ORIGINAL ARTICLE

Cost-Effectiveness of Drug Eluting Stents Versus Bare Metal Stents in Coronary Heart Disease. A Systematic Literature Review

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ABSTRACT

Background
The purpose of this study was to perform a systematic literature review to determine whether coronary disease endovascular therapy with drug eluting stents (DES) compared with bare metal stents (BMS) is cost-effective.

Methods
A systematic review was performed in Pubmed/Medline, Embase, CDRS, NCBI, Hinari, CRD, DARE, NHSEED, HTA, HSRPROJ, HSTAT electronic databases to identify full economic evaluation studies with healthcare system perspective reporting the relationship between cost/absolute risk reduction and cost/QALY, without date or language limitations.

Results
Sixteen studies were included (21807 participants). Paclitaxel or sirolimus DES compared with BMS were evaluated in five studies (31.25%), 31.25% assessed only sirolimus eluting stents, 25% only paclitaxel eluting stents and 12.5% zotarolimus eluting stents. Health care payment perspective was explicit in 93.75% of the studies. The distribution of patient characteristics was similar in all groups and balanced in observational studies. Six of the 16 studies concluded that DES was not cost-effective in their population, but that in subgroups at greater risk of restenosis or with multiple vessel disease the therapy was cost-effective.

Conclusions
The studies were consistent in the reduction of target vessel revascularization frequency with DES compared to BMS without affecting mortality at 12 month follow-up. The intervention was cost-effective in studies at greater risk of restenosis or with multiple vessel disease.

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Key words > Stents - Cost-effectiveness - Coronary disease - Myocardial infarction - Systematic review

Abbreviations >

A£	Pound	**QALY**	Quality-Adjusted Life Year
¥	Yen	**R$**	Brazilian real
€	Euro	**RCEI**	Incremental cost-effectiveness ratio
C$	Canadian dollar	**BMS**	Bare metal stent
MACE	Major adverse cardiovascular events	**DES**	Drug eluting stent
NT$	New Taiwanese dollar	**US$**	Dollar

BACKGROUND
Current healthcare systems are facing fast technological development which is becoming increasingly costly with budget limitations unable to meet those demands.(1-3) In this context, coronary disease has progressed in the knowledge of both physiopathological mechanisms and in medical and interventional treatment. This has led from open cardiovascular surgery to less invasive treatments through interventional endovascular coronary therapy. (4,5) Balloon dilation of a diseased vessel was initially performed, but owing to the incidence of post-angioplasty restenosis,

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percutaneous coronary interventions with stents were developed in which angioplasty was followed by bare-metal stent (BMS) implantation.(4-6) Subsequently, the use of drug-eluting stents (DES) was marketed, releasing drugs at a local level to antagonize cell reactions in the treated vessel segment, thus reducing restenosis rate as compared with BMS.(4,5,7) Henceforth, DES demand increased exponentially, with its related costs increase, seriously impacting in the progressively resource-constrained healthcare systems, even in the best economic scenarios.(5,7)

Published economic evaluations have attempted to determine the cost-effectiveness(11) or cost-utility(11) of DES compared with BMS in eligible patients. The purpose of these models has been to determine the cost per event avoided or per quality-adjusted life year (QALY) gained, by comparing the absolute risk difference between each alternative with the costs generated by them. (8,11) The aim of this study is to systematically compile the available DES cost-effectiveness evidence vs. BMS (8) through a complete review of economical evaluation studies(12) in patients with symptomatic coronary disease in terms of major adverse cardiac events (MACE) during follow-up.

METHODS

A systematic review of the literature was performed to assess cost-effectiveness or cost-utility of DES vs. BMS for endovascular treatment of coronary disease. (9) Complete economic studies comparing two or more alternatives that considered both costs and consequences in patients with coronary disease and percutaneous intervention with DES or BMS were included for analysis. (8, 10, 11) The effectiveness or utility information was obtained from piggy-back controlled clinical trials, observational studies or extrapolations from other studies taking into account the economic evaluation.

Effectiveness measurements were expressed as absolute risk difference of restenosis, mortality, target vessel revascularization or MACE. Regarding costs, studies having adopted a health sector perspective were included using local currency for evaluation. Likewise, the incremental cost-effectiveness ratios (ICER) expressed as cost per event avoided or the cost-utility ratios as cost per QALY gained were included for each study. The sensitivity analysis for each article is reported.

An extensive, objective and reproducible search of original articles was performed in Pubmed/Medline, Embase, CDRS, NCBI, HINARI, CRD, DARE, NHSEED, HTA, HSR-PROJ, HSTAT electronic databases, with no date limit up to November 8, 2011 nor language or type of study restrictions. Search was carried out using "cost-effectiveness analysis OR cost-benefit analysis" terms, which included complete economic cost-effectiveness or cost-utility analyses, and "Drug Eluting Stent" or "Stent" for interventions and comparisons with any type of DES (sirolimus, paclitaxel, zotarolimus) or BMS. Studies were selected by abstract and the quality of the articles was assessed according to the checklist developed by Drummond and suggested by Cochrane Collaboration for this type of studies. (9) Author, year and publication site, sample size, type of stent, stent price, price difference among stents, average number of stents, measurement of health improvement evaluation (effectiveness), follow-up period, absolute risk difference among the alternatives, mean and incremental cost-effectiveness ratio or mean and incremental cost/QALY were acquired using a data collection format generated in Microsoft Office Excel 2007.

Effectiveness measurements are reported as cumulative incidence and absolute risk reduction for restenosis, mortality, target vessel revascularization or MACE. Cost-effectiveness or cost-utility measurements are presented as incremental cost-effectiveness/cost-utility ratios. Decision models used in each study are described, as well as sensitivity analyses. Thresholds considered by the authors to be cost-effective were established. No meta-analysis was performed due to heterogeneity among experimental and observational studies, characteristics of the included population and cost evaluation using the local currency of each country.

RESULTS

Five hundred and thirty seven studies were collected, out of which 489 were discarded due to title, abstract or following content review. From the remaining 48 articles, 21 were excluded because they were repeated studies, 5 because they had no complete economic analysis, one due to inaccessibility after writing to the author, (12) 4 because the alternative stent included surgery and one because it compared elective vs. non-elective procedures. Thus, 16 articles were used for critical review with the quality criteria established by Drummond. (10) Figure 1 shows the flowchart of study selection.

Characteristics of studies and alternatives

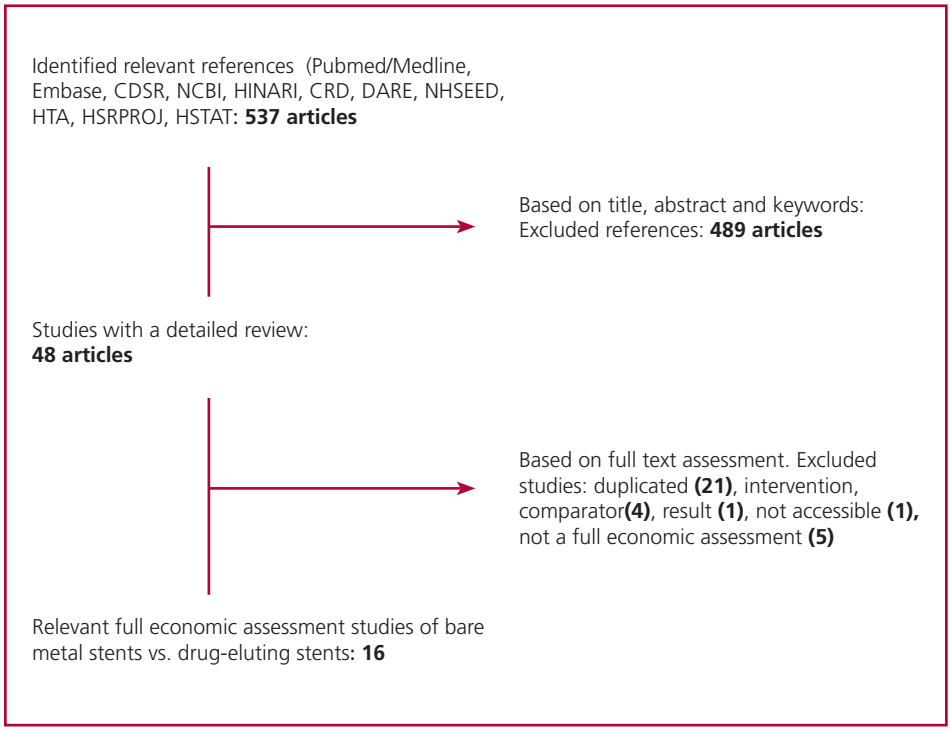
Six studies (37.5%) obtained effectiveness and utility data during the course of clinical trials, (13-18) three (18.75%) used extrapolated effectiveness measurements from clinical trials in other populations, (19-21) five (31.25%) communicated data from prospective studies (22-26) and two (12.5%) from retrospective studies. (27, 28) Sample size was variable probably because cohorts consisted in the systematic collection of subjects submitted to coronary percutaneous interventions within a population (24, 26) and in the case of clinical trials the main objective was the efficacy of DES vs. BMS interventions (13-18) (Table 1)

Payment perspective was explicit in 15 articles (93.75%). Ten articles adopted the payer perspective (66.6%), two a social perspective (13.3%) and three the provider perspective(20%). BMS were compared with paclitaxel or sirolimus DES in five articles (31.25%), (18, 23, 24, 26, 28) only sirolimus in five studies (31.25%), (13, 14, 21, 22, 27) only paclitaxel in four studies (25%) (15, 19, 20, 25) and zotarolimus in two studies (12.5%). (16, 17) Twelve studies (75%) did not establish the type of BMS, two (12.5%) used Driver®(16, 17) and Liberté® stents (18, 25) respectively, (23) and one study (6.25%) included Vision® stents. Only one article described the available stent length. (14)

Population characteristics

The general characteristics of the population were not described in four studies; however, they could be

Fig. 1. Study flowchart



obtained from the original clinical trials from which the effectiveness measurements were retrieved. (19-21, 26) Clinical trial age, diabetes, infarction and previous revascularization distribution were similar due to randomness and balance in most cohort and retrospective studies (Table 2). Average population age ranged between 60 and 70 years for all the groups, the percentage of diabetes varied between 16-60% in the DES group and 5-33% in the BMS group, and history of infarction was present in 24-48% of the patients with DES and in 24-42% of those with BMS. Similarly, previous revascularization, either percutaneous or open surgery was present in 8-45% of the population in studies communicating this event for DES and in 8-24% for BMS. (22-25, 27)

Effectiveness measurements

Thirteen studies used restenosis decrease or revascularization avoided as effectiveness measurements (13-16, 19-22, 24-28) and three used combined measurements such as MACE (17, 18, 23) or revascularization plus infarction. (16, 18) Statistically significant differences were found in the incidence of target lesion revascularization in all the studies, varying from 3.3% (24) to 18% (14) for cumulative incidences. Two studies referred differences in incidence ratios expressed as events per patient (0.021) (23) and events per 100 subjects-year (11.1), (16) respectively. There were no statistically significant differences in mortality or re-infarction between the two alternatives in the studies reporting these outcomes. (14-17, 22, 23, 25, 27, 28) The follow-up period was 12 months in 31.5% of the studies, (13-15, 21, 27) 18 months in 6.25%, (23) 24 months in 43.75% (18-20, 22, 24, 25, 28) and 48 months in 18.75% of the studies (16, 17, 26) (Table 3).

Cost analysis

The included studies assessed DES vs. BMS. Two studies evaluated also the mixed alternative (DES and BMS) (18, 21) and all found a positive cost difference, indicating that at the end of the follow-up period for each of these studies, the DES alternative was more costly than BMS (Table 4). Sensitivity analyses were performed according to the presence of long lesion, (13, 15, 24) vessel diameter, (13, 15) diabetes, (13, 15, 23, 24, 26) length of clopidogrel treatment, (13, 17, 19, 26) longer stent availability, (13, 14, 17)bare metal or drug-eluting stent price, (14, 17, 21, 24) major and minor restenosis probability, (21, 27)and low and high risk groups (18, 20, 23) (Table 5). Cost evaluation was in euros (€) in six studies (37,5%), (18-20, 22, 23, 26) in dollars (US$) in three, (13, 15, 16) in Canadian dollars (C$) in two, (14, 24) in Brazilian real (R$) in two, (21, 25) in yens (¥) in one, (27) in pounds (£) in one (17) and in new Taiwanese dollars (NT$) in one. (28) Four studies (25%) did not perform sensitivity analysis (see Table 5). (16, 22, 25, 28)

Cost effectiveness and cost-utility measurements

Fifteen studies (93.75%) established a cost-effectiveness ratio and eight studies (50%) also included a cost-utility analysis. (13, 15, 17, 20, 21, 23, 24, 26) Four studies did not include the cost-effectiveness threshold used to analyze results (16, 24, 26, 27) and one study did not communicate incremental cost-effectiveness ratio (ICER) results because there were

Table 1. Articles included in the systematic revision per type of study, sample size and type of evaluated stent

Study	Type of study	Sample size	Drug-eluting stent (N)	Bare metal stent (N)	Type of drug-eluting stent	Bare metal stent
Cohen, et al; 2004	CCT	1055	533	522	Sirolimus	BMS (na)
Ong, et al; 2006	CH	958	508	450	Sirolimus	BMS (na)
Rinfret, et al; 2006	CCT	100	50	50	Sirolimus, 8-18 mm	BMS (na))
Bakhai, et al; 2006	CCT	1314	662	652	Paclitaxel	BMS (na)
Russell, et al; 2006	CCT ex	-	-	-	Paclitaxel	BMS (na)
Ekman, et al; 2006	CCT ex	-	-	-	Paclitaxel	BMS (na)
Brunner, et al; 2007	CH	826	545	281	Sirolimus	BMS Vision
Polanczyk, et al; 2007	CCT ex	-	-	-	Sirolimus	BMS (na)
Eisenstein, et al; 2009	CCT	1167	583	584	Endeavor	BMS (Driver)
Sugimoto, et al; 2009	Re	50	25	25	Sirolimus	BMS (na)
Goeree, et al; 2009	CH	13353	5106	8247	Cypher Sirolimus Paclitaxel	 BMS (na)
Neyt, et al; 2010	CH	12287	1435	10852	Sirolimus, paclitaxel	BMS (na)
Ferreira, et al; 2010	CH	217	130	87	Paclitaxel	BMS (Liberté)
Remak, et al; 2010	CCT	1197	598	599	Endeavor	BMS (Driver)
Varani, et al; 2010	CCT	1190	596	594	Sirolimus-Paclitaxel	BMS (Liberté, Boston Scientific or Chromium cobalt alloy)
Hung, et al; 2011	Re	380	186	194	Sirolimus, paclitaxel	CS (na)

CCT: Controlled clinical trial. CH: Cohort. Re: Retrospective. CCT ex: Extrapolation from controlled clinical trial. BMS: Bare metal stent. na: Not available.

Table 2. Distribution of socio-demographic characteristics per study and stent type

Study	Age (years)		Diabetes (%)		Previous Infarction (%)		Previous Revascularization %	
	BMS	DES	BMS	DES	BMS	DES	BMS	DES
Cohen, et al; 2004	62 ± 11	62 ± 11	25	28	28.2	32.9	NA	NA
Ong, et al; 2006	61 ± 11	61 ± 11	18	15	30	40	9	8
Rinfret, et al; 2006	60 ± 11 (42-79)	61 ± 9 (43-77)	24	24	48	42	NA	NA
Bakhai, et al; 2006	63 ± 11	62 ± 11	23	25	30.5	29.0	NA	NA
Russell, et al; 2006	63 ± 11	62 ± 11	23	25	30.5	29.0	NA	NA
Ekman, et al; 2006	63 ± 11	62 ± 11	23	25	30.5	29.0	NA	NA
Brunner, et al; 2007	64 ± 11	64 ± 11	17	22	28	27	13	12
Polanczyk, et al; 2007	62 ± 11	62 ± 11	25	28	28.2	32.9	NA	NA
Eisenstein, et al; 2009	62 (54.70)	63 (55.70)	18	22	39.7	41.5	NA	NA
Sugimoto, et al; 2009	66 ± 12	66 ± 9	16	32	24	24	8	8
Goeree, et al; 2009	62.3 ± 11.5	62.3 ± 11.7	33	33	40.8	42.3	8.5	9
Neyt, et al; 2010	NR	NR	59.9	5	NR	NR	NA	NA
Ferreira, et al; 2010	64.1 (48-85)	65.2 (43-90)	45	18	26.4	39.2	45	24
Remak, et al; 2010	61.6 ± 10.5	61.9 ± 10.5	18	22	40	42	NA	NA
Varani, et al; 2010	64.1 ± 10.5	70.7 ± 10.5	43	22	22	28.5	NA	NA
Hung, et al; 2011	64 ± 11	64 ± 11	38	30	NR	NR	NA	NA

BMS: Bare metal stent. DES: Drug eluting stent. NR: No reference. NA: Not available.

Table 3. Percentage of major cardiac adverse events per study, type of stent and follow-up period

Study	Nº stents per lesion		Mortality		AMI		Repeat revascularization (%)		Absolute risk reduction(%)	Follow-up period (months)
	BMS	DES	BMS	DES	BMS	DES	BMS	DES		
Cohen, et al; 2004	1.4 ± 0.6	1.4 ± 0.8	1.1	0.8	0.8	1.9	28.4	13.3	15.1	12
Ong, et al; 2006	2.0 ± 1	1.8 ± 0.9	NR	NR	NR	NR	10.4	3. 65	6.77	12
									24	
Rinfret, et al; 2006	1.05 ± 0.7	1.05 ± 0.6	0	0	4	4	22	4	18	12
Bakhai, et al; 2006	1.3 ± 0.7	1.3 ± 0.8	0	0.3	2.4	2.1	16.6	6.6	10	12
Russell, et al; 2006	NR	NR	NR	NR	NR	NR	15.9	4.5	11.4	12
							18.3	5.6	12.7	24
Ekman, et al; 2006	NR	NR	NR	NR	NR	NR	15.10	4.4	10.7	12
							17.4	5.6	11.8	24
Brunner, et al; 2007	1.9 ± 1.1	1.9 ± 1.0	0.185	0.206	-	-	-	-	0.021	18
Polanczyk, et al; 2007	NR	NR	NR	NR	NR	NR	21.2	7.3	14	12
Eisenstein, et al; 2009	1.1 ± 0.3	1.1 ± 0.3	5.0	5.2	3.2	4.4	21.5	10.4	11.1	48
Sugimoto, et al; 2009	1.3 ± 0.5	1.4 ± 0.5	0	0	0	0	20	4	16	12
Goeree, et al; 2009	1.5 ± 0.8	1.5 ± 0.8	NR	NR	NR	NR	10.7	7.4	3.3	24
Neyt, et al; 2010	1.09	1.05	NR	NR	NR	NR	(S) 23.6	(S) 7.8	15.2	48
							(P) 10.1		(P) 20	9.9
Ferreira, et al; 2010	NR	NR	0.75	1.2	NR	NR	10.3	2.3	7.7	26
Remak, et al; 2010	1.12	1.11	1.2	0.5	2.7	3.9	12.5	5.6	6.9	48
Varani, et al; 2010	2.7 ± 0.9	1.8 ± 0.9	2.8	5.2	4.4*	5.2*	14.8	12.4	5.7	24
						3.1**		2.1**		
Hung, et al; 2011	1.6	1.29	NR	NR	1	1	22	12	10	24

Median (range). AMI: Acute myocardial infarction. NR: No reference. BMS: Bare metal stent. DES: Drug eluting stent. (S) Sirolimus vs. BMS, (P) Paclitaxel vs. BMS.

* Acute ST elevated myocardial infarction.

** Acute non- ST elevated myocardial infarction.

no cost differences at the end of follow-up. (16) Cohen et al. (13) reported an ICER of US$1650 per revascularization avoided and US$27540 per QALY gained, concluding that the alternative was cost-effective and cost-useful. Ong et al. (22) established an ICER of €20373 and €22267 per revascularization avoided at one and two years, respectively, which was not cost-effective at a threshold of €10000 per event avoided. Rinfret et al (14) found an ICER of US$11275 per revascularization avoided, indicating that DES was cost-effective in this study. Bakhai et al. (15) reported that DES was cost-effective and cost-useful with an ICER of US$4678 and US$47798 per revascularization avoided and QALY gained. Russell et al.(19) determined that incremental cost-effectiveness at one and two years was €1568 and €811 per event avoided, respectively, with a €7700 threshold, indicating that DES was cost-effective in the Spanish population. Ekman et al. (20) calculated an ICER of €46801 and €35607 for cost-effectiveness, and of €257486 and €197827 for cost-utility at one and two years, respectively. In this study, the use of DES was neither cost-effective nor cost-useful at thresholds of €5687 per revascularization avoided and €70000 per QALY gained. Brunner et al. (23) pointed out that DES was not cost-effective or cost-useful at thresholds of €10000 per MACE avoided or €40000 per QALY gained, reporting an ICER of €64732 per MACE avoided and of €40467 per QALY gained. Polanczyk et al. (21) communicated an ICER of R$27403 per restenosis avoided and R$49464 and R$356354 per QALY gained, under the perspective of prívate and unified healthcare systems, respectively, establishing that the alternative was not cost-effective but cost-useful in some subgroups. Eisenstein et al (16) did not report incremental cost-effectiveness results; however, they concluded that there was less target vessel revascularization without cost differences during follow-up. Sugimoto et al (27) established that the alternative was cost-effective without providing an explicit ICER or cost-effectiveness threshold. Goeree et al (24) documented an ICER of C$52585 per revascularization avoided and C$1569875 per QALY gained, concluding that the use of DES was not cost-effective. Neyt et

Table 4. Type of economic analysis, bare metal or drug-eluting stent cost, cost difference during follow-up and sensitivity analysis according to cost and study measurement units

Study	Type of model	Price DES analytic	Price BMS	Price difference	Cost difference	Sensitivity analysis	Currency
Cohen, et al; 2004	NA	2900	900	2000	NR	Stent length, DES cost, DES use in restenosis	Dollar
Ong, et al; 2006	NA, DES vs. pre-DES BMS	1929	692	1237	1968	NR	Euro
Rinfret, et al; 2006	NA, DES vs. BMS	2700	700	2000	-	Stent length, DES use in restenosis ,	Canadian dollar
Bakhai, et al; 2006	DES vs. BMS	2700	800	1900	572 (346-1478)	Only clinical follow-up, Lesion length and vessel size	Dollar
Russell, et al; 2006	Analytic decision, DES vs. BMS	NR	NR	NR	178	Length of treatment	Euro
Ekman, et al, 2006	Analytic decision,surgery vs. DES and BMS	NR	NR	1051	585	Length of clopidogrel, average stent use, restenosis frequency, waiting time for intervention	Euro
Brunner, et al; 2007	NA, DES vs. BMS	2275 1935	1260	1015 674	1358	Patient subgroup, off-label use, age	Euro
Polanczyk, et al; 2007	Analytic decision PCI BMS, DES,	10320	2707	7613	3816		
	DES after BMS, Markov		4527	5793	6619	Public healthcare and supplementary plan, DES or BMS use in restenosis	Brazilian Real
Eisenstein, et al; 2009	NA, Zotarolimus vs. BMS	2100	900	1200	294	NR	Dollar
					(-1185 to 1772)		
Sugimoto, et al; 2009	NA, DES vs. pre-DES BMS	378000	258000	120000	15841	NR	Yen
Goeree, et al; 2009	Analytic decision CE, CU	1899	600	1299	1148-2534	Different stent price	Canadian Dollar
Neyt, et al; 2010	Analytic decision, DES vs. BMS	2500	1000	1500	663-850	Lesion severity and presence of diabetes	Euro
Ferreira, et al; 2010	Analytic decision PCI BMS vs. DES	-	-	-	7238.16	NR	Brazilian Real
Remak, et al; 2010	Markov, Endeavor vs. Driver	799.79	294.92	504.87	103	Number of stents, length of clopidogrel, percentage of lethal AMI	Libra
Varani, et al; 2010	DES vs. BMS vs. Combined	1450-1800	400-600	1050-1200	2883; 3234	Low risk and high risk patients	Euro
Hung, et al; 2011	NA, DES vs. BMS	242248	177871	64377	43548	NR	New Taiwanese dollar

BMS: Bare metal stent. DES: Drug-eluting stent. NA: Not available. NR: No reference. PCI: Percutaneous coronary intervention. CE: Cost-effectiveness. CU: Cost-utility. AMI: Acute myocardial infarction.

al (26) calculated an ICER of €3580-13182 per revascularization avoided and €268375-970400 per QALY gained, deducing that the alternative can be cost-effective in selected subgroups. Ferreira et al (25) referred R$90476.97 per restenosis avoided, which was not cost-effective at a threshold of R$47532 per event avoided. Remak et al (17) determined an ICER of £3757 per MACE avoided, which was cost-effective at a US$20000-30000 threshold. Varani et al. (18) indicated that the drug-eluting stent was not cost-effective at a €20000 threshold per MACE avoided, with an ICER of €28669 per MACE avoided. Hung et al (28) established an ICER of NT$546444 per revascularization avoided, which was not cost-effective at a NT$10000 threshold per event avoided. According to the control case, it was concluded that at the employed thresholds, the DES alternative was cost-effective in 40% of the cases and cost-useful in 50% of the studies where it was included (Table 6).

Similarly, in sensitivity analyses, results were preserved in the case in which the alternative was cost-effective while in those which reported that their

Table 5. Subgroups and sensitivity analyses, informed incremental cost-effectiveness ratio and results per study.

Study	Subgroups and sensitivity analyses	ICER	Threshold Cost-effectiveness/ Cost-utility
Cohen, et al; 2004	Longer stents, 1.3 stents per lesion	US$727/ARR US$16957/QALY	US$10000/ARR, US$50000/QALY
	Longer stents without difference during clopidogrel treatment	Dominant/ARR Dominant/QALY	
	Diabetics	US$2376/ARR	
	Non- diabetics	US$1973/ARR	
	Lesions <15 mm	US$4265/ ARR	
	Lesions 15-20 mm	US$4459/ ARR	
	Reference vessel <2.5 mm	Dominant	
	Vessel 2.5-3.0 mm	US$1345/ ARR	
	Vessel >3 mm	US$6206/QALY	
Rinfret, et al; 2006	1.2 stents/lesion	C$7941/ ARR	C$10000 or
	SES at C$2200 and BMS at C$650	C$4941/ARR	C$12500
	SES at > C$3400 and BMS at C$750	> C$12500/ARR	
	SES for intrastent restenosis	C$5918/ARR	
Bakhai, et al; 2006	Diabetics	Dominant	<US$50000/QALY,
	Non diabetics	US$9387/ARR	<US$10000/ARR
	Anterior descending coronary artery lesion	US$2764/ARR	
	Anterior non-descending coronary artery lesion	US$8746/ARR	
	Vessel diameter <2.5 mm	Dominant	
	Vessel diameter 2.5-3 mm	US$5089/ARR	
	Diameter ≥ 3	US$25571/ARR	
	Length ≤ 20	US$6700/ARR	
	Length > 20	US$4972/ARR	
Ekman, et al; 2006	High risk group, follow-up 1 year	€41791/QALY €8338/ARR	€70000/QALY €5687/ARR
	High risk group, follow-up 2 years	Dominant	
Brunner, et al; 2007	Low risk patients < 65years	€163243/QALY	€10000/ARR
	High risk patients < 65years	€17742/QALY	€40000/QALY
	Low risk 1 or 2 vessel lesion	€269268/MACE	
		€72946/QALY	
	High risk1 or 2 vessel lesion	€11333/MACE	
		€5641/QALY	
	High risk three vessel disease	Dominant	
	Low risk non-diabetes	€69553/MACE €51690/QALY	
	High risk non-diabetes	€10504/MACE €6733/QALY	
	One low risk segment	€146187/QALY	
	One high risk segment	Dominant	
	Off-label use in low risk	€224591/QALY	
	Off-label use in high risk	Dominant	
	Off-label use in low risk	€375927	
	Off-label use in high risk	Cost saving without effect in QALY	

(continue)

Polanczyk, et al; 2007	Non-public perspective	R$27403	US$50000/QALY,
	Public healthcare system	R$47529	US$10000/ARR
	40% greater incidence of restenosis	< R$15000	
	20% lower than expected incidence of restenosis	> R$50000	
	Drug-eluting stent < $6600	Dominant strategy	
	Drug-eluting stent 6600-8000	< R$10000	
	Drug-eluting stent8000-9400	Between R$10000-20000	
	Restenosis cost management < 10000	More than R$20000	
	Restenosis cost management 10000-19000	R$10000-20000	
	Restenosis cost management > 19000	Less than R$10000	
Remak, et al; 2010	Clinical data only Endeavor II	US$5716/QALY	US$20000-30000
	1.4 stents per lesion	US$12005/QALY	
	12 month clopidogrel in drug-eluting stents and 3 months in bare metal stents	US$15641/QALY	
	Outcome extended to 5 years.	US$1607/QALY	
	Price DES = BMS + 300	DES dominate	
	Price DES 529, BMS 131	DES dominate	
Varani, et al; 2010	Low revascularization risk at 1 year	€87539/ ARR	€20000
	Low revascularization risk at 2 years	€25048/ ARR	
	Low revascularization risk at 1 year	€10194/ ARR	
	Low revascularization risk at 2 years	€11247/ ARR	

ICER: Incremental cost-effectiveness ratio. ARR: Absolute risk reduction. QALY: Quality-adjusted life year. SES: Sirolimus-eluting stent

main measurement was not cost-effective, use of DES was cost-effective in high risk or with three-vessel involvement subgroups (18, 20, 23) (see Table 5). In sensitivity analyses, Polanczyk et al. (21) established that DES was cost-effective when the stent cost decreased below R$9400 and the cost of restenosis management was over R$10000.

DISCUSSION

Most studies are consistent in determining no differences between mortality and reinfarction during follow-up in patients with coronary disease treated with DES vs.BMS. However, in the DES group there is less incidence of restenosis, of target vessel revascularization or MACE, the latter used to calculate cost-effectiveness or cost-utility measurements across studies. Evidence suggests that the use of drug–eluting stents is a cost-effective and cost-useful alternative in subgroups at greater risk of restenosis with critical lesions or with multiple vessel disease. However, the characteristics of the apparently similar populations must be considered as they may vary in lifestyle, diet and physical activity, thus probably influencing the outcome. Furthermore, economic studies derived from clinical studies found a lower event incidence as a consequence of patient follow-up during the course of the study, probably resulting in greater compliance to medical treatment and general measures, as opposed to real life scenarios observed in performed cohort analyses.

Similarly, more restrictive inclusion criteria in clinical trials limit the range of disease severity which may influence the assessed result measurements.

One of the main limitations of the summary information was derived from the important heterogeneity in cost determination provided by the authors. Firstly, because the local currency of each country was used to determine stent costs, and also, because DES or BMS prices may differ between a private or public institution which will purchase the product at a higher price in comparison with healthcare systems, taking into account that pharmaceutical companies prices decrease with greater acquisition. Furthermore, the foreign stent production cost in the country where the evaluation was performed is much higher than that of the local manufacturer.

The main strength of the study is the consideration of multiple sources of evidence for the research question, which allowed comparing different results observed in different scenarios. However, this heterogeneity also limits the ability of the study to obtain summarized measurements on the evaluated outcomes.

In conclusion, it can be seen that intervention with drug eluting stents is cost-effective and cost useful in groups at greater risk of restenosis. However, observational studies establishing that DES is not cost-effective should be considered. This could be attributed, in part, to a real life scenario where patient condition, lifestyle and compliance to drug treatment might in-

Table 6. Type of economic analysis, discount rate, outcome measurement, incremental cost effectiveness and cost-utility ratios per type of study and cost-effectiveness threshold

Study	Type of analysis	Discount	Type of health improvement measurement	ICER	QALY	Cost- effectiveness threshold
Cohen, et al; 2004	CE, CU	NA	Revascularization avoided	NA	NA	Revascularization avoided
Ong, et al; 2006	CE	NA	Revascularization avoided	NA	NA	Revascularization avoided
Rinfret, et al; 2006	CE	None	Revascularization avoided	None	None	Revascularization avoided
Bakhai, et al; 2006	CE, CU	NA	Revascularization avoided	NA	NA	Revascularization avoided
Russell, et al; 2006	CE	NA	Revascularization avoided	NA	NA	Revascularization avoided
Ekman, et al; 2006	CE, CU	NA	Revascularization avoided	NA	NA	Revascularization avoided
Brunner, et al; 2007	CE, CU	None	MACE avoided	None	None	MACE avoided
Polanczyk, et al; 2007	CE, CU	3%	Restenosis avoided	3%	3%	Restenosis avoided
Eisenstein, et al; 2009	CE	3%	Revascularization avoided	3%	3%	Revascularization avoided
Sugimoto, et al; 2009	CE	None	Revascularization avoided	None	None	Revascularization avoided
Goeree, et al; 2009	CE, CU	5%	Revascularization avoided	5%	5%	Revascularization avoided
Neyt, et al; 2010	CE, CU	None	Revascularization avoided	None	None	Revascularization avoided
Ferreira, et al; 2010	CE	None	Restenosis avoided	None	None	Restenosis avoided
Remak, et al; 2010	CU	3,5%	MACE avoided	3,5%	3,5%	MACE avoided
Varani, et al; 2010	CE	None	MACE avoided	None	None	MACE avoided
Hung, et al; 2011	CE	NA	Revascularization avoided	NA	NA	Revascularization avoided

ICER: Incremental cost-effectiveness ratio. QALY: Quality-adjusted life year. CE: Cost-effectiveness. CU: Cost-utility. NR: No reference. NA: Not available. ARR: Absolute risk reduction. MACE: Major cardiovascular adverse events. NC: Does not correspond

fluence the revascularization incidence in comparison to supervised settings in clinical trials, or to the small sample size to find statistically significant differences for a relatively prevalent disease in the population. Similarly, the availability of steadily improving BMS compared to initial stents which had greater rate of restenosis, as well as the improvement in coronary disease drug management might influence the fact that no significant differences were found. In view of the above, it is considered necessary to perform further studies comparing both alternatives within the current scenario, including drug management with more aggressive targets, which might decrease MACE incidence in the population.

RESUMEN

Costo-efectividad de los stents liberadores de fármacos versus stents convencionales en el manejo de la enfermedad coronaria. Revisión sistemática de la bibliografía

Introducción
Realizar una revisión sistemática de la bibliografía para determinar si el tratamiento endovascular con stent liberador de fármacos (SLF) para enfermedad coronaria es costo-efectivo en comparación con el stent convencional (SC).

Material y métodos
Se realizó una revisión sistemática de estudios de evaluación económica completa con perspectiva del sistema de salud que informaran relación costo/reducción de riesgo absolutoy costo/QALY sin límite de fecha ni de idioma en las bases dedatos electrónicas Pubmed/Medline, Embase, CDRS, NCBI, HINARI, CRD, DARE, NHSEED, HTA, HSRPROJ y HSTAT.

Resultados
Se incluyeron 16 estudios (21.807 participantes). Se evaluó SLF con paclitaxel o sirolimus comparado con SC en cinco artículos (31,25%), 31,25 % sólo stent con sirolimus, 25 % sólo paclitaxel y 12,5 % zotarolimus. La perspectiva de pago fue especificada en el 93,75 % de los trabajos. La distribución de las características de los pacientes fue similar en todos los grupos y balanceada en los estudios observacionales. Seis de los 16 estudios concluyeron que el stent con medicación no era costo-efectivo en su población; sin embargo, en los subgrupos de mayor riesgo de reestenosis o enfermedad de múltiples vasos esta terapia se consideró como costo-efectiva.

Conclusiones
Los estudios son consistentes en la reducción de la frecuencia de revascularización con stent con fármacos en comparación con stent convencional sin influir en la mortalidad a 12 meses de seguimiento. La intervención fue costo-efectiva en los estudios con mayor riesgo de reestenosiso enfermedad de múltiples vasos.

Palabras clave > Stents - Costo-efectividad - Enfermedad coronaria - Infarto del miocardio - Revisión sistemática

Conflicts of interest
None declared

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