

Summary and Conclusions:

In summary, the review team concluded that the risk of bleeding is clearly higher with prasugrel, and specific information is merited in labeling for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
- patients who undergo CABG, or by extension, probably any surgical procedure

Nonetheless, even in the unmodified population studies in TAAL, overall survival was not impaired by prasugrel, and ICH was similar in both groups.

Although the excess of fatal and non-fatal bleeding in prasugrel patients is obviously unwelcome, it does not outweigh the benefit of prasugrel; both of these are related to greater inhibition of platelet aggregation. Bleeding events are graded in severity from fatal, to severely debilitating (ICH in many cases), to alarming but ultimately transient. We believe outcomes favor prasugrel (and will do so more when patients over 75 and patients with prior stroke or TIA are excluded).

1. Overall mortality slightly favored prasugrel; HR 0.95; 95% CI 0.78-1.16, $p=0.64$
2. Reduction in non-fatal MI: HR=0.76; 95% CI 0.67–0.85, $p<0.001$
3. Non-fatal strokes (ICH and thrombotic): no difference in overall population; but favored prasugrel if patients with prior TIA/stroke or age >75 are excluded: HR=0.64; 95% CI 0.42–1.00, $p<0.05$

In sum, patients receive a 25% reduction in non-fatal MI without survival or ICH cost. There is a great deal of data to indicate that decreasing the frequency of MIs, even silent ones, has a favorable effect on survival, congestive heart failure, etc., although this is difficult to prove vigorously. This probable benefit, however, is weighed against a small excess of bleeding events that were emergent but did not have long-term consequences.

The benefit-risk relation of prasugrel can be assessed in quantitative terms, as follows (see Tables 2 and 3):

For each 1000 subjects treated with prasugrel instead of clopidogrel, there were:

24 endpoint events prevented:

- 21 non-fatal myocardial infarctions
- 3 cardiovascular deaths
- 0 strokes.

10 attributable TIMI Major or Minor bleeding events:

- 2 fatal bleeding events
- 3 non-fatal TIMI Major bleeding events (ICH, or Hgb decrease >5 g/dL)
- 5 TIMI Minor bleeds (Hgb decrease ≥ 3 to ≤ 5 g/dL)

and 19 additional TIMI Minimal bleeds.

The tradeoff between efficacy and bleeding is largely between prevention of non-fatal myocardial infarction versus causation of transient morbidity. The Division believes that this is a worthwhile trade for patients who might receive prasugrel.

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/s/

Ellis Unger
7/6/2009 12:14:08 PM
MEDICAL OFFICER



DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Date: September 25, 2008
NDA: 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets
Eli Lilly and Company

Status: priority
Submitted: 26 December 2007
Goal Date: 26 September 2008
From: Ellis F. Unger, M.D., Deputy Director, DCaRP
To: The File
Re: **Importance of Prasugrel's Conversion from a Salt to the Base Form**

This document is based, in part, on the reviews of:

- Chemistry (Sharmista Chatterjee, Zhengfang Ge, and Kasturi Srinivasachar), May 14, 2008
- Clinical Pharmacology and Biopharmaceutics (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Secondary (Ellis F. Unger), July 10, 2008

Background:

The prasugrel NDA was one of the applications included in the Quality by Design (QbD) pilot program. The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. Gastric pH is an important issue in patients who use anti-platelet medications, because a substantial fraction of these patients take proton pump inhibitors [PPI] or H₂ receptor antagonists to reduce gastric acidity. Thus, with the concurrence of the Division, the sponsor decided to switch the manufacturing process to the HCl salt form of the drug substance.

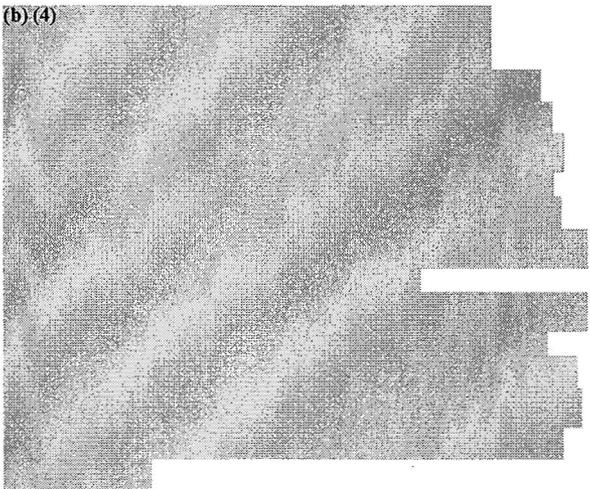
Late in development, at the time that the pivotal efficacy study was nearly completed, the sponsor discovered that an acid-base reaction (b) (4), was converting up to 86% of the salt form to the free base. Using x-ray powder diffraction, the sponsor determined that conversion from salt to base was beginning at the initial (b) (4). Conversion continued during storage to some extent, reaching a plateau after approximately (b) (4). Relative humidity and storage temperature were key factors affecting conversion. Of note, the conversion of a drug product from salt-to-base is a heretofore-unknown phenomenon. For prasugrel, the conversion may have been discovered as a result of following a science-based drug development approach

encouraged under the Quality by Design paradigm of drug development, and might not have been detected otherwise. The degree to which conversion of this nature occurs with other products is unknown.

Extent of Conversion:

The sponsor assayed several lots for salt to base conversion, performing batch analyses of the lots at various times post-manufacture; the extent of conversion ranged from 45 to 86%. They did not report serial data on single lots. When percent conversion of the individual lots is plotted as a function of time since manufacture, it is clear that the degree of conversion is not linear with lot age (Figure 1, from secondary review). The sponsor has added several in-process controls as well as a desiccant to packaging to limit form conversion of the to-be-marketed product to Not More Than (NMT) (b) (4). Importantly, because there are no serial data on conversion of the lots, it is not possible to identify a specific lot administered to a particular subject, and back-calculate the extent of salt to base conversion at the time of administration.

(b) (4)



(b) (4)

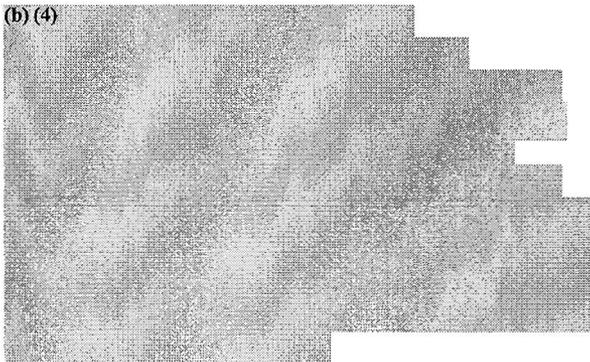
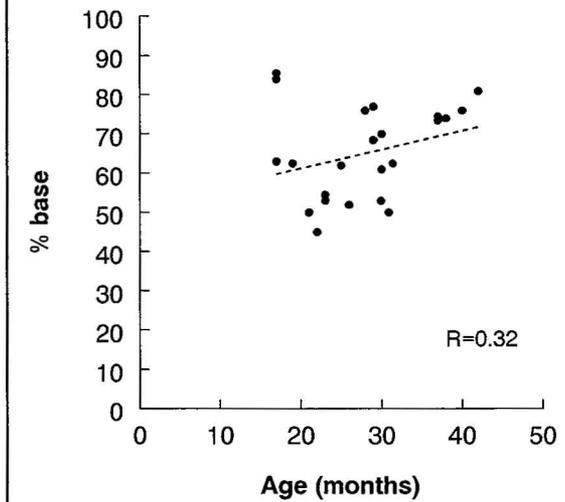


Figure 1: Base Content of Prasugrel as a Function of Time



Bioequivalence of Prasugrel – Low, Medium, and High Salt-to-Base Conversion:

The sponsor conducted two bioequivalence studies in which the bioavailability of lots with low (5%), intermediate (58%), and high (70%) degrees of conversion to base were compared, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. The sponsor concluded that even lots with a high degree of conversion from salt to free base (70%) were

clinically acceptable, both with and without concomitant PPI use. The lots were not, however, bioequivalent.

The prasugrel lots with low, intermediate, and high salt to base conversion were bio-equivalent with respect to R-138727, prasugrel's active moiety, when the drug was administered alone. This was true with respect to both C_{max} and area under the curve (AUC). When prasugrel 60-mg was administered on a background of lansoprazole, however, the three lots were still bio-equivalent for R-138727 with respect to AUC, but *the lots were not bio-equivalent with respect to C_{max}* (Table 1). The mean difference in C_{max} between the low and the high conversion lots was 29% (90% confidence interval [C.I.] 17%, 38%), and there was a 20% difference in C_{max} between the medium and high conversion lots (90% C.I. 8%, 31%). There was no statistically significant difference in C_{max} for the low and medium conversion lots.

Table 1: Relative Bioavailability of R-138727, the Active Moiety of Prasugrel – Comparison of Low, Medium, and High Extents of Conversion with Background 30-mg Lansoprazole (sponsor's table TACS 7.2)

Geometric least square means (90% CI)			Ratio of means (90% CI)		
prasugrel-LC	prasugrel-MC	prasugrel-HC	M-C/LC	H-C/L-C	H-C/M-C
AUC(0-t_{last}) (ng•h/mL)					
470 (424, 522)	467 (421, 518)	409 (368, 454)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C_{max} (ng/mL)					
331 (285, 384)	297 (257, 344)	236 (204, 274)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)

LC ≡ low conversion; MC ≡ medium conversion; HC ≡ high conversion

Pharmacodynamics of Prasugrel – Low, Medium, and High Salt-to-Base Conversion:

What are the consequences of these differences in C_{max} for PPI or H2 receptor antagonist users? The effects of thienopyridines on platelet aggregation last for the life of a platelet and are concentration-dependent. A delay in reaching C_{max} , i.e., a lengthened T_{max} or a lower C_{max} , could delay the full effect of the drug on platelet aggregation. For the 60-mg prasugrel loading dose, these differences translated into disparities in inhibition of platelet aggregation (IPA) of approximately 50% at 0.5 hours post-dose (high versus low- or medium-salt-to-base conversion) and 16% at 1 hour post-dose, when prasugrel is given on a background of lansoprazole (Figure 2). Thus, at the time points that bracket T_{max} , the high salt-to-base conversion lots are not bio-equivalent to lots with medium or low conversion. However, at subsequent time points (2, 4, and 24 hours post-dose), inhibition of platelet aggregation continued to increase, such that IPA was virtually identical with lots of all degrees of conversion by two hours (Figure 2). Thus, the high salt-to-base conversion lots are technically bio-inequivalent from the low- and medium-conversion lots in the presence of a PPI. Inequivalence in platelet aggregation is greatest at 0.5 hours (50%), there is little difference at one hour, and there is no detectable difference at 2 hours and beyond. In essence, the bioinequivalence results in a delay of perhaps 20 minutes in achieving maximal inhibition of platelet inhibition.

This is manifested only with the high salt-to-base conversion product, and only in the presence of PPI or H2 receptor antagonists.

Relevance of Altered Pharmacodynamics of High Salt-to-Base Conversion:

Because percutaneous coronary interventions (PCI) may precipitate periprocedural myocardial infarction, a considerable number of events occur very soon after PCI. Specifically, in TAAL, of the 1095 non-fatal myocardial infarctions recorded during the course of the 15-month study, 332 events, or 30% of them, occurred *within the first hour of the study!*

Clearly, therefore, rapid inhibition of platelet aggregation may be important in preventing periprocedural MIs, and the delay in achieving inhibition of platelet aggregation resulting from use of the high salt-to-base conversion product in the presence of PPIs or H2 receptor blockers has at least the potential to be clinically meaningful.

However, to understand fully the significance of the delay, it is important to contrast the prasugrel's overall IPA activity to that of clopidogrel. Figure 3 shows the IPA in response to 20 μ M ADP for subjects who received prasugrel versus clopidogrel from Study TAAJ (loading and daily maintenance doses). Although prasugrel lots with high salt-to-base conversion exhibit delayed inhibition of platelet aggregation in the presence of high gastric pH, the difference is negligible when placed into context with the effect of clopidogrel, at least on a population basis. Prasugrel has a markedly higher IPA than clopidogrel at all time points following administration (Figure 3).

Figure 2: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP Following 60-mg Prasugrel: Lots with Low, Medium, and High Extents of Salt-to-Base Conversion on Background of Lansoprazole 30-mg (*p<0.01, high conversion versus low or medium conversion, mean \pm SD; calculated by CDER, Study TACS)

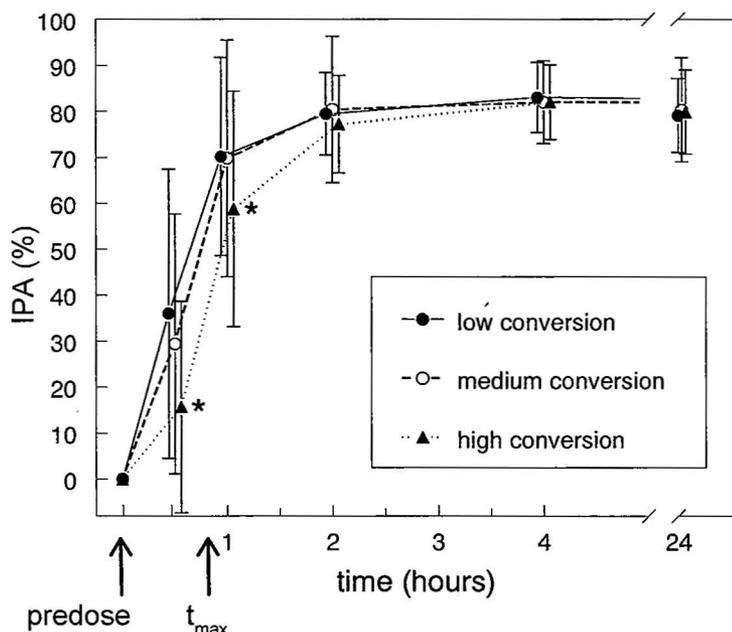
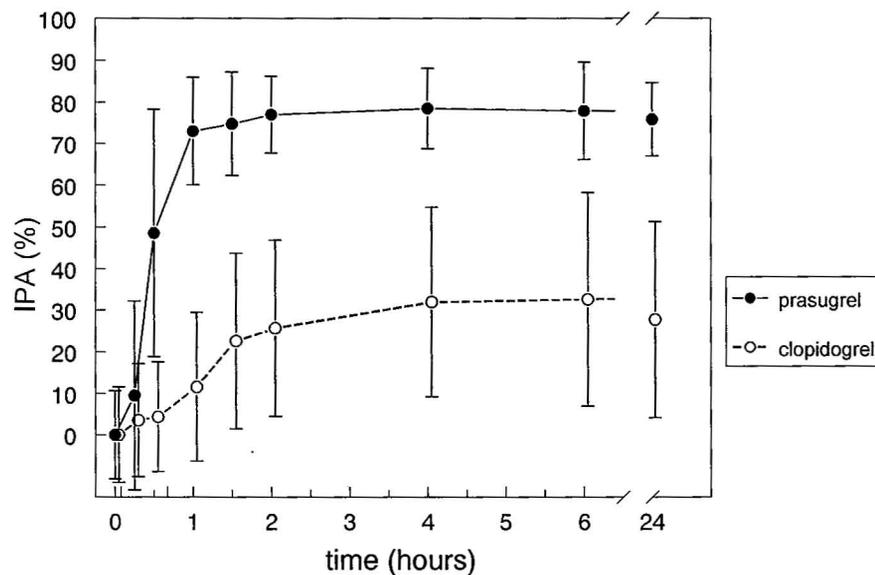


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean \pm SD)



Clinical Relevance of Salt-to-Base Conversion:

Study TAAL was the pivotal, active-control, double-blind, double-dummy, registrational study of prasugrel for subjects with acute coronary syndrome (ACS) who were scheduled to undergo PCI. The primary hypothesis was that prasugrel plus aspirin was superior to clopidogrel plus aspirin in the treatment of these subjects, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke (referred to as the “triple endpoint” in this document), at a median follow-up of ≥ 12 months.

Briefly, subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or a standard regimen of clopidogrel (300-mg load; 75 mg daily maintenance). Randomization was stratified by clinical presentation:

- unstable angina (UA)/ non-ST-segment elevation myocardial infarction (NSTEMI)
- ST-segment elevation myocardial infarction (STEMI).

Aspirin (75-325 mg PO or 250-500-mg IV) was administered within 24 hours prior to the index PCI. Proton pump inhibitors were permitted at the discretion of the treating physician. The intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Median length of follow-up was approximately 15 months.

In total, 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a primary composite endpoint event of cardiovascular death, nonfatal MI, or nonfatal stroke (Table 2). Treatment with prasugrel was associated with a statistically significant reduction in the composite endpoint in both the UA/NSTEMI and STEMI populations, (Table 2 and Figure 4, top and bottoms panels, respectively).

Table 2: Number and Percentage of Subjects Reaching Composite Endpoint

subject population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
	N	n	(%)	N	n	(%)		
UA or NSTEMI	5044	469	9.3	5030	565	11.2	0.82 (0.73, 0.93)	0.002
STEMI	1769	174	9.8	1765	216	12.2	0.79 (0.65, 0.97)	0.019

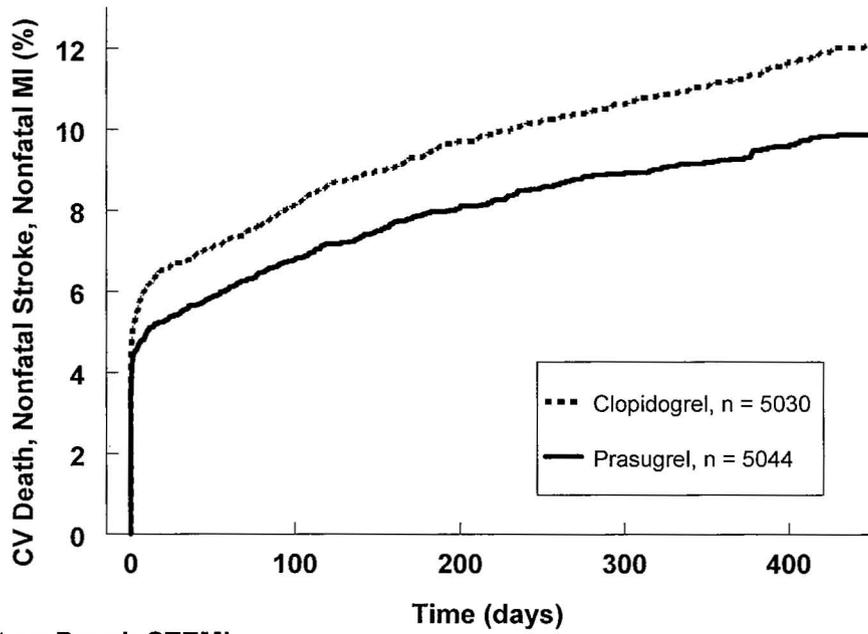
Table 3 displays the individual components of the 1° endpoint for the UA/NSTEMI and STEMI populations. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group in both the UA/NSTEMI and STEMI populations; this component of the composite endpoint drove the overall study results. The CV death component shows a trend in favor of prasugrel in the STEMI population (hazard ratio = 0.74, p = 0.13), and neutrality for the UA/NSTEMI population (representing roughly three-quarters of the overall study population), with only a very weak trend in the overall population (p=0.307). The effect of prasugrel on nonfatal stroke was neutral.

Table 3: Components of 1° Efficacy Endpoint (from table 11.7 in TAAL Study Report)

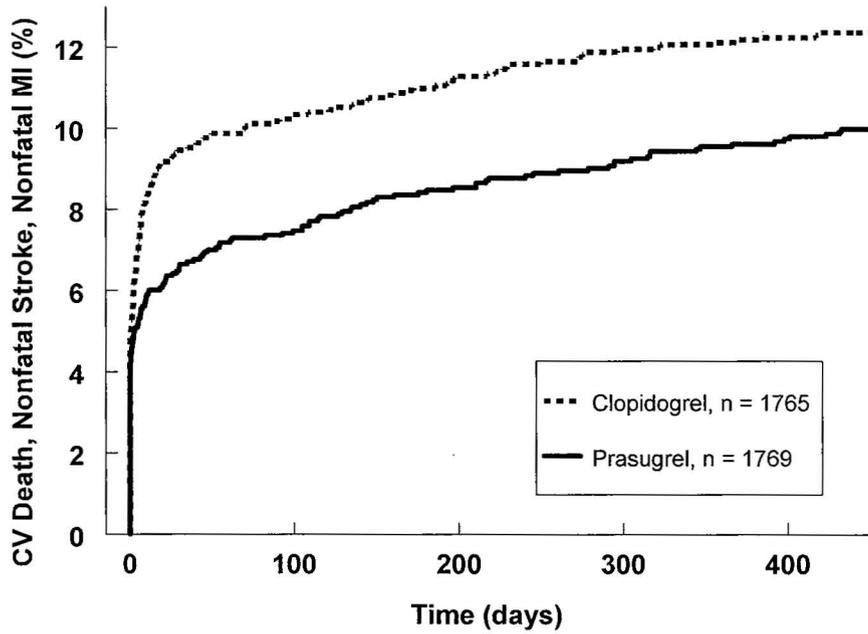
endpoint	Patient population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	0.74 (0.50,1.09)	0.129
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	0.75 (0.59,0.95)	0.016
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	1.10 (0.59,2.04)	0.77

Figure 4: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI



Impact of Salt-to-Base Conversion on Efficacy:

Some estimate of the clinical importance of salt-to-base conversion can be gleaned by considering efficacy as a function of prasugrel lot. Although subjects obtained prasugrel from several lots during the course of the study, the loading dose (6 pills) was obtained from a single lot, and the initial month's supply (Days 2-30) was obtained from a single lot as well. Because more than half of all events occurred between Days 0 and 30, and because the majority of prasugrel's treatment effect was evident during this period, the review team analyzed efficacy on the triple composite endpoint as a function of prasugrel lot used for the loading dose (Figure 5, top) and the lot administered Day 2 to 30 (Figure 5, bottom). Although the salt-to-base conversion at the time of actual use cannot be estimated for the disparate prasugrel lots, it is difficult to interpret event-free survival as importantly different from clopidogrel for any prasugrel lot subgroup with a sizable number of subjects. (Note that the subgroups associated with higher event rates tend to be small in size; fractions indicate N with events/N at risk.)

