UA/NSTEMI	284	18 (6.39%)	291	36 (12.4%)
STEMI	131	17 (12.9%)	113	10 (8.9%)
All ACS	415	35 (8.4%)	404	46 (11.4%)

In the UA/NSTEMI and all ACS populations prasugrel was superior in the poor metabolizers. In the small STEMI group, however, results went the other way, favoring clopidogrel, an inconsistency that is troublesome and precludes a firm conclusion. These data were therefore not included in labeling, although the last paragraph of section 14 (clinical studies) notes the possibility that the greater effect of prasugrel is the result of the presence of clopidogrel poor responders. Further genetic analyses are clearly needed [and are being conducted as a post-marketing commitment in Lilly's ongoing TRILOGY (medically managed ACS) study]. Nonetheless, although the data are not complete, there remains the possibility that the greater platelet inhibition of prasugrel is not the reason for all or most of prasugrel's advantage on CV events, or for its increased rate of bleeding, but that both prasugrel's advantage and bleeding disadvantage comes from the presence of a 2C19 deficient subset in the population, about 1/3 of patients in the TRITON sample. There were more bleeding events in the 2C19 poor metabolizers (5.6% to 1.5%) than in the normal metabolizers (6.8% vs 3.9%), again an observation that needs expansion and replication.

III. Safety

A. Bleeding

The clearest "downside" of prasugrel in the TRITON study is the excess of important bleeding, both TIMI major (clinically overt bleeding with a fall in hemoglobin of ≥ 3g/dL but < 5g/dL or intracranial hemorrhage), and TIMI minor (overt bleeding with a fall in hemoglobin of ≥ 3 g/dL but < 5 g/dL) with an overall rate of TIMI major or minor of 4.5% for prasugrel and 3.4% for clopidogrel (p =0.002). The following tables taken from labeling show these outcomes overall, in the weight < 60 kg and age > 75 subgroups, and in people who underwent CABG, who show a strikingly greater risk of bleeding on prasugrel.

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Table 1: Non-CABG-Related Bleeding[a] (TRITON-TIMI 38)

	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

[a] Patients may be counted in more than one row.

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight <60kg (N=308 Effient, N=356 clop)	10.1	6.5	0.0	0.3
Weight ≥60kg (N=6373 Effient, N=6299 clop)	4.2	3.3	0.3	0.1
Age <75 years (N=5850 Effient, N=5822 clop)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 clop)	9.0	6.9	1.0	0.1

Table 3: CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row.

Note that there was no difference in intracranial hemorrhage and that fatal bleeds occurred at a low rate. Bleeding after CABG was a significant problem.

The risk of bleeding is greatest shortly after PCI, but persists over time, as shown in a figure from labeling.

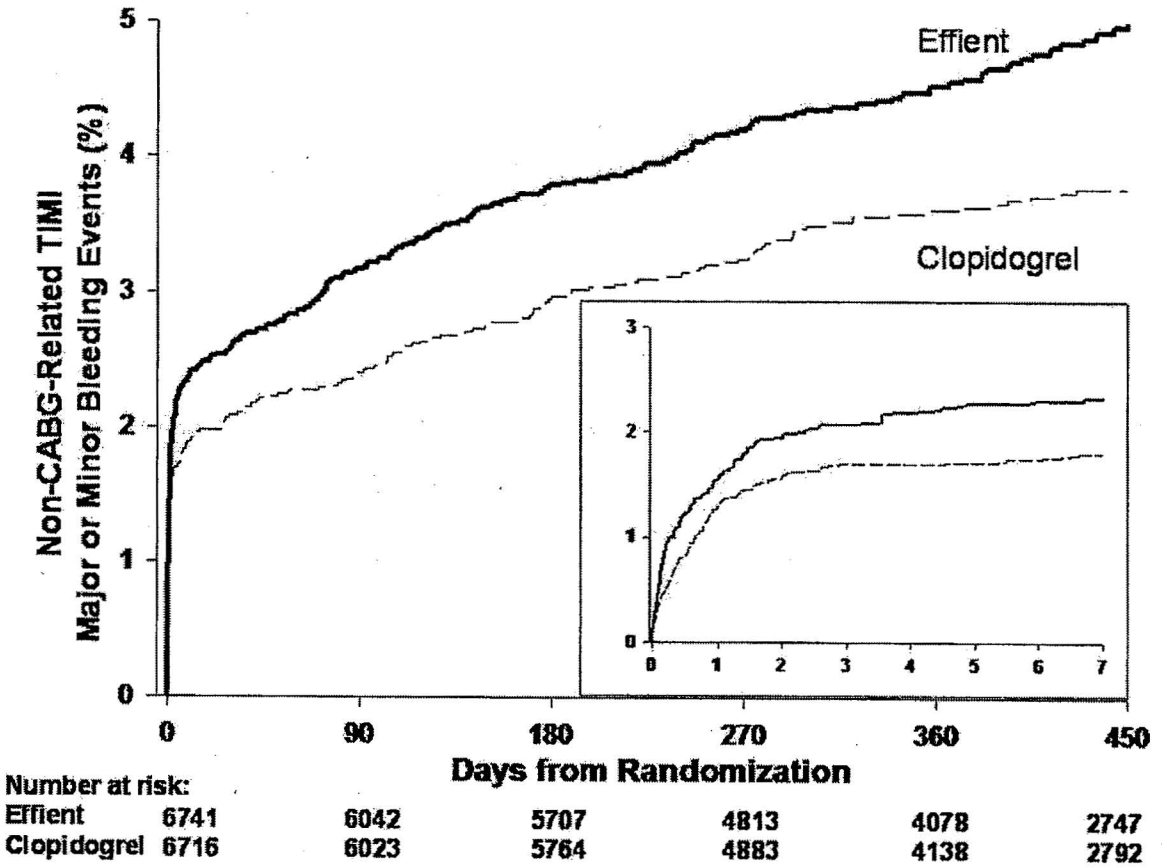

Figure 1: Non-CABG-Related TIMI Major or Minor Bleeding Events

The bleeding risk has led to

1. A boxed warning and warnings about bleeding risk and the particular risk in patients > 75 or who undergo CABG.

2. A statement in Clinical Studies that choice of therapy requires balancing the reduction of total endpoint events against the greater risk of significant bleeding.

3. A REMS consisting primarily of a Medguide warning about bleeding.

4. A post-marketing requirement to study reversal of prasugrel-induced platelet inhibition by exogenous platelets. This study will examine a potential treatment for CABG-related bleeding.

B. Malignancies

It was recognized by the sponsor and the review team that the prasugrel group in TRITON had experienced more malignancies than the clopidogrel group. There have been countless internal discussions, blinded analyses by staff of new (or possibly new) tumors, consideration of whether

our primary interest was in "new" or "new and worse" tumors, and statistical analyses. An early view by the sponsor that the excess of newly diagnosed malignancies, particularly of the GI tract, could be explained by bleeding has, on the whole, not been accepted. Dr. Unger's July 7, 2009 review of this issue covers the discussion and the history and conclusions of our analyses, and Dr. Marciniak (updated review of May 6, 2009) discusses this issue in detail.

There is clearly an excess of newly identified tumors (or new and worse tumors) in the prasugrel group, beginning at about 4 months. This is too soon to represent de novo tumor induction but could suggest tumor growth promotion. The exact risk depends on whether one counts non-melanomatous skin cancer (clinically not important but arguably a pertinent tumor); labeling gives rates as 1.6% and 1.2% for prasugrel and clopidogrel, respectively, a risk increase of about 33% with colon and lung contributing most of the difference. The risk increase and nominal statistical significance depend on which tumors are included. There was also an increase in cancer-related deaths, but overall mortality was somewhat decreased in the prasugrel group for the whole study.

The pre-clinical evaluation (Carcinogenicity Assessment Committee) concluded that there was no evidence that prasugrel promoted malignancies and there is no history of such promotion in a human setting (erythropoietin perhaps representing an exception). They were aware of increased hepatocellular adenomas at high doses and some tendency toward increased hepatocellular carcinoma at the highest dose but did not find these observations critical. The rat showed no suggestion of increased neoplasia. The sponsor, at FDA's request, carried out tumor promotion studies using explants of lung, colon and prostate cell lines in immunodeficient nude mice and in vitro studies of proliferation of cell lines derived from lung, colon, and prostate tumors. Prasugrel did not stimulate cell proliferation or growth of xenografts.

No one believes a definitive answer is possible without further data. Dr. Unger is skeptical about the reality of the increased rate of new tumors, given the benign animal data, including the recent tumor progression studies, the absence of examples of such tumor promotion or any mechanistic explanation, the similarity of its structure to clopidogrel, which shows no suggestion of tumor stimulation, and the inherent multiplicity of our safety analyses. I concur in this and would add to those reservations the marginal statistical support for the increase.

The February 2009 Advisory Committee noted the finding but was skeptical, urging its placement in the Adverse Reactions section, rather than in Warnings/Precautions, which is where it has been placed. There is a post-marketing requirement to collect baseline and subsequent cancer data in the ongoing TRILOGY trial.

Although no one in the Division of Cardiovascular and Renal Products believes the cancer findings should block approval, Dr. Marciniak believes the finding merits restriction of use to one month. This was at least partly because the mouse hepatic adenoma and carcinoma data convinced him that prasugrel may have the ability to stimulate tumor growth, the cardiovascular event rate diminishes with time, and the advantage of prasugrel relative to clopidogrel wanes over time. For the reasons given by Dr Unger, and additional considerations described below, I do not believe that would be appropriate.

IV. Risk-Benefit Considerations, Duration of Use, Time of Administration, Product Quality

A. Risk-Benefit

It is clear that prasugrel reduces the rate of NFMIs by about 20% and increases the rate of serious bleeds by about 30%. Although it might be tempting to add all the events (composite CV and bleeding) that does not appear reasonable, as the specific events must be weighed and judged. Thus, the excess of bleeding is troubling but there was no increase in fatal intracranial hemorrhage, a particular concern, and fatal bleeds were relatively few. Dr. Unger has summarized bleeding events in a review dated 7/6/09 and all cause mortality in a review dated 1/9/2009.

Table 3: CEC Adjudicated Bleeding

Non-CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04,1.66)	0.022
TIMI Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28,1.70)	0.022

CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	213	2	0.9	224	0	0.0		
TIMI Major	213	24	11.3	224	8	3.6	3.50 (1.53,7.99)	0.002

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Table 10: Summary of Deaths in TAAL (adapter from sponsor's Table TAAL.11.10)

	Prasugrel n=6813		Clopidogrel n=6795		delta events per 1000 patients treated (positive = favorable for prasugrel)
	n	%	n	%	
All Cause Death	**188**	**2.76**	**197**	**2.9**	**1.4**
Cardiovascular (conponent of 1° efficacy endpoint)	**133**	**1.95**	**150**	**2.21**	**2.6**
atherosclerotic vascular disease (excluding coronary)	0	0	3	0.04	0.4
CHF/cardiogenic shock	31	0.46	30	0.44	-0.1
related to CABG or PCI	15	0.22	16	0.24	0.2
dysrhythmia	4	0.06	7	0.1	0.4
pulmonary embolism	3	0.04	0	0	-0.4
acute MI	24	0.35	36	0.53	1.8
sudden or unwitnessed	36	0.53	42	0.62	0.9
ICH	9	0.13	5	0.07	-0.6
non-hemorrhagic stroke	5	0.07	6	0.09	0.1
other cardiovascular	6	0.09	5	0.07	-0.1
Non-Cardiovascular	**55**	**0.81**	**47**	**0.69**	**-1.2**
accident/trauma	4	0.06	4	0.06	0.0
hemorrhage, non-ICH	9	0.13	1	0.01	-1.2
infection	11	0.16	10	0.15	-0.1
malignancy	21	0.31	17	0.25	-0.6
suicide	3	0.04	2	0.03	-0.1
other	7	0.1	13	0.19	0.9

The numbers in these tables differ slightly because of different adjudication times. There were 23 hemorrhagic deaths on prasugrel (about 0.3%) vs 5 (about 0.07%) on clopidogrel. Overall CV deaths were decreased on prasugrel by 17, and overall deaths were reduced by about 9. The time course of CV and overall deaths are shown in two figures.

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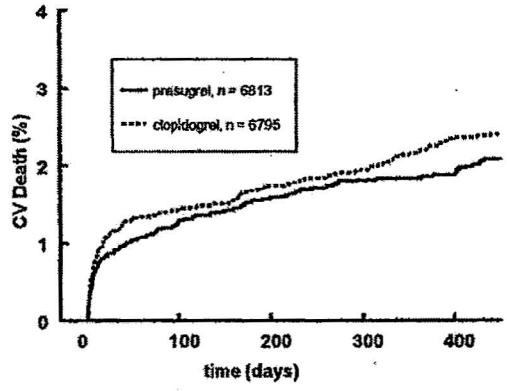

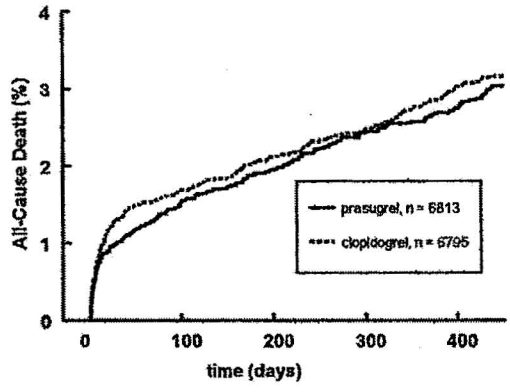

TRITON thus shows no real difference in survival between the two treatment groups. The effort to identify high risk groups in labeling and contraindicate or discourage prasugrel use in them (prior stroke, TIA, age > 75, CABG), should at least somewhat reduce the risk of hemorrhagic deaths. As Dr. Unger shows, in the < 75 group there were 12 bleeding deaths vs 4 (rather than 22/5). With no net adverse effect on deaths, prasugrel showed a decrease of some 145 NFMIs, about 25%. As expressed by Dr. Stockbridge, and as the Advisory Committee agreed, non-fatal MI's, even asymptomatic and peri-procedural ones, about 40% of the events in TRITON, are a concern and are widely thought to have long-term consequences (heart failure, arrhythmias, etc.) Certainly we have treated non-fatal MIs as a major concern with VIOXX, Zelnorm, etc. It must be noted also that much of the effect of clopidogrel in ACS is also on the same, often asymptomatic, MIs. Plainly, there is a judgment involved, but many will value the reduction in NFMIs that prasugrel can provide. Patients and physicians, of course, need to be fully informed, and patient- and physician-directed labeling will do so. What TRITON shows, even before use in high bleeding risk people was discouraged, is that prasugrel does not cause an increase in overall mortality, despite an excess or serious bleeds, but provides a substantial reduction in NFMI.

B. Duration of Use

As shown above, the advantage of prasugrel did not increase in the STEMI population after 30 days, although it does increase over time in UA/NSTEMI. The excess of bleeding does continue to grow slowly after 30 days. The absence of major increasing benefit over time, together with the malignancy finding, has convinced Dr. Marciniak that a switch to clopidogrel after 30 days is warranted. Dr. Hicks, in early reviews, also thought duration of use should be limited, but her most recent review, dated 7/8/09, reached the opposite conclusion, and strongly urges long-term treatment, largely because her detailed analyses showed that prasugrel gives a substantial (as much as 50%, from 1.8% to 0.9%) reduction in stent thrombosis, a potentially fatal event that is often a late event. She also notes, and I concur, that the stable (albeit not increasing) difference favoring prasugrel in the STEMI group after 1 month could represent continued prevention of events in a vulnerable population and that a switch to clopidogrel (something not studied) might lead to loss of the advantage and an increase in events.

C. Timing of Administration

TRITON initiated treatment, particularly in the UA/NSTEMI group, only after coronary anatomy was established, leading to some delay, after symptoms were recognized, in initiation of anti-platelet therapy. This delay to allow assessment of coronary anatomy allows avoidance of prasugrel or clopidogrel in patients who will need CABG, a group with a high rate of bleeding, especially after prasugrel.

As many of the CV events occur early after PCI, however, delay might be expected to increase the risk of CV events, especially in the hour or so after initiation when platelet inhibition was incomplete.

Dr. Marciniak (review of 5/6/2009) has been concerned that the delay might have substantially disadvantaged clopidogrel because of its slower onset of platelet inhibition (about an hour slower, as shown above), allowing events to occur, and that this use did not represent the early use of these agents generally recommended. He analyzed rates of primary endpoint events (first 10 days) for patients with varying times of initiation of treatment compared to the start of PCI, from 2 hours before to 3 hours after, finding a suggestion of greater benefit of prasugrel compared to clopidogrel when initiation was delayed.

The problems with this analysis are several. As Dr. Marciniak notes, the timing of drug administration is not random but could reflect patient conditions. More critical, probably, is that only a tiny fraction of patients received drug prior to PCI. The results of the event vs time of loading dose are shown in the following 2 figures from Dr. Marciniak's review.

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Figure 29: Rates of UA/NSTEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL

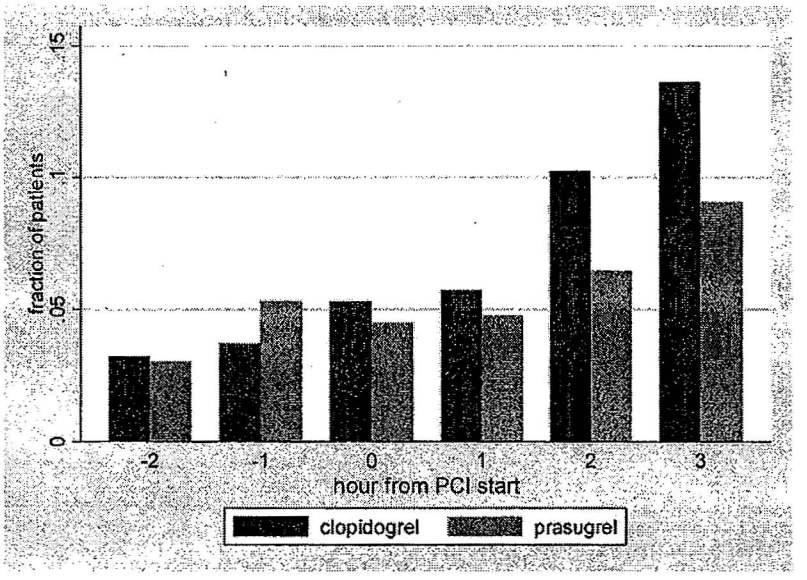
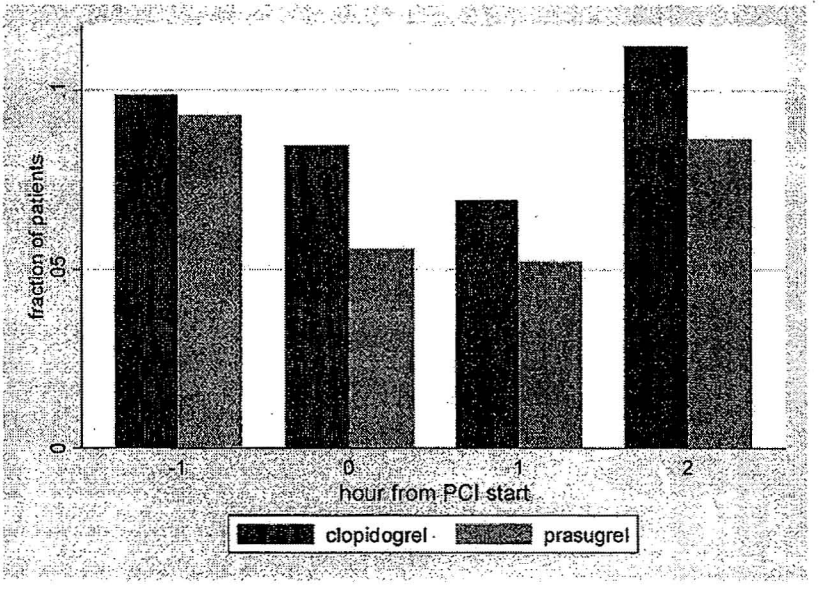


Figure 30: Rates of STEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL



For the UA/NSTEMI group, there is a suggestion that delay might disadvantage both drugs, but especially clopidogrel, but the fraction of patients getting drug at -2 or -1 hours is very small, barely 200 total (vs 4500 with later treatment). For all treatment times with more patients,

prasugrel shows the advantage seen in the overall data. In STEMI (still smaller numbers, it is hard to see any relation of effect to timing.

Labeling for prasugrel will note that many events occur early and that use before coronary anatomy is established can be considered if need for CABG, with its increased risk of bleeding, is considered unlikely.

D) Product Quality

Prasugrel was prepared as a hydrochloride salt after it was recognized that the free base was less well absorbed in a high pH environment, an environment that would occur in patients using proton pump inhibitors (PPIs), a widely used class of drugs in older people. It was found, however, that conversion of salt to base occurred at many stages of manufacturing, so that the product used in TRITON was not entirely the salt but 60-70% base. Dr. Unger, in a memo drafted 7/6/2009 discusses this at length.

It cannot be known exactly what base proportion patients in TRITON received, but it was around 60-70%. Bioavailability studies showed that low (5%) conversion product and medium and high conversion product (58%, 70%) were bioequivalent (C_{max} and AUC) in low pH settings, but were not when given with lansoprazole (i.e., a high pH setting), where the highest conversion product had lower C_{max}.

The main effect of such a difference would be on the speed of inhibiting platelet aggregation (IPA) after the loading dose and indeed, a study of IPA after dosing with low, medium and high conversion lots showed a small delay in reaching 40-50% inhibition (but still well above clopidogrel's effect). Given the prolonged inhibitory effect on platelets of prasugrel or clopidogrel, the main concern would be delayed effect. All dosages reached similar levels of IPA inhibitor by 2 hours and were close at 1 hour. No decreased effect on effectiveness other than in the first 20 minutes seems conceivable even with the highest conversion product. A possible concern would be the greater inhibition in the PPI setting provided by a low conversion product, like the one being developed by the sponsor, but 60% of patients in the trial did not take PPIs and would have been experiencing that level of inhibition already. An examination of the effective of prasugrel vs clopidogrel in people taking vs not taking a PPI showed essentially no difference in effect.

V. Conclusion

It is relatively unusual for a drug within a class to have a greater effect than other members of the class and when this is shown, there is inevitably the question of the cost in adverse effects. In the present case, the advantage shown by prasugrel in TRITON could represent primarily a greater willingness to "push" the dose and inhibit platelets more than the control drug, clopidogrel had, with a resulting greater reduction in NFMIs and a greater likelihood of significant bleeds. It may also represent a drug that does not require metabolic activation by an enzyme missing in many people, so that there are fewer non-responders, i.e., people who both do not receive beneficial effects on CV events and do not face a bleeding risk. Further study will help determine which of these mechanisms is more important.

An ACS population has a risk of CV events that decreases over time, so that how long to treat becomes a difficult question, one not settled in many other situations too. Practitioners will need to weigh benefits and risks over time. It should also be noted that the TRITON study compared prasugrel, not with placebo, but with an active agent, so that the number of CV events was already decreased. In this setting, a further time-related decline in events makes a showing of continued benefit challenging.

Prasugrel represents a useful therapeutic option that will be the subject of further study that will continue to refine its role in cardiovascular therapy.

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