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"Off-Label" Stent Therapy

2-Year Comparison of Drug-Eluting Versus Bare-Metal Stents

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Objective The aim was to compare 2-year outcomes with the routine use of drug-eluting stents (DES) (>75% "off-label") with a comparable group treated with bare-metal stents (BMS).

Background Safety concerns >1 year from implantation have been raised about DES used "off-label." There are limited data comparing DES and BMS in "off-label" patients.

Methods Clinical outcomes (nonfatal myocardial infarction [MI], all-cause mortality) were assessed in 1,164 consecutive patients who received BMS in the year before introduction of DES at Wake Forest University Baptist Medical Center and 1,285 consecutive patients who received DES after it became our routine choice. "On-label" stent use was defined as treatment for a single de novo lesion <30 mm, without recent MI or other major illnesses.

Results At 2 years, the hazard ratio for DES compared with BMS for nonfatal MI or death was 0.77 (95% confidence interval [CI] 0.62 to 0.95), for all-cause mortality 0.71 (0.54 to 0.92), and stent thrombosis (ST) 0.97 (0.49 to 1.91). "On-label" stent procedures were associated with lower risk of MI, death, and ST than "off-label" stent procedures. For "off-label" stent procedures, the hazard ratio for DES compared with BMS for nonfatal MI or death was 0.78 (95% CI 0.62 to 0.98), all-cause mortality 0.72 (0.54 to 0.94), and ST 0.91 (0.46 to 1.80). The hazard of nonfatal MI or death was similar or lower for DES than BMS in high-risk subgroups, including renal failure and recent MI.

Conclusions The routine clinical use of drug-eluting stents for "off-label" indications was associated with lower nonfatal MI and death at 2 years than in a comparable group of patients treated with BMS. (J Am Coll Cardiol 2008;51: 607–14) © 2008 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have reduced the incidence of angiographic and clinical restenosis compared with bare-metal stents (BMS) in randomized clinical trials (RCT) of highly selected patients (1,2). This benefit appears to persist for up to 4 years after stent implantation (3). This has led to the widespread use of DES, including in patients who would not have met the eligibility criteria for inclusion in

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the RCT of DES versus BMS. However, recent data suggest that DES may be associated with an increased rate of late (>1 year) stent thrombosis (ST), myocardial infarction (MI), and death compared with BMS (4–6), particularly in patients not receiving clopidogrel (7). Because of concern of adverse late events with DES, the U.S. Food and Drug Administration (FDA) convened a panel to review available data from both pivotal RCT of DES versus BMS and post-RCT registry and single-center studies (8,9). Based on review of these data, the panel concluded that when DES were used for their approved indications ("on-label") the risk of late DES thrombosis did not outweigh the advantages over BMS in reducing rates of repeat revascularization (10). In contrast, the panel concluded, and the FDA concurred, that adverse late events occurred at a sufficient incidence to raise concern about the safety of "off-label" DES use (10).

Despite the panel's conclusions, there are no RCT comparing outcomes of "on-label" and "off-label" stent treatments between DES and BMS (9). Moreover, it is uncertain that an adequately powered clinical trial to evaluate these comparisons could be performed or that it would be representative of the results under the conditions of routine practice (11). To test the hypothesis that late DES outcomes may be inferior to BMS when used in

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Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
ST = stent thrombosis

"off-label" stent treatments, we assessed the clinical outcomes in consecutive patients treated with DES when DES utilization was ≥90% and compared them with patients who received BMS before the availability of DES. The majority (>75%) of both stent groups were "off-label."

Methods

Patients at our institution undergoing percutaneous coronary intervention (PCI) from April 2002 to April 2005 were included in the study. Of these, 1,164 consecutive patients, representing all patients who underwent coronary artery stenting between April 2002 and April 2003, before FDA approval of DES in the U.S., received BMS and served as the control group. The study group consisted of 1,285 consecutive patients who received DES after these stents were fully available (February 2004) and had replaced BMS as our routine stents of choice (≥90% utilization). Patients were excluded if they received both BMS and DES (n = 8) or were unavailable for follow up (BMS, n = 29; DES, n = 35). Patients were not excluded from the study for any other reason. Thus, 1,135 BMS and 1,242 DES patients composed the control and study groups, respectively. The study was approved by the Institutional Review Board of Wake Forest University Baptist Medical Center. We previously reported the 9-month follow-up of most of these patients (12).

Percutaneous coronary intervention was performed according to standard techniques. Because sirolimus-eluting stents were available much earlier than paclitaxel-eluting stents, they composed most of the DES used in the study: sirolimus-eluting stents, n = 971; paclitaxel-eluting stents, n = 259; both, n = 12. Anticoagulation during PCI was accomplished with unfractionated heparin or bivalirudin per standard protocol. Patients received glycoprotein IIb/IIIa receptor inhibition according to usual protocol with abciximab or eptifibatide at the discretion of the interventionalist (12). All patients were treated with aspirin (81 to 325 mg/day) before PCI and indefinitely thereafter. Patients also received clopidogrel (300 to 600 mg as a loading dose, given before or immediately after the procedure, followed by 75 mg/day). Clopidogrel was given for a minimum of 1 month in BMS-treated patients, for a minimum of 3 months for sirolimus-eluting stent–treated patients, and for a minimum of 6 months for paclitaxel-eluting stent–treated patients. Additional clopidogrel use was at the discretion of the physician responsible for clinical care of the patient.

Before hospital discharge, patient and procedural data and hospital outcomes were entered into the Wake Forest University Baptist Medical Center Cardiovascular Information Services Database. Collection of data and outcomes measures conformed to the American College of Cardiology National Cardiovascular Database Registry definitions for cardiovascular data (13). All patients reported in this study had equivalent follow-up duration. Clinical follow-up was obtained as follows: Independent chart review, including follow-up visit with a cardiologist, was available for 80% of patients; scripted phone interviews were obtained for 18% of patients, who had no clinical follow-up but no reported hospitalization since their index procedures; and review of the Social Security Death Index for 2% of patients, where the death records were the only available follow-up. Follow-up was censored at 2 years ± 30 days, with complete follow-up available in 95% of BMS and 90% of DES patients.

Stent thrombosis was defined following the recommendations of the Academic Research Consortium (ARC) for definite and probable ST as presentation with acute coronary syndrome and definite angiographic or pathologic evidence of ST, unexplained death within 30 days of stent placement, or target vessel infarction in the absence of angiography (14). "On-label" stent use was defined by the study criteria for the initial randomized DES studies (1,2) as follows: >18 years old, single de novo native coronary artery lesions <30 mm in length without thrombus, left ventricular ejection fraction ≥25%, no MI within 7 days of the procedure, and no evidence of renal failure (serum creatinine ≤2.0 mg/dl). Stent use in all other patients was defined as "off-label." This definition of "on-label" use is similar to the indications for both Cypher (Cordis Corporation, Miami, Florida) and Taxus (Boston Scientific, Billerica, Massachusetts), with the exception that renal failure was not specifically listed as a contraindication for DES use in the indications. Nonfatal MI was defined as ischemic symptoms and an elevation of creatine kinase-MB >2× the upper limit of normal, with or without ST-segment elevation or development of Q waves.

Statistical methods. Descriptive statistics (means and standard deviation of continuous factors, frequency counts, and relative frequencies of categoric factors) were calculated and compared using the Wilcoxon rank sum test for continuous factors and chi-square testing for categoric factors. Hazard ratios (HR) are presented along with their 95% confidence intervals (CI). Kaplan-Meier plots of cumulative incidence were constructed from index procedure to 2 years of follow-up. The log rank test was used to test for differences between DES and BMS incidence curves. Cox proportional hazards modeling was used to assess independent predictors of outcomes at 2 years to account for follow-up data censored before 2 years. The proportional hazards assumption was tested for all variables by examining log-log survival curves. No variables in the final models violated the proportional hazards assumption. The SAS version 9.1 statistical