EXAMINATION EXTEND — HCB/2018/0906

Complete study protocol version 1.0. September 12, 2018

(NCT04462315)

Study Design

1. Title Research

Very long-term clinical outcomes of Everolimus-Eluting Stent versus Bare-Metal Stent in ST-segment Elevation Myocardial Infarction. The EXAMINATION EXTEND trial.

2. Investigator Names and sites

EXAMINATION EXTEND principal investigators

dr. Salvatore Brugaletta, MD, PhD, Hospital Clínic de Barcelona

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3. Department & name head of the Department

Interventional cardiology unit, Department of cardiology, Cardiovascular institute, Hospital Clinic of Barcelona, Barcelona Spain. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Prof. Manel Sabaté.

4. Research category

The EXAMINATION trial was originally a multicenter, randomized, controlled, superiority clinical trial to the second-generation everolimus-eluting stent (EES) with the cobalt-chromium balloon-expandable bare-metal stent (BMS) in patients undergoing

percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction, up to 5- year follow-up. The EXAMINATION EXTEND is a retrospective, multicenter, international study to compare the 10-year follow-up clinical outcomes of primary PCI with EES versus BMS. The EXAMINATION EXTEND is an investigator-driven study with limited funding; the Spanish Heart Foundation has committed 50.000 Euro.

5. Background

Percutaneous coronary intervention (PCI) is the standard of treatment in ST-elevation myocardial infarction (STEMI) when performed in experienced Institutions within adequate time delay after the symptoms onset. [1] ST-segment elevation myocardial infarction (STEMI) represents the paradigm of a thrombotic milieu and a challenging clinical scenario to test new intracoronary devices. [2] In this clinical setting, first generation drug-eluting stents (DES) have demonstrated to reduce clinical and angiographic restenosis compared to BMS. [3-9] Conversely, these benefits were counterbalanced by an increased risk of very late stent thrombosis. [10-13] These safety concerns were confirmed by autopsy and intravascular imaging studies, showing evidence of incomplete endothelialization, delayed arterial healing, and vessel remodeling due to chronic inflammation in patients with very late stent thrombosis. [14-19] Development of neotherosclerosis has been identified as an important player in the pathophysiology of the occurrence of very late events.

Second generation everolimus-eluting stent (EES; Xience™ V; Abbott Vascular, Santa Clara, CA) has been designed with a thin (7.8 μm) non-adhesive, durable, biocompatible acrylic polymers and fluorinated copolymer. [20] As compared with first generation DES, the Xience™ V stent was able to reduce both the restenosis and the

thrombosis rates in randomised controlled trials and meta-analyses. [21,22] The EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) all-comers trial was designed to compare clinical outcomes between EES and BMS in STEMI patients. At 5-year follow-up it demonstrated clinical superiority of EES over a BMS in patients with STEMI requiring primary percutaneous coronary intervention. [23]

Currently available data on clinical outcome beyond 5 years are scant, especially in an important clinical scenario such as STEMI. It is therefore unknown if advantages of second-generation DES are maintained at very long-term follow-up, when incidence of neotherosclerosis is high and it may play an important role in the pathophysiology of the occurrence of very late events.

We herein sought to compare 10-year clinical outcomes of EES vs. BMS in the EXAMINATION trial, focusing on differential effects between the first 5 years and subsequent years.

6. Objectives

The EXAMINATION EXTEND study aims to examine patient and device-oriented endpoints after ten years of follow-up in STEMI patients randomly assigned to EES or BMS in the EXAMINATION trial focusing on the differences between 5 and 10 years of follow-up.

7. Methods

The EXAMINATION TRIAL is a multicentre, multinational, prospective, randomised, two-arm, single-blind, controlled trial performed in patients with STEMI (clinicaltrials.gov number: NCT00828087). It has randomized 1.498 patients to receive

either an EES (751 patients) or a BMS (747 patients). At 5 years, complete clinical follow-up was obtained in 97.3% in both arms.

A total of 12 centers in 3 countries were involved in the trial. All these centers have been contacted to prolong follow-up up to 10 years. Nine Institutions agreed to participate in this project for a total of 1.450 patients expected at 10-year follow-up. An excel sheet was sent to all the centers to be fulfilled with 10-year follow-up of the patients included, collecting all-cause death, any myocardial infarction and any revascularization occurred between 5 and 10 years.

The primary endpoint of the study is the patient-oriented combined endpoint of all-cause death, any myocardial infarction or any revascularization at 10 year according to the Academic Research Consortium (ARC). [24] The secondary endpoint of the study is the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction or target lesion revascularization at 10-year. [24] In addition, stent thrombosis (according to the ARC definitions[24]) will be collected.

A clinical event committee, whose members are masked to the assigned stent, will independently adjudicate all deaths, potential myocardial infarctions, stent thrombosis, and revascularization procedures. We expect a 40% incidence of events for a total of 400 events to be adjudicated.

8. Inclusion and exclusion criteria

There are no relevant inclusion and exclusion criteria for the current extended study since this pertains to a follow-up of patients already enrolled in the main EXAMINATION trial.

9. Population

The population was the patients enrolled in the EXAMINATION trial. The study had broad inclusion and few exclusion criteria. Any patient presenting with STEMI with the following electrocardiogram criteria: at least 1 mm in two or more standard leads or at least 2 mm in two or more contiguous precordial leads or left bundle-branch block that was not known to be old, within the first 48 h after the symptoms onset requiring emergent percutaneous coronary intervention with a vessel size ranging between 2·25 mm and 4·0 mm without other anatomical restrictions could be included. Exclusion criteria were age younger than 18 years, pregnancy, patients with known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus or contrast material, and patients on chronic treatment anti-vitamin K agents, and STEMI secondary to stent thrombosis. The patients were enrolled at 11 sites in 3 countries.

10. Endpoints

The prespecified primary endpoint of the EXAMINATION EXTEND study are the patient-oriented combined endpoint of all-cause death, any myocardial infarction, or any revascularization at 10 year according to the Academic Research Consortium (ARC) definition. [24] Secondary endpoints included the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction (MI), or target lesion revascularization (TLR) [24]; all-cause and cardiac death; target vessel revascularization (TVR); and, stent thrombosis (according to ARC definitions). [24] Detailed descriptions of the study endpoints and definitions have been reported previously. [25]

Vital status will be verified in all patients. Independent study monitors (ADKNOMA, Barcelona, Spain) will verify the adequacy of the extended follow-up in 50% of all the patients included, together with all the reported events on-site. All events will be

adjudicated and classified by an independent event adjudication committee blinded to the treatment groups (Barcicore Lab, Barcelona, Spain).

11. Data collection

The EXAMINATION trial protocol was approved by the institutional review board of all 85 sites and is consistent with the International Conference on Harmonisation Guidance of Industry E6 Good Clinical Practice, the Declaration of Helsinki local regulations. Written consent was obtained from all participating patients when enrolled at baseline, for the duration of 5-years of follow-up.

Data collection for the entire cohort of patients will be performed via principal investigators at participating centers. Each center will be contacted by email to gather long-term results for the patients at that particular center. Teleconference calls will be performed for the site training and clarify issues.

The ethical committee will approve the protocol of the coordinating center (Ethics Committee for Drug Research, Hospital Clínic of Barcelona, Spain). After that, the study protocol approval by each site medical ethics committee approval will be requested. Once obtained, survival

status and clinical outcomes will be retrospectively collected. Patient records at hospitals will be checked to assess survival status. If survival is unclear from the patient record, national death registries will be consulted to complete information on death and the specific date. In case a patient has died, the cause of death will be determined from medical records.

12. Data base information

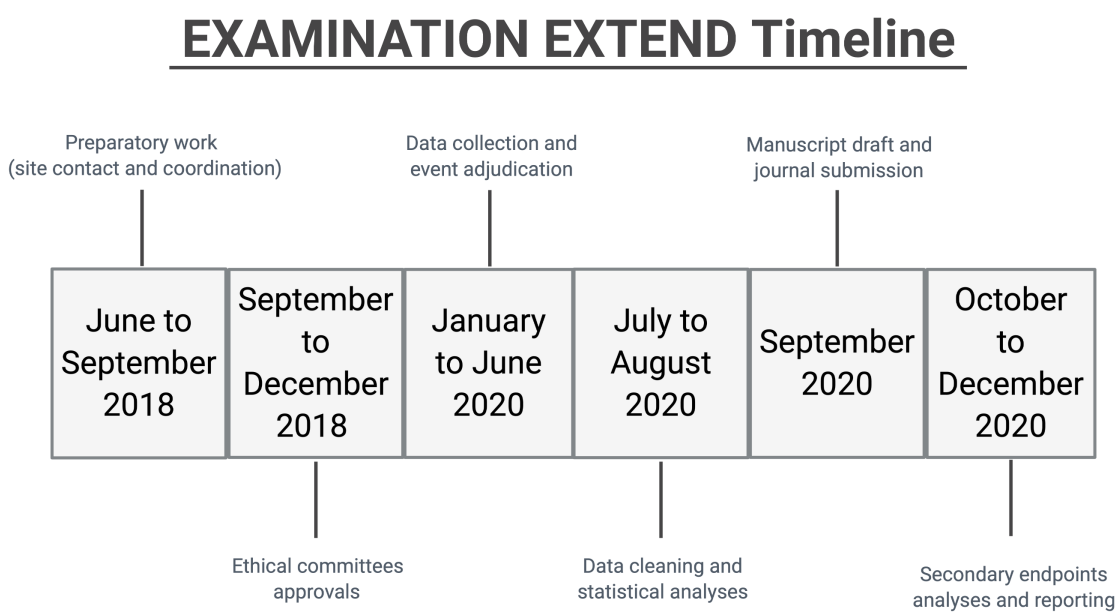
An anonymous database of patients enrolled in the EXAMINATION trial is already available with baseline characteristics, procedural characteristics, and outcome data. All patients included in the database have been assigned a unique study number. Patient information of the patient assigned this study number is only available at individual sites. Local principal investigators will send anonymous data identifiable per unique study number to the study coordinator and principal investigator (dr. Salvatore Brugaletta). A central database will be stored at the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). In comparison to the already existing database, this database will be edited only by changing the duration of follow-up, date of death if this occurred, and the cause of death.

13. Statistics

A specific statistical plan analysis document will be provided. All analyses will be performed according to the intention-to-treat principle. Patients with missing follow-up data will be included in the analysis and censored at the time they are lost to follow-up or at 5-year if their recruiting hospital did not participate in the 10-year follow-up. We will analyze the primary endpoint of 10-year patient-oriented composite endpoint using Kaplan-Meier curves, with a log-rank p-value to test between-groups differences. We will use Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CI) comparing EES with BMS. We will do landmark analyses in the overall population, setting the landmark points at 1 and 5 years to distinguish the EXAMINATION trial results from the extended follow-up of the EXAMINATION EXTEND study. The same will be done for the device-oriented composite endpoint and the other secondary endpoints. Subgroup analyses will include the following specified

variables: gender, age>75, presence of diabetes, post-PCI TIMI <3, multivessel disease, ejection fraction <30%, Killip class >I, ST-segment resolution >70%, use of aspiration thrombectomy catheters, primary PCI (STEMI<12h), and left anterior descending as the infarct-related artery.

14. Time Schedule



15. Administrative aspects and publication

Confidentiality and handling and storage of data and documents

Data will be stored on the Hospital Clínic local network drive with automatic overnight back-up. Stored data regarding patients and personnel included in this study can only be accessed by the investigators and the Ethics Committee for Drug Research of the Hospital Clínic (including Hospital Clínic auditors and monitors, if necessary). The processing, communication, and transfer of personal data of all participants will comply with EU Regulation 2016/679 of the European Parliament and of the Council of 27

April 2016 on the protection of individuals concerning the processing of personal data and the free movement of data, which must be complied with from 25 May 2018. If published in scientific journals or presented at scientific meetings, any information from this study will not reveal patient identity. Data will be stored for a maximum of 25 years after ending the study. Collected data will be secured against unauthorized access and stored and secured by the Hospital Clínic of Barcelona.

16. Relevant articles

1. Wijns W, Kolh P, Danchin N et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501-55.
2. Steg PG, Fox KA, Eagle KA et al. Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events. Eur Heart J 2009;30:321-9.
3. Kastrati A, Dibra A, Spaulding C et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. European heart journal 2007;28:2706-13.
4. Daemen J, Tanimoto S, Garcia-Garcia HM et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH Registries). The American journal of cardiology 2007;99:1027-32.
5. Spaulding C, Henry P, Teiger E et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093-104.
6. Spaulding C, Teiger E, Commeau P et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). JACC Cardiovasc Interv;4:14-23.
7. Valgimigli M, Campo G, Arcozzi C et al. Two-year clinical follow-up after sirolimus-eluting versus bare-metal stent implantation assisted by systematic glycoprotein IIb/IIIa Inhibitor Infusion in patients with myocardial infarction: results from the STRATEGY study. Journal of the American College of Cardiology 2007;50:138-45.
8. Stone GW, Witzenbichler B, Guagliumi G et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193-204.
9. Stone GW, Witzenbichler B, Guagliumi G et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30.
10. Wenaweser P, Daemen J, Zwahlen M et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. Journal of the American College of Cardiology 2008;52:1134-40.
11. Kastrati A, Mehilli J, Pache J et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030-9.
12. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989-97.
13. Stone GW, Moses JW, Ellis SG et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. The New England journal of medicine 2007;356:998-1008.
14. Nakazawa G, Finn AV, Joner M et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138-45.
15. Finn AV, Nakazawa G, Joner M et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500-10.

16. Cook S, Ladich E, Nakazawa G et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391-9.
17. Joner M, Finn AV, Farb A et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.
18. Wilson GJ, Nakazawa G, Schwartz RS et al. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. Circulation 2009;120:141-9, 1-2.
19. Carter AJ, Aggarwal M, Kopia GA et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Cardiovasc Res 2004;63:617-24.
20. Sheiban I, Villata G, Bollati M, Sillano D, Lotrionte M, Biondi-Zoccai G. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (Xience V). Vasc Health Risk Manag 2008;4:31-8.
21. Serruys PW, Ruygrok P, Neuzner J et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. EuroIntervention 2006;2:286-94.
22. Planer D, Smits PC, Kereiakes DJ et al. Comparison of everolimus- and paclitaxel-eluting stents in patients with acute and stable coronary syndromes: pooled results from the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) Trials. JACC Cardiovascular interventions 2011;4:1104-15.
23. Sabate M, Brugaletta S, Cequier A et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. Lancet 2016;387:357-366.
24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115(17): 2344-51.
25. Sabate M, Cequier A, Iniguez A, et al. Rationale and design of the EXAMINATION trial: a randomised comparison between everolimus-eluting stents and cobalt-chromium bare-metal stents in ST-elevation myocardial infarction. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2011; 7(8): 977-84.