Original Article

Instrumental Variable Analysis to Compare Effectiveness of Stents in the Extremely Elderly

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Background—Evaluating novel therapies is challenging in the extremely elderly. Instrumental variable methods identify variables associated with treatment allocation to perform adjusted comparisons that may overcome limitations of more traditional approaches.

Methods and Results—Among all patients aged ≥85 years undergoing percutaneous coronary intervention in nonfederal hospitals in Massachusetts between 2003 and 2009 (n=2690), we identified quarterly drug-eluting stent (DES) use rates as an instrumental variable. We estimated risk-adjusted differences in outcomes for DES versus bare metal stents using a 2-stage least squares instrumental variable analysis method. Quarterly DES use ranged from 15% to 88%. Unadjusted 1-year mortality rates were 14.5% for DES versus 23.0% for bare metal stents (risk difference, −8.5%; $P<0.001$), an implausible finding compared with randomized trial results. Using instrumental variable analysis, DES were associated with no difference in 1-year mortality (risk difference, −0.8%; $P=0.76$) or bleeding (risk difference, 2.3%; $P=0.33$) and with significant reduction in target vessel revascularization (risk difference, −8.3%; $P<0.0001$).

Conclusions—Using an instrumental variable analysis, DES were associated with similar mortality and bleeding and a significant reduction in target vessel revascularization compared with bare metal stents in the extremely elderly. Variation in use rates may be useful as an instrumental variable to facilitate comparative effectiveness in groups underrepresented in randomized trials. **(*Circ Cardiovasc Qual Outcomes*. 2014;7:118-124.)**

Key Words: aged ■ drug-eluting stents ■ percutaneous coronary intervention ■ stents

Comparative effectiveness research has emphasized the use of observational studies to investigate treatment choices within larger and more representative populations. Although randomized trials are the gold standard approach in the comparison of treatments, certain patients, such as those at the extremes of age, are frequently excluded from enrollment. As a result, the effect of new technologies on these groups is often poorly understood. The extremely elderly (≥85 years of age) represent a growing proportion of patients seeking medical care. How to measure true treatment effectiveness in such underrepresented patient populations remains an important challenge in comparative effectiveness research.

Although large databases offer greater power to examine subgroups, a major limitation of observational studies, treatment selection bias (or confounding by indication), is not overcome by size. Treatment selection bias (determined by physician and patient preferences) may be more extreme within subgroups. Clinical characteristics, such as disease severity and patient frailty, relate to both treatment selection and outcome but may not have been prospectively recorded in sufficient detail by clinical databases. As a result, when traditional methods of adjustment (regression or propensity-score analysis) are used to compare treatment effect, residual confounding is expected.[1]

Instrumental variable methods have been used by social scientists[2,3] and, more recently, by clinical researchers[4,5] to overcome treatment selection bias. Similar to randomization, an instrumental variable is related to treatment selection but not directly related to the outcome. Its occurrence creates a natural experiment and can overcome the effect of unmeasured confounders. In the case of the introduction of new medical technology, variation in use rates with time is one such natural experiment that can be used to examine the comparative effectiveness of alternative therapies and devices.[6–8]

Whereas drug-eluting stents (DES) were rapidly adopted for the treatment of most patients undergoing percutaneous coronary intervention (PCI) after their approval in 2003, patterns of use shifted quickly when concerns arose in 2006 about their safety.[9] The clinical guideline recommendations that followed about the need for concurrent dual antiplatelet therapy for an extended duration compared with bare metal stents

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WHAT IS KNOWN

- High-risk subgroups of patients, including the extreme elderly, are often underrepresented in randomized clinical trials of new therapies.
- Additionally, observational comparisons of treatments in these populations may be particularly susceptible to unmeasured confounding.
- Although extensive data exist for outcomes of drug-eluting stents for percutaneous coronary intervention, their relative efficacy and safety compared with bare metal stents in the extreme elderly are less clear because of both the paucity of clinical trial data and potential confounding of observational comparisons.

WHAT THE STUDY ADDS

- We used temporal variation in the use of drug-eluting stents as an instrumental variable to assess their efficacy and safety in patients ≥85 years of age and showed that they are associated with similar mortality and significantly lower target vessel revascularization in this population.
- Traditional regression and propensity-score approaches were not effective at eliminating residual confounding compared with the instrumental variable approach in the study population.
- The article highlights the instrumental variable approach as an underused method that can overcome limitations of more commonly used observational research methods, which may be particularly relevant in high-risk subgroups such as the extreme elderly. Rapid changes in use patterns of new technologies may serve as an effective instrumental variable to enable their evaluation in real-world practice.

(BMS) resulted in pronounced uncertainty about the balance of ischemic and bleeding risk for elderly patients, a growing population of PCI patients who are subject to higher risks of each of these types of clinical outcomes as well as mortality.[10,11] We examined the use of DES with time in patients ≥85 years of age within a mandatory state procedure database. Because of wide swings in DES use rates, particularly among the extremely elderly population, we used quarterly DES use rate as an instrumental variable to determine the independent effect of stent type and associated pharmacological treatment strategies on mortality, revascularization, and bleeding risks.

Methods

Study Population

The Massachusetts Data Analysis Center (Mass-DAC, Harvard Medical School, Boston, MA) collects data on all PCI and cardiac surgeries in all nonfederal hospitals in Massachusetts as mandated by the Massachusetts Department of Public Health. PCI data are collected by using the American College of Cardiology's National Cardiovascular Data Registry data collection instrument (https://www.ncdr.com/webncdr/cathpci). The data are submitted electronically to Mass-DAC, where they are cleaned, audited, and adjudicated by a group of interventional cardiologists and data managers, as previously described.[12] The study was designed and performed by the authors. The Committee on Human Studies of the Harvard Medical School (M10774-145) approved the study.

All patients ≥85 years of age undergoing PCI with stenting between April 1, 2003, and September 30, 2009, were identified (Figure 1). Patients who were not Massachusetts residents and those who could not be linked to hospital discharge billing data were excluded from the analysis to avoid incomplete follow-up. Study subjects were assigned to either a BMS or DES group according to the stent type used in the index hospitalization. Subjects who received both stent types were not included in the analysis.

Study Outcomes

Study outcomes were all-cause mortality, target vessel revascularization (TVR), and bleeding requiring hospitalization at 30 days and 1 year. In-hospital mortality for the index hospitalization is reported directly to Mass-DAC by the hospitals and verified by comparison with the Massachusetts Registry of Vital Records and Statistics. Mortality subsequent to discharge was ascertained via linkage with the Massachusetts Registry of Vital Records and Statistics. In-hospital and long-term bleeding was identified from hospital discharge billing data (*International Classification of Diseases*, Ninth Revision, codes 362.81, 431–432.9, 459.0, 530.82, 578, 578.0, 578.1, 578.9, 719.1, 423.0, 599.7, 786.3, V58.2, and E879.8). TVR was defined as PCI in a vessel previously treated during the index procedure or any coronary artery bypass graft surgery after the index procedure.[13]

Patient and Procedural Characteristics

We identified patient and procedural characteristics among DES- and BMS-treated elderly patients from clinical data assessed at the time of the index procedure. These variables included sociodemographic characteristics (age, sex, race, and insurance), medical history (diabetes mellitus, hypertension, hyperlipidemia, smoking status, previous PCI, previous myocardial infarction [MI], previous coronary artery bypass graft surgery, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, atrial fibrillation, history of neoplasm, history of hospitalized gastrointestinal bleeding, chronic renal insufficiency, hemodialysis), presentation characteristics (ST-segment–elevation MI versus non–ST–elevation MI versus other presentation, emergency, or salvage procedure, duration of acute coronary syndrome, presentation with shock), and angiographic/procedural characteristics (number of diseased vessels, treatment of the left main coronary artery, and high risk/class C lesion). These variables were used for statistical adjustment for all models subsequently described.

Statistical Analysis

We compared patient and procedural characteristics among extremely elderly patients receiving DES or BMS using the χ^2 or Student t test as appropriate. Next, although we prespecified a primary analytic approach using instrumental variables based on previous studies suggesting likely confounding of DES versus BMS comparisons,[6,8,14] we first compared 1-year outcomes via multivariable adjusted ordinary least squares linear regression as well as 1:1 propensity-score matching to motivate this approach further. Covariates used for these models included all sociodemographic, medical history, presentation, and angiographic/procedural characteristics listed above. Linear, and not logistic, regression was used to generate directly comparable risk differences (RDs) to the 2-stage least squares instrumental variable approach. The propensity-score methods used in this analysis have been previously described.[15]

Instrumental Variable Analysis

We first determined quarterly rates of DES use in elderly patients ≥85 years of age in Massachusetts from April 1, 2003, to September 30, 2009. Specifically, the rate of DES use (continuous variable between 0% and 100%) in the concurrent quarter was assigned to each PCI and used as the instrumental variable in the stage 1 model.

We performed both unadjusted and adjusted instrumental variable analyses comparing DES and BMS in our study population using the 2-stage least squares methodology.[16] First, we built a linear regression

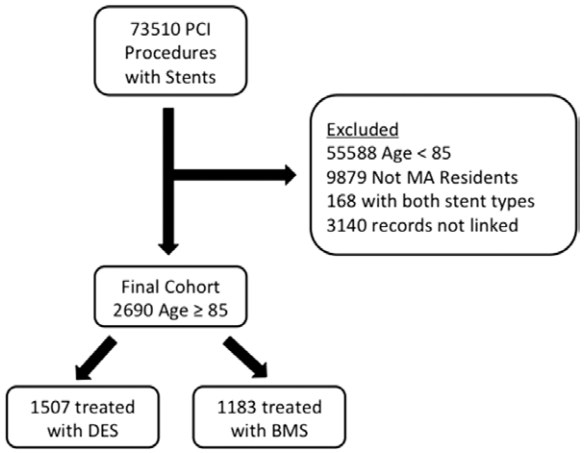

Figure 1. Flow chart of patient selection. BMS indicates bare metal stent; DES, drug-eluting stent; MA, Massachusetts; and PCI, percutaneous coronary intervention.

model predicting DES treatment with the instrument (stage 1). In stage 2, a least squares regression using the predicted values from stage 1 as the primary predictor was performed to obtain instrumental variable-based RDs for 30-day and 1-year mortality, TVR, and bleeding outcomes between DES and BMS. In the unadjusted analysis, only the instrumental variable was incorporated into the regression models; in the adjusted analysis, we adjusted for all variables described above in both stages in addition to the instrumental variable. RDs between DES- and BMS-treated patients for all outcomes were estimated based on the coefficient of the instrumental variable in the stage 2 model. Robust SEs were estimated for all instrumental variables analyses.

Evaluation of Instrumental Variable Assumptions

A valid instrument requires that several assumptions be justified.[17] First, the instrument should strongly predict the exposure of interest. In this case, the assumption is that the statewide rate of DES use in the extremely elderly population would be strongly predictive of the likelihood of receiving DES during the index procedure. We evaluated the strength of this assumption through measurement of the Cragg–Donald Wald F statistic from the stage 1 linear regression model, defining the strength of the association between quarterly DES rate among the extreme elderly population and the likelihood of DES receipt during the index procedure.[18] As a rule of thumb, values >10 for this test have been shown to suggest a sufficiently strong instrument.[19] A second assumption is that the instrument affects the outcome only through its association with the primary predictor of interest, that is, the relationship between quarterly rates of DES use and 30-day and 1-year outcomes after the index procedure would be mediated only through the influence of the likelihood of receiving DES at various points in time, a fundamentally untestable assumption. A third assumption is that the instrumental variable should effectively randomize patients such that patients should be similar with respect to measured and unmeasured factors across levels of the instrument. To indirectly test this assumption for observed characteristics, we compared characteristics of patients undergoing PCI for whom the quarterly rate of DES use in the extreme elderly was ≥50% versus ≤50%.

Dr Normand had full access to the data; Drs Yeh, Mauri, and Normand take full responsibility for the integrity of the data analysis. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC) and STATA version 11.2 (StataCorp LP, College Station, TX).

Results

Patient and Lesion Characteristics

Between April 1, 2003, and September 30, 2009, 73 510 patients underwent PCI with stenting in Massachusetts. Of these patients, 9879 were nonresidents of Massachusetts, and 3140 could not be linked to hospital discharge data and were excluded from analysis. Of the remaining 58 446 patients, 2858 patients (4.89%) were ≥85 years of age. After patients treated with both DES and BMS were excluded, 2690 total patients ≥85 years of age remained in the analysis cohort, 1507 of whom were treated with DES and 1183 of whom were treated with BMS (Figure 1). Of the DES-treated patients, 61.4% received sirolimus-eluting stents, 34.8% received paclitaxel-eluting stents, 4.2% received everolimus-eluting stents, and 2.0% received zotarolimus-eluting stents.

Patients treated with BMS were older and more likely to have a history of atrial fibrillation, neoplasm, and previous gastrointestinal bleed (Table 1). They were more likely to present with ST-segment–elevation MI, congestive heart failure, or cardiogenic shock. DES-treated patients were more likely to have hyperlipidemia or history of previous PCI. They had more vessels and lesions treated compared with BMS-treated patients and were more likely to undergo stenting for left main coronary artery lesions (Table 2).

Stent Types Use With Time

Quarterly DES use rates changed dramatically with time within the ≥85-year-old population, starting at a low rate of 15% shortly after DES approval and rising to as high as 88% in 2006 (Figure 2). Subsequently, coinciding with widely publicized concerns about DES safety, rates of DES use among the extreme elderly rapidly declined to <35% in every quarter after mid-2006. By comparison, in patients between 18 and 85 years of age, DES use rose to similar levels at the peak of use (92% peak) but stayed >50% in all but 1 quarter even after the decline associated with DES safety concerns.

Unadjusted Outcomes

Across the entire study period, the unadjusted 30-day mortality rate was significantly lower for DES- compared with BMS-treated patients (5.6% versus 9.6%; $P<0.0001$). Thirty-day rates of bleeding (DES 5.2% versus BMS 6.3%; $P=0.26$) and TVR (1.7% versus 2.4%; $P=0.24$) did not differ according to stent type. Unadjusted 1-year mortality (14.5% versus 23.0%; $P<0.0001$) and TVR (4.3% versus 9.3%; $P<0.0001$) were significantly lower in DES-treated patients. One-year bleeding rates did not differ according to stent type (DES 10.3% versus BMS 12.4%; $P=0.08$).

Instrumental Variable Comparison

Adjusted instrumental variable analysis demonstrated no significant difference in the rate of mortality or TVR at 30 days associated with DES versus BMS (mortality RD DES–BMS: −1.3%; robust SE, 2.9%; $P=0.50$; TVR RD −2.0%, robust SE 1.1%; $P=0.06$). A difference in hospitalized bleeding of borderline significance was found at 30 days (RD, 3.5%; robust SE, 1.7%; $P=0.05$), although no significant difference was seen at 1 year. At 1 year, mortality was not significantly different for DES- versus BMS-treated patients, and TVR was significantly lower with DES (Table 3). Unadjusted instrumental variables analyses yielded similar results, suggesting that the instrument was less likely to be confounded by measured variables. By comparison, using a traditional

Table 1. Baseline Patient Characteristics

Characteristics	DES (n=1507)	BMS (n=1183)	*P* Value
Age, y (SD)	87.4±2.4	87.8±2.7	<0.0001
Female sex, no. (%)	809 (53.7)	660 (55.8)	0.28
White race, no. (%)	1407 (93.4)	1121 (94.8)	0.13
Insurance, no. (%)			<0.0001
Government	1160 (77.0)	991 (83.8)	
HMO	234 (15.5)	117 (9.9)	
Other commercial or no insurance	113 (7.5)	75 (6.3)	
Insulin-requiring diabetes mellitus, no. (%)	98 (6.5)	58 (4.9)	0.08
Non–insulin-requiring diabetes mellitus, no. (%)	263 (17.5)	211 (17.8)	0.80
Hyperlipidemia, no. (%)	1096 (72.7)	813 (68.7)	0.02
Hypertension, no. (%)	1320 (87.6)	1011 (85.5)	0.11
Smoker, no. (%)			0.87
Current	42 (2.8)	33 (2.8)	
Former	639 (42.4)	490 (41.4)	
Previous PCI, no. (%)	278 (18.5)	140 (11.8)	<0.0001
Previous myocardial infarction, no. (%)	479 (31.8)	346 (29.3)	0.16
Previous CABG, no. (%)	244 (16.2)	189 (16.0)	0.88
Left main disease present, no. (%)	125 (8.3)	82 (6.9)	0.19
Congestive heart failure, no. (%)	357 (23.7)	329 (27.8)	0.02
Peripheral vascular disease, no. (%)	247 (16.4)	206 (17.4)	0.48
Cerebrovascular disease, no. (%)	245 (16.3)	205 (17.3)	0.46
Chronic lung disease, no. (%)	182 (12.1)	171 (14.5)	0.07
Atrial fibrillation, no. (%)	330 (21.9)	322 (27.2)	0.001
History of neoplasm, no. (%)	44 (2.9)	66 (5.6)	<0.001
History of gastrointestinal bleed, no. (%)	47 (3.1)	55 (4.7)	0.04
Chronic renal insufficiency, no. (%)	169 (11.2)	141 (11.9)	0.57
Cardiogenic shock, no. (%)	35 (2.3)	47 (4.0)	0.01
Positive stress test, no. (%)	245 (16.3)	180 (15.2)	0.46
Indication, no. (%)			<0.0001
No angina	122 (8.1)	86 (7.3)	
Stable angina	236 (15.7)	127 (10.7)	
Unstable angina	428 (28.4)	237 (20.0)	
Non-STEMI	492 (32.7)	384 (32.5)	
STEMI	229 (15.2)	349 (29.5)	
Procedure status, n (%)			<0.0001
Elective	376 (25.0)	187 (15.8)	
Urgent	888 (58.9)	622 (52.6)	
Emergency/salvage	243 (16.1)	374 (31.6)	
Ejection fraction <30%	501 (33.2)	438 (37.0)	0.04

ACS indicates acute coronary syndrome; BMS, bare metal stents; CABG, coronary artery bypass graft; DES, drug-eluting stent; HMO, health maintenance organization; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation MI.

Table 2. Procedural Characteristics

Characteristics	DES (n=1507)	BMS (n=1183)	*P* Value
No. diseased vessels	1.80±0.85	1.84±0.83	0.23
No. vessels treated (continuous)	1.26±0.54	1.14±0.39	<0.0001
No. vessels treated (categorical)			<0.0001
1 Vessel treated	1182 (78.4)	1029 (87.0)	
2 Vessels treated	263 (17.5)	139 (11.8)	
≥3 Vessels treated	62 (4.1)	15 (1.3)	
No. lesions treated	1.53±0.80	1.38±0.66	<0.0001
Target vessel(s), n (%)			
Left main artery	85 (5.6)	44 (3.7)	0.02
Left anterior descending artery	775 (51.4)	544 (46.0)	0.005
Left circumflex artery	485 (32.2)	307 (26.0)	<0.001
Right coronary artery	555 (36.8)	455 (38.5)	0.39
Saphenous vein graft	108 (7.2)	95 (8.0)	0.40
High-risk lesion	703 (46.7)	535 (45.2)	0.46
Restenotic target lesion	62 (4.1)	22 (1.9)	<0.001

High-risk lesions were defined as those >20 mm in length, having excessive tortuosity of the proximal segment, extremely angulation >90°, total occlusion >3 mo and/or bridging collaterals, the presence of an unprotectable major side branch, or a degenerated vein graft with friable lesions. BMS indicates bare metal stents; and DES, drug-eluting stent.

linear regression–based approach, DES was associated with significantly lower 1-year mortality (RD, −5.8%; SE 1.7%; *P*=0.001), and similar rates of bleeding (RD, −0.001; SE, 0.15; *P*=0.97). Likewise, propensity-score matching yielded similar results, with significantly lower 1-year mortality (RD, −4.0%; SE, 1.7%; *P*=0.02) and similar rates of 1-year bleeding (RD, 1.1%; SE, 4.6%; *P*=0.45).

Evaluation of the Instrument

The first stage regression demonstrated a Cragg–Donald Wald *F* statistic of 978.6, suggesting a strong instrument that was highly predictive of actual DES use. This large value is attributable to the large shifts in quarterly DES use in the

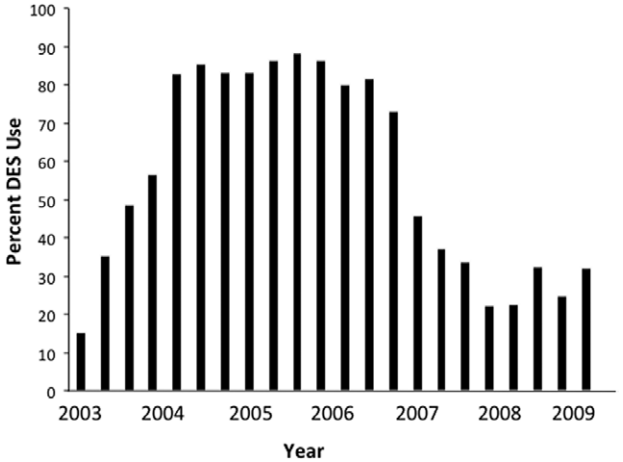

Figure 2. Use of drug-eluting stents (DES) among patients ≥85 years of age with the passage of time.

Table 3. Primary Results—Unadjusted and Instrumental Variable–Based 1-Year Outcomes

	Unadjusted Outcomes				Unadjusted Instrumental Variable Outcomes			Adjusted Instrumental Variable Outcomes		
1-Year Outcomes	DES (n=1507)	BMS (n=1183)	Risk Difference	*P* Value	Risk Difference	Robust SE	*P* Value	Risk Difference	Robust SE	*P* Value
Mortality, %	14.5	23.0	–8.5	<0.0001	–2.7	2.8	0.35	–0.8	2.8	0.76
Bleeding, %	10.3	12.4	–2.1	0.08	1.0	2.4	0.68	2.3	2.4	0.33
Target vessel revascularization, %	4.3	9.3	–5.0	<0.0001	–7.3	1.9	<0.0001	–8.3	2.0	<0.0001

Risk differences represent values for DES outcomes minus BMS outcomes. Unadjusted outcomes represent crude observed results. Unadjusted instrumental variable outcomes represent outcomes using a 2-stage least squares approach but not adjusted for other observed covariates. Adjusted instrumental variable outcomes represent outcomes using a 2-stage least squares approach adjusted for other patient observed covariates. BMS indicates bare metal stent; and DES, drug-eluting stent.

extreme elderly population and greatly exceeded the generally accepted threshold of 10 below which an instrumental variable is considered weak.[19] Clinical characteristics of subjects undergoing PCI when quarterly DES use was >50% were not significantly different from those of subjects undergoing PCI when quarterly DES use was ≥50% in all but 3 variables assessed, evidence that the instrument was rather, effective at randomizing patients in a balanced fashion with regard to measured characteristics (Table 4). The variables for which there were significant differences (insurance status, disease presentation, procedure status) were multilevel variables with greater degrees of freedom, had differences that were small in magnitude at each level, and were included as covariates in the adjusted instrumental variable analysis.

Discussion

We describe the first analysis of medical device use as an instrumental variable to estimate treatment effectiveness of DES and coronary stent as they are used in actual practice to treat extremely elderly patients. We identified marked changes in use patterns during the 6 years after the introduction of this device, more extreme than those observed in the adult patient population <85 years of age. Although evidence of treatment selection bias was present before adjustment, the rapid swings in DES use within the extremely elderly allowed for the use of quarterly DES use rates as an instrumental variable. With such an approach, the estimated treatment effects within the extremely elderly, who are not well represented in clinical trials, were consistent with the treatment effects observed in randomized trials of lower risk populations (ie, DES) were associated with reduction in repeat revascularization procedures but no difference in mortality compared with BMS.

Previous observational studies have examined the efficacy and safety of DES within the extreme elderly population.[20,21] In a study of ≥85-year-old Medicare patients undergoing PCI at hospitals participating in the National Cardiovascular Data Registry, Wang et al[21] found that DES were associated with a significant 20% reduction in the hazard for all-cause mortality and no difference in the rate of repeat revascularization using a propensity score–based approach. In contrast, we observed a reduction in risk of repeat revascularization procedures, consistent with the mechanism of DES benefit, whereby drug elution reduces neointimal hyperplasia and restenosis, and no difference in mortality, consistent with randomized trial results comparing DES and BMS.

Differences in our results compared with previous studies may be explained by differences in the analytic approaches or study populations. In this study, we were concerned that analysis using either regression or propensity score adjustment would not offer sufficient control for confounding as evident by early large differences in unadjusted mortality rates between groups. This pattern of treatment selection bias and suspicion for residual confounding was profound in our own data set, as demonstrated by the significant differences in 1-year mortality using a standard least squares regression approach, and has been previously demonstrated in other studies. Venkitachalam et al[8] compared an instrumental variable analysis with propensity score and regression-based approaches to compare BMS and DES within a broad population of patients undergoing DES within the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. Although the analysis did not focus on the extreme elderly population per se, the authors found results suggesting that a BMS versus DES comparison was best approached using the instrumental variable method, instead of more commonly used propensity score methods or logistic regression because of the strong influence of treatment selection by unmeasured factors. To date, only 1 randomized trial has been performed comparing DES with BMS in an extreme elderly population, with preliminary results suggesting no difference in 1-year mortality or bleeding, but reductions in 1-year TVR rates.[22]

Wide variation in use, in this case, across different time periods allowed for the use of an instrumental variable approach, assuming that use patterns would not be expected to be associated with outcomes aside from through the actual treatment. The approach offered a plausible method to examine treatment effect in actual practice within patient subgroups that are traditionally difficult to study. The main advantage of instrumental variables, in contrast to previous large observational studies that we[15] and others[23,24] have used using propensity score or regression for adjustment, is that the method does not rely on the identification of all confounders to provide unbiased estimators of treatment effect. Rather the method relies on the presence of a strong instrument, not associated directly with outcome, but only associated with outcome through the treatment exposure. We found that the rapid shifts in medical device adoption (both rise and fall) with time provided an unusually strong instrument to allow the evaluation of actual treatment effectiveness in patient groups at risk for adverse events. Although the identification of suitable instrumental variables is challenging, we recommend that the approach

Table 4. Baseline Patient Characteristics Across Levels of the Instrumental Variable

Characteristics	Quarterly DES Rate <50% (n=1359)	Quarter DES Rate ≥50% (n=1331)	*P* Value
DES, %	32.0	80.5	<0.001
Age, y (SD)	87.6	87.5	0.18
Female sex, %	54.2	55.0	0.69
White race, %	94.0	93.9	0.89
Insurance, %			0.04
Government	81.7	78.2	
Commercial	6.8	7.1	
HMO	11.5	14.7	
Insulin-requiring diabetes mellitus, %	6.0	5.6	0.72
Non–insulin-requiring diabetes mellitus, %	17.6	17.7	0.96
Hyperlipidemia, %	71.7	70.2	0.37
Hypertension, %	86.0	87.4	0.27
Smoker, %			0.38
Current	2.4	3.2	
Former	42.3	41.6	
Previous PCI, %	14.2	16.9	0.05
Previous myocardial infarction, %	29.3	32.1	0.12
Previous CABG, %	15.5	16.6	0.48
Left main disease present, %	7.1	8.3	0.27
Congestive heart failure, %	25.9	25.1	0.63
Peripheral vascular disease, %	15.5	18.3	0.05
Cerebrovascular disease, %	15.4	18.1	0.06
Chronic lung disease, %	14.3	12.0	0.07
Atrial fibrillation, %	25.2	23.2	0.22
History of neoplasm, %	4.4	3.8	0.39
History of gastrointestinal bleed, %	4.2	3.4	0.27
Chronic renal insufficiency, %	11.2	11.9	0.58
Cardiogenic shock, %	3.2	2.9	0.72
Positive stress test, %	16.6	15.0	0.23
Indication, %			0.001
No MI	42.8	29.2	
Non-STEMI	33.4	31.7	
STEMI	23.8	19.1	
Procedure status, %			<0.001
Elective	18.3	23.6	
Urgent	55.9	56.4	
Emergency/salvage	25.8	20.0	

The instrumental variable of quarterly DES use rates was maintained as a continuous variable for the analysis. It is dichotomized in this table for presentation only. All but 3 variables had no significant differences across levels of the instrument. The 3 variables with significant differences were categorical variables with multiple levels tested by and r x c χ^2 test, which has an increased power to detect differences. CABG indicates coronary artery bypass graft; DES, drug-eluting stent; HMO, health maintenance organization; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation MI.

be considered for studying treatment effectiveness in settings where strong selection bias is present, sufficient randomized trials are not available, and a strong instrument is identifiable.

The main limitations to our analysis pertain to those associated with the instrumental variable analysis method. Although the strength of the association of instrument and treatment can be tested, other assumptions are mainly evaluated by indirect methods or plausibility rather than formal statistical testing. For example, it is possible that periods of high DES use could have been associated with other differences in medical therapy (eg, duration of dual antiplatelet therapy duration) or differences in observed patient characteristics (eg, disease presentation with ST-segment–elevation MI) compared with periods of low DES use, which could result in confounding of the instrument. In our study, we observed an increase in 30-day bleeding of borderline significance associated with DES using the instrumental variable approach that was not observed at 1 year, which may have been due to this phenomenon, and suggest that for this end point, regression or propensity score approaches may have been more suitable. Furthermore, the power to detect small differences in rates is limited by the lower precision associated with instrumental variables approaches. It is possible that a larger study would identify small differences in outcomes according to treatment. Additionally, we were unable to assess rates of bleeding that did not require hospitalization. Finally, the results of traditional instrumental variable approaches give an estimate of the average treatment effect only for the marginal population, that is, those patients who would have received DES during periods of high DES use but BMS during periods of low DES use. The estimates do not pertain to those patients who would have received only BMS or only DES independent of the quarterly DES use rate.[25] Although methods exist to examine the generalizability of findings to those whose treatment was uninfluenced by the instrumental variable, we think the most conservative approach is to limit the interpretation of the results to the marginal patients alone. Finally, our approach does not identify whether specific subpopulations of extreme elderly patients might benefit more or less from DES.

In conclusion, use rates of new coronary device technology, in this case of DES, served as a strong instrumental variable that allowed comparison of treatment effectiveness and safety within an unselected population of extremely elderly subjects. We found that DES were associated with similar mortality and a significant reduction in TVR compared with BMS in this population. Variation in rates of adoption and use of new technology may be especially useful as an instrumental variable to facilitate comparative effectiveness studies when randomized trial data are not fully representative and existing observational data sources are limited by unmeasured confounding. In certain circumstances, these features may be advantageous for the comparison of the safety and effectiveness of a new therapeutic device in the population in which it is actually being used, during the time frame of adoption, rather than extrapolating from more narrow clinical trial populations.

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