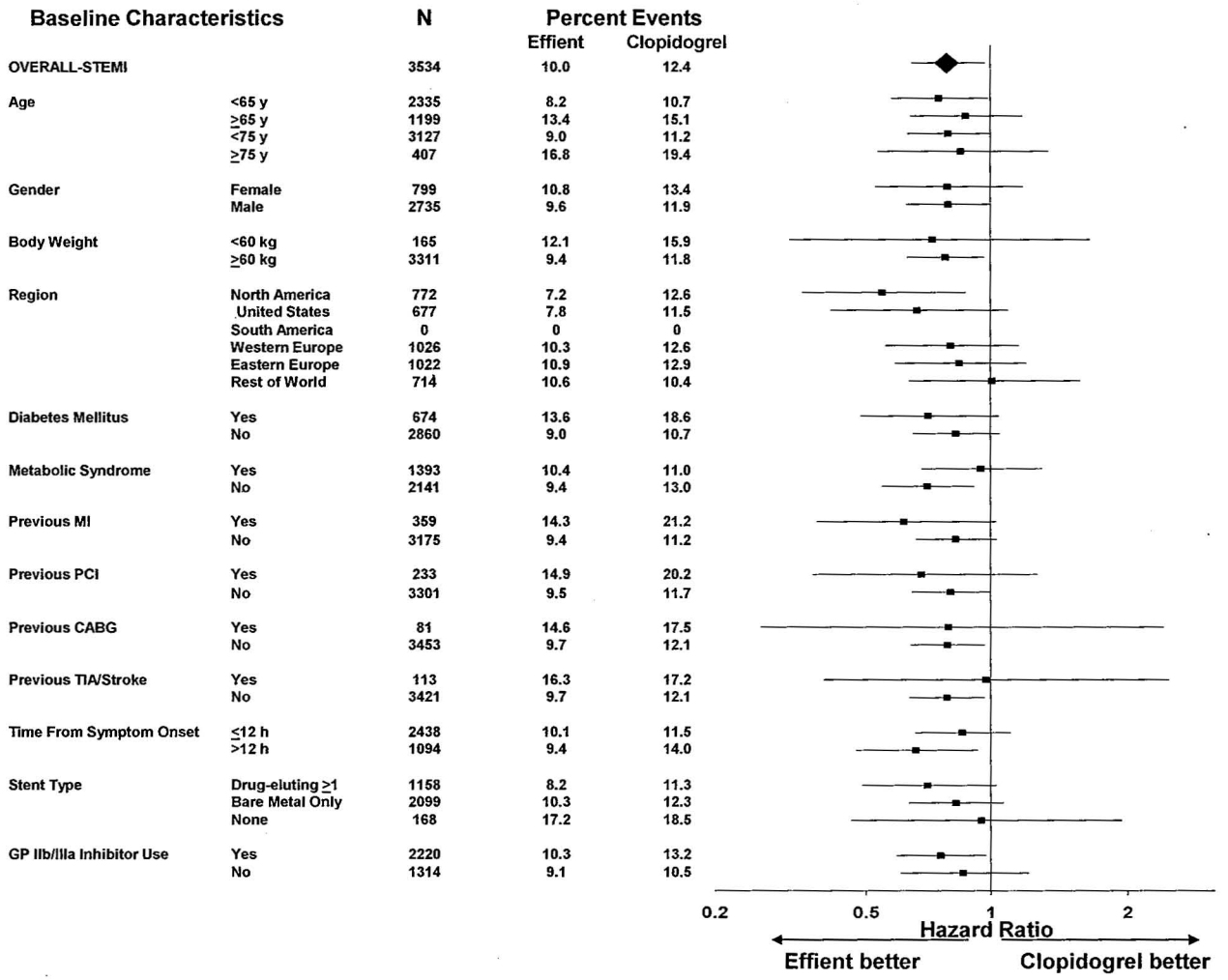


Figure 5: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – STEMI Patients.

Effient is generally not recommended in patients ≥75 years of age, except in high-risk situations (diabetes mellitus or prior MI) where its effect appears to be greater and its use may be considered. These recommendations are based on subgroup analyses (Table 6) and must be interpreted with caution, but the data suggest that Effient reduces ischemic events in such patients.

Table 6: Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke: Patients < or ≥75 Years of Age, ± Diabetes, ± Prior History of MI, All ACS Patient Population

	Effient		Clopidogrel			
	N	% with events	N	% with events	Hazard Ratio (95% CI)	p-value
Age ≥75						
Diabetes - yes	249	14.9	234	21.8	0.64 (0.42, 0.97)	0.034
Diabetes - no	652	16.4	674	15.3	1.1 (0.83, 1.43)	NS
Age <75						
Diabetes - yes	1327	10.8	1336	14.8	0.72 (0.58, 0.89)	0.002
Diabetes - no	4585	7.8	4551	9.5	0.82 (0.71, 0.94)	0.004
Age ≥75						
Prior MI - yes	220	17.3	212	22.6	0.72 (0.47, 1.09)	0.12
Prior MI - no	681	15.6	696	15.2	1.05 (0.80, 1.37)	NS
Age <75						

Prior MI - yes	1006	12.2	996	15.4	0.78 (0.62, 0.99)	0.04
Prior MI - no	4906	7.7	4891	9.7	0.78 (0.68, 0.90)	<0.001

There were 50% fewer stent thromboses (95% C.I. 32% - 64%; p< 0.001) reported among patients randomized to Effient (0.9%) than among patients randomized to clopidogrel (1.8%). The difference manifested early and was maintained through one year of follow-up. Findings were similar with bare metal and drug-eluting stents.

In TRITON-TIMI 38, prasugrel reduced ischemic events (mainly nonfatal MIs) and increased bleeding events *[see Adverse Reactions (6.1)]* relative to clopidogrel. The findings are consistent with the intended greater inhibition of platelet aggregation by prasugrel at the doses used in the study *[see Clinical Pharmacology (12.2)]*. There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. Moreover, certain proton pump inhibitors, widely used in the ACS patient population and used in TRITON-TIMI 38, inhibit CYP2C19, thereby decreasing formation of clopidogrel's active metabolite. Thus, reduced metabolizer status and use of proton pump inhibitors may diminish clopidogrel's activity in a fraction of the population, and may have contributed to prasugrel's greater treatment effect and greater bleeding rate in TRITON-TIMI 38. The extent to which these factors were operational, however, is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

Effient (prasugrel) 5 mg is supplied as a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5 MG" on one side and with "4760" on the other side.

5 mg tablets are supplied as follows:

Bottles of 7 - NDC 0002-4760-76

Bottles of 30 - NDC 0002-4760-30

Effient (prasugrel) 10 mg is supplied as a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "10 MG" on one side and "4759" on the other side.

10 mg tablets are supplied as follows:

Bottles of 30 – NDC 0002-4759-30

Blisters ID 90* NDC 0002-4759-77

(*Identi Dose®, unit dose medication, Lilly)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Dispense and keep product in original container. Keep container closed and do not remove desiccant from bottle. Do not break the tablet.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Effient.
- Tell patients to take Effient exactly as prescribed.
- Remind patients not to discontinue Effient without first discussing it with the physician who prescribed Effient.
- Recommend that patients read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with medications in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Effient before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Effient.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (*e.g.*, warfarin and NSAIDs).

Literature Issued:

490 **Manufactured by Eli Lilly and Company, Indianapolis, IN, 46285**

491 **Marketed by Daiichi Sankyo, Inc. and Eli Lilly and Company**

493 A 12.0 NL 6107 AMP PRINTED IN USA