Very Long-Term Efficacy and Safety of Paclitaxel-Eluting Balloon After a Bare-Metal Stent for the Treatment of ST Elevation Myocardial Infarction: 8-Year Results of a Randomized Clinical Trial (PEBSI Study)

Arturo García-Touchard 1 , Manel Sabaté 2 , Nieves Gonzalo 3 , Vicente Peral 4 , Beatriz B Vaquerizo 5 , Rafael Ruiz-Salmerón 6 , Bruno García del Blanco 7 , Jesús Jiménez-Mazuecos 8 , Eduardo Molina 9 , Pedro Martínez-Romero 10 , José María Hernandez-García 11 , Valeriano Ruiz Quevedo 12 , Cristóbal Urbano 13 , Javier Fernández-Portales 14 , José Ramón Rumoroso 15 , Juan Casanova 16 , Eduardo Pinar 17 , Javier Lopez-Pais 18 , Juan Francisco Oteo 1 , Fernando Alfonso 19

1 Interventional Cardiology department. Hospital Universitario Puerta De Hierro Majadahonda. Madrid. Spain. 2 Interventional Cardiology department. Hospital Clinic i Provincial. Barcelona. Spain. 3 Interventional Cardiology department. Hospital Clínico San Carlos, Madrid, Spain. 4 Interventional Cardiology department. Health Research Institute of the Balearic Islands (IdISBa), Hospital Universitari Son Espases. Palma de Mayorca, Spain. 5 Interventional Cardiology department. Hospital Del Mar. Barcelona. Spain. 6 Interventional Cardiology department. Hospital Virgen Macarena. Sevilla. Spain. 7 Interventional Cardiology department. Hospital Universitari Vall D´Hebron. Barcelona.

Spain. 8 Interventional Cardiology department. Complejo Hospitalario Universitario De Albacete. Albacete. Spain. 9 Interventional Cardiology department. Hospital Universitario Virgen De Las Nieves. Granada. Spain. 10 Interventional Cardiology department. Hospital De Puerto Real. Cadiz. Spain. 11 Interventional Cardiology department. Hospital Universitario Virgen De La Victoria. Málaga. Spain. 12 Interventional Cardiology department. Hospital Universitario De Navarra. Pamplona. Navarra. Spain. 13 Interventional Cardiology department. Hospital Carlos Haya. Málaga. Spain. 14 Interventional Cardiology department. Hospital San Pedro De Alcantara. Cáceres. Spain. 15 Interventional Cardiology department. Hospital De Galdakao. Bizkaia. Spain. 16 Interventional Cardiology department. Hospital Arnau De Vilanova. Valencia. Spain. 17 Interventional Cardiology department. Hospital Virgen De La Arrixaca. Murcia. Spain. 18 Interventional Cardiology department. Hospital Clínico Universitario De Santiago. La Coruña. Spain. 19 Interventional Cardiology department. Hospital Universitario de La Princesa. Madrid. Spain

INTRODUCTION

Drug-eluting stents (DES) are considered the therapy of choice in ST-segment elevation myocardial infarction (STEMI)(1). However, even with latest DES-generation, long-term data shows that there is a low but persistent rate of revascularizations and stent thrombosis (ST) maintained over time(2,3). Target lesion revascularization (TLR) increased from the first to the fifth year, from 1.6% to 4.4% in the EXAMINATION trial(2) and from 1.6 to 4.4%, in the COMFORTABLE AMI trial(3). Similarly, the ST rate rose from 2.2% in the first year to 3.9% at 5-years in the COMFORTABLE-AMI trial and from 0.5% to 1.6% in the EXAMINATION trial.

The use of a paclitaxel-drug coated balloons after a bare metal stent (BMS) implantation (DCB-combined strategy) in STEMI has shown in a randomized trial an excellent efficacy and safety(4). This DCB-combined strategy obtained results comparable to the best results with DES in STEMI trials at one year of follow-up(5,6)**.** Optical coherence tomography (OCT) studies also have suggested that the DCB-combined strategy provides superb strut coverage (99.5%) at 9-months(4) and superior healing at 3-month compared to new-generation DES(7). These favorable clinical, angiographic, and healing characteristics of the DCB-combined strategy might mitigate the problem of the persistent long-term risk associated to current DES.

We sought to investigate the very late clinical safety and efficacy of our DCB-combined strategy in STEMI patients by comparing the 8-year clinical outcomes of patients treated with the DCB-combined strategy versus BMS only, in the PEBSI-1 randomized trial (NCT01839890)(4).

METHODS

The PEBSI-1 trial(4) was a multicenter, single-blind, randomized controlled trial in patients with STEMI. The study was carried out according to the Declaration of Helsinki (as revised in 2013) and approved by the local ethics committees of all participating centers (Nº:19/2019). Signed informed consent was obtained from all patients included in the study. Seventeen tertiary university centers participated in the trial. In addition to an independent on-site monitoring of all cases, an independent clinical events committee, blinded to treatment allocation, adjudicated all clinical events.

The *inclusion criteria* were patients older than 18 years, within the first 12 hours after STEMI onset, with a clinical indication for primary PCI. STEMI was defined as ST-segment elevation of at least 1 mm in two or more contiguous electrocardiographic leads or new left bundle branch block, or a true posterior myocardial infarction, with angiographic evidence of a single culprit lesion in the target vessel.

Exclusion criteria were cardiogenic shock, life expectancy less than 12 months, and women of childbearing age. Procedural exclusion criteria included unprotected left main stenosis >50%, bifurcations with side branch ≥ 2.5 mm, stent thrombosis, lesion length >30 mm (exceeding the longest available paclitaxel-balloon), reference vessel diameter <2.5 mm or >4 mm, more than 1 severe stenosis (≥70% visually) in the same coronary artery, patients considered for CABG within 30 days post STEMI, and overlapping stents required to treat the culprit segment.

All recruited patients were randomly allocated in a 1:1 ratio to the BMS (PRO-Kinetic Energy stent, Biotronik, Berlin, Germany) or the same BMS plus paclitaxel-eluting balloon

(DCB-combined strategy) (Pantera Lux, Biotronik, Berlin, Germany). Interventional treatment type was allocated using opaque sealed and sequentially numbered envelopes using a computer-generated randomization code with block sizes of four or six.

Vascular access (radial or femoral) was left to the interventionalist's discretion. All patients received a pre-procedural loading dose of aspirin (250 to 500 mg) and clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg). Heparin (70-100 U/kg) was administered before the procedure. Use of glycoprotein IIb/IIIa inhibitors and additional boluses of heparin were left to operator discretion. Stent length was selected to cover the stenosis completely and stent size was selected to achieve a stent/distal artery ratio of 1-1.1/1. Pre- and post-dilation before randomization was also left to the operator's discretion. After successful BMS implantation (final TIMI flow 2-3, final residual stenosis <30%, and no post-implantation complications), patients were randomized to one of two groups in a 1:1 ratio: DCB-combined strategy (post-dilation with PTX-B for 45 seconds) and BMS alone group (no further post-dilation).

In the DCB-combined strategy, only one PTX-B was allowed (i.e., treatment of a 30 mm stent segment with two 15 mm PTX-Bs was not allowed) and only a single 45-second PTX-B inflation was allowed. The PTX-B diameter was selected to achieve a 1.1:1 ratio of the final BMS diameter according to the manufacturer's pressure/diameter tables. The length of the PTX-B had to be equal to the length of the previously chosen stent, or slightly longer but taking care to avoid balloon protrusion more than 2 mm from each edge of the stent.

Primary and secondary endpoints of the study have been reported elsewhere(4). Outcomes studied in this follow-up study will follow the ARC-2 criteria(8). Death:

cardiovascular, non-cardiovascular, and undetermined. Cardiovascular death defined as death resulting from cardiovascular causes (acute myocardial infarction, sudden cardiac and death resulting from heart failure). All deaths will be considered cardiac unless an unequivocal noncardiac cause could be established. Myocardial re-infarction as per ARC-2 criteria, will be defined as an absolute rise in cardiac troponin (from baseline) ≥35 times upper reference limit, plus 1 (or more) of the following criteria: a) New significant Q waves or equivalent, b) Flow-limiting angiographic complications, C) New "substantial" loss of myocardium on imaging.

Repeated revascularizations (ischemia driven): target lesion revascularization (including the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent) will be defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. For ischaemia demonstration, priority to functional assessment with fractional flow reserve (FFR) or equivalent techniques will be needed. Target vessel revascularization (included upstream and downstream branches and the target lesion). Stent thrombosis: definitive and probable will be considered. Definite stent thrombosis will be defined as an angiographic confirmation of stent thrombosis (or in the segment 5 mm proximal or distal to the stent or in a side branch originating from the stented segment) and the presence of at least 1 of the following criteria: a) Acute onset of ischemic symptoms at rest, b) New electrocardiographic changes suggestive of acute ischemia, c) Typical rise and fall in cardiac biomarkers. Probable stent thrombosis will be defined as any myocardial infarction that is related to documented acute ischemia in

the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Device-oriented combined endpoint including cardiovascular death, target vessel myocardial infarction (not clearly attributable to a non-target vessel), or target lesion revascularization.

Patient-oriented combined endpoint including all-cause mortality, any myocardial infarction (including non-target vessel territory), or any revascularization (including all target and non-target vessel).

All the above endpoints will be assessed by yearly contact up to the 8-year follow-up by a clinical visit, telephone contact or by electronic records and blindly adjudicated by the clinical events committee. The study began in April 2012. Follow-up will end in July 2021 in order to have complete 8-years clinical follow-up in all patients included in the study.

Statistical analysis

The 8 years-follow up analysis of outcomes is not specified in the study protocol and, therefore, represents a post hoc analysis. Continuous variables will be presented as mean and SD, and categorical data will be presented as counts and percentages. The Kolmogorov-Smirnov test will be used to analyze the normal distribution of quantitative variables. Patients who were lost to follow-up will be censored at their last known contact. For quantitative variables with normal distribution, the Levene test and the t-test will be used; for quantitative variables with non-normal distribution, non-parametric tests will be used (the Mann Whitney test). For qualitative variables: Chi-square test or, where appropriate, Fisher's exact test, will be used. A two-sided p value <0.05 will be considered statistically significant.

Survival curves for time-to-event variables will be constructed using Kaplan-Meier estimates. Hazard ratios (HR) and their confidence intervals will be calculated using the Mantel-Cox

method for comparisons of clinical outcomes between groups The log-rank test will be used to calculate corresponding p values.

Subgroup analyses will be the following: sex, age (>75 years), cardiovascular risk factors (hypertension, dyslipidemia, smoker, diabetes, peripheral vascular disease, previous myocardial infarction, previous revascularization, ischemia time (<3h), multivessel disease, TIMI flow post-PCI (<3), left anterior descending coronary artery culprit vessel, use of aspiration thrombectomy catheters, Killip class (>1) and left ventricular ejection fraction <35%. This trial is registered with ClinicalTrials.gov identifier, NCT01839890

DISCUSSION

We will assess if our DCB-combined strategy for STEMI patients' treatment, sustains its favorable effects over time. Second-generation DES in STEMI provide excellent clinical results but are associated with a low but persistent requirement of repeat revascularization over time. TVR rates from the first to the fifth year, increased from 4% to 7% in the EXAMINATION trial(2). The same was found in the COMFORTABLE-AMI trial where TVR increased from 2 to 6.5%(3). Similar results were seen regarding TLR that increased from 1.6% to 4.4% in EXAMINATION and from 1.6 to 4.4%, in COMFORTABLE AMI. We previously demonstrated in the PEBSI-1 clinical trial(4) that the DCB-combined strategy achieved an excellent clinical efficacy, with one-year results comparable to the best DES results published in STEMI patients (TVL and TLR: 1.8%). The present extended follow-up study will provided further insights regarding long-term efficacy of this unique strategy. It also will address the burning question of whether a brief and single application of paclitaxel from a balloon can maintain favorable antirestenotic effects in the very long term.

Despite the in-stent restenosis´ drastic reduction obtained with DES, there is also a never-ending concern regarding very late stent thrombosis risk which, although rare, still persists with newer generation DES devices(1). This concern has been also seen in STEMI patients. In the only 2 clinical trials with long-term data at 5 years, both almost doubled their rate of stent thrombosis. In the COMFORTABLE-AMI trial, the definite stent thrombosis rate rose from 2.2% in the first year to 3.9% at 5-years, and from 2.5% to 4.1% when the combined definition of "definitive or probable stent thrombosis" was used(3). Similarly, in the EXAMINATION trial, the definite stent thrombosis rate rose from 1 year to 5 years from 0.5% to 1.6% and from 0.9% to 2% in the "definitive or probable" stent thrombosis definition

was used(2). Our results in our DCB-combined strategy will investigate the long term stent thrombosis rate in this challenging scenario.

Finally, in the past years there has been great concern with paclitaxel containing devices due to a possible increased late all-cause mortality at 2 and 5 years in peripheral artery disease. In our follow-up study we will study any increase in mortality signal when paclitaxel is used at the coronary level.

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