Second vs. First generation drug eluting stents in multiple vessel disease and left main stenosis: Two-year follow-up of the observational, prospective, controlled, and multicenter ERACI IV registry

Authors:


Abstract

Objective

To compare second generation drug eluting stents (2DES) with first generation (1DES) for the treatment of patients (pts) with multiple coronary vessel disease (MVD).

Background

Although 2DES improved safety and efficacy compared to 1DES, MVD remains a challenge for percutaneous coronary interventions.

Methods

ERACI IV was a prospective, observational, and controlled study in pts with MVD including left main and treated with 2DES (Firebird 2, Microport). We included 225 pts in 15 sites from Argentina. Primary endpoint was the incidence of major adverse cardiovascular events (MACCE) defined as death, myocardial infarction (MI), cerebrovascular accident (CVA) and unplanned revascularization; and to compare with 225 pts from ERACI III study (1DES). PCI strategy was planned to treat lesions ≥70% in vessels ≥ 2.00 mm, introducing a modified Syntax score (SS) where severe lesions in vessels < 2.0 mm and intermediate lesions were not scored.

Results

Baseline characteristics showed that compared to ERACI III, ERACI IV pts had higher number of diabetics (P = 0.02), previous revascularization (P = 0.007), unstable angina
Ilb/IIIc (P < 0.001) and three vessels/left main disease (P = 0.003). Modified SS was 22.2 ± 11. At 2 years of follow-up ERACI IV group had significantly lower incidence of death+ MI + CVA, (P = 0.01) and MACCE (P = 0.001). MACCE rate was similar in diabetics, (5.8%) and nondiabetics (7.0%). After performing a matched propensity score, MACCE remain significantly lower in ERACI IV (P = 0.005).

Conclusion

This registry showed that 2DES in MVD has a remarkable low incidence of MACCE in unadjusted and adjusted analysis.

INTRODUCTION

In the past decade, several randomized clinical trials (RCT) compared PCI with 1st generation DES versus CABG in complex patient subsets such as three-vessel coronary artery disease (CAD), unprotected left main and diabetics. End points of these trials were, in general, a composite of hard clinical end points such as death, myocardial infarction (MI) and cerebrovascular accident (CVA), with 1, 3, and 5 years of follow-up. Long-term outcome of these randomized studies comparing DES versus CABG demonstrated poorer outcome with PCI in over 70% of the patient population included [1-6].

However, a likely major flaw of the above trials was the stent design used, 1st generation DES in most cases. In the past few years, several RCT either comparing 2nd or 3rd generation DES versus the 1st generation were conducted. All of them consistently showed a significant reduction in the incidence of cardiac late events including cardiac death and/or MI, death/MI and very late stent thrombosis with the newer DES [7-10].

One of the major limitations in these studies was the fact that they were performed generally in well selected low risk populations and there is limited information [11, 12] at the present time on whether these new devices will also be able to improve outcome in patients such as those included in SYNTAX and FREEDOM, with multiple vessel CAD, unprotected left main, diabetes and/or with intermediate or high Syntax Score (SS).

The ERACI IV study was a prospective, multicenter, observational, and controlled registry in patients with multiple vessel disease and left main, treated with second generation DES, and a conservative strategy during DES implantation which was compared with ERACI III, a study with a similar population treated with 1st generation DES.

At mid-term follow-up, a remarkable low incidence of adverse events was reported, although it was unknown whether those results would still remain at long term outcome [13-15].

The purpose of this presentation is to report the 2-year follow-up of this study.
METHODS

The ERACI IV registry was a multicenter and prospective open label study that evaluated a chromium cobalt rapamycin second generation DES (Firebird2™, Microport Inc. Shanghai, China). The Firebird2™ Rapamycin-Eluting chromium cobalt is the second generation DES by MicroPort, which is based on the new cobalt chromium alloy stent platform. It uses polyolefin polymer, which makes the coating property quite remarkable. Firebird 2 compared to Firebird has shown 34% increase in flexibility, 15% increase in supporting strength, lower strut thickness, abluminal coating and drug release rate at 30 day over 80% [16, 17].

Patients were candidates for inclusion if they had multiple vessel CAD including left main stenosis and indication for myocardial revascularization, both clinical objective evidence of myocardial ischemia and angiographic evidence of severe coronary obstruction (stenosis ≥70% by visual estimation).

Patients were excluded from the study if they had: prior PCI with BMS in the preceding 6 months, previous PCI with DES in target or non-target vessel, acute MI in the preceding 72 hr, poor left ventricular function (ejection fraction <35%), two or more chronic total occlusions, severe concomitant valvular or myocardial heart disease, limited life expectancy, history of cerebrovascular accident, neutropenia or thrombocytopenia, aspirin or thienopyridine intolerance, a requirement for concomitant vascular or general surgery, or if they were deemed unsuitable for long-term antiplatelet therapy, or not amenable to treatment with DES therapy.

Patient population and study design of the study were previously published [13] and described in Fig. 1. After 11 months, from 4,030 patients assessed for eligibility, 1,917 patients were initially eligible with severe CAD, 233 patients were initially included, and 8 patients were excluded because they didn't meet clinical or angiographic inclusion criteria, therefore 225 were finally included (11.8% of the overall PCI performed in those centers). This number of subjects was in accordance with the ERACI III population [15], which included an identical number of patients treated with 1st generation DES (Cypher™, Cordis/Johnson & Johnson, Miami Lakes, FL, and Taxus Express™, Boston Scientific, Boston, MA).
Patient population and study design. STEMI = ST elevation myocardial infarction; PCI = percutaneous coronary intervention; DES = drug eluting stent; CRF = chronic renal failure; CI = contraindication; DAPT = dual antiplatelet therapy; ES = eluting stent; MACCE = major adverse cardiovascular events.

Primary and secondary endpoints at 2 years of follow up. CVA: cerebrovascular accident, MI = myocardial infarction; MACCE = major adverse cardiovascular events.

Primary end point was the incidence of major adverse cardiac and cerebrovascular events (MACCE) in the Firebird2™ arm and subsequently an indirect comparison with ERACI III patients (1st generation DES) was done. The end point was recorded at 30 days, 6, 12, 18, and 24 months of follow-up. Secondary end points included the incidence of target lesion and vessel revascularization (TLR and TVR respectively) and stent thrombosis.
**End Point Definitions**

MACCE was defined as the composite of any cause of death, MI (both ST and Non-ST elevation), cerebrovascular accident (CVA) and unplanned target vessel or nontarget vessel revascularization (TVR). During the initial procedure, only ST elevation MI was recorded. Target lesion failure (TLF) was defined as any ischemia driven revascularization of the target lesion, cardiac death (if the event could not be determined with certainty, it would be assumed to be cardiac), MI and target lesion revascularization (TLR). TVR refers to an ischemic driven revascularization of the treated coronary artery. Stent thrombosis was defined in agreement with the definition used in previous studies [18, 19] including the Academic Research Consortium definition.

Dual anti-platelet therapy (DAPT) was required for all included patients. A 100 mg of aspirin was administrated orally at least 1 hr prior to catheterization with an oral loading dose of thienopyridines (P2Y12): either clopidogrel (300–600 mg), prasugrel (60 mg), or ticagrelor (180 mg). During PCI, unfractionated heparin was recommended as necessary to maintain an activated clotting time as current guidelines suggest. Alternatively, enoxaparin, bivalirudin or other antithrombotic agents could be administered per standard of care and operator's choice. In ERACI IV, DAPT was mandatory for 6 months, but strongly recommended for the entire follow-up period, and included either clopidogrel (75 mg day$^{-1}$), prasugrel (10 mg day$^{-1}$), or ticagrelor (90 mg/12 hr). As part of the revascularization strategy, the protocol suggested that prasugrel and/or ticagrelor would be the first P2Y12 selected in patients with diabetes, complex left main or high Syntax Score [20, 21].

An independent blind clinical events committee adjudicated all reported events of MACCE and other clinical events, including stent thrombosis. An independent data monitoring committee was responsible for oversight of all reported adverse events and evaluating safety data.

The study fulfilled all regulatory steps according to Argentina's requirements for this kind of registry, and all patients signed an Informed Consent Form previous to the procedure.

**PCI Technique**

The revascularization strategy was planned prior to the procedure and the aim was to achieve complete functional revascularization (CFR). Percutaneous revascularization was considered functionally complete if no residual severe stenosis (≥70%) remained in any major epicardial vessel and all severe stenosis had been successfully treated with stents [22]. Chronic totally occluded vessels supplying akinetic left ventricular segments were usually not attempted. The strategy of staged procedures was allowed. If this was the case, medical records would reflect this information. Treatment of a nonplanned coronary vessel after baseline PCI was evaluated by the Clinical Committee.
In addition, mild or intermediate stenosis (50–<70%) was not treated and stent was indicated (by visual estimation) in severe stenosis only; secondly, provisional stent strategy in all bifurcations was recommended and, lastly, severe stenosis in vessels <2.0 mm was strongly discouraged and usually not attempted.

In ERACI IV patients, original SS was calculated [23], however, we also used a modification of the original SS, excluding from the analysis all intermediate lesions and severe stenosis in vessels <2.0 mm. In-stent restenosis was scored as heavy calcified stenosis. This new scoring was in agreement with the PCI strategy used in the study and was reported in detail elsewhere [24].

**Statistical Analysis Plan for the Primary End Points**

In ERACI IV, sample size was estimated according to similar population included in ERACI III DES arm [15]. In that study, there was an incidence of the primary end point of MACCE at 1 year of follow-up among patients treated with 1st generation DES (12% of MACCE and 7% of death/MI/CVA). Taking into account that second generation DES—either Xcience V (Abbott,Vascular), Promus Element (Boston Scientific), or Endeavor Resolute (Medtronic)—compared to the 1st generation ones, Taxus Express or Taxus Element (Boston Scientific) in most cases, reported a reduction of major adverse events of 50% during the first and second year [7-9, 11, 12], using a two-sided test for differences in independent binomial proportions with a level of 0.05, we estimated that if we included 225 patients, the power of the study would be 80% to detect differences between both kind of stents. Continuous variables were compared using ANOVA with Bonferroni correction. Categorical variables were compared using ×2 analysis or Fisher's exact test. Continuous variables were expressed as mean + SD and categorical variables as percentages. Freedom from survival end points at follow-up were obtained using Kaplan–Meier curves and compared by log-rank test. Because these treatment comparisons were not randomized, we used multivariable statistical methods to adjust for possible confounding factors. Univariate and multivariate Cox regression analysis were performed using SPSS version 17.0 to determine independent predictors of outcome at follow-up (all variables introduced in block in a single step). Variables of statistical significance after univariate analysis and clinically relevant covariates including all demographic, clinical, angiographic, and procedural variables were included into the model. We also performed a propensity score to analyze results in matched population of patients. The propensity score was constructed using a logistic model. The logistic model included independent predictors such as age, sex, diabetes, hypertension, hypercholesterolemia, smoking, prior MI, proximal left anterior descending disease, three vessel CAD, left main stenosis, prior revascularization, and unstable angina symptoms. We used a greedy matching algorithm to identify pairs of patients, one of whom received a 1st generation DES while the other one received a Firebird2™.
Study Organization and Ethical Considerations

An independent clinical events committee adjudicated all reported events of MACCE and other clinical events, including stent thrombosis. An independent data monitoring committee was responsible for the oversight of all reported adverse events and evaluating safety data.

All the required patient's information needed to fulfill the research was incorporated to the database by each site's researchers, trained with that purpose, using a password protected electronic case report form (CRF).

The Centro de Estudios en Cardiología Intervencionista (CECI) was responsible for the development of the protocol registry, database, e-CRF and statistics analyses. The Informed Consent Form (ICF) was presented to the National Direction of Personal Data from Argentina, and the database was approved by this national bureau, following the personal data protection law (No. 25326). The protocol was presented to the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) from Argentina. The registry followed Good Clinical Practice and Helsinki’s declaration for human research. All patients signed an ICF.

RESULTS

Baseline clinical, demographic, angiographic, and procedural characteristics of the two studies were described in Table 1. Briefly compared to ERACI III 1st generation DES, ERACI IV had a greater number of diabetic patients (P = 0.01), more patients with Braunwald IIB/IIIC angina (P < 0.001), with more three vessels plus left main compromise (P = 0.003), and also more stent length deployed per patient (P < 0.001). In contrast, elderly patients (P = 0.02) and those with high cholesterol (P = 0.04) were more frequent in ERACI III.

Table 1. Baseline Demographic, Clinical, Angiographic, and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ERACI III</th>
<th>ERACI IV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.5 ± 10.6</td>
<td>63.9 ± 11.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td>83.6%</td>
<td>85.6%</td>
<td>0.89</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>32.4%</td>
<td>33.3%</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.9%</td>
<td>30.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>22.7%</td>
<td>34.7%</td>
<td>0.007</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>79.6%</td>
<td>78.7%</td>
<td>1.00</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>79.1%</td>
<td>66.7%</td>
<td>0.04</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11.6%</td>
<td>6.7%</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>ERACI III</td>
<td>ERACI IV</td>
<td>P value</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Unstable angina IIb/IIIc</td>
<td>40.7%</td>
<td>64.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left main disease (LMD)</td>
<td>5.8%</td>
<td>9.8%</td>
<td>0.11</td>
</tr>
<tr>
<td>3 vessel CAD+LMD</td>
<td>38.2%</td>
<td>54.3%</td>
<td>0.003</td>
</tr>
<tr>
<td>N° stents per patient</td>
<td>1.79 ± 0.7</td>
<td>1.8 ± 0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>36.1 ± 8.9</td>
<td>40.8 ± 10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete anatomical revascularization</td>
<td>48.0%</td>
<td>50.2%</td>
<td>0.63</td>
</tr>
<tr>
<td>Complete functional revascularization</td>
<td>88.4%</td>
<td>82.0%</td>
<td>0.08</td>
</tr>
<tr>
<td>Original SYNTAX score</td>
<td>NA</td>
<td>27.7 ± 11.3</td>
<td>NA</td>
</tr>
<tr>
<td>Low (&lt;23)</td>
<td>NA</td>
<td>33.8%</td>
<td>NA</td>
</tr>
<tr>
<td>Intermediate (23–32)</td>
<td>NA</td>
<td>32.4%</td>
<td>NA</td>
</tr>
<tr>
<td>High (&gt;32)</td>
<td>NA</td>
<td>33.8%</td>
<td>NA</td>
</tr>
<tr>
<td>Modified SYNTAX score</td>
<td>NA</td>
<td>22.2 ± 11.0</td>
<td>NA</td>
</tr>
<tr>
<td>Low</td>
<td>NA</td>
<td>54.8%</td>
<td>NA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NA</td>
<td>27.9%</td>
<td>NA</td>
</tr>
<tr>
<td>High</td>
<td>NA</td>
<td>17.2%</td>
<td>NA</td>
</tr>
</tbody>
</table>

All other clinical, demographic, and procedural variables were not significantly different. In ERACI IV, 1.8 stent per patient was used, 27.2% of patients had overlapping stents and 14.2% of bifurcations were treated. Completeness of revascularization either anatomic (CAR) or CFR were achieved similarly in both studies, CAR was 48 and 50.2% in ERACI III and IV respectively, P = 0.63; whereas CFR was 88.4% vs. 82% in ERACI III and IV respectively, P = 0.08 (Table 1).

ERACI IV patients were classified at low SS in 33.8%, intermediate in 32.4% and high in 33.8%. However, when we used the modified SS, patients with low SS rose to 54.9%, intermediate dropped to 27.9% and only 17.2% of ERACI’s patients scored at high SS. At hospital discharge, all patients in ERACI III DES arm and ERACI IV were taking P2Y12. In ERACI III, clopidogrel was the only P2Y12 available, while in ERACI IV clopidogrel was used in 58.7%, and more active P2Y12 such as prasugrel and ticagrelor were taken in 27.2 and 14.1%, respectively.

### 30 Days and One Year Results

Briefly, at 30 days, there were no differences in death, MI, CVA, emergent TVR or stent thrombosis; MACCE rate was greater in ERACI III (4.4% vs. 1.3%, respectively, P = 0.04).

At 1 year, Firebird2™ DES of ERACI IV, compared to ERACI III 1st generation DES, had a significantly lower incidence of each component of the primary end point: death (0.4% vs.
3.1%, respectively P = 0.03), death/MI/CVA (0.9% vs. 6.7%, respectively P = 0.001), TVR (1.8% vs. 8.9%, respectively, P < 0.001), and MACCE (2.2% vs. 12%, respectively, P < 0.001).

At 1 year, patients with second generation DES had significantly better free survival events than those treated with 1st generation DES (97.8% vs. 88%, respectively, P < 0.001).

**Two-Year Follow-Up Results**

At 2 years of follow-up, 24.5 ± 3.8 months, at univariate analysis, a significant advantage of second generation DES was seen.

The incidence of the composite of death/MI/CVA (3.6% vs. 9.3%, respectively P = 0.01); unplanned new revascularization (4% vs. 11.6%, respectively P = 0.003) and MACCE (16.9% vs. 6.7% P = 0.001), were significantly lower in ERACI IV 2nd generation DES compared to the 1st generation DES. Incidence of stent thrombosis was also lower, (0.9% vs. 3.1% in ERACI IV and III respectively, P = 0.09/Fig. 2). Very late stent thrombosis was not seen in ERACI IV patients.
Figure 3.

MACCE and death/MI and CVA survival curves at two years of follow-up. MACCE: major adverse cardiovascular events (any cause of death, myocardial infarction, cerebrovascular accident and unplanned revascularization); MI = myocardial infarction; CVA = cerebrovascular accident.

Cumulative 2-year events of the two groups were described in Table 2.

Table 2. Cumulative Events at 2 years of Follow-up

1. FU = follow-up; CVA = cerebrovascular accident; MI = myocardial infarction; TVR = unplanned revascularization-target vessel revascularization; MACCE = major adverse cardiovascular events; RR = risk ratio; CI = confidence interval.
<table>
<thead>
<tr>
<th>Event</th>
<th>1 year FU</th>
<th>2 years FU (cumulative)</th>
<th>2 years FU (cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7 (3.1%)</td>
<td>1 (0.4%)</td>
<td>0.13 (0.17–1.13)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>6 (2.7%)</td>
<td>1 (0.4%)</td>
<td>0.16 (0.01–1.36)</td>
</tr>
<tr>
<td>Non-fatal CVA</td>
<td>5 (2.2%)</td>
<td>0 (0%)</td>
<td>0.49 (0.45–0.54)</td>
</tr>
<tr>
<td>Death/MI/CVA</td>
<td>15 (6.7%)</td>
<td>2 (0.9%)</td>
<td>0.12 (0.02–0.55)</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>20 (8.9%)</td>
<td>4 (1.8%)</td>
<td>0.18 (0.06–0.55)</td>
</tr>
<tr>
<td>MACCE (Death/MI/CVA/TVR)</td>
<td>27 (12%)</td>
<td>5 (2.2%)</td>
<td>0.16 (0.06–0.44)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>6 (2.7%)</td>
<td>2 (0.9%)</td>
<td>0.32 (0.06–1.64)</td>
</tr>
</tbody>
</table>

**Death**

- **1 year FU**: 7 (3.1%) events, 1 (0.4%) non-events, p-value: 0.03
- **2 years FU (cumulative)**: 7 (3.1%) events, 5 (2.2%) non-events, p-value: 0.56

**Acute myocardial infarction**

- **1 year FU**: 6 (2.7%) events, 1 (0.4%) non-events, p-value: 0.057
- **2 years FU (cumulative)**: 10 (4.4%) events, 3 (1.3%) non-events, p-value: 0.049

**Non-fatal CVA**

- **1 year FU**: 5 (2.2%) events, 0 (0%) non-events, p-value: 0.07
- **2 years FU (cumulative)**: 7 (3.1%) events, 1 (0.4%) non-events, p-value: 0.07

**Death/MI/CVA**

- **1 year FU**: 15 (6.7%) events, 2 (0.9%) non-events, p-value: 0.001
- **2 years FU (cumulative)**: 21 (9.3%) events, 8 (3.6%) non-events, p-value: 0.013

**Unplanned revascularization**

- **1 year FU**: 20 (8.9%) events, 4 (1.8%) non-events, p-value: 0.001
- **2 years FU (cumulative)**: 26 (11.6%) events, 9 (4.0%) non-events, p-value: 0.003

**MACCE (Death/MI/CVA/TVR)**

- **1 year FU**: 27 (12%) events, 5 (2.2%) non-events, p-value: <0.001
- **2 years FU (cumulative)**: 38 (16.9%) events, 15 (6.7%) non-events, p-value: 0.001

**Stent thrombosis**

- **Definitive/probable**
  - **1 year FU**: 6 (2.7%) events, 2 (0.9%) non-events, p-value: 0.28
  - **2 years FU (cumulative)**: 7 (3.1%) events, 2 (0.9%) non-events, p-value: 0.17
At 2 years of follow-up, the survival curves from major adverse cardiovascular events and death/MI/CVA were lower with 2nd generation DES (Fig. 3A and B).

Even though an adverse cardiac events progression (4.4%) in patients treated with 2nd generation DES was seen between the first and second year, death/MI/CVA and MACCE were significantly lower compared to the ERACI III DES arm.

**Diabetic vs. Nondiabetic Patients**

At 1 year of follow-up, no differences in outcome were seen between diabetic (1.5%) and nondiabetic patients (2.6%) included in ERACI IV, and significant differences with 1st generation DES of ERACI III were seen (23.4% and 9%, respectively). At 2 years of follow-up, the advantages of 2nd generation DES remained both in diabetics, 5.8% vs. 25.4%, respectively (P < 0.001) and nondiabetes 7% vs. 12.4%, respectively (P < 0.02). In ERACI IV MACCE rate at 2 years was similar in both populations (5.8% and 7.0%).

Cumulative cardiac and cerebrovascular events in diabetics were described in Fig. 4.

**Multivariate Analysis**

We analyzed independent predictors of the primary end point (MACCE) using multivariate Cox regression analysis. The variables analyzed were sex, age, hypertension, diabetes, high cholesterol, renal failure, smoking, angina pectoris, unstable angina, Braunwald class angina, previous MI, previous PCI, previous stroke, left ventricular ejection fraction, three vessel disease, left main, number of stents, stent length, overlapping stents, reference vessel diameter, and treatment group.
On univariate analysis, previous revascularization, hypertension, peripheral vascular disease, and DES treatment group were associated with MACCE and were entered into Cox regression model. At 2 years, only 1st generation DES (ERACI III) was an independent predictor of poor outcomes (RR: 2.46; 95% CI: 1.25–4.75, P = 0.008) (Table 3).

Table 3. Multivariate Cox Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Significance level</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>ERACI III vs ERACI IV</td>
<td>0.008</td>
<td>2.446</td>
<td>1.258</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.307</td>
<td>0.728</td>
<td>0.395</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>0.189</td>
<td>0.576</td>
<td>0.253</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>0.099</td>
<td>0.607</td>
<td>0.335</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.090</td>
<td>0.521</td>
<td>0.246</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.297</td>
<td>1.551</td>
<td>0.680</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0.886</td>
<td>0.958</td>
<td>0.530</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>0.512</td>
<td>0.803</td>
<td>0.417</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.497</td>
<td>1.139</td>
<td>0.783</td>
</tr>
<tr>
<td>IIb/IIIc Braunwald classification</td>
<td>0.720</td>
<td>0.897</td>
<td>0.494</td>
</tr>
<tr>
<td>3 vessel and LM CAD</td>
<td>0.214</td>
<td>0.692</td>
<td>0.388</td>
</tr>
</tbody>
</table>

1. LM = unprotected left main; CAD = coronary artery disease.

While analyzing 2nd generation DES group only, we introduced 21 demographic, clinical, angiographic and procedural variables in the model including original and modified SS and completeness of revascularization either anatomic or functional. No independent predictor of poor outcomes was identified in the multivariate model.

Because ERACI IV study was not randomized, we performed a propensity score matching to control for differences between Firebird2-DES and 1st generation-DES treated patients. We were able to match 108 patients who received a Firebird2-DES with 108 patients who received a 1st generation-DES. Incidence of MACCE [0.22 (0.07–0.6) P = 0.005] unplanned revascularization [0.23 (0.06–0.78) P = 0.01] and death/MI/CVA [0.22 (0.04–1.00) P = 0.05] were still significant in favor to 2nd generation DES similar to results in general population albeit with wider confidence interval due the smaller sample size (Table 4).
Table 4. Propensity Score Analysis (Matched population, n = 216).

<table>
<thead>
<tr>
<th>Event</th>
<th>ERACI III</th>
<th>ERACI IV</th>
<th>RR (CI 95%)</th>
<th>Sig level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause of death (%)</td>
<td>3.7</td>
<td>0.9</td>
<td>0.25 (0.02–2.20)</td>
<td>0.21</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.6</td>
<td>0.9</td>
<td>0.16 (0.02–1.36)</td>
<td>0.09</td>
</tr>
<tr>
<td>Non-fatal CVA (%)</td>
<td>1.9</td>
<td>0.0</td>
<td>0.2 (0.009–4.11)</td>
<td>0.29</td>
</tr>
<tr>
<td>Death/myocardial infarction/CVA (%)</td>
<td>8.3</td>
<td>1.9</td>
<td>0.22 (0.04–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Unplanned revascularization (%)</td>
<td>12.0</td>
<td>2.8</td>
<td>0.23 (0.06–0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>MACCE (death/myocardial infarction/CVA/TVR) (%)</td>
<td>16.7</td>
<td>3.7</td>
<td>0.22 (0.07–0.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

DISCUSSION

Main results of this prospective, multicenter, controlled, and observational study in patients with multiple vessel disease including unprotected left main, revealed that at 24.5 months of follow-up a remarkable low incidence of MACCE, the composite of death/MI/CVA and unplanned revascularization was observed. Moreover, this low MACCE rates were also seen in the diabetic population.

Additionally, when we compared these results with a similar cohort of patients treated with 1st generation DES, there were significant differences in favor to 2nd generation DES either in adjusted or unadjusted matched comparisons.

Our low events rate were in agreement with several randomized and observational studies comparing 2nd or 3rd generation DES versus the first ones [7-10], although limited information has been reported so far in patients with complex lesion subsets such as we are reporting here [11, 12]. The 2nd and 3rd generation DES showed significant improvement in stent design, polymer characteristics, drug release and stent struts coverage, and all of these new features significantly enhanced the safety/efficacy compared to previous ones [25].
In recent years several randomized studies compared PCI with DES implantation—1st generation DES the most [1-6]- versus CABG, and consistently demonstrated advantages with the latter one in more complex lesion subsets. In all of them an aggressive PCI strategy was selected in order to achieve a more complete revascularization; for this reason, all intermediate stenosis (50–69%) and severe stenosis in vessels of 1.5 mm or more were part of the revascularization strategy, and this also included complex bifurcation techniques.

Therefore the potential flaw of these studies would be both, stent design used and the PCI strategy selected [26].

Park et al. [27] recently reported the first randomized study utilizing everolimus-eluting stents (EES) vs. CABG for multivessel disease. Major coronary events at 2 years were higher with PCI (11.0%) vs. 7.9% for CABG. At long term follow-up (average 4.6 years), the event rates were 15.3% for PCI and 10.6% for CABG, P = 0.04 and this was mainly driven by the need for repeat revascularization. There were no significant differences in the rates of death or MI between the two treatment strategies, although spontaneous MI was still significantly higher with EES.

Results of the above study [27] suggested that they made an improvement compared to those trials with 1st generation DES in a similar cohort of patients [1-6], however, the total stent length of this trial was 85.3 mm with an average original SS of 24.2, meaning that a multiple stent deployment strategy instead of a conservative PCI strategy was probably selected by study investigators. It is unknown whether, had they used a more conservative strategy, a lower MACCE rate would have been seen at follow-up.

In contrast, in our ERACI IV we used a 2nd generation DES plus a conservative functional PCI technique [15, 28], treating severe stenosis in large vessels (≥2.0 mm) but intermediate stenosis was not treated. The 6.7% MACCE rate reported here at 2 years suggested that we don't have any penalty with this PCI strategy for each of the primary end points, including repeat revascularization procedures either in the treated or nontreated vessels and that included those patients with intermediate nonstented lesions. However, whether this more conservative strategy will result in lower 5-year MACCE rates is presently unknown.

Finally, for the first time in ERACI trials [15, 22, 28] MACCE rates and repeat revascularization procedures were similar between diabetic and non-diabetic patients.

**Study Limitations**

This study had some limitations taking into account the no randomized nature of the study.
Patients treated with 2nd generation DES were prospectively included years later than those treated with the first generation ones, and during those years, significant improvement in medical therapies were introduced, in fact ERACI IV patients with complex CAD were under more active P2Y12 such as prasugrel or ticagrelor in 40%, whereas for patients in ERACI III clopidogrel was the only P2Y12 available [15, 19, 20] and we could not discard that these new P2Y12 were, in part, responsible for the large outcome differences between both groups.

Second it is clear that functional flow reserve (FFR) is the most accurate tool to assess functional revascularization strategy [29, 30] and lesion assessment and has become a gold standard to guided PCI in most of elective cases. FFR was not used in this study; however most of our patients had stress tests before the PCI procedure where areas of myocardial ischemia were usually detected [28]. Incomplete revascularization [31], either anatomic or functional, were linked with poor outcome after PCI, however, long-term outcome of those patients with IAR or IFR would be different if the residual nontreated lesions were intermediate or critical.

Third, in spite that the study was powered for primary end point of MACCE, the study group size was small and the propensity group even smaller, therefore we were not able to detect differences for each component of the end points.

Finally, baseline clinical and angiographic characteristics between both groups were not equal, although all differences associated with poor outcome during PCI were more frequently present in ERACI IV; moreover, low MACCE rate in patients treated with 2nd generation DES remained after a matched propensity score was performed.

In conclusion, this observational, prospective and controlled study in patients with multiple vessel disease including left main stenosis, showed at 2 years a remarkable low MACCE rate, just as lower rates for all individual components of the end points. Stent design and a conservative strategy during PCI appeared to be associated with these findings.

**APPENDIX**

ERACI IV study organization

Data monitoring committee:

Clinical Events Committee: David Antoniucci, MD (CEC Chairperson); Eduardo Gabe, MD (Sanatorio Otamendi y Miroli, Buenos Aires, Argentina); Fernando Sokn, MD (Clínica IMA. Adrogué, Argentina) and Pablo Stutzbach, MD (Sanatorio Las Lomas. San Isidro, Argentina).
Angiocorelaboratory: Claudio Llauradó, Bs and Alejandro Incarbone, Bs (Centro de Estudios en Cardiología Intervencionista. Buenos Aires, Argentina).

Clinical Project Management: Centro de Estudios en Cardiología Intervencionista (Alfredo M. Rodriguez-Granillo, Project Manager; Alfredo E. Rodriguez, Director).

Biostatistical analysis: Centro de Estudios en Cardiología Intervencionista. (Gastón Rodríguez-Granillo, MD, PhD; Alfredo M. Rodríguez-Granillo, MD).

Safety monitoring: Comité de Ética en Investigación Clínica, Buenos Aires, Argentina.

Study sites and PI: Sanatorio Otamendi y Mirolí, Buenos Aires (Alfredo E. Rodríguez); Clínica IMA, Adrogué, Buenos Aires (Carlos Fernández-Pereira, Carlos Mauvecín); Sanatorio Las Lomas, San Isidro, Buenos Aires (Juan Mieres); Sanatorio de la Trinidad, Quilmes, Buenos Aires (Carlos Haiek); Clínica provincial de Merlo, Merlo, Buenos Aires (Omar Santaera); Sanatorio San Miguel, San Miguel, Buenos Aires (Juan Lloberas); Hospital Español, Mendoza (Miguel Larribau); Hospital El Cruce, Buenos Aires (Ricardo Sarmiento); Instituto de Diagnóstico y Tratamiento de Afecciones Cardiovasculares, La Plata, Buenos Aires (Ignacio Rifourcat); Centro Médico Talar, Pacheco, Buenos Aires (Antonio Pocoví); Hospital Militar Central, Buenos Aires (Oscar Carlevaro); Clínica Privada Angiocor, La Plata, Buenos Aires (Elías Sisu); Sanatorio Belgrano, Mar del Plata, Buenos Aires (Alejandro Delacasa); Sanatorio San Lucas, San Isidro, Buenos Aires (Antonio Pocoví); Clínica de Nefrología, Urología y Enfermedades Cardiovasculares, Santa Fe (Víctor Moles).

REFERENCES


