Cardiovascular Revascularization Medicine 20 (2019) 752–757

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Health Economic Evaluation of an Ultrathin, Bioresorbable-Polymer Sirolimus-Eluting Coronary Stent Compared to a Thin, Durable-Polymer Everolimus-Eluting Stent

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ARTICLE INFO

Article history:
Received 10 September 2018
Received in revised form 22 October 2018
Accepted 6 November 2018

Keywords:
Drug-eluting stent
Peri-procedural myocardial infarction
Health economics
Simulation

ABSTRACT

Objectives: The study estimated the health economic impact of a latest generation coronary stent with ultrathin struts and bioresorbable polymer coating.
Background: The recent BIOFLOW V trial, an international FDA approval trial (ClinicalTrials.gov: NCT02389946), has shown that an ultrathin, bioresorbable polymer sirolimus-eluting stent had a significantly lower rate of target lesion failure and target vessel-related myocardial infarction than a thin, durable polymer everolimus-eluting stent at 12 months, driven by a lower rate of peri-procedural myocardial infarction (ppMI).
Methods: We used a Markov model to project mortality and cost outcomes of that lower ppMI rate from a U.S. health system perspective over a 12-month horizon. Model parameters were derived from BIOFLOW V trial data, a systematic literature review and expert interviews.
Results: Use of the bioresorbable polymer sirolimus-eluting stent compared to durable polymer everolimus-eluting stent is associated with net reductions in medical cost of $124 (Interquartile Range (IQR) $97–154) per patient in 2018 US$, of which $115 (IQR $76–124) accrues to the initial admission and $10 (IQR $7–72) to cost of follow-up. The lower rate of ppMI translates into a gain of 0.000017 (IQR 0.000011–0.000022) quality-adjusted life-years (QALY) per patient.
Conclusions: Lower ppMI rates of bioresorbable polymer sirolimus-eluting stent translate into reductions in direct medical cost, while improving patient outcomes. Most of the cost reduction is attributed to the initial admission with moderate savings up to 12 months post-discharge.

1. Introduction

Implantation of latest generation drug eluting stents (DES) has become the standard of care for patients undergoing percutaneous coronary intervention (PCI) [1]. Nonetheless, the design of coronary stents continues to evolve with the intention to further improve short- and long-term outcomes. Latest generation DES feature thinner struts to improve device deliverability and reduce arterial vessel wall injury during implantation, and coating with bioresorbable polymers to reduce the stimulus for chronic inflammation. The recent BIOFLOW V trial (ClinicalTrials.gov: NCT02389946) compared one such stent, the Orsiro ultrathin, bioresorbable polymer sirolimus-eluting stent (BIOTRONIK, Buelach, Switzerland) to an established reference stent, the Xience thin, durable polymer everolimus-eluting stent (Abbott Vascular, Santa Clara, CA). This FDA approval trial enrolled 1334 patients in 90 hospitals in 13 countries that were 2:1 randomly assigned to the bioresorbable polymer sirolimus-eluting stent (n = 884) or the durable polymer everolimus-eluting stent (n = 450). Approximately one-third of patients had medically treated diabetes mellitus and 50% of patients presented with acute coronary syndromes. Earlier trials had compared the bioresorbable polymer sirolimus-eluting stent against other drug-eluting stents in all-comers populations [2,3].

Results showed significant differences in target lesion failure and target vessel-related myocardial infarction in favor of the bioresorbable polymer sirolimus-eluting stent at 12-month follow-up. An analysis of the temporal pattern, with which these events occurred after stent placement, revealed that the difference was driven by a lower rate of peri-procedural myocardial infarction (ppMI), whereas rates of spontaneous myocardial infraction during 12-month follow-up were numerically lower for the bioresorbable polymer sirolimus-eluting stent without reaching statistical significance [4].

Abbreviations: DES, drug eluting stent; PCI, percutaneous coronary intervention; ppMI, peri-procedural myocardial infarction; CK-MB, creatine kinase myocardial band; ULN, upper limit of normal; QALY, quality-adjusted life-year; IQR, inter-quartile range; CPT, current procedure terminology.

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https://doi.org/10.1016/j.carrev.2018.11.006
1553-8389/

While not formally designed as superiority trial [5], the BIOFLOW V findings suggest that this particular bioresorbable polymer sirolimus-eluting stent could improve outcomes in patients undergoing PCI compared to an established reference durable polymer everolimus-eluting stent. The objective of our study is to estimate the implications of these results for the health status of populations as well as costs to the U.S. health care system using a simulation model.

2. Methods

2.1. Model development

We developed a Markov-type decision analytic model in Microsoft Excel Visual Basic for Applications to evaluate the comparative mortality and cost impact of the two stent types over 12 months. As the superiority of the bioresorbable polymer sirolimus-eluting stent over the durable polymer everolimus-eluting stent rests on the lower incidence of ppMI [4], projecting the effect of ppMI is the cornerstone of our model. As illustrated in Fig. 1, our model starts with the index procedure and the differential ppMI rates for the two stent types, estimates the implication for resource utilization during the initial hospital admission and then differential cost and mortality rates over 12 months post discharge. The model uses the perspective of the U.S. health system and all cost estimates are expressed in 2018 U.S. dollars. The study was reviewed and considered exempt by the Institutional Review Board of the Kanton of Zurich, Switzerland.

2.2. Evidence review

We conducted a comprehensive review of the peer-reviewed and grey literatures to obtain model parameters and consulted with eight experts in interventional cardiology and health services research to assist with model design, fill in missing parameters, and guide parameter selection. Our search included studies published between January 2000 and March 2018, with monitoring of the literature afterwards, in English with the following keywords covered four databases (PubMed, Web of Science, Embase and Scopus):

((stent OR DES OR BMS OR PCI OR "percutaneous coronary intervention") AND (coronary OR cardiac)) AND (peri-procedural OR periprocedural OR post-procedural OR postprocedural OR peri-operative OR perioperative OR post-operative OR postoperative) AND ((myocard* AND (ischem* OR infarct*) OR MI OR myonecrosis OR necrosis) AND (relevance OR consequences OR prognosis OR outcome OR cost OR utilization OR resource OR admission OR death OR mortality)

We mined the reference sections of included articles and reviewed abstract volumes of selected conferences (ISPOR, AHA and ACC). The searches returned 3012 articles. Two reviewers (MB and SM) first screened titles and retained 319 potentially relevant items for abstract review, which yielded 102 unique articles for full-text review. Of those, 62 were rejected after full-text review, as they did not contain data on the relationship between ppMI and patient outcomes and 11 because they were review articles, commentaries or editorials.

The remaining 29 papers were independently abstracted into a database by the two reviewers, who then met, reconciled their abstracted information and prioritized publications as parameter sources. Criteria for prioritization were use of contemporary DES, ppMI identification based on creatine kinase myocardial band (CK-MB) elevation, prospectively collected data, inclusion of consecutive patients and adjustment for procedure indication (stable angina or acute coronary syndrome), procedure complexity and patient comorbidities. Mortality, usually expressed in risk-adjusted hazard ratios, was the only outcome that was evaluated in the identified articles.

2.2.1. Criteria for ppMI detection

The ongoing debate about the definition of ppMI and its clinical significance means that the choice of definition is critical for the selection of parameters for the model. Based on our review of the literature, we decided to follow the Society for Cardiovascular Angiography and Intervention [6] recommendation and define ppMI based on elevation of CK-MB rather than troponin for two reasons.

First, CK-MB assays have been in use for much longer than troponin assays and have historically been the biomarker to diagnose ppMI. The resulting rich body of evidence that links peri-procedural CK-MB elevations to clinical outcomes and resource use constitutes a solid basis for selection of model parameters. Second, it is still being discussed which threshold of troponin elevation to use for ppMI diagnosis and whether thresholds should differ for different types of assays. Troponin assays, especially contemporary high sensitivity assays, have been optimized to quickly rule out or confirm myocardial ischemia in patients presenting with symptoms like chest pain. Their ability to detect small elevations of troponin levels means that results are difficult to interpret in the context of coronary revascularization procedures that commonly entail minor biomarker release [7]. Hanna and Hennebry, for example, have argued that troponin assays could pick up minor myonecrosis with uncertain prognostic relevance [8]. Cavallini et al. have shown that an isolated increase in troponin after PCI without a rise in CK-MB

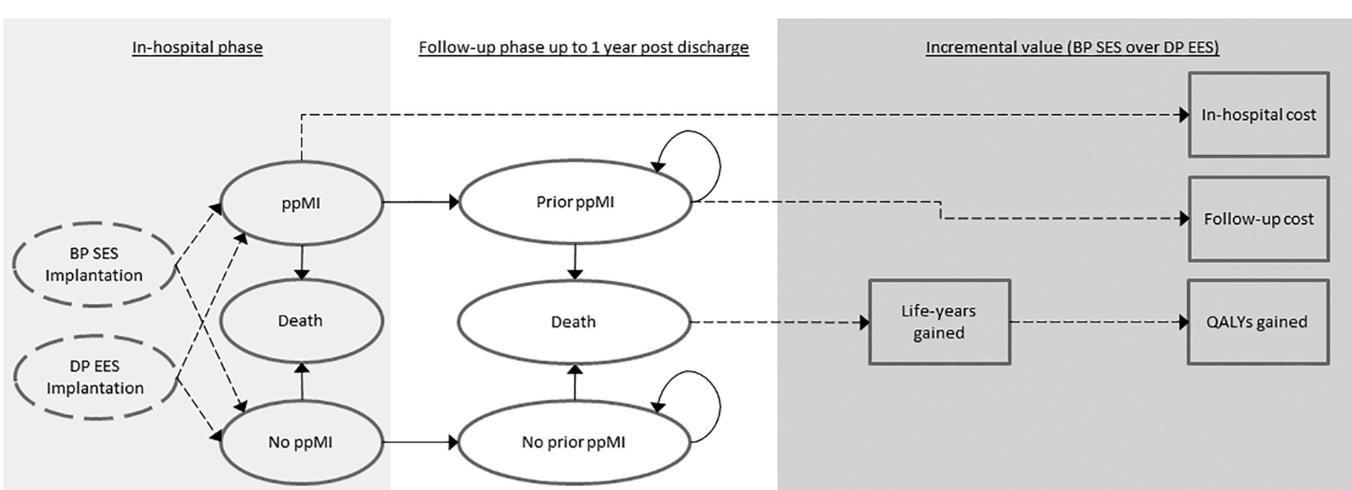

Fig. 1. Conceptual depiction of the model. Legend: BP-SES: bioresorbable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; ppMI: peri-procedural myocardial infarction, QALY: quality-adjusted life-year.

was not associated with increased mortality over two years, after accounting for patient risk factors [9]. Lim et al. found that patients with elevated CK-MB but not with elevated troponin were more likely to have wall motion abnormalities [10]. The recently updated endpoint definition of the Academic Research Consortium (ARC-2) proposes to settle this question by setting a threshold for isolated troponin elevation of >70 times the upper limit of normal (ULN) for all assays but this recommendation has not yet been prospectively validated [11].

Our review also suggested that ppMI represents a spectrum of events, ranging from a minor and asymptomatic release of cardiac enzymes to severe events akin to spontaneous myocardial infarction. For example, Tricoci et al. [12], Ndrepapa et al. [13] and Park et al. [14] have demonstrated a dose-response relationship between the degree of CK-MB elevation and clinical impact. In these studies, even a CK-MB elevation >3× ULN, irrespective of concomitant ECG changes or symptoms suggestive of myocardial ischemia, was consistently correlated with a small but measureable effect on risk-adjusted mortality. Higher elevations and elevations accompanied by clinical signs of myocardial ischemia were associated with higher relative risk of mortality. The limited effect size of isolated CK-MB elevations might also explain why some smaller studies [15,16] have failed to detect a relationship between ppMI and mortality: The study by Tricoci et al., for example, included 13,038 patients with 657 ppMI events but only 23 deaths over one year [12]. We therefore decided to use a CK-MB >3× ULN elevation as criterion for ppMI, irrespective of presence of symptoms or ECG changes. We apply the higher threshold of a CK-MB >5× ULN elevation as sensitivity analysis.

2.2.2. Estimates for excess mortality in ppMI patients

Based on data from the BIOFLOW V trial, 2.27% (20/882) patients in the bioresorbable polymer sirolimus-eluting stent arm and 4.45% (20/449) in the durable polymer everolimus-eluting stent arm experienced ppMI based on our definition and excluding cases, in which ppMI had been diagnosed based on troponin elevation without corroborating CK-MB data. When applying the higher threshold, the rates were 0.79% (7/882) and 2.45% (11/449), respectively [4]. For patients with CK-MB >3× ULN, we assumed an adjusted hazard ratio of 12-month mortality of 1.20 based on the largest follow-up study to date, which pooled data for 23,604 patients from 11 studies [14], with a range of 1.00 based on expert opinion and 1.84 based on a study by Lindsey et al. [17].

For cases with CK-MB >5× ULN elevation, we assumed an adjusted hazard ratio of 12-month mortality of 1.33 [14] with a range of 1.25 [13] to 2.10 [18]. Excess mortality estimates were used to project incremental life-years lost for patients experiencing ppMI, and data from the BIOFLOW trial program to derive corresponding quality-adjusted life-years (QALY) lost.

2.2.3. Estimates for cost impact of ppMI

Tamez et al. had analyzed data from a subset of the CHAMPION PHOENIX study to determine the incremental cost of ppMI patients during the index procedure using resource-based accounting and regression adjustment for patient risk. Based a definition for ppMI of CK-MB >3× ULN irrespective of symptoms or ECG changes, they estimated adjusted mean direct medical cost of $4391 (in 2012 US$) with a 95% confidence interval from $2475 to $6307 [19]. We used their estimates for the midpoint and upper limit in our model, but followed expert guidance and applied a lower limit of zero incremental cost to acknowledge the possibility of silent events under real-world conditions.

Based on expert opinion, we assumed average incremental cost of $446 for ppMI patients in the 12 months after the index procedure, representing average Medicare payments for one additional office visit (CPT 99205) with an echocardiogram (CPT 93306) and ECG (CPT 93000). We used a lower bound of zero incremental cost and an upper bound of $17,918, which is the average attributable Medicare cost of medical care in the first 12 months after discharge for spontaneous myocardial infarction [20].

2.3. Sensitivity analyses

We conducted three types of sensitivity analyses. The first was to apply the more restrictive definition of ppMI with a CK-MB >5× ULN elevation. The second was a univariate sensitivity analysis, in which we varied each model parameter individually by ±10% from its midpoint estimate. The third was a probabilistic sensitivity analysis that varied all parameters simultaneously to reflect the overall uncertainty in our model parameters. This analysis used cohorts of 1 million patients and ran the model 10,000 times for each cohort, drawing for each run a value for every parameter at random from its underlying distribution.

2.4. Model parameters

Midpoint estimates, ranges and distributions of our model parameters are summarized in Table 1 together with their respective sources.

3. Results

3.1. Model predictions

For our base case assumption, we estimate that use of bioresorbable polymer sirolimus-eluting stent compared to durable polymer everolimus-eluting stent is associated with average net reductions in direct medical cost of $124 per patient, of which $115 accrues to the initial admission for stent placement and $10 to cost of follow-up over 12 months, as shown in Fig. 2. The model predicts that the lower ppMI rates translates into a gain of 0.000019 life-years and 0.000017 (IQR 0.000011–0.000022) quality-adjusted life-years (QALY) per patient (or 19 life-years and 17 QALYs gained per one million patients) for the bioresorbable polymer sirolimus-eluting stent compared to the durable polymer everolimus-eluting stent.

Applying the more restrictive threshold of CK-MB >5× ULN reduced the estimated economic benefit of the bioresorbable polymer sirolimus-eluting stent to $94 per patient. Of this amount, $87 stems from lower cost during the index admission and $7 from lower cost of follow-up.

3.2. Sensitivity analyses

Fig. 3 shows the result from the univariate sensitivity analysis that varies each parameter individually by ±10% of the midpoint estimate. Assumptions for the ppMI rates for the two stent types have the largest effect on the predicted economic benefit, followed by the midpoint assumption for the attributed cost during the index admission. All other parameters have limited influence on the prediction.

Fig. 4 displays the results from the probabilistic sensitivity analysis as a boxplot. The results suggest a median for the predicted reductions in medical cost for the bioresorbable polymer sirolimus-eluting stent of $123 per patient with an interquartile range from $97 to $154.

Applying the more restrictive definition for ppMI of a CK-MB elevation >5× ULN to the probabilistic sensitivity analysis yielded median predicted savings of $93 per patient with an interquartile range from $78 to $112 for the bioresorbable polymer sirolimus-eluting stent.

4. Discussion

The BIOFLOW V trial had shown that the bioresorbable polymer sirolimus-eluting stent has a lower rate of ppMI than an established reference durable polymer everolimus-eluting stent. In the study presented, we use a simulation model to estimate how this better performance would translate into both better outcomes for patients and lower healthcare cost over a 12-month time horizon.

Table 1
Model parameters.

Parameter	Midpoint estimate	Range	Distribution	Source
ppMI rate (CK-MB >3× ULN)			Uniform	[4]
BP-SES	2.27%	2.04%–2.49%		
DP-SES	4.45%	4.01%–4.90%		
ppMI rate (CK-MB >5× ULN)			Uniform	[4]
BP-SES	0.79%	0.71%–0.87%		
DP-EES	2.45%	2.20%–2.69%		
Baseline mortality rate after PCI	0.87%	0.78%–0.96%	Uniform	[4]
Adjusted HR for mortality ppMI with			Poisson	
CK-MB >3× ULN	1.20	1.00–1.84		[13,14,17,18], expert opinion
CK-MB >5× ULN	1.33	1.25–2.10		
Attributable cost for ppMI			Poisson	
Index admission	$5243	$0–$7530		[19,20], expert opinion
12 month follow-up	$446	$0–$17,918		

Legend: BP-SES: bioresorbable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; PCI: percutaneous coronary intervention; ppMI: peri-procedural myocardial infarction; HR: hazard ratio, CK-MB: creatine kinase myocardial band; ULN: upper limit of normal.

Our results suggest that the mortality benefit is modest in that use of bioresorbable polymer sirolimus-eluting stent would lead to a gain of 17 quality-adjusted life-years per one million patients. This limited gain is a testament to the level of safety that PCI procedures have achieved. A recent pooled analysis of 11 randomized controlled trials including 11,518 patients found an all-cause mortality rate of about 1% in the first year after stent placement [21]. Given this low baseline risk of mortality, the relative increase of mortality after ppMI of 20–30% that is consistently found in larger studies [14] does not have a large absolute effect on patient outcomes.

Conversely, use of bioresorbable polymer sirolimus-eluting stent was estimated to reduce direct medical cost by $124 per patient over one year compared to the durable polymer everolimus-eluting stent, an estimated reductions in medical cost that corresponds to about 10% of the price of a DES [22]. With about 600,000 coronary stent procedures per year in the U.S. alone, the savings could add up to $74 million per year, with a range of $58 million to $92 million based on the probabilistic sensitivity analysis. This effect could become larger still, if the ongoing analysis of the BIOFLOW V trial data confirmed an early trend towards a lower rate of target-vessel myocardial infarction events beyond 30 days in patients with bioresorbable polymer sirolimus-eluting stent compared to durable polymer everolimus-eluting stent.

While not designed as a cost-effectiveness analysis, our results imply that the bioresorbable polymer sirolimus-eluting stent would dominate the durable polymer everolimus-eluting stent because of the combination of lower cost and improved patient outcomes. This is an important finding in light of the growing concerns about financial sustainability of health care systems, as historically improved medical devices and drugs have almost always increased cost, even if their increased price met established criteria for value for money. To illustrate, an analysis by Nelson and colleagues looked at 887 published cost-effectiveness studies to assess how many medical innovations led to actual savings, as opposed to meeting thresholds for cost-effectiveness. They found that about three out of four innovations (72%) had better outcomes at higher cost and only 16% improved outcomes at lower cost [23]. As the share of U.S. gross domestic product that is spent on health care is projected to reach 20% by 2025 [24], reducing cost and improving value of care has become a policy priority [25]. Redirecting research and development in medical devices towards cost-saving innovation has been pointed out as one potential avenue to reach this objective [26].

It is equally important that the projected savings materialize in a manner that is compatible with the incentives created by the prevailing payment system. Over 90% of the savings would accrue during the index admission for stent placement and thus directly to the hospital or clinic that is at risk for the episode cost under prospective payment. The remaining savings during the 12-month follow-up could be captured under so-called bundled payment models for coronary interventions that include cost after discharge into a fixed price per procedure [27]. Such incentive compatibility is important for the dissemination of cost-saving technology that is commonly hindered by the fact that savings do not accrue to the stakeholder making the initial investment [28]. A recent example is the controversy about transcatheter aortic valve replacement (TAVR): While results from a cost-effectiveness analysis suggest that cost are lower and outcomes better for TAVR than surgical

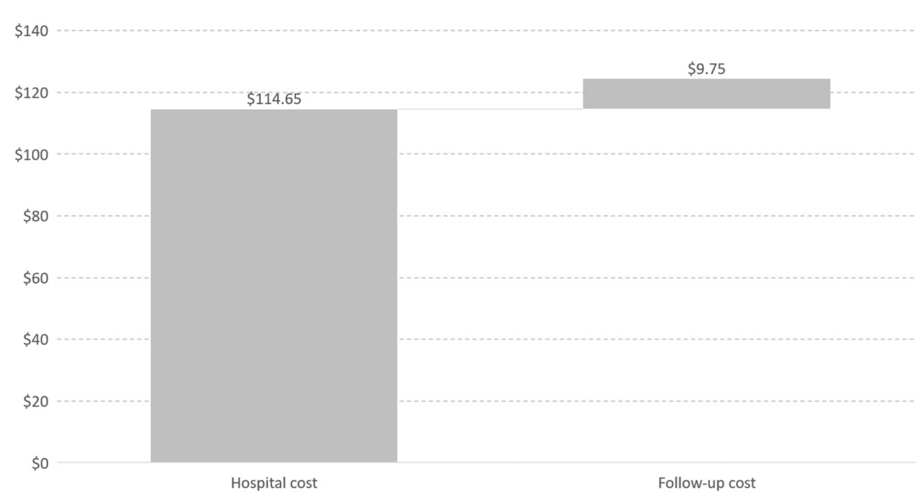

Fig. 2. Incremental value of the bioresorbable polymer sirolimus-eluting stent over the durable polymer everolimus-eluting stent.

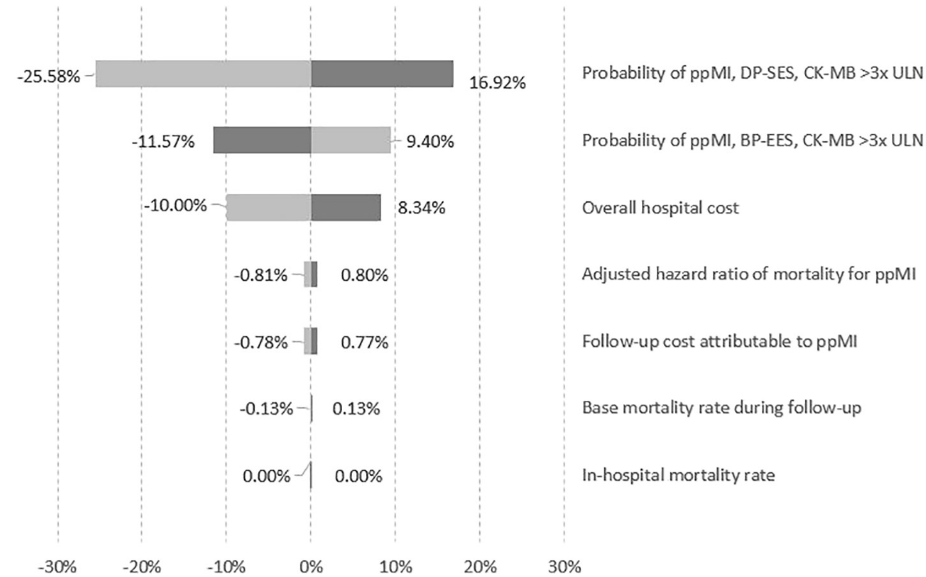

Fig. 3. One-way sensitivity analysis of overall incremental value. Legend: BP-SES: bioresorbable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; ppMI: peri-procedural myocardial infarction; CK-MB: creatine kinase myocardial band; ULN: upper limit of normal.

valve replacement (SAVR) in intermediate risk patients [29], payment rates make SAVR more attractive to hospitals [30], which could interfere with the uptake of TAVR.

4.1. Limitations

Our analysis is not without limitations. First, there is an ongoing debate about the significance of ppMI outside of clinical trials, as low-severity events might remain undetected without routine monitoring of biomarkers [11,31]. We would argue that our modeling approach reflects this consideration correctly, as our distributions imply no incremental cost in about a third of ppMI cases with a midpoint and upper limit derived from published estimates. Thus, our predictions should correctly reflect the average difference between the two stent types, and the predicted ranges capture the uncertainty.

Second, some concerns were voiced over residual imbalances between the two arms of the BIOFLOW V trial, which may have favored the bioresorbable polymer sirolimus-eluting stent and contributed to the differences in ppMI. However, the difference in ppMI persisted in after multivariate adjustment for these differences [32].

Lastly, we acknowledge that model prediction do not constitute direct evidence, as they are based on data from various sources and expert opinion, but point out that the estimates for differential ppMI rates and attributable in-hospital cost, as the most influential model parameters based on our sensitivity analyses, were derived from direct empirical evidence.

5. Conclusions

Our findings suggest that the ultrathin, bioresorbable polymer sirolimus-eluting stent tested might be a valuable option for patients undergoing percutaneous coronary intervention from a population health and economic perspective. The results may help clinicians, payers and purchasers in making future decisions about the choice of

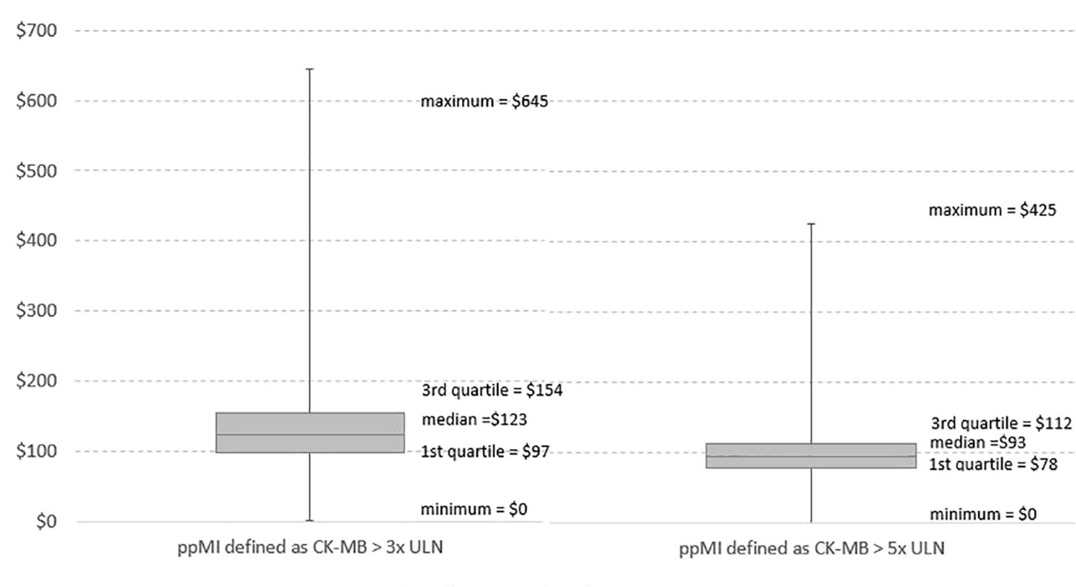

Fig. 4. Distribution of estimates for overall incremental economic value of bioresorbable polymer sirolimus-eluting stent based on probabilistic sensitivity analyses. Legend: ppMI: peri-procedural myocardial infarction; CK-MB: creatine kinase myocardial band; ULN: upper limit of normal.

coronary stents. Additional research is needed to establish the long-term impact on cost and clinical outcomes past the 12 months covered by the current data.

Clinical perspective

What's known?

The recent BIOFLOW V trial compared the Orsiro ultrathin, bioresorbable polymer sirolimus-eluting coronary stent to the Xience thin, durable polymer everolimus-eluting stent. Its results showed significant differences in target lesion failure and target vessel-related myocardial infarction in favor of the bioresorbable polymer sirolimus-eluting stent, driven by a lower rate of peri-procedural myocardial infarction (ppMI).

What's new?

This study analyzed the effect of that difference in ppMI rates on cost of care and patient outcomes over 12 months with a simulation model and estimated that the bioresorbable polymer sirolimus-eluting stent was associated with average net reductions in direct medical cost of $124 per patient and 17 QALYs gained per one million patients.

What's next?

Additional research is needed to establish the long-term impact on cost and mortality.

Disclosures

Supported through a contract from BIOTRONIK, Switzerland to Benecit Research. The sponsor provided comments on an earlier draft of the paper, but the authors had full control over study design and execution, interpretation of the data, preparation, review and approval of the manuscript and decision to submit.

Soeren Mattke serves on the board of directors of Senscio Systems, Inc. and the scientific advisory board of aicure technologies, Boston Millennia Partners and ZanoZano. He has received consulting fees from AARP, Biotronik, Bristol-Myers Squibb, Philips, TEVA Pharmaceuticals and UCB Pharma, and honoraria from Defined Health and Gerson Lehman Group. Mark Hanson has received consulting fees from Biotronik. Anissa Dallmann has received consulting fees from Biotronik and holds stock in Biogen. Marc Bentele is an employee of Biotronik.

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