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Impact of Drug-Eluting Stents on the Comparative Effectiveness of Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention

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Abstract

Background—Drug-eluting stents (DES) have largely replaced bare-metal stents (BMS) for percutaneous coronary intervention (PCI). It is uncertain, however, whether introduction of DES had a significant impact the comparative effectiveness of PCI versus coronary artery bypass graft surgery (CABG) for death and myocardial infarction (MI).

Methods—We identified Medicare beneficiaries 66 years of age and older who underwent multivessel CABG or multivessel PCI, and matched PCI and CABG patients on propensity score. We defined the BMS era as January 1999 through April 2003 and the DES era as May 2003 through December 2006. We compared five-year outcomes of CABG and PCI using Cox proportional hazards models, adjusting for baseline characteristics and year of procedure, and tested for an interaction (P_{int}) of DES era with treatment (CABG or PCI).

Results—Five-year survival improved from the BMS era to the DES era by 1.2% for PCI and by 1.1% for CABG, and the CABG:PCI hazard ratio was unchanged (0.90 vs. 0.90, $P_{\text{int}} = 0.96$). Five-year MI-free survival improved by 1.4% for PCI and 1.1% for CABG, with no change in the CABG:PCI hazard ratio (0.81 vs. 0.82, $P_{\text{int}} = 0.63$). By contrast, survival-free of MI or repeat coronary revascularization improved from the BMS era to the DES era by 5.7% for PCI and 0.9% for CABG, and the CABG:PCI hazard ratio changed significantly (0.50 vs. 0.57, $P_{\text{int}} = 0.0001$).

Conclusions—The introduction of drug-eluting stents did not alter the comparative effectiveness of CABG and PCI with respect to hard cardiac outcomes.

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Keywords

comparative effectiveness research; outcomes research; percutaneous coronary intervention; coronary artery bypass

Percutaneous coronary intervention (PCI) has evolved considerably since its original introduction by Gruentzig in 1977, with numerous technological improvements in the procedure, as well as improvements in concomitant drug therapy and general management of patients with coronary disease. Two technologic innovations in PCI stand out against this background of continual incremental improvements: the approval of coronary stents in 1994, and the introduction of drug-eluting stents (DES) in 2004 (1). Coronary stents dramatically reduced the risk of acute vessel closure and of restenosis. Head-to-head trials comparing PCI using DES with PCI using bare metal stents (BMS) have shown that DES significantly reduces the rate of repeat procedures (2–4) without changing the rate of hard cardiac endpoints (death or myocardial infarction (MI)). The beneficial effect of DES on repeat procedures has led to their essentially replacing BMS during PCI (5).

PCI is an alternative to coronary artery bypass graft surgery (CABG) for treatment of multivessel coronary disease, and these procedures have been compared in a number of randomized trials (6–8). Several waves of randomized trials have been conducted based on the widespread belief that newer PCI devices (first BMS, then DES) altered the comparative balance between CABG and PCI for patients with multivessel disease. The relative effectiveness of CABG and PCI upon mortality did not, however, differ significantly between randomized clinical trials in which PCI was performed using balloon angioplasty and trials in which PCI was performed using BMS (8), and mortality has been lower after CABG compared with PCI in more recent trials that used DES for PCI (9, 10). The recently reported ASCERT study used observational data to compare CABG and PCI using DES, and also found improved survival after CABG (11).

The continuing evolution of medical technologies, such as PCI, presents a dilemma for evidence-based medical practice: have recent changes altered clinical outcomes to the extent that older evidence is out of date? This “moving target problem” (12, 13) is especially acute in comparing CABG and PCI, since each procedure continues to be refined, and background management of coronary disease continues to improve, which could lead to better outcomes after both procedures (14–16). The need to compare clinical outcomes over long-term follow-up further complicates this assessment, since five-year results can only be assessed based on patients with five years or more of follow-up, who necessarily have been treated with earlier technology.

One potential solution to the moving target problem is to track outcomes over time using continuously collected data, and then test explicitly for changes in comparative effectiveness. In this study, we therefore sought to test whether the comparative effectiveness of CABG and PCI on hard clinical outcomes has changed over time, and specifically by the introduction of DES. We reasoned that a time series approach would allow us to isolate any specific effect of DES from general secular trends towards improved outcomes by comparing the difference in outcomes between CABG and PCI prior to the

introduction of DES with this difference after the introduction of DES. We hypothesized that a “difference-in-differences” approach would directly test whether the availability of DES altered the balance between CABG and PCI on hard cardiac outcomes.

Methods

The study population consisted of fee-for-service Medicare beneficiaries who underwent either multivessel CABG or multivessel PCI between January 1999 and December 2006. In order to permit a one-year look-back period to define comorbidities, we restricted the population to individuals aged 66 years and older who had both Part A and Part B coverage and were not in a Medicare HMO plan. We identified CABG and PCI procedures in the 20% sample of Medicare Part A data, and defined relevant comorbidities using both Part A and Part B data.

We identified patients by ICD-9 procedure codes for multivessel CABG (36.12, 36.13, 36.14, 36.16 or 36.11 plus 36.15), or multivessel PCI (ICD.9 code 36.05 and, from October 2005, ICD.9 code 00.66, and either an ICD-9 code of 00.41, 00.42, 00.43 or a CPT code of 92981 or 92984). We excluded patients who had single-vessel PCI or CABG, had concomitant cardiac procedures (such as valve replacement) at the time of CABG, were of unknown race, or were receiving chronic dialysis for end-stage renal disease. We defined comorbid conditions using outpatient and inpatient encounters in the year prior to the index procedure. We considered a comorbidity to be present if it was recorded as a primary or secondary diagnosis code on an inpatient admission or outpatient encounter (17).

We matched patients on propensity score to create the final analysis cohort. We used all of the baseline characteristics listed in Table 1 as predictors of receiving CABG or PCI, as well as a history of: ventricular tachycardia ventricular fibrillation, other arrhythmias, implantation of a cardioverter defibrillator, valvular heart disease, stroke, transient ischemic attack, intracranial hemorrhage, other cerebrovascular disease, fluid and electrolyte abnormalities, gastrointestinal bleeding, anemia, pulmonary vascular disease, hypothyroidism, chronic liver disease, acquired immunodeficiency syndrome, systemic cancer, obesity, dementia, depression, psychosis, alcohol abuse, or drug abuse. We matched each patient who received a multivessel PCI with one patient who received a multivessel CABG using a greedy matching algorithm (18) that first matched propensity scores at seven digits, then at six digits, and so forth, down to a two-digit match (i.e., agreement at the 0.01 level of propensity score). We additionally required that patients be matched on year of index procedure, diabetes status, and age within one year.

Outcomes

We limited analyses of follow-up events to five years after the initial CABG or PCI in order to compare medium-term outcomes between patients treated before and after the introduction of DES. The primary outcome was all-cause mortality within five years of the initial procedure, determined from the Medicare denominator file through December 31, 2011. Acute MI in follow-up was defined as a subsequent hospital admission (i.e., excluding the index admission) with a primary diagnosis code of 410.x0 or 410. x1 (19). To test the sensitivity of our analysis method to detect an expected signal, we also analyzed the

outcome of repeat coronary revascularization, which we defined as an admission with a procedure code for either CABG (36.1x) or PCI (00.66, 36.0x, but excluding 36.04).

Analytic Approach

Our analysis strategy was to compare the outcomes between CABG vs. PCI in the BMS era (January 1999 through April 2003) with the outcomes between CABG vs. PCI in the DES era (May 2003 through December 2006). We first compared rates of death from any cause after CABG and PCI on mortality during the first five years of follow-up using a Cox proportional hazards model that adjusted for baseline covariates and year of procedure. We then tested whether an indicator variable for “DES era,” defined as after the date that DES was approved by the Food and Drug Administration, had a significant interaction with treatment (i.e., whether there was a significant change in the adjusted CABG:PCI hazard ratio after the introduction of drug-eluting stents). This study was approved by the Stanford University Institutional Review Board.

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Results

In the propensity-score matched cohort, a total of 38,277 patients underwent multivessel CABG or PCI in the BMS era and another 43,645 patients underwent one of these procedures in the DES era. The baseline characteristics of patients in the BMS era were generally different ($p<0.0001$) from those of patients in the DES era (Table 1), but most differences were small (less than 2% in absolute magnitude). The clinical characteristics of the CABG and PCI patients were well balanced as a result of the propensity score matching, both overall (Table 1) and within the BMS and DES eras (data not shown).

Patients in the BMS era had a procedure code for a coronary stent in 93% of all PCI procedures, while in the DES era 97% of patients had a procedure code for a coronary stent ($p<0.0001$), the vast majority (85%) of whom received a DES. An internal mammary artery graft was used in 80% of CABG patients in the BMS era and in 87% of the CABG patients in the DES era ($p<0.0001$).

Unadjusted Kaplan-Meier survival rates at five years were improved from the BMS era to the DES era (Figure 1) by 1.2% for patients who underwent PCI (from 70.8% to 72.0%), and by 1.1% for patients who underwent CABG (from 73.6% to 74.7%). Similar trends were evident for the composite outcome of survival free of acute MI (Figure 2), with a 1.4% improvement (from 65.1% to 66.5%) for PCI, and a 1.1% improvement (from 70.6% to 71.7%) for CABG. The composite outcome of major adverse cardiac events (death, MI, or repeat coronary revascularization) improved by 5.7% for patients who underwent PCI (from 45.6% to 50.3%), and by just 0.9% for patients who underwent CABG (from 66.1% to 67.0%) (Figure 2).

The CABG:PCI hazard ratio for mortality in the BMS era was 0.90 (CI 0.87 to 0.93), compared with 0.90 (CI 0.87 to 0.93) in the DES era. The interaction between treatment and DES era was not significant ($P_{\text{int}} = 0.96$). There was also no effect of DES era on the CABG:PCI hazard ratio for the composite endpoint of death or MI (Figure 3). As expected, DES era had a significant effect upon the comparative effectiveness of CABG and PCI for the composite endpoint of death, MI or repeat coronary revascularization ($P_{\text{int}} < 0.0001$). The results of all analyses were essentially unchanged after further adjustment for interactions between treatment and the baseline characteristics of diabetes, heart failure, peripheral vascular disease, and tobacco abuse (17).

Discussion

The use of drug-eluting stents has unquestionably reduced the rate of repeat coronary revascularization procedures after PCI, and DES are now used in almost all PCI procedures (5). The key clinical question is whether this shift to using DES for PCI altered the comparative effectiveness of CABG and PCI for patients with multivessel coronary disease. Our analysis suggests that the introduction of DES for multivessel PCI did not significantly change subsequent risks of death and MI relative to multivessel CABG, even though it did significantly reduce the rate of repeat revascularization. Our findings also suggest that since hard outcomes were not affected, earlier studies of CABG and PCI continue to provide useful information about their comparative effects.

The evolution of coronary revascularization procedures exemplifies the “moving target” of medical technology (12, 13). Assessment of clinical outcomes are, of necessity, performed at a specific time, but results of treatment may improve over time as physicians gain more experience, techniques are improved, and background therapies advance (e.g., greater use of guideline recommended drug therapies such as statins; better control of cardiac risk factors, such as smoking and blood pressure; and greater use of reperfusion therapy for acute MI). Tracking clinical outcomes over time can address the “moving target.” A breakthrough technology should lead to a distinct break in the time trend in outcomes. The difference-in-difference approach can isolate any changes in outcomes due to introduction of a new treatment by controlling for background improvements and secular trends. Our study shows that mortality after multivessel coronary revascularization has steadily improved, both for CABG and for PCI, without a clean break in the overall trend coincident with the introduction of DES. In addition, the results of clinical trials comparing multivessel PCI and CABG have yielded similar results where PCI used balloon angioplasty, BMS, or DES. The “snapshots” from clinical trials, and the continuous comparison based on our analysis help to address the “moving target” of coronary revascularization.

Other studies have compared PCI using DES with CABG for multivessel disease. The SYNTAX (SYNERgy between percutaneous coronary intervention with TAXus and cardiac surgery) trial randomized 1800 patients to multivessel CABG or multivessel PCI using DES, and reported a higher rate of survival free of MI at five years after CABG (20). The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial also found a reduction by CABG in death, MI, or stroke among 1900 patients with diabetes randomized to CABG or PCI with

DES for multivessel coronary disease (21). Park and associates (22) found an insignificant difference in mortality between CABG and PCI with DES among 3,042 patients from Korea. In contrast, Weintraub and associates (11) found a lower mortality in the DES era after multivessel CABG and after multivessel PCI among 189,793 patients in clinical registries (23) linked to Medicare (HR 0.79, CI 0.76–0.82). We are not aware of any prior study that compared multivessel CABG with multivessel PCI before and after the introduction of DES, and to assess, as this study has, the impact of DES on CABG vs. PCI outcomes.

Our study also provides indirect evidence about the effect of DES on hard outcomes of multivessel PCI, using contemporary CABG as a benchmark. Evaluation of the impact of DES upon clinical outcomes has been difficult because of the rapid and virtually complete adoption of DES soon after its introduction (5). Meta-analyses of randomized trials (4) comparing PCI using DES with PCI using BMS found no difference in the rate of death (HR 0.97, CI 0.81 to 1.15) or MI (HR 0.95 CI 0.79–1.13), despite substantial reductions in repeat revascularization (HR 0.45, CI 0.37–0.54). By contrast, a meta-analysis of observational studies found a lower mortality rate with DES than BMS (HR 0.87, CI 0.78–0.97) (4). The strong treatment selection bias for DES over BMS after DES became available makes comparisons between concurrently treated PCI patients difficult, because residual selection bias may remain despite multivariable statistical adjustment. In order to overcome the strong selection bias for DES over BMS, several studies compared the outcomes of PCI performed prior to the introduction of DES with the outcomes after DES became available, essentially using time of procedure as an instrumental variable. These studies found less striking effects of DES on clinical outcomes, probably because very similar patients were undergoing PCI, despite quite different use of PCI technology by physicians. Hannan and associates (24) found no difference in New York State in mortality between patients treated before DES became available and after DES was approved. Malenka and co-workers (25) found no difference in mortality among Medicare beneficiaries who underwent PCI before and after the introduction of DES, although analyses by Groeneveld (26) and by Ryan (27) of Medicare data did show a lower mortality after PCI in the DES era compared with the BMS era. Yeh and associates (28) analyzed data from Kaiser Permanente Northern California in both a pre/post analysis and a contemporary comparison of BMS and DES patients. They found a strong association of DES selection upon mortality using contemporary controls (HR 0.70, $p=0.01$), but no effect on mortality when comparing PCI outcomes before and after DES became available (HR 0.92, $p=0.12$). Venkitachalan and associates used the “natural experiment” of liberal DES use between 2004 and 2006 (29) and more conservative DES use during 2007 (30). Their time series, instrumental variable analysis found no difference in mortality between contemporary BMS and DES treated patients (HR=0.94, $p=0.30$). While the question of whether hard clinical outcomes were reduced by DES compared with BMS is of interest, the well-established effect of DES in reducing repeat coronary revascularization procedures has made this an academic question, since DES has almost completely replaced BMS in contemporary PCI.

This study has several limitations, the most important of which is the non-random selection of patients for treatment of multivessel CABG or multivessel PCI. Consequently, there may be residual treatment selection bias even after statistical adjustments. The effect of any such

bias is mitigated, however, by the study design comparing the earlier BMS era with the later DES era, as the selection between CABG and PCI was likely to be similar over time. Second, since this study analyzed Medicare claims, data on several clinical variables that affect outcomes, such as the number of diseased vessels or patient frailty, were unavailable. Again, this limitation applies to both the BMS and DES eras, and is therefore likely to have been “subtracted out” by the difference-indifference comparison of CABG and PCI between the BMS and DES eras.

In summary, our analysis suggests that the introduction of drug-eluting stents was not associated with a material change in the comparative effectiveness of multivessel CABG vs. multivessel PCI for the hard outcomes of death or MI. Overall, multivessel CABG remained associated with lower hazards of death and MI over five years of follow-up in the DES era.

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Figure 1.

Kaplan-Meier survival curve for mortality for CABG and PCI in the BMS era (January 1999 through April 2003), and the DES era (May 2003 through December 2006). The differences between five year survivals between the DES era and the BMS era are indicated to the right of the CABG (top) and PCI (bottom) survival curves.

Figure 2.

Improvement in five-year event-free survival between the BMS era and DES era for CABG (blue bar) and PCI (red bar). The improvements between eras in five-year event-free rates are shown for death (left-hand pair of bars), death or MI (middle pair of bars), and major adverse cardiac events (MACE=death, MI or repeat revascularization) (right-hand pair of bars). The difference in improvements between CABG and PCI for each endpoint is shown at the top of the figure.

CABG:PCI HR by Era

Figure 3.

CABG:PCI hazard ratios, with 95% confidence limits, in the BMS era and the DES era. The effects on death alone (top), death or MI (middle), and major adverse cardiac events (bottom) over five years are shown. The p-values indicate the results of a test for an interaction between treatment (CABG or PCI) and treatment era (BMS or DES).

Table 1

Baseline Characteristics by Treatment Era and by Treatment

	Era of Treatment		Treatment Received	
	BMS (N=38,277)	DES (N=43,645)	CABG (N=40,961)	PCI (N=40,961)
Age				
66–70 years	29.3	30.5	30.0	29.9
71–75 years	28.2	27.3	27.6	27.8
76–80 years	23.4	23.0	23.1	23.3
81–85 years	14.2	14.7	14.5	14.5
86 years	4.8	5.6	4.8	4.6
Female	43.1	41.0	41.7	42.4
Race				
White	92.7	91.8	92.3	92.1
Black	4.3	4.9	4.6	4.7
Other	3.0	3.4	3.2	3.2
Diabetes	31.6	34.7	33.2	33.2
Hypertension	75.8	81.6	79.0	78.8
Hyperlipidemia	28.7	29.6	28.9	29.5
Tobacco Abuse	17.3	20.9	18.9	19.5
Chronic Kidney Disease	4.2	5.8	5.0	5.1
Peripheral Arterial Disease	16.6	18.6	17.3	18.0
Cerebrovascular Disease	15.8	17.3	16.5	16.8
Prior MI	13.7	9.1	11.0	11.5
Heart Failure	14.2	12.1	12.7	13.4
Unstable Angina	33.7	26.6	30.2	29.6
Atrial Fibrillation/Flutter	11.6	11.4	11.3	11.6
Stent Used in PCI	92.9	97.2	--	95.2
IMA Used in CABG	80.3	87.2	84.0	--