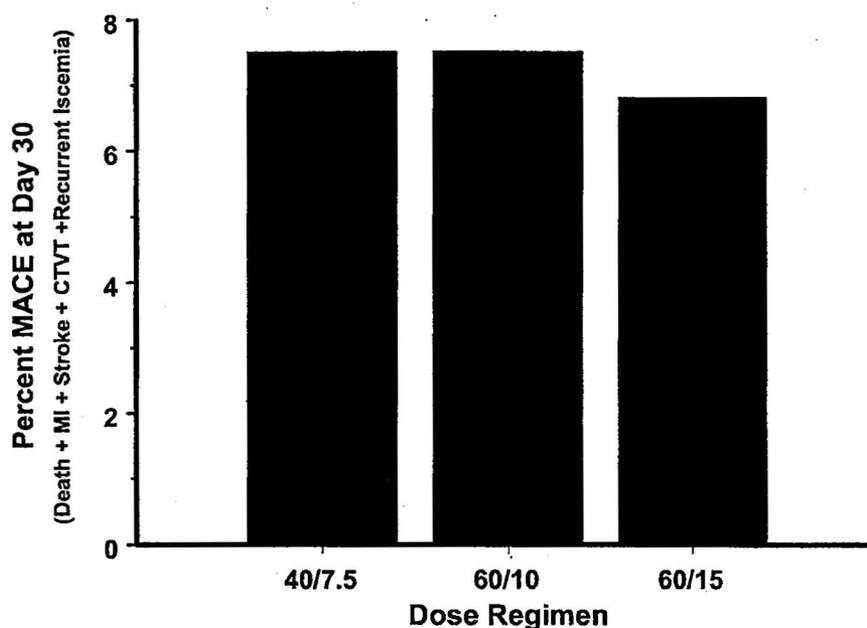


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dose-response analysis could not be performed. However, in a double blind, randomized dose-ranging trial in patients undergoing PCI (Study TAAH), no consistent relationship between the dose of prasugrel and the clinical outcome (major adverse cardiovascular event [MACE] at 30-day visit) was observed as shown in **Figure 2**. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small (N=200 for 40/7.5 and 60/10 groups and N=251 for 60/15 group).

Figure 2: No relationship between dose and major cardiovascular events (MACE - Death+MI+Stroke+Clinical Target Vessel Thrombosis (CTVT) +Recurrent Ischemia at 30-day visit)



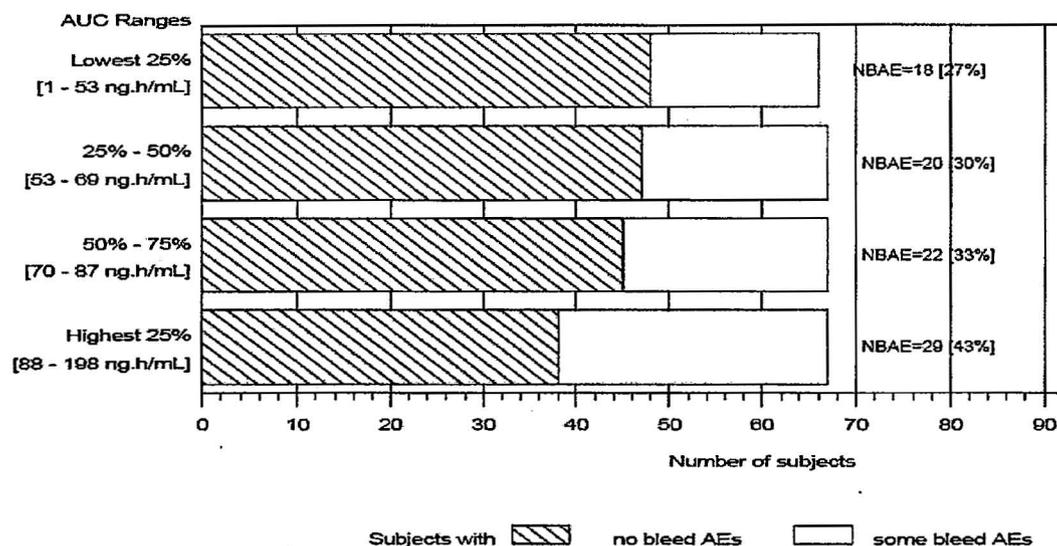
2) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies (TAAS, TAAZ, TABS, TABV and TACG) found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites as shown in **Figure 3** below.

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Figure 3: Increase in the active metabolite exposures trends to increase in number of bleeding adverse events (NBAE).

(Source: Figure APP.2.7.4.4 of sponsor report summary-clin-safe-app)



In the phase 1b study TAAD, in subjects with stable atherosclerosis, the rate of epistaxis was higher in subjects treated with prasugrel 15-mg MD (5%) than in subjects treated with prasugrel MD of 10 mg (1%), 7.5 mg (1%) or 5 mg (1%).

In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding.

All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

3) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?

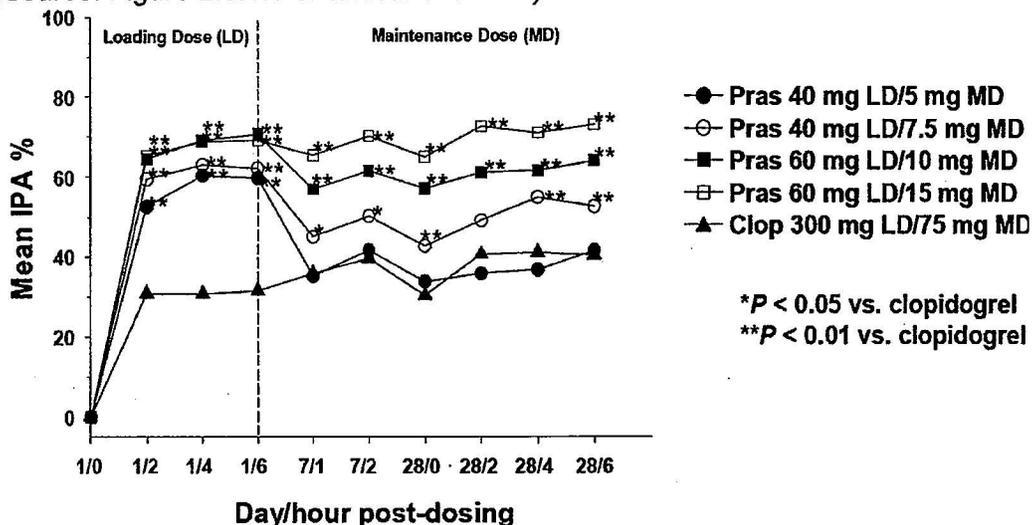
Dose selection for the pivotal trial was based primarily on the effect of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding compared to clopidogrel in subjects with stable atherosclerosis.

In Study TAAD, 4 prasugrel LD/MD regimens were compared with the approved clopidogrel LD/MD regimen. As seen in Figure 4, both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA to 20 μ M ADP from 2 to 6 hours after administration than the 300-mg LD of clopidogrel.

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Figure 4: Prasugrel LD of 60 mg achieves highest IPA. Maintenance doses of 10 mg and 15 mg achieve significantly greater IPA compared to clopidogrel MD of 75 mg.

(Source: Figure 2.5.1.1 of clinical overview)



The 60-mg prasugrel LD consistently achieved the highest level of platelet inhibition. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD. However, the 15-mg MD of prasugrel was associated with higher bleeding adverse events (AEs) hence 10-mg prasugrel MD was selected. This effect of increased trend for bleeding with 15-mg prasugrel MD compared to 10-mg prasugrel MD was also observed in Study TAAH. Further, 10-mg prasugrel MD had 0% PD responders (IPA <20% to 20 μ M ADP) compared to about 20% with 7.5-mg prasugrel MD.

Hence, the dose regimen of prasugrel is a single 60-mg loading dose (LD), followed by a 10-mg once-daily maintenance dose (MD) was selected to be studied in the registration trial TAAL.

However, given the lack of consistent relationship between the inhibition of platelet aggregation and the risk for cardiovascular events, it is not known whether a mean 10% increased effect (LD prasugrel 60 mg Vs 40 mg) on platelet inhibition would translate into a meaningful incremental reduction of cardiovascular risk. Hence it is not known whether a lower dose would have provided similar benefit with decreased risk for bleeding. The current submission does not have enough data to explore the value of lower doses.

4) Should the maintenance dose be reduced to 5 mg QD in patients with body weight below 60 Kg?

Relationship between body weight and efficacy

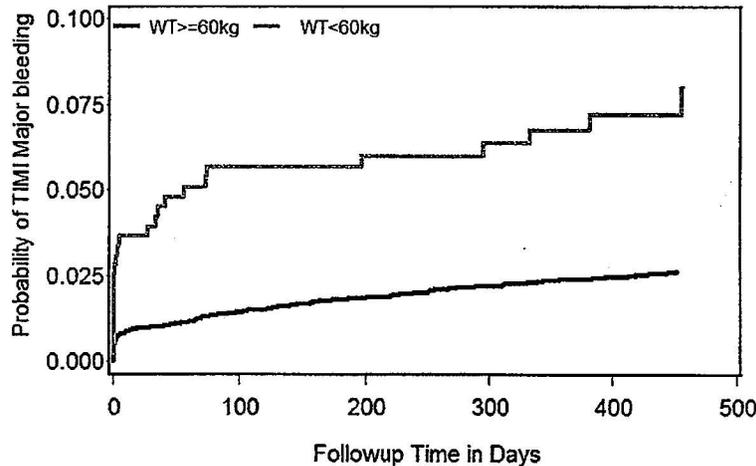
Exploratory univariate Cox model showed inconsistent results for the impact of bodyweight on efficacy depending on whether it is used as a

continuous or categorical variable. Further, multivariate analysis did not reveal body weight as a significant predictor of risk for efficacy event in multivariate analyses.

Relationship between body weight and TIMI major bleeding

The risk for TIMI major bleeding with prasugrel was found to be higher in lower body weight group as shown in the Kaplan-Meier plot (Figure 5). Univariate Cox regression showed that the relative risk for TIMI major bleeding on prasugrel for patients with body weight less than 60 Kg was 4 fold higher (HR: 3.051. (2.013 – 4.623), $p < 0.0001$) compared to patients with higher body weight. Body weight was retained as the significant predictor of TIMI major bleeding risk in multivariate analyses too (HR: 2.826; $p < 0.0001$). Similar relationship was observed for the NCABG TIMI major bleeding.

Figure 5: Risk for TIMI Major bleeding is higher in patients with body weight less than 60 Kg.



Relationship between exposure and bleeding

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies (TAAS, TAAZ, TABS, TABV and TACG) found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites.

In the phase 1b study TAAD, in subjects with stable atherosclerosis, the rate of epistaxis was higher in subjects treated with prasugrel 15-mg MD (5%) than in subjects treated with prasugrel MD of 10 mg (1%), 7.5 mg (1%) or 5 mg (1%).

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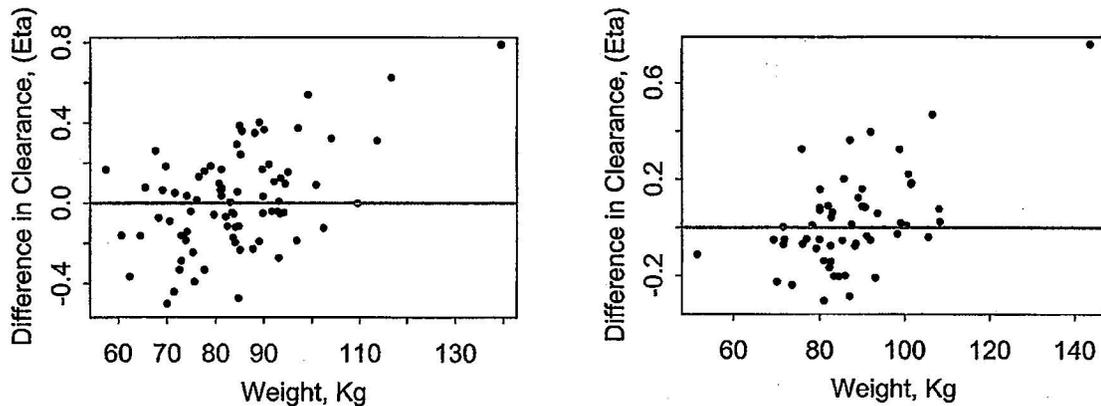
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All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

Relationship between body weight and exposure

Population pharmacokinetic analyses of studies TAAD and TABR reveal that the clearance of the active metabolite R-138727 increases with increase in the body weight as shown in Figure 6. This indicates a decrease in exposures with increase in body weight.

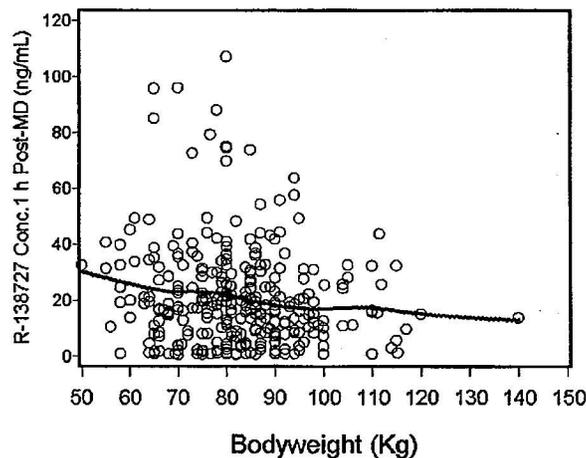
Figure 6: Clearance of R-138727 increases with increase in body weight (Left: Study TAAD; Right: Study TABR).



This decreased exposure with increase in bodyweight is also evident in the pivotal trial (Study TAAL) as shown in the Figure 7.

Figure 7: Decreased Exposures of R-138727 with increased body weight in Study TAAL.

(Circles represent plasma concentrations 0.75-1.25 h post MD; Blue line is a smooth trend line)



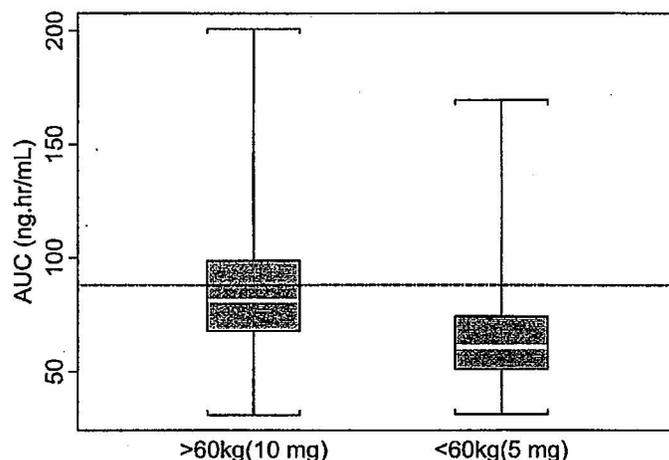
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Simulation of R-138727 exposure (model based AUC for the maintenance dose) show that the proposed dose adjustment of 5 mg MD by the sponsor is able to shift the exposure of majority of subjects with body weight less than 60 Kg from the upper quartile to lower quartile of those seen in patients with body weight greater than 60 Kg.

Figure 8: Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight < 60kg will result in exposures predominantly corresponding to lower two quartiles of those expected with 10 mg MD in patients with body weight >60 kg.

(The red dashed line represent the concentration range beyond which the bleeding related adverse events were highest from Figure 3)

(CL = $123 \times (WT/85)^{0.798}$; Between-subject variability (%CV) = 24% - Obtained from Reviewer's POPPK analysis of TABR for Simulation)



5) Should the maintenance dose be reduced to 5 mg QD in patients with age \geq 75 years?

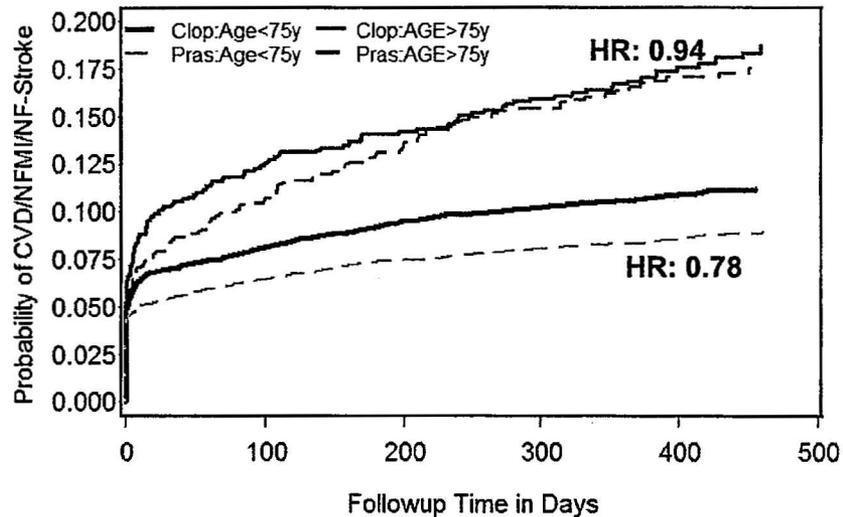
Relationship between age and efficacy

Age was found to be a significant predictor of the CVD/Non-fatal MI/Non-fatal stroke (HR: 1.031, $p < 0.0001$). When age was tested as a categorical covariate, the risk for CVD/Non-fatal MI/Non-fatal Stroke on prasugrel for patients with age greater than 75 years was 98% higher (HR: 1.982 (1.647 – 2.386), $p < 0.0001$) compared to patients with age less than 75 years. The Kaplan-Meier curve depicting the effect of age is shown in **Figure 9**. This effect of age was also evident in the multivariate Cox proportional model (HR: 1.98; $p < 0.0001$). Similar

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relationship was observed for the clopidogrel treatment arm. Further prasugrel was shown to be better (numerically but not statistically significant) than clopidogrel in patients with age ≥ 75 years.

Figure 9: Risk for CVD/Non-fatal MI/ Non-fatal Stroke is high in patients above 75 years of age compared to patients below 75 years.
(The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)



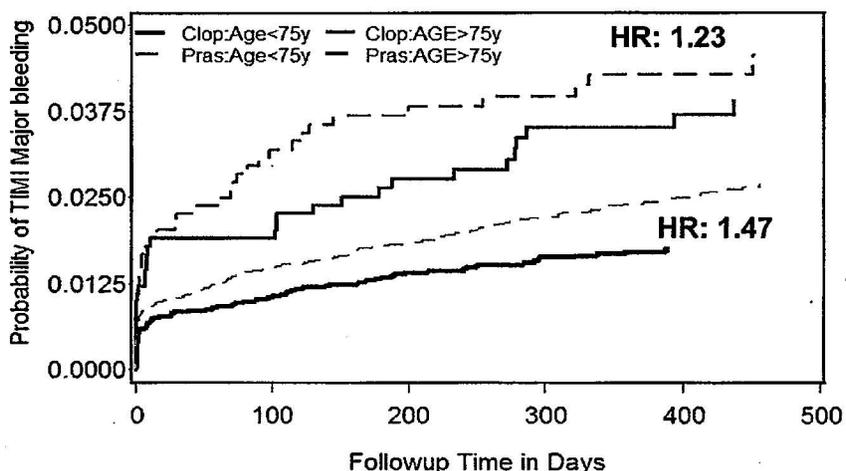
Relationship between age and TIMI major bleeding

Univariate analysis with age as a continuous measure was found to be a significant predictor of TIMI Major bleeding risk with 3.2% increase in risk per year (HR:1.032; $p < 0.0001$). When tested as categorical covariate (cutoff 75 years) the relative risk for TIMI major bleeding with prasugrel was significant (HR: 1.818 (1.265 – 2.612); $p = 0.00120$). The Kaplan-Meier curves showing the effect of age on bleeding risk is shown in **Figure 10**. Age was found to be an independent predictor of TIMI major bleeding risk in multivariate analyses too (HR: 1.650; $p = 0.0069$). Similar relationship was observed for the NCABG TIMI major bleeding in a multivariate analysis.

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Figure 10: Risk for TIMI Major bleeding is high in patients above 75 years of age compared to patients below 75 years.

(The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)



Since prasugrel is better (numerically) than clopidogrel with similar risk for bleeding and no appreciable increase in body-weight adjusted exposure of the active metabolite with age, reduction of maintenance dose to 5 mg QD is not justified.

6) What is the impact of early loading dose (6 hours prior to the start of PCI) on the incidence of cardiovascular events?

The range for the time difference between loading dose and start of PCI across the octiles are shown in the table below:

Group	N	Range of Loading Dose Time - PCI Start Time (hrs)	Median (hrs)
1	1667	-234.83 - -0.12	-0.45
2	1703	-0.10 - 0.00	-0.05
3	1616	0.02 - 0.25	0.15
4	1658	0.27 - 0.43	0.35
5	1665	0.45 - 0.62	0.53
6	1773	0.63 - 0.83	0.73
7	1487	0.85 - 1.15	0.96
8	1699	1.17 - 530.00	1.45
<6 h*	231	-234.83 - -6.00	-19.82
>6 h*	13037	-5.90 - 530.00	0.45

* For comparing the range of differences in the loading dose time and the start of PCI in patients who were early pre-treated (<6 hrs Vs >6 hrs)

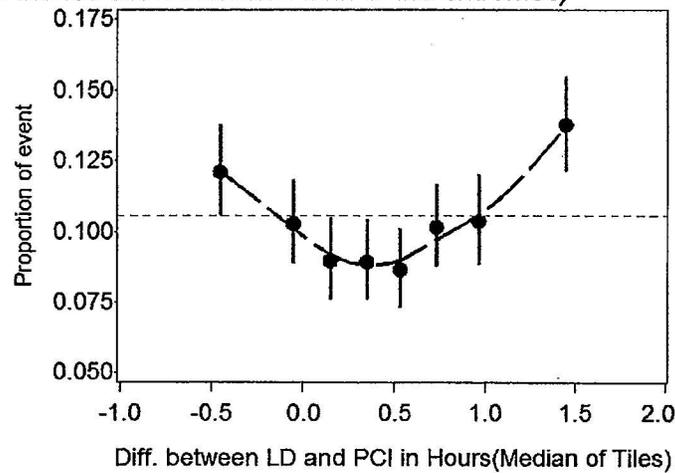
Irrespective of the treatment arms, lowest incidence of CVD/Non-fatal MI/Non-fatal Stroke was observed when the loading dose was administered at

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the start of PCI or within 30 minutes of the start of the procedure as shown in Figure 11.

Figure 11: Maximum effectiveness is achieved when the loading dose is administered at the start or within 30 min of start of PCI

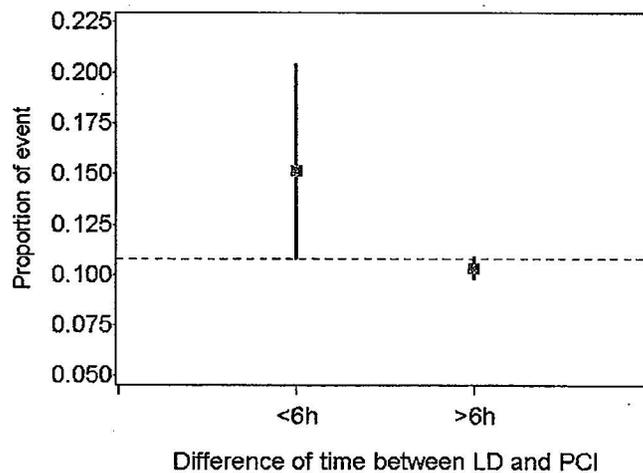
(Red dots – represent proportion of events corresponding to the midpoints of the octiles; Blue bars – 95% Confidence interval; Black line – Smooth trend line; Green line – is the lowest confidence limit of the extremes)



Further the proportion of events were consistently higher when the time difference between the loading dose and the start of PCI were divided into groups based on whether the patient received the loading dose at least 6 hours or before as shown in the Figure 12.

Figure 12: Pre-treatment with clopidogrel/prasugrel 6 hrs before the start of PCI results in decreased effectiveness compared to no pre-treatment

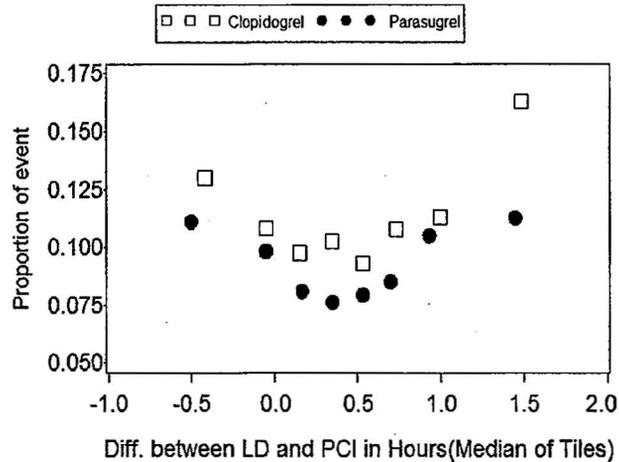
(Orange squares – represent proportion of events; Black bars – 95% Confidence interval)



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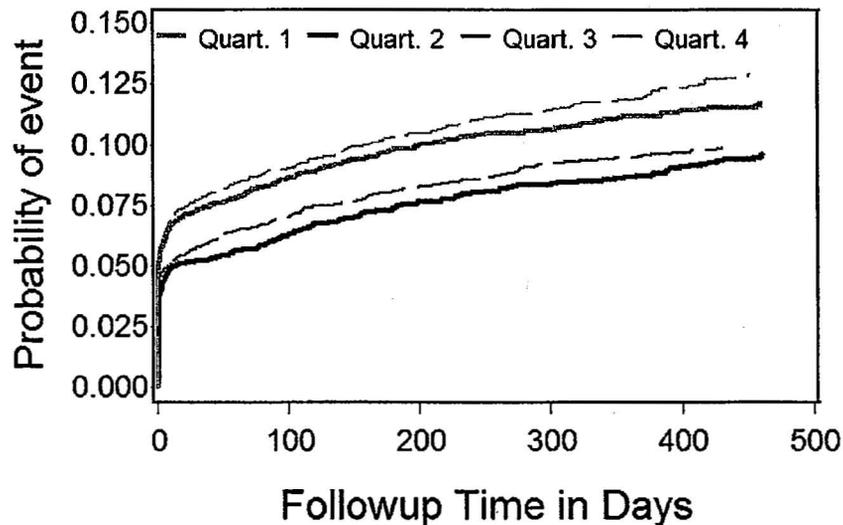
Similar relationship was seen across both the treatment arms as shown in **Figure 13**. However, it can be clearly seen that prasugrel consistently performs better than clopidogrel.

Figure 13: The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel



The value of administering the loading dose at the start of PCI is also evident from the Kaplan-Meier curves across the quartiles of difference between loading dose and start of PCI as shown in **Figure 14**. Similar relationship was also seen when the data was divided into octiles instead of quartiles.

Figure 14: Cumulative event rate of the cardiovascular event is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective.



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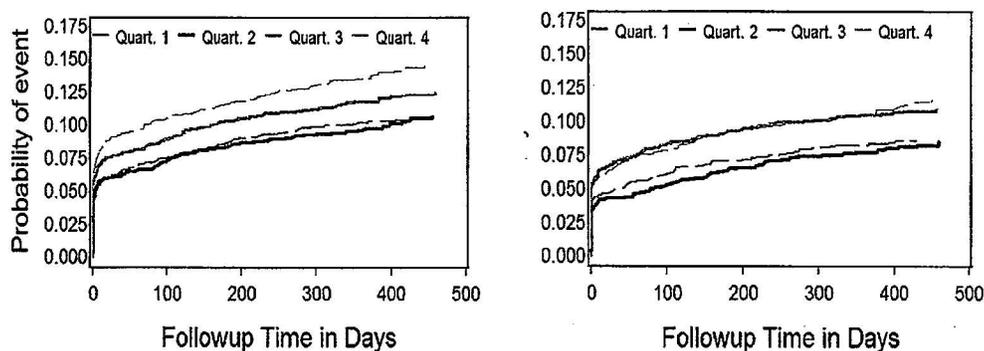
Cox Proportional regression shows that the relative risk for CVD/Non-fatal MI/Non-fatal Stroke is 28% and 24% lower for Quartiles 2 and 3 compared to Quartile 4. The details are presented in the table below:

Quartile	N	Range of Loading Dose Time – PCI Start Time (hrs)	Hazard Ratio (95% Confidence Limit)	p-value
4*	3186	0.85 – 530.13	-	-
1	3370	-234.83 - 0	0.91 (0.79 – 1.05)	0.1858
2	3274	0.02 – 0.43	0.72 (0.62 – 0.84)	<0.0001
3	3438	0.45 – 0.83	0.76 (0.66 – 0.89)	0.0004

* Quartile – 4 was used as reference to compute the relative risk for rest of the quartiles using Proc TPHREG

This relationship was consistent between prasugrel and clopidogrel as shown in Figure 15.

Figure 15: Cumulative event rate of the cardiovascular events across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right).



Exploratory analyses revealed a weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use upto PCI or hospital discharge.

Further, prior CABG was found to be a statistically significant predictor (χ^2 statistic $p < 0.0001$) of the timing of loading dose when a 2x2 contingency table was constructed between prior CABG and the timing of the loading dose (dichotomized by at least 6 hrs before PCI or not) in only those patients who received the loading dose before the start of PCI. After controlling for the prior CABG, no statistically significant association (CMH Statistics: General association $p = 0.1146$) was seen between timing of loading dose (at least 6hrs before PCI or not) and observing the efficacy endpoint. This could likely explain