EDITORIAL COMMENT

Late Ischemic Events After Clopidogrel Cessation Following Drug-Eluting Stenting

Should We Be Worried?*

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Among patients with obstructive coronary artery disease, percutaneous coronary intervention (PCI) has become a widely used therapy, especially among those presenting with acute ischemic events such as myocardial infarction and unstable angina (1). Since its introduction into clinical practice, PCI has had two Achilles’ heels: early thrombosis and delayed restenosis, leading to the need for repeat procedures. Advances in antithrombotic therapy have lowered the risk of acute thrombosis and the associated ischemic complications of death and myocardial infarction (2). Coronary stenting has had a major impact on our ability to successfully treat the acute problem of plaque dissection and abrupt closure and markedly reduce late restenosis and the need for repeat revascularization procedures (3).

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As the procedure has moved from one largely involving balloon angioplasty to one centered around stenting, first with bare-metal stents (BMS) and now with drug-eluting stents (DES), the distribution of procedural complications also has changed, especially regarding the timing of risk. In the era of balloon angioplasty, abrupt closure was mainly concentrated in the first 24 h after the procedure. If patients survived that very early period without an ischemic complication, then there was a gradually increasing risk of restenosis over approximately the next 6 months. Advances in antithrombotic therapy lowered the risk of abrupt closure, and the risk of restenosis with subsequent repeat revascularizations was dramatically lowered with the increasing use of stents. However, simultaneously, subacute stent thrombosis emerged as a new, dramatic clinical problem with severe clinical consequences (4). Fortunately, treatment with dual antiplatelet therapy with the combination of aspirin and a thienopyridine was found in randomized clinical trials to reduce this risk substantially (5). Observational studies then suggested that this combination of drugs was needed for 2 to 4 weeks after the procedure because there seemed to be an early clustering of risk and ischemic events attributable to subacute stent thrombosis (6).

Because the putative mechanism of benefit of DES would be less neointimal proliferation within the stented segment compared with that induced by BMS, it was acknowledged that implantation of a DES might require antiplatelet therapy beyond the 1-month period standard for BMS. The key trials performed with the DES chose durations of antiplatelet therapy based largely on preclinical experience coupled with knowledge of the local drug release kinetics. These trials, largely performed in low-risk patients based on clinical and angiographic criteria, suggested that this strategy was reasonable (7,8); thus, dual antiplatelet therapy for 3 months (sirolimus) and 6 months (paclitaxel) became standard therapy after DES implantation (2,9,10). Data from the CREDO (Clopidogrel for Reduction of Events During Observation) (11) and CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trials (12) supported more prolonged therapy up to 1 year with the combination of aspirin and clopidogrel, especially among specific groups of patients, including those with a recent acute coronary syndrome.

Several months after the introduction of the sirolimus-eluting stents into U.S. clinical practice, the Food and Drug Administration issued a warning to physicians regarding the risk of these new stents and subsequent thrombosis (13). During the last few years questions have been raised about the thrombotic risks that may be associated with delayed endothelization of the DES (14), and the sponsors and clinical investigators in the field provided reassurances based on the low absolute risk of these events (15). The latest perspective on this evolving controversy with the highest level of clinical evidence to date is put forward by Pfisterer et al. (16) in this issue of the Journal.

The BASKET-LATE (BAasel Stent Kosten-Effekivitäts Trial-LAtte Thrombotic Events) Investigators present the long-term follow-up of a cohort of patients from the BASKET trial (17), a study of a randomized comparison of BMS with DES among a broad spectrum of unselected patients from a single practice. In the BASKET trial, all patients received the combination of aspirin plus clopidogrel for 6 months; after the cessation of clopidogrel, the investigators prospectively followed patients who had had survived the first 6 months without an ischemic event. Between 7 and 18 months, they observed an increase in the death/myocardial infarction composite among the DES patients compared with the BMS patients (adjusted hazard ratio 2.2,
The investigators had limited angiographic data to document these clinical events as definite late thromboses, but the data available are consistent with the overall observation. Their conclusion is carefully worded to note that there was an observed continued lesser incidence of target vessel revascularization with the DES and that the late clinical events may only "possibly" be related to late stent thrombosis.

Comments are warranted on the clinical dilemma leading to this report, the study methodology and conduct, and the limitations of the data and its interpretation. The incorporation of DES technology into clinical practice occurred over approximately 18 months and has resulted in the use of this technology in at least 80% of all U.S. PCI procedures (18,19). As is frequently seen with new cardiac devices, a rapid increase in clinical adoption quickly outstripped what is known about the device from limited clinical trials. Although BASKET-LATE was a single-center study from a hub-and-spoke hospital system, the investigators should be congratulated for efficiently using a previously randomized study cohort for this long-term observational study that preserves some, but not all, of the internal validity of a randomized comparison. Because most of the effort and resources go into the organization and conduct of the original trial, adding a second question and extending follow-up is logistically efficient and scientifically helpful.

These investigators also demonstrate great commitment to the research process, giving their study broader applicability than might be typically ascribed to a single center study, as they enrolled 84% of 988 consecutive patients during a 13-month period. This complete integration of clinical research and clinical practice deserves recognition and praise. It also makes the results applicable to the broader world of clinical practice as demonstrated by the large percentage of patients with high-risk clinical characteristics (including acute coronary syndromes) as well as challenging anatomic subsets (chronic total occlusions, bifurcations, and vein graft disease). The rate of follow-up was very high, and the suspected clinical events were adjudicated by a committee blinded to the type of stent. The investigators also quite cautiously and conservatively offer up their observations, taking care to point out that the events were infrequent, that their sample size was small, and that they had limited angiographic data to confirm the events as definite stent thrombosis, which is noteworthy as important discussions can be sidetracked and further investigation delayed by emotional displays on both sides of the argument (20).

It deserves mention, congratulations, and some discussion that the authors received no industry sponsorship for this study. The medical products industry provides most of the financial support for clinical research involving drugs and devices (21,22) in the U.S. This is neither surprising nor intrinsically bad or improper. Our own research group at the Duke Clinical Research Institute receives the majority of its funding from industry sources. Little funding from public sources is devoted to the study of drugs, devices, or technology despite the fact that the public health as well as criteria for use and reimbursement are completely dependent on having an adequate knowledge base. During the last 20 years, there has been much productive collaboration between academic investigators and industry sponsors. Collaborative investigation into fibrinolysis, statins, angiotensin-converting enzyme inhibitors, beta-blockers, antithrombotic therapies, and implantable defibrillators has resulted in knowledge about drugs and devices that has dramatically improved the plight of patients with cardiovascular disease.

However, the BASKET-LATE findings point to potentially troubling changes in the clinical research world. Although the possible risk of DES thrombosis was identified in preclinical studies and unproven signals have been seen in clinical data, studies funded by the stent industry have been slow to follow-up. It took an independent study funded by the Swiss government and a registry funded by a pharmaceutical firm (23) to raise this signal to a high level of consciousness. Research focusing on regulatory approval focuses on the appropriate need of companies that market medical products to optimize individual products as financial assets. Although this system obviously advances better public health through appropriate product approval and labeling, it does not necessarily have the imperative either to fine-tune the posing of research questions to maximize the impact on clinical care or to improve the public health. Important questions that might lead to less use of a product often lack sufficient funding to be pursued, and comparative trials of commonly used therapeutic strategies infrequently are performed, particularly when the alternative is generic and not driven by marketing concerns. One disconcerting feature of this issue is the continued growth of research as a business that is disconnected from the continuum of knowledge needed to inform patients and their doctors about therapeutic options. Some members of the commercial contract research industry have identified academic health centers as the competition rather than collaborators in a mutual effort to improve the knowledge base for improved health outcomes (24); the commercial contract research industry, as with any profit-making entity, seeks mainly and legitimately to pursue that profit without the ethical imperative to improve either the research process or the public health. Clinical practitioners and academic leaders need to push for collaboration with industry that is mutually respectful of each other's goals while maintaining a critical degree of independence, especially regarding data management and analysis and result interpretation. To do otherwise is to abdicate our contract with society.

What might the results from BASKET-LATE mean for our patients and for the continued development of DES technology? Given the unprecedented uptake of DES into cardiovascular care, are we committing millions of patients to lifelong potent antithrombotic therapy with its attendant costs and risks, especially regarding bleeding or ischemia after interruption? Spertus et al. (23) recently reported that, among a group of patients receiving DES after acute

\[ p = 0.03 \]
myocardial infarction, 13.6% had discontinued clopidogrel by 30 days after hospitalization and had a highly significant increased risk of death during the next 11 months (adjusted hazard ratio 9.0, 95% confidence interval 1.3 to 60.6). These findings, coupled with BASKET-LATE, have led us to the view that patients with DES should remain on clopidogrel and aspirin if at all possible until adequate studies are completed that, first, fully depict the trade-off of the benefit of DES with the risk of late thrombosis and, second, lead us to understand the time-oriented risk of stopping thienopyridine treatment over a course of years rather than months. Wise clinicians also should carefully consider the likelihood that a patient will be able to adhere to a long-term thienopyridine regimen and should consider a BMS strategy when the risk of discontinuation exceeds the potential benefit of the well-proven prevention of restenosis with DES. Understanding barriers to access to medications and strategies to improve adherence are desperately needed (25).

Given the infrequent occurrence of many late events, it is difficult, as with BASKET-LATE, to enroll enough patients in studies to place a high degree of certainty around an observation. Investigators with access to relevant databases, including academics, industry colleagues, and regulatory authorities, should figure out efficient ways to collaborate and share data and observations. This information should be rapidly published and disseminated and should serve as hypotheses for more prospective studies. Analyses need to consider how best to balance the competing issues of inhibiting neointimal proliferation and reducing endothelial healing. Some appropriate answers might use techniques of decision analysis that incorporate knowledge of patient values and choices while other answers will come from further consideration of the technology itself. Local drug delivery is intuitively appealing, and perhaps the next generation of polymers, stent materials, including bioabsorbable materials, and drugs may help address some of these risks.

Equally important is a call to improve the research process so that questions vital to society’s health can be quickly prioritized and answered by a better integrated system of clinical care and clinical research. Regarding the specific clinical question of late ischemic events, understanding the relationships among choice of stenting, risk of restenosis, adherence to antithrombotic therapies, and risk of late cardiac events is critical. Clearly the best way to answer this question would be through a randomized clinical trial. Nay-sayers point out that a trial focusing on late cardiac events is critical. Clearly the best way to answer this question would be through a randomized clinical trial.

However, there are many other unanswered questions being asked every day by concerned clinicians who are limited in their ability to have them enter the national discussion or to see them quickly answered. That should worry all of us enough to be inspired to develop a more effective and responsive clinical research system.

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