Effect of PON1 Q192R Genetic Polymorphism on Clopidogrel Efficacy and Cardiovascular Events in the CURE and ACTIVE Trials

Running title: Pare et al.; Effect of PON1 Q192R polymorphism on clopidogrel efficacy

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Abstract:

**Background** - A recent report suggested that carriers of the Q allele of the PON1 Q192R polymorphism had decreased biotransformation of clopidogrel into its active metabolite and decreased efficacy of clopidogrel in preventing cardiovascular events. Furthermore, PON1 has been reported to have a central role in the antioxidant function of HDL and the Q192R polymorphism has been previously associated with cardiovascular risk in patients not treated with clopidogrel.

**Methods and Results** - 5,059 patients from the CURE randomized trial that demonstrated benefits of clopidogrel versus placebo in preventing cardiovascular events in acute coronary syndromes were genotyped for the PON1 Q192R polymorphism. Clopidogrel compared to placebo significantly reduced the first primary efficacy outcome, irrespective of PON1 Q192R genotype (P=0.07 for heterogeneity). No association was observed between the Q192R polymorphism and cardiovascular events in the overall sample (HR= 1.09 per allele; 95%CI 0.95–1.24; p=0.23). However, an association was observed between the Q allele and increased cardiovascular events in the placebo group (HR=1.23 per allele; 95%CI 1.03-1.47; p=0.03), but not in the clopidogrel group (HR=0.93 per allele; 95%CI 0.76-1.13; p=0.46). In 1,156 atrial fibrillation patients from the ACTIVE trial, there was no evidence of interaction between PON1 genotype and clopidogrel for any outcome or for an association between genotype and cardiovascular events.

**Conclusions** - In conclusion, our study shows that PON1 Q192R genotype does not modify the efficacy and safety of clopidogrel in ACS patients. Further studies are needed to confirm or refute the association of the Q allele with adverse cardiovascular events independently of clopidogrel in secondary prevention patients.

**Key words**: antiplatelet therapy, atrial fibrillation, clopidogrel, paraoxonase 1 gene, pharmacogenetics
Introduction

Clopidogrel when added to aspirin reduces major vascular events in patients with acute coronary syndromes (ACS). Clopidogrel is a prodrug that requires biotransformation into the active metabolite in order to inhibit the platelet P2Y12 receptor. Differences in the extent of clopidogrel biotransformation are believed to account for inter-individual variability in platelet response to clopidogrel. Most of the variability appears to be genetically determined but common cytochrome P450 2C19 polymorphisms account for only a minority of this variability. The PON1 enzyme has been reported to play a crucial role in clopidogrel biotransformation and a common non-synonymous genetic variant Q192R has recently been associated with decreased conversion of clopidogrel to its active metabolite, implying that the benefits of clopidogrel may be attenuated in affected patients. Specifically, carriers of the Q allele were found to have a significantly higher risk of stent thrombosis following stent percutaneous coronary intervention (PCI), with an odds ratio of 3.6 (95%CI 1.6–7.9; P = 0.003) for QQ homozygous individuals as compared to individuals with either the RR or QR genotype.

The PON1 gene encodes an esterase that hydrolyzes endogenous and exogenous esters, most notably organophosphate pesticides and nerve gas. PON1 is also believed to enhance the antioxidant properties of high-density lipoproteins (HDL) by breaking down biologically active oxidized phospholipids and oxidized cholesteryl esters, thereby preventing oxidation of low-density lipoproteins (LDL). Because of the importance of oxidized LDL in the initiation and progression of atherosclerotic plaque, PON1 has also been proposed as an atherosclerotic susceptibility gene. The PON1 Q192R polymorphism results in the substitution of glutamine (Q) for arginine (R) at position 192 and the Q allele has been associated with lower enzymatic
activity\textsuperscript{11,12} and an increased risk of cardiovascular disease independently of clopidogrel action, although this remains controversial\textsuperscript{13-15}.

We hypothesized that the PON1 polymorphism Q192R is associated with both a decreased efficacy of clopidogrel and an increased risk of cardiovascular (CV) events. To test this hypothesis, we investigated the efficacy and safety of clopidogrel among carriers of the Q192R polymorphism compared with non-carriers and the association between genotype and risk of cardiovascular disease in the placebo-controlled Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial that enrolled patients with ACS; and the placebo controlled Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A) trial that enrolled patients with atrial fibrillation (AF).

Methods

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Study

The design and results of the CURE trial have been described previously\textsuperscript{16,17}. In brief, CURE was a randomized, double-blind, placebo-controlled trial comparing clopidogrel (75 mg per day) with placebo on a background of aspirin (75-325 mg per day) in 12,562 patients with ACS without ST-segment elevation. For the current analyses we used the same primary efficacy and safety outcomes as in the CURE trial\textsuperscript{16}. The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or stroke, and the second primary outcome was the composite of the first primary outcome, recurrent ischemia, or hospitalization for unstable angina. The main safety outcome was major bleeding. Results are presented only for individuals of European and Latin American ancestry. Individuals from other
ethnic groups were excluded because of small numbers (N=99 for the next largest group) and concerns about the potential for population stratification.

**Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) Study**

The design and results of the ACTIVE A study have been described previously\(^\text{18,19}\). ACTIVE A was a randomized double blind trial comparing clopidogrel 75mg/d with placebo for stroke prevention on a background of aspirin therapy (75-100 mg per day) in patients with AF and at least one additional risk factor for stroke who were not eligible for warfarin therapy. We adopted the primary efficacy and safety outcomes used in the ACTIVE trial\(^\text{18}\). The primary efficacy outcome was any major vascular event (stroke, non–central nervous system systemic embolism, MI, or death from vascular causes). Major hemorrhage was defined as any overt bleeding requiring transfusion of at least two units of blood or any overt bleeding meeting the criteria for severe hemorrhage. The 58 individuals of non-European ancestry were excluded.

The Institutional Review Board at each center approved each study, and all patients provided written informed consent. Only those patients who also consented to participate in either of the two genetic studies were eligible for this analysis (without any further selection criteria). Baseline characteristics of both genetic groups were similar to those of the CURE and ACTIVE study population, as previously reported\(^\text{20}\).

**Genotyping**

Genotyping of the PON1 Q192R polymorphism (rs662) was performed using TaqMan assays from stored DNA. The call rate was >98% and Hardy-Weinberg equilibrium was tested within each ethnic group (P>0.05 in all groups).

**Statistical Analysis**
We first explored the effect of PON1 Q192R genotypes on efficacy and safety of clopidogrel and then we looked the association between genotype and outcome. These analyses were restricted to CURE trial participants of European and Latin American ancestry. The effect of clopidogrel compared with placebo according to genotype was assessed using Cox proportional hazard regression under additive and dominant genetic models. No statistically significant (P>0.05) effect modification by ethnicity was observed for any of the pharmacogenetic effects described (data not shown) and results from Europeans and Latin Americans were therefore combined (with adjustment for ancestry).

We used separate models to adjust for (1) age, sex, and ethnicity, and (2) age, sex, ethnicity, revascularization (PCI with or without stent, coronary artery bypass surgery), smoking, waist-to-hip ratio, diabetes, blood pressure, and country of origin. Similar results were obtained with both models and therefore only results obtained with the parsimonious model are presented. A two-sided P<0.05 was considered significant throughout.

The same analytic approach that was used for CURE was used for ACTIVE A.

**Results**

**Effect of PON1 genotype on clopidogrel efficacy in CURE**

Characteristics of study participants are presented in Table 1. A total of 5,059 participants of European and Latin American self-defined ancestry were successfully genotyped, of whom 2510 were randomized to placebo and 2,549 to clopidogrel. The benefit of clopidogrel treatment on the first primary composite efficacy outcome (231 events, 9.1% versus 316 events, 12.6%; HR=0.71 95% CI 0.60-0.84, p<0.001) was similar to the parent study\(^1\) (582 events, 9.3 % versus 719 events, 11.4%; HR=0.80 95% CI 0.72-0.90, p<0.001).
Figure 1 presents estimates of the hazard ratios of the first and second primary composite efficacy outcomes in patients treated with clopidogrel compared with placebo stratified by PON1 Q192R genotype. A trend was observed for the first primary outcome whereby carriage of the Q allele was associated with greater efficacy of clopidogrel as compared to placebo, albeit this apparent heterogeneity was not statistically significant (p=0.07). Individuals carrying two Q alleles derived an increased benefit of clopidogrel (HR=0.60; 95% CI 0.47-0.77; p<0.001) as compared to individuals with either the QR (HR=0.80; 95% CI 0.62-1.05; p=0.10) or RR (HR=0.90; 95% CI 0.50-1.64; p=0.74) genotypes. This trend was less pronounced for the second primary endpoint or for major bleeds. The corresponding Kaplan-Meier survival curves are shown in Figure 2. For survival analysis, individuals of the QR and RR genotypes were grouped and compared to individuals of the QQ genotype, corresponding to a dominant genetic model. Results were consistent, with individuals of the QR and RR genotypes collectively deriving a similar benefit of clopidogrel (HR=0.82; 95% CI 0.65-1.05; p=0.12). Likewise, no effect was observed in the smaller CURE-PCI datasets (734 individuals with genotype; Supplementary Figure 1). Power to detect an effect size similar as the one described by Bouman et al. ³ was estimated at >99% in clopidogrel-treated participants from the CURE dataset for the first and second primary efficacy outcomes.

**Effect of PON1 genotype on cardiovascular events in CURE**

To further explore the association of PON1 Q192R polymorphism with CV events, we performed similar analysis but stratifying individuals by treatment allocation and testing for association with Q192R genotype using an additive genetic model (Figure 3). Overall, there was no association between the Q allele and the first primary outcome when combining clopidogrel and placebo treated participants (HR= 1.09 per allele; 95% CI 0.95–1.24; p=0.23), and no
Our results are consistent with the recently published null association of PON1 Q192R mainly because the Q allele was associated with adverse events in placebo-treated individuals (HR=0.97 per allele; 95% CI 0.84-1.12; p=0.70). A similar trend was observed for the second primary outcome in placebo treated individuals (HR=1.13 per allele; 95% CI 0.99-1.30; p=0.08) but not in clopidogrel-treated individuals (HR=0.97 per allele; 95% CI 0.84-1.12; p=0.70).

**Effect of PON1 genotype on clopidogrel efficacy and cardiovascular events in ACTIVE**

Characteristics of study participants are summarized in Table 1. A total of 1156 participants of European self-defined ancestry were successfully genotyped, of whom 586 were randomized to placebo and 570 to clopidogrel. The benefit of clopidogrel on the primary composite efficacy outcome (114 events, 20.0% vs 154 events, 26.3%; HR=0.74; 95% CI 0.58-0.94; p=0.01) was comparable with the benefit reported in the parent study\(^1\) (432 events, 22.1% vs 924 events, 24.4%; HR=0.89; 95% CI 0.81-0.98; p=0.01). The results were consistent in subgroups based on PON1 genotype (Figure 4). No effect of PON1 on CV events was observed in either clopidogrel-treated or placebo-treated participants.

**Discussion**

Our results suggest that PON1 Q192R genotype does not modify the effect of clopidogrel. We also found that contrary to a previous report, the QQ genotype was not associated with an increased hazard of major CV events in individuals treated with clopidogrel. In fact, a trend was observed towards greater benefit of clopidogrel in individuals carrying two Q alleles in CURE, mainly because the Q allele was associated with adverse events in placebo-treated individuals.

Our results are consistent with the recently published null association of PON1 Q192R.
polymorphism with stent thrombosis\textsuperscript{21} and CV events\textsuperscript{22, 23}. They also support the lack of association between Q192R genotype and platelet aggregation\textsuperscript{22, 23}.

Several reports have investigated the association of Q192R with coronary heart disease, with mixed results. A large meta-analysis of 39 studies comprising 10,738 cases and 17,068 controls reported a pooled odds ratio of 1.10 (95% CI 1.06-1.13) per R allele for coronary heart disease\textsuperscript{13}. The prospective REGRESS study of 793 secondary prevention patients reported a hazard ratio of 1.71 (95% CI 1.0-2.8; p=0.03) per Q allele for death due to ischemic disease\textsuperscript{24}. Finally, the GeneBank study of 1,399 sequential patients undergoing diagnostic coronary angiography reported that the Q allele was associated with lower PON1 activity, increased levels of systemic indices of oxidative stress, and an increased risk of major adverse CV events (HR 1.48 95% CI 1.09-2.03 for QQ versus QR and RR)\textsuperscript{25}. These latter two reports are particularly relevant to our study since they included a large fraction of individuals with established CV disease (100% and 80%, respectively). Although the use of clopidogrel was not reported, neither study is likely to have included a substantial number of patients on clopidogrel therapy since the REGRESS study was conducted between 1989 and 1993 (i.e., before the approval of clopidogrel) and the GeneBank study recruited patients undergoing elective diagnostic coronary angiography in 2002 and 2003.

Our results offer a further caution against the interpretation of pharmacogenetic data in the absence of a non-treated control group. Such analyses should ideally be performed in the context of a randomized controlled trial to minimize the potential for confounding. Prior reports have provided evidence for a role of \textit{PON1} genotype in atherosclerosis irrespective of clopidogrel treatment. Thus, any pharmacogenetic analysis performed exclusively in clopidogrel-treated individuals could reflect a genetic effect that is independent of clopidogrel
treatment, as opposed to a therapeutic failure of clopidogrel. Our data support an effect of PON1 genotype on cardiovascular risk in patients not receiving clopidogrel although we cannot explain the lack of association between PON1 Q192R genotype and outcome in individuals treated with clopidogrel. Our results could reflect a hitherto unknown pharmacologic interaction but might also be explained by lack of statistical power given the smaller number of events in individuals treated with clopidogrel. Nevertheless, our data argue against a detrimental effect of the Q allele on clopidogrel metabolism.

In conclusion, our study shows that PON1 Q192R genotype do not modify the efficacy and safety of clopidogrel in ACS or AF patients. Further studies will be needed to confirm the association of the Q allele with adverse CV events independently of clopidogrel in secondary...
prevention patients. Taken together, these results emphasize the need for randomized
collection groups in pharmacogenetic studies.

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consulting and grant fees from Portola Pharmaceuticals and a research grant from Johnson and
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References:

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in
addition to aspirin in patients with acute coronary syndromes without st-segment elevation. N

of cytochrome p450 2c19 genotype with the antiplatelet effect and clinical efficacy of


Table 1. Baseline characteristics of CURE-Genetics and ACTIVE-Genetics participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CURE-Genetics Study</th>
<th>ACTIVE-Genetics Study</th>
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<td>Placebo</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Number</td>
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<td>2549</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
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<tr>
<td>European</td>
<td>85.7</td>
<td>86.2</td>
</tr>
<tr>
<td>Latin American</td>
<td>14.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>40.9</td>
<td>41.2</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>63.9 (11.0)</td>
<td>63.8 (11.0)</td>
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<tr>
<td>Body mass index, mean (SD)</td>
<td>27.6 (4.2)</td>
<td>27.7 (4.2)</td>
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<tr>
<td>Diabetes (%)</td>
<td>21.5</td>
<td>20.7</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>21.6</td>
<td>23.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>134.6 (22.0)</td>
<td>135.5 (22.3)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>78.3 (13.6)</td>
<td>78.6 (13.6)</td>
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<tr>
<td>PCI without stent (%)</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>PCI with stent (%)</td>
<td>13.5</td>
<td>15.5</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>10.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Follow-up time (days), mean (SD)</td>
<td>277.8 (101.1)</td>
<td>279.7 (99.9)</td>
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<tr>
<td>PON1 Q192R Genotype (%)</td>
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</tr>
<tr>
<td>QQ</td>
<td>48.5</td>
<td>49.2</td>
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<tr>
<td>QR</td>
<td>42.4</td>
<td>40.8</td>
</tr>
<tr>
<td>RR</td>
<td>9.0</td>
<td>10.0</td>
</tr>
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</table>

No variable was significantly different between treated and untreated subjects (p>0.05) for both the CURE and ACTIVE datasets.

Figure Legends

Figure 1. Effect of clopidogrel compared with placebo on clinical outcomes stratified by PON1 Q192R genotype in CURE. The first primary outcome was the composite of death from cardiovascular causes, nonfatal MI, or stroke, and the second primary outcome was the composite of the first primary outcome, recurrent ischemia, or hospitalization for unstable angina. P-value refers to the effect of clopidogrel versus placebo, for each genotype sub-group. Interaction p-
value refers to heterogeneity of effect of clopidogrel versus placebo between genotype sub-
groups.

**Figure 2.** Kaplan-Meier event-free survival according to PON1 Q192R genotype status in CURE. The first primary outcome was the composite of death from cardiovascular causes, nonfatal MI, or stroke, and the second primary outcome was the composite of the first primary outcome, recurrent ischemia, or hospitalization for unstable angina.

**Figure 3:** Effect of PON1 Q192R genotype clopidogrel on clinical outcomes stratified by treatment allocation in CURE. The first primary outcome was the composite of death from cardiovascular causes, nonfatal MI, or stroke, and the second primary outcome was the composite of the first primary outcome, recurrent ischemia, or hospitalization for unstable angina. P-value refers to the additive (per allele) genetic effect of the R allele, for each treatment group. Interaction p-value refers to heterogeneity of additive genetic effects of the R allele between treatment groups.

**Figure 4:** Effect of clopidogrel compared with placebo on clinical outcomes stratified by PON1 Q192R genotype in ACTIVE. The primary efficacy outcome was any major vascular event (stroke, non–central nervous system systemic embolism, MI, or death from vascular causes). P-value refers to the effect of clopidogrel versus placebo, for each genotype sub-group. Interaction p-value refers to heterogeneity of effect of clopidogrel versus placebo between genotype sub-groups.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carrier Status</th>
<th>Clopidogrel Participants</th>
<th>Placebo Participants</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Primary Outcome</strong></td>
<td>RR 9.1% (23/253)</td>
<td>9.0% (21/234)</td>
<td>0.90 (0.50-1.64)</td>
<td>0.742</td>
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<tr>
<td></td>
<td>QR 9.5% (98/1035)</td>
<td>11.8% (123/1046)</td>
<td>0.80 (0.62-1.05)</td>
<td>0.104</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>QQ 8.5% (106/1246)</td>
<td>13.9% (168/1206)</td>
<td>0.60 (0.47-0.77)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td></td>
<td><strong>Total</strong> 9.0% (227/2534)</td>
<td>12.6% (312/2486)</td>
<td>0.70 (0.59-0.84)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Second Primary Outcome</strong></td>
<td>RR 17.8% (45/253)</td>
<td>16.7% (39/234)</td>
<td>0.92 (0.67-1.27)</td>
<td>0.911</td>
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<tr>
<td></td>
<td>QR 16.1% (167/1035)</td>
<td>19.8% (207/1046)</td>
<td>0.80 (0.66-0.99)</td>
<td>0.036</td>
<td></td>
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<td></td>
<td>QQ 16.3% (203/1246)</td>
<td>21.4% (258/1206)</td>
<td>0.74 (0.62-0.89)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td></td>
<td><strong>Total</strong> 16.4% (415/2534)</td>
<td>20.3% (504/2486)</td>
<td>0.79 (0.69-0.90)</td>
<td>&lt;0.001</td>
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<td><strong>Major Bleed</strong></td>
<td>RR 4.0% (10/253)</td>
<td>3.8% (9/234)</td>
<td>0.98 (0.40-2.43)</td>
<td>0.972</td>
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<td></td>
<td>QR 4.1% (42/1035)</td>
<td>2.7% (28/1046)</td>
<td>1.55 (0.96-2.50)</td>
<td>0.072</td>
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<td></td>
<td>QQ 3.9% (49/1246)</td>
<td>3.1% (37/1206)</td>
<td>1.30 (0.85-1.99)</td>
<td>0.232</td>
<td></td>
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<tr>
<td></td>
<td><strong>Total</strong> 4.0% (101/2534)</td>
<td>3.0% (74/2486)</td>
<td>1.36 (1.01-1.83)</td>
<td>0.045</td>
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</table>
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SUPPLEMENTAL MATERIALS
Supplemental Figure Legend

Supplementary Figure 1. Effect of clopidogrel compared with placebo on clinical outcomes stratified by PON1 Q192R genotype in stented ACS patients from the CURE trial
### Supplementary Figure 1.

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<th>Placebo Participants</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Primary Outcome</strong></td>
<td>RR</td>
<td>5.4% (2/37)</td>
<td>5.6% (2/36)</td>
<td>1.17 (0.16–8.74)</td>
<td>0.878</td>
<td>0.706</td>
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<tr>
<td></td>
<td>QR</td>
<td>9.4% (16/171)</td>
<td>16.2% (24/148)</td>
<td>0.55 (0.29–1.04)</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QQ</td>
<td>7.5% (14/186)</td>
<td>14.1% (22/156)</td>
<td>0.51 (0.26–1.00)</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>RR</td>
<td>8.1% (32/394)</td>
<td>14.1% (48/340)</td>
<td>0.55 (0.35–0.87)</td>
<td><strong>0.010</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Second Primary Outcome</strong></td>
<td>RR</td>
<td>27.0% (10/37)</td>
<td>22.2% (8/36)</td>
<td>1.22 (0.47–3.15)</td>
<td>0.682</td>
<td>0.982</td>
</tr>
<tr>
<td></td>
<td>QR</td>
<td>21.1% (36/171)</td>
<td>32.4% (48/148)</td>
<td>0.58 (0.38–0.90)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QQ</td>
<td>22.0% (41/186)</td>
<td>26.9% (42/156)</td>
<td>0.80 (0.52–1.24)</td>
<td>0.315</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>RR</td>
<td>22.1% (87/394)</td>
<td>28.8% (98/340)</td>
<td>0.73 (0.55–0.97)</td>
<td><strong>0.033</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleed</strong></td>
<td>RR</td>
<td>2.7% (1/37)</td>
<td>5.6% (2/36)</td>
<td>0.43 (0.04–5.20)</td>
<td>0.508</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>QR</td>
<td>2.9% (5/171)</td>
<td>2.0% (3/148)</td>
<td>1.53 (0.36–6.56)</td>
<td>0.563</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QQ</td>
<td>5.9% (11/186)</td>
<td>2.6% (4/156)</td>
<td>2.49 (0.79–7.83)</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>RR</td>
<td>4.3% (17/394)</td>
<td>2.6% (9/340)</td>
<td>1.63 (0.73–3.66)</td>
<td><strong>0.235</strong></td>
<td></td>
</tr>
</tbody>
</table>