Five-year follow-up of the ERACI IV-score study of modified SYNTAX as the ERACI risk score of patients with multivessel and left main coronary artery disease

Cinco años de seguimiento del estudio ERACI IV - score de SYNTAX modificado como score de riesgo ERACI para pacientes con enfermedad de múltiples vasos y enfermedad de tronco de la coronaria izquierda

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ABSTRACT

Objective: To compare the long-term follow-up ofa population with coronary artery disease treated conservatively with percutaneous coronary intervention (PTA) with second-generation drug-eluting stents (DES 2) compared to first-generation drug-eluting stents (DES 1).

History: Although DES 2 improved the safety and efficacy profile compared to DES 1, the disease progression of patients with multivessel coronary artery disease (MVD) including the left main coronary artery treated with PTA is still controversial

Methods: A total of 225 patients with MVD and a 72-month follow-up were prospectively included in a registry. These patients were treated with DES 2 and represented the ERACI IV registry. They were compared to 225 patients treated with DES 1 from the ERACI III trial. Patients with a clinical indication for myocardial revascularization with PTA with DES were included in the study. The study primary endpoint was a composite ofmajor adverse cardiovascular and cerebrovascular events (MACCE) including all-cause mortality, acute myocardial infarction (AMI), stroke, and new revascularization. The PTA strategy in the ERACI IV registry excluded small vessels and the management of intermediate lesions. Keeping up with this PTA strategy, a new angiographic risk score called ERACI score (ES) was built. Baseline and residual data were compared tothe Syntax score (SS). The study primary endpoints were used in a crude and adjusted comparison.

Results: ES was significantly lower compared to the SS (22.2 and 27.7;P =.0004). Residual ES and SS were also < 3.5 vs 8.7, respectively; P = .003. The 5-year composite endpoint of death, AMI, stroke, new revascularization, and MACCE was significantly lower in the ERACI IV compared to the ERACI III in a non-adjusted (P = .001; P = .01 andP < .001, respectively), and population adjusted way (P < .001; P < .01; andP < .001 respectively).

Conclusions: Patients with complex lesions treated with DES 2 as part of a conservative implantation strategy showed a significantly lower rate of adverse events at 5-year follow-up.

Keywords: *coronary artery disease, DES, drug-eluting stent, MVD, multivessel coronary artery disease, SYNTAX score,* ***ERACI score,*** *PTA, percutaneous transluminal angioplasty, complete revascularization.*

RESUMEN

Objetivo. Comparar el seguimiento a largo plazo en una población con enfermedad coronaria entre una estrategia conservadora de intervención percutánea coronaria (ATC) con stents con drogas de segunda generación (DES 2) y otra con stents con drogas de primera generación (DES 1).

Antecedentes. Aunque los DES 2 mejoraron la seguridad y eficacia comparados con los DES 1, en la evolución de los pacientes con enfermedad de múltiples vasos (EMV) incluyendo el tronco de la coronaria izquierda, el tratamiento con ATC sigue siendo controvertido.

Métodos. Se incluyeron prospectivamente 225 pacientes con EMV con un seguimiento de 72 meses en un registro. Estos pacientes fueron tratados con DES 2 y representaron al registro ERACI IV y fueron comparados con 225 pacientes tratados en DES 1 que fueron pacientes del estudio ERACI III. Los pacientes fueron incluidos con indicación clínica de revascularización miocárdica con ATC con DES. El punto final primario fue la incidencia de eventos cardiovasculares mayores (MACCE), definido como mortalidad de cualquier causa, infarto agudo de miocardio (IAM), accidente cerebrovascular (ACV) y nueva revascularización. La estrategia de la ATC en el registro ERACI IV excluyó pequeños vasos y el tratamiento de lesiones intermedias. Siguiendo con esta estrategia de ATC, se construyó un nuevo score de riesgo angiográfico llamado ERACI score (ES), los datos basales y residuales se compararon con el SYNTAX score (SS). Los puntos finales primarios fueron comparados en forma cruda y ajustada.

Resultados. El ES fue significativamente menor que el SS (22,2 vs. 27,7; p=0,0004). El score residual de ES fue también menor que el de SS (3,5 vs. 8,7; p=0,003). A 5 años, el punto final combinado de muerte/IAM/ACV, nueva revascularización y MACCE fue significativamente menor en el ERACI IV que en el ERACI III en forma no ajustada (p=0,001; p<0,01 y p=<0,001, respectivamente) y en población ajustada (p=<0,001; p<0,01 y p<0,001, respectivamente).

Conclusiones. Los pacientes con lesiones complejas con DES 2, con una estrategia de implantación conservadora, presentaron en forma significativa una incidencia menor de eventos adversos a 5 años de seguimiento.

Palabras clave: *enfermedad coronaria, DES, enfermedad de múltiples vasos, SYNTAX score, ERACI score, ATC, revascularización completa.*

Revista Argentina de Cardioangiología Intervencionista 2022;13(4):174-181. https://doi.org/10.30567/RACI/202204/0174-0181

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Conflicts of interest: Dr. Ming Zheng is an employee of MicroPort. The other authors do not report conflicts of interest with respect to this publication.

Received: 28/09/2022 | Accepted: 30/11/2022

INTRODUCTION

Over the past few years, the revascularization strategy of patients with multivessel coronary artery disease has been the center of attention of multiple controlled clinical trials (CCT) to define the best therapeutic alternative between percutaneous coronary procedures and myocardial revascularization surgery (MRS). Several CCTs compared PTA with drug-eluting stents (DES) vs MRS in several subgroups of patients with complex disease like 3-vessel coronary artery disease, unprotected left main coronary artery disease, and in diabetic patients. (1-7)

Several CCTs compared second-and-third generation vs first-generation DES. All these trials showed a significant reduction of late cardiovascular events including cardiac death and/or acute myocardial infarction (AMI), late and very late thrombosis with new-generation stents (8-10). One of these studies major limitations is that they were conducted in a selected population. Also, that there was limited information on whether these devices could improve disease progression in the patients included in the SYNTAX and FREEDOM clinical trials with MVD, unprotected left main coronary artery, in diabetic patients, and in those with intermediate or high SS. The long-term results of CCT between DES and MRS were controversial in the PTA group including a higher mortality rate in some subgroups of patients. (11)

The results favorable to MRS did not change with the introduction of DES 2 and new-generation stents as the BEST, NOBLE, and EXCEL trials confirmed. Regardless of the design of DES, these CCT revealed an aggressive strategy of PTA followed by stratification using SS to achieve complete revascularization.

As a matter of fact, the SYNTAX (DES 1) and BEST clinical trials (new-generation DES 2) included all intermediate and small-vessel lesions as part of a revascularization strategy, which is suggestive that the design of the stent was not the only reason for this unfavorable progression(12-14).

The ERACI IV was a prospective, multicenter, observational trial of patients with DES 2 treated with a conservative PTA strategy in stent implantation compared to the ERACI III, a similar population study where patients were treated with DES 1. During the trial patient recruitment process, a new anatomical angiographic score was built, the ERACI risk score—both baseline and residual RES—by modifying the Syntax score from www.syntaxscore.org, both baseline and residual (SS and RSS). This re-categorized patients into a lower risk anatomical angiographic class turning PTA into a more viable option compared to MRS for many more patients.

The 2- and 3-year follow-up short-and-mid-term results published revealed low rates of adverse events (15-17).

The objective of this study is to expose the long-term follow-up clinical outcomes (up to 5 years) and assess whether the conservative strategy of reaching reasonable yet incomplete revascularization after residual score-based PTA was associated with acceptable results at long-term follow-up.

MATERIALS AND METHODS

The ERACI IV is a prospective and multicenter clinical trial to assess a cobalt-chromium rapamycin-release stent (Firebird2™, Shanghai MicroPort Medical (Group) Co., Ltd., Shangahi, China). The Firebird2™ is a second-generation

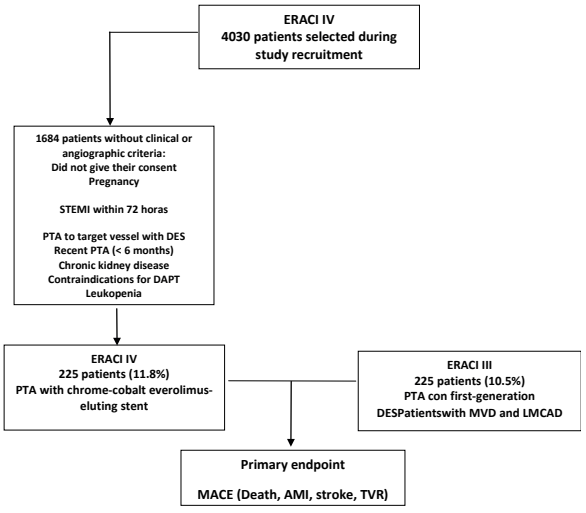


Figure 1. *Study population and design. AMI, acute myocardial infarction; angioplasty;DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MACE, major adverse cardiovascular events; PTA, percutaneous transluminal.*

stent mounted on a cobalt-chromium platform. Patients met the inclusion criteria in the presence MVD including left main coronary artery disease, an indication for myocardial revascularization, evidence of overt myocardial ischemia, and evidence of severe coronary obstruction (stenosis ≥ 70% through visual estimation) in the culprit vessel. The patients' exclusion criteria were previous PTA over the past 6 months with bare metal stent (BMS), patients with previous PTA with DES in the culprit and non-culprit vessel, acute myocardial infarction 72 hours prior to admission, poor left ventricular ejection fraction ≤ 35%, 2 or more chronic total coronary occlusions, severe valve disease, previous stroke, intolerance to aspirin and thienopyridines, blood dyscrasia or patients ineligible to receive long-term antiplatelet therapy, patients treated with non-cardiac surgery due to brief or low life expectancy. The study protocol (18) was previously published with the study design and is shown on the supplementary data.

Eleven months later, 4030 patients were assessed for prospective inclusion in the study. A total of 1917 patients were initially selected and, finally, 233 patients were included in the registry. However, 8 patients who did not meet the study clinical or angiographic criteria were excluded. Therefore, a total of 225 patients were selected according to the population of the ERACI III that included a similar number of patients treated with DES 1 like the Cyher™, Cordis, Johnson & Johnson, Miami Lakes, FL, and Taxus Express™ (Boston Scientific, Boston, MA, United StatesI (figure 1).

The study primary endpoint was the presence of major adverse cardiovascular and cerebrovascular events (MACCE) with DES 2 and then a comparison with patients from the ERACI III registry, DES 1.

Each composite endpoint of MACCE was also reported as secondary endpoints.

All patients received a 100 mg oral aspirin formulation indefinitely 1 hour prior to cardiac catheterization with a load dose of a thienopyridine (P_2Y_{12}), which could be clopidogrel

600 mg, prasugrel 60 mg or ticagrelor 180 mg. During PTA, the patients received 100 U/kg of unfractionated heparin. Patients could also receive enoxaparin or bivalirudin in anticoagulant doses depending on their routine prescriptions and on the treating interventional cardiologist.
In the ERACI IV, dual antiplatelet therapy (DAPT) was mandatory for 6 months. However, it was strongly advised for the entire follow-up period with clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg every 12 hours. As part of the protocol, prasugrel or ticagrelor should be the first choice in patients with diabetes, left main coronary artery disease or high ERACI scores.
The primary endpoint was recorded at 30-day, 6-,12-,18-,36- and 60-month follow-up.
Secondary endpoints included the rate of target vessel revascularization (TVR) and target lesion revascularization (TLR), and the presence of stent thrombosis (ST). The follow-up of the patients was conducted within the first follow-up year through personal visits and, then, also through personal visits, phone calls or contact with the general practitioner.

Definitions of endpoints

MACCE was defined as a composite of all-cause mortality, acute myocardial infarction, stroke, and repeat target vessel revascularization (TVR) or non-target vessel revascularization (non-TVR). During the index PTA, only STEMI was registered. Target lesion failure (TLF) was defined as cardiac death (when death could not be defined exactly it was assumed as cardiac death), AMI, and target lesion revascularization (TLR). TVR stands fro target vessel revascularization. ST was defined based on the definition established by the Academic Research Consortium. DAPT was mandatory for all the study patients. A blind independent committee adjudicated all the MACCE and events reported including ST. An independent data monitoring committee was responsible for the follow-up of all adverse event reports, and assessment of data safety.
The study completed all regulatory steps based on the requirements established by the Argentine regulatory authorities. The study was approved by each participant center ethics committee. All patients signed the informed consent form before being included in the study(18).
The study was sponsored by Microport Inc, Shangai, China during the 3-year follow-up. However, the 5-year follow-up was conducted by investigators.

ERACI Risk Score-based PCI strategy

The ERACI IV registry revascularization strategy was planned before each procedure to achieve complete functional revascularization. PTA was considered functionally complete in the absence of residual lesion ≥ 70 % in a major epicardial vessel, and all stenoses initially considered severe were successfully treated with stents. Lesions with chronic total coronary occlusions of an akinetic territory of the compromised ventricular sector were not approached. The staged approach strategy was allowed. Management of an unscheduled coronary vessel in the early strategy after the baseline PTA was left to the operator's discretion. Intermediate lesions (50% up to 69%) were not approached regularly, and stents were only indicated in severe lesions through visual estimation. In all bifurcation lesions, the use of provisional stenting was advised. Management of severe lesions in vessels ≤ 2.0 mm was strongly ill-advised and often not attempted.
In patients from the ERACI IV we estimated the anatomical risk score SS using the calculator from the SS website. Let's remember that the SS calculator requires entering all coronary lesions including lesions ≥ 50% in vessels ≥ 1.5 mm. We used a modified definition method where we only scored lesions ≥ 70% in vessels > 2 mm and defined this new strategy as the risk score of our ERACI (ERS) cath lab. Bifurcations, trifurcations, and chronic total coronary occlusions were also included. Restenosis was scored as a heavily calcified lesion. All the remaining anatomical variables were included in the early SS procedure and then incorporated to our cath lab new anatomical score like the ESR. This score has already been described above (19-20).
With this new score in the ERACI IV, 82.7% of the patients were included in the low or intermediate ES while only 17.2% had a high-risk score. However, in the baseline SS the elevated risk score reached up to 33.8%. We used a post-hoc analysis to assess the predictive value of residual lesions in complete revascularization using the value of the angiographic residual risk score defined with cut-off values < 6 in residual SS scores and < 8 in residual ES scores.
Complete functional revascularization was defined post-hoc when the angiographic residual score was < 6 in RES or < 8 in RSS that was classified as reasonable incomplete revascularization. Arbitrary agreement between residual SS and residual ES scores was agreed of no more than 2 points of difference. All the risk scores were reported to our core lab where each angiographically scored lesion was independently studied (HP, JM, and AER).

Statistical analysis

The ERACI IV sample size was estimated based on a similar population included in the ERACI III registry in the DES branch. In this study, a rate of primary endpoint of MACCE at 1-year follow-up in patients treated with DES 1 was reported (where the rates of MACCE and composite endpoint of death/AMI/stroke were 12% and 7%, respectively). We should mention that, compared to DES, DES 2 like the Xcience V (Abbott, Chicago, Illinois, United States), the Promus Element (Boston Scientific, Marlborough, Massachusetts, United States), and the Endeavor Resolute (Minneapolis, Minnesota, United States) reported, in many cases, a lower rate of MACCE of 50% within the first and second years in a two-tailed test due to differences in the independent bimodal proportion with P values of .05. We estimated that if we included 225 patients, the study statistical power should have been 80% to detect differences in that class of stents. Continuous variables were compared using the ANOVA test with Bonferroni correction. Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were expressed as means of SD while categorical variables were expressed as percentages. Event-free survival at follow-up was obtained using the Kaplan-Meier curves and compared using the long-rank test. Since comparison of these treatments was not randomized, we used multivariate statistical methods to adjust for all the possible confounding factors. We conducted a propensity score analysis to study results in a homogeneous population. Propensi-

ty score matching was conducted using a logistics model. Logistics model included independent predictors such as age, sex, diabetes, hypertension, dyslipidemia, smoking, previous infarction, damage to the proximal third of left anterior descending coronary artery, three-vessel disease, left main coronary artery disease, previous revascularization, and unstable angina. We used an intense matching algorithm to identify pairs of patients, one of whom received DES 1 and the other received the DES 2. To assess the predictive value of incomplete revascularization determined by residual ES, a Cox regression analysis (uni and multivariate) was conducted using SPSS version 17.0 to determine independent predictors of results at follow-up (all the variables introduced *en bloc* in one step). Statistically significant variables after the univariate analysis and clinically significant covariables including all demographic, clinical, angiographic, and procedural variables were included in the model.

RESULTS

The clinical, demographic, angiographic, and procedural characteristics of the studies are shown on table 1. In a brief comparison between the 2 registries, the ERACI IV DES 2 had more diabetic patients (P = .01), more patients with angina IIB/IIIC according to Braunwald classification (P < .001), more 3-vessel disease and left main coronary artery disease (P = .003), and longer stents per patient (P < .001). Compared to the ERACI III DES 1 there were more elderly patients (P = .02) and with dyslipidemia (P = .04). All the remaining clinical, demographic, angiographic, and procedural variables were similar between both studies. The ERACI IV used 1.8 stents per patient. A total of 27.2% of the patients received overlapping stents while 14.2% of the patients were treated in bifurcation. Angiographic complete revascularization was achieved similarly in both groups (48% in the ERACI III and 50.2% in the ERACI IV; P = .63).

In the ERACI IV registry, patients were categorized as low, intermediate, and high-risk patients in 33.8%, 32.4%, and 33.8%, respectively. However, with the ES was used, patients with low scores went up to 54.9%, the intermediate group dropped down to 27.9% while only 17.2% remained at high risk. All patients from both registries were on DAPT at hospital discharge. In the ERACI III, clopidogrel was the only P_2Y_{12} receptor inhibitor available. In the ERACI IV, clopidogrel, prasugrel, and ticagrelor were used in 58.7%, 27.2%, and 14.1% of the patients.

1-, 2-, and 3-year follow-up

1-, 2-, and 3-year follow-up periods were reported in the ERACI IV compared to the ERACI III (15-17) previously reported. DES 2 had significantly lower rates of all-cause mortality, death/AMI/stroke, new revascularization, and MACCE compared to patients from the ERACI III treated with DES at 1 year (P = .03; P = .001; P < .001; P < .001, respectively).

At 2-year follow-up, DES 2 had lower rates of death/AMI/stroke (P = .01), new revascularization (P = .003), and MACCE (P = .001).

At 3-year follow-up, DES 2 had lower rates of AMI, composite endpoint of death/AMI/stroke, new revascularization, and MACCE (P = .01; P < .001; P < .001, and P < .001, respectively).

TABLE 1. Baseline demographic, clinical, angiographic, and procedural characteristics.

	ERACI III	ERACI IV	*P value*
Age	65.5 ± 10.6	63.9 ±	0.06
Masculine sex	83.6	85.6	0.89
Previous myocardial infarction	32.4	33.3	0.68
Diabetes mellitus	20.9	30.7	0.02
Previous revascularization	22.7	34.7	0.007
Arterial hypertension	79.6	78.7	1.00
Dyslipidemia	79.1	66.7	0.04
Peripheral vascular disease	11.6	6.7	0.07
Unstable angina	40.7	64.2	<0.001
Left main coronary artery disease	5.8	9.8	0.11
3-vessel + LMCAD	38.2	54.3	0.003
Number of stents per patient	1.79±0.7	1.80±0.9	0.8
Syntax Score	NA	27.7±11.3	NA
Low and intermediate Syntax score	NA	66.2	NA
High Syntax score	NA	33.8	NA
Modified ERACI score	NA	22.2±11	NA
Low and intermediate ERACI score	NA	82.7	NA
High ERACI score	NA	17.2	NA
Residual Syntax score < 8	NA	48	NA
Residual ERACI score <8	NA	93.5	NA
Residual Syntax score <6	NA	35	NA
Residual ERACI score <6	NA	80	NA

ST was not significantly different between the ERACI III and the ERACI IV (3.1% and 0.9%; P = .18). Very late ST was not reported in patients from the ERACI IV.

Final follow-up results

At 5-year follow-up, patients from the ERACI III had longer follow-ups (93.3% vs 81.2%, P = .02). However, duration of follow-up was longer in the ERACI IV (60 ± 16.8 months in the ERACI III, and 72.6 ± 18.2 months in the ERACI IV; P < .001).

At 5-year follow-up, the survival curves of death/AMI/stroke and MACCE were significantly better with the DES 2 (figure 2). Since these studies were not randomized, homogenization was attempted using propensity score matching to control for the differences between patients treated with DES 2 and those treated with DES 1. We ended up pairing 108 patients who received DES 2 with other 108 patients who received DES 1. All primary endpoints and each component were significantly lower in the ERACI IV with DES 2 (death, AMI, death/AMI/stroke, and MACCE), which means that less event progression was seen in both an adjusted and unadjusted way in the population (table 2) where we can also see the progression of events in both groups at 1-, 2-, 3-, and 5-year follow-up.

The rate of new revascularization was 19.6% vs 12%, the composite endpoint of death/AMI/stroke was 22.7% vs 9.3% (P = .001), and the rate of MACCE was 33.8% and 18.7% (P < .001). All these rates were significantly lower in the ERACI IV with DES 2 compared to the ERACI III with DES 1. When homogenization of the population was attempted using propensity score matching, the composite endpoint of death/AMI/stroke was seen in 25.9% vs 5.6% (P < .001), the rate of repeat revascularization was 22.2% vs 9.3% (P = .01), and the rate of MACCE was 38.9% vs 13.9% (P < .001), all statistically significant in favor of ERACI IV with DES 2 (table 2).

Table 3 details cardiovascular event progression at 1-, 2-, 3-, and 5-year follow-up.

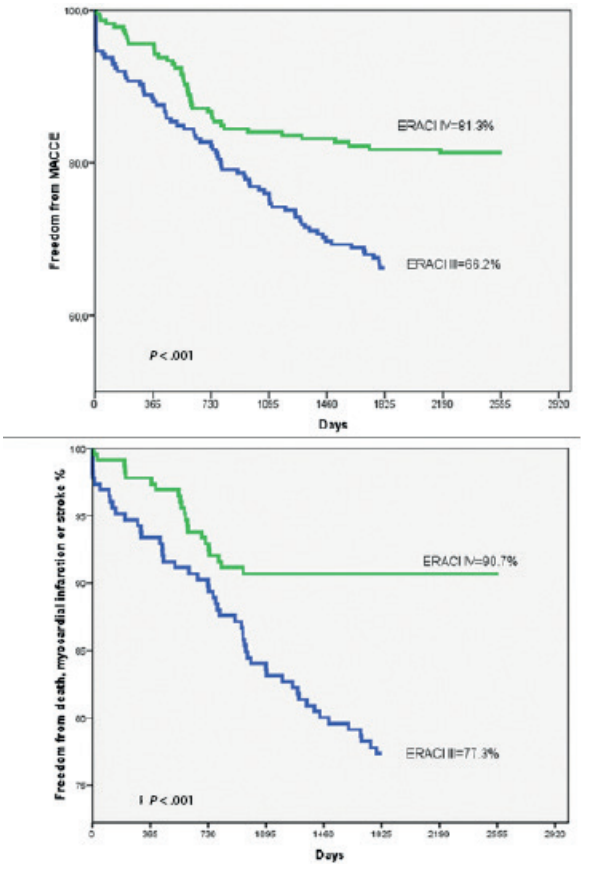


Figure 2. *Curves showing the 5-year follow-up of MACCE and composite endpointsof death, AMI, and stroke. AMI, acute myocardial infarction, stroke; MACCE (major adverse cardiovascular and cerebrovascular events, all-cause mortality acute myocardial infarction, stroke, and TVR); TVR, target vessel revascularization.*

Diabetic patients

At 1-, 2-, and 3-year follow-up significant differences of adverse events were reported among diabetic patients from the DES 2 and the DES 1 groups. Differences that were reported at 5-year follow-up (figure 3). Patients treated with DES 2 had significantly lower rates of death, the composite endpoint of death/AMI/stroke, new revascularization, and MACCE compared to DES1 (P = .002, P = .002, P = .014, and P < .001, respectively).

Multivariate analysis

We analyzed independent predictors of primary endpoints (MACCE) using a multivariate Cox regression analysis. The 2-year univariate analysis confirmed previous revascularization, hypertension, peripheral vascular disease, family history, and hereditary family history. Groups treated with DES were associated with MACCE and included in a Cox regression model.

At 2-year follow-up, DES 1 (ERACI III) (OR, 2.46; CI, 1.25-4.75; P = .08) was the only predictor of poor disease progression. At 5-year follow-up—as shown on table 4—the DES group (OR, 3.24; CI, 1.82-5.78; P < .001), presence of diabetes (OR, 054; CI, 0.30-0.97; P = .04), and 3-vessel disease (OR, 0.60; CI, 0.34-1.03; P = .06) were independent predictors of poor disease progression.

Although we only analyzed DES 2 group, we included 21 different demographic, clinical, angiographic, and procedural variables into a model that included baseline and residual SS and ES scores. No independent predictors of poor disease progression in the multivariate analysis were found.

TABLE 2. Propensity score analysis (matched population).

%	ERACI III n=108 (%)	ERACI IV n=108 (%)	*P* value
All-cause mortality	18 (16.7)	4 (3.7)	.002
Acute myocardial infarction	14 (13.0)	2 (1.9)	.002
Nonfatal stroke	3 (2.8)	0 (0.0)	.12
Death, AMI or stroke	28 (25.9)	6 (5.6)	<.001
Unscheduled revascularization	24 (22.2)	10 (9.3)	.009
MACCE	42 (38.9)	15 (13.9)	<.001

MACCE (death, acute myocardial infarction, stroke, and unscheduled revascularization).

TABLE 3. Cumulative events at 1-, 2-, and 5-year follow-up.

	ERACI III n=225 (%)	ERACI IV n=225 (%)	*P* value
All-cause mortality			
1 year	7 (3.1)	1 (0.4)	.03
2 years	7 (3.1)	5 (2.2)	.56
3 years	13 (5.7)	6 (2.7)	.07
5 years	31 (13.8)	12 (5.3)	.002
Acute myocardial infarction			
1 year	6 (2.7)	1 (0.4)	.057
2 years	10 (4.4)	3 (1.3)	.049
3 years	14 (6.2)	4 (1.8)	.01
5 years	23 (10.2)	8 (3.6)	.005
Nonfatal stroke			
1 year	5 (2.2)	0 (0)	.07
2 years	7 (3.1)	1 (0.4)	.07
3 years	7 (3.1)	2 (0.9)	.23
5 years	9 (4.0)	2 (0.9)	.03
Death/Acute myocardial infarction/Stroke			
1 year	15 (6.7)	2 (0.9)	.001
2 years	21 (9.3)	8 (3.6)	.013
3 years	31 (13.7)	11 (4.9)	< .001
5 years	51 (22.7)	21 (9.3)	< .001
Target vessel revascularization			
1 year	20 (8.9)	4 (1.8)	.001
2 years	26 (11.6)	9 (4.0)	.003
3 years	32 (14.2)	12 (5.3)	< .001
5 years	44 (19.6)	27 (12)	.01
Major adverse cardiovascular events			
1 year	27 (12)	5 (2.2)	< .001
2 years	38 (16.9)	15 (6.7)	.001
3 years	51 (22.7)	21 (9.3)	< .001
5 years	76 (33.8)	42 (18.7)	< .001

Complete revascularization

Residual SS and residual ES were significantly different. This study mean residual SS was 8.7 ± 5.9, which is significantly higher compared to residual ES of 3.5 ± 4.6 (P = .003). In addition, concordance was found in only 34.4% of residual SS and ES. Also, only 35% of the patients had residual SS < 6 compared to 80% if residual ES was used (P < .001). Also, if cut-off values < residual 8 were used, 48% of the patients were included with SS, which went up to 93.5% if ES was used (P = .002) (figure 4).

The number of residual SS of the ERACI IV matched the degree of complete angiographic revascularization obtained after the PTA. On the contrary, residual ES was consistent with complete functional revascularization.

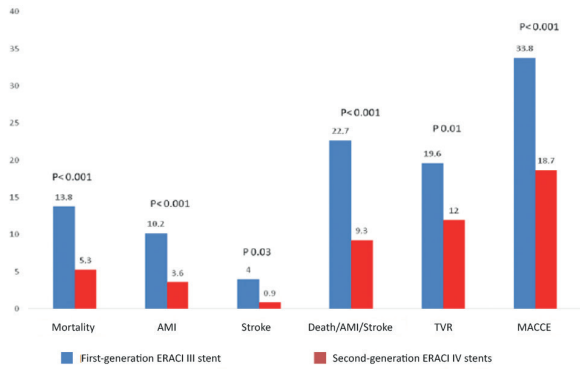
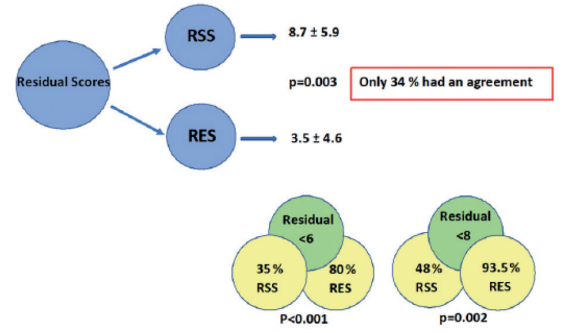


Figure 3. *Primary and secondary endpoints at 5-year follow-up. AMI, acute myocardial infarction; MACCE, major adverse cardiovascular and cerebrovascular events.*



The RSS numbers are consistent with the degree of complete revascularization achieved after angioplasty. RES is associated with complete functional revascularization. RSS, residual Syntax score; RES, residual ERACI score.

Figure 4. *Complete revascularization based on the residual score after angioplasty.*

DISCUSSION

The main results of this prospective, multicenter, and observational study of patients with MVD including the left main coronary artery demonstrated a low rate of MACCE, composite endpoint of death/AMI/stroke, and new revascularization in patients treated with DES 2 at 5-year-follow-up.

However, although the rates of MACCE went up at follow-up, they remained lower compared to a cohort study of high-risk patients, and these advantages were seen in non-adjusted and adjusted patients.

When DES 2 were included in the routine clinical practice, they improved safety significantly compared to DES 1 regarding poor stent apposition and stent strut coverage, which were soon removed due to a significant low rate of late and very late ST and need for long-term DAPT (7-10).

However, despite this improvement, when DES 2 were compared to MRS, the rate of long-term cardiovascular adverse events was higher compared to surgery as seen by the high rate of spontaneous AMI seen in all randomized clinical trials between DES 2 and MRS like the BEST, NOBLE, and EXCEL trials. (5-7,12)

TABLA 4. Análisis de regresión logística en el seguimiento a largo plazo para análisis de predictores de MACCE.

Variables	*P* value	Odds ratio (95%CI)
ERACI III vs ERACI IV	< .001	3.24 (1.82-5.78)
Population of non-diabetic patients	.040	0.54 (0.30-0.97)
3-vessel disease	.067	0.60 (0.34-1.03)
Dyslipidemia	.30	0.70 (0.35-1.38)
Arterial hypertension	.34	0.69 (0.33-1.44)
Previous AMI	.42	1.27 (0.70-2.27)
Acute coronary syndrome at presentation	.96	1.01 (0.58-1.77)

AMI, acute myocardial infarction; ACS, acute coronary syndrome; MACCE, major adverse cardiovascular and cerebrovascular events (death, AMI, stroke or target vessel revascularization).

The presence of early neoatherosclerosis could be associated with a high rate of spontaneous AMI reported in this observational study of new-generation DES (21-23)

Therefore, if the advanced designed of DES is not enough to improve long-term results, we may want to change our PTA and stent strategy like we did in the ERACI IV study.

It seems logical somehow to think that, if we prevent unnecessary stenting, we can minimize the rate of future complications associated with the biology of stents.

When fractional flow reserve (FFR) joined routine clinical practice it was used with conservative strategy like in the FAME and SYNTAX II trials where, in the FFR groups, the authors used fewer DES and obtained better results compared to the angiography-guided groups.

It is well known that FFR has become the gold standard of functional assessment during PTA (24-26). Also, it is known that FFR is not available while PCI is being performed in many cath labs across the world due to financial constraints. Also, some anatomical constraints have been associated with FFR with controversial results (27-29). In addition, not treating small vessel disease and intermediate lesions in the revascularization strategy resulted in better disease progression, which is suggestive that FFR is not necessary for a delayed strategy in most angiographically assessed intermediate lesions.

Although we found no predictors of poor progression in the ERACI IV, which may have been due to the sample size, the low rate of events, few revascularizations performed in treatment-naïve vessels (5.7%) at 72-month follow-up added to the low frequency of adverse events support our therapeutic strategy for the management of lesions with PTA. Similarly, the large number of patients who reached reasonably incomplete revascularizations determined by residual ES also points in this direction.

Additionally, recently, a landmark randomized clinical trial could become an indirect validation of our new and redefined score, the ERS. The EXCEL trial—that was one of the largest randomized clinical trials that compared DES to MRS for the management of left main coronary artery disease—excluded, per protocol, patients with high SS. The authors reported high discrepancies in score measurement when they compared the determinations made by the operator and those made at the study core lab. As a matter of fact, in the determinations made in the field no patient with high SS was considered. However, when analyzed by the core lab, 25% of the patients selected had high SS, and the main reason for this is that operators did not count all small-vessel lesions like we did. (7,33)

STUDY LIMITATIONS

This study had some limitations. The first thing we should consider is that it was not a randomized clinical trial conducted among patients with DES 2 who were followed and included prospectively compared to patients with DES 1 years ago. During that time, DAPT therapies like prasugrel or ticagrelor improved significantly while for patients from the ERACI III clopidogrel was the only P_2Y_{12} receptor inhibitor available. (30-32) Actually, we could not discard that these new P_2Y_{12} receptor inhibitors were, in part, responsible for the differences seen in disease progression between both groups. As a matter of fact, per protocol, prasugrel and ticagrelor were the first DAPT indicated in patients with diabetes, left main coronary artery disease or angiographically high-risk scores.

Despite the study was statistically powered regarding the primary endpoint of MACCE, the study sample was very small, and, therefore, propensity score matching groups were also small. The baseline and angiographic characteristics between the two groups were not identical. Even after propensity score matching, all the characteristics of poor progression were more common in the ERACI IV group. Also, many of the patients contacted from the ERACI IV at long-term follow-up were contacted by phone or by their GP, meaning we cannot discard a small rate of NSTEMI or TVR-AMI that may have gone unnoticed or inadequately interpreted.

Finally, a huge number of patients were followed for a long time in the ERACI III. However, in patients from the ERACI IV, follow-up was much longer with *P* values < .001.

In conclusion, this multicenter, prospective, observational registry of patients with MVD including left main coronary artery stenosis demonstrated a significantly low rate of MACCE and each primary component at 5-year follow-up.

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