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Original Studies

Cost-Effectiveness of Percutaneous Coronary Intervention with cobalt-Chromium Everolimus Eluting Stents versus Bare Metal Stents: Results from a Patient Level meta-Analysis of Randomized Trials

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Background: Second-generation drug eluting stents (DES) may reduce costs and improve clinical outcomes compared to first-generation DES with improved cost-effectiveness when compared to bare metal stents (BMS). We aimed to conduct an economic evaluation of a cobalt-chromium everolimus eluting stent (Co-Cr EES) compared with BMS in percutaneous coronary intervention (PCI). Objective: To conduct a cost-effectiveness analysis (CEA) of a cobalt-chromium everolimus eluting stent (Co-Cr EES) versus BMS in PCI. Methods: A Markov state transition model with a 2-year time horizon was applied from a US Medicare setting with patients undergoing PCI with Co-Cr EES or BMS. Baseline characteristics, treatment effects, and safety measures were taken from a patient level meta-analysis of 5 RCTs ($n = 4,896$). The base-case analysis evaluated stent-related outcomes; a secondary analysis considered the broader set of outcomes reported in the meta-analysis. Results: The base-case and secondary analyses reported an additional 0.018 and 0.013 quality-adjusted life years (QALYs) and cost savings of $236 and $288, respectively with Co-Cr EES versus BMS. Results were robust to sensitivity analyses and were most sensitive to the price of clopidogrel. In the probabilistic sensitivity analysis, Co-Cr EES was associated with a greater than 99% chance of being cost saving or cost effective (at a cost per QALY threshold of $50,000) versus BMS. Conclusions: Using data from a recent patient level meta-analysis and contemporary cost data, this analysis found that PCI with Co-Cr EES is more effective and less costly than PCI with BMS.

Key words: drug-eluting stent; bare metal stent; percutaneous coronary intervention; cost-effectiveness

INTRODUCTION

As the first major drug-device combination product for cardiovascular disease, drug-eluting stents (DES) represented a clinical breakthrough in treatment of patients with coronary artery disease (CAD) [1]. The technology continues to evolve, with the recent development of second-generation DES platforms such as the cobalt chromium (Co-Cr) everolimus-eluting stent (EES). These platforms are comprised of permanent polymer coatings, less toxic antiproliferative drugs (e.g., everolimus or zotarolimus), and thin strut stent designs compared with first-generation DES.

Robust randomized controlled trials (RCTs) and several meta-analyses of RCTs have shown that Co-Cr EES is significantly safer and more effective than bare metal stents (BMS), with lower rates of stent thrombosis (ST), myocardial infarction (MI), and cardiac mortality [2–8]. A recent patient level meta-analysis of 4,896 patients from five RCTs (including three all comer studies) found that patients receiving Co-Cr EES had significant reductions in cardiac mortality, MI, definite ST, definite or probable ST, and target vessel revascularization (TVR) versus patients receiving BMS [5]. There are also some indications that second-generation DES reduce costs and improve clinical outcomes compared to first-generation DES [9], with improved cost-effectiveness versus BMS [10–12].

The current study leverages the availability of data from the patient level meta-analysis of RCTs to address the cost effectiveness of Co-Cr EES compared to BMS.

METHODS

Type of Analysis and Perspective. The cost-effectiveness analysis (CEA) was conducted for a 2-year time horizon from the US Medicare perspective [13]. A 2-year time horizon was selected to align with the patient level meta-analysis [5] and previous cost-effectiveness studies of DES compared to BMS [10,14–17]. Costs and outcomes at year 2 were discounted at a rate of 3%.

Study Population

The mean age of patients included in the patient level meta-analysis was 67 years and the majority of patients included were male (76%). Type 2 diabetes mellitus was present in approximately 19% of patients. Forty-four percent of all patients received stenting in the setting of primary PCI and more than 87% underwent PCI treatment for an unstable presentation. The methods and results of the meta-analysis have been reported in detail by Valgimigli et al. [5].

Model Overview

A Markov state transition model was developed in Microsoft Excel 2007 using effectiveness and safety data from the patient level meta-analysis (Fig. 1) [5]. Patients started the model in the "alive" health state, and during each model cycle of 1 year, could transition to deceased. During each 1-year model cycle, "event-free" patients could also experience one or more of the following transient events: MI, ST or TVR. Event risks

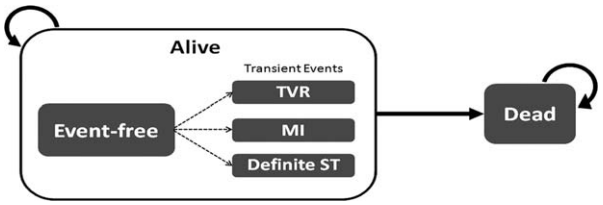

Fig. 1. Overview of the model structure. The model captured both base-case (i.e., TVR, TVR-related MI, ST, and cardiac mortality) and secondary analysis (i.e., TVR, MI, ST, all-cause death) outcomes. MI = myocardial infarction; ST = stent thrombosis; TVR = target vessel revascularization.

were only available to inform the probability of moving from event-free to a transient event; data was not available to inform movement between the transient events. The data inputs used in the CEA are summarized in Table I.

Transition Probabilities and Event Risks

The risks of mortality, MI, ST, and TVR were informed by the patient level meta-analysis [5]. The authors of the meta-analysis provided the number of patients at risk and the number of events for each treatment group, stratified by year 1 and year 2. The authors also provided cause of mortality (i.e., all-cause or cardiac-related) and type of MI (i.e., TVR-related, any MI).

Resource Use and Unit Costs

The focus of the CEA was costs borne by the US Medicare program, including costs associated with the percutaneous coronary intervention (PCI) procedure (including the stent), TVR, MI, and dual antiplatelet therapy (DAPT). Estimates of resource use and unit costs (2015 US dollars) were obtained from the published literature. Additional technology costs associated with DES versus BMS were included in diagnosis-related group (DRG) payments.

For patients who experienced TVR, re-intervention could be performed by means of coronary artery bypass graft (CABG) or PCI (with stent or without stent). The proportions of patients receiving CABG (10%) or PCI (90%) were taken from a publication reported by Garg et al. [18]. The breakdown of re-intervention with PCI was assumed to be PCI with DES (56%) and PCI without stent (44%) [18].

In the patient level meta-analysis, the duration of DAPT (i.e., clopidogrel in addition to aspirin) ranged from 3 months to 24 months for both DES and BMS [5]. The European Society of Cardiology (ESC) guidelines recommend a DAPT duration of at least 1 month for BMS and 6 months for DES [19]. The ACC guidelines recommended a DAPT duration of 1 month for BMS and 12 months for DES [20]. For the base-case analysis, we assumed a DAPT duration of 6 months for BMS and 12 months for DES. Generic pricing of clopidogrel (75 mg) was based on the wholesale acquisition cost (WAC) published in the US Redbook online pricing database [21]. A 20% mark-up was added to the WAC to be more conservative and to arrive at a total monthly acquisition cost of $23.64 that more closely reflected the average wholesale price (AWP) [22]. An alternative monthly DAPT cost of $91.82 (assuming 50% generic and 50% brand clopidogrel) was evaluated in the sensitivity analyses.

Health Utility

Quality of life impacts were included for CAD, MI, and TVR. A health utility value of 0.85 was applied in the model to patients with CAD and no symptoms [18]. For patients experiencing TVR a health utility decrement of −0.06 was applied for 1 year following the re-intervention, irrespective of revascularization with CABG or PCI [18]. For patients experiencing MI, a health utility of 0.75 was applied for 1 year following the MI [18].

Analysis

The base-case analysis included clinical outcomes from the patient level meta-analysis that were considered to be stent-related: TVR, TVR-related MI, definite ST, and cardiac-related mortality. A secondary analysis was conducted that considered the broader set of clinical outcomes from the meta-analysis: TVR, all MI, definite ST, and all-cause mortality.

One-way sensitivity analyses were conducted in order to test the robustness of the base-case analysis to alternative assumptions and data inputs related to transition probabilities, risks of events, resource use, DAPT therapy costs, and health utility (Table II) [20,23–25]. A probabilistic sensitivity analysis (PSA) was conducted to simultaneously quantify the uncertainty in all key model input parameters.

RESULTS

Base-Case Analysis

Results of the base-case analysis (Table III) demonstrated that Co-Cr EES was more efficacious than BMS. Patients who received PCI with Co-Cr EES experienced fewer cardiac-related deaths, TVR-related MIs, ST, and TVRs, 0.015 additional life years, and 0.018 additional QALYs compared with patients who received PCI with BMS. PCI with Co-Cr EES was also associated with cost savings of $236 per patient. The primary drivers of the cost savings were the reduction in TVR and MI rates, which offset the increased costs

TABLE I. Summary of Model Parameters for the Base-Case and Secondary Analyses

Input parameter	Intervention		Sources
Event risks (%) (years 0–2)	Co-Cr EES	BMS	
All-cause mortality[a]	4.9	5.9	Valgimigli et al. [5]
Cardiac-related mortality[b]	2.7	4.1	
TVR[a,b]	4.3	10.2	
Any MI[a]	4.0	5.6	
TVR-related MI[b]	0.9	1.8	
Definite ST[a,b]	0.6	1.4	
Procedure proportions	Both interventions		
PCI with DES			Medicare claims data [34]
Inpatient (index procedure)	64%		
Outpatient (index procedure)	36%		
Inpatient with MCC; w/o CC or MCC	18%; 82%		HCUPnet [35]
Outpatient with AMI or CTO; w/o AMI or CTO	5%; 95%		
PCI with BMS			Medicare claims data [34]
Inpatient (index procedure)	64%		
Outpatient (index procedure)	36%		
Inpatient with MCC; w/o CC or MCC	25%; 75%		HCUPnet [35]
Outpatient with atherectomy; w/o atherectomy	0%; 100%		
Unit costs (USD)	Both Interventions		
Procedure reimbursement [36,37]			References 36,37
PCI with DES			
Inpatient with MCC; w/o CC or MCC	$19,009		DRG 246
Inpatient w/o CC or MCC	$12,090		DRG 247
Outpatient with AMI or CTO	$14, 841		APC 319
Outpatient w/o AMI or CTO	$9,624		APC 229
PCI with BMS			
Inpatient with MCC	$17,860		DRG 248
Inpatient w/o CC or MCC	$11,046		DRG 249
Outpatient with atherectomy	$14,841		APC 319
Outpatient w/o atherectomy	$9,624		APC 229
PCI (no stent)			
Inpatient with MCC	$17,551		DRG 250
Inpatient w/o CC or MCC	$11,980		DRG 251
Outpatient with PTA	$4,537		APC 083
Outpatient w/o PTA	–		
CABG [36], Inpatient market estimator, unpublished data, 2015	$30,669		DRG 231–236[c]
Event costs			
MI [35,36]	$7,814		DRG 231–236[d]
TVR-Treated with CABG	See above		
TVR-Treated with PCI DES	See above		
TVR-Treated with PCI no Stent	See above		
DAPT costs and duration			
Generic clopidogrel (75 mg) monthly cost [21]	$23.64		
Brand clopidogrel (75 mg) monthly cost [23]	$160.00		
Clopidogrel duration–Co-Cr EES [5]	12 months		
Clopidogrel duration–BMS [5]	6 months		
Health Utilities [18]	Both Interventions		
CAD (no symptoms)	0.85		
TVR			
PCI (0–6, 6–12 months)	0.79		
CABG (0–6, 6–12 months)	0.79		
MI (12 months)	0.75		

[a]Variables used in base-case analysis.
[b]Variables used in secondary analysis.
[c]Procedure weights based on Cardiovascular Inpatient Market Estimator.
[d]Procedure weights based on HCUPnet.
AMI = acute myocardial infarction; APC = ambulatory patient classification; CABG = coronary artery bypass graft; CC = complications or comorbidities; CTO = chronic total occlusion; CV = cardiovascular; DAPT = dual antiplatelet therapy; DES = drug eluting stent; DRG = diagnosis-related group; HCUP = Healthcare Cost Utilization Project; MCC = major complications or comorbidities; MI = myocardial infarction; PCI = percutaneous coronary intervention; PTA = percutaneous transluminal angioplasty; ST = stent thrombosis; TVR = target vessel revascularization; USD = United States dollars; w = with; w/o = without.

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TABLE II. Summary of Model Inputs for Additional One-Way Sensitivity Analyses

	Base-case value(s)		Alternative value(s)	
Input parameter	Co-Cr EES	BMS	Co-Cr EES	BMS
DAPT duration				
Turco 2012 [23]	12 months	6 months	12 months	12 months
2011 ACC/AHA/SCAI guidelines for PCI [20]			12 months	1 month
2014 ESC/EACTS guidelines on revascularization [30]			6 months	1 month
Clopidogrel cost (50% generic & 50% brand price)	$23.64		$91.82	
Cost of MI				
Patient receiving CABG [25]	$7,814		$9,344	
Patient receiving PCI [25]			$6,230	
Health utility for MI [24]	0.75		0.72	
Health utility for TVR (0–6 months, 6–12 months) [24]	0.79		0.75	
TVR procedure (%)[a]	CABG = 10; PCI = 90		CABG = 13.2; PCI = 86.8	

[a]Based on unpublished 2012 data from HCUP.net and MEDPAR data.

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; HCUP = Healthcare Cost Utilization Project; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCAI =Society Cardiovascular Angiography Interventions; TVR = target vessel revascularization.

TABLE III. Model Predicted Results for Base-Case (A) and Secondary (B) Analyses

Outcome	Co-Cr EES	BMS	Difference (Co-Cr EES-BMS)
(A) Base-case analysis			
Cardiac-related deaths*	27	41	−14
TVR-related MI*	9	18	−9
Definite stent thrombosis*	6	14	−8
TVR*	43	102	−59
Life years per patient	1.935	1.920	0.015
QALYs/patient	1.642	1.624	0.018
Total costs (USD)*	$12,999,798	$13,235,578	-$235,780
Index procedure*	$12,093,215	$11,624,320	$468,895
TVR*	$553,758	$1,329,344	-$775,586
MI*	$69,145	$140,074	-$70,929
DAPT*	$283,680	$141,840	$141,840
(B) Secondary analysis			
All-cause deaths*	49	59	−10
Any MI*	40	56	−16
Definite stent thrombosis*	6	14	−8
TVR*	43	102	−60
Life years per patient	1.909	1.900	0.009
QALYs/patient	1.616	1.603	0.013
Total costs (USD)*	$13,237,583	$13,525,567	-$287,984
Index procedure*	$12,093,215	$11,624,320	$468,895
TVR*	$551,574	$1,327,315	-$775,741
MI*	$309,114	$432,092	-$122,978
DAPT[a]	$283,680	$141,840	$141,840

[a]Per cohort of 1,000 patients; model predicted clinical outcome results differ slightly from clinical results reported in the Valgimigli 2014 meta-analysis due to model calculation and rounding requirements.

DAPT = dual antiplatelet therapy; MI = myocardial infarction; QALYs = quality-adjusted life years; TVR = target vessel revascularization; USD = United States dollars.

of the index procedure and DAPT observed with Co-Cr EES versus BMS.

Results of the secondary analysis (not shown) demonstrated similar results to the base-case analysis. PCI with Co-Cr EES was both more effective (0.009 additional life years and 0.013 additional QALYs per patient) and less costly (-$288 per patient) versus BMS.

One-Way Sensitivity Analysis

The base-case results were robust to a number of sensitivity analyses. When inputs were varied by ±20%, results remained cost savings for Co-Cr EES relative to BMS in all cases (not shown). Similarly, when base-case inputs were varied using alternative values taken from published literature [20,23–25], all analyses showed that

TABLE IV. Results of Sensitivity Analyses Using Alternative Published Values, Reported for the Base-Case Analysis Only

Analysis description	Incremental cost (USD)	Incremental QALY	Cost per QALY gained (USD)
Base-case analysis	−$235.78	0.0178	Cost savings
TVR procedures (CABG: 13.2%, PCI: 86.8%)	−$272.77	0.0178	Cost savings
DAPT duration (Co-Cr EES: 12 months, BMS: 12 months)	−$377.62	0.0178	Cost savings
DAPT duration (Co-Cr EES: 12 months, BMS: 1 month)	−$117.58	0.0178	Cost savings
DAPT duration (Co-Cr EES: 6 months, BMS: 1 month)	−$259.42	0.0178	Cost savings
Clopidogrel cost (50% generic; 50% brand)	$173.30	0.0178	$9,754.88
Cost of MI (CABG patients)	−$249.67	0.0178	Cost savings
Cost of MI (PCI patients)	−$221.40	0.0178	Cost savings
Utility for MI (0.72)	−$235.78	0.0180	Cost savings
Utility for PCI; 0–6, 6–12 (0.75)	−$235.78	0.0199	Cost savings

CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization; QALY = quality-adjusted life year; USD = United States dollars.

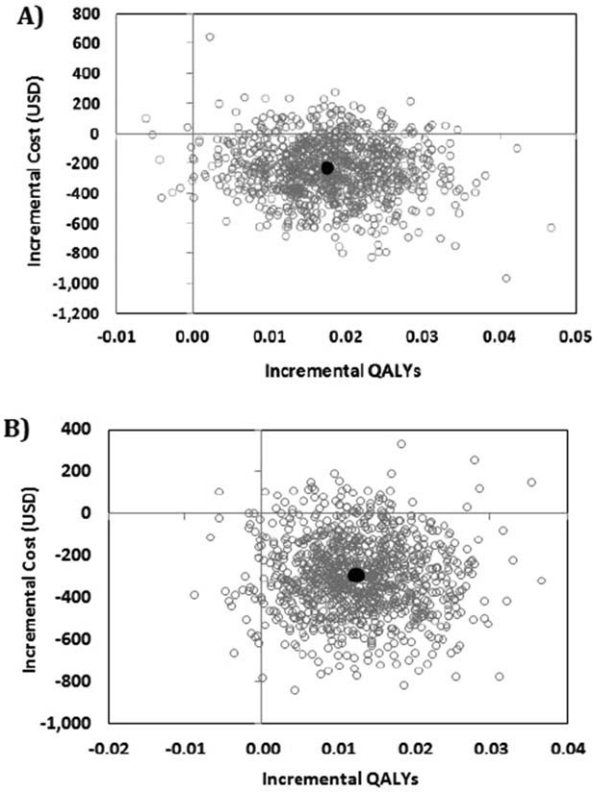

Fig. 2. Results of the probabilistic sensitivity analysis on the cost-effectiveness scatter plot for the base-case analysis (A) and the secondary analysis (B) [28]. QALY = quality-adjusted life year; USD = United States dollars.

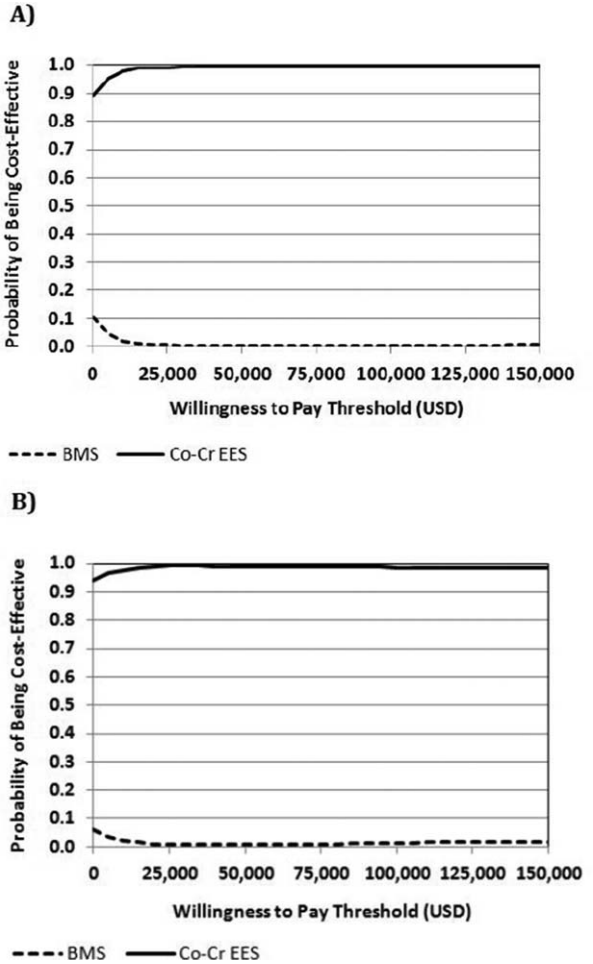

Fig. 3. Results of the probabilistic sensitivity analysis using cost-effectiveness acceptability curves for the base-case analysis (A) and the secondary analysis (B) [28]. BMS = bare-metal stent; Co-Cr EES = cobalt chromium everolimus-eluting stent; USD = United States dollars.

Co-Cr EES was more effective and less costly versus BMS, with the exception of the cost of clopidogrel, which resulted in a cost of $9,755 per QALY gained (Table IV).

Probabilistic Sensitivity Analysis

Figure 2 depicts the results of the PSA on the cost-effectiveness scatter plot for the base-case analysis (A) and the secondary analysis (B). Each point on each scatterplot represents the incremental QALYs for Co-Cr EES versus BMS (x-axis) and the incremental cost of Co-Cr EES versus BMS (y-axis) for each of the

1,000 model simulations [26,27]. For the base-case analysis, 88.5% of the model iterations showed Co-Cr EES to be cost savings versus BMS. In 10.6% of the model iterations, Co-Cr EES was more effective and more costly than PCI with BMS. In the remaining model iterations, Co-Cr EES was less effective [28].

Very similar results were observed for the secondary analysis; Co-Cr EES was cost savings versus BMS in 91.1% of the model iterations and Co-Cr EES was more effective and more costly than BMS in 5.8% of the model iterations.

Figure 3 shows the CEACs for both the base-case and secondary analyses. At willingness-to-pay (WTP) thresholds of $50,000 per QALY, the base-case PSA predicted that Co-Cr EES was associated with a 99.5% likelihood of being cost-savings or cost effective. For the secondary analysis, the PSA predicted that Co-Cr EES was associated with a 99.2% likelihood of being cost-savings or cost effective.

DISCUSSION

Statement of Principal Findings

This 2-year CEA found that PCI with Co-Cr EES is more effective and less costly compared with PCI with BMS in contemporary US clinical practice. The base-case analysis found that a patient who received Co-Cr EES experienced an additional 0.018 QALYs and cost savings of $236 compared with a patient who received a BMS. The findings were consistent between the base-case analysis and the secondary analysis that included broader outcomes.

Strengths and Limitations

The evaluation was based on a patient level meta-analysis of RCTs, a research methodology that is widely regarded as the highest level of evidence and has inherent advantages over individual RCTs and aggregate data meta-analyses [29–31]. Furthermore, the patient population of the RCTs included in the meta-analysis is generally reflective of real-world clinical practice. This analysis was also based on several conservative assumptions, including a short-term time horizon and the assumption that a high proportion of re-interventions employed angioplasty only [32]. Finally, the results of our analyses were robust across a range of sensitivity analyses.

Uncertainty remains regarding the appropriate duration of DAPT for patients receiving Co-Cr EES. A recent meta-analysis of 10 RCTs of DES showed that patients using DAPT for less than 12 months showed lower risk of major bleeding with no significant increase in thrombotic outcomes compared with patients using DAPT for 12 months [33]. A 12-month duration of DAPT for Co-Cr EES was assumed for the base-case analysis, and the results were found to be robust to a wide range of alternative assumptions. However, care should be exercised when generalizing the results of the economic evaluation to environments in which practice patterns, resource utilization, and costs differ from those assumed in this analysis.

Comparison With Other Studies

To our knowledge, this CEA is the first to find that Co-Cr EES is economically dominant versus BMS. Cost savings were driven primarily by significant reductions in MI, ST, and cardiac mortality with Co-Cr EES relative to BMS. Other key drivers of the analysis include the declining price differential between DES and BMS and the availability of generic clopidogrel.

Other recent economic evaluations have reported conflicting results regarding the economic value of DES. In 2010, Remak et al. [11] reported a CEA of patients treated with the Endeavor DES or BMS over 4 years and reported a low cost per QALY of £3,575. Like our analysis, Remak et al. incorporated a reduction in the risk of MI and death for DES, a smaller price difference between DES and BMS (~£500), and relatively low cost of generic clopidogrel (~£35 per month). It is noteworthy that the magnitude of the clinical benefit at 2 years was reported to be lower in the Remak study compared to the current study; however the Remak data extended to 4 years. Schafer et al. [10] reported an economic evaluation of first-generation DES using 3-year, real-world, observational data from the US and reported a high cost per QALY of $87,705 for DES versus BMS. Importantly, Schafer and colleagues did not incorporate a reduction in the risk of MI for DES and assumed a relatively high cost of clopidogrel (i.e., $140 per month). The authors noted that lower generic clopidogrel and DES costs would result in overall cost-savings for DES versus BMS.

In contrast, Barone-Rochette et al. [12] reported that DES was not cost-effective (i.e., at a WTP threshold of €10,000 per revascularization avoided) at a price differential of €1,200 (€2,008), but that it became cost effective at a price differential of €400 (€2,012). No differences in MI, ST, or cardiac mortality were modeled in this analysis. Finally, a 2013 economic evaluation based on Canadian observational data for patients with stable coronary disease also questioned the cost effectiveness of DES and recommended broad use of BMS [24]. However, the observational data were based on patients receiving first-generation stents from 2003 to 2005 and the unit costs of DES vs. BMS (i.e., $2,519 vs. $657, respectively) used in the analysis were also presumably from that timeframe.

Impact on Daily Practice

The findings of this study hold practical importance for payers, policymakers and clinicians evaluating the clinical and economic value of Co-Cr EES and other cardiovascular innovations. As PCI technology and clinical practice rapidly advanced from first-generation DES to Co-Cr EES, it has represented a "moving target" that underscores the importance of updating health technology assessment (HTA) and economic evaluations to reflect changes in economic value over time. In contrast to early analyses involving first-generation DES, our economic analysis based on the highest level of clinical evidence finds that PCI with Co-Cr EES is more effective and less costly than PCI with BMS in contemporary US clinical practice.

CONCLUSIONS

Studies assessing the cost effectiveness of DES versus BMS have reported mixed results due to multiple factors including limitations of first-generation DES. Utilizing the latest data from the US Medicare program and clinical results from a high-quality, patient level meta-analysis of RCTs our study finds that Co-Cr EES is an economically attractive strategy compared with BMS in patients undergoing PCI.

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