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EDITORIAL COMMENT

Selection of Patients for Drug-Eluting Stents Based on Insurance Coverage

Pay or Don't Play*

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The introduction of coronary artery stents revolutionized percutaneous coronary intervention (PCI). Once the problem of early thrombosis was successfully attacked with the use of more aggressive dilation (1) and dual antiplatelet therapy (DAPT) (2), then stents became used routinely, initially to deal with issues of acute vessel dissection or acute vessel closure to greatly enhance the safety of the procedure itself (3), but with the hope that late restenosis would be minimized (4). It soon became apparent that the uncoated or bare-metal stents (BMS) or even heparin-coated stents did not solve the problem of late restenosis (5). To solve that problem, polymer-coated stents eluting antiproliferative drugs (also known as drug-eluting stents [DES]) were developed. The pivotal studies with both the sirolimus-eluting stent (6) and the paclitaxel-eluting stents documented dramatic reduction in restenosis at 6 months (7). By 2005, DES were used in 95% of hospitals in the U.S. sampled in the DEScovery registry (8) and in 90% of stent implantations (9).

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Concerns about the thrombogenicity of the DES arose soon after introduction into the U.S. market (10). Virmani et al. (11) reviewed the available literature in addition to their own observations showing delayed endothelialization, hypersensitivity reactions, and positive remodeling and called for more outcomes data before concluding the stents were safe. In mid-2006, a series of studies reporting increased stent thrombosis or even death after stopping antiplatelet therapy were presented (12–14) and were highly publicized (15). The effect of these early revelations on stent usage was dramatic. The percentage of DES usage dropped rapidly starting in the third quarter of 2006 (15). The U.S. Food and Drug Administration convened an advisory committee that supported the DES as safe, but did recommend that DAPT be continued for 1 year in complex lesions (off-label usage) (16). This early alert led to a chaotic situation in which physicians became aware that critical data were lacking. Hundreds of studies in 2007 and 2008 attempted to fill the void. These reports were composed of a number of post-hoc analyses: single-center data (17), multicenter national (18), regional registries (18), or the Medicare database (19,20). The studies mostly showed a low incidence of late thrombosis or late infarction and death in patients given DES (18–20). However, some studies did show an increased risk of thrombosis but not mortality in patients with DES placement (21,22).

A number of reports emphasized the need for prolonged DAPT. In many cases (definitely not all), DES stent thrombosis was related to discontinuation of clopidogrel (23) or occasionally both aspirin and clopidogrel for surgical procedures (24–26) or even endoscopies and dental extractions, often after a year past implantation. This relationship was addressed in the updated PCI guidelines published in early 2008 (27), which emphasized the need for uninterrupted DAPT for at least 1 year and preferably longer and never stopping aspirin. The updated guidelines specifically state: "For example, the clinician should not select a DES for a patient who does not have access to DAT for financial reasons or who is unlikely to be compliant in taking DAT" (27).

The importance of uninterrupted DAPT in the year after DES implantation was emphasized in a science advisory issued under the auspices of the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with Representation From the American College of Physicians (28).

The long-term studies have clarified the need for prolonged DAPT (29). Cessation of antiplatelet therapy has been identified as a major risk factor for DES thrombosis. Iakovou et al. (30) looked at the predictors of stent thrombosis in patients prospectively followed after DES placement. The single greatest predictor of risk for stent thrombosis was premature antiplatelet discontinuation (hazard ratio: 89.78, $p < 0.001$) resulting in a stent thrombosis rate of 29%. Ho et al. (31) proposed that part of the risk may stem from a "rebound" effect, noting increased thrombosis rates in the 90 days after discontinuing clopidogrel.

Recent evidence suggests that continuing DAPT beyond 1 year may provide additional protection against stent thrombosis for patients with DES. In a registry of 4,666 patients who underwent PCI, Eisenstein et al. (32) found that in patients with DES who were event-free at 12 months, continued DAPT out to 24 months was associated with a decreased risk of death (0% vs. 3.5%, $p = 0.004$) and

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death or myocardial infarction (0% vs. 4.5%, p = 0.001). It is noteworthy that continuing DAPT in patients receiving BMS provided no additional benefit. Taken all together, the data indicate that DAPT be maintained without interruption for a minimum of 1 year, with an increased potential for stent thrombosis if this guideline is not met. Clearly, patient compliance with the DAPT is exceptionally important. Thus, it is particularly unsettling that Spertus et al. (33), following patients who had a DES inserted for acute ST-segment elevation myocardial infarction and followed in the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery), have shown that nearly 14% of patients had stopped taking the drug within 30 days, with a 10-fold increase in mortality.

This brings us to the paper by Gaglia et al. (34) in this issue of *JACC: Cardiovascular Interventions.* They showed that in their own practice, they chose to insert DES less often in patients without insurance or on Medicaid than in other patients with private insurance. They also chose not to insert a DES in some African American patients as well. Unfortunately, there is no way to determine exactly why the decision was made not to insert the DES. We also do not know if this disparity was present in the early years or only after the importance of DAPT became known in late 2006.

As the investigators state, there are many reasons why the operator would choose not to implant a DES. A recent analysis, considering the cost of hospitalizations for myocardial infarction and the cost of long-term clopidogrel, suggests that DES are, in fact, more expensive over the long term than BMS (35) so that the cost of the device initially may be a factor. Reliability of the patient to take DAPT without interruption is a major consideration. A very important criterion is the ability to pay for the clopidogrel. Clopidogrel (sold in the U.S. under the brand name Plavix [Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, New York]) can be expensive. In St. Louis, Missouri, at a local independent pharmacy it costs $199.50 per month. (As an aside it is worth noting if one needs this drug and is in Paris, France, clopidogrel by the same manufacturer [and called Plavix] can be purchased for €56.82 [$77.82] or the generic version at €30.75 [$42.13] for a 28-day supply at any neighborhood pharmacy. Therefore, the price of Plavix in the U.S. is nearly 2.5 times the cost of Plavix in Paris, France. Gaglia et al. [34] imply that the cost of Plavix played a role in the decision not to insert a DES in patients without insurance. One can only speculate about the effects of clopidogrel costing less than 40% of the current price on the percent usage of the DES in these patients without insurance.)

Before concluding that this is strictly an economic issue, the fact that patients with Medicaid also were less likely to get a DES is noteworthy. The investigators do not state explicitly which Medicaid plans cover the cost of Plavix, but in my state of reference, Missouri, it does. Therefore, cost alone cannot be the sole determining factor in selecting who gets the DES and who gets a BMS or no stent. Whereas the multivariable logistic analyses did identify lack of insurance and race as the only independent variables associated with DES insertion, the patients without insurance had a higher incidence of shock on presentation, acute coronary syndrome, and a lower incidence of previous PCI, all of which have been shown to be associated with a lower likelihood to insert a DES (9).

The fact that patients without insurance and those on Medicaid were less likely to be given DES does suggest that the physicians at Washington Hospital were making a decision partly based on likelihood to maintain DAPT therapy, either on the basis of economics or patient reliability. Until the need for prolonged uninterrupted DAPT is reduced, presumably through reengineering of the stents themselves, or possibly by reducing the cost of the DAPT, perhaps to at least the cost comparable to that in other developed countries, these disparities will continue.

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