Published in final edited form as:

Catheter Cardiovasc Interv. 2008 April 1; 71(5): 636–643. doi:10.1002/ccd.21417.

Survival Advantage in Medicare Patients Receiving Drug-Eluting Stents Compared With Bare Metal Stents: Real or Artefactual?

Fen Wei Wang, MD, PhD¹, Barry F. Uretsky, MD^{1,*}, Jean L. Freeman, PhD^{2,3,4}, Dong Zhang, PhD³, Sharon H. Giordano, MD⁵, and James S. Goodwin, MD^{2,4}

¹Division of Cardiology, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas

²Division of Geriatric Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas

³Division of Epidemiology and Biostatistics, Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas

⁴Sealy Center on Aging, University of Texas Medical Branch, Galveston, Texas

⁵Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Background—Concerns have been raised regarding late mortality, particularly from late stent thrombosis, from drug-eluting stents (DES). Randomized clinical trials have shown that DES decrease restenosis but do not decrease mortality compared with bare metal stents (BMS). These studies utilized well-defined clinical and angiographic subsets. In the “real world” drug-eluting stents are used in a much broader crosssection of patients. We evaluated mortality in the first year after implantation of DES, specifically the sirolimus-eluting stent (SES), Cypher vs. BMS in “real world” older patients using the Medicare claims database.

Methods and Results—Data for the years 2002 ($n = 6,890$; pre-DES) and 2003 ($n = 7,566$; first year of DES use) (May through December of each year) were analyzed. BMS and DES groups had similar baseline characteristics except for small but significant differences with BMS patients being somewhat older, having more males and African Americans, and a higher percentage of peripheral artery disease and heart failure while DES patients had a higher percentage of diabetics and patients with prior revascularization procedures. A significant improvement in mortality using both unadjusted and adjusted analyses was observed for DES (6.0% vs. 11.4%, $P < 0.0001$; hazard ratio 1.98, 95% CI 1.68–2.34). Controlling for comorbidity, extent of disease, and other characteristics by multivariable analysis or by propensity analysis had little impact on these results. On the other hand, there was no change in overall mortality in all stented patients in 2003 compared with all stented patients in 2002.

Conclusion—An observed mortality benefit for DES compared with BMS in 2003 was observed, demonstrating the safety of DES, and suggesting the possibility of superiority in outcome in older patients with DES vs. BMS. However, the lack of improved survival from 2002 to 2003 in all stented patients suggests that the mortality advantage with DES finding may be due to unidentified selection biases. Our data suggest that DES in the Medicare population is as safe as, and possibly superior, to BMS for survival over the first year after implantation.

Keywords

drug-eluting stents; coronary intervention; mortality; outcome; observational data

INTRODUCTION

The introduction of drug-eluting stents (DES) in April 2003 has been described as a “transforming” event because it has significantly changed clinical practice [1,2]. Randomized trials have demonstrated a marked reduction in long-term restenosis after DES compared with bare metal stents (BMS) with comparable mortality [3–6]. These studies have compared well defined clinical and angiographic subsets. “Real world” DES use is much broader with as many as 50% or more of stented patients being “off-label,” i.e. patients being stented with clinical or angiographic features not well studied in randomized trials [7]. Further, “off-label” patients have shown an increased frequency of adverse outcomes compared with patients who would have been eligible for randomized clinical trials [7]. Recently there have been concerns raised about the risk of late myocardial infarction and death from stent thrombosis [8–10]. We examined the effect of DES vs. BMS on mortality during the first year after stent implantation using the population-based Medicare claims database in 2003, the first year of Medicare coverage of DES [11]. We also evaluated the mortality of BMS from 2002 and compared these results to 2003.

PATIENTS AND METHODS

Data Source

Data were obtained from the 5% nationwide random sample of Medicare Denominator File and Standard Analytic Files (SAFs) from 2002 to 2004. The claims cover services for hospitalizations, outpatient services, and physician services (inpatient and outpatient).

Study Populations

It was assumed that all patients were admitted as inpatients for stent placement. Study cohorts were identified using International Classification of Diseases (ICD)-9 procedure codes for BMS (ICD-9 code 36.06) and DES (ICD-9 code 36.07). As the sirolimus-eluting stent, Cypher, (Johnson and Johnson, New Brunswick, NJ) was approved for payment by CMS in April 2003, a sample of 8,369 patients age 66 undergoing coronary stenting between May 1, 2003, and December 31, 2003 were identified from the SAF files and linked to the denominator file. The paclitaxel-eluting stent, Taxus (Boston Scientific Corporation, Watertown MA) was not approved until 2004; as such this analysis is limited to results of the Cypher stent. After excluding 427 patients with both implantation of DES and BMS during the same hospitalization and 376 patients enrolled in an HMO, the remaining 7,566

patients comprised the 2003 study population. Using the same approach, 6,890 patients undergoing coronary stenting (only BMS used) between May 1, 2002, and December 31, 2002 were identified, comprising the 2002 study population. Patients who had multiple coronary stenting procedures in both 2002 and 2003 were excluded.

Study Variables

Data on survival was obtained from the Medicare Denominator File. The mortality outcome was defined as death within 1 year following the date of coronary stenting. Patient covariates such as diabetes, chronic renal failure, heart failure, and peripheral vascular disease were identified from diagnoses recorded on hospital discharge abstracts by ICD-9 coding. With the exception of age, which was coded into discrete ranges, the patient covariates were coded into categories indicating its presence or absence.

Statistical Analysis

The primary purpose of the data analyses was to determine whether 1-year mortality differed significantly between DES and BMS patients on unadjusted analysis and after controlling for potential confounders [12]. We also determined whether 1 year mortality for all stented patients differed significantly between the year before the adoption of DES (only BMS being implanted) and the year of DES adoption. This analysis was followed by a Cox proportional-hazards model which controlled for risk factors while testing for differences in mortality between patients who received DES and BMS. Multivariable Cox proportional-hazards analysis was also used to compare mortality differences between patients who had stenting in 2002 and in the year of adoption of DES (2003). Parameters in the multivariable analysis included age, gender, race, the indication of acute myocardial infarction (MI) for index coronary stenting, diabetes, chronic renal failure, heart failure and prior PCI, coronary artery bypass surgery (CABG) or acute MI.

We compared baseline characteristics of patients receiving DES and BMS in 2003 and characteristics of all patients stented in May to December of 2002 vs. May to December of 2003. Comparisons were made with either a nonpaired Student's *t* test for continuous variables or a χ^2 test for categorical data. Unadjusted survival curves were estimated by the Kaplan–Meier method. Differences in survival were tested using the log rank test.

In an attempt to control for selection bias, a propensity score-matched multivariable analysis was performed. Propensity score analysis has been used as a method to balance covariates between the different treatment groups and reduce bias [13]. Propensity score was defined as the conditional probability of DES use. The predicted probability of receiving DES (propensity score) was estimated with a logistic regression model of all covariates. The propensity score was tabulated for each patient and categorized into five groups or strata of increasing score. After calculating the propensity scores, and stratifying each group according to the propensity score, we performed Cox analysis for each stratum using stent type groups and propensity score as covariates.

Finally, we performed sensitivity analyses to assess the potential effects of unmeasured confounders on the associations observed between mortality and different stent groups. The

purpose of the method is to obtain a realistic picture of the potential impact of biases [14,15]. The unmeasured confounder in our study could be unmeasured disease severity, difference in operator skill, unmeasured risk factors (e.g. tobacco use), and other factors. The prevalence of the unmeasured confounder(s) was set to different levels with both DES and BMS groups. Over the different prevalence levels, the hazard ratio (HR) between the unmeasured confounder and mortality ranged from 1.5 to 3.0. The range for the prevalence estimates and for the HRs was obtained by inspection of the prevalence and hazard associated with the measured confounders in this study. We then generated multivariate models (which included this unmeasured confounding variable) to determine the effect of unmeasured factors on the result.

All analyses were performed using SAS version 9.1 (Cary, NC). For all comparisons, a two sided value of $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

There were 4,149 BMS and 3,417 DES patients during the 2003 study period (May 1, 2003 to December 31, 2003). Utilization increased from 34.4% of cases in May 2003 to 51.9% of cases in December 2003 (Fig. 1). There were 6,890 BMS patients during the 2002 study period (May 1, 2002 to December 31, 2002).

Patient Characteristics by Stent Type (BMS vs. DES)

Characteristics of the 2003 DES and BMS groups were similar except for the following (Table I) BMS patients were older, were more likely to be male and black, have peripheral vascular disease, and have heart failure. DES patients were more likely to be white, have diabetes, and have had a prior coronary revascularization.

Mortality by Stent Type

Figure 2 displays the 1-year survival curves of DES and BMS in 2003. Mortality at 1-year was higher for BMS than DES patients [11.4% vs. 6.0%, $P < 0.0001$; unadjusted HR 1.98, 95% CI 1.68–2.34] (Table II, model 1). After adjustment for potential confounders, including demographic characteristics, clinical indications, and comorbidities, the observed improved survival with DES persisted [HR 1.86, 95% CI 1.57 to 2.19] (Table II, model 2).

Propensity Score-Matched Analysis

To further address potential confounders, we performed propensity analyses. Those covariates that were statistically unbalanced between the DES and BMS groups as shown in Table I were adjusted with propensity score in the analysis. Patients were sorted into five equal groups by increasing probability of undergoing DES (propensity score) obtained from the multivariable logistic regression model containing all baseline characteristics. The 1-year mortality rate for each propensity score group for patients undergoing DES or BMS within each group is shown in Table III. The observed mortality rate remained higher in all five groups for the patients receiving BMS than DES.

In the multivariable analysis using the Cox model with propensity score matching, the HR for 1-year all-cause death was significantly higher in the BMS compared with the DES group (HR 1.83, 95% CI 1.56–2.16) (Table II, model 3).

Mortality Assessment in Different Years

We reasoned that if the mortality rate was truly lower with DES than BMS, then the overall mortality rate of stenting procedures from May to December 2003 should be lower than the overall mortality rate from May to December 2002. In a Cox proportional hazards analysis controlling for all the factors included in Table II, there was no significant difference in hazard of 1-year mortality after stenting in 2003 vs. 2002 (HR = 0.92; 95% CI 0.82–1.02). Figure 3 shows that 1-year survival curve for all stent patients in May to December 2002, all stent patients in May to December 2003, and May to December 2003 stent patients stratified by whether they received DES or BMS. The overall survival for stent patients between 2002 and 2003 was unchanged. However, in 2003 patients receiving BMS experienced substantially worse survival compared with the patients in 2002, who all received BMS. In contrast, 2003 patients receiving DES did substantially better.

Sensitivity Analysis

We also conducted sensitivity analyses to estimate the potential effect of unmeasured confounder(s) on the study results (Table IV). The estimated prevalence and HR of an unmeasured confounder was based on the prevalence and HR of measured variables shown in Table IV. For example, if the prevalence of an unmeasured confounding variable was 80% in BMS and 20% in DES group, and the HR for mortality associated with this unmeasured confounder was 3.0, then the adjusted HR of mortality for BMS relative to DES would be 1.00 (95% CI 0.85–1.18) (Table IV) instead of 1.86 (95% CI 1.57–2.19), as shown in Table II. These analyses show that an unmeasured confounder could be responsible for the results obtained if it has a difference of ~60% in prevalence between the two groups and if it is associated with an HR of 2.5 or greater.

DISCUSSION

We examined survival after stenting with DES vs. BMS in a population-based sample of patients using the Medicare claims database. A substantial improvement with DES compared with BMS in mortality in the first year of Medicare DES coverage (2003) was observed. Using multivariable analysis, adjusted for patient demographics and comorbidity, there was still a large, statistically significant improvement in survival with DES [adjusted HR 1.86, (95% CI 1.57–2.19); $P < 0.0001$ and the model including propensity score showed a HR 1.83, (95% CI 1.56–2.16); $P < 0.0001$]. These data suggest that in the “real world” of older (Medicare) patients, use of DES (vs. BMS) may produce a true survival advantage. This conclusion must be tempered, however, by the fact that overall mortality in stented patients in 2003 compared with 2002 was unchanged which suggests to us that the observed mortality improvement with DES may have been due to an unidentified selection bias or biases. The apparent improved outcome with DES is mirrored by an apparent worsening of outcome with BMS in 2003 compared with 2002.

These Medicare 2003 “real world” data are also consistent with results from other “real world” registries [16–19]. Analysis of 6,906 patients in the DES cover registry showed that at 1 year, the unadjusted cumulative incidence of death was higher in BMS than in sirolimus-eluting stent patients (5.90 % vs. 3.10%; $P = 0.005$). After adjustment, however, the risk of death was similar in the two groups [16]. We used statistical methods to adjust for demographic and clinical differences between groups, including propensity-score matching and stratification. However, we could not adjust for unmeasured variables between groups. In this large database, we did not have detailed angiographic data such as lesion type, length, location, number of vessels diseased, or prior restenosis. We also could not adjust for the socioeconomic status of the patients and the experience of the operators. Thus, the ability to adjust was not as robust as in a registry specifically designed to study the problem such as the DES cover registry. A single center American stent registry of somewhat more than 2,400 patients showed an improved 1-year survival with DES vs. BMS which, similar to our study, was unchanged by adjustment [17]. An observational analysis of 6,033 DES and 13,738 BMS patients (Swedish Coronary Angiography and Angioplasty Registry) showed a higher risk of death in the group with DES than in the group with BMS adjusted by propensity-score Cox regression analysis (RR, 1.18; 95% CI 1.04–1.35) [20]. At 6 months the risk of death was similar in the two groups. After 6 months, the risk of death became significantly higher in the DES group, with increased separation of the event curves over time (RR, 1.32; 95% CI 1.11–1.57) [20]. Four-year follow-up was recently presented which showed similar outcomes as opposed to the 2.5-year data [21]. A contemporaneous registry from a neighboring country to Sweden, Denmark, showed a different outcome with a significant improvement in survival with DES vs. BMS at the end of 1 year [19]. Adjusted mortality was similar in the two groups. Neither our study nor the above four registries have detailed information regarding the use of antiplatelet agents during follow-up which may account for some of the differences observed as discontinuation of dual antiplatelet therapy appears to be an important factor in developing late stent thrombosis [22].

Randomized clinical trials have not shown a survival advantage with DES. In a meta-analysis of 11 clinical trials of 5,103 patients [23], pooled mortality rate (6–12 month) was 0.90% for DES vs. 0.86% for BMS (OR 1.11, CI, 0.61–2.06). It is likely that the higher mortality in the current analysis and other observational data bases reflects the broader use of stents in the Medicare population than randomized patients where stent use was limited to a single stent in rather straightforward lesions versus use in a broader more complex set of lesions, often in multiple lesions, in patients with prior revascularization procedures, in older patients with multiple comorbidities. In another meta-analysis of 17 trials of 8,221 patients [24], the OR for 1-year total mortality in patients treated with DES when compared with patients treated with BMS was 0.94 (CI: 0.66–1.34). A recent analysis of 14 randomized trials of 4,958 patients comparing sirolimus-eluting stents vs. BMS with mean follow-up interval of 12.1–58.9 months showed similar findings (HR 1.03, 95% CI 0.80–1.30) [18]. Thus, existing clinical trial data do not support the notion that DES decreases 1-year mortality compared with BMS.

Limitations of an Observational Study

Observational studies may provide important insights in evaluating new treatments. Although randomized, controlled trials are the “gold standard” for proof of therapeutic efficacy and safety, observational databases have been considered useful to determine whether efficacy found in controlled clinical trials translates into effective treatment in an unselected “real world” group of patients. Observational studies, however, have one crucial limitation: each patient’s treatment is deliberately chosen rather than randomly assigned, so there is an unavoidable risk of selection bias and of systematic differences in outcomes not necessarily attributable to the treatment itself. Although statistical techniques such as multivariable analysis, stratification, matching, and propensity analysis are used to “control” for potential biases, it is difficult to totally eliminate the effect of confounders [25]. We should keep in mind that all standard risk-adjustment methods, including multivariable analysis and propensity score methods, have the same limitations regarding removal of unmeasured treatment selection biases [25]. Although our data are reassuring that DES appears safe over the first year after implantation, our report should also serve as a warning in relying on retrospective observational data—no matter how large the sample size—when comparing outcomes of DES vs. BMS because of potential selection biases.

There are many examples in the medical literature of observational data, often from multiple studies with large sample sizes, which have led to erroneous conclusions, and which were subsequently corrected in randomized controlled trials. Recent examples include the use of estrogen to decrease cardiovascular risk in postmenopausal women, vitamin E to prevent cardiovascular events, and the combination of beta carotene and vitamin A to prevent lung cancer [26–29]. Even the largest and best observational studies may provide the wrong answer if there are confounding unrecognized or unrecorded risk factors.

In conclusion, recent reports have questioned the long-term safety of DES. Using observational data from a large administration database of older patients, DES appeared to be as safe as, and possibly safer than BMS. Larger “real world” experience and more long-term controlled data will be useful in placing DES in its proper place in the treatment of coronary disease.

Acknowledgments

We thank Prof. Daniel H. Freeman, PhD and Jue Wang, MD for their helpful review and suggestions.

References

1. Tung R, Kaul S, Diamond GA, Shah PK. Narrative review: Drug-eluting stents for the management of restenosis: A critical appraisal of the evidence. *Ann Intern Med.* 2006; 144:913–919. [PubMed: 16785479]
2. Rao SV, Shaw RE, Brindis RG, Klein LW, Weintraub WS, Krone RJ, Peterson ED. Patterns and outcomes of drug-eluting coronary stent use in clinical practice. *Am Heart J.* 2006; 152:321–326. [PubMed: 16875917]
3. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. RAVEL Study Group. Randomized study with the sirolimus-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions. A randomized comparison of a sirolimus-eluting stent with a

- standard stent for coronary revascularization. *N Engl J Med*. 2002; 346:1773–1780. [PubMed: 12050336]
4. Holmes DR, Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE. Analysis of 1-year clinical outcomes in the SIRIUS trial—A randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation*. 2004; 109:634–640. [PubMed: 14769686]
 5. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. TAXUS-IV Investigators. One-year clinical results with the slow-release polymer-based, paclitaxel-eluting TAXUS stent. *Circulation*. 2004; 109:1942–1947. [PubMed: 15078803]
 6. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *JAMA*. 2005; 294:1215–1223. [PubMed: 16160130]
 7. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulka S, Nassif D, Cohen DJ, Kleiman NS. Event Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug eluting stents. *JAMA*. 2007; 297:2001–2009. [PubMed: 17488965]
 8. Muni NI, Gross TP. Problems with drug-eluting coronary stents—The FDA perspective. *N Engl J Med*. 2004; 351:1593–1595. [PubMed: 15483274]
 9. Shuchman M. Trading restenosis for thrombosis? New questions about drug-eluting stents. *N Engl J Med*. 2006; 355:1949–1952. [PubMed: 17093244]
 10. Maisel WH. Unanswered questions—Drug-eluting stents and the risk of late thrombosis. *N Engl J Med*. 2007; 356:981–984. [PubMed: 17296826]
 11. Malenka DJ, Kaplan AV, Sharp SM, Wennberg JE. Postmarketing surveillance of medical devices using Medicare claims. *Health Aff (Millwood)*. 2005; 24:928–937. [PubMed: 16012135]
 12. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR Jr. A critical appraisal of current models of risk stratification for percutaneous coronary interventions. *Am Heart J*. 2005; 149:753–760. [PubMed: 15894953]
 13. D'Agostino RB Jr. Propensity score methods for bias reduction in comparison of a treatment to a non-randomized control group. *Stat Med*. 1998; 17:2265–2281. [PubMed: 9802183]
 14. Greenland, S. Basic methods for sensitivity analysis and external adjustment. In: Rothman, KJ.; Greenland, S., editors. *Modern Epidemiology*. 2. Philadelphia: Lippincott-Raven; 1998. p. 343–357.
 15. Du XL, Key CR, Osborne C, Mahnken JD, Goodwin JS. Discrepancy between consensus recommendations and actual community use of adjuvant chemotherapy in women with breast cancer. *Ann Intern Med*. 2003; 138:90–97. [PubMed: 12529090]
 16. Williams DO, Abbott DA, Kip KE. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents report of the DEScover registry. *Circulation*. 2006; 114:2154–2162. [PubMed: 17060386]
 17. Applegate RJ, Sacrinty MT, Kutcher MA, Baki TT, Gandhi SK, Santos RM, Little WC. Comparison of drug-eluting versus bare metal stents on later frequency of acute myocardial infarction and death. *Am J Cardiol*. 2007; 99:333–338. [PubMed: 17261393]
 18. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbæk H, Menichelli M, Sabaté M, Suttrop M, Baumgart D, Seyfarth M, Pfisterer M, Schömig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007; 356:1030–1039. [PubMed: 17296823]
 19. Jensen LO, Maeng M, Kaltoft A, Thayssen P, Hansen HHT, Bottcher M, Lassen JF, Krussel LR, Rasmussen K, Hansen KN, Pedersen L, John SP, Soerensen HF, Thuesen L. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol*. 2007; 50:463–470. [PubMed: 17662400]
 20. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med*. 2007; 356:1009–1019. [PubMed: 17296822]

21. James, S.; Carlsson, J.; Lindback, J.; Nilsson, T.; Stenestrand, U.; Wallentin, L.; Lagerqvist, B. for the SCAAR Study Group. Long-term outcome with drug eluting stents vs. bare metal stents in Sweden-one additional year of follow-up. Presented at the European Society of Cardiology; Vienna, Austria. September 3, 2007; Sep 4. 2007 Reported on mgibson@clinicaltrialresults.org
22. Iakovou I, Schmidt T, Bonizonni F, Sangiorgi G, Stankovic G, Airolidi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Brigouri C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005; 293:2126–2130. [PubMed: 15870416]
23. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomized clinical trials of drug-eluting stents. *Lancet*. 2004; 364:583–591. [PubMed: 15313358]
24. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: A meta-analysis. *Eur Heart J*. 2006; 27:2784–2814. [PubMed: 17020889]
25. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: Effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007; 297:278–285. [PubMed: 17227979]
26. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, Speizer FE, Hennekens CH. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med*. 1996; 335:453–461. [PubMed: 8672166]
27. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998; 280:605–613. [PubMed: 9718051]
28. The Heart Outcomes Prevention Evaluation Study investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2002; 342:154–160.
29. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996; 334:1150–1155. [PubMed: 8602180]

Fig. 1.

Patients underwent DES or BMS placement from January to December in year 2003 DES = drug eluting stents; BMS = bare metal stents. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Fig. 2.

Kaplan–Meier survival curves for 2003 stented patients according to stent type.

Fig. 3.

Kaplan–Meier survival curves for stented patients according to different years and stent type.

TABLE I

Characteristics of the Patients by Stent Type

Characteristics	All patients, <i>n</i> = 7566 (<i>n</i>)	BMS patients, <i>n</i> = 4149 (<i>n</i>)	DES patients, <i>n</i> = 3417 (<i>n</i>)	<i>P</i> -value
Mean age (yr)		76 ± 6	75 ± 6	<0.0001
66–69	1,533	19.4%	21.3%	<0.0001
70–74	2,135	27.2%	29.4%	
75–79	1,965	25.8%	26.2	
80–84	1,327	18.6%	16.3	
85	606	9.0%	6.8%	
Male	4,288	57.9%	55.3%	0.02
Female	3,278	42.1%	44.7%	
Caucasian	6,936	90.9%	92.6%	0.0031
African-American	369	5.6%	4.0%	
Other racial groups	261	3.5%	3.4%	
Acute myocardial infarction	882	11.9%	11.3%	0.41
Diabetes	2,293	29.1%	31.7%	0.013
Heart failure	1,206	16.6%	15.1%	0.07
Chronic renal failure	297	4.1%	3.7%	0.4
Peripheral vascular disease	620	8.8%	7.5%	0.035
History of stroke	687	9.2%	8.9%	0.67
Prior coronary intervention ^a	600	6.9%	9.2%	0.0002
Prior coronary bypass surgery ^a	72	0.8%	1.2%	0.075

BMS = bare metal stent; DES = drug-eluting stent.

^aPrior coronary intervention or coronary bypass surgery in the past 1 year.

TABLE II

Multivariable Predictors of Overall Mortality at 1 year

Risk factor	Unadjusted model 1		Adjusted model 2		Model 3 including propensity score	
	HR	CI	HR	CI	HR	CI
Stents group						
BMS vs. DES	1.98	(1.68, 2.34)	1.86	(1.57, 2.19)	1.83	(1.56, 2.16)
Age			1.08	(1.07, 1.10)		
Gender			0.92	(0.79, 1.08)		
Female vs. male						
Race			0.92	(0.71, 1.19)		
Caucasian vs other						
Acute myocardial infarction			0.91	(0.73, 1.13)		
Diabetes			1.34	(1.14, 1.57)		
Heart failure			1.89	(1.58, 2.26)		
Chronic renal failure			2.01	(1.55, 2.59)		
Peripheral vascular disease			1.41	(1.14, 1.75)		
Prior stroke			1.13	(0.91, 1.42)		
Other comorbidity			1.89	(1.60, 2.22)		
Prior PCI ^a			0.81	(0.60, 1.08)		
Prior CABG ^a			0.71	(0.30, 1.73)		

^aPrior PCI or CABG in the past 1 year;

CI= confidence interval; BMS = bare metal stent; DES = drug-eluting stent; CABG= coronary artery bypass grafting; PCI = percutaneous coronary intervention; HR = hazard ratio.

TABLE III

Stratification by Propensity to Undergo DES and 1-Year Mortality

	Group 1	Group 2	Group 3	Group 4	Group 5	Total
Propensity score	0.24966–0.41394	0.41395–0.44062	0.44063–0.46132	0.46133–0.48853	0.48854–0.67871	
Number of subjects						
BMS, <i>n</i>	929	857	827	814	722	4,149
DES, <i>n</i>	584	659	676	706	792	3,417
Death within 365 days						
BMS (%)	18.95	12.49	11.37	6.51	6.09	11.4
DES (%)	13.53	7.44	3.99	3.68	2.90	6.0

TABLE IV

Sensitivity Analyses of the Hazard Ratio (HR) of Mortality for Patients With BMS Compared With Those With DES Controlling for an Unmeasured Binary Confounder

Assumed prevalence (%) of unmeasured confounder in the BMS group	Assumed prevalence (%) of unmeasured confounder in the DES group	HR unmeasured confounder	HR (95 % CI) adjusted for unmeasured confounder
0	0	1	1.86 (1.57–2.19)
100	0	2	0.93 (0.79–1.09)
100	20	2.5	0.96 (0.82–1.14)
60	0	2.5	0.98 (0.83–1.15)
80	20	3.0	1.00 (0.85–1.22)
80	0	2.0	1.03 (0.87–1.22)
40	0	3.0	1.03 (0.87–1.22)
80	20	2.5	1.10 (0.93–1.29)
100	40	3.0	1.11 (0.94–1.31)