CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

OFFICE DIRECTOR MEMO

Office Director's Memo to File

Date: July 10, 2009

From: Robert Temple, MD
Director, ODE-I

To: File, NDA 22-307 – Effient (prasugrel hydrochloride) Tablets; Sponsor – Eli Lilly

Subject: Approval with REMs (Medguide)

I. Background

This review is based, in part, on the secondary review of Dr. Stockbridge, Director, HFD-110 (4/25/09), the revised CDTL review of Dr. Unger, the Deputy Director, HFD-110 (1/9/09), supplemented by his three additional reviews of chemistry, carcinogenicity, and bleeding issues (dated July 6 and 7, 2009), and the primary reviews cited by Dr. Unger, including particularly the primary medical review by Dr. Hicks, with an addendum dated July 8, 2009, and the Clinical Team Leader review by Dr. Marciniak, dated May 9, 2009.

The labeling Indications and Usage for prasugrel is:

> 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:
>
> - Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI)
> - Patients with ST- segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.
>
> Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death.
>
> It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was

established. For the small fraction of patients that required urgent coronary CABG after treatment with Effient, the risk of significant bleeding was substantial. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if 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.

There have been few questions raised about the overall results of the clinical trial (TRITON-TIMI 38, TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) conducted to establish the effectiveness of prasugrel. TRITON-TIMI-38 was a 13,608 patient, double-blind, randomized, controlled trial comparing prasugrel and clopidogrel in patients with acute coronary syndrome (ACS, including unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) who were to be managed with percutaneous coronary intervention (PCI). The trial showed a reduction in the combined endpoint of cardiovascular (CV) death, non-fatal MI, or non-fatal stroke in the UA/NSTEMI population (the primary endpoint), and in the entire ACS and STEMI populations, endpoints that could be analyzed after success in the UA/STEMI population. As noted in labeling, however, this represented primarily a reduction in the overall rate of non-fatal MIs, which included both clinically apparent (investigator reported) and "chemical" (CK-MB changes; seen especially in the early, in-hospital phase of the study). Much, but not all of the advantage of prasugrel was observed in the first 30 days of the study.

The TRITON-TIMI 38 trial also clearly showed a higher rate of serious bleeding on prasugrel, leading to an important concern: whether the benefit of reduced NFMI (many of them not clinically recognized) outweighed the risk of increased bleeding.

Many other concerns arose, and these were discussed at length internally and at the Cardiovascular and Renal Drugs Advisory Committee meeting on February 3, 2009 (which recommended approval by a 9 to 0 vote). They have also been raised in letters to FDA as well as in public discussion. These concerns include:

- Some instability of the prasugrel salt (conversion to base) in the lots of drug used in TRITON-TIMI 38 (and in the to-be-marketed drug). The base has poorer bioavailability (primarily C_{max}) in high pH environments (e.g., with concomitant use of proton pump inhibitors [PPIs]), and use of the salt was intended to avoid that. Correcting the instability would increase bioavailability relative to the product used in TRITON-TIMI-38, in patients receiving PPIs, so that there might be greater platelet inhibition.
- A finding of an increased rate of newly diagnosed malignancies in the prasugrel group after several months, raising the question whether the duration of recommended use should be limited, especially given that much of the advantage of prasugrel was early.
- Whether the delay in giving both drugs compared to recommended (although not uniform) practice disadvantaged clopidogrel compared to prasugrel (see third paragraph of Indications, above).
- Whether, in seeking a superior effect on platelet inhibition, and thus a greater reduction in CV events, Lilly chose too high a dose of prasugrel, thereby causing excess bleeding that might have been avoided. This question is not easily separated from the question of the underlying reason for prasugrel's greater effect in TRITON. There are two candidate explanations: 1) greater inhibition of platelet function by the chosen dose (60 mg loading, 10 mg

maintenance), or 2) the presence in the population (about 1/3) of CYP 2C19 poor metabolizers, who do not form any, or as much, of the active metabolite of clopidogrel that is wholly responsible for its platelet-inhibiting effect, leading to a significant fraction of clopidogrel "non-responders." This potential non-responder subset may be enlarged by concomitant use of proton pump inhibitors (PPIs), at least some of which are strong inhibitors of CYP 2C19 and cause reduced active metabolite formation. There is evidence, mainly from observational data, that there is, in fact, a clopidogrel non-responder subset. Whether this group, or part of it, could gain improved benefit from a higher clopidogrel dose is under study, but the question is not yet settled, and there are suggestions of decreased clopidogrel CV endpoint response in the presence of PPIs, as would be predicted.

II. Effectiveness

A. Overall Results

The principal evidence of effectiveness of prasugrel comes from a study called TAAL or TRITON-TIMI-38 that is described at length by Dr. Unger and Dr. Hicks (Clinical Review dated April 28, 2008). As noted earlier, it was a randomized double-blind (double dummy) trial comparing prasugrel (loading dose 60 mg plus 10 mg daily maintenance) with clopidogrel (300 mg loading dose plus 75 mg daily), in patients with ACS scheduled to undergo PCI. The objective was to show a reduction in a composite endpoint of CV death, NFMI, and NF stroke, over a median follow up of ≥ 12 months. It was an international study (30 countries) conducted at 725 study sites.

ACS included 1) UA: patients with a history of chest discomfort for ≥ 10 minutes at rest within 72 hours of randomization with persistent or transient ST segment deviation ≥ 1mm in ≥ 1 ECG leads but without CK-MB or troponin T elevation 2) NSTEMI: all of the above but without persistent ST elevation, and with elevated CK-MB or troponin T, or 3) STEMI: ≥ 20 minutes chest discomfort within 14 days and one of a) ST elevation ≥ 1min in ≥ 2 ECG leads, b) new LBBB, or c) ST depression ≥ 1min in 2 anterior precordial leads with history suggesting true posterior infarction. Patients were not to have had a thrombolytic within 24 hours, or streptokinase within 48 hours, active bleeding, a history of hemorrhagic or ischemic stroke within 3 months, INR > 1.5, platelets < 100,000/mm, or anemia (Hgb < 10 gm/dL), recent thienopyridine, need for anticoagulants or daily NSAID.

Randomization was stratified by presentation (UA/NSTEMI vs STEMI) and subjects could be randomized only after coronary arteriography with anatomy confirmed suitable for PCI, except that STEMI-patients within 12 hours of symptoms could be randomized at time of diagnosis if PCI was planned. Dosing could occur at any time between randomization and PCI.

All patients were given ASA, and anti-thrombin treatment was given as part of care. Essentially all other treatments (statins, anti-HTs, CCBs, BBs) could be given as needed.

Evaluations took place at 24 hours post PCI or discharge and at days 30, 90, 180, 270, 360, and 450.

The primary endpoint was based on a time to event analysis for a composite of CV death, NFMI and NF stroke in the UA/NSTEMI population, with further primary endpoints being the same composite in the total ACS and in the STEMI populations using a hierarchical approach. Secondary endpoints included effects at other times (day 30, day 90). In addition, and appropriately, analyses of total events (i.e., that were not the first event) were performed. This would include, e.g., deaths that occurred after an earlier acute MI. Results were generally similar for all of these analyses and for UA/NSTEMI and STEMI. All reported endpoints were adjudicated by a blinded clinical events committee.

As will be seen below, there is considerable interest in a variety of population subsets and their impact on both benefit (reduced NFMI) and risk (bleeding). These must be considered with care. Nonetheless, although we recognize the uncertainties inherent in unplanned subset analyses and treat subset results with caution, we also believe that efforts to optimize the benefit/ risk relationship for prasugrel, as is true for many drugs, demands attention to such subgroups.

Study results are shown in the following table from the approved labeling.

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 composite endpoint results are based on an analysis of time to first event (of CV death, NFMI, and NF stroke) and show statistically significant results in UA/NSTEMI (n=10,074) and in the smaller STEMI population (n=3534), with results clearly driven by NFMI. The individual endpoints reflect both primary and second events. There is a favorable trend on survival in the STEMI population but no evidence of an effect on survival in UA/NSTEMI. Labeling does not show results for the whole ACS population, as we felt the effect in the combined group was less informative, but this was a prospective primary endpoint (sequentially), and this larger population (n=13,608) there was a 19% risk reduction in the prasugrel group (9.4% vs 11.5%, p< 0.001).

The timing of benefit is of interest and shows an effect that is predominantly early in both UA/NSTEMI and STEMI, as shown in 2 figures from labeling:

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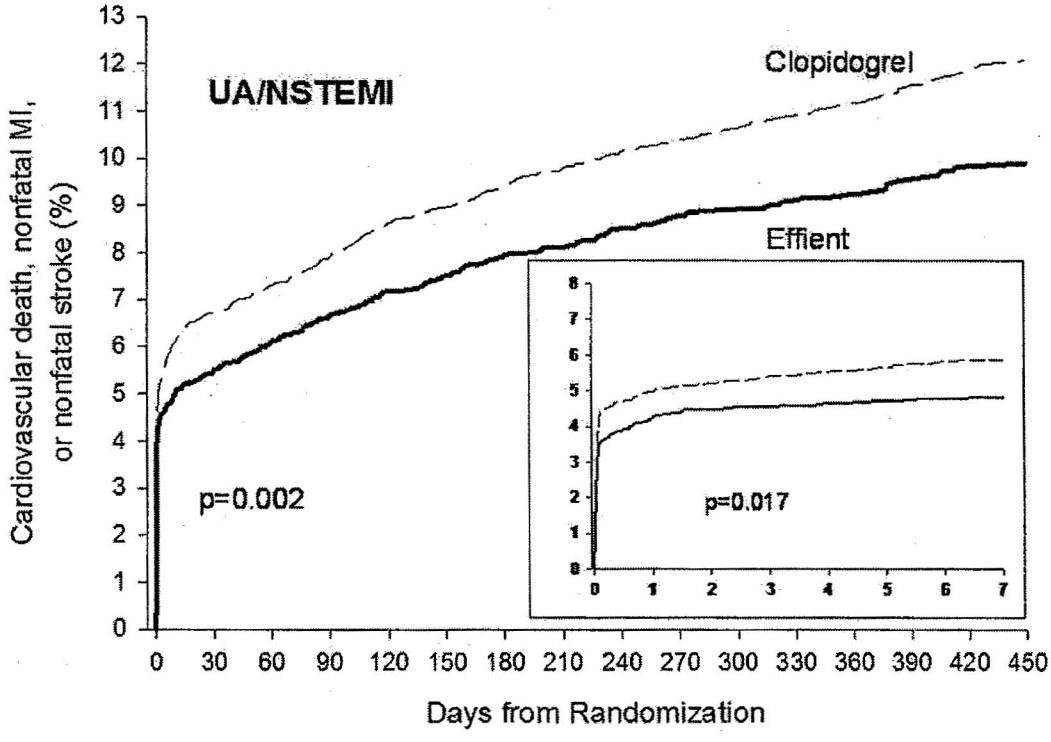
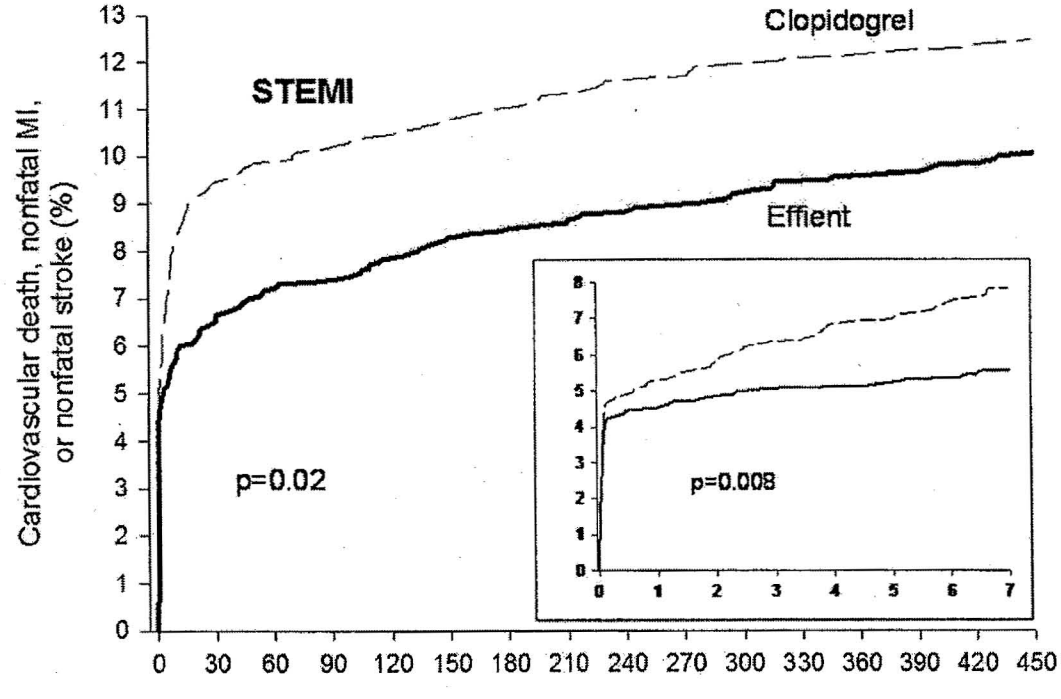

UA/NSTEMI
Clopidogrel
Effient
p=0.002
p=0.017
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)
Days from Randomization
0 30 60 90 120 150 180 210 240 270 300 330 360 390 420 450
0 1 2 3 4 5 6 7 8 9 10 11 12 13

12


STEMI
Clopidogrel
Effient
p=0.02
p=0.008
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)
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

These figures show clearly that many events occurred within hours of PCI (most of these were NFMIs detected by CK-MB blood tests), and that the advantage of prasugrel was also seen early, especially for UA/NSTEMI; in this group, however, there was a continued increase in between-group difference after 30 days. In the STEMI population, the advantage of prasugrel was seen over the first 7 and 30 days, with little further increase in that advantage after 30 days. This will be considered further when duration of treatment with prasugrel is discussed.

Labeling also notes a 50% reduction in stent thrombosis in the prasugrel-treated patients.

In any outcome trial, there is interest in effects in a variety of subsets of the population and forest plots, also taken from the label, are shown in the following two figures, one for UA/NSTEMI, the second for STEMI.

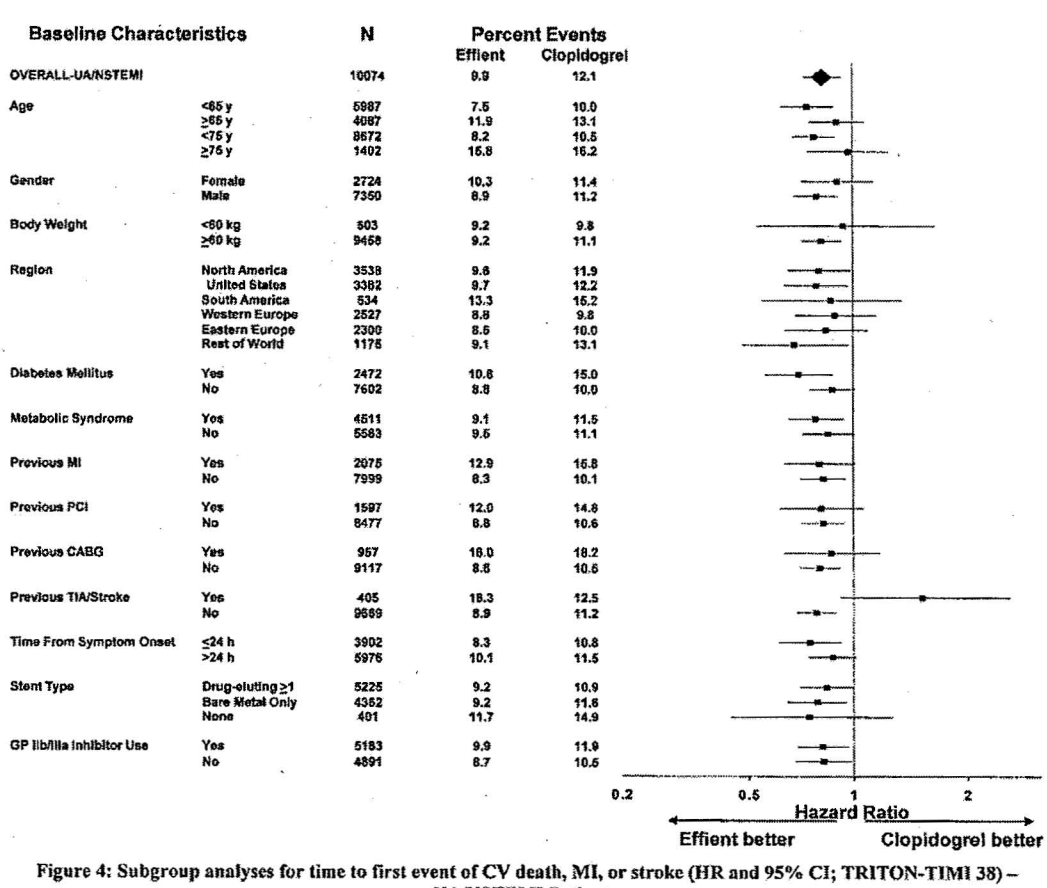


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

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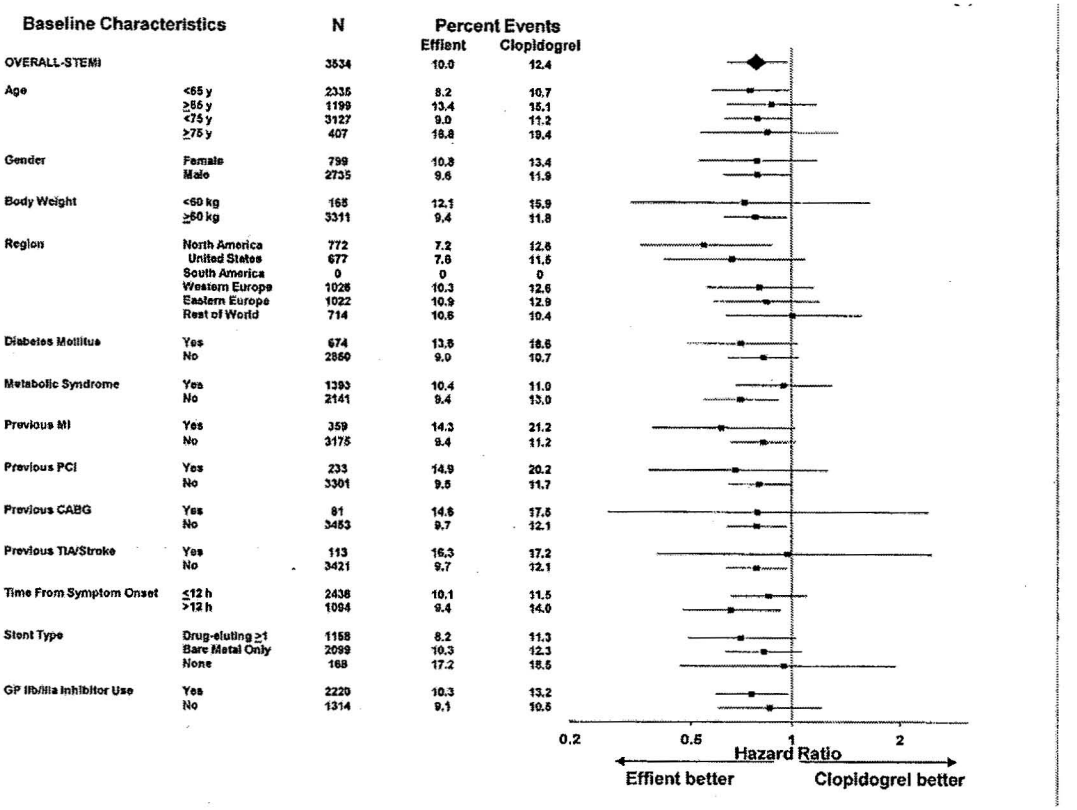

In any such display, there will be subgroups that appear to have greater or lesser effects. Such displays must be interpreted carefully, but several subgroups should be noted:

1. Age > 75

In the larger UA/NSTEMI group, the effect seems smaller in the subset of patients > 75 years, a group that probably also has only a small benefit from clopidogrel (CURE study). This minimal effect in the > 75 patients was notable because these patients also had more bleeding. Labeling therefore does not recommend use in most patients > 75. It was also noted, however, that high risk patients (patients with diabetes or prior MI) over 75, considering the entire ACS (UA/NSTEMI and STEMI) population, did appear to benefit, as shown in the following table from labeling

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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

The labeling notes that such subgroup analyses must be interpreted with caution, but the data fairly strongly suggest that it would be reasonable to consider use in patients over 75 who are at high risk because of, for example, diabetes or a remote history of MI, but not in other patients over 75.

2. Previous Transient Ischemic Attack/Stroke

In both UA/ NSTEMI and STEMI, patients with a prior transient ischemic attack (TIA) or stroke did badly on prasugrel (UA/NSTEMI) or show no advantage over clopidogrel (STEMI) on the composite endpoint. Indeed, they had a strikingly higher rate of stroke, both thrombotic and hemorrhagic.

	Prasurgel	Clopidogrel
Total Stroke	6.5%	1.2%
Thrombotic	4.2%	1.2%
Hemorrhagic	2.3%	0

In patients without a history of prior TIA or stroke, total strokes occurred at a rate of about 1% in both groups.

Use of prasugrel in patients with a prior history of stroke (even long ago; patients with a stroke or TIA within 3 months were excluded from TRITON) is contraindicated.

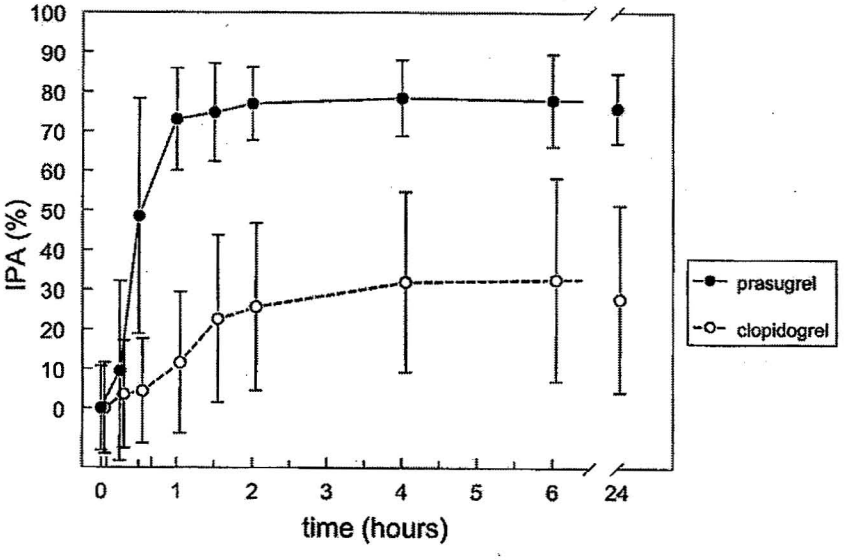
B. Reasons for effectiveness advantage and bleeding disadvantage of prasugrel.

1. Greater inhibition of platelet aggregation

As described in Dr. Unger's CDTL review of 1/1/09, the prasugrel dose was chosen based on two relatively small studies (TAAD and TAAH) comparing effects of clopidogrel and prasugrel on inhibition of platelet aggregation (IPA) and bleeding. TAAD showed that a loading dose of 60 mg

prasugrel gave more rapid and higher IPA than clopidogrel 300 mg and that maintenance doses above 10 mg caused excess bleeding. A small phase 2 study in patients undergoing PCI showed that a dose of 60 mg loading/ 10 mg daily did not seem to cause excess bleeding. The greater platelet inhibition by the 60 mg loading dose is shown in the following figure from Dr. Unger's review.

Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μM ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean ± SD)



Note that prasugrel rapidly (within an hour) gives 75-80% IPA inhibition, compared to about 30% after 1½-2 hours with 75 mg clopidogrel. There have been suggestions that the clopidogrel loading dose should be increased, but this has not been fully tested and, of course, the bleeding consequences have not been fully examined.

The 60/10 regimen thus represented a dose with greater IPA than clopidogrel and it was hoped and expected that this would yield a greater effect on CV events. And, indeed, a greater effect was seen. The same reasoning of course, leads to an expectation of more bleeding. But the relationship between the effect on IPA (a biomarker surrogate) to the effect on actual CV events is not established (we don't know, for example if, beyond some IPA inhibition, say 50%, no further reduction in CV events occurs) and thus can only be determined in outcome trials (like TRITON). Unfortunately, the size of these outcome trials makes good dose finding (say, randomization to low, medium, and high doses of prasugrel and to a standard dose of clopidogrel) difficult and, at least in most cases, such studies are not carried out. The early studies are not large enough to predict accurately the event rates and bleeding rates in a large study. We therefore do not have a good dose-response outcome study for CV events or for bleeding. It should be appreciated that there have also been suggestions that the loading dose of clopidogrel should be increased, both for the whole population and in patients who do not form as much of the active metabolite (see below).

The results of TRITON could be interpreted as confirming the sponsor's hypothesis that greater platelet inhibition would indeed yield greater reduction of CV events and, perhaps not surprisingly, greater numbers of bleeding events (see below), a known consequence of treatment with any thienopyridine platelet inhibitor. Although this may indeed be true, there is, however, an alternative explanation for at least some of that advantage.

2. Prasugrel is potentially effective in 100% of patients.

Both prasugrel and clopidogrel must be converted to an active metabolite to inhibit platelet aggregation. This is done by a number of CYP P450 enzymes for prasugrel but primarily by CYP 2C19 for clopidogrel; 2C19 is subject to genetic variations such that as much as a third of the population may form limited amounts of the active metabolite. In addition, some proton pump inhibitors, commonly used in older populations receiving anti-clotting drugs, can inhibit formation of the active metabolite. If, say, 25-30% of patients given clopidogrel have a diminished response, that might account for some of the TRITON results, both the greater effectiveness of prasugrel and the greater bleeding rate, depending on what the effect size of clopidogrel was in this study. In CURE (ACS study of clopidogrel) the overall effect vs placebo was about 2%. If 1/3 of patients could not respond, the effect in responders might be 3% vs placebo, or a 1% difference. If TRITON and CURE had the same clopidogrel effect, then if prasugrel differed from clopidogrel only in being effective in all patients, it should be about 1% better. In TRITON, however, the difference was 2%, suggesting that the advantage of prasugrel could have more than one basis.

Genomic data (specifically 2C19 deficiency) were collected from a 2534-patient subset of the TRITON study (about 20%); unfortunately, not all the samples were collected at baseline and many patients had had events by the time of sampling. The subset is thus a "convenience sample" that may not have been a random subset.

Of particular concern is the fact that the whole sampled population did not show the effect seen in the overall ACS population, i.e., a 19% reduction by prasugrel in event rate (11.5% vs 9.4%) but instead showed essentially no effect (both 8.8-8.9%). The results in the subset are nonetheless of interest. The following data come from the analysis (5/2/2007) of Dr. Ququan Liu.

In the extensive metabolizer group there was little difference between prasugrel and clopidogrel; in fact, clopidogrel was somewhat favored.

	Prasugrel		Clopidogrel	
	N	events	N	events
UA/NSTEMI	596	58 (9.7%)	623	47 (7.5%)
STEMI	243	18 (7.4%)	253	22 (8.7%)
All ACS	839	76 (9.1%)	876	69 (7.9%)

In the clopidogrel poor metabolizer group, in contrast, there was a suggestion of a substantial prasugrel advantage, but it was not consistent.

	Prasugrel		Clopidogrel	
	N	events	N	events