Revascularization strategies for patients with multiple vessel coronary disease and unprotected left main.

A prospective, multicenter and controlled Argentina registry with a cobalt-chromium rapamycin eluting stent, FIREBIRD 2™: protocol design and methods of the ERACI IV Registry

Estrategias de revascularización en pacientes con enfermedad de múlples vasos y tronco no protegido: protocolo y métodos del Registro ERACI IV

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ABSTRACT

The ERACI IV Registry is a multicenter and prospective open label study that evaluates the cobalt-chromium alloy sirolimus eluting stent Firebird 2™ for the treatment of patients with multiple vessel coronary artery disease and indication for revascularization. 225 patients were evaluated and included in the registry. Patients inclusion criteria are acute coronary syndromes, excluding ST elevation myocardial infarction (MI), reference vessel diameter >2.5 mm and target lesion diameter stenosis ≥70%. Exclusion criteria were poor left ventricular ejection fraction, previous treatment with drug eluting stent (DES) in an epicardial vessel or contraindication to ASA or thienopyridines. All patients signed an informed consent form according to the National Direction of Personal Data from Argentina following the current law. All data will be incorporate to a database by an electronic case report form. Primary end-point was to know the incidence of cardiovascular events defined as any cause of death, MI, cerebrovascular accident (CVA) and target lesion revascularization (TLR), compared with ERACI III population (Cypher™ and Taxus™ arm and by-pass arm) at 30 days, 6 and 12 months of follow-up. Secondary endpoints includes incidence of target lesion failure (TLF) defined as any ischemia driven revascularization of the target lesion, cardiac death, MI and TLR; incidence of Target vessel revascularization (TVR) and stent thrombosis, according to Academic Research Consortium (A.R.C.) definition. An independent clinical events committee will adjudicate adverse events.

Key words: *DES, multiple vessel disease, unprotected left main.*

RESUMEN

El Registro ERACI IV es un estudio multicéntrico, prospectivo y abierto que evalúa el ***stent*** de aleación de cromo cobalto liberador de sirolimus Firebird 2® para el tratamiento de pacientes con enfermedad coronaria múltiple e indicación de revascularización. Se incluyeron 225 pacientes en el registro; los criterios de inclusión fueron: síndrome coronario agudo como motivo de internación, excluyendo al infarto de miocardio con elevación del segmento ST; diámetro de referencia >2,5 mm y estenosis de la lesión a tratar >70%, por estimación visual. Los criterios de exclusión fueron: mala función ventricular, tratamiento previo con ***stent*** liberador de fármacos o contraindicación para el tratamiento con aspirina y/o tienopiridinas. Todos los pacientes firmaron un consentimiento informado de acuerdo con la Dirección Nacional de Datos Personales de la Inspección General de Justicia de la Nación. Todos los datos relevantes para la investigación se incorporaron a la base de datos utilizando un formulario electrónico de formulario de datos, mediando una contraseña para cada sitio e investigador. El objetivo primario del registro fue conocer la incidencia de eventos cardiovasculares definidos como muerte de cualquier causa, infarto de miocardio (IM), accidente cerebrovascular y revascularización de la lesión tratada (TLR), para posteriormente compararla con la población del estudio ERACI III (rama Taxus® y Cypher® y rama cirugía de ***bypass***) a 30 días, 6 y 12 meses de seguimiento. Los objetivos secundarios: la incidencia de falla de la lesión tratada (TLF), definida como cualquier revascularización debido a isquemia de la lesión tratada, muerte cardíaca, MI y TLR; incidencia de revascularización del vaso tratado (TVR) y trombosis del ***stent*** de acuerdo con la definición del ***Academic Research Consortium***. Un comité clínico Independiente adjudica los eventos adversos.

Palabras clave: *DES, enfermedad de múltiples vasos, tronco no protegido.*

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BACKGROUND

In the past, several randomized clinical trials comparing Coronary Artery By-pass Graft surgery (CABG) vs Percutaneous Coronary Interventions (PCI), using either balloon or bare metal stents (BMS),[1-4] were performed. Results showed similar rates of survival and freedom from acute myocardial infarction (AMI). Among them, the ***E**studio **R**andomizado **A**rgentino angioplastia vs.**CI**rugía (ERACI)* randomized trial presented better results in BMS group for the endpoints of death and AMI at 30 days and after one year of follow-up. This advantage remained, although non-significant, at 5 years of follow-up.[5]

Using the results from these pivotal clinical trials two meta-analyses[6,7] were set and published using the individual data from each of them; of significance, one included multiple vessel coronary disease patients and other patients treated either treated with balloon angioplasty or BMS. The first one, by Mark Hlatky et al.,[6] showed almost identical survival freedom from death, AMI and cerebrovascular accident (CVA) between BMS and CABG. At six years of follow-up the results were similar. In both articles neither the number of coronary vessels involved, left anterior descendent artery or poor left ventricular ejection fraction were associated to worst survival in PCI arm; meaning that coronary disease extension was not a predictor of poorer outcome in the randomized trials done during 1986/2000.

With the introduction of the first generation Drug Eluting Stents (DES) designs during the beginning of this century, the angiographic and clinical restenosis linked to BMS diminished significantly; this advantages were consistent during late follow-up,[8-10] apparently without increasing the incidence of "hard" cardiac clinical events such as AMI and/or death, indicating that future comparisons with CABG were imperative, despite that some reports of late stent thrombosis with these first DES designs and the need of long double antiplatelet therapy could moderate the benefits.[11,12]

At the end of the last decade the most ambitious randomized trial comparing DES with CABG in patients with multiple vessel disease presented the one year results: the "SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX)" trial. This study, conducted by Patrick Serruys, was a multinational trial (85 sites) with a randomization block 1:1 that compared the incidence of major adverse cardiovascular events (MACCE: death, AMI, CVA and new revascularization) between the first generation of DES and CABG in patients with coronary disease in three vessels and unprotected left main disease (ULMD). One year results[13] showed similar incidence in death and AMI, with a significant difference in favor to DES when comparing CVA (p=0.003), no differences in death, AMI and CVA (p=0.89) and a major incidence in revascularization procedures with DES (p=0.001). Numbers that affected the incidence of MACCE resulting in non-inferiority margins that didn't fulfill the primary endpoint.

In this trial the authors stratified results according to the SYNTAX Score, an index that take in account the complexity of the patients, classifying them in tertiles of low (<22), moderate (between 22 and 32) and high risk (>32).

At five years of follow-up[14] DES arm showed higher incidence of cardiac death (p=0.003), MI (p<0.001) and new revascularization procedure (p<0.001), meanwhile CVAs was still in favor of DES, although non-significantly (p=0.09). These unfavorable findings in PCI group where mainly caused by higher incidence of events in patients with 3 vessels treated with PCI. On the contrary, in most patients with left main stenosis, long term outcome was similar between both revascularization strategies, and the only advantage of CABG was due to revascularization procedures. The old DES design used in this trial was a major limitation; in fact, any definition of stent thrombosis (definite, probable and possible) from the SYNTAX trial showed 15.4% rate of stent thrombosis, and this was translated to a higher incidence of death. Patients with definite or probable stent thrombosis have 41.3% of death rate.

Another important multicenter and prospective randomized trial especially design for diabetic patients with multiple vessel disease was the FREEDOM trial, sponsored by NLHI, comparing DES vs. CABG.[15] At five years the composite endpoint of death, MI and CVA was significantly better in CABG arm (p=0.005). Once again, both DES designs used in the trial were first generation devices, outdated. In fact, pooled data from the 8 stents trials suggested poorer long term safety outcome compared with CABG when first DES generation was used.[16]

In the last years we witness the introduction of new DES designs[17,18] with better platforms and biocompatible and/or biodegradable polymers that shown an important reduction in severe cardiac events including cardiac death and MI in almost all analyzed subgroups, comparing to first generation DES, as randomized clinical trials showed.

Firebird-2 is a cobalt-chromium alloy sirolimus eluting stent completely different from those used in ERACI III,[19] SYNTAX and FREEDOM trial.

METHODS/DESIGN

Device description

The Firebird 2™ Sirolimus-Eluting Cobalt-chromium Coronary Stent is a second generation DES, which based on a cobalt chromium alloy stent platform. It has a strut thickness of 0.0034'' and a crossing profile or 0.039''. The pharmacological agent, rapamycin, in incorporated into a polyolefin polymer that provides

controlled release of the available drug, with a drug-release rate at 30-days of 80%.

Study design

The ERACI IV Registry is a multicenter and prospective open label study that evaluates the Firebird-2™ DES for the treatment of patients with multiple vessel coronary artery disease and indication for revascularization. Subjects with acute coronary syndromes (ACS), excluding ST elevation myocardial infarction as clinical presentation and reference vessel diameter (RVD) ≥ 2.5 mm and ≤ 3.5 mm by visual estimation will be included; additional inclusion and exclusion criteria are given in this manuscript. The number of subjects to evaluate was 225, in accordance with the ERACI III population. Primary end point is the rate of major adverse cardiovascular events (MACCE). Subsequently a comparison with ERACI III patients (DES and CABG arms) will be done at 30 days, 6 and 12 months of follow-up. Secondary end points includes the incidence of TLF at one year of follow-up, incidence of TVR and incidence of stent thrombosis, according to the Academic Research Consortium definition (A.R.C.).

Endpoints definitions

MACCE is defined as the composite of any cause of death, myocardial infarction (MI; both ST elevation and Non-ST elevation), cerebro-vascular accident (CVA) and any ischemia-driven revascularization of the target lesion (TLR). Target lesion failure (TLF) is defined as any ischemia driven revascularization of the target lesion, cardiac death (if the event could not be determined with certainty, it will be assumed to be cardiac), MI and TLR. Target vessel revascularization (TVR) refers to an ischemic driven revascularization of the treated coronary artery. Stent thrombosis is defined per the Academic Research Consortium (A.R.C.) definition.

Follow up schedule

For the study, clinical endpoints measurements were conducted in-hospital and at 30 days and are planned at 3, 6 and 12 months. After the first follow-up visit, the next ones could be done by personal visit, telephone or reference physician.

Antiplatelet and other concomitant medical therapy

Dual Anti-Platelet Therapy (DAPT) was required for all included patients. Aspirin ≥ 300 mg was administrated orally at least 1 hour prior to catheterization and an oral loading dose of tienopiridnes: either clopidogrel (300 to 600 mg), prasugrel (60 mg) or ticagrelor (180 mg), preferably ≥ 6 hours prior to procedure. During PCI unfractionated heparin was recommended as necessary to maintain an activated clotting time as current guidelines suggested. Alternatively, enoxaparin, bivalirudin or others antithrombotic agents could be administrated per standard of care and operator´s choice. DAPT will be maintained at least 6 months and, recommended, indefinitely; includes either clopidogrel (75 mg/day), prasugrel (10 mg/day) or ticagrelor (90 mg/12 hours).

Criteria for multiple and staged interventions

This registry evaluated patients with multiple vessel coronary disease (MVD). The strategy of staged procedures was allowed. If this was the choice, the medical records must reflect this information. Treatment of a non-planned coronary vessel after baseline PCI it will be evaluated by the Clinical Committee, either an original target or non-target lesion or vessel.

Statistical analysis plan for the primary endpoints

For the primary endpoint analysis, most frequent methods will be use. No power calculation were done taking in account that this is an observational study. For the later indirect comparison with ERACI III population, we will do a matching-adjusted indirect comparison incorporating individual patient data and using an approach similar to propensity score weighting, so we can estimate the difference in 12 months MACCE rate between the ERACI IV group and the ERACI III trial (DES and CABG groups).

Study Organization and Ethical Considerations

An independent clinical events committee will adjudicate all reports events of MACCE and other clinical events, including stent thrombosis. An independent data monitoring committee is responsible for oversight of all reported adverse events and evaluate safety data.
All the required patient´s information needed to fulfill the research was incorporated to the database by each site researchers, trained with that purpose, using a password protected electronic case report form (CRF).
The Centro de Estudios en Cardiología Intervencionista (CECI) is 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 (Inspección General de Justicia) from Argentina, and the database was approved by this national bureau, following the personal data protection law (n° 25326). The protocol was presented to the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) from Argentina.
The registry follows Good Clinical Practice (GCP) and Helsinki declaration for human research. All patients signed an Informed Consent Form (ICF).

Limitations and study design

Taking in account that this is a multicenter registry that evaluates a "real world" population, not a ran-

domized clinical trial,[20,21] a matched-adjusted indirect comparison between ERACI IV and ERACI III trial will be done, considering that the devices used in ERACI III, Taxus and Cypher stents, were 1st generation eluting stents (paclitaxel and rapamycin respectively) approved by ANMAT, FDA and with CE-mark and widely used around the world, and that Firebird 2™ is a later generation sirolimus eluting stent, approved by ANMAT and other agencies.

LIST OF ABBREVIATIONS

ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
ARC: Academic Research Consortium
BMS: Bare Metal Stent
CECI: Centro de Estudios en Cardiología Intervencionista.
CRF: Case Report Form
CABG: Coronary Artery by-pass Graft Surgery.
CVA: Cerebro-Vascular Accident
DES: Drug Eluting Stent.
ERACI: Estudio Randomizado Argentino Angioplastia versus CIrugía.
GCP: Good Clinical Practice.
ICF: Informed Consent Form.
IGJ: Inspección General de Justicia
MI: Myocardial Infarction.
MACCE: Major Adverse Cardiovascular Events.
PCI: Percutaneous Coronary Intervention.
SYNTAX: The SYNergy between PCI with TAXUS Cardiac Surgery Trial
ULMD: Unprotected Left Main Disease.
TLF: Target Lesion Failure.
TLR: Target Lesion Revascularization.
TVR: Target Vessel Revascularization.

APPENDIX

Firebird-2™ platform

TABLE 1. Firebird 2 charactaristics.

Component & Characteristics	Firebird 2
Stent material	L605 Cobalt-Chromium super alloy laser-cut stent
Drug	Sirolimus
Polymer	Polyolefin
Strut thickness	0.0034″
Crossing profile	0.039″
Metal coverage area	11.6%-13.7%
Nominal balloon pressure	9-12
Balloon rated burst pressure	16-21

Inclusion and exclusion criteria

A complete list of inclusion and exclusion criteria, both clinical and angiographic, is listed below.

1. ***Inclusion criteria. Clinical and angiographic***
   - Subject is ≥ 18 years old.
   - Eligible for percutaneous coronary intervention (PCI).
   - Documented stable angina pectoris or acute coronary syndrome (ACS), excluding ST elevation myocardial infarction (MI) at the moment of inclusion.
   - Left ventricular ejection fraction >35%
   - Subject understands the nature of the study and provides informed consent before inclusion to registry.
   - Patient willing to comply with follow up evaluations.
   - Target lesions located in native coronary artery.
   - Target lesions diameter stenosis ≥ 70%.
   - Reference vessel diameter ≥ 2.50 mm and ≤ 4.0 mm, by visual estimation.
2. ***Exclusion criteria. Clinical and angiographic***
   - Pregnancy.
   - Patients with left ventricular ejection fraction ≤ 35%
   - Patients with documented ST elevation MI between 72 hours prior to baseline PCI.
   - Patients treated with one or more drug eluting stent/s (DES) in an epicardial target vessel.
   - Patients with previous treatment of a target epicardial vessel with a bare metal stent (BMS) within 6 months of the index procedure.
   - Patients with impaired renal function (serum creatinine > 2.0 mg/dl)
   - Contraindication to ASA, or both clopidogrel, prasugrel or ticagrelor.
   - Known hypersensitivity to sirolimus.
   - Known allergy to Cobalt chromium alloy.
   - Any prior true anaphylactic reaction to contrast agents defined as known anaphylactoid or other non-anaphylactic allergic reactions to contrast agents that cannot be adequately treated prior to index procedure.
   - Leukopenia (<3000 cel/mm^3), thrombocytopenia (<100000 cel/mm^3) or other blood diseases.
   - Active peptic ulcer or active gastrointestinal bleeding.
   - Any known disease, to investigator criteria, that could interfere with the optimal participation of the patient in the current registry.
   - Currently participating in another investigational drug or device study.
   - Programmed surgical intervention within 30 days posterior to the index procedure.

Definitions

Death

Death is divided in two categories: Cardiac and Non-cardiac.

1. **Cardiac death** is defined as death due to any of the following:
   - Acute myocardial infarction.
   - Arrythmia or any conduction abnormality.
   - Cerebrovascular accident after hospital discharge or cerebrovascular accident suspected to be related to the index procedure.
   - Death due to procedure complication, including bleeding, vascular repair, transfusion reaction or by-pass surgery.
   - Any death in which cardiac cause cannot be excluded.
   - Cardiac perforation/pericardial tamponade.
2. **Non-cardiac death** is defined as a death not due to any of the above.

Major adverse cardiovascular event (MACCE).

MACCE is defined as the composite of any cause of death, myocardial infarction (MI; both Q and non Q), cerebro-vascular accident (CVA) and any ischemia-driven revascularization of the target lesion (TLR).

Myocardial infarction (MI)

MI will be defined as either:

- Q wave: development of new pathological Q-waves in 2 or more leads lasting ≥ 0.04 segs with post procedure cardiac enzyme levels elevated above normal.
- Non Q wave: de novo elevation of enzyme levels (CK > 2 the upper normal limit without the presence of new Q waves)

Target lesion revascularization (TLR)

TLR is defined as any ischemia driven repeat revas-

cularization procedure of the previously successfully treated lesion. It will be considered ischemia driven if the diameter stenosis is ≥ 50% by QCA and there is presence of clinical or functional ischemia which cannot be explained by other coronary or graft lesions.

Target lesion failure (TLF)

TLF is defined as any ischemia driven revascularization of the target lesion, cardiac death (if the event could not be determined with certainty, it will be assumed to be cardiac), MI and TLR.

Target vessel revascularization (TVR)

TVR refers to an ischemic driven revascularization of the treated coronary artery.

Stent thrombosis

Stent thrombosis is defined per the Academic Research Consortium (ARC):

- Definite: symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis)
- Probable: unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis.
- Possible: any unexplained death after 30 days.

Based on the elapsed time since stent implantation, stent thrombosis can be classified as:

  - Acute: 0-24 hours post stent implantation.
  - Subacute: > 24 hours – 30 days post implantation.
  - Late: > 30 days – 1 year post implantation.
  - Very Late: > 1 year post implantation.

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