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Original Studies

Economic Outcomes of Percutaneous Coronary Intervention with Drug-Eluting Stents versus Bypass Surgery for Patients with Left Main or Three-Vessel Coronary Artery Disease: One-Year Results from the SYNTAX Trial

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Objectives: To evaluate the cost-effectiveness of alternative approaches to revascularization for patients with three-vessel or left main coronary artery disease (CAD). Background: Previous studies have demonstrated that, despite higher initial costs, long-term costs with bypass surgery (CABG) in multivessel CAD are similar to those for percutaneous coronary intervention (PCI). The impact of drug-eluting stents (DES) on these results is unknown. Methods: The SYNTAX trial randomized 1,800 patients with left main or three-vessel CAD to either CABG (*n* = 897) or PCI using paclitaxel-eluting stents (*n* = 903). Resource utilization data were collected prospectively for all patients, and cumulative 1-year costs were assessed from the perspective of the U.S. healthcare system. Results: Total costs for the initial hospitalization were $5,693/patient higher with CABG, whereas follow-up costs were $2,282/patient higher with PCI due mainly to more frequent revascularization procedures and higher outpatient medication costs. Total 1-year costs were thus $3,590/patient higher with CABG, while quality-adjusted life expectancy was slightly higher with PCI. Although PCI was an

Additional Supporting Information may be found in the online version of this article.

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economically dominant strategy for the overall population, cost-effectiveness varied considerably according to angiographic complexity. For patients with high angiographic complexity (SYNTAX score > 32), total 1-year costs were similar for CABG and PCI, and the incremental cost-effectiveness ratio for CABG was $43,486 per quality-adjusted life-year gained. Conclusions: Among patients with three-vessel or left main CAD, PCI is an economically attractive strategy over the first year for patients with low and moderate angiographic complexity, while CABG is favored among patients with high angiographic complexity.

Key words: cost-benefit analysis; revascularization; randomized controlled trial; restenosis

INTRODUCTION

Previous randomized trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with multivessel coronary artery disease (CAD) have demonstrated similar rates of adverse events including death and myocardial infarction (MI) over 5–10 years [1–6]. Given comparable outcomes for irreversible cardiovascular events, secondary considerations including quality of life and cost-effectiveness become increasingly relevant in choosing between these alternative revascularization strategies.

Previous economic studies have compared both conventional balloon angioplasty and bare metal stents with CABG. In general, these studies have demonstrated that PCI is less costly as an initial strategy, but that follow-up costs are substantially higher—driven predominantly by higher rates of repeat revascularization—resulting in roughly comparable costs within the first several years of follow-up [7–9]. More recently, the introduction of drug-eluting stents (DES) has led to substantial reductions in restenosis and rates of repeat revascularization compared with previous PCI techniques [10]. Although numerous studies have examined the cost-effectiveness of DES versus bare metal stents [11–13], whether the benefits of DES have led to important changes in the balance of costs and benefits between PCI and CABG is unknown. In addition, most previous studies of coronary revascularization in multivessel CAD have excluded patients with left main disease. Consequently, the economic benefits of a contemporary PCI strategy for these complex patient subsets are unknown as well.

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial is the first randomized clinical trial to compare PCI with DES versus CABG for patients with three-vessel and left main CAD. Given the increasing importance of economic considerations in the current healthcare environment, a prospectively designed health economic evaluation was embedded within the SYNTAX trial. By collecting detailed resource utilization data, we sought to directly evaluate the cost-effectiveness of DES versus CABG and to extend insights from previous clinical trials to patients with the most complex forms of CAD. This report describes the 1-year results of this ancillary economic study, performed from the perspective of the U.S. healthcare system.

METHODS

Trial Design and Treatment Protocol

The SYNTAX trial design and methods have been described previously [14,15]. Between March 2005 and April 2007, a total of 1,800 patients with three-vessel or left main CAD suitable for equivalent revascularization by either PCI or CABG were randomized to either technique. In both groups, patients were treated with the goal of achieving complete revascularization of all vessels at least 1.5 mm in diameter. Patients randomized to CABG underwent treatment using standard techniques. All PCI procedures utilized paclitaxel-eluting stents (TAXUS Express; Boston Scientific, Natick, MA).

The Institutional Review Board at each center approved the protocol, and all patients provided written informed consent. The study was designed collaboratively by the SYNTAX trial steering committee and the sponsor, Boston Scientific and is registered at the National Institute of Health website (www.clinicaltrials.gov) as identifier NCT00114972.

Assessment of Resource Utilization and Clinical Follow-up

Case report forms documenting patient characteristics, procedural details, medical resource utilization, and clinical outcomes during the initial hospitalization and 1-year follow-up period were completed by a research coordinator at each site. All components of the primary clinical endpoint (death, MI, stroke, repeat revascularization) were reviewed by an independent clinical events committee that was blinded to treatment assignment. Other clinical outcomes (e.g., wound infection, arrhythmias etc.) and measures of resource utilization (e.g., length of stay) were based on site-reported data that were independently monitored.

Determination of Medical Care Costs

Medical care costs for the index hospitalization and for the 1-year follow-up period were assessed by a combination of resource-based and event-based methods as described below. All costs were assessed from the perspective of the U.S. health care system and are reported in 2007 U.S. dollars.

Procedural Costs

Detailed resource use was recorded for each PCI procedure, and the cost for each item was estimated on the basis of the mean hospital acquisition cost for the item at U.S. hospitals in 2007 (IMS Hospital Supply Index, Millennium Research Group). The IMS Hospital Supply Index reports national average acquisition costs (weighted for volume purchased) for a broad range of medical devices across a representative sample of US hospitals. In particular, each DES was assigned a cost of $2,200 and each bare metal stent was assigned a cost of $800. Costs of antithrombotic therapy were based on average wholesale prices from the Drug Topics Red Book [16]. Costs of additional disposable equipment, overhead and depreciation for the cardiac catheterization laboratory, and non-physician personnel were estimated using data from the micro-cost accounting systems of Saint Luke's Mid America Heart Institute and Beth Israel Deaconess Medical Center and adjusted for actual procedure duration. Costs for each bypass operation including the pump circuit and associated disposable supplies were estimated in a similar fashion. For analytic purposes, resource utilization and cost data for the initial PCI procedure and any planned staged PCI procedures were combined and reported as the index procedural cost.

Other Hospital Costs

All other hospital costs associated with coronary revascularization procedures were estimated using regression models based on SYNTAX-eligible Medicare patients who underwent either PCI (n = 116,883) or CABG (n = 41,710) and whose hospitalization data were included in the 2007 Medicare Provider and Review (MedPAR) database. For each hospitalization, total costs were estimated by multiplying hospital charges by the hospital and cost-center specific cost-to-charge ratio [17,18]. We then constructed separate linear regression models for each procedure in which total hospital costs were the dependent variable and independent variables included sociodemographic factors, comorbid conditions, and in-hospital complications identified on the basis of ICD-9-CM codes [19,20]. Of note, length of stay was not included as a predictor in these models because of substantial differences in length of stay across the countries that participated in the SYNTAX trial. Finally, to avoid double-counting procedural costs, the intercept for each model was adjusted to remove the costs directly related to the revascularization procedures themselves (based on national averages for procedure duration and resource use). Details of each model are provided in Supporting Information Table I.

For hospitalizations that did not involve a revascularization procedure, the hospital admission was mapped to the appropriate diagnosis-related group (DRG) based on the principal diagnosis and any procedures performed during the admission. The cost for each admission was then assigned based on mean Medicare reimbursement rates for the DRG obtained from the Medicare Part A data file [21].

Physician Costs

Physician costs for revascularization procedures and their associated hospitalizations were estimated based on the Medicare fee schedule. For all other hospitalizations, physician costs were estimated as a percentage of hospital costs according to DRG as previously described [22,23].

Outpatient Cost

Costs for outpatient cardiovascular testing and procedures as well as cardiac rehabilitation were estimated using Medicare reimbursement rates. Outpatient medication use was assessed by patient self-report at the time of each follow-up visit, and costs were assigned using average wholesale prices from the Red Book based on a weighted average of the three most frequently used medications in each medication class [16].

Quality of Life

Quality of life was assessed directly from patients at baseline, 1, 6, and 12 months using the EuroQOL (EQ-5D) health status instrument and converted to utility weights using an algorithm developed for the U.S. population [24]. Quality-adjusted life expectancy was calculated for each patient as the time-weighted average of his or her utility values, using the mid-point between assessments as the transition between health states [25]. Missing utility values were estimated using multiple imputation techniques, taking into account

TABLE I. Baseline Characteristics

	All randomized patients (ITT)			Economic analysis population		
	PCI ($N = 903$)	CABG ($N = 897$)	P value	PCI ($n = 891$)	CABG ($n = 849$)	P value
Sociodemographic characteristics						
Age, years	65.2 ± 9.7	65.0 ± 9.8	0.55	65.3 ± 9.6	64.9 ± 9.7	0.43
Male, %	76.4	78.9	0.20	76.3	79.9	0.08
Body mass index (kg/m2)	28.1 ± 4.8	27.9 ± 4.5	0.37	28.1 ± 4.8	27.9 ± 4.4	0.26
Enrolling country, %						
United States	13.6	13.6	0.99	13.6	13.3	0.87
Rest of world	86.4	86.4	0.99	86.4	86.7	0.87
Clinical characteristics						
Treated diabetes, %	28.2	28.5	0.89	28.2	27.9	0.91
Insulin-dependent, %	9.9	10.4	0.72	9.9	10.2	0.80
Current smoker, %	18.5	21.9	0.08	18.2	21.8	0.07
Previous myocardial infarction, %	31.9	33.8	0.32	31.8	33.5	0.45
Peripheral vascular disease, %	9.1	10.6	0.28	9.2	10.5	0.37
Chronic obstructive pulmonary disease, %	7.9	9.3	0.29	7.7	9.3	0.24
Prior stroke or transient ischemic attack, %	7.7	9.1	0.28	7.6	9.1	0.27
History of congestive heart failure, %	4.0	5.3	0.18	4.1	5.0	0.33
Left ventricular ejection fraction, %	59 ± 13	58 ± 13	0.32	59 ± 13	58 ± 13	0.31
Left main disease (any), %	39.5	38.8	0.75	39.8	39.6	0.91
Left main + 0/1/2 vessel disease, %	24.5	25.2	0.72	24.7	25.7	0.60
Left main + three-vessel disease, %	15.1	13.6	0.38	75.3	74.3	0.42
Three-vessel disease (no left main), %	60.5	61.2	0.75	60.2	60.4	0.91
Number of lesions	3.9 ± 1.7	4.0 ± 1.7	0.44	3.9 ± 1.7	4.0 ± 1.7	0.73
SYNTAX score	28.4 ± 11.5	29.1 ± 11.4	0.19	28.4 ± 11.5	29.1 ± 11.3	0.19
Initial treatment received, %						
PCI	98.0	1.8	< 0.001	98.5	1.9	< 0.001
CABG	1.2	95.2	< 0.001	1.0	97.5	< 0.001
None	0.8	3.0	< 0.001	0.4	0.6	0.75

CABG = coronary artery bypass grafting; ITT = intent to treat; PCI = percutaneous coronary intervention.

baseline patient characteristics, clinical events, number of hospitalizations, and previous utility values.

Statistical Analysis

To avoid bias due to slightly higher rates of withdrawal before treatment among patients assigned to CABG, the analytic population for the primary economic analysis consisted of all randomized patients for whom complete data were available through 1-year of follow-up ($n = 1740$). Sensitivity analyses using the full intention to treat population ($n = 1,800$), the population who underwent at least one revascularization procedure (revascularized population, $n = 1,766$) and the population who were treated as assigned (per protocol population; $n = 1,739$) demonstrated similar results.

Categorical data are reported as frequencies, and continuous data are reported as mean ± standard deviation. Discrete variables were compared by Fisher's exact test. Normally distributed continuous variables were compared by Student's t-test, and non-normally distributed data were compared by the Wilcoxon rank-sum test. Cost data are reported as both mean and median values and were compared by t-tests, which are appropriate given the large sample size and our focus on comparing mean costs between groups (rather than the underlying distributions) [26]. Confidence intervals for the differences in costs between the two treatment groups were obtained using the bootstrap method [27]. Unless otherwise indicated, all analyses were performed according to intention-to-treat.

Cost-Effectiveness Analyses

Cost-effectiveness was assessed from the perspective of the U.S. healthcare system over the 1-year observation period. The primary endpoint for this analysis was the incremental cost-effectiveness ratio (ICER) for the more costly therapy (generally CABG) compared with the less costly therapy, measured in terms of cost per quality-adjusted year of life gained ($/QALY). Since the main benefit of CABG during the timeframe of this analysis was a reduction in the need for repeat revascularization [15], a secondary cost-effectiveness analysis was performed in terms of cost per repeat revascularization event avoided. For each analysis, bootstrap methods (1,000 replicates) were used to estimate the joint distribution of cost and effectiveness differences and the proportion of replicates with ICERs less than commonly accepted benchmarks [28,29]. Stratified analyses of 1-year costs, clinical outcomes, and cost-effectiveness were performed according to prespecified subgroups defined by gender, age terciles, diabetic status, the presence of significant left main disease, enrolling country (U.S. vs. others), and SYNTAX score terciles (a measure of angiographic complexity) [15].

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Patient Population

A total of 1,800 patients with either three-vessel or left main coronary disease were randomized to either PCI with paclitaxel-eluting stents ($n = 903$) or bypass surgery ($n = 897$). One-year follow-up was available for 891 patients assigned to initial PCI and 849 patients assigned to initial CABG. Baseline characteristics were well-matched within the overall study population as well as among those patients for whom follow-up data were available (Table I).

Initial Treatment Costs

Among patients assigned to PCI, 98% underwent initial PCI, 1.2% underwent CABG, and 0.8% underwent no revascularization (Table I). Among patients assigned to initial CABG, 95.2% underwent CABG, 1.8% underwent PCI, and 3.0% underwent no procedure. Resource utilization for the initial revascularization procedures (including any staged PCI procedures) is summarized in Table II. Among patients treated with initial PCI, 14.0% required two planned procedures and 0.1% required three planned procedures. On average, the index PCI procedures required 2.1 guiding catheters (range 1–15), 3.5 guidewires (range 1–19), 3.7 angioplasty balloons (range 0–21), and 4.5 DES (range 0–14). Although procedure duration was substantially shorter for PCI than for CABG, total cost for the index procedure(s) was ~$6,000/patient higher with PCI ($14,407 vs. $8,100, $P < 0.001$) reflecting the much higher cost of consumable resources for the PCI procedures.

TABLE II. Index Procedural Resource Utilization and Cost (Per Protocol Population)

	PCI ($N = 885$)	CABG ($N = 854$)	P value
Number of PCI procedures, %			
1	85.9	–	
2	14.0	–	
3	0.1	–	
Procedure duration (minutes)			
Index procedure	91 ± 44	209 ± 62	<0.001
Staged procedures	10.2 ± 29.7	–	
Total	101 ± 55	209 ± 62	<0.001
Guiding catheters	2.1 ± 1.2	–	
Guidewires	3.5 ± 2.3	–	
Paclitaxel-eluting stents	4.5 ± 2.3	–	
Bare metal stents	0.0 ± 0.3	–	
Angioplasty balloons	3.7 ± 2.8	–	
Rotablator burrs	0.1 ± 0.3	–	
Intravascular ultrasound catheters	0.1 ± 0.4	–	
Contrast volume, ml	415 ± 203	–	
Antithrombotic agents used, %			
Bivalirudin	7.2	–	
Abciximab	15.6	–	
Eptifibatide	9.5	–	
Tirofiban	10.7	–	
Index procedure costs, $	14,407 ± 6,887 [13,537]	8,100 ± 1,878 [7,959]	<0.001

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.
Values in brackets are medians.

Resource utilization and costs for the initial hospitalization (including repeat hospitalizations for staged procedures) are summarized in Table III. There were no differences in death or MI between the treatment groups, but post-procedural stroke was more frequent with CABG. Several other in-hospital complications were more common among patients assigned to CABG as well including respiratory failure, renal failure, serious infections, and atrial fibrillation. On the other hand, the need for unplanned PCI was more common among patients assigned to initial PCI. Not surprisingly, post-procedure length of stay (9.4 vs. 3.3 days) and ICU duration (2.4 vs. 0.9 days) were both substantially longer among patients assigned to initial CABG. Although procedural costs were higher for the PCI group, other hospital costs including room/ancillary costs and costs for physician services were substantially higher with CABG. As a result, total costs for the index revascularization procedures and associated hospitalization were $5,693/patient higher for the CABG group compared with the PCI group (95% CI: $4,699 to $6,689; $P < 0.001$).

Follow-up Resource Utilization and Costs

During the 1-year follow-up period, cardiovascular resource utilization was substantially greater among patients assigned to initial PCI as compared with CABG (Table IV). In particular, patients assigned to initial PCI experienced higher rates of repeat revascularization (14.1 vs. 4.8 procedures per 100 patients treated) and cardiovascular hospitalizations (18.9 vs. 12.1 per 100 patients) during follow-up. As a result, costs for re-hospitalization were $1,502/patient higher after initial PCI with parallel increases in follow-up physician costs and outpatient costs. Costs for cardiovascular medications were $1,247/patient higher after initial PCI—driven almost entirely by the cost of

TABLE III. Index Hospitalization Events, Resource Utilization, and Costs (Revascularized Population)

	PCI (*N* = 896)	CABG (*N* = 870)	Difference (95% CI)	*P* value
Death, %	1.8	1.4	0.4 (−0.8 to 1.6)	0.27
Myocardial infarction, %	2.7	2.4	0.3 (−12 to 1.7)	0.72
Stroke, %	0.1	1.0	−0.9 (−1.6 to −0.2)	0.01
Unplanned PCI, %	1.8	0.5	1.3 (0.3 to 2.3)	0.008
Unplanned CABG, %	0.8	1.1	−0.04 (−1.3 to 0.5)	0.22
Staged PCI, %	13.6	0.2	13.4 (11.1 to 15.7)	<0.001
Complications, %				
Major bleeding	4.5	4.8	−0.4 (−2.3 to 1.6)	0.72
Respiratory failure	0.0	1.6	−1.6 (−2.4 to −0.8)	<0.001
Renal failure	0.7	2.4	−1.7 (−2.9 to −0.6)	0.003
Wound infection	0.0	4.1	−4.1 (−5.5 to −2.8)	<0.001
Other infection	0.4	2.2	−1.7 (−2.8 to −0.7)	0.001
Atrial fibrillation	1.3	17.9	−16.6 (−19.2 to −13.9)	<0.001
Cardiac tamponade	0.3	0.8	−0.5 (−1.2 to 0.2)	0.22
Other procedures, %				
Permanent pacemaker	0.2	0.6	−0.4 (−0.9 to 0.2)	0.28
Implantable cardioverter-defibrillator implantation	0.0	0.2	−0.2 (−0.5 to 0.1)	0.24
Carotid endarterectomy	0.0	0.5	−0.5 (−0.9 to 0.0)	0.06
Length of stay (post-procedure), days				
Intensive care unit /cardiac care unit	0.9 ± 1.9 [0]	2.4 ± 3.9 [1]	−1.5 (−1.7 to −1.2)	<0.001
Total	3.3 ± 4.5 [2]	9.4 ± 7.4 [7]	−6.0 (−6.6 to −5.5)	<0.001
Initial hospitalization costs, $				
Procedural costs	14,509 ± 7,014 [13,527]	8,206 ± 2,154 [7,973]	6,303 (5,815 to 6,791)	<0.001
Hospital stay + ancillary services	10,909 ± 6,205 [8,094]	20,536+8,634 [17,763]	−9,626 (−10,327 to −8,926)	<0.001
Physician fees	2,141 ± 939 [1,778]	4,511 ± 807 [4,267]	−2,370 (−2,451 to −2,288)	<0.001
Total	27,560 ± 11,443 [24,729]	33,254 ± 9,782 [30,554]	−5,693 (−6,689 to −4,699)	<0.001

CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.
Values in brackets are medians.

prolonged dual antiplatelet therapy. On the other hand, costs for rehabilitation services were substantially lower after initial PCI compared with CABG

Overall, follow-up medical care costs averaged $8,426 after PCI versus $6,143 after CABG—a difference of $2,282/patient (95% CI: $1,304–$3,261).

Despite these lower follow-up costs after CABG, total 1-year costs remained $3590/patient higher with initial CABG as compared with initial PCI (95% CI: $2,124–$5,056). The net 1-year cost difference was similar when the analysis was performed among all patients who underwent revascularization ($3,411) or among the per protocol population ($3,622).

Cost-Effectiveness

Although there was no significant difference in 1-year survival between the two groups, quality-adjusted life expectancy was greater for the PCI group as compared with the CABG group (0.82 vs. 0.80 QALYs, $P = 0.003$)—driven largely by differences in utility weights during the early recovery period (Baseline: PCI-0.75 vs. CABG-0.74, $P = 0.11$; 1-month: 0.85 vs. 0.77, $P < 0.001$; 6-months: 0.86 vs. 0.85, $P = 0.09$; 12-months: 0.86 vs. 0.85, $P = 0.92$). Thus, in our primary cost-effectiveness analysis, PCI was an economically dominant treatment strategy with both lower overall costs and greater quality-adjusted life expectancy at 1-year. Bootstrap simulation demonstrated that PCI remained economically dominant in 100% of replicates (Fig. 1).

In our secondary cost-effectiveness analysis (in which avoidance of the need for repeat revascularization was the measure of clinical benefit), the ICER for CABG versus PCI was $35,491 per repeat revascularization avoided. Bootstrap simulation demonstrated that this ratio remained >$10,000 in 100% of replicates and >$20,000 per repeat revascularization avoided in 94.1% (Fig. 2).

Subgroup Analyses

Results from stratified analyses according to prespecified baseline characteristics are displayed in Tables V and VI. There were significant interactions between treatment assignment and total 1-year cost according to the presence of diabetes, left main disease, and SYNTAX score. The interaction with SYNTAX score was particularly strong with a 1-year cost difference of $6,154/patient among patients with SYNTAX scores < 23, $3,889/patient for those with SYNTAX scores 23–32 and only $466/patient for those with SYNTAX scores >32. There was also a statistically significant interaction between treatment assignment and SYNTAX score for quality-adjusted life expectancy with differences ranging

TABLE IV. Follow-up Events, Resource Utilization, and Costs (Revascularized Population)

	PCI (N = 896)	CABG (N = 870)	Difference (95% CI)	P value
Clinical outcomes				
Repeat revascularization, %				
PCI	10.2	4.1	6.0 (3.6 to 8.4)	<0.001
CABG	2.0	0.1	1.9 (0.9 to 2.8)	<0.001
Any	11.6	4.1	7.5 (5.0 to 9.9)	<0.001
Re-hospitalization, %				
Cardiovascular	15.8	10.2	5.6 (2.5 to 8.7)	<0.001
Non-cardiovascular	22.2	21.7	0.5 (−3.4 to 4.3)	0.81
Any	32.4	27.6	4.8 (0.5 to 9.0)	0.03
Resource utilization (events/100 pts)				
Repeat revascularization, n/100 pts				
PCI procedures	11.9 ± 38.7	4.7 ± 23.8	7.2 (4.2 to 10.2)	<0.001
CABG procedures	2.1 ± 15.2	0.1 ± 3.4	2.0 (1.0 to 3.0)	<0.001
Total procedures	14.1 ± 43.9	4.8 ± 24.5	9.2 (5.9 to 12.6)	<0.001
Diagnostic catheterization, n/100 pts	11.5 ± 34.6	3.6 ± 19.7	7.9 (5.3 to 10.6)	<0.001
Re-hospitalization, n/100 pts				
Cardiovascular	18.9 ± 48.6	12.1 ± 37.8	6.8 (2.7 to 10.9)	0.001
Non-cardiovascular	30.8 ± 67.4	31.5 ± 74.3	−0.7 (−7.3 to 5.9)	0.84
Total	49.7 ± 86.7	43.6 ± 88.1	6.1 (−2.1 to 14.3)	0.14
Follow-up Costs				
Re-hospitalizations, $				
Cardiovascular	3,978 ± 9,179 [0]	2,041 ± 5,428 [0]	1,937 (1,231 to 2,644)	<0.001
Non-cardiovascular	479 ± 2,422 [0]	914 ± 3,663 [0]	−435 (−724 to −146)	0.003
Total	4,457 ± 9,460 [0]	2,955 ± 6,616 [0]	1,502 (738 to 2,266)	<0.001
Physician fees, $	1,058 ± 1,948 [0]	829 ± 1,751 [0]	230 (57 to 403)	0.009
Outpatient services, $	441 ± 943 [0]	303 ± 700 [0]	139 (61 to 216)	<0.001
Rehabilitation services, $	218 ± 1,101 [0]	1,052 ± 102 [0]	−834 (−979 to −690)	<0.001
Medications, $	2,253 ± 857 [2,165]	1,006 ± 768 [741]	1,247 (1,171 to 1,323)	<0.001
Total follow-up cost, $	8,426 ± 11,750 [2,839]	6,143 ± 8,983 [2,958]	2,282 (1,304 to 3,261)	<0.001
Cumulative outcomes and costs[a]				
Death, %	4.4	3.5	0.8 (−1.0 to 2.7)	0.37
Myocardial infarction, %	4.8	3.3	1.5 (−0.3 to 3.4)	0.11
Stroke, %	0.6	2.2	−1.7 (−2.8 to −0.6)	0.003
Repeat revascularization, %	13.5	5.9	7.6 (4.8 to 10.3)	<0.001
Quality-adjusted life years	0.82 ± 0.19	0.80 ± 0.16	0.02 (0.01 to 0.04)	0.003
Total 1-year cost, $	35,991 ± 17,149 [30,720]	39,581 ± 13,753 [34,496]	−3,590 (−5,056 to −2,124)	<0.001

[a]Total 1-year costs and QALYs are based on the population with complete economic data (n = 891 PCI, 849 CABG) and are analyzed by intention to treat.
CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

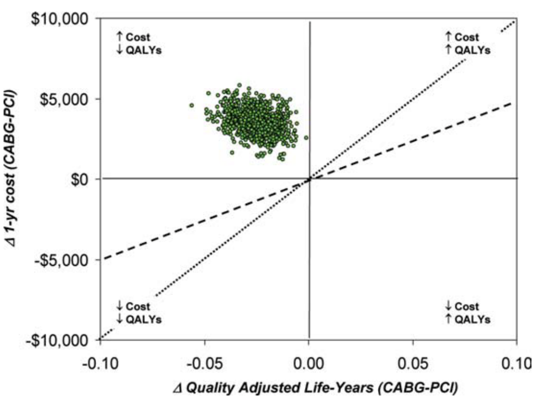

Fig. 1. Scatter plot showing the joint distribution of the difference in cost and quality-adjusted life expectancy between PCI and CABG at 1-year according to bootstrap simulation (1,000 replicates). The lines indicate ICER thresholds of $50,000/QALY gained (long dashes) and $100,000/QALY gained (short dashes). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

from 0.056 QALYs in favor of PCI for the lowest SYNTAX score tercile versus 0.011 QALYs in favor of CABG for the highest SYNTAX score tercile.

These interactions led to important differences in the incremental cost-effectiveness of CABG versus PCI according to SYNTAX score. Whereas PCI was an economically dominant strategy for patients with low and intermediate SYNTAX scores, for patients in the highest SYNTAX score tercile, the ICER for CABG versus PCI was $43,486/QALY gained and remained $50,000/QALY in 48.9% of bootstrap simulations. Similar findings were noted in the disease-specific cost-effectiveness analysis. The ICER for CABG versus PCI ranged from $78,660/repeat revascularization avoided in the lowest SYNTAX score tercile to $3,602/repeat revascularization avoided in the highest SYNTAX score tercile (with 68% of bootstrap replicates < $10,000/repeat revascularization avoided).

DISCUSSION

This is the first direct economic comparison of PCI using DES versus CABG for patients with three-vessel and left main CAD. Within this highly complex patient population, we found that although PCI required an average of 4.5 stents and incurred procedural costs of >$14,000/patient, initial treatment costs were ~$6,000 per patient higher with CABG-reflecting a combination of higher costs for the hospitalization and ancillary services, more frequent complications, and higher physician fees. Over the first year, however, patients assigned to CABG underwent fewer repeat revascularization procedures and lower medication costs, resulting in cost offsets of ~$2,500/patient. Nonetheless, for the overall population, total 1-year medical care costs remained ~$3,500/patient higher with CABG than with PCI. Since there were early differences in QOL that favored PCI but no late differences in either QOL or survival between the two groups, quality-adjusted life expectancy also tended to favor PCI. Taken together, these results suggest that for the "average" SYNTAX patient, PCI was an economically dominant strategy (with lower costs and greater quality-adjusted life expectancy) over the first year of follow-up.

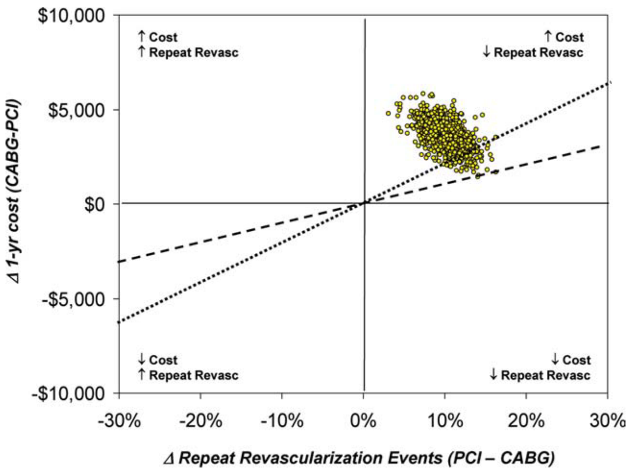

Fig. 2. Scatter plot showing the joint distribution of the difference in cost and repeat revascularization events between PCI and CABG at 1-year according to bootstrap simulation (1,000 replicates). The lines indicate ICER thresholds of $10,000 per repeat revascularization avoided (long dashes) and $20,000 per repeat revascularization avoided (short dashes). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The results of prespecified subgroup analyses suggest a somewhat more complex pattern, however. In particular, we found that both clinical and economic differences between CABG and PCI were highly dependent on angiographic complexity. For patients with low (<23) or intermediate (23–32) SYNTAX scores, PCI remained economically dominant with 1-year cost savings of $3,800–$6,100 and quality-adjusted life expectancy benefits of 0.013–0.048 QALYs. On the other hand, for patients with high (>32) SYNTAX scores, total 1-year costs were similar for PCI and CABG and quality-adjusted life expectancy tended to favor CABG, resulting in a favorable ICER for CABG of ~$43,000/QALY gained. These results parallel those for the primary clinical outcome of the SYNTAX trial, which did not differ significantly between PCI and CABG for patients with low or intermediate SYNTAX scores but strongly favored CABG for patients with high SYNTAX scores [15].

TABLE V. Subgroup Analyses—Cost Per Quality-Adjusted Life Year Gained (CABG vs. PCI)

Subgroup	Δ Cost (95% CI)	P_{int}	ΔQALYs (95% CI)	P_{int}	ICER for CABG ($/QALY)	% < $50K per QALY gained
Overall (*n* = 1,740)	−3,590 (−5,056 to −2,124)	–	0.016 (−0.001 to 0.033)	–	PCI Dominant	0.0
Male (*n* = 1,358)	−4,192 (−5,771 to −2,614)	0.12	0.017 (0.000 to 0.034)	0.62	PCI Dominant	0.0
Female (*n* = 382)	−1,728 (−5,364 to −1,908)		0.027 (−0.016 to 0.071)		PCI Dominant	9.9
Age < 61 (*n* = 600)	−4,157 (−6,401 to −1,914)	0.75	0.027 (0.003 to 0.052)	0.63	PCI Dominant	0.0
Age 62–70 (*n* = 589)	−3,275 (−5,687 to −864)		0.003 (−0.023 to 0.029)		PCI Dominant	1.1
Age > 70 (*n* = 551)	−3,480 (−6,432 to −527)		0.019 (−0.018 to 0.056)		PCI Dominant	1.0
Diabetes (*n* = 488)	−1,289 (−4,409 to 1,829)	0.02	0.019 (−0.019 to 0.058)	0.85	PCI Dominant	13.6
No diabetes (*n* = 1,252)	−4,500 (−6,120 to −2,879)		0.015 (−0.003 to 0.033)		PCI Dominant	0.0
LM disease, any (*n* = 691)	−6,341 (−8,729 to −3,954)	<0.001	0.032 (0.005 to 0.058)	0.15	PCI Dominant	0.0
Three-vessel disease, no LM (*n* = 1,301)	−1,768 (−3,609 to 74)		0.006 (−0.016 to 0.028)		PCI Dominant	5.3
SYNTAX score <23 (*n* = 554)	−6,154 (−8,599 to −3,709)	0.001	0.048 (0.018 to 0.077)	0.007	PCI Dominant	0.0
SYNTAX score 23–32 (*n* = 590)	−3,889 (−6,345 to −1,433)		0.013 (−0.014 to 0.041)		PCI Dominant	0.3
SYNTAX score >32 (*n* = 589)	−466 (−3,132 to 2,199)		−0.011 (−0.042 to 0.020)		43,486	48.9
U.S. patients (*n* = 234)	−7,897 (−12,423 to 3,371)	0.02	0.011 (−0.033 to 0.053)	0.85	PCI Dominant	0.0
Non-U.S. patients (*n* = 1,506)	−2,930 (−4,467 to −1,391)		0.017 (−0.001 to 0.034)		PCI Dominant	0.0

CABG = coronary artery bypass grafting; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LM = left main; PCI = percutaneous coronary intervention; QALY = quality-adjusted life year.

TABLE VI. Subgroup Analyses—Cost Per Repeat Revascularization Avoided (CABG vs. PCI)

Subgroup	Δ Cost (95% CI)	P_{int}	Δ Repeat Revasc (events/100 patients) (95% CI)	P_{int}	ICER for CABG ($/RR avoided)	% < $10K per RR avoided
Overall (*n* = 1,740)	−3,590 (−5,056 to −2,124)	–	10.1 (6.5 to 13.9)	–	35,491	0.0
Male (*n* = 1,358)	−4,192 (−5,771 to −2,614)	0.12	9.2 (5.1 to 13.5)	0.29	45,356	0.0
Female (*n* = 382)	−1,728 (−5,364 to −1,908)		13.2 (5.6 to 21.1)		13,072	41.6
Age < 61 (*n* = 600)	−4,157 (−6,401 to −1,914)	0.75	6.9 (1.6 to 12.7)	0.20	60,111	0.3
Age 62–70 (*n* = 589)	−3,275 (−5,687 to −864)		11.2 (4.8 to 17.3)		29,225	6.3
Age > 70 (*n* = 551)	−3,480 (−6,432 to −527)		12.4 (5.7 to 20.4)		28,095	8.9
Diabetes (*n* = 488)	−1,289 (−4,409 to 1,829)	0.02	13.6 (8.4 to 24.4)	0.20	7,895	56.7
No diabetes (*n* = 1,252)	−4,500 (−6,120 to −2,879)		7.7 (3.4 to 11.9)		58,630	0.0
LM disease, any (*n* = 691)	−6,341 (−8,729 to −3,954)	<0.001	7.2 (1.4 to 13.5)	0.14	88,377	0.0
Three-vessel disease, no LM (*n* = 1,301)	−1,768 (−3,609 to 74)		12.1 (7.5 to 17.1)		14,664	30.1
SYNTAX score <23 (*n* = 554)	−6,154 (−8,599 to −3,709)	0.001	7.8 (1.0 to 15.6)	0.23	78,660	0.1
SYNTAX score 23–32 (*n* = 590)	−3,889 (−6,345 to −1,433)		9.4 (3.7 to 15.7)		41,604	2.7
SYNTAX score >32 (*n* = 589)	−466 (−3,132 to 2,199)		13.0 (6.8 to 19.2)		3,602	68.0
U.S. patients (*n* = 234)	−7,897 (−12,423 to 3,371)	0.02	−4.4 (−15.8 to 6.4)	<0.001	PCI Dominant	0.1
Non-U.S. patients (*n* = 1,506)	−2,930 (−4,467 to −1,391)		12.4 (8.6 to 16.3)		23,696	3.6

CABG = coronary artery bypass grafting; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LM = left main; PCI = percutaneous coronary intervention; QALY = quality-adjusted life year; RR = repeat revascularization.

Comparison with Previous Studies

Over the past 20 years, numerous studies have evaluated the cost-effectiveness of PCI versus CABG among patients with multivessel coronary disease. In general, these studies have demonstrated much higher initial revascularization costs with CABG and lower costs during follow-up, resulting in roughly comparable costs over the long-term [7,8,30–36]. Only three studies, however, have been performed from the perspective of the U.S. healthcare system.

The bypass angioplasty revascularization investigation (BARI) compared conventional balloon angioplasty and CABG among 1,829 patients with two- or three-vessel disease. Although initial costs were ~$11,000 higher with CABG, by 1-year this difference had narrowed to ~$5,000 and by 5-years the difference was $2,500 with an ICER of $26,117 per year of life gained [7]. Among the 387 BARI patients with three-vessel CAD, CABG was an economically dominant strategy with lower costs and better survival. Extended follow-up to 12-years demonstrated roughly comparable results [30].

The Emory angioplasty versus surgery trial (EAST) randomized 392 patients with two- or three-vessel CAD (60% two-vessel disease) to balloon angioplasty or CABG. Initial hospital costs were ~$8,000/patient higher with CABG, but this difference decreased to ~$1,500/patient by 3-years [8] with similar results at 8-years [31]. A formal cost-effectiveness analysis was not performed.

Most recently, Stroupe et al. reported the results of an economic evaluation performed alongside the Angina with Extremely Serious Operative Mortality Evaluation (AWESOME) trial [37]. They randomized 454 patients with an urgent need for revascularization and who had one or more high risk features for CABG to either CABG or PCI (using a combination of balloon angioplasty and bare metal stents). In contrast to most other studies, the AWESOME trial demonstrated little difference in follow-up costs; the initial cost difference of ~$24,000/patient (higher with CABG) only decreased to $20,000 by 3-years and remained nearly $19,000 at 5-years. Coupled with improved survival in the PCI group, the AWESOME investigators concluded that for patients requiring urgent revascularization and at high risk of complications, PCI was an economically dominant strategy.

The SYNTAX economic study thus extends previous research in several ways. Most importantly, our study is the first prospective economic evaluation of PCI with DES versus CABG. Since the main limitation of previous PCI strategies has been restenosis leading to frequent repeat revascularization, it might be expected that the lower restenosis rates seen with DES would translate into more durable economic benefit. Indeed, we found that follow-up hospital costs were only ~$1,500 higher with PCI than with CABG—a much lower difference than had been reported previously. Moreover, our study extends the population of patients for whom comparative economic data are available to patients with the most complex forms of CAD including left main disease. Based on the SYNTAX data, it appears that patients with left main disease may derive substantial economic advantage from a DES–PCI strategy. Since the overall clinical trial failed to meet its primary endpoint, however, these findings should be considered hypothesis-generating and will require independent confirmation.

Study Limitations

Our study has several important limitations. First, as with any clinical trial, our results may not be applicable to all patients with three-vessel or left main CAD-many of whom were excluded from randomization on the basis of unfavorable anatomy for PCI or excessive surgical risk. These patients were treated in parallel nested registries that were not included in this study.

Second, although our analysis was performed from the perspective of the U.S. healthcare system, it was based on data collected from patients who were enrolled and treated in 18 countries of which only ~15% were actually treated in the U.S. (Supporting Information Table II). Although it would have been possible to restrict the economic analysis to U.S. patients, given the limited sample size we felt that this approach would have led to highly unstable results. Instead, we used costing methodology that depended only on the assumption that clinical outcomes and complications (the primary determinants of cost) would be similar across healthcare systems [38]—an assumption that underlies the design of the overall trial as well. It is also important to recognize that extension of our economic analysis to other health care systems may demonstrate very different results because of different cost and payment structures.

Moreover, although we used the most current cost data available at the time of the analysis, changes in unit costs since 2007 (particularly for DES) may have altered the relative cost of the two strategies somewhat. Recently, several clinical trials have demonstrated that the paclitaxel drug-eluting stent that was used in the SYNTAX trial has higher rates of target lesion revascularization and MI compared with the second-generation everolimus-eluting stent [39,40]. Whether use of everolimus-eluting stents would have increased the economic advantage of PCI is unknown.

Finally, the time frame encompassed by our study is relatively brief compared with the life expectancy of the underlying population. Nonetheless, previous studies have demonstrated that cost differences between PCI and CABG are minimal beyond the first 2–3 years [30,31] suggesting that even a shorter follow-up duration may provide useful insight. On the other hand, if meaningful differences in long-term survival emerge either within the overall SYNTAX population or important subgroups, it will be important to incorporate these benefits in future economic assessments. Indeed, 5-year clinical and economic follow-up is currently planned for the SYNTAX trial and will be the subject of separate reports at that time.

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REFERENCES

1. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. N Engl J Med 1996;335:217–225.
2. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomised controlled trial. Lancet 2002;360:965–970.
3. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schönberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: The final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575–581.
4. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic review: The comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147:703–716.
5. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: A meta-analysis with 5-year patient-level data from the ARTS. ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–1154.
6. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, D, Danchin N, Flather M, Hamm CW, Hueb WA, Kähler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: A collaborative analysis of individual patient data from ten randomized trials. Lancet 2009; 373:1190–1197.
7. Hlatky MA, Rogers WJ, Johnstone I, Boothroyd D, Brooks MM, Pitt B, Reeder G, Ryan T, Smith H, Whitlow P, Wiens R, Mark DB. Medical care costs and quality of life after randomization to coronary angioplasty or coronary bypass surgery. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. N Engl J Med 1997;336:92–99.
8. Weintraub WS, Mauldin PD, Becker E, Kosinski AS, King SB. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995;92:2831–2840.
9. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schönberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA; Arterial Revascularization Therapies Study Group. Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery

and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–1124.
10. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, Brodie B, Hannan E, Harjai K, Jensen LO, Park SJ, Perry R, Racz M, Saia F, Tu JV, Waksman R, Lansky AJ, Mehran R, Stone GW. Safety and efficacy of drug-eluting and bare metal stents: Comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119:3198–3206.
11. Cohen DJ, Bakhai A, Shi C, Githiora L, Lavelle T, Berezin RH, Leon MB, Moses JW, Carrozza JP Jr, Zidar JP, Kuntz RE; SIRIUS Investigators. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: Results from the Sirolimus-eluting balloon expandable stent in the treatment of patients with de novo native coronary leisons (SIRIUS) trial. Circulation 2004;110:508–514.
12. Bakhai A, Stone GW, Mahoney E, Lavelle TA, Shi C, Berezin RH, Lahue BJ, Clark MA, Lacey MJ, Russell ME, Ellis SG, Hermiller JB, Cox DA, Cohen DJ; TAXUS-IV Investigators. Cost-effectiveness of paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization: Results from the TAXUS-IV trial. J Am Coll Cardiol 2006;48:253–261.
13. Groeneveld PW, Greenhut A, Matta MA, Yang F. The costs of drug-eluting coronary stents among medicare beneficiaries. Am Heart J 2008;155:1097–1105.
14. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: Design, rationale, and run-in phase. Am Heart J 2006;151:1194–1204.
15. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–972.
16. Drug Topics Red Book. 111th edition. Florence, KY: Thompson Healthcare; 2007.
17. Ashby J. The accuracy of cost measures derived from medicare cost report data. Hosp Cost Manag Acount 1992;3:1–8.
18. Taira DA, Seto TB, Siegrist R, Cosgrove R, Berezin R, Cohen DJ. Comparison of analytic approaches for the economic evaluation of new technologies alongside multicenter clinical trials. Am Heart J 2003;145:452–458.
19. Kugelmass AD, Cohen DJ, Brown PP, Simon AW, Becker ER, Culler SD. Hospital resources consumed in treating complications associated with percutaneous coronary interventions. Am J Cardiol 2006;97:322–327.
20. Brown PP, Kugelmass AD, Cohen DJ, Reynolds MR, Culler SD, Dee AD, Simon AW. The frequency and cost of complications associated with coronary artery bypass grafting surgery: Results from the United States Medicare program. Ann Thorac Surg 2008;85:1980–1986.
21. Centers for Medicare and Medicaid Services. 100% MEDPAR Inpatient Hospital National Data for Fiscal Year 2007. Short Stay Inpatient Diagnosis Related Groups. Available at: http://www.cms.hhs.gov/MedicareFeeforSvcPartsAB/Downloads/DRG07.pdf. Accessed on August 27, 2010.
22. Mitchell J, Burge R, Lee AJ, McCall NT. Per Case Prospective Payment for Episodes of Hospital Care. Springfield, VA: U.S. Department of Commerce National Technical Information Service; 1995.
23. Weintraub WS, Mahoney EM, Lamy A, Culler S, Yuan Y, Caro J, Gabriel S, Yusuf S. CURE Study Investigators. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. J Am Coll Cardiol 2005;45:838–845.
24. Shaw JW, Johnson JA, Coons SJ. U.S. valuation of the EQ-5D health states: Development and testing of the D1 valuation model. Med Care 2005;43:203–220.
25. Weintraub WS, Barnett P, Chen S, Hartigan P, Casperson P, O'Rourke R, Boden WE, Lewis C, Veledar E, Becker E, Culler S, Kolm P, Mahoney EM, Dunbar SB, Deaton C, O'Brien B, Goeree R, Blackhouse G, Nease R, Spertus J, Kaufman S, Teo K. Economics methods in the clinical outcomes utilizing percutaneous coronary revascularization and aggressive guideline-driven drug evaluation (COURAGE) trial. Am Heart J 2006;151:1180–1185.
26. Polsky D, Glick H. Costing and cost analysis in randomized controlled trials: Caveat emptor. Pharmacoeconomics 2009;27: 179–188.
27. Efron B, Tibshirani RJ.An Introduction to the Bootstrap. New York, NY: Chapman and Hall; 1993.
28. Mark DB, Hlatky MA. Medical economics and the assessment of value in cardiovascular medicine: Part I. Circulation 2002; 106:516–520.
29. Ryan JW, Cohen DJ. Are drug-eluting stents cost-effective? It depends on whom you ask. Circulation 2006;114:1736–1744.
30. Hlatky MA, Boothroyd DB, Melsop KA, Brooks MM, Mark DB, Pitt B, Reeder GS, Rogers WJ, Ryan TJ, Whitlow PL, Wiens RD. Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multivessel coronary artery disease. Circulation 2004;110:1960–1966.
31. Weintraub WS, Becker ER, Mauldin PD, Culler S, Kosinski AS, King SB. Costs of revascularization over eight years in the randomized and eligible patients in the Emory Angioplasty versus Surgery Trial (EAST). Am J Cardiol 2000;86:747–752.
32. Sculpher MJ, Seed P, Henderson RA, Brooks MM, Mark DB, Pitt B, Reeder GS, Rogers WJ, Ryan TJ, Whitlow PL, Wiens RD. Health service costs of coronary angioplasty and coronary artery bypass surgery: The Randomised Intervention Treatment of Angina (RITA) trial. The Lancet. 1994;344:927–930.
33. Henderson RA, Pocock SJ, Sharp SJ, Nanchahal K, Sculpher MJ, Buxton MJ, Hampton JR. Long-term results of RITA-1 trial: Clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet 1998;352:1419–1425.
34. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998;352:673–681.
35. Legrand VM, Serruys PW, Unger F, van Hout BA, Vrolix MC, Fransen GM, Nielsen TT, Paulsen PK, Gomes RS, de Queiroz e Melo JM, Neves JP, Lindeboom W, Backx B. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004;109:1114–1120.
36. Weintraub WS, Mahoney EM, Zhang Z, Chu H, Hutton J, Buxton M, Booth J, Nugara F, Stables RH, Dooley P, Collinson J, Stuteville M, Delahunty N, Wright A, Flather MD, De Cock E. One year comparison of costs of coronary surgery versus percutaneous coronary intervention in the stent or surgery trial. Heart 2004;90:782–788.
37. Stroupe KT, Morrison DA, Hlatky MA, Barnett PG, Cao L, Lyttle C, Hynes DM, Henderson WG. Cost-effectiveness of coronary artery bypass grafts versus percutaneous coronary intervention for revascularization of high-risk patients. Circulation 2006;114:1251–1257.

38. Reed SD, Anstrom KJ, Bakhai A, Briggs AH, Califf RM, Cohen DJ, Drummond MF, Glick HA, Gnanasakthy A, Hlatky MA, O'Brien BJ, Torti FM, Tsiatis AA, Willan AR, Mark DB, Schulman KA. Conducting economic evaluations alongside multinational clinical trials: Toward a research consensus. Am Heart J 2005;149:434–443.
39. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): A randomised trial. The Lancet 2010;375:201–209.
40. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ; Spirit IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–1674.