Comparative effectiveness at five years of drug-eluting stents, bare metal stents, and coronary bypass surgery: the ERACI III study

Comparación de la efectividad a cinco años de seguimiento de los pacientes tratados con stents farmacológicos, stents convencionales y cirugía de revascularización miocárdica: resultado final del estudio ERACI III

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Abstract

Background. Drug-eluting stents (DES) reduce the rate of repeat revascularization compared with bare metal stents (BMS), however the effect of DES on long-term clinical outcomes is not well documented.

Methods and results. We compared the five-year outcomes of 225 patients who received a DES with patients randomized in an earlier trial to BMS or coronary artery bypass graft surgery (CABG). We applied multivariable adjustment and propensity score matching to control for differences between patient groups. Compared with patients who received a BMS, patients who received a DES had similar major adverse cardiac and cerebrovascular events (MACCE), with a DES:BMS hazard ratio (HR) of 0.75 (95% confidence interval (CI) 051 to 1.12), but had higher mortality (HR=1.84, CI: 0.92-3.68) and fewer repeat revascularizations (HR=0.52, CI: 0.31-0.85). Patients receiving DES did not differ significantly from patients receiving CABG with respect to MACCE (HR=1.03, CI: 0.67-1.60) or mortality (HR=1.33 (CI: 0.70-2.55), but had more repeat revascularizations (HR=2.11, CI: 1.05-4.24). Differences remained after propensity score DES: BMS hazard ratios in the propensity score matched patients were generally higher than the point estimates in the entire population albeit with wider confidence intervals due to the smaller sample size MACCE 1.20, CL: 0.75-1.90, p=0.45; for death 2.53, CL: 1.10-5.83, p=0.03; death, MI and stroke 3.31, CL: 1.62-6.76, p=0.001.

Conclusions. Use of first generation DES may be associated with a higher risk of cardiac events in routine clinical practice when the time use of clopidogrel is less than the recommendated by guidelines.

Palabras clave: *DES, CABG, BMS, stent thrombosis, clopidogrel, restenosis.*

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Abbreviations	
BMS	bare metal stent
CABG	coronary artery bypass graft surgery
CI	confidence interval
DES	drug-eluting stent
ERACI	Estudio Randomizado argentino Angioplastia coronaria y Clrugía de ***bypass*** coronario en la enfermedad de múltiples vasos
MACCE	major adverse cardiac and cerebrovascular events
MI	myocardial infarction

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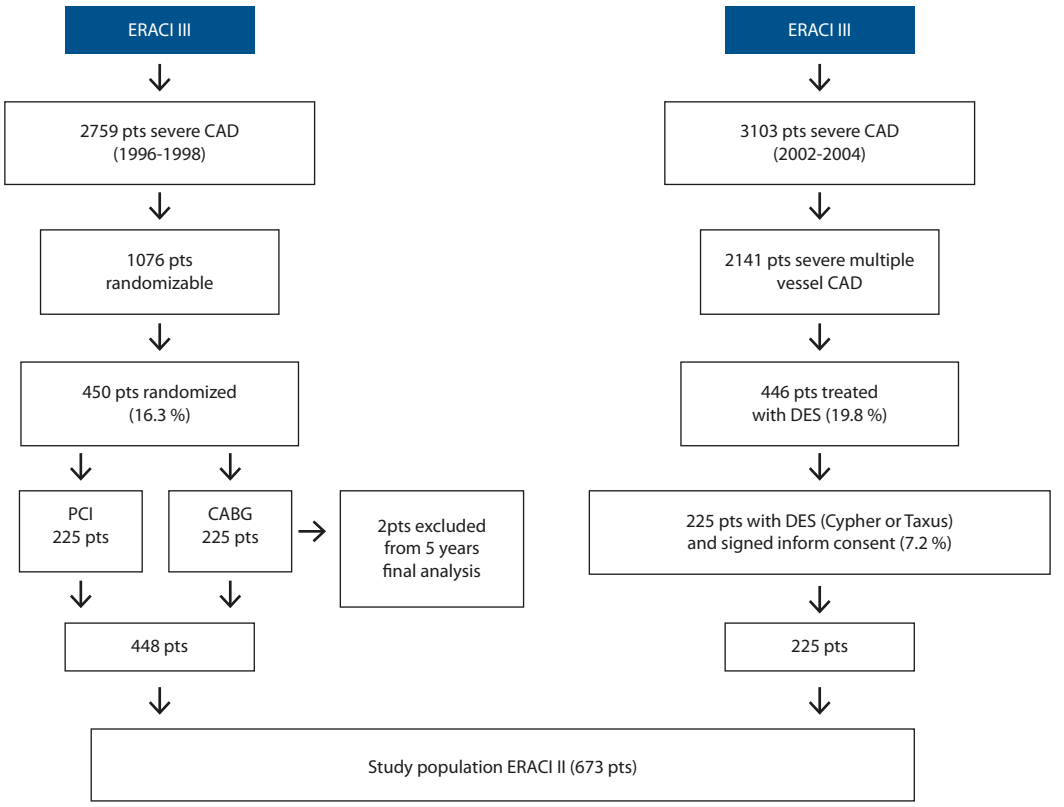

Figure 1. *Flow chart of ERACI trials and study population of ERACI III. CAD: Coronary Artery Disease, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, DES: Drug Eluted Stents. In CABG 2 patients assigned but not treated were excluded in the five years analysis.*

INTRODUCTION

Drug-eluting stents (DES) have had lower rates of repeat coronary intervention than bare-metal stents (BMS) in head-to-head randomized clinical trials.[1,2] The long-term effects of DES on hard cardiac events compared with BMS has been less clear,[2,3] especially in routine clinical practice settings.[4] The comparative efficacy of DES and coronary artery bypass graft surgery (CABG) is also uncertain, as randomized trials of DES and CABG have not yet completed long term follow-up.[5-7] The purpose of the present study was to compare five-year clinical outcomes of patients undergoing DES implantation for multivessel coronary disease with the outcomes of similar patients who had undergone either BMS implantation or CABG.

METHODS

ERACI III was a multicenter, prospective, non-randomized registry of patients undergoing DES implantation for multivessel coronary disease in one of five centers in Argentina.[8,9] The ERACI III registry was designed to permit comparisons with the previous ERACI II randomized trial,[10,11] which compared BMS implantation with CABG among patients with multivessel coronary disease. The same clinical centers participated in the ERACI III registry and the ERACI II trial, and they used the same patient inclusion and exclusion criteria and data collection methods in order to facilitate comparisons among the treatment groups (**Figure 1**). The design and early results of the ERACI III registry have been presented previously.[8,9] In brief, patients were eligible if they had anginal symptoms that warranted coronary revascularization, and significant obstruction of two or more coronary arteries (including the left main) with a reference diameter of 2.5 mm or more that were amenable to complete functional revascularization by either percutaneous coronary intervention (PCI) or CABG. Patients were excluded if they had any of the following: single-vessel disease, prior PCI within the past year, prior CABG at any time, two or more total coronary occlusions, an ejection fraction less than 35%, a history of in-stent restenosis, unsuitability for long-term anti-platelet therapy, acute myocardial infarction (MI) within 48 hours, need for concomitant valvular, vascular, or general surgery, or limited life expectancy. After PCI in ERACI III, patients were prescribed 75 mg of clopidogrel daily for three months (after a sirolimus DES) or six months (after a paclitaxel DES) and 325 mg of aspirin indefi-

nitely. After PCI in ERACI II, patients were prescribed ticlopidine for one month and aspirin indefinitely. The primary study endpoint was major adverse cardiac and cerebrovascular events (MACCE), a composite consisting of death from any cause, MI, stroke, or repeat coronary revascularization with either CABG or PCI. The endpoint of MI included Q-wave MIs related to the initial revascularization procedure, and both Q wave and non-Q-wave MIs during follow-up; all MIs required a three-fold rise in CKMB. Confirmed and suspected stent thromboses were adjudicated as previously described.[12,13] All clinical end points were adjudicated separately by an independent safety and clinical adverse events committee, a list of the study organization committee and participating centers were previously published.[8,10]

Statistical analysis

Follow-up for clinical outcomes commenced with the date of revascularization and extended to five years. Event-free survival rates were calculated by the Kaplan-Meier method. The primary comparisons were between the patients who received a DES in the ERACI III registry and (a) patients who were randomized to receive a BMS in the ERACI II trial, and (b) the patients who were randomized to receive a CABG in the ERACI II trial. Two patients randomized to CABG who did not undergo any revascularization were omitted, as they did not have a defined procedure date. Since these treatment comparisons were not randomized, we used multivariable statistical methods to adjust for possible confounding factors. We performed two analyses of each endpoint, including direct adjustment for baseline covariates in a Cox proportional hazards model among all patients, and an additional analysis in a propensity score matched subset of patients. The propensity score was constructed using a logistic model in which the outcome was receipt of a DES in the ERACI III registry. Patients randomized to BMS or CABG in the ERACI III trial were pooled in the propensity score model, since their baseline clinical characteristics were equivalent within the play of chance as a result of randomization. The logistic model included as independent predictors age, sex, diabetes, hypertension, hypercholesterolemia, smoking, prior MI, proximal left anterior descending disease, Euroscore, prior BMS implantation and unstable angina symptoms. We used a greedy matching algorithm to identify pairs of patients, one of whom received a DES and one of whom received a BMS, who had propensity scores within 0.05 units of one another. We used the same procedure to matchpatients who received a DES with patients who underwent CABG. The standard intention-to-treat analysis of the ERACI II trial data includes all patients in their originally assigned groups, whether or not they actually received their assigned treatment. In order to more closely match the analysis method applied to the ERACI III registry patients, we performed a secondary "actual treatment" analysis, in which 19 patients in ERACI II who crossed over were analyzed according to treatment received, rather than treatment assigned.

Table 1. Demographic, clinical, and angiographic characteristics by treatment.

	DES (n=225)	BMS (n=225)	CABG (n=225)*	P value
Sex (male)	188 (84%)	174 (78%)	182 (82%)	0.23
Age (years)	65.4 +/- 10.6	60.5 +/- 10.2	60.7 +/-10.3	<0.0001
Previous MI	73 (32%)	64 (28%)	62 (28%)	0.51
Hyperlipidaemia	178 (79%)	141 (63%)	132 (59%)	<0.0001
Diabetes	47 (21%)	39 (17%)	39 (17%)	0.55
Smoking	148 (66%)	122 (54%)	109 (49%)	0.001
EuroSCORE				<0.0001
High risk	32 (14%)	23 (10%)	14 (6%)	
Medium risk	152 (68%)	133 (59%)	174 (78%)	
Low risk	41 (18%)	69 (31%)	35 (16%)	
Unstable angina	155 (69%)	208 (92%)	202 (91%)	<0.0001
Left main	13 (6%)	12 (5%)	9 (4%)	0.68
Three-vessel CAD	90 (40%)	123 (55%)	128 (57%)	0.0004
Prior BMS	51 (23%)	0 (0%)	0 (0%)	<0.0001

BMS: bare metal stent. DES: drug-eluting stent. CABG: coronary artery bypass surgery. MI: myocardial infarction. CAD: coronary artery disease.
**Two patients randomized in ERACI II to CABG who did not undergo revascularization were excluded from all analyses.*

RESULTS

The study population consisted of 673 patients with multivessel coronary disease, 448 of whom were enrolled between 1996 and 1998 in the ERACI II trial and were randomized to receive either BMS (225 patients) or CABG (223 patients), and an additional 225 patients who were enrolled between 2002 and 2004 in the ERACI III registry and received a DES. At baseline, the DES group was significantly older, more likely to be hypertensive and to smoke, and less likely to have unstable angina and triple-vessel disease (**Table 1**).

One and three years outcome

One and three years results were previously reported.[8,9] Briefly, one year incidence of MACCE[8] was significantly lower in ERACI III-DES compared to ERACI II-BMS arm (p=0.005) and ERACI II-CABG (p=0.038). One year incidence of death, was similar in the ERACI III-DES (3.1%) and ERACI II-BMS (3.1%) arms, although death in ERACI II-CABG arm was significantly higher (p=0.031). The incidence of repeat revascularization was significantly lower in ERACI III-DES compared to ERACI II-BMS arm (p=0.016) and similar to the CABG arm of ERACI II (8.8% vs. 4.9%, respectively; p= ns).

At three years MACCE[9] rate was still significantly lower in ERACI III-DES (22.7%) than in ERACI II-BMS (29.8%, p= 0.015) reflecting less target vessel revascularization in DES group (14.2 vs. 24.4%; p=0.009). MACCE rates at 3 years were similar in

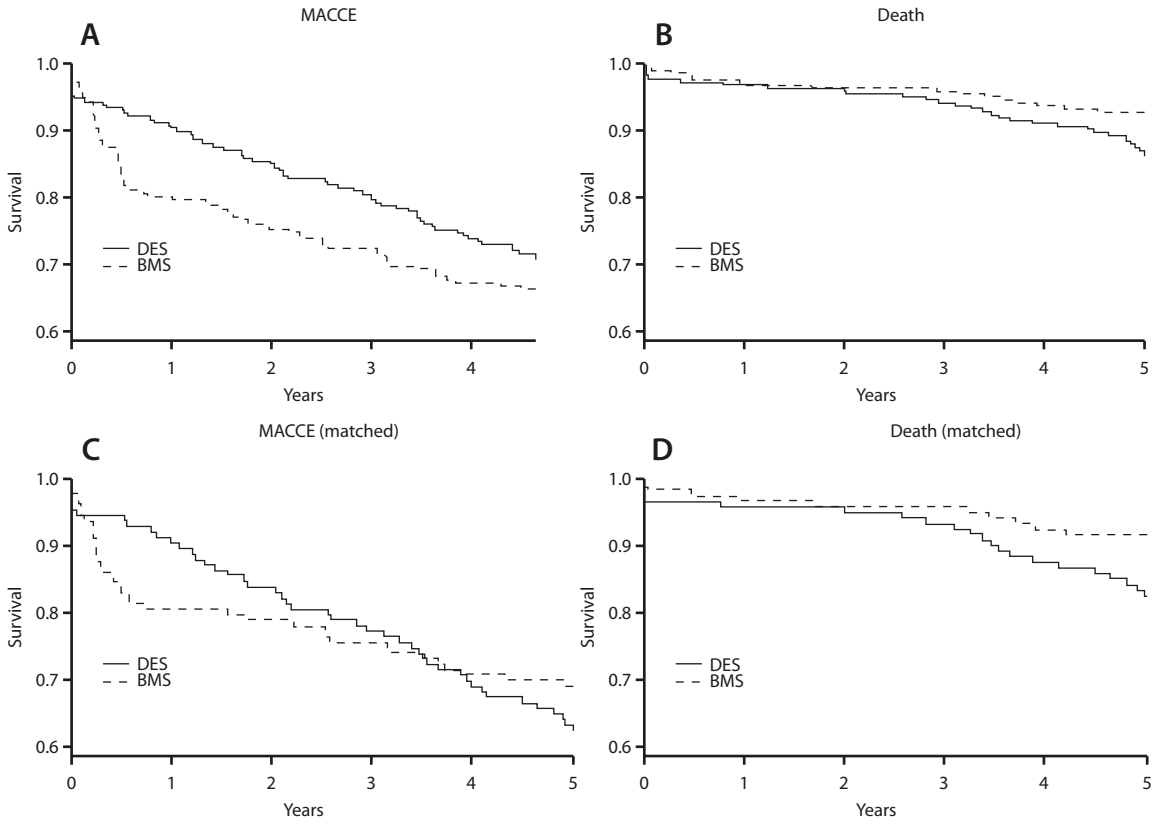

Figure 2. *Major adverse cardiovascular events (MACCE) and death in the entire group (A and B) and in matched population (C and D); after DES (solid line) and BMS (dashed line). DES: drug eluring stents, BMS: bare metal stents.*

Table 2. Long-term outcomes by treatment.

	Five-year fee event rates			Unadjusted Hazard ratio (confidence limits)	
	DES (n=225)	BMS (n=225)	CABG (n=223)	DES: BMS	DES: CABG
MACCE	66.8%	65.4%	76.4%	0.88 (0.64-1.21)	1.34 (0.94-1.91)
Death	85.6%	92.7%	89.0%	1.99 (1.09-3.63)	1.25 (0.73-2.12)
Death/MI/ stroke	78.3%	88.2%	81.8%	1.87 (1.16 -3.02)	1.11 (0.73-1.69)
Repeat revascularization	80.3%	71.0%	92.6%	0.63 (0.43-0.93)	2.81 (1.56-5.06)

BMS: bare metal stent. CABG: coronary artery bypass surgery. DES: drug-eluting stent. MI=myocardial infarction. MACCE=major adverse cardiac and cardiovascular events.

DES and CABG treated patients. Stent thrombosis was observed in 4.4% of DES treated patients.

Five years follow up results

At five years, 31 (14%) of the DES patients had died, compared with 16 (7%) of the BMS patients and 24 (11%) of the CABG patients. The composite outcome of death, MI, or stroke occurred in 47 (21%) of the DES patients compared with 26 (12%) of the BMS patients and 40 (18%) of the CABG patients. Stent thromboses were documented in 14 of the DES patients (6.2%), which were categorized as definite in six patients (2.7%), probable in one patient (0.4%), and possible in seven patients (3.1%).

DES vs. BMS

The five year event rates were lower after DES than BMS for MACCE, but higher for death and for hard cardiac events (death, MI, or stroke) (**Figure 2, Table 2).** Since use of DES was not randomized, we applied multivariable statistical methods to adjust for differences in baseline clinical characteristics. In an analysis that included all patients and adjusted directly for baseline covariates, use of DES was associated with a HR for MACCE of 0.75 (CL: 0.51-1.12, p=0.16) compared with use of BMS (**Table 3).** The outcome of all-cause mortality had a DES:BMS HR of 1.84 (CL: 0.92-3.68, p=0.09), and the endpoint of death, MI or stroke had a DES:BMS HR of 1.66 (CL: 0.95-2.88, p=0.074). There were more non-cardiac deaths among DES patients (6.7%) than BMS patients (1.8%, p=0.04). Repeat revascularization was significantly less frequent after DES than after BMS, with a HR of 0.52 (CL: 0.31-0.85, p=0.009).

We performed an alternative analysis that used propensity score matching to control for differences between DES and BMS treated patients. In this analysis, we excluded 51 patients in the DES group who had a

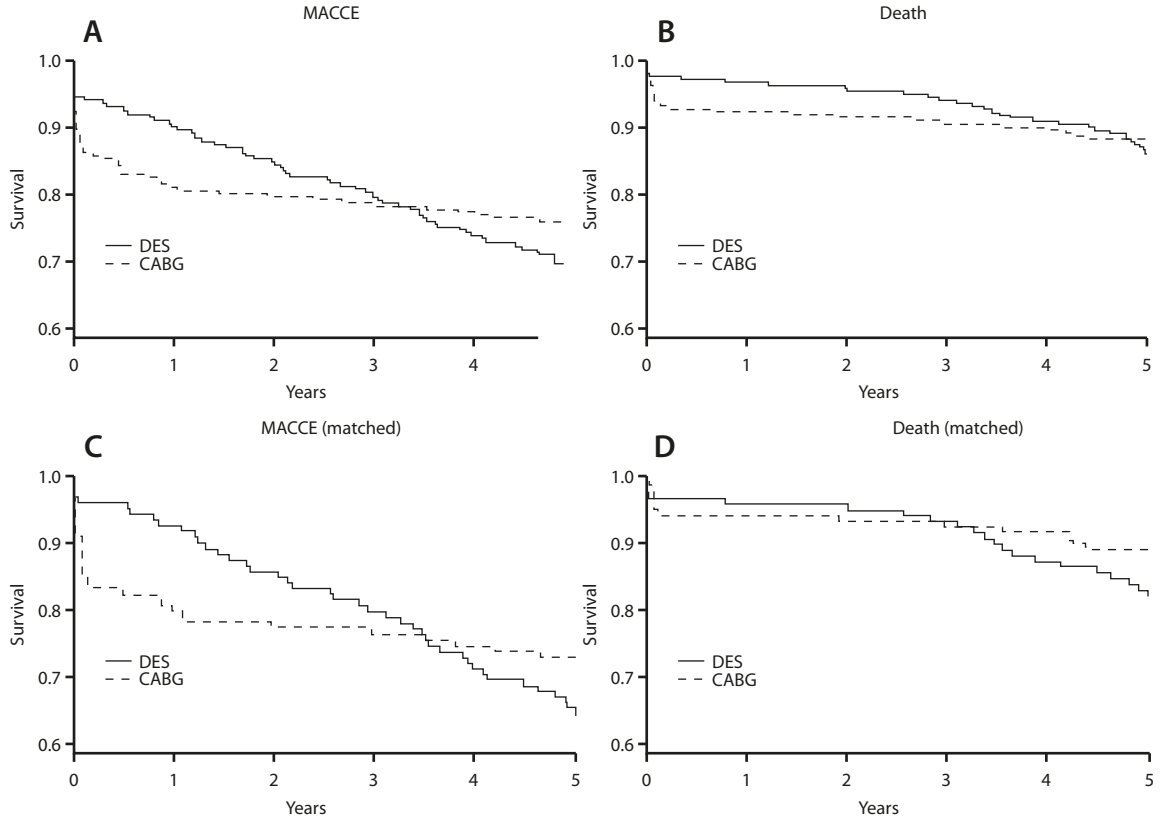

Figure 3. *Major adverse cardiovascular events (MACCE) and death in the entire group (A and B) and in matched population (C and D); after DES (solid line) and CABG (dashed line). DES: drug eluring stents, CABG: coronary artery bypass graft.*

previous PCI procedure in which they received a BMS. We were able to match 121 patients who received a DES with 121 patients who received a BMS. The point estimates of the DES: BMS hazard ratios in the propensity score matched patients were generally higher than the point estimates in the entire population albeit with wider confidence intervals due to the smaller sample size (DES:BMS HR for MACCE=1.20, CL: 0.75-1.90, p=0.45; HR for death2.53, CL: 1.10-5.83, p=0.03; HR for death, MI and stroke=3.31, CL 1.62-6.76, p=0.001; **Table 3**).

Table 3. DES:BMS Hazard Ratios (95% Confidence Limits) in Multivariable Cox Models Adjusted for Baseline Characteristics

Endpoint	All patients (n=450)	P values	Propensity score matched points (n=242)	P values
MACCE	0.75 (0.51-1.12)	0,1562	1.20 (0.75-1.90)	0,45
Death	1.84 (0.92-.3.68)	0,0864	2.53 (1.10-5.83)	0,03
Death, MI or Stroke	1.66 (0.95-2.88)	0,0744	3.31 (1.62-6.76)	0,001
Repeat Revascularization	0.52 (0.31-0.85)	0,0096	0.84 (0.48-1.47)	0,37

BMS: bare metal stent. DES: drug-eluting stent. MI: myocardial infarction. MACCE: major adverse cardiac and cardiovascular events.

Actual treatment analysis

In a secondary "actual treatment" analysis, we compared outcomes of 238 patients in the ERACI II trial population who received a BMS with the 225 patients in the ERACI III registry who received a DES. The baseline characteristics of the two patient groups were essentially unchanged from those presented in **Table 1** (data not shown). The hazard ratios comparing DES and BMS for MACCE among all patients were minimally changed in this secondary analysis (to 0.81 from 0.75), as were the hazard ratios for all-cause mortality (to 1.95 from 1.84), with similar levels of statistical significance. In the matched patient analysis, the DES:BMS HR for MACCE was also minimally changed (to 1.21 from 1.20), as was the HR for mortality (to 2.60 from 2.53), with similar levels of statistical significance.

DES vs. CABG

Five year outcomes were generally similar in patients who received a DES and patients who underwent CABG (**Figure 3, Table 2**). In a multivariable Cox model that included all patients and adjusted for baseline clinical factors, there was no significant difference in the primary outcome of MACCE between DES and CABG treated patients, with a DES:CABG

Table 4. DES:CABG hazard ratios (95% confidence limits) in multivariable Cox models adjusted for baseline characteristics.

Endpoint	All patients (n=448)	P values	Propensity score matched points (n=230)	P values
MACCE	1.03 (0.67-1.60)	0,8845	1.48 (0.90-2.45)	0,12
Death	1.33 (0.70-2.55)	0,3841	2.17 (0.89-5.29)	0,09
Death, MI or Stroke	0.90 (0.54-1.51)	0,6999	1.48 (0.81-2.69)	0,20
Repeat Revascularization	2.11 (1.05-4.24)	0,0366	2.96 (1.32-6.64)	0,01

BMS: bare metal stent. DES: drug-eluting stent. MI: myocardial infarction. MACCE: major adverse cardiac and cardiovascular events.

HR of 1.03 (CL: 0.67-1.60, p=0.95). The incidence of death and of the composite outcome of death, MI or stroke were also not significantly different between patients who had DES compared with patients who had CABG (**Table 4**). Repeat revascularization was significantly higher after DES than after CABG, with a HR of 2.11 (CL: 1.05-4.24, p=0.04). All results were similar in the subset of 230 propensity score matched patients (DES: CABG HR for MACCE=1.48, CL: 0.90-2.45, p=0.12; HR for death=2.17, CL: 0.89-5.29, p=0.09; HR for death, MI and stroke=1.48, CL: 0.81-2.69, p= 0.20; **Table 4**).

DISCUSSION

In this non-randomized comparison, patients with multivessel coronary disease treated with a drug-eluting stent, bare metal stent or CABG had similar incidence of MACCE at five years of follow up. However, patients treated with DES had higher than expected risk of hard cardiac events over the subsequent five years compared with patients treated with a BMS, despite a substantial reduction in the rate of repeat coronary revascularization procedures. These differences do not appear to be explained by the more adverse risk profile among DES treated patients (**Table 1**), as multivariable statistical adjustment for baseline factors did not materially affect the results (**Table 3**).

The reasons for these results remain uncertain. In light of current understanding of the importance of prolonged dual antiplatelet therapy after DES implantation,[14,15] in retrospect it is possible that patients who received a DES in the ERACI III registry had clopidogrel treatment discontinued earlier than is now recommended. Unfortunately, we do not have data on the use of clopidogrel in follow-up, so we could not test this hypothesis directly. Alternatively, the higher rate of hard cardiac events may be due to the more adverse risk profile at entry among the DES patients (**Table 1**); although we applied multivariable adjustment methods, they can correct only for measured confounding factors, and unmeasured differences between the DES and BMS groups may have contributed to the higher rate of adverse outcomes in the DES group. Finally, it is possible that participation in the randomized ERACI II trial may have led to closer monitoring and more aggressive drug treatment among the BMS treated patients than among the DES treated patients in the ERACI III registry.

During late outcome, some randomized studies have also reported an increased incidence of hard cardiac events after one year of follow-up among patients who received a first generation of DES designs.[16-19] Pooled data from the SIRIUS trials showed a higher rate of hard cardiac events beyond one year among patients with diabetes receiving DES compared with patients with diabetes who received a BMS, despite a lower rate of restenosis.[17]

Similarly, the SYNTAX trial has reported an incremental risk for death, cardiac death and myocardial infarction between first and third year of follow-up among patients receiving a DES, which was significant among patients with three-vessel disease. The SYNTAX trial also reported a 7.4% rate of stent thrombosis at three years,[19] and the ARTS II study reported a 9% rate of definite, probable, or possible stent thrombosis over five years,[20] each of which is higher than the 6.2% rate of stent thrombosis over five years among DES treated patients in this study. Patients in our study who received a DES had a significantly lower rate of repeat revascularization over five years than patients who received a BMS. This reduction is consistent with the outcomes reported after one to three years of follow up in randomized trials of DES vs. BMS,[1,2] as well as the lower rate of MACCE in the DES group at one and three year of follow-up.[8,9]

We also found little difference between DES and CABG with respect to five year outcomes among patients with multivessel coronary disease. The study had relatively limited statistical power, however, to detect modest yet clinically important differences in the rate of hard cardiac outcomes such as death or the composite outcome of death, MI or stroke, although the sample size was small and the propensity score diminished it more. Large randomized trials comparing the use of CABG and DES for multivessel coronary disease are ongoing,[5-7] and should clarify the comparative effectiveness of these alternative modes of coronary revascularization. Thus far, only short-term outcomes are available from a few of these studies. The higher rate of repeat revascularization after DES compared with CABG that we observed in this study confirms the recent reports of the SYNTAX[5] and CARDia[6] trials and has been reported consistently after each technologic improvement in PCI technique.[21]

This study has a number of limitations. The patients underwent DES several years later than patients underwent BMS and CABG. The non-concurrent patient accrual may have introduced clinical differences between these patient cohorts be-

yond those recorded in the baseline characteristics (**Table 1**). Any unmeasured differences may have affected the outcomes observed. In particular, we do not have data on the SYNTAX angiographic score, which appears to be a useful predictor of prognosis after PCI, and thus may not have completely controlled for differences in the extent of coronary disease. Lastly, we recognized that results of this study are in disagreement with other registries reported long term outcome with DES and BMS[20,22] and we don't have an explanation for these discordances. However, the increased rate of death/MI beyond one year observed in ERACI III is accorded with other studies with similar DES designs in complex lesion subsets.[17,19,23] In agreement, at 3 years of follow up, in SYNTAX trial, DES patients treated with Taxus stents compared to CABG patients had significant higher incidence of cardiac events including raise of cardiac death and MI, and these findings were not observed at the first year of follow up.[5] Furthermore, in SYNTAX the subgroup of patients with three vessels disease, incidence of death, MI and the composite of death/MI/stroke were also significantly higher in the PCI group.[19] More over a lack of clinical improvement with first DES designs at late follow up have been also seen in a large registry of PCI and CABG from USA recently published; in that study PCI in patients older than 65 years had significant increase rate of death at 4 years compared to CABG in spite of use of first DES designs in 78% of cases.[24] In the past, previous meta-analysis from randomized studies before DES era has shown similar trend in elderly patients,[25] thus, these new findings suggested a lack of clinical improvement with DES and strengthen results presented here. Furthermore, and in agreement with us, differences in favor to CABG was not present during the first year of follow up.

Finally, first generation DES were used in this study and introduction of later generation DES might have led to different results as was reflected by recent randomized data[26,27] which observed a significant lower incidence of cardiac events including cardiac death and MI in those patients treated with "best in class" DES design.

In conclusion, patients included in the ERACI III registry at five years of follow up had similar incidence of MACCE independently which revascularization strategy was selected for. The results of this study underscore the importance of weighing the reduction in repeat procedures against the potential for increased late risk of death, MI and stroke.

RESUMEN

Comparación de la efectividad a cinco años de seguimiento de los pacientes tratados con stents farmacológicos, stents convencionales y cirugía de revascularización miocárdica: resultado final del estudio ERACI III

Objetivos. Comparar los resultados a cinco años de los pacientes tratados con *stents* liberadores de fármacos (DES), *stents* de metal desnudo (BMS) o cirugía de revascularización miocárdica (CABG).

Antecedentes. Los DES reducen la tasa de revascularización en comparación con el BMS, pero pueden predisponer la *stent* trombosis. Los resultados de los DES en el seguimiento clínico a largo plazo en pacientes complejos en comparación con BMS o CABG no están definidos.

Métodos. Se compararon los resultados a cinco años de 225 pacientes que recibieron primera generación de DES con los de 448 pacientes randomizados en un ensayo previo donde fueron tratados con BMS o CABG. Se utilizó análisis multivariado y el método de *propensity score* para homogeneizar las variables entre los tres grupos.

Resultados. En comparación con los pacientes que recibieron un BMS, los pacientes que recibieron un DES tuvieron similares eventos cardíacos adversos mayores (MACCE), con DES:BMS (cociente de riesgo 0,75, LC: 0,51-1,12), pero mayor mortalidad (cociente de riesgo 1,84, IC: 0,92-3,68 (y menor número de revascularizaciones (cociente de riesgo 0,52, IC 0,31- 0,85 (. En comparación con los pacientes que recibieron CABG, los que recibieron DES no presentaron diferencias significativas en la tasa de eventos cardíacos adversos (p=0,88) o en la mortalidad (p=0,38), pero tuvieron más revascularizaciones (p=0,03).

Conclusiones. El uso de DES de primera generación puede estar asociado a mayor riesgo de eventos cardíacos en pacientes con lesiones complejas.

Palabras clave: enfermedad coronaria, angioplastia coronaria, *stents* liberadores de fármacos, cirugía de revascularización miocárdica, *stent* trombosis.

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