Rev Esp Cardiol. 2015;68(5):382–389

Original article

Sex-related Impact on Clinical Outcome of Everolimus-eluting Versus Bare-metal Stents in ST-segment Myocardial Infarction. Insights From the EXAMINATION Trial

Ander Regueiro,[a] Diego Fernández-Rodríguez,[a] Salvatore Brugaletta,[a] Victoria Martín-Yuste,[a] Monica Masotti,[a] Xavier Freixa,[a] Ángel Cequier,[b] Andrés Íñiguez,[c] Patrick W. Serruys,[d] and Manel Sabaté[a,*] on behalf of the EXAMINATION trial investigators[◇]

[a] *Servicio de Cardiología, Hospital Clínic, IDIBAPS, Barcelona, Spain*
[b] *Área de Enfermedades del Corazón, Hospital Universitario de Bellvitge, IDIBELL, Barcelona, Spain*
[c] *Servicio de Cardiología, Complejo Hospitalario Universitario de Vigo, Pontevedra, Spain*
[d] *Thoraxcenter, Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands*

Article history:
Received 12 November 2013
Accepted 11 April 2014
Available online 29 October 2014

Keywords:
Sex
Myocardial infarction
Stent

ABSTRACT

Introduction and objectives: The use of second-generation drug-eluting stents compared with bare-metal stents in patients with ST-segment elevation myocardial infarction reduces the rate of major adverse cardiac events. We aimed to evaluate the impact of sex on the performance of everolimus-eluting stents vs bare-metal stents in ST-segment elevation myocardial infarction at 2-year follow-up.
Methods: This is a sub-study of the EXAMINATION trial that randomized 1498 patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention to everolimus-eluting or bare-metal stents. Primary end point was combined all-cause death, any recurrent myocardial infarction, and any revascularization. All end points were analyzed according to sex at 2-year follow-up.
Results: Of 1498 patients included in the trial, 254 (17.0%) were women. Women were older and had higher prevalence of hypertension and lower prevalence of smoking compared with men. In contrast with men, stent diameter was smaller in women. After multivariate analysis, the primary end point was similar between women and men (hazard ratio = 0.95; 95% confidence interval, 0.66-1.37), and among women, between those treated with bare-metal vs everolimus-eluting stents (hazard ratio = 2.48; 95% confidence interval, 0.95-6.46). Women showed a lower rate of repeat revascularization than men (hazard ratio = 0.55; 95% confidence interval, 0.32-0.95) despite worse baseline characteristics. This difference was driven by better performance of the everolimus-eluting stent in women.
Conclusions: Despite poorer baseline clinical characteristics, women with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention showed outcomes similar to men. The use of everolimus-eluting stents may represent an added value in women as it showed a reduced rate of repeated revascularization compared to men.

Influencia del sexo en los resultados clínicos de los *stents* liberadores de everolimus en comparación con los *stents* metálicos sin recubrimiento en el infarto agudo de miocardio con elevación del segmento ST. Perspectivas del ensayo EXAMINATION

Palabras clave:
Sexo
Infarto de miocardio
Stent

RESUMEN

Introducción y objetivos: Los *stents* liberadores de fármaco (farmacoactivos) de segunda generación, en comparación con los *stents* metálicos sin recubrimiento, reducen la tasa de eventos adversos cardiacos mayores de los pacientes con infarto agudo de miocardio con elevación del segmento ST. El objetivo es evaluar la influencia del sexo del paciente en el resultado obtenido con los *stents* liberadores de everolimus en comparación con los *stents* metálicos sin recubrimiento en pacientes con infarto agudo de miocardio con elevación del segmento ST a los 2 años de seguimiento.
Métodos: Se llevó a cabo un subestudio del ensayo clínico EXAMINATION, en el que se aleatorizó a 1.498 pacientes con infarto agudo de miocardio con elevación del segmento ST tratados con intervención coronaria percutánea al grupo de *stents* liberadores de everolimus o al de *stents* metálicos sin recubrimiento. El objetivo principal fue la combinación de muerte por cualquier causa, cualquier recurrencia de infarto agudo de miocardio y cualquier revascularización. Todos los objetivos se analizaron en función del sexo del paciente en el seguimiento realizado a los 2 años.

* Corresponding author: Servicio de Cardiología, IDIBAPS, Universidad de Barcelona, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: masabate@clinic.ub.es (M. Sabaté).
◇ The complete list of collaborators is included in the Appendix.

http://dx.doi.org/10.1016/j.rec.2014.09.001
1885-5857/

Resultados: De los 1.498 pacientes incluidos en el ensayo, 254 (17,0%) eran mujeres. Las mujeres eran de más edad y tenían mayor prevalencia de hipertensión arterial y menor prevalencia de tabaquismo que los varones. Respecto a los varones, el diámetro máximo del *stent* en las mujeres resultó menor. Tras realizar un análisis multivariable, el objetivo principal fue similar entre mujeres y varones (*hazard ratio* = 0,95; intervalo de confianza del 95%, 0,66-1,37), y en el análisis realizado sobre las mujeres, fue similar entre tratadas con *stents* metálicos sin recubrimiento y tratadas con *stents* liberadores de everolimus (*hazard ratio* = 2,48; intervalo de confianza del 95%, 0,95-6,46). Las mujeres presentaron una tasa de revascularización repetida menor que los varones (*hazard ratio* = 0,55; intervalo de confianza del 95%, 0,32-0,95), a pesar de sus peores características basales. Esta diferencia se explica por un mejor resultado del *stent* liberador de everolimus en las mujeres.

Conclusiones: Pese a tener características basales peores, las mujeres con infarto agudo de miocardio con elevación del segmento ST tratadas con intervención coronaria percutánea obtuvieron resultados similares a los de los varones. El uso de *stents* liberadores de everolimus puede aportar un valor añadido en las mujeres, puesto que se demostró una reducción de la tasa de revascularización repetida en comparación con los varones.

Abbreviations

BMS: bare-metal stent
DES: drug-eluting stent
EES: everolimus-eluting stent
PCI: percutaneous coronary intervention
STEMI: ST-segment elevation myocardial infarction

INTRODUCTION

In Europe, more than one million women die from ischemic heart disease every year. Mortality is higher in women than in men.[1] Sex may exert an independent influence on the results after percutaneous coronary intervention (PCI)[2] with a similar or even lower restenosis rate despite smaller vessels than men.[3] In addition, women appear to have a greater medical advantage from treatment with drug-eluting stent (DES)[4] and more specifically after second-generation DES.[5]

The use of DES compared with bare-metal stent (BMS) reduces restenosis rate and target lesion revascularization in patients with chronic stable coronary artery disease, including high-risk patients such as diabetics.[6–9] Two trials have studied second-generation DES vs BMS in ST-segment elevation myocardial infarction (STEMI) patients. In the EXAMINATION (Evaluation of the Xience-V stent in Acute Myocardial INfarcTION) trial, the use of everolimus-eluting stent (EES) did not reduce the rate of the patient-oriented primary end point (combined all-cause death, any recurrent myocardial infarction, and any revascularization) compared with BMS; however, a significantly lower incidence of repeat revascularization and stent thrombosis was observed in patients with EES, compared to those with BMS[10] at 2-year follow-up.[11] In the COMFORTABLE AMI trial, there was a reduced rate of major adverse cardiovascular events (cardiac death, target vessel-related reinfarction and ischemia-driven target lesion revascularization) at one year with the use of biolimus-eluting stent compared with BMS.[12] There is scarce information about the performance of second-generation DES in women with STEMI.

The objective of this study was therefore to analyze the impact of sex on EES vs BMS performance in patients with STEMI at 2-year follow-up.

METHODS

This is a substudy of the all-comers, multicenter, controlled, randomized, EXAMINATION trial (NCT00828087).[10] The EXAMINATION Trial randomized 1:1 a total of 1498 patients with STEMI undergoing PCI to EES (Aience®, Abbott Vascular; Santa Clara, California, United States) or BMS (Multi-Link Vision®, Abbott Vascular). The rationale of the EXAMINATION trial has been previously reported.[13] Briefly, all patients with STEMI within the first 48 h after the onset of symptoms who underwent emergent PCI were eligible for the study.

Exclusion criteria included lesions requiring stent sizes < 2.25 mm or > 4 mm, STEMI caused by stent thrombosis, age < 18 years, pregnancy, patients with known intolerance to acetylsalicylic acid, clopidogrel, heparin, cobalt-chromium, or other stent components. Patients on chronic treatment with antivitamin-K agents were also excluded. The PCI was performed according to the standard medical practice. Either unfractionated heparin, bivalirudin, or glycoprotein IIb/IIIa inhibitors were used according to the operator criteria. Before PCI, loading doses of acetylsalicylic acid (≥ 250 mg) and clopidogrel (≥ 300 mg) were administered to the patient. Acetylsalicylic acid (≥ 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) was prescribed for ≥ 1 year in both groups.

All participating centers submitted and received the approval of their medical ethics committee for the protocol and for the informed consent. The study was conducted in compliance with the Declaration of Helsinki, BS EN ISO 14155 part 1 and part 2, and applicable local requirements. All patients provided written informed consent.

Study End Points

Study end points have been previously reported.[13] Briefly, the primary end point was the patient-oriented end point of all-cause death, any recurrent myocardial infarction, and any revascularization. Secondary end points included the device-oriented combined end point of cardiac death, target vessel myocardial infarction, and target-lesion revascularization; all-cause and cardiac death; recurrent myocardial infarction (World Health Organization extended definition)[14]; target lesion revascularization; target-vessel revascularization; stent thrombosis (according to the Academic Research Consortium definitions);[15] device and procedure success; and major and minor bleeding. All clinical events were adjudicated by an independent clinical event committee (Cardialysis, Rotterdam, The Netherlands) according to the Academic Research Consortium definitions.[15] For the purpose of this substudy, all end points were analyzed according to sex (female group vs male group).