Editorial Comment

Vascular Responses to Percutaneous Coronary Intervention With Bare-Metal Stents and Drug-Eluting Stents: A Perspective Based on Insights From Pathological and Clinical Studies*

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The era of percutaneous coronary intervention (PCI) has led to substantial changes in the management of patients with acute coronary syndromes and stable coronary heart disease, with an associated range of impacts on the course and outcomes of subsets of patients with these conditions. Interventional cardiology has moved from percutaneous transluminal coronary angioplasty (PTCA), with or without administration of tissue plasminogen activator or other thrombolytic agent, to the combined use of PTCA and implantation of a bare-metal stent (BMS) or multiple stents, to PTCA and implantation of 1 or more drug-eluting stents (DES) (1–3). As first-generation DES, paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) have had extensive clinical application. The evolution in treatment has been associated with a progressive decrease in short-term complications, including early thrombosis, and a decrease in short-term and long-term restenosis (2,3). Optimal results with PTCA and stent placement requires concomitant antithrombotic drug therapy to avoid short-term thrombotic occlusion (4). Although the implementation of first-generation DES has resulted in a marked decrease in the incidence of restenosis, the DES are affected by a certain incidence of late and very late coronary thrombosis (2–4). The first-generation DES are now being followed by second-generation and newer DES (3).

The number of patients receiving PCI and stent implants now numbers in the millions (2–4). Follow-up of these patients with clinical evaluation and imaging studies has yielded abundant data regarding clinical outcomes based on these parameters. Clinical features and imaging results also serve as the basis for assessment in randomized clinical trials. Conversely, relatively few published studies have provided information derived from direct pathological evaluation of stented coronary arteries, and these observations are necessarily limited to autopsy series of a relatively limited number of patients. The relative paucity of pathological observations is related to a constellation of factors, including the relatively low autopsy rates in most countries and the technical challenges of adequately examining coronary arteries with implanted stents. Nevertheless, direct pathological examination has an important role in providing observations and insights not available by any other approach.

Insights from pathology studies have served as a basis for evolution in approaches to PCI. Pathology studies showed that PTCA results in arterial injury of variable degree, including endothelial damage, plaque fractures, variable damage and dissection of the media, and mural platelet and fibrin thrombus deposition (5–7). The vascular responses to PTCA were identified as: 1) recoil and negative remodeling or contraction of the coronary artery segment after dilation; 2) endothelial damage, often with associated thrombosis; and 3) concomitant progressive fibrocellular intimal thickening involving perturbation of vascular smooth muscle cells leading to deposition of extracellular matrix and variable proliferation (8,9).

These vascular responses to PTCA, characterized by remodeling and neointimal proliferation, were found to be responsible for the rapidly progressive and frequent restenosis within several months after PTCA. With the modification of PCI to include BMS placement, the development of restenosis was reduced in frequency and average time of onset, largely due to elimination of the elastic recoil and negative remodeling (9). However, in coronary artery segments with BMS and restenosis, pathology studies demonstrated the same neointimal proliferation as the culprit process (10,11). Proliferation of smooth muscle cells and extracellular matrix synthesis were identified as key components of the process (9–11). Recent studies have demonstrated colonization of the neointima by extravascular cells, including endothelial progenitor, dendritic, and neural crest-derived cells as well as inflammatory cells, and have identified a counterbalancing role for apoptosis, adding further complexity to the process (12,13). Predisposing factors for in-stent restenosis were identified as stenting that is accompanied by medial damage or penetration of the stent struts into the lipid core of plaques. Both of these factors were implicated in inducing increased arterial inflammation, which in turn can drive increased intimal proliferation (10).
The basic concept for the development of DES is that coating the stents with a drug with antiproliferative properties will significantly reduce post-PTCA intimal proliferation and subsequent restenosis (2). First-generation DES, including PES and SES, have markedly decreased the occurrence of post-PTCA restenosis. However, DES have been found to have the complication of late thrombosis and very late thrombosis (4). Virmani et al. (10,11,14,15) have contributed significantly to the investigation of the pathological correlates of BMS and DES implantation, including comparative findings in DES and BMS. In a previous study, multiple features of coronary segments with DES were characterized from a registry of 81 autopsied patients with DES (14). The basic feature of neointimal thickening was again identified. However, multiple logistic modeling with generalized estimation equations demonstrated that impaired endothelialization was the best predictor of thrombosis. The measured parameter that best correlated with endothelialization was the ratio of uncovered to total stent struts per histological section. Nevertheless, multiple factors contributing to delayed re-endothelialization with DES have been identified, including an inflammatory response to the PTCA and stent placement as well as hypersensitivity reactions to the polymers employed in the DES, before the recent advent of polymer-free DES (16). The findings, taken together, have pointed to the importance of heterogeneity of healing and incomplete healing of the stented segment in the pathophysiology of late stent thrombosis.

In this issue of the Journal, Nakazawa et al. (15) report on another pathological change, namely, atherosclerosis in the neointima, or neoatherosclerosis, in a registry series of 299 autopsies with 406 coronary stented segments (lesions), including 197 BMS and 209 DES (103 SES and 106 PES) with implant duration >30 days. Neoatherosclerosis was identified as clusters of peristrut lipid-laden foamy macrophages within the neointima with or without necrotic core formation. Approximately one-third of the neoatherosclerotic lesions lacked advanced features and appeared to be equivalent to fatty streaks in native arteries. The other two-thirds of the lesions had features of advanced lesions, including fibroatheromas, thin-cap fibroatheromas, and ruptures with thrombosis. Several of these lesions had features equivalent to vulnerable or unstable plaques of native coronary arteries (17). In all cases, however, there was no communication between the lesion within the stent and the underlying native atherosclerotic plaque.

In this registry series, the overall incidence of neoatherosclerosis was significantly greater in DES (31%) than in BMS (16%) lesions ($p < 0.001$). The median duration of stent implantation showing neoatherosclerosis was shorter in DES than in BMS: 420 days for DES and 2,160 days for BMS ($p < 0.001$). Complicated lesions characterized as thin-cap fibroatheromas or plaque rupture were more frequent but not significantly different in BMS ($n = 7, 4\%$) compared with DES ($n = 3, 1\%; p = 0.17$), but with relatively shorter implant times for DES (1.5 ± 0.4 years) compared with BMS (6.1 ± 1.5 years). By multiple logistic regression analysis, independent determinants of neoatherosclerosis were younger age ($p < 0.001$), longer implant durations ($p < 0.001$), SES usage ($p < 0.001$), PES usage ($p < 0.001$), and underlying unstable plaques ($p = 0.004$).

Thus, based on data from this autopsy registry series, neoatherosclerosis was found to be a more frequent pathological change in DES than in BMS and to occur earlier in DES than in BMS. Although unstable features of neoatherosclerosis occurred with BMS and DES, unstable neoatherosclerosis occurred with shorter implant duration with DES than BMS. These findings suggested a higher rate and more rapid onset of significant complications with first-generation DES than BMS. However, the incidence of thin-cap fibroatheromas and ruptured plaques with thrombosis were low for both groups, namely, BMS ($n = 7, 4\%$) and DES ($n = 3, 1\%$). The authors reached the general conclusion that the frequency of the development of neoatherosclerosis is such that the phenomenon likely represents an additional factor contributing to late thrombotic events in some patients and after shorter duration of implantation with DES than BMS implantation. However, the findings and conclusions regarding neoatherosclerosis need to be put into the context of other characteristics of the case series. The incidence of causes of death from stent-related thrombosis, restenosis without diffuse coronary artery disease, and diffuse coronary artery disease with restenosis were different in the 2 groups, with stent-related thrombosis higher in the DES group (20% vs. 4%) and the other 2 causes higher in the BMS group (13% vs. 3% and 14% vs. 3%). The DES group also had significantly more native unstable plaques and significantly longer stents implanted.

Clinical trials present a different perspective on the incidence of various complications of coronary stenting. A large meta-analysis including 18,023 patients in 38 randomized controlled trials with follow-up of up to 4 years and additional data on clinical outcomes for 29 other trials focused on risks of death, myocardial infarction, and stent thrombosis comparing BMS, SES, and PES (18). Mortality was similar in the 3 groups. The SES were associated with the lowest risk of myocardial infarction. There were no significant differences in the risk of definite stent thrombosis, confirmed by angiography or autopsy, during the interval of 0 days to 4 years. However, the risk of late definite stent thrombosis (>30 days) was increased with PES. Both SES and PES reduced the target lesion revascularization rate compared with BMS, but the effect was more pronounced with SES than with PES. In another meta-analysis of 35 trials involving 3,852 subjects with diabetes mellitus and 10,947 without diabetes, hazard ratios were near 1 for all comparisons in subjects with diabetes (19). Both types of DES were associated with a decrease in revascularization rates compared with BMS in subjects with and without diabetes. These meta-analyses support the overall safety and effectiveness of DES in patients with and without diabetes.
from a general population perspective. These conclusions are also supported by data from the largest registry (Swedish Coronary Angiography and Angioplasty Registry) reported by Langerqvist et al. (20). Similar results have been obtained with next-generation DES (21). Clinical studies also have provided direction for selection of patients for either BMS or DES according to criteria aimed at obtaining good outcomes with either BMS or DES (22–24).

The apparent discrepancies between the pathological and clinical studies need to be reconciled. A recommended approach is to focus on the strengths and limitations of the 2 types of studies. Randomized, controlled clinical trials, appropriately powered with large numbers of patients, clearly represent the strongest and statistically validated approach to determining clinical outcomes of a drug or intervention as well as comparative outcomes of different therapeutic approaches. A caveat, however, is that clinical trials necessarily provide a detailed analysis of a subset of an entire treated population in which trends may occur and not be captured in the clinical trial.

Conversely, whereas pathological studies, particularly autopsy series, are typically subject to selection bias regarding population outcomes, the pathological studies are uniquely capable of providing information regarding pathobiological phenomena that predispose to both good and adverse clinical outcomes. In other words, the strength and importance of the pathological studies is on identifying underlying mechanistic factors rather than on incidence of clinical outcomes, which is one of the strengths of the clinical trials. These considerations certainly pertain to the discussion regarding the coronary vascular responses to BMS and DES, including PES and SES. A related consideration is that advanced imaging techniques increasingly are being used to investigate vascular responses to interventions in living patients. This includes intravascular ultrasound coupled with what is called virtual histology as well as other approaches (25,26). Although virtual histology is an appealing concept, there remains a need for direct pathological confirmation of such imaging studies (17).

The pathological findings regarding vascular responses to BMS and DES clearly point to the importance of complete and effective covering of the stented neointima by endothelium, namely, endothelialization, or the lack thereof, in leading to good or adverse outcomes, including late thrombosis. However, the approach of evaluating endothelialization by determining numbers and percent of covered and uncovered struts is not a definitive approach to evaluating the extent and quality of endothelial covering of stented segments. Additional approaches are warranted, including en face scanning electron microscopy and immunocytochemistry in pathological studies as well as functional assessments (27–30). There also is an important place for experimental studies to evaluate pathophysiological phenomena, including extent of endothelial formation and maturation and control of fibrocellular intimal thickening, as new approaches to DES are being developed (31–33). Adverse reactions to stents involve multiple interrelated mechanisms including stent characteristics, procedural factors, individual susceptibility influenced by genetic predisposition and clinical factors, and the inflammatory response (9,16). Delayed or impaired re-endothelialization needs to be considered in the context of this complex milieu. Continued attention to the basic pathobiology of vascular responses to injury and interventions is of paramount importance in developing improved therapeutic interventions and optimal clinical outcomes.

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