SUPPLEMENTARY DATA

Study protocol for amenable non-culpable lesions

Amenable lesions are initially studied with pressure guidance based on the standard procedure of each cath lab.[1,2] In conclusion, the use of an, at least, 6-Fr guiding catheter, anticoagulation, administration of intracoronary nitroglycerin, and correct equalization of aortic pressure with an intracoronary pressure guide prior to the lesion functional assessment is recommended. After advancing the wire sensor toward the distal third of the artery—distal to the lesion—fractional flow reserve (FFR) is evaluated by inducing maximum hyperemia. The use of any 0.014 in pressure wires, any access routes for the hyperemic agent (whether intravenous or intracoronary bolus), and the hyperemic agent of choice in each center is allowed. By protocol, researchers are recommended to assess the non-hyperemic index of the lesion, coronary flow reserve, and microcirculation resistance indices by thermodilution with saline injections when using a pressure guidewire with a thermistor (PressureWire X, Abbott, United States).[1,2]

Patients with more than 1 non-culprit lesion

The study requires the local investigator to categorize and locate non-culprit lesions into 3 groups: *a)* amenable lesions for the study to be assessed using the FFR (meeting inclusion criteria); *b)* lesions in which the operator decides on percutaneous coronary intervention a without functional study (e.g., lesions with ≥ 70% percent diameter stenosis); and *c)* lesions for which the optimal medical therapy is decided without any studies being performed, such as secondary vessels not amenable to revascularization at the operator's discretion.

The inclusion of patients presenting, at least, 1 lesion meeting eligibility criteria for the study is allowed. In the presence of multiple eligible lesions, those meeting the inclusion criteria of the randomized clinical trial (FFR > 0.80 and presence of vulnerable plaque by optical coherence tomography [OCT]) are prioritized, while other lesions will not be considered for patient analysis. Patients without lesions with inclusion criteria in the randomized clinical trial with, at least, 1 lesion with FFR > 0.80 will be included in the study registry group. Patients in whom all amenable lesions show FFR ≤ 0.80 will be considered search failures.

Special situations during non-culprit lesion assessment

Lesions that could not be evaluated with the pressure wire, or OCT for technical or anatomical reasons will be recorded but not included in the analysis. Complications from using both diagnostic techniques will also be reported.

In cases in which OCT assessment of functionally nonsignificant lesions shows criteria of unstable plaque, such as a fibrous cap rupture or intraluminal thrombus, the operator's decision to treat will be respected. These specific cases in which the operator decides to treat the non-culprit lesion will not be included in any study group but recorded and included in the study flowchart. If the fibrous cap rupture of a thrombus-free vulnerable plaque is observed and suspected as caused by lesion manipulation with various

intracoronary diagnostic techniques, operators can include this lesion in the randomized clinical trial. If angiographic thrombus is documented, it is recommended not avoid including such lesion in the study.

Procedure for optimal coherence tomography-guided stent implantation

Patients with FFR > 0.80 and characteristics of vulnerable plaque by OCT allocated to the percutaneous coronary intervention group with stent implantation will undergo everolimus-eluting stent implantation (Xience, Abbott, United States). OCT-guided stent implantation is required by protocol. Implantation criteria are summarized in table 4 of the supplementary data. Of note, the correct assessment of vulnerable plaque length and reference diameters proximal and distal to the lesion. Post-implantation control pullback is recommended to rule out any major dissections towards the media layer at the stent edges (> 3 mm in length and 60° in arc from the center of the vessel) or stent malapposition (> 450 µm separation between the stent and the vessel wall in > 3 mm extension), and confirm correct stent expansion (≥ 80% relative to the reference area obtained in the OCT software according to the chosen reference model depending on the presence or absence of branches causing caliber loss).[3]

Angiographic and optical coherence tomography quantification analyses

There is an available independent imaging laboratory associated with the study to perform angiographic and OCT quantification analyses for the study purposes (Barcelona Cardiac Imaging Core-Laboratory [BARCICORELab]) to monitor compliance with the study criteria associated with vulnerable plaque diagnosis. A blind analysis of the study results will be conducted, and patients will be adjudicated as per protocol to conduct an exploratory analysis.

Angiographic quantitative analysis will be performed with the specific software QAngio XA 7.3 (Medis, Netherlands). Calibration by isocenter or guiding catheter diameter will be used to analyze the target vessel stenosed segment to obtain lesion length, the minimum lumen diameter, the reference diameter obtained by interpolation, and the percent diameter stenosis through standard laboratory procedures.[4]

The OCT analyses will be performed with the Apqvue program (Abbott, United States) for acquisitions with the Opq system (Abbott, United States), or the QIVUS Research Edition 3.1 program (Medis, Netherlands) for acquisitions with other systems. The lesion minimum lumen area will be automatically estimated. Manual measurement of the vessel reference area will be performed by tracking the external elastic membrane contour as close as possible, and if feasible, distal to the site where the minimum lumen area is located.[5] Minimum fibrous cap thickness will be assessed based on pre-established methods by the imaging laboratory.[5]

Monitoring of optical coherence tomography images

The study imaging laboratory will monitor the first 5 cases studied by OCT at each center. If discrepancies arise in the decision to allocate a vulnerable plaque between the local investigator and the central laboratory, a teleconference will be held to discuss the case with the principal investigators.

Single-blind procedure and blinding monitoring

Eligible patients will be informed that if they meet the inclusion criteria for the randomized clinical trial, they will not be verbally informed of the assigned treatment. Since information on the treatment received must be included in the procedural report, the patient's health care staff and dedicated personnel performing the follow-up staff have both been trained to not reveal the assigned treatment.

To monitor the patients' knowledge of their assigned treatment in the randomized clinical trial, they will be asked immediately after the intervention and at the 4 scheduled annual follow-ups whether they know their allocated treatment group. Search failures or patients included in the registry will be informed of the test results and the treatment received.

Table 1 of the supplementary data

List of principal investigators and participant centers

	Principal investigator	**Center**
1	Enrique GuQérrez Ibañes	Hospital Gregorio Marañón, Madrid
2	Salvatore Brugale.a	Hospital Clínic de Barcelona, Barcelona
3	Alejandro GuQérrez Baños	Hospital Universitario Puerta del Mar, Cádiz
4	Fernando Rivero Crespo	Hospital Universitario La Princesa, Madrid
5	Tamara García Camarero	Hospital Universitario Marqués de Valdecilla, Santander
6	Antonio Gómez Menchero	Hospital Juan Ramon Jiménez, Huelva
7	Ramón López Palop	Hospital Universitario Virgen de la Arrixaca, Murcia
8	Carlos Cortés Villar	Hospital Clínico Universitario de Valladolid, Valladolid
9	Íñigo Lozano Marvnez-Luengas	Hospital Universitario de Cabueñes, Gijón
10	Rosa María Cardenal Piris	Hospital Universitario Virgen del Rocío, Seville
11	Jean Paul Vílchez Tschischke	Hospital Universitari i Politècnic La Fe, Valencia
12	Raúl Millán Segovia	Hospital Universitari Son Espases, Palma de Mallorca
13	Beatriz Vaquerizo MonQlla	Hospital del Mar, Barcelona
14	Loreto Oyarzabal Rabanal	Hospital Universitari de Girona Doctor Josep Trueta, Girona
15	Juan Sánchez Rubio	Hospital Universitario Miguel Servet, Zaragoza
16	Xacobe Flores Ríos	Complexo Hospitalario Universitario A Coruña, A Coruña
17	Alfonso Jurado Román	Hospital Universitario La Paz, Madrid
18	Sergio García Blas	Hospital Clínic Universitari de Valencia, Valencia

19	Fernando Sarnago Cebada	Hospital Universitario 12 de Octubre, Madrid
20	Soledad Ojeda Pineda	Hospital General Universitario Reina Soga, Córdoba
21	José Valencia Marvn	Hospital General Universitario de Alicante, Alicante
22	Miren Telleria Arrieta	Hospital Universitario de DonosQa, San SebasQán
23	Pablo Avanzas Fernández	Hospital Universitario Central de Asturias, Oviedo
24	José Antonio Linares Vicente	Hospital Clínico Universitario Lozano Blesa, Zaragoza
25	Eva Rumiz González	Hospital General Universitari de Valencia, Valencia
26	Estefanía Fernández Peregrina	Hospital de la Santa Creu i Sant Pau, Barcelona
27	Oriol Rodríguez Leor	Hospital Universitari Germans Trias i Pujol, Badalona
28	Paula Tejedor Viñuela	Hospital General Universitario de Elche, Elche
29	Alfonso Freites Esteves	Hospital General Universitario de Ciudad Real, Ciudad Real
30	Juan Gabriel Córdoba Soriano	Hospital General Universitario de Albacete, Albacete
31	Manuela Romero Vazquianez	Hospital Universitario de Torrevieja, Torrevieja
32	Ana Belén Cid Álvarez	Hospital Clínico Universitario, SanQago de Compostela
33	Renier Goncalves Ramírez	Complejo Asistencial Hospitalario de León, León
34	Alejandro Diego Nieto	Complejo Asistencial Universitario de Salamanca, Salamanca
35	Guillermo Sánchez Elvira	Complejo Hospitalario de Navarra, Pamplona
36	Juan Caballero Borrego	Hospital Universitario Clínico San Cecilio, Granada
37	José Antonio Fernández Díaz	Hospital Universitario Puerta de Hierro Majadahonda, Madrid
38	Pedro Luis Marvn Lorenzo	Complejo Hospitalario Universitario de Gran Canaria Dr. Negrín, Las Palmas
39	Miguel Jerez Valero	Hospital de Manises, Manises
40	Alberto Pernigo|	Hospital Universitari Joan XXIII, Tarragona
41	Raquel Pimienta González	Hospital Universitario Nuestra Señora de la Candelaria, Tenerife
42	José Moreu Burgos	Hospital Universitario de Toledo, Toledo
43	Eduardo Arroyo Úcar	Hospital Universitario San Juan de Alicante, Alicante
44	Blanca Trejo Velasco	Hospital General Universitario de Castellón, Castellón
45	Bruno García del Blanco	Hospital Universitari Vall d'Hebron, Barcelona
46	Josep Gómez Lara	Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat

Table 2 of the supplementary data

Participants in the VULNERABLE trial committees

Steering committee		
President	Héctor García García	Medstar Washington Hospital Center, Washington, United States
Participants	Josep Gómez-Lara	Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain
	Enrique GuQérrez-Ibañes	Hospital Universitario Gregorio Marañón, Madrid, Spain
	Joan Antoni Gómez-Hospital	Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain
	Javier Bermejo Thomas	Hospital Universitario Gregorio Marañón, Madrid
	Armando Pérez de Prado	Hospital Universitario de León, León, Spain Fundación EPIC
Secretary	Teresa Carretero García	Fundación EPIC
Data and safety monitoring board		
President	Xavier Rosselló Lozano	Hospital Universitari Son Espases, Palma de Mallorca, Spain
Participants	Víctor Jiménez Díaz	Complejo Hospitalario Universitario de Vigo, Vigo, Spain
	José Ramón Rumoroso Cuevas	Hospital Galdakao-Usansolo, Bilbao, Spain
Biostatistics	Alicia Quirós Carretero	Universidad de León, León, Spain
Secretary	Teresa Carretero García	Fundación EPIC
Independent event adjudication committee		
President	José Ramón Rumoroso Cuevas	Hospital Galdakao-Usansolo, Bilbao, Spain
Participants	Xavier Rosselló Lozano	Hospital Universitari Son Espases, Palma de Mallorca, Spain
	Víctor Jiménez Díaz	Complejo Hospitalario Universitario de Vigo, Vigo, Spain
Secretary	Teresa Carretero García	Fundación EPIC

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Table 3 of the supplementary data

Definition of study endpoints

All-cause mortality

Death from any cause. Based on the ARC-II criteria, the causes of death will be categorized as cardiac or non-cardiac.[6]

Cardiac death

All deaths suspected to be primarily due to a cardiac condition will be considered cardiac death. Of note that deaths without a clear non-cardiac origin and those with an indeterminate etiology will be categorized as cardiac.
Cardiac death will be subcategorized into:

a) Sudden death.
b) Myocardial infarction.
c) Heart failure.
d) Other causes.
e) Unknown cause.

Acute myocardial infarction

The fourth universal definition of myocardial infarction[7] will be used to estimate primary and secondary endpoints. Exploratory data on myocardial infarctions as defined by ARC-II will be collected too.[6]
Myocardial infarctions will be subcategorized into:

a) Target vessel-related: in the presence of angiographic or ECG evidence of target vessel-related infarction.
b) Non-target vessel-related.

Target vessel-related infarctions will be further subcategorized into:

a) Target lesion-related: those with angiographic evidence originating in the segment under study.
b) Non-target lesion-related.

Spontaneous acute myocardial infarction

Acute myocardial infarction is defined based on the fourth universal classification.[7] This definition requires a rise and fall of cardiac troponin with, at least, 1 value above the 99th percentile of the upper reference limit (defined as myocardial injury), along with, at least, 1 of the following ischemic indicators:

a) Angina symptoms.
b) Presence of new changes on the ECG.
c) Development of pathological Q waves on the ECG.
d) Evidence of myocardial viability loss, or new segmental wall motion abnormality by cardiac imaging.
e) Identification of thrombus by angiography or autopsy.

This definition includes:

a) Type II myocardial infarctions caused by an imbalance between oxygen supply and demand not related to an atherothrombotic mechanism.

b) Type III myocardial infarctions in patients with death preceded by symptoms suggestive of myocardial ischemia and new electrical changes, in whom blood samples for troponin analysis could not be obtained.

Myocardial revascularization-related myocardial infarction

Patients are considered to have perioperative revascularization myocardial infarction, according to the fourth universal definition of infarction,[7] if:

a) Within the first 48 hours after percutaneous revascularization, they exhibit a rise and fall in troponin levels > 5 times the reference value in patients with normal pre-catheterization levels, along with, at least, 1 of the following:

- New changes on the ECG
- Development of Q waves on the ECG.
- Cardiac imaging evidence of presumably new, ischemic myocardial viability loss.
- Angiographic evidence of perioperative slow coronary flow associated with a complication, such as dissection, side branch occlusion, or distal embolization.

b) Within the first 48 hours following surgical revascularization, they exhibit a rise and fall in troponin levels > 10 times the reference value, along with, at least, 1 of the following:

- Development of Q waves on the ECG.
- Angiographic documentation of new graft occlusion or new native artery occlusion.
- Cardiac imaging evidence of presumably new, ischemic myocardial viability loss.

*In cases (common in the study) in which myocardial markers remain elevated prior to the procedure, a re-elevation of troponin levels > 20% of the last pre-revascularization value plus the above-mentioned additional criteria will be required.

**Additionally, exploratory data will be collected on myocardial revascularization-related myocardial infarctions based on the ARC-II criteria.[6]

Target vessel revascularization

All coronary revascularizations will be cataloged and categorized into:

a) Target vessel revascularization, including, or not, the target lesion.

b) Revascularization of another vessel.

Additionally, any revascularization will be categorized as clinically indicated in the presence of:

a) Evidence of ischemia by a non-invasive imaging modality.

b) Evidence of ischemia by an intracoronary functional test with fractional flow reserve values ≤ 0.80.

c) Angina symptoms, and if angiography shows progressive stenosis with a percent diameter stenosis ≥ 70%.

Stent thrombosis

Stent thrombosis will be categorized based on to ARC-II criteria.[6]

ECG, electrocardiogram.

Table 4 of the supplementary data
Optical coherence tomography-guided stent implantation

Pre-stent implantation evaluation

The following findings, summarized as MLD, will be evaluated:

- *Morphology*. For fibrolipidic plaques, direct stent implantation can be considered in the absence of calcium. For mixed plaques with presence of calcium, predilatation with a semi-compliant or non-compliant balloon at a 1:1 balloon-to-artery ratio is recommended.
- *Length*. Optical coherence tomography (OCT) pullback with angiographic co-registration is recommended to accurately measure and adjust lesion length. Only lesions treatable with a single stent will be accepted. Select 2 points—proximal and distal to the lesion—with a "normal" artery appearance and larger lumen caliber, covering the entire segment with characteristics of vulnerable plaque. The stent length based on the distance between these 2 points will be estimated.
- *Diameter*. Based on reference luminal diameters, stent sizes will be estimated and, if necessary, subsequent postdilatation balloon sizes too. If the external elastic membrane can be assessed, this value can be used, rounding the stent size to the smallest diameter. Per protocol, only stents with luminal diameters between 2.0 mm and 4.5 mm can be implanted.
-

Post-stent implantation evaluation

Per-protocol post-stent implantation evaluation is recommended. The following findings, summarized as MAX, will be evaluated:

- *Medial dissection.* The presence of an edge dissection reaching the medial layer (or a hematoma in this location), covering ≥ 60° of the vessel perimeter and extending ≥ 3 mm in length will be considered a major dissection. Treatment with an overlapping stent is recommended.
- *Apposition.* Post-dilatation is recommended in case of stent malapposition ≥ 3 mm in length with a strut-to-vessel distance ≥ 450 µm until proper stent apposition is achieved.
- *Expansion.* Minimum stent area ratio ≥ 80% compared with the reference area is considered appropriate stent expansion. The "tapered" or "double" reference area will be selected based on the presence of significant caliber branches in the treated area. In the presence of under-expansion, postdilatation with a non-compliant balloon adjusted to the reference diameters is recommended.

Table 5 of the supplementary data

Rate of target vessel failure in non-culprit lesions in patient with acute coronary syndrome

Study	Study group	n	TVF (%)	Time	Notes
COMPLETE[8]	Complete revascularization	2016	8.9[b]	3 years	Randomized clinical trial on angiography-guided complete revascularization vs no revascularization. Elevated rate of lesions with a PDS ≥ 70%.
	Culprit lesion-only revascularization	2025	16.7[b]		
FLOWER-MI[9]	Angiography-guided complete revascularization	586	5.5[b]	1 year	Randomized clinical trial on FFR-guided vs angiography-guided complete revascularization. A total of 40% of lesions with a PDS of 40% up to 69%.
	FFR-guided complete revascularization	577	4.2[b]		
PROSPECT II[10]	Non-culprit lesions with plaque burden ≥ 70%	787	4.6	4 years	Observational trial with non-culprit lesions on OMT. Elevated rate of lesions with a PDS < 50%.
	Non-culprit lesions with plaque burden < 70%	2842	0.4		
PROSPECTAbsorb[11]	Bioresorbable stent implantation in vulnerable lesions	93	4.3	4 years	Substudy of PROSPECT II. Vulnerable lesions defined as FFR > 0.80 and plaque burden > 65% by IVUS. Angiographic control at 2 years. OMT in vulnerable lesions.
	OMT in vulnerable lesions	89	10.7		
FRAME-AMI[12a]	Angiography-guided complete revascularization	278	19.7[b]	3.5 years	Randomized clinical trial on angiography-guided vs FFR-guided complete revascularization. Elevated rate of lesions with a PDS ≥ 70%.
	FFR-guided complete revascularization	284	7.4[b]		
FIRE[13a]	Physiology-guided complete revascularization	720	15.7[b]	1 year	Randomized clinical trial on angiography-guided vs FFR-guided complete revascularization in patients ≥ 75 years. A total of 40% of lesions with a PDS of 50% up to 69%.
	Culprit lesion-only revascularization	725	21.0[b]		
PECTUS-obs[14a]	Vulnerable lesions	143	4.9	2 years	Observational study with OMT of non-culprit lesions.
	Non-vulnerable lesions	277	1.4		

Study	Study group	n	TVF (%)	Time	Notes
					Non-culprit lesions with a PDS of 30% up to 90% and FFR values > 0.80 by OCT.
PREVENT[15a]	Bioresorbable or drug-eluting stent implantation in vulnerable lesions	803	0.4	2 years	Lesions in patients with chronic coronary syndrome and FFR > 0.80. Vulnerable plaque defined by various imaging modalities, mostly IVUS based on minimal lumen area ≤ 4 mm² and plaque burden ≥ 70%.
	OMT in vulnerable lesions	803	3.4		

FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OMT, optimal medical therapy; PDS, percent diameter stenosis; TVF, target vessel failure.
Note: TVF is a composite of cardiac death, non-fatal target vessel myocardial infarction, or symptom-driven target vessel revascularization.
[a] Studies published after the sample size calculation in this study.
[b] Data per patient (not per lesion), being a composite of all-cause mortality, any myocardial infarction, or revascularization.

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