LETTERS TO THE EDITOR

For How Long Should Treatment With Clopidogrel Be Continued After Coronary Stent Implantation?

In their editorial (1) in *JACC* on the analysis of the results of the TARGET study (2), Tcheng and Campbell try to provide answers to five key questions regarding clopidogrel therapy as an adjunct to percutaneous coronary intervention (PCI). The fifth question is: How long should treatment be continued? The recommendation in the editorial is to continue therapy for one year. This is based on results of the PCI-CURE and CREDO studies (3,4). However, both these studies compared a strategy that included both pretreatment (before PCI) and long-term treatment after PCI to a strategy of treatment for one month only after PCI. In both these trials, the first strategy was superior; however, it is not clear whether the long-term benefit (from one month to one year) is related to the pretreatment or to the continuation of clopidogrel beyond one month after PCI.

Data presented in the analysis of TARGET (2) show that pretreatment is associated with additional benefit, beyond one month. Death or myocardial infarction (MI) rates at one month were 6.2% and 10.1%, with and without pretreatment, respectively (3.9% absolute difference). This absolute difference increased to 5.2% at six months (7.8% compared to 13% with and without pretreatment). Thus, the pretreatment itself explains additional absolute reduction of 1.3% in death or MI (from one to six months). The conclusion from this analysis is that most of the benefit in PCI-CURE and CREDO is from the pretreatment rather than from the continuation of clopidogrel treatment to one year. I believe that Tcheng and Campbell should alter their fifth recommendation because, based on the above analysis, it is unclear whether continuation of clopidogrel treatment beyond one month after PCI is associated with any benefit. I would certainly agree that pretreatment is highly recommended.

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REPLY

By his letter, Dr. Rozenman raises not only one but several critical issues regarding the optimal duration of clopidogrel treatment. These include the interpretation of clinical trial results relative to primary versus substudy analyses, and (implicitly) the impact of economics on applying trial findings to the real world.

The interpretation of clinical trial results is best approached with rigor and caution. The PCI-CURE analysis (1), though prospectively defined, is nevertheless a post-randomization substudy better considered as "hypothesis-generating." Confounders may have been introduced that could account for some of the differences observed at both 30 days and long-term. It is not possible to determine the relative contributions of pre-treatment versus treatment after one month to the long-term efficacy results observed in PCI-CURE. What is clear is that additional benefits accrue to patients in the active treatment arm between 30 days and one year.

The approach to answering the duration-of-therapy question ultimately will require a series of randomized, prospective trials. A component of this question is approached in CREDO (2) (direct comparison of pre-PCI loading followed by long-term therapy, versus "uncovered" PCI, followed by post-PCI treatment without loading, followed by four weeks of short-term therapy). Conducted in a prospective, randomized fashion, the result was actually *negative* at the primary 28-day end point (relative risk reduction [RRR] of 18.5%, 95% confidence interval [CI] −14.2% to 41.8%, p = 0.23). What was observed in the CREDO trial was a *greater* absolute difference in the composite end point rates between 29 days and one year (after patients in the comparator arm had been placed on placebo treatment) than that seen between PCI and 28 days. In CREDO, it was not until after the first 28 days that the event curves separated sufficiently to have a statistically significant difference (29-day to one-year RRR of 37.4%, 95% CI 1.8% to 60.1%, p = 0.04, resulting in an overall one-year RRR of 26.9%, 95% CI 3.9% to 44.4%, p = 0.02). Given the similar trend observed in PCI-CURE (and the absence of the definitive trials to address the issue), it would appear that short-term therapy is best thought of as reducing the propensity for early subacute stent thrombosis, whereas longer-term therapy is efficacious in reducing adverse cardiovascular events including death, myocardial infarction, and stroke.

Economics become central to rational treatment when a therapeutic imparts a high direct cost to the consumer and when the cost-effectiveness is marginal. Duration of therapy would not be an issue if clopidogrel were inexpensive. Economic issues, however, do not invalidate efficacy considerations. Instead, we should focus on the "cost of living" component by identifying strategies, both locally and nationally, for assuring the delivery of optimal treatments to those who stand to benefit.

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