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Effects of Genetic Variation in Protease Activated Receptor 4 after an Acute Coronary Syndrome: Analysis from the TRACER trial

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Abstract

Variation in platelet response to thrombin may affect the safety and efficacy of PAR antagonism. The Thr120 variant of the common single nucleotide polymorphism (SNP) rs773902 in the protease-activated receptor (PAR) 4 gene is associated with higher platelet aggregation compared to the Ala120 variant. We investigated the relationship between the rs773902 SNP with major bleeding and ischemic events, safety, and efficacy of PAR1 inhibition in 6177 NSTE ACS patients in the TRACER trial. There was a lower rate of GUSTO moderate/severe bleeding in patients with the Thr120 variant. The difference was driven by a lower rate in the smaller homozygous group (recessive model, HR 0.13 [0.02–0.92] p=0.042). No significant differences were observed in the ischemic outcomes. The excess in bleeding observed with PAR1 inhibition was attenuated in patients with the Thr120 variant, but the interactions were not statistically significant. In summary, lower major bleeding rates were observed in the overall TRACER cohort with the hyperreactive PAR4 Thr120 variant. The increase in bleeding with vorapaxar was attenuated with the Thr120 variant, but we could not demonstrate an interaction with PAR1 inhibition. These findings warrant further exploration, including those of African ancestry where the A allele (Thr120) frequency is ~65%.

Keywords

platelets; PAR1; PAR4; bleeding; pharmacogenetics

1. Introduction

Patients with acute coronary syndromes are at risk of subsequent coronary events due to platelet thrombosis on a lipid-rich plaque [1, 2]. Antiplatelet therapies are critical to mitigate the risk of atherothrombotic events but at the same time increase the risk of bleeding [2–5]. Bleeding complications are associated with increased mortality, and decision of potency and duration of antiplatelet medications should be based on the assessment of the risk of thrombotic events vs. bleeding complications [6, 7]. There are well-established inter-individual variations in platelet reactivity and platelet response to anti-platelet agents, and we have shown there is a substantial genetic component to both types of variations [8, 9] that may play a role in determining the risk of bleeding and coronary events [10–12]. Many of the challenges with platelet functional assays for assessing bleeding and thrombosis risk that can be overcome with nucleic acid-based assays [13]. Thus, identifying genetic biomarkers of variation in platelet reactivity may help with risk stratification of ischemia and bleeding and improve individual tailoring of antiplatelet medications [14–18].

Thrombin is the most potent platelet activator, acting through the protease-activated receptors (PARs) [19]. The PAR1 receptor has classically been identified as the primary mediator of thrombin effects on human platelets since it is activated at a lower thrombin concentration [20]. However, PAR1 signaling is a rapid-on and rapid-off mechanism, whereas thrombin-induced PAR4 signaling has slower activation kinetics, but a sustained response. PAR4 has an overall greater contribution to platelet calcium flux than PAR1 [21, 22]. We have previously reported that a single nucleotide dimorphism (G/A), rs773902 of the PAR4 gene (*F2RL3*) determines the Ala120 or Thr120 variants and that the Thr120 variant was associated with higher PAR4 induced platelet aggregation in humans [23]. Notably, the allele frequency of rs773902 G or A varies by race, with the G allele more common in whites than blacks (~80% vs. 37%, respectively) and the A allele less common in whites than blacks (~20% vs. 63%, respectively) [24]. Another rare SNP, rs2227346 (only seen on the rs773902 A allele in blacks), results in a Phe296Val substitution and the Val 296 variant markedly reduces PAR4 signaling [24]. An increased response to thrombin via PAR4 could favor platelet-mediated hemostasis and thrombosis events, but it is unknown whether either PAR4 variant modifies the risk of bleeding or ischemic events i*n vivo*. In addition, under conditions where PAR1 is nearly fully inhibited, such as with the use of the potent PAR1 antagonist vorapaxar, the residual response of platelets to thrombin is due to PAR4 activation [25]. Therefore, inter-individual variation in platelet PAR4 reactivity could also influence bleeding and thrombotic events in patients treated with PAR1 antagonists, and especially bleeding when two different platelet signaling pathways are inhibited by aspirin or P2Y12 blockade.

Using the platform of the TRACER trial of vorapaxar vs. placebo in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) and the DNA samples collected as part of the trial biorepository, we genotyped participants for the rs773902 and rs2227346 SNPs [26]. The overarching hypothesis of our analysis was that genetically determined variability in PAR4 function would influence the risk of bleeding and thrombotic events among patients who were treated with vorapaxar. In particular, our goals were to test whether rs773902 G or A could mitigate the increased risk of major bleeding observed with vorapaxar and to assess the effect of PAR4 genetic variability in patients following NSTE ACS.

2. Materials and methods

2.1. The TRACER trial

The design and results of the TRACER trial have been reported [26]. In brief, the TRACER trial included 12,944 patients with NSTE ACS and high-risk features within 24h of hospital presentation. Patients were randomized to vorapaxar 40 mg loading dose and 2.5 daily maintenance dose or matching placebo. Patients had to be treated for a minimum of one year and for the entire duration of the study, which was an event-driven trial. The trial was halted 5 months prior to its planned conclusion after a Data Safety Monitoring Board review, which reported an increased risk of intracranial hemorrhage after the enrollment was completed and the minimum number of endpoint events had been reached (median follow up 502 days). In TRACER vorapaxar was associated with a non-significant reduction of the primary

endpoint, a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization and a nominally significant reduction in death from cardiovascular causes, myocardial infarction, stroke. Vorapaxar significantly increased GUSTO moderate or severe bleeding and intracranial hemorrhage.

A TRACER trial biorepository was created which included blood samples for genetic and biomarker analysis. A total of 7,927 consented to the supplemental collection of the genetic sample (blood for DNA and RNA analysis).

2.2. Genotyping

Blood samples from patients who consented to voluntary participation in the genetic substudy were collected in DNA PAXgene tubes (PreAnalytiX, Hombrechtikon, Switzerland) for DNA analysis. Because the additional collection of DNA samples was voluntary and subject to individual country regulations, about 60% of the trial cohort had available DNA for genetic analysis. Samples were genotyped for rs773902 and rs222736 using TaqMan SNP Genotyping Assays (Life Technologies Carlsbad, CA) as previously described [24]. Control DNAs for each allele (that had been sequenced) were included on each plate.

2.3. Statistical Analysis

Based on the prior platelet function studies, we hypothesized that patients with at least one copy of the hyperreactive rs773902 A allele had a decreased rate of major bleeding. We also hypothesized that bleeding liability with the PAR1 antagonist vorapaxar would be lower in presence of the A allele, as the increased PAR4 function would provide a more effective pathway for thrombin-mediated platelet activation through the PAR4. Finally, we hypothesized that patients with at least one copy of the rs773902 A allele would have increased risk of ischemic events and reduced efficacy from vorapaxar. For this analysis patients were classified in 3 groups: *F2RL3* rs773902 AA homozygous (Thr/Thr120); AG heterozygous (Thr/Ala120), GG homozygous (Ala/Ala120)

Similarly, we hypothesized that patients with at least one copy of the rs2227346 G allele (encodes Val296) are at increased risk of bleeding and relatively higher bleeding risk when treated with vorapaxar, compared with placebo.

The main bleeding outcomes for the study were non-CABG related GUSTO Moderate and Severe and intracranial hemorrhages. The main ischemic outcome was the composite of cardiovascular death, myocardial infarction or stroke. The event accrual period for the analysis was from hospital discharge to 24 months.

To describe the relationship between the rs773902 and clinical events and their timing, Kaplan-Meier (KM) rates stratified by genotype were computed for each endpoint and were compared across genotype using the log-rank test. The relationship between the *F2RL3* variant rs773902 genotype and clinical events was assessed by fitting a Cox proportional hazards model for the time-to-first event. The association is characterized by the genotype hazard ratio (HR) and the corresponding 95% confidence interval (CI) and p-value.

TRACER used self-identified race and ethnicity (called “race”). To minimize population confounders, self-identified non-white patients were excluded in the primary analysis. This analysis was repeated modeling the rs773902 genotype under an additive, dominant, and recessive model.

To describe the relationship between rs773902 and rs227346 variants, vorapaxar and clinical event Kaplan-Meier rates were calculated by genotype overall and by treatment arm for each endpoint of interest. Event counts were compared across genotype using the log-rank test. To determine if the relationship between vorapaxar and clinical events differ by rs773902 genotype, an interaction term between genotype and treatment arm was included in the model and tested. The relationship between treatment and outcome was characterized by the vorapaxar vs. placebo HR and the corresponding 95% CI within each genotype and by the interaction p-value.

3. Results

3.1. TRACER PAR4 Genetic Substudy participants

Of the 12944 patients included in the TRACER trial 7927 individual agreed to participate in the Genetic Substudy (Figure 1). Among these, sufficient material for DNA analysis was collected in 6890 subjects. 632 non-white patients were not included. For 81 patients it was not possible to match the sample ID to the main trial database (i.e., genetic data are de-identified and not kept into the main trial database). The final sample size for this PAR4 Genetic Study analysis included 6177 patients, and the baseline characteristics are shown in Table 1. The PAR4 Genetic Study is representative of the entire TRACER study except for the limitation to white subjects in the PAR4 Genetic Study; the demographic variables are similar across all genotypes.

3.2. F2RL3 Genotypes

The rs773902 SNP was successfully genotyped in 99.5% of samples; 31 could not be definitively assigned a genotype. The rs773902 genotypes for the entire cohort showed that 3884 (63.2%) patients were G/G genotype, 1995 (32.4%) were A/G and 267 (4.3%) were A/A genotype. The rare rs2227346 G allele was present in 15 patients (0.2%), all of whom were heterozygous G/T; no homozygous G/G subjects were present in our cohort. Given the small number of patients with the rare rs2227346 G allele, we did not test for associations of this allele with further event rates or interaction with vorapaxar.

3.3. F2RL3 Genotypes and Bleeding Outcomes

In the PAR4 Genetic Study, there was a lower rate of GUSTO moderate or severe bleeding with the presence of the A allele (p=0.053) (Table 2). As shown in Table 3, the association between bleeding and genotype was not statistically significant using the additive genetic model (HR 0.84, 95% CI 0.64 – 1.11) or dominant genetic model (HR 0.93, 95%CI 0.68–1.28). The recessive genetic model showed a significant reduction in the risk of bleeding associated with the allele A (HR 0.13, 95%CI 0.02–0.92), suggesting a bleeding risk reduction with the presence of 2 copies of the hyperactive A allele.

In our analysis cohort, only 22 intracranial hemorrhages were observed by 24 months post-discharge. None of the ICH as observed in the homozygous AA group, while the rate of ICH was 0.4% in the AG and 0.8% in the GG group.

3.4. F2RL3 Genotypes and Ischemic Outcomes

There were no significant differences in the occurrence of cardiovascular death, myocardial infarction or stroke according to the *F2RL3* genotypes (Table 2). Numerical imbalances observed were contrary to the study hypothesis, with lower rates in the AA group. The additive, dominant and recessive models were all non-significant (Table 3).

3.5. Vorapaxar Effect on Bleeding by F2RL3 Genotypes

We next estimated the treatment difference among genotypes. The relative increase in GUSTO moderate or severe bleeding observed with vorapaxar was higher in the GG group, known to have lower platelet PAR4 reactivity (Table 4). Because the number of bleeding events was too small to perform a recessive model analysis, we considered patients with at least one copy of the A allele (i.e., a dominant model). As shown in Table 5, the Hazard Ratio of bleeding with vorapaxar in this group was 1.06 (95% CI 0.64 – 1.78), while in the GG group the HR was 1.45 (95% CI 0.99 – 2.13). The interaction term was not statistically significant.

The number of intracranial hemorrhages was overall low. There were no intracranial hemorrhages in patients with AA genotypes. In patients with AG genotypes, there was a doubled rate of intracranial hemorrhage with vorapaxar v. placebo (0.3% vs. 0.6%). In patients in the GG group there we observed a 7-fold increase in the occurrence of intracranial hemorrhage with vorapaxar compared to placebo (1.4% vs. 0.2%). In the dominant model, among patients with at least one copy of the A allele, the Hazard Ration of intracranial hemorrhage with vorapaxar was 1.50 (95% CI 0.25 – 8.98), while in the GG group the HR was 2.69 (95% CI 0.71– 10.13).

3.6. Vorapaxar Effect on Ischemic Outcomes by F2RL3 Genotypes

A reduction in cardiovascular death, myocardial infarction or stroke with vorapaxar was observed in all groups (Table 2), but there was no significant interaction between genotypes and treatment using the additive, dominant or recessive models.

4. Discussion

Inhibition of the PAR1 thrombin receptor provides benefit in the secondary prevention of ACSs in some settings, but its use has been limited due to concerns of major bleeding. The rationale for the current study was to identify a genetic predictor that could identify patients with a lower bleeding risk in the setting of anti-platelet therapies. To our knowledge this is the first study testing for associations between a common thrombin receptor polymorphism and clinical outcomes in a large, randomized clinic trial of patients with NSTE ACS [26]. Although thrombin receptors have a broad tissue distribution, our hypotheses were based on abundant *in vitro* data using human blood that demonstrated enhanced platelet activation and aggregation from healthy individuals expressing the rs773902 A allele encoding Thr in the

PAR4 thrombin receptor [23, 24, 27]. The most important finding from our work was that the rs773902 AA genotype conferred a significant reduction in GUSTO moderate or severe bleeding. Our findings may have implications for the future development of PAR inhibitors generally, and for PAR4 inhibitors specifically [28, 29].

The major physiologic role for platelets is to maintain hemostasis, and thrombocytopenia and platelet dysfunction are well-established risks for bleeding. Anti-platelet therapy with aspirin and P2Y12 inhibition block secondary feedback pathways of platelet activation and have become standards of care for secondary prevention of ACSs. The development of effective anti-platelet agents that inhibit a third, though primary, activation pathway has the difficult challenge of demonstrating clinical benefit in the face of likely enhanced bleeding with triple anti-platelet therapy. Indeed, this challenge has appeared to be the case with vorapaxar, which inhibits the PAR1 thrombin receptor. Our analyses showed that patients homozygous for the rs773902 A allele had less GUSTO severe/moderate bleeding, which is consistent with a mechanism whereby the hyperactive Thr120 PAR4 isoform promotes normal hemostasis. Smaller numbers of patients met the criteria for TIMI major or minor bleeding, but trends in the same direction were observed (not shown). While we could not demonstrate an interaction between vorapaxar use and rs773902, a significant increase in bleeding was observed in the GG group only. And since most patients in TRACER were using both aspirin and a P2Y12 inhibitor, the enhanced hemostasis with the A allele is also consistent with *in vitro* studies showing platelets from donors expressing the rs773902 A allele are less sensitive to the inhibitory effects of both aspirin and P2Y12 inhibition [27]. Notably, our modeling of the effect of the A alleles showed a significant reduction in bleeding in the whole population only with the recessive model, suggesting that two copies of the A allele may be required to significantly modify the bleeding tendency in TRACER. The additive and dominant model showed a directionally consistent result but were not statistically significant. The Thr for Ala substitution at residue 120 in the 2nd transmembrane domain of PAR4 changes a nonpolar residue to a polar residue, which could favor PAR4 homodimerization [30] and enhanced signaling in the homozygous state.

We did not observe an association between rs773902 A and ischemic events. This observation was not entirely unexpected since, unlike hemostasis where platelets play a central and critical role, atherothrombosis is a complex and multifactorial disease, involving other pathophysiologic mechanisms such as elevated blood pressure, altered glucose or lipid metabolism, endothelial dysfunction, etc. Our hypotheses were based on *in vitro platelet* studies, but PARs have other platelet-independent functions, and are involved in response to injury and inflammation and their proteases may signal differently in other cells. There are no data on the functional effect of the PAR4 variant in non-platelet tissues [31, 32], and perhaps the lack of an association of rs773902 with ischemic outcomes in TRACER is related to unknown effects of the PAR4 variants to the vasculature [33, 34]. Moreover, atherothrombosis is a complex and multifactorial disease and not determined by single gene, therefore a single genetic variant may have a relatively minor effect on the onset and progression of the disease.

This study had several limitations. First, this was a selected cohort of patients randomized in a clinical trial after suffering an NSTE ACS. Because patients during the acute period were

treated with multiple antithrombotic therapies and had undergone invasive procedures, we decided to start the accrual period for the analyses at the time of discharge from the index hospitalization. While this selection was arbitrary, it is a standard time point for post-ACS studies, and we believe that this selection allowed an adequate assessment of the effect of the genotypes in our cohort. Finally, the prevalence of homozygous AA in our cohort was small, accounting for slightly over 4% of the populations. This low prevalence means that, if in fact, a significant effect on bleeding requires homozygous status, our study may have been underpowered. At the same time, although biologically plausible and in line with the study hypothesis, a chance finding is also possible given the small group size.

The findings of this analysis are limited to an NSTE ACS cohort of patients who were discharged from an acute event. Despite these limitations, our analysis is the first assessment in a large cohort of the association between PAR4 genotypes and bleeding and the potential impact of PAR4 genotypes on safety and efficacy of concomitant PAR1 inhibition.

We conclude that the SNP rs7773902 of PAR4 gene may influence the bleeding risk and bleeding liability with vorapaxar after an NSTE ACS, especially in allele A homozygotes. Further studies are needed to confirm this finding. Our findings may be of particular relevance for patients of African descent ~40% of whom are homozygous AA for rs7773902, while the TRACER population only included 2.5% of African American [24]. In data not shown, when blacks were included in our analyses, none of the results materially changed, with only a minimal change in the rate of GUSTO moderate or severe bleeding with the presence of the A allele (p=0.035). Our study should serve as basis for future studies that include sufficient numbers of African Americans or patients with other cardiovascular conditions, such as those with chronic stable disease. It will also be important to consider PAR4 functional variants in those on-going trials of PAR4 antagonists in platelet-mediated cardiovascular diseases [28, 29] or other conditions where PAR4 or race may play a pathophysiologic role.

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Abbreviations

PAR	protease activated receptor
NSTE ACS	non-ST-segment elevation acute coronary syndromes
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction

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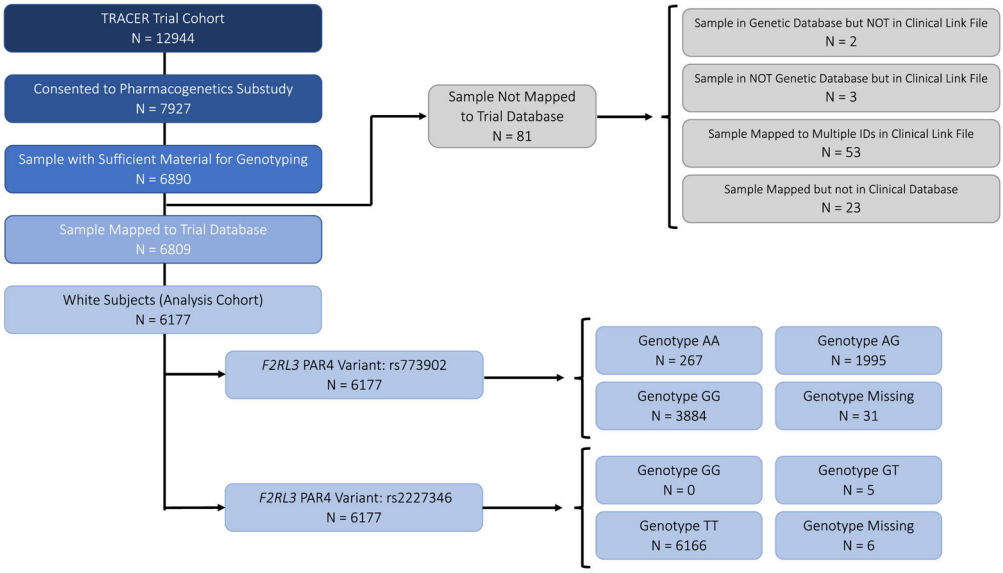

Figure 1.
Consort Diagram

Table 1

Baseline characteristics by study cohort and by genotype of the *F2RL3* variant rs773902

			By Genotype of the *F2RL3* Variant rs773902		
	TRACER Trial Cohort	**Analysis Cohort**	**A/A**	**A/G**	**G/G**
Cohort Size	12944	6117	267	1995	3884
Age	64.0 (58.0 – 72.0)	64.0 (58.0 – 72.0)	64.0 (58.0 – 72.0)	64.0 (58.0 – 72.0)	64.0 (58.0 – 72.0)
Male	9312 (71.9%)	4414 (71.5%)	190 (71.2%)	1431 (71.7%)	2772 (71.4%)
Race					
White	11039 (85.3%)	6177 (100.0%)	267 (100.0%)	1995 (100.0%)	3884 (100.0%)
Asian	1056 (8.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	814 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg)	80.0 (70.0 – 92.4)	83.0 (73.0 – 95.0)	83.9 (74.4 – 95.0)	82.5 (72.0 – 95.0)	83.0 (73.0 – 95.0)
Hypertension	9128 (70.5%)	4349 (70.4%)	180 (67.4%)	1427 (71.5%)	2721 (70.1%)
Hyperlipidemia	8062 (62.3%)	3901 (63.2%)	162 (60.7%)	1239 (62.1%)	2476 (63.7%)
Diabetes	4070 (31.5%)	1813 (29.4%)	92 (34.5%)	589 (29.5%)	1119 (28.8%)
Current Tobacco Use	3536 (27.3%)	1666 (27.0%)	74 (27.7%)	562 (28.2%)	1026 (26.4%)
History of MI	3791 (29.3%)	1814 (29.4%)	80 (30.0%)	576 (28.9%)	1152 (29.7%)
History of PCI	3090 (23.9%)	1461 (23.7%)	55 (20.6%)	450 (22.6%)	948 (24.4%)
History of CABG	1543 (11.9%)	758 (12.3%)	41 (15.4%)	245 (12.3%)	468 (12.0%)
History of Stroke	553 (4.3%)	236 (3.8%)	12 (4.5%)	79 (4.0%)	142 (3.7%)
Region					
Asia/Pacific	1366 (10.6%)	258 (4.2%)	12 (4.5%)	81 (4.1%)	164 (4.2%)
Eastern EU	1487 (11.5%)	1081 (17.5%)	42 (15.7%)	349 (17.5%)	688 (17.7%)
North America	3404 (26.3%)	1837 (29.7%)	76 (28.5%)	589 (29.5%)	1153 (29.7%)
South America	848 (6.6%)	119 (1.9%)	4 (1.5%)	45 (2.3%)	70 (1.8%)
Western EU	5839 (45.1%)	2882 (46.7%)	133 (49.8%)	931 (46.7%)	1809 (46.6%)
Clopidogrel at Randomization	11608 (89.7%)	5562 (90.0%)	238 (89.1%)	1784 (89.4%)	3510 (90.4%)
MI at enrollment	12050 (93.7%)	5778 (94.2%)	252 (95.5%)	1859 (93.8%)	3637 (94.3%)

Table 2

Event rates by rs773902 genotypes, overall and by treatment arm

	Overall				Vorapaxar Arm				Placebo Arm			
Genotype	**A/A**	**A/G**	**G/G**	**P**	**A/A**	**A/G**	**G/G**	**P**	**A/A**	**A/G**	**G/G**	**P**
Cohort Size	267	1995	3884	---	138	1002	1941	---	129	993	1943	---
Bleeding												
Gusto Severe/Moderate	1 (0.4%)	57 (3.8%)	108 (3.8%)	0.053	0 (0.0%)	30 (3.8%)	64 (4.6%)	0.092	1 (0.9%)	27 (3.7%)	44 (2.9%)	0.357
Intracranial Hemorrhage	0 (0.0%)	6 (0.4%)	16 (0.8%)	0.483	0 (0.0%)	4 (0.6%)	13 (1.4%)	0.440	0 (0.0%)	2 (0.3%)	3 (0.2%)	0.856
Ischemic Outcomes												
CV Death/MI/Stroke	14 (6.1%)	179 (11.5%)	328 (10.9%)	0.102	5 (3.7%)	76 (9.5%)	153 (10.1%)	0.190	9 (8.6%)	103 (13.4%)	175 (11.8%)	0.303
CV Death	4 (1.5%)	47 (3.2%)	77 (2.6%)	0.475	2 (1.5%)	22 (3.0%)	37 (2.5%)	0.743	2 (1.6%)	25 (3.3%)	40 (2.7%)	0.639
MI	11 (4.7%)	130 (8.1%)	245 (8.2%)	0.280	4 (3.0%)	54 (6.7%)	109 (7.1%)	0.391	7 (6.6%)	76 (9.5%)	136 (9.3%)	0.575
Stroke	1 (0.7%)	27 (2.3%)	38 (1.4%)	0.201	0 (0.0%)	9 (1.2%)	20 (1.5%)	0.476	1 (1.4%)	18 (3.3%)	18 (1.3%)	0.103

Table 3

Models of effect of rs773902 genotypes on bleeding and ischemic outcomes in the analysis cohort

	Additive Genetic Model		Dominant Genetic Model		Recessive Genetic Model	
Endpoint	**HR (95% CI)♦**	**P-Value**	**HR (95% CI) ♦**	**P-Value**	**HR (95% CI) ♦**	**P-Value**
Bleeding						
Gusto Severe/Moderate	0.84 (0.64 – 1.11)	0.221	0.93 (0.68 – 1.28)	0.666	0.13 (0.02 – 0.92)	0.042
Intracranial Hemorrhage*	0.61 (0.26 – 1.45)	0.265	0.65 (0.25 – 1.66)	0.367	---	---
Efficacy						
CV Death/MI/Stroke	0.96 (0.82 – 1.11)	0.565	1.02 (0.85 – 1.21)	0.867	0.59 (0.34 – 1.00)	0.049
CV Death	1.06 (0.79 – 1.42)	0.717	1.14 (0.80 – 1.63)	0.459	0.70 (0.26 – 1.88)	0.475
MI	0.95 (0.79 – 1.13)	0.548	0.99 (0.81 – 1.22)	0.956	0.63 (0.34 – 1.14)	0.126
Stroke	1.09 (0.72 – 1.64)	0.689	1.27 (0.78 – 2.08)	0.330	0.33 (0.05 – 2.37)	0.269

Hazard Ratios show risk associated with allele A

Table 4

Safety and Efficacy of Vorapaxar by rs773902

Genotype	A/A			A/G			G/G			
	Vorapaxar	Placebo	HR (95% CI)	Vorapaxar	Placebo	HR (95% CI)	Vorapaxar	Placebo	HR (95% CI)	P-Int
Cohort Size	138	129		1002	993		1941	1943		
Bleeding										
Gusto Severe/Moderate	0 (0.0%)	1 (0.9%)	NA	30 (3.8%)	27 (3.7%)	NA	64 (4.6%)	44 (2.9%)	NA	0.678
Intracranial Hemorrhage	0 (0.0%)	0 (0.0%)	NA	4 (0.6%)	2 (0.3%)	NA	13 (1.4%)	3 (0.2%)	NA	NA
Ischemic Outcomes										
CV Death/MI/Stroke	5 (3.7%)	7 (5.7%)	0.60 (0.36 – 1.01)	76 (9.5%)	9 (8.6%)	0.72 (0.55 – 0.92)	153 (10.1%)	103 (13.4%)	0.85 (0.69 – 1.05)	0.225
CV Death	2 (1.5%)	2 (1.6%)	0.87 (0.32 – 2.34)	22 (3.0%)	2 (1.6%)	0.89 (0.55 – 1.44)	37 (2.5%)	25 (3.3%)	0.91 (0.59 – 1.40)	0.932
MI	4 (3.0%)	6 (5.0%)	0.60 (0.33 –1.11)	54 (6.7%)	7 (6.6%)	0.69 (0.51 – 0.93)	109 (7.1%)	76 (9.5%)	0.78 (0.61 – 1.00)	0.469
Stroke	0 (0.0%)	0 (0.0%)	NA	9 (1.2%)	1 (1.4%)	NA	20 (1.5%)	18 (3.3%)	NA	NA

HR comparing vorapaxar vs. placebo in each of genotypes. HR and P-value not calculated when one of the group had 0 events. P-int: P-value for interaction.

Table 5

Hazard of bleeding and ischemic event with vorapaxar by dominant genotype

	HR (95% CI) Vorapaxar vs. Placebo		
Genotype	**A/A and A/G**	**G/G**	**P-Int**
Bleeding			
Gusto Severe/Moderate	1.06 (0.64 – 1.78))	1.45 (0.99 – 2.13)	0.342
Intracranial	2.02 (0.37 – 11.04)	4.39 (1.25 –15.40)	0.472
Hemorrhage			
Ischemic Outcomes			
CV Death/MI/Stroke	0.70 (0.53 – 0.94)	0.85 (0.69 – 1.06)	0.292
CV Death	0.88 (0.51 – 1.53)	0.92 (0.59 – 1.43)	0.917
MI	0.68 (0.49 – 0.95)	0.78 (0.61 – 1.01)	0.342
Stroke	0.47 (0.21 – 1.03)	1.10 (0.58 – 2.08)	0.100

P-int: P-value for interaction.