Effect of PON1 Q192R Genetic Polymorphism on Clopidogrel Efficacy and Cardiovascular Events in the Clopidogrel in the Unstable Angina to Prevent Recurrent Events Trial and the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events

Guillaume Paré, Stephanie Ross, Shamir R. Mehta, Salim Yusuf, Sonia S. Anand, Stuart J. Connolly, Keith A.A. Fox and John W. Eikelboom

Circ Cardiovasc Genet 2012;5;250-256; originally published online February 24, 2012;
DOI: 10.1161/CIRCGENETICS.111.961417

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Effect of PON1 Q192R Genetic Polymorphism on Clopidogrel Efficacy and Cardiovascular Events in the Clopidogrel in the Unstable Angina to Prevent Recurrent Events Trial and the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events

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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 high-density lipoprotein, and the Q192R polymorphism has been previously associated with cardiovascular risk in patients not treated with clopidogrel.

Methods and Results—Patients (n = 5059) from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (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 with 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 (hazard ratio [HR], 1.09 per allele; 95% confidence interval [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 1156 atrial fibrillation patients from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events, 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 patients with acute coronary syndromes. Further studies are needed to confirm or refute the association of the Q allele with adverse cardiovascular events independent of clopidogrel in secondary prevention patients. (Circ Cardiovasc Genet. 2012;5:250-256.)

Key Words: antiplatelet therapy ■ atrial fibrillation ■ clopidogrel ■ paraoxonase 1 gene ■ pharmacogenetics
been proposed as an atherosclerotic susceptibility gene.9,10

with individuals with either the RR or QR genotype.3

numbers (n

Individuals from other ethnic groups were excluded because of small

data. only for individuals of European and Latin American ancestry.

outcome, recurrent ischemia, or hospitalization for unstable angina.

The second primary outcome was the composite of the first primary

deadth from CV causes, nonfatal myocardial infarction, or stroke, and

The effect of clopidogrel compared with placebo according to
genotype was assessed using Cox proportional hazard regression

usual risk of cardiovascular (CV) disease independent of clopidogrel action, although this remains
controversial.13–15

We hypothesized that the PON1 polymorphism Q192R is

associated with both a decreased efficacy of clopidogrel and

an increased risk of CV events. To test this hypothesis, we

investigated the efficacy and safety of clopidogrel among

carriers of the Q192R polymorphism compared with noncarriers

and the association between genotype and risk of CV disease in the placebo-controlled Clopidogrel in Unstable

Angina to Prevent Recurrent Events (CURE) trial that en-
rrollepd patients with ACS and the placebo-controlled Atrial

Fibrillation Clopidogrel Trial With Irbesartan for Prevention

of Vascular Events (ACTIVE A) that enrolled patients with

atrial fibrillation.

Methods

The CURE Study

The design and results of the CURE trial have been described

previously.16,17 In brief, CURE was a randomized, double-blind,

placebo-controlled trial comparing clopidogrel (75 mg/d) with pla-
cebo 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.16 The first primary outcome was the composite of
death from CV causes, nonfatal myocardial infarction, 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.

The ACTIVE Study

The design and results of the Atrial Fibrillation Clopidogrel Trial

With Irbesartan for Prevention of Vascular Events (ACTIVE A) study

have been described previously.18,19 ACTIVE A was a ran-
domized, double-blind trial comparing 75 mg/d clopidogrel with

placebo for stroke prevention on a background of aspirin therapy

(75–100 mg/d) in patients with atrial fibrillation and at least 1

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.18 The primary efficacy outcome was any major

vascular event (stroke, non–central nervous system systemic embo-

lism, myocardial infarction, or death from vascular causes).

Major hemorrhage was defined as any overt bleeding requiring transfusion

of at least 2 units of blood or any overt bleeding meeting the criteria

for severe hemorrhage. The 38 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 2 genetic

studies were eligible for this analysis (without any further selection

criteria). Baseline characteristics of both genetic groups were similar

tо those of the CURE and ACTIVE study population, as previously

reported.20

Genotyping

Genotyping of the PON1 Q192R polymorphism (rs6622) 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 we then looked at 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 signif-
cy (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 com-
bined (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 2-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 the Table. A total of 5059 participants of European and Latin American self-defined ancestry were successfully genotyped, of whom 2510 were randomly assigned to placebo and 2549 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 study16 (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 with placebo, albeit this apparent heterogeneity was not statistically significant (P=0.07). Individuals carrying 2 Q alleles derived an increased benefit of clopidogrel (HR, 0.60; 95% CI, 0.47–0.77; P<0.001) as compared with individuals
with either the QR (HR, 0.80; 95% CI, 0.62–1.05; *P*/H11005 0.10) or RR (HR, 0.90; 95% CI, 0.50–1.64; *P*/H11005 0.74) genotypes. This trend was less pronounced for the second primary end point 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 with 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*/H11005 0.12). Likewise, no effect was observed in the smaller CURE-PCI datasets (734 individuals with genotype; online-only Data Supplement Figure I). Power to detect an effect size similar as the one described by Bouman et al3 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 CV 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CURE-Genetics Study</th>
<th>ACTIVE-Genetics Study</th>
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<tr>
<td>No.</td>
<td>Placebo 2510</td>
<td>Clopidogrel 2549 Total 5059</td>
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<tr>
<td>Ethnicity, %</td>
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<tr>
<td>European</td>
<td>85.7</td>
<td>86.2</td>
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<tr>
<td>Latin American</td>
<td>14.3</td>
<td>13.8</td>
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<tr>
<td>Female, %</td>
<td>40.9</td>
<td>41.2</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>63.9 (11.1)</td>
<td>63.8 (11.0)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>27.6 (4.1)</td>
<td>27.7 (4.2)</td>
</tr>
<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 (13.8)</td>
<td>78.6 (13.6)</td>
</tr>
<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, d, mean (SD)</td>
<td>277.8 (101.1)</td>
<td>279.7 (99.9)</td>
</tr>
</tbody>
</table>

*CURE* indicates Clopidogrel in Unstable Angina to Prevent Recurrent Events trial; *ACTIVE*, Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

No variable was significantly different between treated and untreated subjects (*P*/H11005 >0.05) for both the CURE and ACTIVE datasets.

Figure 1. Effect of clopidogrel compared with placebo on clinical outcomes stratified by *PON1* Q192R genotype in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, 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 subgroup. Interaction *P* value refers to heterogeneity of effect of clopidogrel versus placebo between genotype subgroups.

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Table. 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>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Placebo 2510</td>
<td>Clopidogrel 2549 Total 5059</td>
</tr>
<tr>
<td>Ethnicity, %</td>
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<td></td>
</tr>
<tr>
<td>European</td>
<td>85.7</td>
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<tr>
<td>Latin American</td>
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</tr>
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<td>Age, y, mean (SD)</td>
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<td>3.2</td>
</tr>
<tr>
<td>PCI with stent, %</td>
<td>13.5</td>
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<tr>
<td>CABG, %</td>
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<td>Follow-up time, d, mean (SD)</td>
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<td>279.7 (99.9)</td>
</tr>
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</table>

*PON1* Q192R genotype, %

<table>
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<tr>
<th></th>
<th>QQ 48.5</th>
<th>QR 42.1</th>
<th>RR 9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, d, mean (SD)</td>
<td>277.8 (101.1)</td>
<td>279.7 (99.9)</td>
<td>278.8 (100.5)</td>
</tr>
</tbody>
</table>

Figure 1. Effect of clopidogrel compared with placebo on clinical outcomes stratified by *PON1* Q192R genotype in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, 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 subgroup. Interaction *P* value refers to heterogeneity of effect of clopidogrel versus placebo between genotype subgroups.
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 evidence of heterogeneity (P = 0.07). The Q allele was significantly associated with incidence of the first primary outcome in placebo-treated participants (HR, 1.23 per allele; 95% CI, 1.03–1.47; P = 0.03) but not in clopidogrel-treated individuals (HR, 0.93 per allele; 95% CI, 0.76–1.13; P = 0.46). A similar trend was observed for the second primary outcome (P = 0.03).

Figure 2. Kaplan-Meier event-free survival according to PON1 Q192R carrier status in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, and the second primary outcome was the composite of the first primary outcome, recurrent ischemia, or hospitalization for unstable angina. A represents the survival curves for the first primary composite endpoint; B represents the survival curves for the second primary composite endpoint; and C represents the survival curves for major bleeding.
and CV Events in ACTIVE benefit reported in the parent study (832 events, 22.1% per allele; 95% CI, 0.84–1.12; P = 0.74; 95% CI, 0.58–0.94; 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 toward greater benefit of clopidogrel in individuals carrying 2 Q alleles in the context of a randomized, controlled trial to minimize the potential for confounding. Prior reports have provided evidence for a role of 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 CV 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 pharmacological 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.

Our study has a few potential limitations. First, despite the large number of participants and events in the CURE genetic datasets, our study cannot exclude smaller interactions, especially for the PCI subgroup. Furthermore, stent thrombosis was not adjudicated in CURE, precluding direct comparison with the study by Bouman et al. Nev-
ertheless, our data provide randomized confirmation of a lack of deleterious effect of the Q allele on clopidogrel efficacy on spontaneous CV events not induced by PCI. The ACTIVE genetic dataset contained fewer participants and outcome events than the CURE dataset and therefore had less statistical power. Second, our results might be specific to our patient population and how they were treated. Third, only participants of European and Latin American ancestries could be adequately analyzed. Even though there is no reason to suspect different results in other populations a priori, further studies in diverse populations will be needed. It should be noted that inclusion of randomized groups lessens the risk of confounding by population stratification because individuals in any sub-strata were equally likely to receive clopidogrel or placebo.

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

Acknowledgments

Dr Yusuf is Co-Chair and Principle Investigator of CURE and the Chair of ACTIVE; Dr Connolly is Principle Investigator of ACTIVE; Dr Fox is Co-Chair of CURE; and Dr Mehta is Project Officer of CURE. Dr Paré holds the Canada Research Chair in Genetic and Molecular Epidemiology. Dr Yusuf holds the Heart and Stroke Foundation of Ontario/Marion W. Burke Chair in Cardiovascular Disease. Dr Anand holds the Michael DeGroote and Heart and Stroke Foundation of Ontario Endowed Chair in Population Health and the May Cohen Eli Lily Endowed Chair in Women’s Health. Dr Connolly holds the Salim Yusuf Chair in Cardiology. Dr Eikelboom holds the Canada Research Chair in Cardiovascular Medicine. We acknowledge Alexandre Belisle from the Genome Quebec Innovation Centre for expert genotyping assistance. We also acknowledge Sue McMillan for expert administrative assistance.

Sources of Funding

The CURE and ACTIVE A studies were funded by Sanofi-Aventis and Bristol-Myers-Squibb.

Disclosures

Dr Paré reports receiving consulting and speaker fees from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer-Ingelheim and research grant support from Bristol-Myers-Squibb and Sanofi-Aventis; Dr Mehta reports receiving consulting and speaker fees from AstraZeneca, Bristol-Myers-Squibb, and Sanofi-Aventis as well as speaker fees from Eli Lilly; Dr Connolly reports receiving consulting, speaker, and grant support from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer-Ingelheim, speaker and grant fees from Boston Scientific and St Jude Medical, consulting and speaker fees from Bayer Pharmaceuticals Inc, consulting and grant fees from Portola Pharmaceuticals, and a research grant from Johnson and Johnson; Dr Fox reports receiving research grant support from Bayer and Eli Lilly and speaker fees from Bayer, Eli Lilly, Sanofi-Aventis, and Boehringer-Ingelheim; Dr Eikelboom reports receiving speaker and consulting fees from Boehringer-Ingelheim, Sanofi-Aventis, and Bristol-Myers-Squibb.


**CLINICAL PERSPECTIVE**

It has recently been suggested that efficacy of the antiplatelet agent clopidogrel depends on biotransformation by the PON1 enzyme. The *PON1* gene carries a common genetic variant—Q192R—which has been shown to be associated with stent thrombosis in patients treated with clopidogrel. In this latter study, carriers of the Q allele had decreased biotransformation of clopidogrel and increased cardiovascular events. In contrast to previous results, we show that the *PON1* genetic variant Q192R does not influence efficacy and safety of clopidogrel in 2 large, randomized studies. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial of clopidogrel versus placebo in non–ST-elevation–myocardial infarction (NSTEMI) patients, clopidogrel was equally effective at reducing cardiovascular events irrespective of the presence of the Q allele. Similarly, in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events of clopidogrel versus placebo in high-risk atrial fibrillation patients, no effect of the *PON1* genetic variant was observed. In conclusion, our study shows that the Q192R genetic variant does not modify the efficacy and safety of clopidogrel in NSTEMI and atrial fibrillation patients.
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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<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>
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<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>
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<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>
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<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>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>8.1% (32/394)</td>
<td>14.1% (48/340)</td>
<td>0.55 (0.35–0.87)</td>
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<td><strong>Second Primary Outcome</strong></td>
<td>RR</td>
<td>27.0% (10/37)</td>
<td>22.2% (8/36)</td>
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<td>QR</td>
<td>21.1% (36/171)</td>
<td>32.4% (48/148)</td>
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<td>QQ</td>
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<td>26.9% (42/156)</td>
<td>0.80 (0.52–1.24)</td>
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<td><strong>Total</strong></td>
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<td>22.1% (87/394)</td>
<td>28.8% (98/340)</td>
<td>0.73 (0.55–0.97)</td>
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<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>
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<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>
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<td>5.9% (11/186)</td>
<td>2.6% (4/156)</td>
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<td><strong>Total</strong></td>
<td></td>
<td>4.3% (17/394)</td>
<td>2.6% (9/340)</td>
<td>1.63 (0.73–3.66)</td>
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