Number Needed to Treat With Rosuvastatin to Prevent First Cardiovascular Events and Death Among Men and Women With Low Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)

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Background—As recently demonstrated, random allocation to rosuvastatin results in large relative risk reductions for first cardiovascular events among apparently healthy men and women with low levels of low-density lipoprotein cholesterol but elevated levels of high-sensitivity C-reactive protein. However, whether the absolute risk reduction among such individuals justifies wide application of statin therapy in primary prevention is a controversial issue with broad policy and public health implications.

Methods and Results—Absolute risk reductions and consequent number needed to treat (NNT) values were calculated across a range of end points, timeframes, and subgroups using data from Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized evaluation of rosuvastatin 20 mg versus placebo conducted among 17 802 apparently healthy men and women with low-density lipoprotein cholesterol <130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/L. Sensitivity analyses were also performed to address the potential impact that alternative statin regimens might have on a similar primary prevention population. For the end point of myocardial infarction, stroke, revascularization, or death, the 5-year NNT within JUPITER was 20 (95% CI, 14 to 34). All subgroups had 5-year NNT values for this end point below 50; as examples, 5-year NNT values were 17 for men and 31 for women, 21 for whites and 19 for nonwhites, 18 for those with body mass index ≤25 kg/m² and 21 for those with body mass index greater than 25 kg/m², 9 and 26 for those with and without a family history of coronary disease, 19 and 22 for those with and without metabolic syndrome, and 14 and 37 for those with estimated Framingham risks greater or less than 10%. For the net vascular benefit end point that additionally included venous thromboembolism, the 5-year NNT was 18 (95% CI, 13 to 29). For the restricted “hard” end point of myocardial infarction, stroke, or death, the 5-year NNT was 29 (95% CI, 19 to 56). In sensitivity analyses addressing the theoretical utility of alternative agents, 5-year NNT values of 38 and 57 were estimated for statin regimens that deliver 75% and 50% of the relative benefit observed in JUPITER, respectively. All of these calculations compare favorably to 5-year NNT values previously reported in primary prevention for the use of statins among hyperlipidemic men (5-year NNT, 40 to 70), for antihypertensive therapy (5-year NNT, 80 to 160), or for aspirin (5-year NNT, >300).

Conclusions—Absolute risk reductions and consequent NNT values associated with statin therapy among those with elevated high-sensitivity C-reactive protein and low low-density lipoprotein cholesterol are comparable if not superior to published NNT values for several widely accepted interventions for primary cardiovascular prevention, including the use of statin therapy among those with overt hyperlipidemia.

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Key Words: statins ■ outcomes research ■ prevention and control ■ epidemiology ■ primary prevention ■ risk factors
In the recently completed Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) conducted among apparently healthy men and women with low levels of low-density lipoprotein cholesterol (LDLC; <130 mg/dL) but elevated levels of high-sensitivity C-reactive protein (hsCRP; ≥2 mg/L), random allocation to rosuvastatin 20 mg daily was associated with a 54% reduction in myocardial infarction (P=0.0002), a 48% reduction in stroke (P=0.002), a 46% reduction in need for bypass surgery or angioplasty (P<0.0001), a 43% reduction in venous thromboembolism (P=0.007), and a 20% reduction in all-cause mortality (P=0.02).1-3 However, despite these large relative risk reductions, absolute risk reductions within JUPITER were modest as incidence rates for the primary trial end point were 1.36 and 0.77 per 100 person-years in the placebo and statin groups, respectively. Differences between relative and absolute risk reductions are common in primary prevention trials and can be a source of controversy for those seeking to interpret trial data in the context of new clinical guidelines and already accepted therapies.

The number needed to treat (NNT) to prevent one clinical event is a commonly used metric of treatment benefit that combines aspects of both absolute risk and relative treatment effects and thus can be helpful for the translation of clinical trial data into practice.4 For example, a 5-year NNT of 100 implies that 100 individuals would need to be treated for a 5-year period to prevent one specified clinical end point.

NNT values have been of particular utility for comparing the relative clinical benefits of statin therapy in the prevention of myocardial infarction, stroke, and all-cause mortality. Interpretation of NNT values requires data on the magnitude of baseline risk, the comparator group, the duration of therapy, and the end points evaluated.5 In primary prevention among those with overt hyperlipidemia, 5-year NNT values ranging between 40 and 70 have been observed in the AFCAPS/TexCAPS trial of lovastatin and in the WOSCOPS trial of pravastatin.6-8 As would be anticipated, smaller NNT values have been reported when statin therapy is given to higher risk populations, such as those with prior myocardial infarction.9 In this regard, among participants in the Cholesterol and Recurrent Events trial of secondary prevention patients with average cholesterol levels, the 5-year NNT for pravastatin was 33,10 whereas in the 4S trial of secondary prevention among those with elevated LDLC, the 5-year NNT for simvastatin was approximately 15.11 All of these values compare favorably to 5-year NNT values ranging between 80 and 160 for the treatment of hypertension among comparable middle-aged individuals12-13 and 5-year NNT values exceeding 300 for aspirin in primary prevention.14-16

To inform policy and public health discussions regarding the net utility of statin therapy for primary prevention among those with low levels of LDLC but elevated levels of hsCRP, we used the JUPITER trial database to calculate relative risk reductions, absolute risk reductions (incidence rate differences), and NNT values across a range of clinical end points, time intervals, and in multiple different prespecified participant subgroups. To address the robustness and generalizability of these data, we also performed sensitivity analyses to calculate estimated NNT values that might be achieved by statin therapy across a more conservative range of relative risk reductions than those directly observed in the JUPITER trial.

WHAT IS KNOWN

- The JUPITER trial demonstrated that rosuvastatin reduces by half first vascular events among men and women with low levels of low-density lipoprotein cholesterol but elevated high-sensitivity C-reactive protein.
- However, although this relative risk reduction is large, whether the absolute risk reduction justifies wide application of statin therapy in this setting is controversial.

WHAT THE STUDY ADDS

- In an analysis of absolute risk reductions and consequent number needed to treat values within the JUPITER trial, the utility of rosuvastatin among those with elevated high-sensitivity C-reactive protein and low low-density lipoprotein cholesterol is comparable if not superior to published number needed to treat values for several widely accepted interventions for primary cardiovascular prevention, including the use statins among hyperlipidemic men, antihypertensive therapy, or aspirin.
- These data have implications in policy discussions regarding new guidelines for the primary prevention of cardiovascular disease.

Methods

Details of JUPITER, a randomized, double-blind, placebo-controlled trial evaluating rosuvastatin 20 mg in the prevention of first ever cardiovascular events among 17 802 men and women free of diabetes or prior cardiovascular disease that was conducted between 2003 and 2008 in 26 countries worldwide, have been presented elsewhere.1-3,17 The primary eligibility criteria for JUPITER were a low level of LDLC (<130 mg/dL) and an elevated level of hsCRP (≥2 mg/L). All participants were followed prospectively for the trial primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death) and for incident venous thromboembolism as well as all-cause mortality. All components of the trial primary end point were adjudicated by an independent end points committee unaware of randomized treatment assignment. Analyses of total mortality included any reported death; regardless of whether cause of death could be ascertained from available medical records.

As in the primary JUPITER reports,1-3 Cox proportional-hazards models were used to calculate relative risks for the comparison of event rates in the 2 study groups, and absolute incidence rates (and incidence rate differences) were calculated as events per 100 person years of exposure. For the purpose of these analyses, NNT values at years 1, 2, 3, and 4 were calculated directly as the reciprocal of the absolute difference between risks of the outcome of interest at the specified time-point of interest based on Kaplan–Meier estimates. Estimated 95% confidence intervals for the NNT were based on inversion of the confidence intervals for risk differences with standard errors of risks estimated by Greenwood formula. As most prior studies of cardiovascular interventions have reported 5-year NNT values, 5-year NNT values were computed based on 4-year
absolute rates projected over an average 5-year period according to the methods of Altman and Anderson.4

When comparing NNT values, specification must be made not only of the timeframe but also the clinical end point of interest. Further, within any given clinical trial, NNT values may vary widely in specific participant subgroups. Although we observed no significant heterogeneity in the relative effectiveness of rosuvastatin between any subgroups,1 the consistency of estimated NNT values within subgroups can be of clinical interest. We computed NNT values within JUPITER not only for the primary trial end point, but also for a series of alternative end points to better allow direct comparison to prior studies, including a restricted “hard clinical end point” of myocardial infarction, stroke, or all-cause mortality. By so doing, values of 5-year NNT within JUPITER could then be compared to 5-year NNT values obtained in prior statin trials in both primary and secondary prevention, as well as 5-year NNT values deriving from other prevention settings including the treatment of hypertension among middle aged men and women as well as the prophylactic use of aspirin.6–16 We additionally computed NNT values on the basis of a “net vascular benefit” end point that included incident venous thromboembolism in addition to the trial primary end point and all-cause mortality.

To address the robustness and generalizability of these data as well as the potential impact that might come from use of alternative statin regimens in a similar population, we also performed sensitivity analyses to calculate estimated NNT values assuming more conservative relative risk reductions than those observed in the JUPITER trial. Specifically, we estimated 5-year NNT values for the hard end point of myocardial infarction, stroke, and death that might accrue in scenarios where the use of statin therapy delivered 75% and 50% of the relative benefit actually observed in the JUPITER trial.

## Results

Randomized participants in JUPITER had a median age of 66 years, 38% were women, and 25% were black or Hispanic.

Table 1 presents incidence rates, incidence rate difference, relative risk reductions, and annual NNT values in the JUPITER trial.

### Table 1. Incidence Rates, Incidence Rate Difference, Relative Risk Reductions, and Annual NNT Values in the JUPITER Trial

<table>
<thead>
<tr>
<th></th>
<th>Primary End Point*</th>
<th>Primary End Point or Any Death</th>
<th>Primary End Point, VTE, or Any Death</th>
<th>Primary Revascularization or Any Death</th>
<th>MI, Stroke, or Any Death</th>
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<tr>
<td>Events, placebo</td>
<td>251</td>
<td>441</td>
<td>483</td>
<td>431</td>
<td>353</td>
</tr>
<tr>
<td>Events, rosuvastatin</td>
<td>142</td>
<td>295</td>
<td>320</td>
<td>291</td>
<td>239</td>
</tr>
<tr>
<td>Incidence rate,† placebo</td>
<td>1.36</td>
<td>2.39</td>
<td>2.62</td>
<td>2.23</td>
<td>1.90</td>
</tr>
<tr>
<td>Incidence rate,† rosuvastatin</td>
<td>0.77</td>
<td>1.59</td>
<td>1.73</td>
<td>1.57</td>
<td>1.28</td>
</tr>
<tr>
<td>Incidence rate difference†</td>
<td>0.59</td>
<td>0.80</td>
<td>0.89</td>
<td>0.76</td>
<td>0.62</td>
</tr>
<tr>
<td>Relative risk reduction, %</td>
<td>44</td>
<td>33</td>
<td>34</td>
<td>33</td>
<td>32</td>
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<tr>
<td>1-year NNT</td>
<td>215</td>
<td>158</td>
<td>147</td>
<td>167</td>
<td>164</td>
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<tr>
<td>2-year NNT</td>
<td>95</td>
<td>73</td>
<td>65</td>
<td>76</td>
<td>95</td>
</tr>
<tr>
<td>3-year NNT</td>
<td>49</td>
<td>38</td>
<td>33</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>4-year NNT</td>
<td>31</td>
<td>25</td>
<td>23</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>5-year NNT</td>
<td>25</td>
<td>20</td>
<td>18</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

†Incidence rate per 100 person-years.

NNT values were 23 (95% CI, 18 to 41). These values were 25 (95% CI, 18 to 40) and 20 (95% CI, 14 to 32), respectively for this end point when all-cause mortality was also included. Hospitalization for unstable angina was rare in JUPITER, and thus the 4-year and 5-year NNT values for the end point of myocardial infarction, stroke, arterial revascularization, and any death were similar (25 [95% CI, 18 to 42] and 20 [95% CI, 14 to 34], respectively). For the restricted end point of myocardial infarction, stroke, or death, 4-year and 5-year NNT values were 36 (95% CI, 24 to 70) and 29 (95% CI, 19 to 56). For the net vascular benefit end point that included venous thromboembolism in addition to the primary end point and death, 4-year and 5-year NNT values were 23 (95% CI, 16 to 36) and 18 (95% CI, 13 to 29), respectively.

Table 2 presents absolute incidence rates for the JUPITER primary end point among those allocated to placebo, stratified by clinically relevant subgroups. As anticipated, absolute risks were higher among men than among women, among smokers than among nonsmokers, among those with a family history compared to those without, among older individuals as compared to younger individuals, and among those with higher as compared to lower Framingham risk scores or with multiple Adult Treatment Panel III (ATP-III) risk factors. By contrast, no significant increase in absolute risk was observed with higher body mass index, among those with impaired fasting glucose, or among those with metabolic syndrome. As all JUPITER study participants had elevated levels of hsCRP at baseline, this measure of overall inflammatory status likely captures the excess risk attributed to these variables.

Using these stratum-specific absolute risk data, Table 2 also presents 5-year NNT values in JUPITER for each of the study end points, stratified by clinically relevant subgroups. For example, 5-year NNT values were 17 for men and 31 for women using the end point of myocardial infarction, stroke, revascularization, or all-cause mortality, whereas comparable NNT values were 23 and 16 for those below or above age 70; 21 and 19 for white and nonwhite participants; 9 and 26 for those with and without a family history of premature athero-
As additionally shown in Table 2, NNT values ranged between 12 and 60 for the end point that included only myocardial infarction, stroke, or death from any cause. For this restricted end point, subgroups with the smallest NNT values included men (5-year NNT, 23), smokers (5-year NNT, 22), those with a family history (5-year NNT, 12), nonwhite participants (5-year NNT, 14), and those with Framingham Risk Scores greater than 10 (5-year NNT, 20). By contrast, for this restricted end point, subgroups with the largest NNT values were women (5-year NNT, 52), those with metabolic syndrome but no other ATP-III risk factor (5-year NNT, 54). However, all of these subgroups had 5-year NNT values comparable to those observed in prior prevention studies limited to men with hyperlipidemia, and superior to those observed in prior evaluations of diuretics, β-blockers, and aspirin when used either to treat hypertension or as cardiovascular prophylaxis (Table 3). To assist interpretation, Table 3 also provides the specific end point used in each comparison. All data in Table 3 are calculated for the same time period (5 years).

The Figure presents cumulative incidence curves for first vascular events within the JUPITER trial for the primary trial end point (Figure, A), the primary trial end point plus incident venous thromboembolism (Figure, B), and for the primary trial end point plus venous thromboembolism and all cause mortality (Figure, C). These latter data demonstrate how the NNT reflects aspects of both relative and absolute risk reductions and can be useful for clinical decision making; as...
shown, although there is some attenuation of the relative risk reduction with the addition of VTE and all-cause mortality, the absolute number of events prevented increases from 109 to 163 and the consequent 5-year NNT declines from 25 to 18.

Table 4 presents results of the sensitivity analyses in which a range of more conservative relative risk reductions than those observed in the JUPITER trial are assumed. As shown, for an hypothetical statin regimen that delivers 75% of the observed relative benefit in the JUPITER trial, the estimated 5-year NNT value is 38. For an hypothetical statin regimen that delivers 50% of the observed relative benefit in the JUPITER trial, the estimated 5-year NNT value is 57.

Discussion

For clinical decision making and effectiveness analyses, absolute risk reductions require consideration as well as
relative risk reductions. In this analysis of statin therapy for the primary prevention of cardiovascular events among those with low LDLC but elevated hsCRP, we have presented absolute rates and differences in these rates for a variety of end points, time frames, and patient subgroups. However, understanding of rate differences by both patients and clinicians is limited, and clinician surveys as well as randomized evidence indicate that the NNT is more readily understood and interpreted.18–20 Using this metric, our analysis indicates that the magnitude of benefit of statin therapy in primary prevention is substantial, relative to estimated benefits reported for other interventions widely used in this setting. Moreover, in sensitivity analyses designed to address the robustness of these data, the 5-year NNT for statin therapy among those with low LDLC but elevated hsCRP remains comparable to that of published NNT values for the use of statin therapy among those with overt hyperlipidemia, even if the assumed benefit is only half the magnitude of that actually observed in the JUPITER trial. Further, as shown in Table 3, the 5-year NNT values for rosuvastatin, pravastatin, and lovastatin in the primary prevention of cardiovascular disease (whether among those with elevated hsCRP or elevated LDLC) are all substantially smaller than 5-year NNT values associated with the use of antihypertensive therapy or aspirin, preventive strategies already in wide use and endorsed by current guidelines.

We believe the current data have clinical relevance and may be informative for policy discussions regarding guidelines for the primary prevention of cardiovascular disease. In contrast to almost all prior statin trials, participants in JUPITER had low levels of LDLC at entry (median, 108 mg/dL) and high levels of HDLC (median, 49 mg/dL), and thus were widely considered by their physicians to have “optimal lipid levels” that did not require lipid-lowering therapy. Nonetheless, the overall 5-year NNT values observed in JUPITER (ranging between 18 and 29 depending on end point) are all smaller than those observed in prior primary prevention trials of statin therapy that almost exclusively enrolled men with adverse lipid profiles.6–8 This is remarkable when considering that JUPITER enrolled 6801 women who would have been anticipated to further lower absolute event rates for the trial. Nonetheless, the 5-year NNT for women in JUPITER was only 52 for the most restrictive end point evaluated, despite the fact that 76% of enrolled women had Framingham risk scores predicting a 10-year risk at or below 10%. Similarly, using the most restrictive end point of myocardial infarction, stroke, or death, the 5-year NNT was 54 for those with elevated hsCRP and no other major ATP-III risk factor. Thus, using the NNT as a metric, these data demonstrate that several groups excluded from current guidelines for prophylactic statin therapy have substantive benefit on both relative and absolute risk scales when compared to interventions already considered to be effective. Further, in contrast to data from AFCAPS/TexCAPS6 and WOSCOPS7 that inform current prevention guidelines, JUPITER additionally demonstrated a statistically significant 20% reduction in all-cause mortality.

Because JUPITER was stopped early after a median follow-up of just under 2 years (maximal follow-up 5.0 years), a theoretical limitation of our analysis is that the true magnitude of benefit observed with statin therapy might be smaller or wane with longer periods of follow-up. However, in a test for interaction between the study-group assignment and follow-up time, no violation of the proportional hazards assumption was observed. Further, among the nearly 8000 JUPITER participants followed between 2 and 5 years, relative risk reductions were just as large as those followed for 2 years or less, and absolute risk reductions were actually larger. As also demonstrated by the narrow 95% CIs in these data, the range of potential effect estimates is small. Thus, there is no evidence in JUPITER that early termination had any substantive impact on the magnitude of these effects, an observation consistent with analyses of stopping rules in several other settings.21–22 Despite these data, we nonetheless calculated NNT values in our sensitivity analysis assuming benefits from statin therapy as small as 50% of the actual benefit observed and still found NNT values comparable to those already accepted for the treatment of overt hyperlipidemia. These sensitivity analyses are consistent with our own prior data in which randomized allocation to lovastatin (20 to 40 mg daily) as compared to placebo among 1428 primary prevention patients with LDLC <150 mg/dL and hsCRP >2 mg/L was associated with a significant reduction in acute coronary events and a 5-year NNT of 48.23

Although our data are internally consistent, caution is nonetheless needed when comparing NNT values across different trials or between different treatments. Most importantly, when comparing NNT values, specification must be made not only of the timeframe but also the clinical end point of interest. For this reason, we computed NNT values within JUPITER not only for the primary trial end point, but also for a series of alternative end points to better allow direct comparison to prior studies, including a restricted “hard clinical end point” of myocardial infarction, stroke, or all-cause mortality. We also include in Table 3 the specific end points used in prior NNT studies so that readers can judge for themselves the validity of this approach. Further, to demonstrate the robustness of these findings across a wide range of considerations regarding net clinical benefit, we performed an additional sensitivity analysis in which the actual benefit observed in JUPITER was reduced as much as 50%. As shown in Table 4, even in this analysis NNT values at 5 years associated with the diagnostic and treatment strategy tested in

<table>
<thead>
<tr>
<th>Statin Regimen</th>
<th>Estimated Risk Difference at Year 5</th>
<th>Estimated 5-y NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin regimen delivering 100% of the observed JUPITER benefit</td>
<td>3.50</td>
<td>29</td>
</tr>
<tr>
<td>Statin regimen delivering 75% of the observed JUPITER benefit</td>
<td>2.63</td>
<td>38</td>
</tr>
<tr>
<td>Statin regimen delivering 50% of the observed JUPITER benefit</td>
<td>1.75</td>
<td>57</td>
</tr>
</tbody>
</table>

*End point of myocardial infarction, stroke, or any death.
the JUPITER trial remained favorable. Nonetheless, we recognize that comparing NNT values across trials and across treatments is a complex issue. For example, changes in quality of care or in the distribution of background risk factors over time can make comparisons of treatment effects difficult even if, as done in Table 3, all trials compared use a similar primary prevention population. It is also difficult to predict the direction of effect any such bias over time might present for the calculation of NNT values. In general, an improvement in background cardiovascular risk over time would tend to adversely impact on a more recent NNT calculation because absolute benefit would have to be shown against a lower background event rate. However, such an effect, would be unlikely to lead to an overestimation of benefit in our analysis or to a falsely low NNT value because our study is the more recent.

In sum, the current analyses indicate that NNT values associated with statin therapy among men and women with low levels of LDLc but elevated hsCRP are at least comparable to NNT values observed in prior primary prevention trials evaluating statin therapy for the treatment of hyperlipidemia. Further, these data demonstrate that the use of statin therapy in primary prevention—whether targeting those with elevated LDLc or elevated hsCRP—is associated with substantially better NNT values than those reported for antihypertensive therapy or aspirin. These data may be informative in policy discussions regarding new guidelines for the primary prevention of cardiovascular disease.

Sources of Funding

The JUPITER trial was investigator-initiated and supported by AstraZeneca. The sponsor of the study collected the trial data and monitored the study sites but had no role in the conduct of the analyses or drafting of the report. All statistical analyses were done by the investigators and the academic study statistician (Dr. Glynn). Drs. Ridker and Glynn had full access to all study data and had final responsibility for the decision to submit for publication.

Disclosures

During the period of this project, Dr. Ridker reports having received investigator-initiated research grant support from the National Heart, Lung, and Blood Institute, the National Cancer Institute, the Donald W. Reynolds Foundation, the Leducq Foundation, Astra-Zeneca, Novartis, Merck, Abbott, Roche, and Sanofi-Aventis; consulting fees or lecture fees from Astra-Zeneca, Novartis, Merck, Merck-Schering Plough, Sanofi-Aventis, ISIS, Dade-Behring, and Vascular Biogenics; and is listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. These patents have been licensed to several entities, including Astra-Zeneca. Dr. Fonseca reports having received research grants, lecture fees, and consulting fees from Astra-Zeneca, Pfizer, Schering-Plough, Sanofi-Aventis, and Merck.

Dr. Genest reports having received lecture fees from Astra-Zeneca, Merck-Schering Plough, Pfizer, Novartis, and Sanofi-Aventis and consulting fees from Astra-Zeneca, Merck, Merck Fosst, Schering-Plough, Pfizer, Novartis, Resverlogix, and Sanofi-Aventis. Dr. Gotto reports having received consulting fees from Dupont, Novartis, Aegerion, Arisaph, KOWA, Merck, Merck Schering Plough, Pfizer, Genentech, Martek, and Reliant, having served as an expert witness, and as having received publication royalties. Dr. Kastelein reports receiving research grant support from Astra-Zeneca, Pfizer, Roche, Novartis, Merck, Merck Schering Plough, ISIS, Genzyme, and Sanofi-Aventis; lecture fees from Astra-Zeneca, Glaxo Smith Kline, Pfizer, Novartis, Merck-Schering Plough, Roche, ISIS, and Boehringer-Ingelheim; and consulting fees from Astra-Zeneca, Abbott, Pfizer, ISIS, Genzyme, Roche, Novartis, Merck, Merck Schering Plough, and Sanofi-Aventis. Dr. Koenig reports receiving research grant support from Anthera, Dade-Behring and Glaxo-Smith-Kline; lecture fees from Astra-Zeneca, Pfizer, Novartis, Glaxo-Smith-Kline, DiaDexus, Roche, and Boehringer-Ingelheim; and consulting fees from Glaxo-Smith Kline, Medlogix, Anthera, and Roche. Dr. Libby reports receiving lecture fees from Pfizer and lecture or consulting fees from Astra-Zeneca, Bristol-Myers Squibb, Glaxo-Smith-Kline, Merck, Pfizer, Sanofi-Aventis, VIA Pharmaceutical, Interleukin Genetics, Kowa Research Institute, Novartis, and Merck Schering Plough. Dr. Lorenzatti reports receiving research grant support, lecture fees, and consulting fees from Astra-Zeneca, Takeda, and Novartis. Dr. Nordestgaard reports receiving lecture fees from Astra-Zeneca, Abbott, Sanofi-Aventis, Pfizer, Boehringer Ingelheim and Merck; and consulting fees from Astra-Zeneca and BG Medicine. Dr. Shepherd reports receiving lecture fees from Astra-Zeneca, Pfizer, and Merck and consulting fees from Astra-Zeneca, Merck, Roche, Glaxo SmithKline, Pfizer, Nicox, and Oxford Biosciences. Dr. Glynn reports receiving research grant support from the National Heart, Lung, and Blood Institute, Astra-Zeneca, and Bristol-Myers Squibb.

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