

7.2.3. Baseline Characteristics

As expected in a study of this size, there were no important imbalances in baseline demographic or disease characteristics (Table 2). From the standpoint of generalizability of the results, however, several points are worth noting. Roughly a quarter of the subjects were female; only 3% of subjects were of African ancestry. Approximately 30% of subjects were from the U.S.; eastern and western Europe each accounted for approximately 25% of subjects. The median (and mean) age was 61, with 13% of subjects age 75 or older. Concomitant medical history (Table 3) and pharmacotherapy (Table 4) were typical of an ACS population. The majority of subjects were taking statins and beta blockers; about half of the subjects were taking GPIIb/IIIa inhibitors and ACE inhibitors.

7.2.4. Index Procedure

Essentially all subjects (98.6% in each treatment group) underwent PCI as directed per protocol, and 94% received at least one stent, divided fairly equally between bare metal stents (47%) and drug eluting stents (42%) (Table 5). Of the 1.4% of subjects who did not undergo PCI, one-fourth (0.35% overall) underwent CABG and three-fourths (1.1% overall) were managed medically without revascularization.

7.3. Primary Efficacy Endpoint

For the study as a whole (All ACS), 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a 1° triple endpoint event of cardiovascular death, nonfatal MI, or nonfatal stroke. Treatment with prasugrel was associated with a statistically significant reduction in the triple composite endpoint in the UA/NSTEMI population (Cox proportional hazard ratio in favor of prasugrel 0.82, 95% C.I. 0.73 to 0.93, p=0.002, Table 6, Figure 5, top panel). Therefore, as prospectively specified in the analytic plan, the analysis was carried out in the overall ACS patient population (Figure 6). Prasugrel was associated with a statistically significant treatment effect, with a hazard ratio of 0.81 (95% C.I. 0.73 to 0.90,

	Prasugrel n=6813	Clopidogrel n=6795
Age (years)		
mean ± SD	60.9 ± 11.2	60.9 ± 11.4
median	61	61
25th, 75th percentile	53, 69	53, 70
≥ 75 yrs	13.2	13.4
Female sex		
	25.0	26.8
Ethnicity		
Caucasian	91.9	92.3
African	3.0	2.8
Hispanic	3.9	3.8
Asian	0.9	0.9
Other	0.2	0.2
Region of enrollment		
U.S.	29.9	29.7
North America, non-U.S.	1.9	1.9
South America	4.0	3.9
Western Europe	26.1	26.1
Eastern Europe	24.3	24.5
Rest of world	13.8	13.9
Body Mass Index (kg/m²)		
mean ± SD	28.5 ± 5.0	28.5 ± 5.1
median	27.8	27.8
25th, 75th percentile	25.1, 31.1	25.1, 31.1
Weight (kg)		
mean ± SD	83.6 ± 16.8	83.2 ± 16.9
median	82.0	81.0
25th, 75th percentile	72.6, 93.0	72.0, 92.1

Table 3: Medical History (%)

	Prasugrel n=6813	Clopidogrel n=6795
Hypertension	64.1	64.3
Hypercholesterolemia	55.6	55.8
Diabetes	23.1	23.1
treated with insulin	5.6	5.8
not treated with insulin	17.5	17.3
Metabolic syndrome	43.5	43.2
Tobacco use		
ever	65.5	66.1
current	38.3	38.0
Hepatic impairment	0.5	0.6
Renal impairment		
Ccr ≤ 60 mL/min	10.7	11.6
Ccr ≤ 30 mL/min	0.8	0.8
Prior MI	18.0	17.8
Prior PCI	13.3	13.6
Prior CABG	7.9	7.3
History of CHF	3.9	3.6
Atrial fibrillation	3.1	3.1
History of carotid/vertebral artery disease	2.8	2.9
Prior Stroke	2.6	2.4
Prior TIA	1.4	1.7
History of peripheral vascular disease	5.1	5.3
Peptic ulcer disease	5.9	6.1

Table 4: Concomitant Pharmacotherapy (%)

	Prasugrel n=6813	Clopidogrel n=6795
Statins	78.8	78.6
ACE inhibitor	52.0	49.4
Beta blocker	74.0	73.9
Calcium channel blocker	14.7	14.2
Aspirin within 7 days prior to symptom onset	34.1	34.3
GPIIb/IIIa use through 3 days	53.4	54.9

Table 5: Index Procedure (%)

	Prasugrel n=6813	Clopidogrel n=6795
PCI	98.6	98.6
no stent	4.0	3.6
bare metal stent only	46.8	46.9
≥ 1 drug-eluting stent	42.0	42.3
CABG	0.4	0.3
Medically managed	1.1	1.1

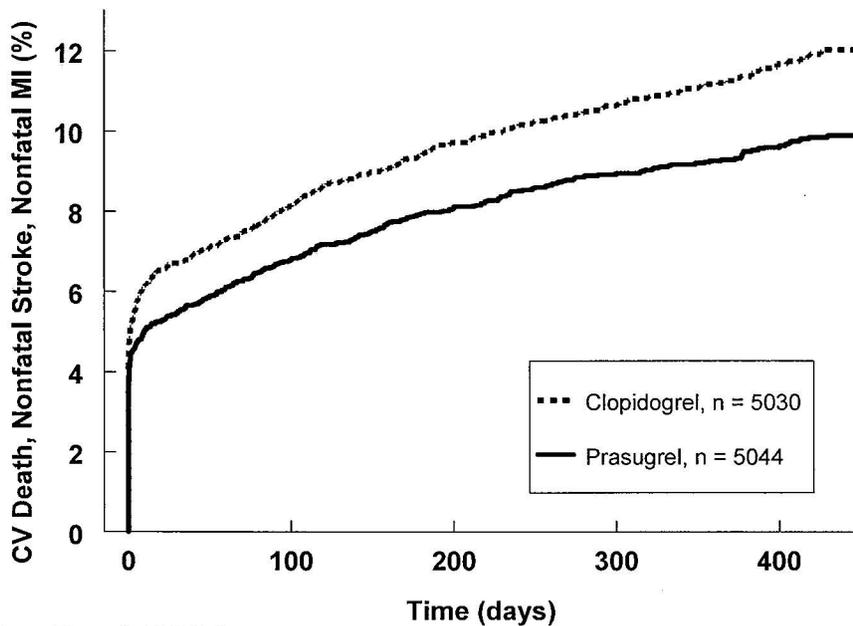
p<0.001, Table 6, Figure 6). Results were also statistically significant for prasugrel in the STEMI population alone (Table 6, Figure 5, bottom panel). The efficacy results for the 1° endpoint were verified by Dr. Ququan Liu in her statistical review.

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
Overall	6813	643	9.4	6795	781	11.5	0.81 (0.73, 0.90)	<0.001

For the entire ACS population, Figure 6 shows the Kaplan-Meier estimates for the composite triple endpoint. The top panel shows the events over the full 450 days; the bottom panel displays the same data but is limited to the first 30 days only. In order to better delineate how prasugrel's treatment advantage is manifested with respect to time, Figure 7 shows the *delta %* with a primary endpoint event as a function of time for both the STEMI and NSTEMI/UA populations. In essence, the Kaplan Meier time-to-event lines in Figure 5 are subtracted to produce Figure 7, and the *delta %* of Figure 7 represents the distance between the curves in Figure 5, the *cumulative* difference in event rates. For STEMI, the advantage begins immediately, reaches its maximum at 18 days, and remains unchanged thereafter. In the NSTEMI/UA population, approximately 60% of the cumulative treatment advantage occurred within 3 weeks, but the *delta* continues to increase fairly linearly through 450 days, supporting the concept that prasugrel's treatment advantage persists throughout the entire study.

Figure 5: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI

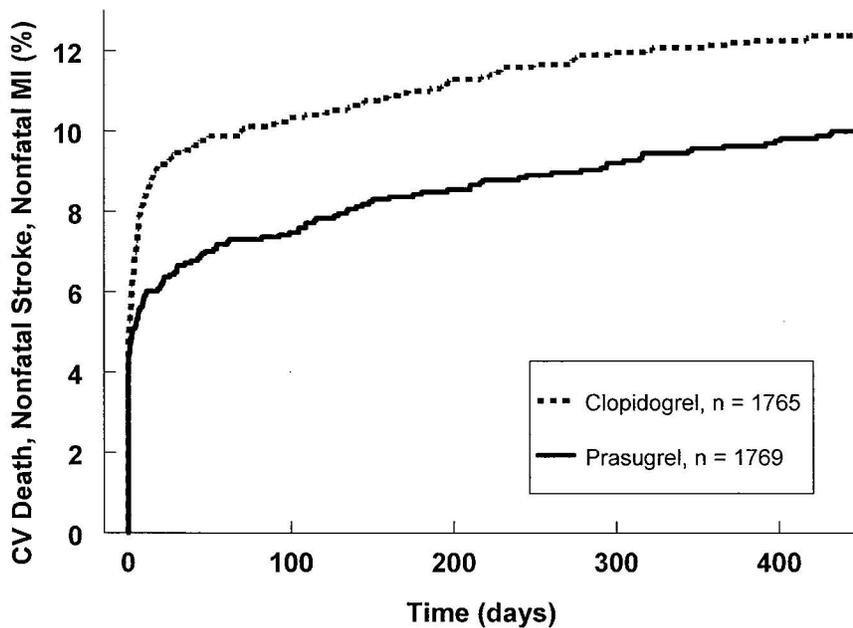
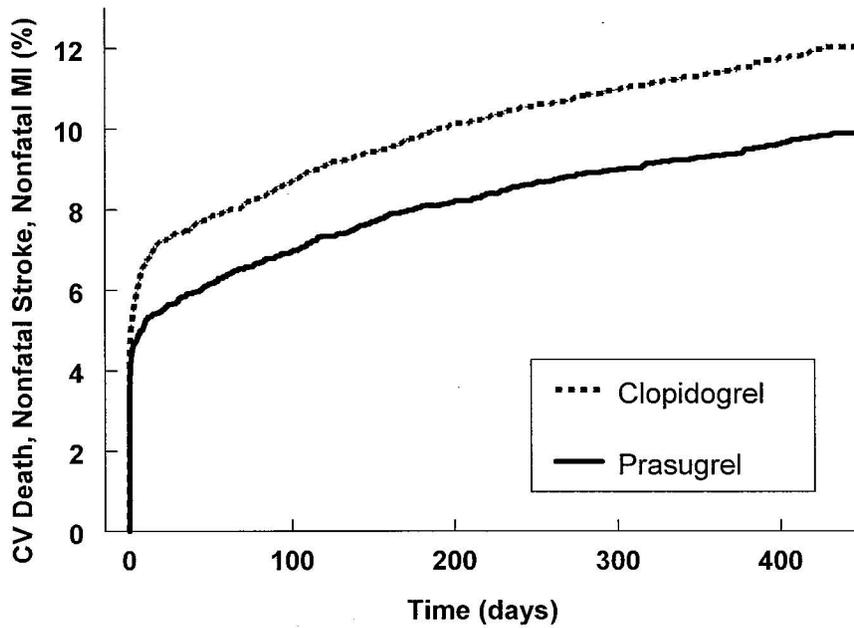


Figure 6: Kaplan-Meier Estimates of the 1^o Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke, All ACS Subjects

Top Panel: 0 – 450 Days;



Bottom Panel: 0 – 30 Days:

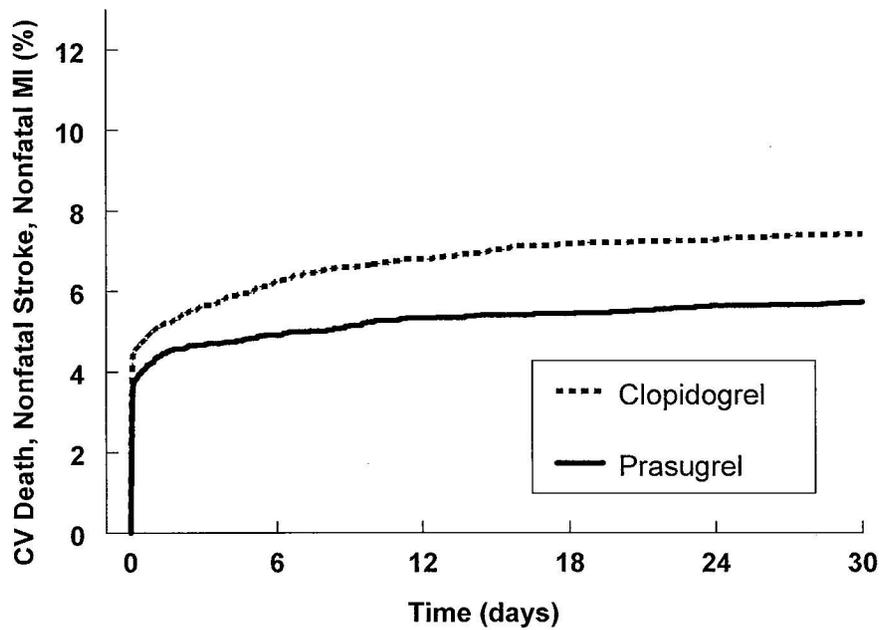
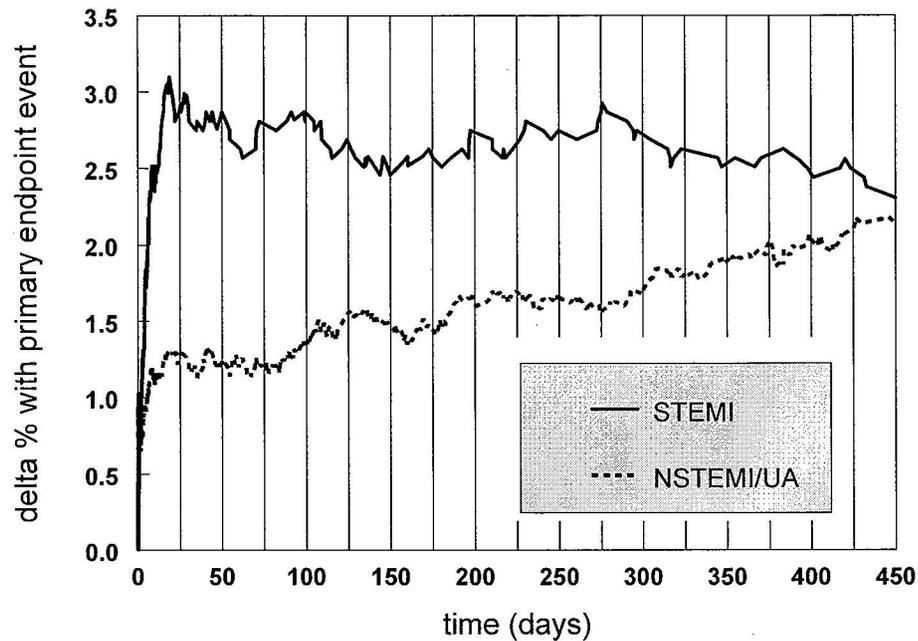


Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations



7.3.1. Explorations on the Primary Endpoint

Sponsor's Sensitivity Analyses:

The sponsor conducted sensitivity analyses, restricting the analysis of the 1° endpoint to subjects on treatment, and subjects on treatment and compliant to study drug. For both analyses, the results were consistent with the study results on the whole.

Individual Components of the Endpoint:

The individual components of the 1° endpoint are shown for the UA/NSTEMI, STEMI, and the All ACS populations in Table 7, as reported by the sponsor and confirmed by the statistical reviewer. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group in both the UA/NSTEMI and STEMI populations, and in the ACS population overall; this component of the composite endpoint is what drives 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. The statistical reviewer noted that prasugrel was associated with a higher incidence of nonfatal stroke in the All ACS and STEMI populations, but the numbers of events were small, with a hazard ratio fairly close to unity (Table 7).

Table 7: Components of 1° Efficacy Endpoint (from table 11.7 in TAAL Study Report)

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	10074	182	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	3534	101	2.9	0.74 (0.50,1.09)	0.129
	All ACS	6813	133	2.0	6795	150	2.2	13608	283	2.1	0.89 (0.70,1.12)	0.307
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	10074	821	8.1	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	3534	274	7.8	0.75 (0.59,0.95)	0.016
	All ACS	6813	475	7.0	6795	620	9.1	13608	1095	8.0	0.76 (0.67,0.85)	<0.001
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	10074	81	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	3534	40	1.1	1.10 (0.59,2.04)	0.77
	All ACS	6813	61	0.9	6795	60	0.9	13608	121	0.9	1.02 (0.71,1.45)	0.93

Definition of MI:

The protocol's original definition of peri-procedural MI required an elevation of CK-MB to >3X ULN on at least two samples within 48 hours of PCI. A modified definition, specified in protocol amendment "A" dated January 10, 2006, extended the definition of peri-procedural MI to a CK-MB >5X ULN on a single sample if it was the last available sample drawn and obtained ≥12 hours after PCI. This change resulted in the addition of 38 and 44 endpoint events to the prasugrel and clopidogrel groups, respectively, with no substantive change in the overall findings.

Statistical Assumptions of the Cox Model:

Non-informative censoring is a key assumption of the Cox model; the study design must ensure that mechanisms leading to the censoring of subjects are not related to the probability of an event. Dr. Liu, the statistical reviewer, examined the censoring distributions between the two treatment groups in all three subject populations and found them to be similar. Another key assumption of the Cox's regression analysis is the assumption of proportionality of the hazard ratio over time. Dr. Liu created log(-log survivor) plots for the UA/NSTEMI, STEMI, and overall ACS populations. For all 3 populations, the two relations were reasonably parallel over time, supporting the concept that the hazard ratio was fairly constant over time. Thus, the statistical reviewer found no important issues with the statistical assumptions of the Cox Model.

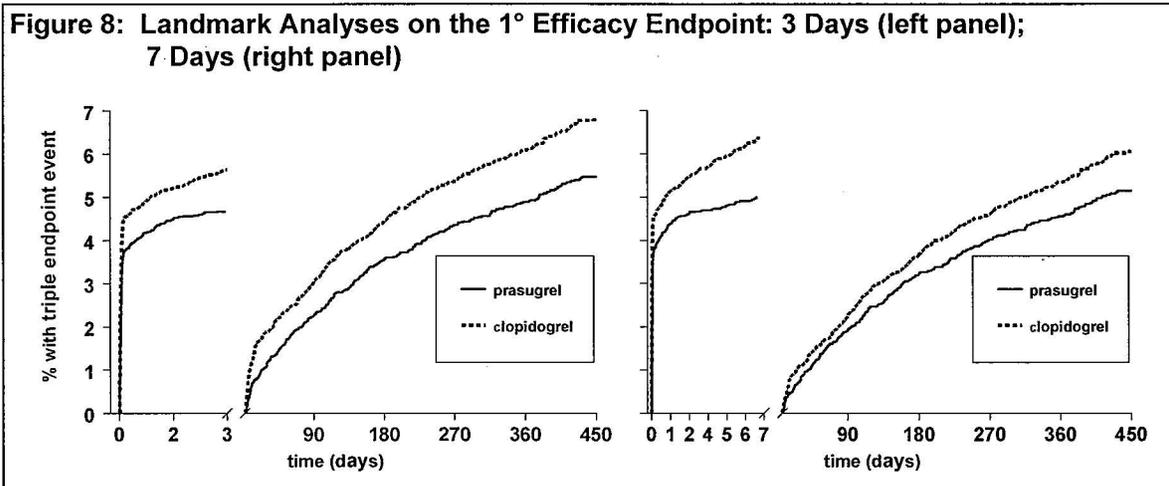
Landmark Analyses:

There is support for the concept that a clopidogrel LD of 600-mg is associated with more rapid inhibition of platelet aggregation than the standard LD of 300-mg (used in TAAL), and OASIS7 is being conducted to examine this hypothesis in a randomized controlled trial (ClinicalTrials.gov Identifier: NCT00335452). Thus, some have argued that in TAAL, an inadequate clopidogrel LD provided prasugrel with an advantage during the initial hours of therapy, during the interval when patients were subjected to PCI and at risk of peri-procedural myocardial infarctions.¹

This reviewer conducted landmark analyses, in essence time-to-event analyses before and after cut-points of 3 days (Figure 8, left panel) and 7 days (Figure 8, right panel). These consider event-free survival beginning at points in time beyond which the adequacy of the LD would be

¹ *N Engl J Med.* 2008;358:1298-9

expected to influence events, and beyond which peri-procedural events are likely to occur. The landmark analyses have limitations in that the original randomization is not preserved; therefore, the analyses are somewhat observational in nature. The point can also be argued that events occurring at the beginning of the study might influence events later on; however, it is also true that subjects at the highest risk experience events early in the study. As such, the clopidogrel group is “de-enriched” through removal of subjects at highest risk. Although interpretation is not straightforward, the analyses show a treatment effect of prasugrel from both Day 3 and Day 7 forward, and are consistent with the concept that the superiority of prasugrel is not merely a function of the LD, or simply a reduction in early peri-procedural events.



Multiplicity:

Given the nature and interrelations of the indications supported by the study, multiplicity is a complex issue. Although the statistical reviewer noted that a number of reviewers had comments on multiplicity in their reviews of the study protocol, she opined that the pre-specified strategy for dealing with multiplicity was reasonable. She noted also that adjustment of multiplicity is a moot issue, given the very small nominal p-values for the 1° composite endpoint and the pre-specified 2° endpoints.

Site-Reported Endpoint Events:

Dr. Marciniak performed a number of exploratory analyses to assess the robustness of the 1° efficacy endpoints. In light of his concerns regarding neoplasia (see section 7.4.15), the strength of the efficacy findings are particularly important to the risk-benefit profile.

In TAAL, events could be referred to the CEC by site, or triggered by a review of laboratory values. Dr. Marciniak noted (page 28 of his review): “The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events, as shown in Table 19.” (reproduced here):

Table 19: CEC MI Adjudications by Type of Referring Event

referring event	clopidogrel		prasugrel	
	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

*PPMI = peri-procedural myocardial infarction

He concluded that site reported MI's appear to be better predictors of death than the CEC-adjudicated MI's, and noted, therefore, that site-reported events are clinically more important than those that are not site-reported. He went on to assess the efficacy endpoint (death, non-fatal MI, non-fatal stroke) in the UA/NSTEMI, STEMI, and overall ACS populations, counting only site-reported events. (Site-reported events represented approximately 60-70% of the total events; therefore, some 30-40% of events were not included in his sensitivity analyses.) With omission of these events, results were not statistically significant. He also noted that there is no substantial treatment effect after 30 days, when considering site-reported events. This is essentially in line with the standard analysis, where the treatment effect waned after 18 days (in STEMI subjects), and waned more gradually in STEMI subjects (Figure 7). Dr. Marciniak has also emphasized that the numbers of events decrease greatly after 30 days. Thus, if there is ongoing risk, it must be considered against a background of diminishing benefit.

This reviewer strongly agrees with the latter point, that is, that the treatment effect is front-loaded. In the opinion of this reviewer, however, these sensitivity analyses do not raise important questions regarding the validity or persuasiveness of the results. My rationale can be summarized as follows:

- 1) Based on Table 19, above, there was essentially no evidence of differential reporting or biased adjudication for the two treatment groups.
- 2) "Enzyme leaks" are widely believed to be of clinical importance. TAAL was designed with the knowledge that many non-fatal myocardial infarctions would be asymptomatic, manifested only as "chemical MIs" or "enzyme leaks." However, because these "events" are believed to have clinical significance,² the trial was designed in such a way as to attempt to ensure that they would be detected and included in efficacy analyses.
- 3) The Division prospectively agreed with the protocol design, to ensure that these events would be counted.

In some clinical trials, it can be important to assess the adjudication of events by a central committee. This is particularly true in studies where there is the potential for unblinding of subjects or investigators (e.g., because of side effects, changes in laboratory values, injection site reactions, etc.), and ascertainment bias is suspected or possible. In such cases, a disparity between treatment groups in terms of the percentages of events adjudicated as positive (versus negative) might suggest that bias was operational. In TAAL, adjudication seems less critical, considering that unblinding would be unlikely, and given that strict criteria were used to analyze laboratory data. (Although these criteria were revised at one point during the study, there is no reason to suspect a differential effect by treatment group.)

² *Eur Heart J.* 2004;25:313-21