
We thank Dr Nezami and colleagues for their interest in our study. As they note, statin therapy has been associated with improved clinical outcomes after percutaneous coronary intervention. Although an early observational study suggested an interaction between atorvastatin and the antiplatelet effect of clopidogrel in the acute phase of treatment, presumably due to shared metabolism via the CYP3A4 pathway, this does not occur during maintenance clopidogrel therapy and was not confirmed in subsequent randomized pharmacodynamic studies. In addition, clinical outcome studies have failed to identify a clear impact of statins on the ability of clopidogrel to reduce recurrent ischemic events. In order to address the questions of Dr Nezami and colleagues about our trial, we assessed the effect of statin use in GRAVITAS by incorporating this covariate into our time-dependent multivariable regression model. Statin use was not associated with clinical outcome at 60 days (adjusted hazard ratio [HR] 0.89, 95% confidence interval [CI], 0.27–3.02) or 6 months (adjusted HR 0.86, 95% CI, 0.39–1.91), nor did it affect the relationship between on-treatment reactivity <208 PRU and outcome at either time point (adjusted HR 0.23, 95% CI, 0.05–0.98, p=0.047 at 60 days and adjusted HR 0.54, 95% CI, 0.28–1.04, p=0.064 at 6 months). Admittedly, the power to detect differences in outcomes according to statin use was severely limited because periprocedural myocardial infarction was not a component of the primary end point and 88% of the enrolled patients were taking a statin at discharge. We unfortunately did not systematically collect the types of statin used, and therefore we cannot address potential differences between lipophilic and hydrophilic statins. However, posthoc analyses of several large randomized clinical trials, including Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22), found no impact of adding atorvastatin to patients already on clopidogrel.

Dr De Miguel Castro and colleagues posit that a threshold value for on-treatment reactivity may depend on clinical presentation. Yet in GRAVITAS we found that the threshold of on-treatment reactivity ≥208 PRU was independently associated with clinical events even after adjustment for acute coronary syndrome. In the recently reported Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study, which involved >8000 patients treated with percutaneous coronary intervention, on-treatment reactivity >208 PRU was associated with a >5-fold risk of definite stent thrombosis after adjustment for acute coronary syndrome presentation. Similarly, in a pooled patient-level meta-analysis of observational studies, there was no interaction between clinical presentation with or without acute coronary syndrome and the risk of death, myocardial infarction, or stent thrombosis in patients with high on-treatment reactivity. Differences in analytic approaches, combined with differences in population characteristics, may also explain differences in risk thresholds identified by different studies. Receiver operator characteristic (ROC) curve analysis like that used by de Miguel Castro and other investigators defines a statistically optimal threshold by identifying the cut-off that provides the greatest sum of sensitivity and specificity. However, this approach has several limitations, because (1) if the sample size is small, the event rate low, or both, the error of the estimate for the optimal cutoff increases (exemplified by a stair-step rather than smooth appearance of the ROC curve); (2) the statistically optimal cut point may not be clinically relevant, because a clinician may not afford equal weight to sensitivity and specificity when assessing risk; and (3) ROC curve analysis may underestimate the prognostic strength of a risk marker, and therefore HRs or reclassification analysis may be more appropriate to assess the utility of prognostic tests. Although identifying the best cut-off for on-treatment reactivity is a laudable goal, the GRAVITAS analysis demonstrates that patients who achieved on-treatment reactivity <208 PRU did better, regardless of clinical presentation; moreover, this cut-off has subsequently been prospectively validated in an independent study.

Although temporal variation in platelet reactivity represents a potential challenge in patient management, we believe that the findings of our study support the prognostic utility of platelet function testing both early and late after percutaneous coronary intervention, as noted by other investigators. Since percutaneous coronary intervention may itself perturb platelet reactivity, platelet function assessment and intensive treatment preceding angiography and intervention, as proposed by de Miguel Castro and colleagues, would seem to be a reasonable approach, although this was not evaluated in GRAVITAS.

Disclosures

Dr Price reports receipt of consulting fees from Bristol-Myers Squibb/sanofi aventis, Daiichi Sankyo/Eli Lilly & Co, Accumetrics, AstraZeneca, Johnson & Johnson, The Medicines Company, Merck, Janssen Pharmaceuticals, and Medicare; speaker’s fees from Daiichi Sankyo/Eli Lilly & Co and AstraZeneca, and grant support from Bristol-Myers Squibb/sanofi aventis, Accuretics, and Quest Diagnostics. Dr Angiolillo reports receipt of consulting fees from Bristol-Myers Squibb/sanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, AstraZeneca, The Medicines Company, Portola, Novartis, Medicare, Accuretics, Arena Pharmaceuticals, and Merck; and speaker’s fees from Bristol Myers Squibb/sanofi-aventis and Daiichi Sankyo/Eli Lilly & Co. Dr Tanguay reports receipt of consulting and speaker’s fees from Bristol-Myers Squibb/sanofi aventis, Daiichi Sankyo/Eli Lilly & Co, GlaxoSmithKline, Abbott Vascular, and AstraZeneca; and speaker’s fees from Boehringer Ingelheim. Dr Berger reports receipt of consulting fees from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo/Eli Lilly & Co, Medicare, and Ortho McNeil. Dr Cannon reports receipt of consulting fees from Bristol-Myers Squibb/sanofi aventis, Alynlam, and Novartis and grant support from Intekrin Therapeutics, and he serves on the advisory board for GlaxoSmithKline and Merck. Dr Teirstein reports receipt of consulting fees from Daiichi Sankyo/Eli Lilly & Co and Accuretics. Dr Topol reports receipt of consulting fees from Bristol-Myers Squibb/sanofi aventis and Daiichi Sankyo/Eli Lilly & Co. The other authors report no conflicts.

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_Circulation_. 2012;125:e571-e572
doi: 10.1161/CIRCULATIONAHA.112.092239
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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