Regulatory Perspective on Embolic Protection Device Approval for Saphenous Vein Graft Stenting With a Single-Arm Trial Using Risk-Adjusted Prediction Model

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The article by Coolong et al1 in this issue of Circulation identifies potential predictors of 30-day major adverse cardiac events (MACE) after saphenous vein graft (SVG) percutaneous coronary intervention (PCI) with embolic protection devices (EPDs). These predictors, angiographic estimates of plaque volume and SVG degeneration, were derived from patient-level data on 3958 patients enrolled in 6 clinical trials of SVG EPDs. As discussed in their article, the authors have incorporated these predictors into a model that seeks to accurately predict 30-day MACE rates for such devices. The authors make an intriguing proposal that their covariate-adjusted, historically derived model could be used to construct an objective performance goal for the evaluation of novel EPDs. The implementation of such a model seems an attractive goal not only because of savings in time and cost for future clinical trials but also because of the potential to allow effective devices to reach patients more expeditiously. However, putting the model into practice will likely need some additional forethought and further collaborative effort to ensure that the effectiveness and safety of these devices are adequately evaluated. Although the investigators did not submit the actual predictive model within their article, we appreciate this opportunity to provide our insight into how such a model could potentially be integrated into future trials supporting regulatory approval.

Regulatory Approaches to SVG EPDs for PCI

The Food and Drug Administration (FDA) regulates devices in 3 classes, with the highest-risk devices in class III, moderate-risk devices in class II, and lowest-risk devices in class I. Medical devices in class III support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury. These devices reach the market through the premarket approval process. Because of the level of risk associated with class III devices, the FDA has determined that adequate clinical trials are required to ensure the safety and effectiveness of class III devices. Class II devices, which involve moderate risk, generally require 510(k) premarket submission. The 510(k) submission must demonstrate that the device to be marketed is at least as safe and effective as, ie, substantially equivalent to, a legally marketed device, or “predicate device,” that is not subject to premarket approval. About 10% of devices submitted to the FDA through the 510(k) process require clinical data.

EPDs used during PCI in SVGs are regulated as class II devices, requiring clearance of a 510(k) before marketing. Although 510(k) devices may be shown through laboratory and bench testing to be substantially equivalent to a marketed device, clinical data also may be needed to establish safety and effectiveness and therefore substantial equivalence. In line with this regard, the FDA required adequate clinical trials to ensure reasonable safety and effectiveness for EPDs used in the setting of PCI for SVGs. On the initial introduction of these devices, there was some uncertainty regarding the most appropriate control group. It was not clear whether a concurrent control was needed or whether an adequate performance goal could be generated from historical data (or other means). This question was discussed by a Circulatory System Devices Advisory Panel meeting on February 5, 2001.2 The advisory panel agreed that the most appropriate control would be the “standard of practice,” which at the time was no EPD use, and recommended that randomized controlled trials were necessary. After the first EPD was cleared and marketed, the standard of practice shifted to become use of an EPD; thus, ongoing and new clinical trials incorporated cleared devices as active controls in noninferiority comparisons.

Implementing the Prediction Model for New EPDs

There are a number of important considerations regarding the validity of the proposed model, including confirmation of the poolability of the studies within the model, generalizability of the model itself to outside patient populations (external validity), and the modeling procedure (internal validity).

Trial poolability of the predictive model will be an important issue for a new EPD market approval using this method. The authors performed an analysis using a Bayesian hierarchical model to estimate the intratrial correlation coefficient and concluded that there was little unexplained variation between trials used to generate the model. Although the Bayesian analysis indicated that the between-trial variation is relatively small, those trials nevertheless may be somewhat heterogeneous from a regulatory perspective. For instance, the
CardioShield Application Protects During Transluminal Intervention of Vein Grafts by Reducing Emboli (CAPTIVE) trial, which evaluated the EmboShield device, failed to show both superiority to conventional guidewire and noninferiority to GuardWire. Second, the Embolic Protection Transluminally with the FilterWire EZ Device in Saphenous Vein Grafts (BLAZE) II study, unlike the others, was a single-arm trial in which the reported 30-day MACE rate was 3.8%, much lower than in the other 11 EPD treatment arms in the analysis (range, 8.2% to 11.4%).

Generalizability is another critical component for evaluating the prediction model for use in single-arm trials seeking market clearance of new EPDs for SVG PCI. The assumption that poolability of trials in this type of prediction model is appropriate rests on accepting that the study populations are homogeneous. In this respect, the prediction model may have powerful advantages for future trials with study populations homogeneous to those used to generate the prediction model. However, this advantage may not apply to specific indications for an EPD evaluated in populations dissimilar to those used to generate the model.

The 2 novel angiographic risk factors proposed, estimated plaque volume and SVG degeneration score, are conceptually intriguing and appear to be clinically sound. However, consistency and reproducibility in their measurement in practice may need to be further demonstrated before their acceptance. It also appears that these variables are not entirely objective, despite being measured by a quantitative coronary angiography system. This may introduce a level of bias, especially in single-arm studies, that could unpredictably affect the validity of the predictive model. The use of angiographic core laboratories with prospectively outlined and detailed performance procedures may minimize this potential measurement bias but with some uncertainty likely remaining.

Additionally, the univariate logistic regression analysis used to assess the relationship between the presence of diabetes and 30-day MACE showed that there was a protective relationship with this covariate. This is a curious finding in that diabetes is a significant risk factor for PCI procedures. However, the authors note that the univariate analysis was confounded by the finding that diabetics tended to be younger and had lower SVG degeneration scores and smaller estimated plaque volumes. Because the actual model was not provided in the article, we cannot confirm whether this bias was sufficiently adjusted for by the multiple logistic regression model selection; thus, it seems that the presence of diabetes should be included in multivariate logistic regression analysis.

Most critically, sensitivity analyses using external data sets such as other trials not used to generate the model might be a way to validate the prediction model. Such an analysis is important primarily to evaluate whether the model can actually predict 30-day MACE. Moreover, even after adoption of the prediction model, it would seem most appropriate for the model to be continuously updated as new data become available, understanding that clinical settings, adjunctive medical treatments, and novel or iterative devices may be introduced or change over time. Furthermore, it should be noted that although the authors’ study may appropriately conclude that EPDs used for PCI in SVGs are beneficial compared with conventional guidewire use, across multiple EPD types, this does not guarantee that future EPDs will have similar safety and effectiveness profiles.

Conclusions
A number of elements need to be considered when studies are designed to support medical device market approval. These include defining appropriate target populations, establishing the correct risk-to-benefit ratio based on safety and effectiveness, and choosing appropriate end points for the assessment of device performance. In regard to EPDs for PCI of SVG lesions, the FDA has historically considered randomized controlled trials most appropriate to address variation between studies, including differences in lesion or vessel characteristics, device types, treatment modalities (such as stent type or use of glycoprotein IIb/IIIa antagonists), and patient populations.

Coolong et al conclude that their covariate-adjusted prediction model of 30-day MACE can be used to generate patient- and trial-specific objective benchmarks for the evaluation of novel devices in single-arm studies. Accumulating data and increased knowledge about the performance of EPDs in SVGs have made this approach possible. It follows that our regulatory approach toward these devices should evolve as we gain more detailed understanding of the devices and diseases that they are designed to treat. Such a philosophy is incorporated into the “least burdensome” approach that the agency is mandated by law to follow. Discussions between the agency and its stakeholders is strongly recommended early in the planning stages of clinical trials to reach agreement on the most appropriate, least burdensome path.

However, in many circumstances, clinical data are held by proprietary interests, limiting the free exchange of data across the various stakeholders within the medical community. For predictive models to be adopted broadly, a cooperative approach between the relevant stakeholders is of paramount importance. Collaboration between industry, academia, and regulatory bodies will be necessary if we are to learn fully from previous clinical trials. Such cooperation will be key to developing novel regulatory pathways for promising medical devices.

We are pleased to see that such efforts are ongoing, as exemplified by the Coolong et al article, and we encourage all stakeholders to adopt and expand such collaboration. Moreover, we believe that such an approach can be applied to other areas of cardiovascular research and medical devices, and we welcome further discussion on the implementation of similar approaches.

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Disclosures
None.
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