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, MD, MSc, FRCPC; Stephanie Ross, MSc; Shamir R. Mehta, MD, FRCPC; Salim Yusuf, DPhil, FRCPC; Sonia S. Anand, MD, PhD; Stuart J. Connolly, MD; Keith A.A. Fox, MBChB, FRCP; John W. Eikelboom, MBBS, MSc

**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

Clotidogrel when added to aspirin reduces major vascular events in patients with acute coronary syndromes (ACS).1 Clopidogrel is a produg that requires biotransformation into the active metabolite to inhibit the platelet P2Y12 receptor. Differences in the extent of clopidogrel biotransformation are believed to account for interindividual variability in platelet response to clopidogrel.2 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 nonsynonymous 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.3 Specifically, carriers of the Q allele were found to have a significantly higher risk of stent thrombosis after stent percutaneous coronary intervention (PCI), with an odds ratio

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From the Population Health Research Institute, Hamilton Health Sciences and Departments of Medicine, Epidemiology, and Pathology, McMaster University, Hamilton, Ontario, Canada; and the Center for Cardiovascular Science, Edinburgh University and Royal Infirmary, Edinburgh, United Kingdom.

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Correspondence to Guillaume Paré, MD, Hamilton Health Sciences–General Site, Population Health Research Institute (DBCVSRI); C3-103, 237 Barton St E, Hamilton, ON, Canada L8L 2X2. E-mail pareg@mcmaster.ca

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been proposed as an atherosclerotic susceptibility gene.9,10 The potential for population stratification.

The 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 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; \( P = 0.10 \)) or RR (HR, 0.90; 95% CI, 0.50–1.64; \( P = 0.74 \)) genotypes. This trend was less pronounced for the second primary 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; \( P = 0.12 \)). 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 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 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

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Table. Baseline Characteristics of CURE-Genetics and ACTIVE-Genetics Participants

<table>
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<tr>
<th>Characteristic</th>
<th>CURE-Genetics Study</th>
<th>ACTIVE-Genetics Study</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>Clopidogrel</td>
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<tr>
<td>No.</td>
<td>2510</td>
<td>2549</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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<td>Female, %</td>
<td>40.9</td>
<td>41.2</td>
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<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>

**PON1 Q192R genotype, %**

| QQ    | 48.5    | 49.2    | 48.8    | 50.3    | 52.3    | 51.3    |
| QR    | 42.1    | 40.8    | 41.5    | 41.7    | 39.3    | 40.5    |
| RR    | 9.4     | 10.0    | 9.7     | 7.9     | 8.4     | 8.1     |

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 (\( P > 0.05 \)) for both the CURE and ACTIVE datasets.

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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 (HR, 1.44 in placebo-treated participants; HR, 0.97 in clopidogrel-treated participants; \( P = 0.46 \)).

**Figure 2.** Kaplan-Meier event-free survival according to \( PON1 \) Q192R carrier status in 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.

**Figure 3.** Effect of \( PON1 \) Q192R genotype clopidogrel on clinical outcomes stratified by treatment allocation in 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 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.
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 CV Events in ACTIVE**

Characteristics of study participants are summarized in the Table. A total of 1156 participants of European self-defined ancestry were successfully genotyped, of whom 586 were randomly assigned to placebo and 570 to clopidogrel. The benefit of clopidogrel on the primary composite efficacy outcome (114 events, 20.0% versus 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 study18 (832 events, 22.1% versus 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 toward greater benefit of clopidogrel in individuals carrying 2 Q alleles in combination with clopidogrel. Our results 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 offer a further caution against the interpretation of pharmacogenetic data in the absence of a nontreated 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 \( PON1 \) 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.

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References
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.
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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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>Outcome</th>
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<th>Placebo Participants</th>
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<th>p-value</th>
<th>Interaction p-value</th>
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<td>RR 5.4% (2/37)</td>
<td>5.6% (2/36)</td>
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<td>QR 9.4% (16/171)</td>
<td>16.2% (24/148)</td>
<td>0.55 (0.29–1.04)</td>
<td>0.067</td>
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<td></td>
<td>QQ 7.5% (14/186)</td>
<td>14.1% (22/156)</td>
<td>0.51 (0.26–1.00)</td>
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<td></td>
<td><strong>Total</strong> 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>
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<td>QR 21.1% (36/171)</td>
<td>32.4% (48/148)</td>
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<td>QQ 22.0% (41/186)</td>
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<td><strong>Total</strong> 22.1% (87/394)</td>
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<td>0.73 (0.55–0.97)</td>
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<td><strong>Major Bleed</strong></td>
<td>RR 2.7% (1/37)</td>
<td>5.6% (2/36)</td>
<td>0.43 (0.04–5.20)</td>
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<td>1.53 (0.36–6.56)</td>
<td>0.563</td>
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<td></td>
<td>QQ 5.9% (11/186)</td>
<td>2.6% (4/156)</td>
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<td><strong>Total</strong> 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>
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