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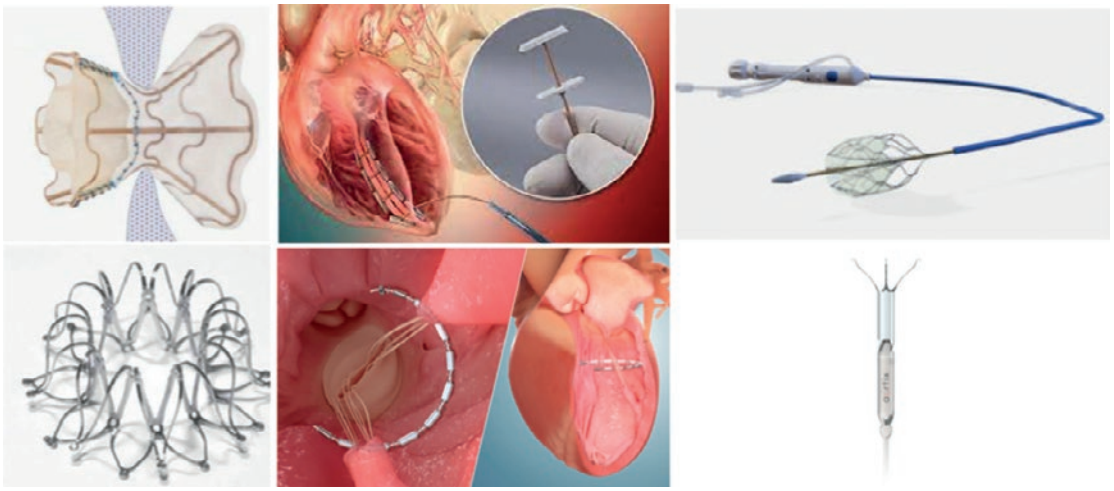

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Editorial

Stent delivery during primary angioplasty: speed doesn't matter

Despliegue del stent en la angioplastia primaria: no es cuestión de velocidad

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Although mechanical reperfusion has been shown to achieve epicardial recanalization in almost all acutely occluded arteries, the optimal myocardial reperfusion still remains a major issue, and it is only achieved in barely 50% to 70% of the patients with ST-segment elevation myocardial infraction (STEMI).[1] Several factors have been demonstrated to have an impact on myocardial reperfusion including preoperative Thrombolysis in Myocardial Infarction (TIMI) flow, ischemia time, ageing, diabetes, thrombus burden, and vessel size.[1-3] Therefore, over the last few decades, several studies have been conducted on adjunctive therapies and devices to improve reperfusion such as antithrombotic therapies,[4-5] and thrombectomy.[6]

The use of coronary stents, in particular drug-eluting stents, currently represents the standard of care,[7] and considerable attention has been paid over the last decade on stenting techniques,[8] and their impact on procedural results and outcomes.

In a paper recently published in *REC: Interventional Cardiology*, Vega et al.[9] conducted a randomized trial to address the impact of the delivery system speed deflation on myocardial perfusion and the outcomes of patients with STEMI treated with direct stenting.

In fact, fast balloon deflation has been suggested to cause abrupt changes in coronary flow that may trigger the detachment of thrombotic material, and plaque fragments, disrupted by the stent strut coverage.[10] Also, variations of intravascular pressure may increase the wall shear stress, which has been shown to promote plaque destabilization, endothelial dysfunction,[11] and also the hydrostatic pressure inside the interstitial space favoring myocardial oedema, and cellular damage.[12]

Indeed, in post-conditioning strategies, balloon inflation has been proposed as a mechanism of protection against ischemic damage by inducing repeated sequences of ischemia-reperfusion that have been proven to reduce the infarct size.[13]

In a previous randomized study that recruited 211 patients, Gu et al.[14] reported an improvement of coronary flow with the stent delivery system slow deflation strategy, yet with a not significant reduction of the no-reflow phenomenon, and null effects on the long-term outcomes.

However, this study primary endpoint was the corrected TIMI frame count, an index of coronary flow, whereas Vega et al.[9] assessed the myocardial blush grade (MBG) and the ST-resolution, both parameters of myocardial perfusion that may be conditioned by several other factors.

In fact, the Spanish study[9] was consistent with previous larger reports,[8] and diabetes, hypertension, kidney disease, hemodynamic parameters, and lesion location emerged as independent predictors of MBG. Therefore, it may be argued that slow balloon deflation may have facilitated a successful epicardial reperfusion, although this did not translate into microcirculation differences or myocardial salvage.

Furthermore, although the extensive use of thrombectomy and glycoprotein IIb/IIIa inhibitors in the overall cohort of patients, as the authors very well pointed out, is not representative of the current guidelines-indicated strategies regarding primary percutaneous coronary intervention (PCI), it may have prevented such complications and minimized any potential benefits with the delivery system slow deflation strategy. Indeed, former studies and meta-analyses have demonstrated that the administration of these potent antiplatelet agents during a primary PCI, mainly as a downstream strategy,[15] could translate into better myocardial perfusion, and reduce mortality.

In addition, the recruitment restriction to those lesions eligible for direct stenting in the study conducted by Vega et al.[9] may have led to the selection of a very low-risk population where the occurrence of an impaired MBG was extremely low (observed in about 25% of the study population).

Finally, since the study was stopped after the recruitment of 50% of the predefined sample size for futility, we cannot discard that, with a larger population and different endpoints, any differences would have emerged. Future larger studies with a more

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heterogeneous and higher-risk population of patients with STEMI, more complex lesions, a higher rate of comorbidities, less extensive use of glycoprotein IIb/IIIa inhibitors, are certainly justified to better define the potential role of slow balloon deflation during primary PCI in terms of periprocedural complications, myocardial reperfusion, short- and long-term outcomes.

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CONFLICTS OF INTEREST

None declared.

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Editorial

Utility of the pressure guidewire in diabetic patients

Utilidad de la guía de presión en pacientes diabéticos

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Blood pressure indices like fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) measure the distal-to-aortic pressure ratio of a lesion in a similar way using a pressure guidewire. FFR requires the induction of maximal hyperemia while the iFR is an index based on the assessment of pressure curves at rest. There is solid confirmation of the validity and efficacy of such indices from multiple studies while their use is widely backed by the clinical practice guidelines.[1]

However, the efficacy of blood pressure indices is based on 2 fundamental objectives. The first one is to prove that they are useful to indicate the revascularization of a lesion when the resulting value is below the cut-off point (≤ 0.80 for the FFR, and ≤ 0.89 for the iFR). The second one is to demonstrate that lesions with values above the cut-off point (> 0.80 or > 0.89, respectively) have a low risk of requiring revascularization, and lack of ischemic events at follow-up. Conceptually, the first indication is clear: a lesion with pathological values is an obstructive lesion that causes ischemia now. Therefore, if clinically indicated (and technically feasible) the best thing to do is to revascularize such a lesion. The second indication has a higher degree of uncertainty because a lesion that does not cause ischemia (now) does not necessarily mean that it will not cause it at some point in the future. This is so because the capacity of blood pressure indices (with normal results) to detect vulnerable plaques is limited, and they show a greater tendency towards progression or destabilization. Therefore, the negative predictive value of pressure indices is supposed to be worse when used in patients with a higher risk of progression into atherosclerotic cardiovascular disease.

Proof of this is that recent studies conducted in patients with acute myocardial infarction (AMI) and multivessel disease have demonstrated that the FFR of non-culprit lesions does not provide any clinical benefits regarding the revascularization of such lesions estimated visually and, therefore, under angiographic guidance.[2,3] The prevalence of vulnerable plaques causing visual stenosis between 50% and 69% in non-culprit vessels of patients with AMI is estimated at around 30%. Actually this rate is probably higher when lesions with a greater degree of angiographic obstruction are studied.[4] The COMBINE OCT-FFR trial also reported a similar rate of vulnerable plaques (25%) on the optical coherence tomography performed in diabetic patients with angiographic stenoses between 40% and 80% and normal FFR values.[5] In this study, angiographic lesions with normal FFR values associated with vulnerable plaques had more adverse events (cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization) compared to those not associated with vulnerable plaques (13% vs 3%; $P < .001$).

The article by Castro-Mejía et al.[6] recently published in *REC: Interventional Cardiology* provides the mid-term follow-up (3.5 years) of a large single-center registry of patients with intermediate angiographic lesions assessed using blood pressure indices and with normal results. This study compared the adverse events between diabetic and nondiabetic patients with the necessary statistical adjustments to compensate for the inherent differences of the baseline characteristics of both groups. The authors conclude that blood pressure indices (FFR and iFR) had a similar efficacy in diabetic and nondiabetic patients for not predicting future target vessel myocardial infarctions or the need for target lesion revascularization. However, we should mention that diabetic patients had higher rates of all-cause mortality, AMI, and need for revascularization compared to nondiabetic patients.[6] We should specifically mention that there was a 2.6-fold higher risk of infarction in any vessels at the follow-up in diabetic compared to nondiabetic patients ($P < .063$ after adjustments). However, only 13% of the AMIs registered were adjudicated to the study vessel in diabetic vs 38% in nondiabetic patients.[6] This difference can be due to chance alone or to the fact that the lesions that cause AMIs at the follow-up are scarcely susceptible to be studied with a pressure guidewire at the index procedure in diabetic patients. It is well known that these patients have more diffuse atherosclerotic cardiovascular disease, which complicates the correct angiographic assessment of the lesions (and, also, prevents the use of a pressure guidewire in such vessel for assessment purposes). It is highly likely that a strategy based on intravascular imaging modalities alone or in combination like in the COMBINE OCT-FFR trial can be of greater utility to detect this type of lesions.

Three recent studies have reported contradictory outcomes regarding the negative predictive value of blood pressure indices in diabetic patients. Kennedy et al.[7] found more AMIs and a greater need for

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target lesion revascularization with normal FFR values in diabetic patients at the 3-year follow-up. On the contrary, Van Belle et al.[8] found no differences between diabetic and nondiabetic patients who were deferred (for having normal FFR values) in 2 large registries conducted in Portugal, and France at the 1-year follow-up. No significant differences were seen either in the DEFINE-FLAIR substudy that analyzed adverse events between diabetic and nondiabetic patients in deferred patients at 1-year follow-up.[9] It should be interesting to assess the long-term follow-up of these last 2 studies to see if the negative predictive value of blood pressure indices stays the same in diabetic and nondiabetic patients.

Finally, Castro-Mejía et al.[6] propose that resting physiological indices with nonpathological findings may have a better negative predictive value compared to the FFR values of diabetic patients. This would be explained by the fact that one of the causes of discrepancy between the FFR and the iFR is microvascular dysfunction (that is more common in diabetic patients). Patients with microvascular dysfunction can have smaller drops of the pressure index during maximal hyperemia since not enough hyperemia is induced. However, resting physiological indices are not hyperemia-dependent, meaning that they should be more sensitive to detect significant epicardial lesions. However, this hypothesis was not confirmed by the DEFINE-FLAIR substudy on deferred diabetic patients.[9]

In conclusion, diabetic patients still remain as one of the challenges of interventional cardiology because they have more adverse events compared to nondiabetic patients (despite the proper optimal medical therapy). A more aggressive strategy to assess intermediate coronary lesions using pressure guidewires is advisable to guide complete revascularization in diabetic patients. Future studies should also assess whether a mixed strategy with intravascular imaging modalities of nonfunctionally significant arteries can be useful to prevent future events in this group of patients.

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CONFLICTS OF INTEREST

J. Gómez-Lara has received speaking fees for presentations on behalf of Abbott Vascular, Boston Scientific, and Terumo. R. Romaguera declared no conflicts of interests whatsoever.

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Original article

Deflation speed of the stent delivery system and primary angioplasty results: a randomized study

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ABSTRACT

Introduction and objectives: Distal embolization and no-reflow are common complications in primary angioplasty and the information available on the role played by the deflation speed of the stent delivery system is scarce. Our aim is to analyze how the deflation speed of the stent delivery system impacts the results of primary angioplasty.
Methods: From December 2016 through February 2019, all consecutive patients with ST-segment elevation myocardial infarction undergoing urgent coronary angiography at our institution and who were eligible for thrombectomy, IIB-IIIA inhibitors, and direct stenting were randomized in a 1:1 ratio to rapid (group 1, n = 103) or slow deflation of the stent delivery system, at 1 atm/second, (group 2, n = 107). Pre- and postdilatation was not allowed per protocol. The primary outcomes were myocardial blush ≥ 2 and ST-segment resolution ≥ 70% while the size of myocardial damage, the ejection fraction both at discharge and at the 12-month follow-up, and the overall and 12-month cardiovascular mortality rates were the secondary outcomes.
Results: The study was stopped prematurely with 50% of the estimated sample size due to futility. Myocardial blush ≥ 2 occurred in 77 (74.7%) vs 79 (75.2%) of the patients, $P = .93$, and ST-segment resolution ≥ 70% occurred in 54 (53.9%) vs 59 (55.5%) of the patients, $P = .75$ in groups 1 and 2, respectively without any differences being reported in any of the secondary endpoints.
Conclusions: In our series, the deflation speed of the stent delivery system in primary angioplasty did not modify the myocardial blush ≥ 2, the ST-segment resolution ≥ 70% or impacted the clinical outcomes, the size of myocardial infarction according to the biomarkers or the ejection fraction.

Keywords: Primary angioplasty. ST-segment-elevation myocardial infarction. No-reflow. ST-segment resolution. Myocardial blush.

Velocidad de desinflado del sistema de liberación del *stent* en la angioplastia primaria: estudio aleatorizado

RESUMEN

Introducción y objetivos: La embolización distal y el fenómeno de *no-reflow* son complicaciones frecuentes de la angioplastia primaria. La información disponible sobre la influencia de la velocidad de desinflado del sistema de liberación del *stent* es escasa. Nuestro objetivo es analizar la influencia de este factor en los resultados de la angioplastia primaria.
Métodos: Entre diciembre de 2016 y febrero de 2019, todos los pacientes consecutivos con infarto de miocardio con elevación del segmento ST sometidos a coronariografía urgente en nuestro centro y que eran susceptibles de trombectomía, inhibidores de IIB-IIIA e implante directo de *stent* fueron aleatorizados 1:1 a un desinflado rápido del sistema de liberación (grupo 1, n = 103) o a un desinflado lento a 1 atm/s (grupo 2, n = 107). Por protocolo, no se permitió la predilatación previa ni posterior. Los objetivos primarios fueron el grado de *blush* miocárdico ≥ 2 y la resolución del segmento ST ≥ 70%. Los objetivos secundarios fueron el tamaño del infarto, la fracción de eyección al alta y a los 12 meses, y las mortalidades total y cardiovascular a los 12 meses.
Resultados: El estudio se detuvo prematuramente con el 50% del tamaño muestral calculado por futilidad. Se encontró *blush* ≥ 2 en 77 (74,7%) frente a 79 (75,2%) pacientes (p = 0,93) y resolución del segmento ST ≥ 70% en 54 (53,9%) frente a 59 (55,5%) pacientes (p = 0,75) en los grupos 1 y 2, respectivamente, sin diferencias en ninguno de los objetivos secundarios.
Conclusiones: En nuestra serie, la velocidad de desinflado del sistema de liberación del *stent* en la angioplastia primaria no modificó el *blush* miocárdico ni la resolución del segmento ST, y tampoco demostró tener influencia en los resultados clínicos, el tamaño del infarto según los biomarcadores ni la fracción de eyección.

Palabras clave: Angioplastia primaria. Infarto con elevación del segmento ST. *No-reflow*. Resolución del segmento ST. *Blush* miocárdico.

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Abbreviations

MB: myocardial blush. **pPCI:** primary percutaneous coronary intervention. **STR:** ST-segment resolution. **STEMI:** ST-segment elevation myocardial infarction. **TIMI:** Thrombolysis in Myocardial Infarction.

INTRODUCTION

Distal embolization and slow coronary flow often limit the success of primary percutaneous coronary angioplasty (pPCI). In 25% to 50% of the cases, despite satisfactory flow restoration, poor microvascular reperfusion can be seen, which leads to worse prognoses.[1] This is a field of ongoing discussion because strategies that initially showed positive results have later been questioned like direct stenting,[2] thrombus aspiration,[3,4] and the administration of beta-blockers,[5] and IIB-IIIA inhibitors.[6]

It has been confirmed that aggressive balloon dilatation with a high balloon-to-artery ratio may favor the presence of no-reflow and it has been speculated that the deflation speed of the stent delivery system may impact the results too, although the information available on this regard is scarce.

No-reflow may be due to different pathophysiological factors such as distal embolization, ischemia-reperfusion injury, and the susceptibility of coronary microcirculation to injury.[7,8] Rapid stent balloon deflation may trigger the so-called siphon effect and rapid changes in coronary hemodynamics that can be associated with distal embolization, and microcirculatory dysfunction.[9] As part of a published report, the investigators built an in vitro experimental study and combined it with a computer model to eventually find that the wall shear stress due to the different balloon deflation strategies used triggered differences in the flow final velocity as well.

Our objective is to analyze the impact of the deflation speed of the stent delivery system on myocardial blush (MB), and the ST-segment resolution (STR) in the acute phase, as well as the prognosis and ejection fraction at the 12-month follow-up.

METHODS

Patients

A randomized, parallel, single-center study was conducted with a 24-hour program of pPCI including 440 000 patients. Recruitment was carried out by convenience sampling and eligible patients were all consecutive subjects with ST-segment elevation myocardial infarction (STEMI) referred to receive a pPCI who had a culprit lesion eligible for direct stenting. Patients should have ST-segment elevations ≥ 0.1 mV in 2 contiguous leads or new left bundle branch block.

Exclusion criteria were contraindications to acetylsalicylic acid, clopidogrel or IIB-IIIA inhibitors, impossibility to complete the follow-up, life expectancy < 12 months, lesion not amenable to direct stenting, culprit lesions located at grafts or in-stent thrombosis, and previous oral anticoagulation.

After performing the coronary angiography, the patients who met the inclusion criteria and had no exclusion criteria gave their initial oral consent and were allocated by simple randomization through a computer-generated list that would create individual codes. These codes were inserted one by one in identical envelopes—prepared by personnel not involved in the study—that were thick enough so the codes could not be seen. All patients were asked to confirm their participation by giving their written informed consent within 24 hours. The study protocol was designed in full compliance with the ethical guidelines of the 1975 Declaration of Helsinki as shown in a prior approval granted by the center human research committee.

Parallel groups were created by *a)* direct stenting with fast deflation of the stent delivery system after 20 seconds of balloon inflation (group 1), or *b)* direct stenting with slow deflation at 1 atm/second after the same period of inflation (group 2).

Procedure

Patients and outcome evaluators were blind to the procedure. To minimize variability and any potential confounders the protocol was strict and included the administration of 250 mg of acetylsalicylic acid followed by 600 mg of clopidogrel at the first medical contact (according to the myocardial infarction protocol of our unit), 70 mg/kg of IV heparin, and IV abciximab or tirofiban at the beginning of the procedure for a 12-hour administration course. Manual thrombectomy and posdilatation of the stent were performed systematically, but implantation of a second stent was not allowed per protocol. Intention-to-treat and per protocol analyses were performed. The former dictated the main analysis. The volume of contrast per injection was 6 mL administered for 3 seconds into the left main coronary artery followed by 4 mL administered for 2 seconds into the right coronary artery using the ACIST device (ACIST Medical Systems Inc., United States). Intracoronary nitroglycerine (100 µg to 200 µg) was administered before the final injection to assess MB. Myocardial blush was studied in the right anterior oblique 20-degree projection with 20-degree caudal angulation, and in the left anterior oblique 45-degree projection with 20-degree cranial angulation regarding the left main coronary artery, and in the anteroposterior projection with 20-degree cranial angulation regarding the right coronary artery. Recordings were acquired at 30 images/second without image magnification with a prolonged duration until the venous phase of the myocardial circulation was completed.

Within the first 30 minutes upon arrival to the coronary care unit, patients underwent a 12-lead electrocardiogram and blood samples were obtained for troponin I assessment 6 and 24 hours after the procedure, as well as additional measurements until a reduction in the levels reported was confirmed.

Optimal medical management according to guidelines was recommended with statins, beta-blockers, or renin-angiotensin system blockers. Also, dual antiplatelet therapy was indicated for 12 months. Switching to ticagrelor during admission was also recommended in the absence of significant risk of bleeding.

Outcomes

The 2 primary endpoints were how the deflation speed of the stent delivery system impacted MB at the end of the procedure, and the

STR. The final MB was analyzed blindly by an external core laboratory in a different region and the variable analyzed was the percentage of MB grade ≥ 2 vs < 2 between both groups by visual assessment. Two interventional cardiologists with > 10 years of experience grading MBs[10] were involved in the evaluation and, in case of disagreement, a third opinion was requested. The STR was analyzed by evaluators not involved in the study who were blind to the procedure. The J-point was manually identified with respect to the nearest 0.5 mm in all leads except in the aVR lead. Using the TP segment as the isoelectric baseline interval, the extent of the ST-segment elevation with respect to the nearest 0.05 mV was measured 80 ms after the J-point. The STR was estimated by a reduction in the sum of the ST-segment elevation in all leads except in the aVR from the baseline ECG compared to the ECG performed upon arrival at the coronary care unit. The variable was a binary outcome, the ≥ 70% resolution of the sum of millimeters of ST-elevation between both recordings.

The secondary endpoints were: *a)* size of the myocardial damage comparing the maximum levels of troponin I; *b)* ejection fraction at discharge; *c)* ejection fraction at 12 months; *d)* all-cause mortality rate at 12 months; and *e)* 12-month cardiovascular mortality rate.

Definitions

Angiographic thrombus burden was defined according to Sianos' classification[11] while collateral supply was defined according to Rentrop classification.[12]

Quantitative coronary angiography

The Medis Suite XA system (Medis Medical Imaging, Israel) was used for the analysis according to the experts' standards.[13] Lesion length was measured once the vessel flow had been restored after thrombectomy. The diameter parameters were taken at the end of the procedure after the stent was deployed due to the difficulties reported while performing analyses in thrombotic vessels. The following data were used: reference vessel diameter (the average lumen diameter assumed without atherosclerotic disease), minimal lumen diameter, postoperative stenosis, and the stent-to-artery ratio.

Sample size calculations

Based on a primary endpoint of STR of 50% in the control group[14,15] and an increase up to 62.5% in the procedural group following, the principle of minimum clinically significant difference between treatments of 25%,[16] and a dropout rate of 10%, 420 patients, 210 per group, were needed.

Interim analysis

Given the uncertainty of the results and the lack of data available on the medical literature, an interim futility analysis was planned after recruiting 50% of the sample size.

Statistical analysis

Quantitative variables with normal distribution were expressed as means and standard deviation, and those without a normal distribution as median and interquartile range. Categorical variables were expressed as absolute values and percentages. The mean comparison was carried out using the Student *t* test in normal distribution or the Mann-Whitney *U* test when that assumption was not met. The chi-square test or Fisher's exact test were used to compare proportions. Two-tailed tests were used to analyze all studies. *P* values ≤ .05 were considered statistically significant. A logistic regression analysis was performed to adjust for possible imbalances and measure how the deflation speed rate of the stent delivery system impacted each of the 2 primary endpoints. The variables that met the 2 criteria of a reasonable association with the outcomes and *P* values < .20 in the univariate analysis were tested in the multivariate analysis. The calculations were performed using the SPSS 27.0.0.0 statistical software (IBM Corp, United States).

RESULTS

Baseline

From December 2016 through February 2019 a total of 447 patients were referred to our cath lab with a diagnosis of STEMI (figure 1, flow diagram). A total of 237 (53%) were not eligible for randomization and the remaining 210 (47%) were allocated to fast (103, 49%) or slow balloon deflation (107, 51%). The initially calculated sample size was 420 patients but, after an interim analysis with 50% of the sample recruited, the study was terminated early due to futility. There was 1 protocol violation in the first group and 4 in the second group. The intention-to-treat analysis is seen in this section and the per protocol analysis on tables 3 to 5 of the supplementary data. The baseline and procedural characteristics of the study cohort are shown on table 1 and table 2. There were no statistical differences between both groups although, despite the randomization process, there was a non-significant trend towards a larger vessel diameter in the slow deflation group. All cases were performed with 6-Fr guiding catheters.

Endpoints

The primary endpoint, MB grade ≥ 2compared to < 2, occurred in 77 (74.7%) vs 79 (75.2%), *P* = .93, of the patients, and STR ≥ 70% in 54 (53.9%) vs 59 (55.5%), *P* = .75, of the patients from the rapid and slow deflation groups, respectively. Also, there were no differences in any of the secondary endpoints regarding the size of myocardial damage, the ejection fraction at discharge, the ejection fraction at 12 months, the overall mortality rate at 12 months or in the cardiovascular mortality rate at 12 months (table 3).

Predictors of myocardial blush

The univariate analysis was performed with the variables shown on table 1 of the supplementary data. The variables age, creatinine clearance levels < 60 mL/min, postoperative maximum lumen diameter, past medical history of hypertension, systolic blood pressure at admission, Rentrop grade ≥ 2 collateral circulation, and the first medical contact to balloon time were tested using a logistic regression model. Systolic blood pressure at admission, creatinine clearance levels < 60 mL/min, and the postoperative maximum lumen diameter were predictors of blush ≥ 2 while in the final model hypertension remained with *P* values = .074 (table 4). The predictive power was moderate with an area under the ROC curve of 0.71 (0.63-0.80) (figure 2).

Predictors of ST-segment resolution ≥ 70%

The univariate analysis was performed with the variables listed on table 2 of the supplementary data. The variables tested in the

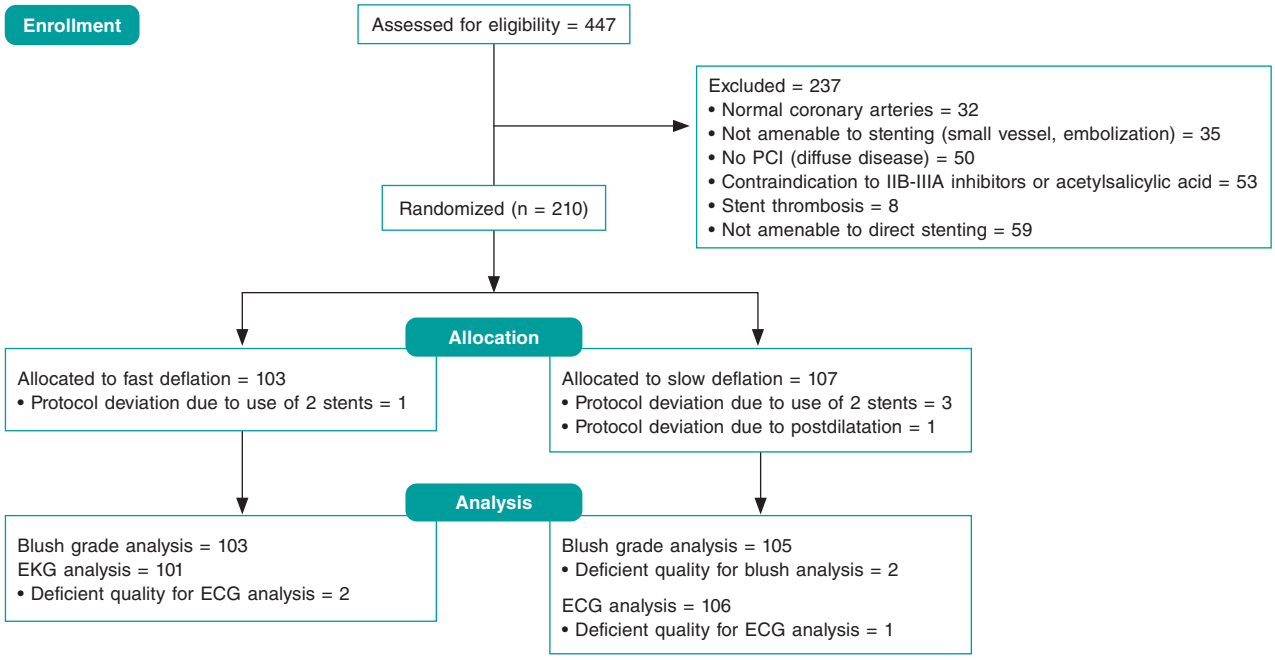

Figure 1. Study flow-chart. ECG, electrocardiogram; PCI, percutaneous coronary intervention.

Table 1. Baseline clinical characteristics

	Fast deflation N = 103	Slow deflation N = 107	*P*
Age	59.73 (10.56)	59.33 (10.71)	.78
Sex (female)	26 (25.2)	20 (18.7)	.25
Diabetes	14 (13.6)	21 (19.6)	.24
Hypertension	40 (38.9)	48 (44.8)	.37
Hypercholesterolemia	37 (35.9)	45 (42.1)	.36
Smoking	65 (63.1)	71 (66.3)	.62
Previous myocardial infarction	4 (3.9)	6 (5.6)	.75
Previous percutaneous coronary intervention	3 (2.9)	4 (3.7)	1.00
Previous coronary artery bypass graft	0 (0)	1 (0.1)	1.00
Previous stroke	1 (0.1)	0 (0.0)	.49
Creatinine clearance levels < 60 mL/min	14 (13.6)	22 (20.5)	.18
Blood pressure at admission	123.4 (30.8)	129.6 (28)	.13
Shock	4 (3.9)	1 (0.09)	.21
Radial access	103 (100)	105 (98.1)	.50
Number of diseased vessels	1.38 (0.61)	1.45(0.66)	.42
Total ischemic time	192 (125-295)	169 (120-260)	.21
First medical visit to balloon time	87 (66-130)	80 (65-114)	.22
ST elevation before procedure (mm)	11.40 (6.74)	12.63 (8.06)	.24

Quantitative variables with normal distribution are expressed as means and standard deviation (SD), variables with non-normal distribution as median and interquartile range, and categorical variables are expressed as absolute values and percentages.

Table 2. Characteristics of the procedure

	Fast deflation N = 103	Slow deflation N = 107	*P*
Vessel			.60
Left anterior descending coronary artert	44 (42.7)	40 (37.4)	
Left circumflex artery	13 (12.6)	18 (16.8)	
Right coronary artery	46 (44.7)	49 (45.8)	
Preoperative TIMI ≥ grade 2 flow[a]	10 (9.7)	17 (15.9)	.21
Rentrop ≥ 2	15 (14.6)	19 (17.8)	.53
Thrombus grade score ≥ 4	46 (44.6)	50 (46.7)	.76
Drug-eluting stent	100 (97.1)	101 (94.4)	.50
Percent diameter stenosis	99.28 (3.43)	98.89 (6.48)	.58
RVD[b]	2.74 (0.42)	2.86 (0.47)	.07
Lesion length	14.07 (5.94)	13.44 (4.71)	.39
Stent diameter	3.23 (0.47)	3.32 (0.57)	.17
Maximum inflation pressure	14.68 (1.48)	14.77 (1.69)	.67
MLD[c]	2.89 (0.38)	3.00 (0.49)	.06
Minimum lumen diameter	2.63 (0.39)	2.67 (0.48)	.48
Postoperative stenosis	8.92 (4.75)	11.20 (6.25)	.01
Stent-to-artery ratio	1.05 (0.07)	1.05 (0.08)	.95

Quantitative variables with normal distribution are expressed as means and standard deviation (SD), variables with non-normal distribution as median and interquartile range, and categorical variables are expressed as absolute values and percentages.

[a] TIMI, Thrombolysis in Myocardial Infarction risk score.

[b] RVD, reference vessel diameter after the procedure.

[c] MLD, maximum lumen diameter after the procedure.

Table 3. Results

	Fast deflation N = 103	Slow deflation N = 107	*P*
Myocardial blush ≥ 2	77 (74.7)	79 (75.2)	.93
Postoperative ST-segment elevation (mm)	4.26 (5.19)	4.03 (4.69)	.73
ST-segment elevation resolution (mm)	7.03 (6.99)	8.56 (8.11)	.15
Percentage of resolution (%)	64.97 (33.35)	65.40 (34.69)	.92
Resolution ≥ 70 %	54 (53.4)	59 (55.6)	.75
TIMI grade flow after the procedure			.38
0	1	0	
1	0	1	
2	5	9	
3	97	97	
Maximum troponin-I levels	47.84 (14-129)	72 (29.7-144.75)	.14
Ejection fraction at discharge	53.9 (8.58)	54.62 (8.71)	.55
Ejection fraction at 12 months	57.43 (8.20)	57.75 (6.48)	.76
In-hospital mortality rate	1 (0.9)	2 (1.8)	1.00
Overall mortality rate at 12 months	3 (2.9)	3 (2.8)	1.00
Cardiovascular mortality rate at 12 months	2 (1.9)	3 (2.8)	1.00
Myocardial infarction	1 (0.9)	1 (0.9)	1.00
Target vessel revascularization	0	1 (0.9)	1.00

Quantitative variables with normal distribution are expressed as means and standard deviation (SD), variables with non-normal distribution as median and interquartile range, and categorical variables are expressed as absolute values and percentages. TIMI, Thrombolysis in Myocardial Infarction risk score.

multivariate analysis were sex, diabetes, hypercholesterolemia, smoking, shock, left anterior descending coronary artery, previous myocardial infarction, preoperative TIMI grade ≥ 2 flow, postoperative TIMI grade 3 flow, and Rentrop grade ≥ 2 collateral circulation, number of millimeters of ST elevation before the procedure, and creatinine clearance levels < 60 mL/min. The logistic regression model included diabetes, previous myocardial infarction, left anterior descending coronary artery, preoperative TIMI grade ≥ 2 flow, postoperative TIMI grade 3 flow, and Rentrop grade ≥ 2 collateral circulation as predictors of ST-segment resolution ≥ 70% (table 4). The area under the ROC curve was 0.75 (0.68-0.82) (figure 3).

Per protocol analysis

Protocol deviation was seen in 5 patients. In the rapid deflation group 2 stents were needed in 1 patient. In the slow deflation group 3 patients received 2 stents followed by 1 postdilatation (figure 1). Tables 3, 4 and 5 of the supplementary data show the per protocol analysis without any significant differences compared to the intention-to-treat analysis.

Table 4. Predictors of myocardial blush ≥ 2 and ST-segment resolution

	OR	95%CI	*P*
Predictors of myocardial blush ≥ 2			
Systolic blood pressure at admission	1.02	1.02-1.03	.011
Creatinine clearance levels <60 mL/min	0.29	0.13-0.66	.003
Postoperative maximum lumen diameter	3.08	1.24-7.63	.015
Hypertension	0.52	0.26-1.06	.074
Predictors of ST-segment resolution			
Diabetes	0.16	0.06-0.43	< .001
Previous myocardial infarction	13.54	1.47-124.91	.022
Left anterior descending coronary artery	0.46	0.24-0.91	.025
Preoperative TIMI grade flow ≥ 2	3.95	1.36-11.46	.011
Postoperative TIMI grade 3 flow	7.10	1.76-28.68	.006
Rentrop grade ≥ 2 collateral circulation	0.31	0.13-0.75	.010

Quantitative variables with normal distribution are expressed as means and standard deviation (SD), variables with non-normal distribution as median and interquartile range, and categorical variables are expressed as absolute values and percentages. 95%CI, 95% confidence interval; OR, odds ratio; TIMI, Thrombolysis in Myocardial Infarction risk score.

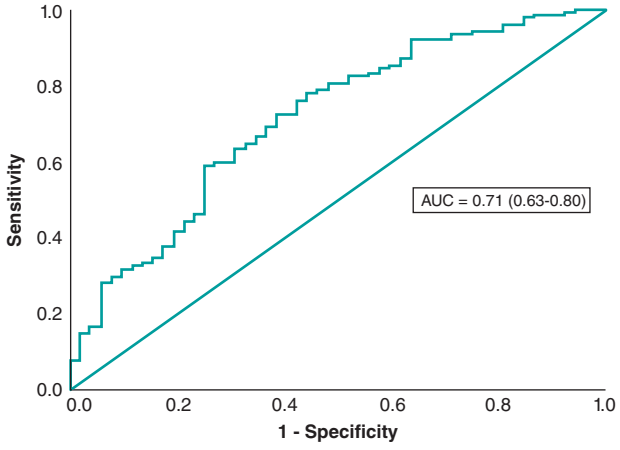

Figure 2. Receiver operating characteristic curve of the logistic regression model for myocardial blush prediction.

Missing values

In 2 patients from the slow deflation group, the quality of the angiogram did not allow us to perform a proper analysis. Regarding the electrocardiogram, suboptimal quality was recorded in 2 patients from the rapid deflation group and in 1 patient from the slow deflation group. All of them may be considered as missing values completely at random, which means that the randomization balance was never affected.

DISCUSSION

In this randomized study we assessed how the deflation speed of the stent delivery system impacted myocardial blush ≥ 2, and ST-segment resolution ≥ 70%. The most important findings are: *a)* the study was stopped with 50% of the predefined sample sized

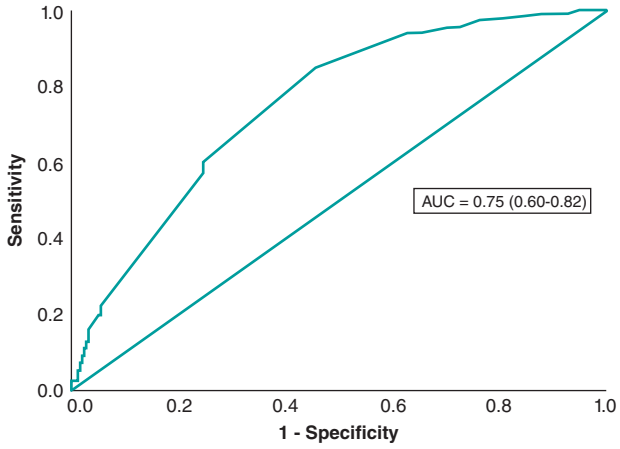

Figure 3. Receiver operating characteristic curve of the logistic regression model for ST-segment resolution.

due to futility and neither MB nor STR were modified by the intervention; *b)* no differences were seen in the size of myocardial damage, ejection fraction at 12 months and discharge or in the all-cause and 12-month cardiovascular mortality rates; *c)* systolic blood pressure at admission, creatinine clearance levels < 60 mL/min, and postoperative maximum lumen diameter played a role in MB while the past medical history of hypertension would have probably been included in the final model if the sample size would have been larger; and *d)* STR was influenced by diabetes, previous myocardial infarction, left anterior descending coronary artery, preoperative TIMI grade ≥ 2 flow, postoperative TIMI grade 3 flow, and Rentrop grade ≥ 2 collateral circulation.

The data available on the medical literature on this research topic is significantly scarce and, to our knowledge, only 1 group has provided information. Gu et al.[17] also studied the association of balloon deflation during stent deployment with coronary flow and clinical outcomes regarding pPCI in a series of 211 patients. They found that slow deflation led to favorable coronary flow and infarct size compared to conventional rapid deflation. These contradictory results may be justified by the remarkable differences seen between both cohorts. Former studies have reported on the role of balloon inflation,[18] thrombectomy,[19,20] and IIB-IIIA inhibition[21] in the management of MB. In our series, we designed a strict protocol to control these potential confounders, which is why pre- and post-dilatation was not allowed, and both thrombus aspiration and IIB-IIIA inhibitors were essential components of the procedure. The study conducted by Gu et al. allowed both pre- and postdilatation while the use of thrombectomy, and IIB-IIIA inhibitors was left to the operator's discretion. Indeed, predilatation was performed in > 80% of the patients from both groups, postdilatation in roughly 40%, thrombus aspiration in only 20%, and IIB-IIIA inhibitors were administered in 70% of the patients. Undoubtedly, the approach conducted by Gu et al. favored external validity although, in our opinion, the influence of these 4 factors may have influenced the results deeply, mainly when no adjustment was performed through a multivariate analysis. Finally, although closely related, the TIMI frame count and MB are not the same endpoint, and the ST-segment resolution was not assessed in the study conducted by Gu et al. Regarding the clinical endpoints, no differences were seen between the 2 strategies in any of the 2 studies.

As we mentioned, we were not able to show that the deflation speed of the stent delivery system impacted MB. In the multivariate analysis performed, blood pressure levels at admission, creatinine clearance levels, and the postoperative maximum lumen diameter were all predictors of MB while a past medical history of hypertension would have probably reached statistical significance with a larger sample size. Former reports have underlined how blood pressure impacts MB during the procedure.[22] Also, patients with hypertension due to an increased microvascular resistance have shown an impaired flow.[22] In addition, it has been reported that the adverse event of renal function regarding cardiovascular events may be mediated by an increased microvascular resistance.[23] Time to treatment has impacted MB in previous studies.[24] In our cohort, there were significant differences in the univariate analysis, but in the last step of the multivariate analysis it was removed from the final model, although it would have probably been present with a larger sample size. However, in the comparison of our series with the aforementioned study, we tested the vessel size as a predictor of MB while this variable was not analyzed in Luca's study, but it had played a role in previous cohorts.[25]

Consistent with this, the deflation speed of the stent delivery system did not seem to play a role in STR. We found up to 6 factors that proved its impact on the ST-segment resolution, most of them already described in former studies. As it leads to a lower ST-segment elevation, collateral circulation reduces the impact of pPCI in STR.[26] Anterior infarctions with culprit lesion in the left anterior descending coronary artery also led to lower ST-segment recoveryies in previous cohorts.[27-29] This was also seen with preoperative TIMI grade < 2 flow, and final TIMI grade flow < 3,[14,27,28,30] and diabetes.[14,28] In our series, previous myocardial infarction was a predictor of STR, although we found no explanation for this finding.

Limitations

The study was stopped in the interim analysis based on the criterion of futility. However, we do not expect the results of primary endpoints to have been any different with the whole sample size. We could have probably found more predictors and a higher predictive power of the MB and STR models, but this was not the endpoint of our study. The risk profile of the patients was low because the inclusion criteria of direct stenting, use of IIB-IIIA inhibitors, and thrombectomy focused the study on lesions more frequently associated with younger patients with a low bleeding risk and less calcification, which are features associated with better outcomes. This limits the external validity of the study because, as shown on figure 1, roughly 50% of the patients were ineligible to enter the study. This may have also played a role in the lack of differences seen between the study groups. However, as we have already explained, the purpose of our study was to avoid any confounders. Clopidogrel was the $P2Y_{12}$ inhibitor at the first medical visit according to the protocol of the regional myocardial infarction network of our area. This may also limit the external validity of the results. Myocardial blush was visually assessed and, although it was performed by 2 experienced operators, certain degree of subjectivity cannot be ruled out. The predictive power for both MB and STR was low, but it has also occurred in former series[28] being the concordance between those factors described as moderate.[31] Finally, we could not find any explanations for the role of previous myocardial infarction predicting STR as this factor was not present in former series.

CONCLUSIONS

In our series, the deflation speed of the stent delivery system in primary angioplasty did not change myocardial blush or ST-segment resolution and no influence was seen on the clinical outcomes, size of myocardial infarction assessed by biomarkers, and ejection fraction at discharge and after 12 months.

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AUTHORS' CONTRIBUTIONS

B. Vega, J. M. Vegas, J. Rondan, E. Segovia, and Í. Lozano: design, data mining, manuscript drafting, and manuscript revision. A. Pérez de Prado, C. Cuellas-Ramon, M. López-Benito, T. Benito-González, and F. Hernández-Vázquez: blush measurements, and manuscript revision.

CONFLICTS OF INTEREST

The authors declared no conflict of interests whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Distal embolization and slow coronary flow frequently reduce the success of primary angioplasty.
- Several interventions have been tested but it is a field of ongoing debate because the strategies that showed positive results at the beginning have now been questioned such as direct stenting, thrombus aspiration, and use of beta-blockers and IIB-IIIA inhibitors.
- It has been demonstrated that aggressive balloon dilatation with a high balloon to artery ratio may favor the presence of no-reflow. Also, it has been speculated that the deflation speed of the stent delivery system may impact the results, although the information available on this regard is scarce.

WHAT DOES THIS STUDY ADD?

- Our objective is to analyze how the deflation speed of the stent delivery system impacts myocardial blush, ST-segment resolution in the acute phase, prognosis, and the ejection fraction at 12months.
- The study was prematurely stopped due to futility because the speed of deflation of the stent delivery system did not change the primary outcomes or impacted the size of the infarction, prognosis or the ejection fraction at 12 months whatsoever.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000234.

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Original article

Diabetes mellitus and long-term safety of FFR and iFR-based coronary revascularization deferral

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ABSTRACT

Introduction and objectives: The safety of physiology-based revascularization in patients with diabetes mellitus has been scarcely investigated. Our objective was to determine the safety of deferring revascularization based on the fractional flow reserve (FFR) or the instantaneous wave-free ratio (iFR) in diabetic patients.
Methods: Single-center, retrospective analysis of patients with intermediate coronary stenoses in whom revascularization was deferred based on FFR > 0.80 or iFR > 0.89 values. The long-term rate of major adverse cardiovascular events, a composite of all-cause mortality, myocardial infarction, and target vessel revascularization (TVR), was assessed in diabetic and non-diabetic patients at the follow-up. The rate of TVR based on the type of physiological index used to defer the lesion was also evaluated.
Results: We evaluated 164 diabetic (214 vessels) and 280 non-diabetic patients (379 vessels). No significant differences in the rate of major adverse cardiovascular events was seen between diabetic and non-diabetic patients (20.1% vs 13.2%; $P = .245$) at a median follow-up of 43 months. All-cause mortality and cardiac death were not statistically different between both groups in the adjusted analysis ($P > .05$). A trend towards a higher rate of myocardial infarction was seen in diabetic patients (6.7% vs 2.9%; $P = .063$). However, the rate of target vessel myocardial infarction was similar in both groups ($P = .874$). Overall, TVR was similar in diabetics and non-diabetics (4.7% vs 4.2%; $P = .814$); however, when analyzed based on the physiological index, numerically, diabetics had a higher rate of TVR when the FFR was used in the decision-making process compared to when the iFR was used (6.4% vs 0.0%; $P = .064$).
Conclusions: Deferring the revascularization of intermediate stenoses in patients with DM based on the FFR or the iFR is safe regarding the risk of TVR or target vessel myocardial infarction, with a rate of events at the long-term follow-up similar to that seen in non-diabetic patients.

Keywords: Fractional flow reserve. Instantaneous wave-free ratio. iFR. Diabetes mellitus.

Diabetes mellitus y seguridad a largo plazo del diferimiento de la revascularización coronaria basado en FFR e iFR

RESUMEN

Introducción y objetivos: La seguridad de la revascularización fisiológica en pacientes diabéticos ha sido poco investigada. El objetivo fue determinar la seguridad de diferir la revascularización basándose en la reserva fraccional de flujo (FFR) o en el índice instantáneo libre de ondas (iFR) en pacientes con diabetes mellitus.
Métodos: Análisis retrospectivo, unicéntrico, de pacientes con estenosis coronarias intermedias en quienes se había diferido la revascularización en función de unos valores de FFR > 0,80 o de iFR > 0,89. Se analizó la incidencia a largo plazo de eventos cardiovasculares adversos mayores, una combinación de muerte por cualquier causa, infarto miocárdico y revascularización del vaso diana (RVD) en pacientes con y sin diabetes. También se evaluó la incidencia de RVD según el tipo de índice fisiológico utilizado para diferir la revascularización.
Resultados: Se evaluaron 164 pacientes diabéticos (214 vasos) y 280 pacientes no diabéticos (379 vasos), con una mediana de seguimiento de 43 meses. No se observaron diferencias significativas en los eventos cardiovasculares adversos mayores entre pacientes con y sin diabetes mellitus (20,1 frente a 13,2%; p = 0,245). La mortalidad por cualquier causa y de causa cardiaca no

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fue estadísticamente diferente entre ambos grupos en el análisis ajustado (p > 0,05). Se observó una tendencia a una mayor incidencia de infarto de miocardio en los pacientes con diabetes mellitus (6,7 frente a 2,9%; p = 0,063), pero el infarto relacionado con el vaso diana fue similar en ambos grupos (p = 0,906). En general, la RVD fue similar en diabéticos y no diabéticos (4,7 frente a 4,2%; p = 0,787); sin embargo, cuando se analizó según el índice fisiológico, los diabéticos tuvieron una mayor tasa numérica de RVD cuando se utilizó la FFR en la toma de decisiones en comparación con el iFR (6,4 frente a 0,0%; p = 0,064).
Conclusiones: Diferir la revascularización de estenosis intermedias en pacientes con diabetes mellitus según la FFR o el iFR es seguro en términos de RVD e infarto relacionado con el vaso diana, con una tasa de eventos en el seguimiento a largo plazo similar a la observada en pacientes sin diabetes mellitus.

Palabras clave: Reserva fraccional de flujo. Índice instantáneo libre de ondas. iFR. Diabetes mellitus.

Abbreviations

DM: diabetes mellitus. **FFR:** fractional flow reserve. **iFR:** instantaneous wave-free ratio. **MACE:** major adverse cardiovascular events. **TVR:** target vessel revascularization.

INTRODUCTION

Physiological evaluation has a class IA recommendation to guide coronary revascularization in the current clinical practice guidelines.[1] Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) have proven to be safe tools to guide revascularization therapy in several clinical scenarios.[2-4]

The results of the DEFER trial at the 15-year follow-up showed the long-term safety of FFR to defer therapy in functionally non-significant stenosis.[5] Afterwards, the DEFINE-FLAIR and the iFR-SWEDEHEART trials proved the non-inferiority of the iFR compared to the FFR to guide revascularization of moderate stenosis at the 1-year follow-up.[3,6] The utility of physiological guidance to guide revascularization in multivessel disease has been confirmed in the FAME and the SYNTAX II clinical trials.[7,8]

However, the prognostic value of pressure guidewire assessment in certain high-risk groups has not been firmly established yet. A pooled analysis of the DEFINE-FLAIR and the iFR-SWEDEHEART trials found a higher rate of events in patients with acute coronary syndrome in whom revascularization of non-culprit vessels was deferred based on the FFR or the iFR compared to stable patients.[3,6] Patients with diabetes mellitus (DM) are a high-risk group with a well-known higher burden of cardiovascular disease and worse prognosis including more extensive atherosclerosis, more prevalence of multivessel disease, and a faster disease progression compared to non-diabetic patients.[9-11] The special characteristics of the extent and spread of atherosclerosis in patients with DM raises concerns on the safety surrounding deferring revascularization in this population. Our objective was to evaluate the safety of revascularization deferral based on pressure guidewire interrogation in diabetic patients at the long-term follow-up.

METHODS

Study population

This is a single center, retrospective, and open-label trial. The study population was recruited from a total of 1321 consecutive patients with coronary artery disease in whom the iFR or the FFR indices were used to determine the need for coronary revascularization from January 2012 through December 2016. In 444 patients (34%) the revascularization of ≥ 1 lesions was deferred based on FFR values > 0.80 or iFR values > 0.89. Patients with stable angina and acute coronary syndrome (with non-culprit stenosis interrogated with pressure guidewires) were included in the study. For the analysis, the overall population was divided into 2 groups: DM and non-DM. The DM group was defined based on their past personal history included in their medical records. The study flow chart depicting patient selection is shown on figure 1.

This retrospective, cohort study was conducted according to the principles established by the Declaration of Helsinki. Both the informed consent and the research committee assessment were spared due to the retrospective nature of the study; each patient included in the database was encrypted and de-identified to protect everyone's privacy.

The physiological procedure

Pressure guidewire assessment was performed using a commercial guidewire (Verrata, Philips Healthcare, United States; PressureWire [Certus. Aeris, X] St. Jude Medical, United States) and the standard technique previously reported.[3,12] As a standard practice, an intracoronary bolus of nitrates (200 mcg) was administered before the FFR or iFR measurements. The cases submitted for FFR assessment received IV adenosine at a rate of 140 µg/kg/min. The cut-off values to defer revascularization were FFR > 0.80 or iFR > 0.89. The presence of significant drift was discarded by placing the sensor of the pressure guidewire on the tip of the guiding catheter at the end of the physiological measurements acquisition.

In patients with stable angina, the physiological evaluation was performed as part of the same procedure, and all intermediate stenoses were assessed. In patients with acute coronary syndrome, interrogation with the pressure guidewire was performed at a staged procedure in non-culprit vessels only.

Endpoints

The primary endpoint was the 4-year risk of major adverse cardiovascular events (MACE) defined as a composite endpoint of all-cause mortality, myocardial infarction or unplanned target vessel revascularization (TVR). The secondary endpoints were *a)* the individual components of MACE, *b)* the rate of target vessel myocardial infarction, and *c)* the rate of unplanned TVR based on the physiological index used (FFR or iFR)

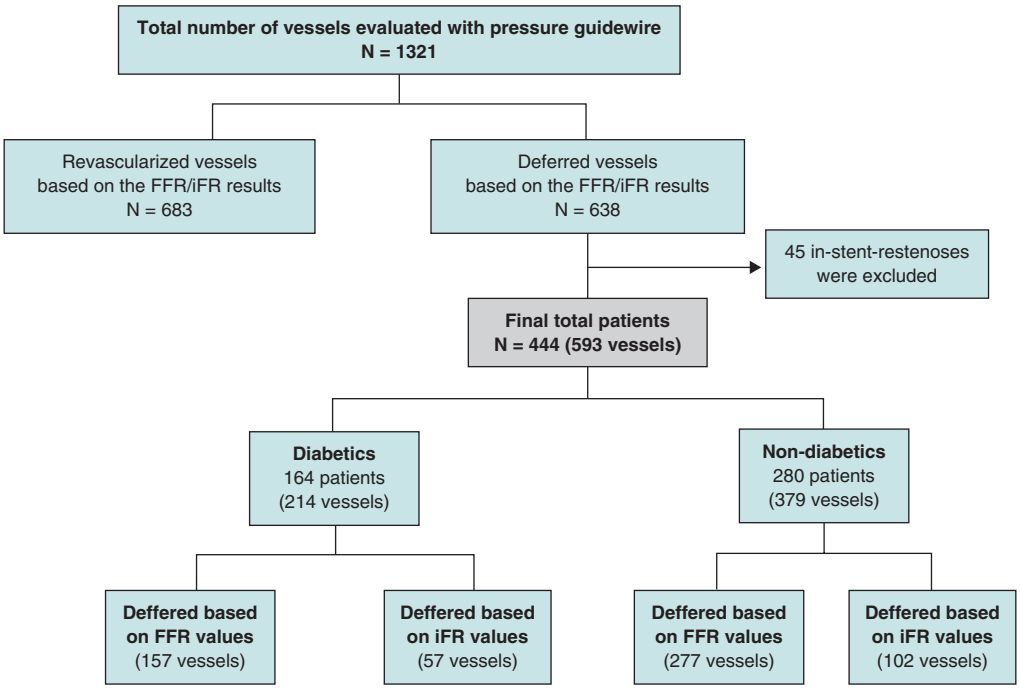

Figure 1. Study flow chart. iFR, instantaneous wave-free ratio; FFR, fractional flow reserve.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Discrete variables are summarized as frequency (percentages). Under baseline conditions, group comparisons were made using the Student *t* test or the Mann Whitney U test for continuous variables and Pearson's chi-square test for discrete data.

Time-to-event analysis was performed using the Kaplan-Meier method, and group comparison was performed using the Mantel-Cox (log-rank) test. For the primary and secondary endpoint comparison between diabetics and non-diabetics, a Cox Proportional hazards model was used to estimate hazard ratios (HR). The adjusted analysis was performed based on age, sex, hypertension, dyslipidemia, smoking habit, chronic kidney disease, previous stroke, previous percutaneous coronary intervention, and coronary artery bypass grafting surgery.

All probability values were 2-sided with 95% confidence intervals (95%CI). *P* values < .05 were considered statistically significant. The SPSS version 23.0 (IBM Corp, Armonk, NY, United States) and STATA version 15 (Stata Corp, College Station, TX, United States) statistical packages were used for statistical analyses.

RESULTS

Baseline clinical and angiographic characteristics

The baseline clinical characteristics are shown on table 1. In the overall study population, mean age was 68.4 years, and 39.6% were patients with DM (164 patients). As expected, patients with DM had more cardiovascular risk factors and comorbidities compared to patients without DM. There were no significant differences in the clinical presentation between both study groups (*P* > .05). Most patients received optimal medical treatment at the hospital discharge without significant differences between DM and non-DM patients (*P* > .05).

Characteristics of vessels with deferred revascularization

On average, deferred revascularization was performed in vessels with stenoses of intermediate severity (percent diameter stenosis, 59.73% ± 9.2%). The most frequently interrogated artery was the left anterior descending coronary artery (43.2%). In most patients, only 1 vessel was deferred (72.7%). Nevertheless, in about 4% of patients, revascularization was deferred in 3 vessels within the same procedure.

In our study population, revascularization deferral was based more frequently in the FFR (434 vessels, 73.2%) compared to the iFR (159 vessels, 26.8%). The same ratio applied to patients with DM: revascularization was deferred in 157 vessels (73.4%) based on FFR values compared to 57 vessels (26.6%) based on iFR values. The mean FFR and iFR values of the overall population were 0.87 ± 0.46 and 0.94 ± 0.41, respectively without any significant differences between diabetic and non-diabetic patients (table 2).

Clinical outcomes at the long-term follow-up based on the presence of diabetes

The median follow-up was 43 months [interquartile range, 31.1-55.8] without any differences being reported between DM and non-DM patients. The clinical outcomes are shown on table 3. Diabetic patients had higher rates of MACE (33 [20.1%] vs 37 [13.2%] in non-DM patients) although this difference did not reach statistical significance in the adjusted analysis (HR, 0.98, 95%CI, 0.46-2.11; *P* = .964). The all-cause mortality rate was higher in diabetics (18 [10.8%] vs 15 [5.3%] in non-diabetics), but the rates of cardiovascular death were not statistically different in either group (3.1% vs 2.1%). A trend towards a higher rate of myocardial infarction was seen in patients with DM (6.7% vs 2.9%; *P* = .063), yet target vessel myocardial infarction was similar in both groups (HR, 0,87; 95%CI, 0.15-4.89; *P* = .906). Similar rates of unplanned revascularization and TVR were seen between diabetics and non-diabetics (figure 2 and table 3).

Table 1. Baseline characteristics

	Total (N = 444)	Diabetics (N = 164)	Non-diabetics (N = 280)	*P*
Clinical characteristics, N (%)				
Sex				.026
Male	340 (76.5)	116 (70.7)	224 (80.0)	
Female	104 (23.4)	48 (29.3)	56 (20.0)	
Age (year)	68.41	70.02	67.46	.003
Arterial hypertension	321 (72.3)	138 (84.1)	183 (65.4)	<.001
Hyperlipidemia	287 (64.6)	124 (75.6)	163 (58.2)	<.001
Current smoker	253 (57.0)	85 (51.8)	168 (60.0)	.093
Chronic kidney disease	41 (9.2)	29 (17.7)	12 (4.3)	<.001
COPD	30 (6.8)	9 (5.5)	21 (7.5)	.415
Previous cerebrovascular disease	21 (4.7)	12 (7.3)	9 (3.2)	.049
Peripheral vascular disease	38 (8.6)	18 (11.0)	20 (7.1)	.164
Previous AMI	47 (10.6)	17 (10.4)	30 (10.7)	.908
Previous PCI	220 (49.5)	70 (42.7)	150 (53.6)	.027
Previous CABG	13 (2.9)	9 (5.5)	4 (1.4)	.019
Clinical presentation, N (%)				
Myocardial infarction	148 (33.3)	46 (28.0)	102 (36.4)	.302
Unstable angina	89 (20.0)	33 (20.1)	56 (20.0)	
Stable angina	112 (25.2)	44 (26.8)	68 (24.3)	
Silent ischemia	46 (10.4)	22 (13.4)	24 (8.6)	
Other	49 (11.0)	19 (11.6)	30 (10.7)	
Therapy at discharge, N (%)				
Aspirin[a]	408 (93.8)	150 (94.3)	258 (93.5)	.720
Clopidogrel[a]	165 (37.9)	53 (33.3)	112 (40.6)	.134
Prasugrel[a]	22 (5.1)	9 (5.7)	13 (4.7)	.663
Ticagrelor[a]	78 (17.9)	30 (18.9)	48 (17.4)	.699
DAPT	332 (56.3)	111 (52.6)	221 (58.3)	.181
Statins[b]	396 (93.2)	148 (93.1)	248 (93.2)	.952
Beta-blockers[b]	334 (78.6)	121 (76.1)	213 (80.1)	.334
ACEI[b]	324 (76.2)	126 (79.2)	198 (74.4)	.260
Acenocoumarol[a]	41 (9.4)	18 (11.3)	23 (8.3)	.304
Insulin	53 (8.9)	53 (24.8)		

ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.
[a] N = 435.
[b] N = 425.

Table 2. Characteristics of the deferred arteries

	Total (N = 593)	Diabetics (N = 214)	Non-diabetics (N = 379)	*P*
Deferred vessel				
LMCA	25 (4.2)	8 (3.7)	17 (4.5)	.664
LAD	256 (43.2)	90 (42.1)	166 (43.8)	.681
LCX	173 (29.2)	59 (27.6)	114 (30.1)	.519
RCA	138 (23.3)	57 (26.6)	81 (21.4)	.145
*Number of deferred vessels per patient**				
1 vessel	323 (72.7)	122 (74.4)	201 (71.8)	.475
2 vessels	98 (22.1)	35 (21.3)	63 (22.5)	
3 vessels	19 (4.3)	7 (4.3)	12 (4.3)	
4 vessels	4 (0.9)	4 (1.4)	0 (0.0)	
Coronary physiological parameters				
Mean FFR	0.87 ± 0.46	0.86 ± 0.41	0.87 ± 0.48	.387
Mean iFR	0.94 ± 0.41	0.94 ± 0.43	0.95 ± 0.40	.091
Deferred based on FFR values	434 (73.2)	157 (73.4)	277 (73.1)	.942
Deferred based on iFR values	159 (26.8)	57 (26.6)	102 (26.9)	.942

FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery.
* N = 444.

Clinical outcomes at the long-term follow-up based on the physiological index used to defer revascularization

In patients with DM the physiological index used (FFR or iFR) that led to revascularization deferral was not associated with a significant difference in the rate of MACE (*P* = .688) or with significant differences in all-cause mortality, cardiovascular death, myocardial infarction or unplanned revascularization. Similar rates of target vessel myocardial infarction were seen in patients deferred with both techniques (DM or non-DM) (table 4).

The rate of TVR was significantly higher in patients deferred based on FFR values compared to patients deferred based on iFR values (24 [5.5%] vs 2 [1.3%], *P* = .037). This result was mainly driven by a significant trend towards a higher rate of TVR in patients with DM deferred based on FFR values compared to diabetic patients deferred based on iFR values (10 [6.4%] vs 0 [0%]), a result that did not achieve statistical significance (*P* = .065). This trend towards a lower rate of TVR in iFR-deferred vessels was not seen in non-DM patients (14 [5.1%] vs 2 [2.0%], *P* = .244) (figure 3).

DISCUSSION

The main findings of this study are: *a)* patients with DM had high rates of MACE. However, deferring the revascularization of intermediate stenoses in patients with DM based on the physiological assessment results with pressure guidewires is safe regarding the risk of TVR or target vessel myocardial infarction with a similar rate of events at the long-term follow-up compared to that seen in non-diabetic patients; *b)* both the FFR and the iFR can be used

Table 3. Clinical events at the 4-year follow-up based on the presence of diabetes

	Diabetics (N = 164)	Non-diabetics (N = 280)	Unadjusted analysis		Fully adjusted analysis*	
			HR (95%CI)	*P*	HR (95%CI)	*P*
MACE	33 (20.1)	37 (13.2)	1.58 (0.99-2.53)	.058	0.98 (0.46-2.11)	.964
All-cause mortality	18 (10.8)	15 (5.3)	2.10 (1.06-4.17)	.034	2.01 (0.92-4.40)	.079
Cardiovascular death	5 (3.1)	6 (2.1)	1.45 (0.44-4.74)	.543	0.72 (0.19- 2.76)	.641
Myocardial infarction	11 (6.7)	8 (2.9)	2.54 (1.02-6.32)	.045	2.56 (0.95- 6.91)	.063
Unplanned revascularization	17 (10.4)	20 (7.1)	1.53 (0.80-2.93)	.195	1.55 (0.77- 3.10)	.219
	Diabetic vessels (N = 214)	**Non-diabetic vessels (N = 379)**	**Unadjusted analysis**		**Fully adjusted analysis***	
			HR (95%CI)	*P*	HR (95%CI)	*P*
Target vessel myocardial infarction	2 (0.9)	4 (1.1)	0.96 (0.18-5.23)	.971	0.87 (0.15-4.89)	.874
Target vessel revascularization	10 (4.7)	16 (4.2)	1.15 (0.52-2.54)	.767	1.14 (0.38-3.42)	.814

95%CI, 95% confidence interval; HR, hazard ratio; MACE, mayor adverse cardiovascular events (all-cause mortality, myocardial infarction, target vessel revascularization).
* HR and *P* values are obtained after adjusting the model with different baseline variables (age, hypertension, dyslipidemia, smoking habit, chronic kidney disease, previous percutaneous coronary intervention, and previous coronary artery bypass grafting).

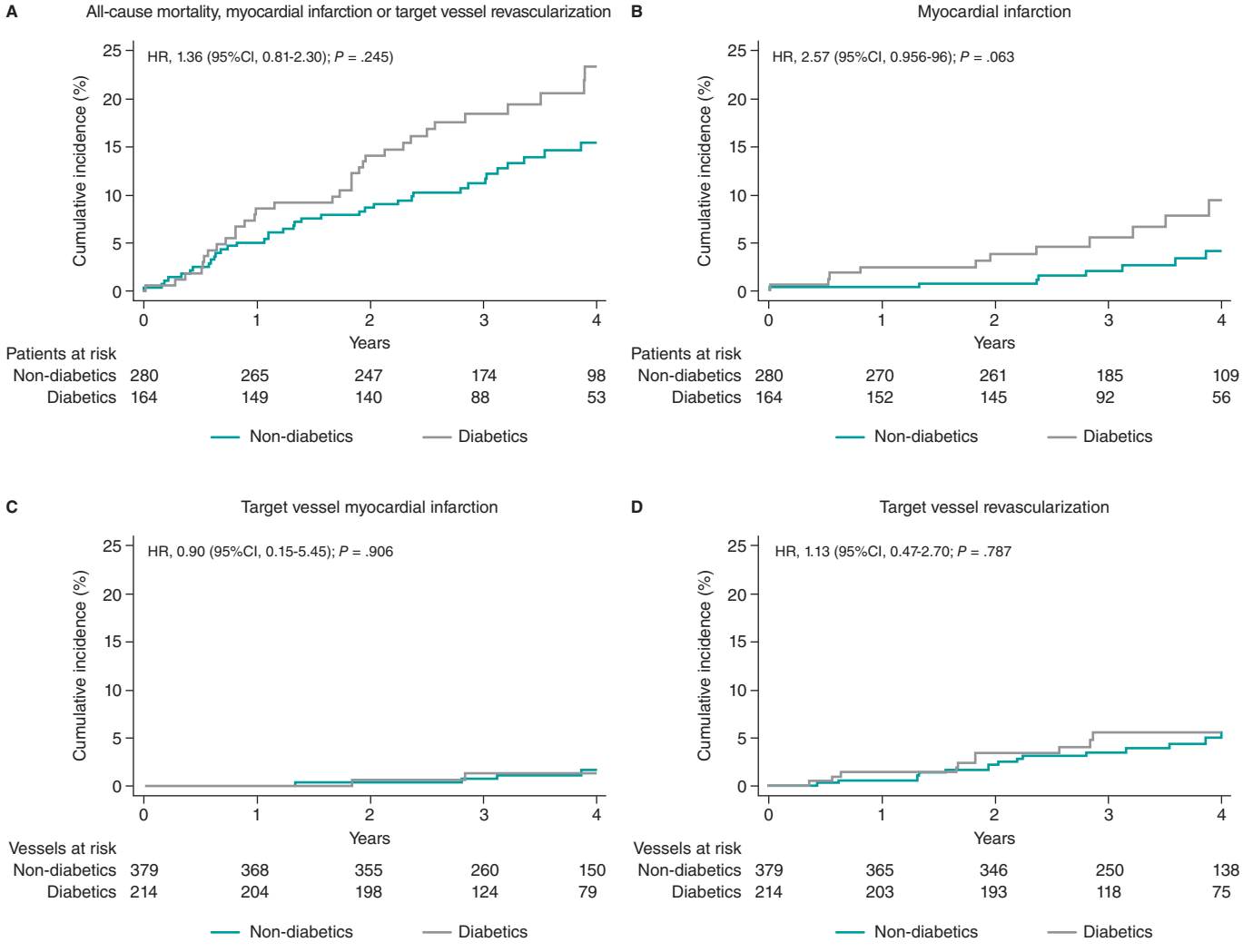

Figure 2. Clinical outcomes in diabetic and non-diabetic patients at the 4-year follow-up. 95%CI, 95% confidence interval; HR, hazard ratio.

Table 4. Clinical outcomes at the 4-year follow-up based on the technique to defer revascularization

	Patients deferred based on FFR values (N = 347)	Patients deferred based on iFR values (N = 97)	*P* (log-rank)
MACE	59 (17.0)	11 (11.3)	.288
Diabetics	27 (21.1)	6 (16.7)	.688
Non-diabetics	32 (14.6)	5 (8.2)	.277
All-cause mortality	25 (7.2)	8 (8.3)	.574
Diabetics	13 (10.2)	5 (13.9)	.417
Non-diabetics	12 (5.5)	3 (4.9)	.972
Cardiovascular mortality	8 (2.3)	3 (3.1)	.593
Diabetics	4 (3.1)	1 (2.8)	.964
Non-diabetics	4 (1.8)	2 (3.3)	.436
Myocardial infarction	16 (4.6)	3 (3.1)	.762
Diabetics	10 (7.8)	1 (2.8)	.396
Non-diabetics	6 (2.7)	2 (3.3)	.596
Unplanned revascularization	33 (9.5)	4 (4.1)	.133
Diabetics	16 (12.5)	1 (2.8)	.112
Non-diabetics	17 (7.8)	3 (4.9)	.542
	Patients deferred based on FFR values (N = 434)	**Patients deferred based on iFR values (N = 159)**	***P*** **(log-rank)**
Target vessel myocardial infarction	4 (0.9)	2 (1.3)	.527
Diabetics	2 (1.3)	0 (0.0)	.433
Non-diabetics	2 (0.7)	2 (2.0)	.172
Target vessel revascularization	24 (5.5)	2 (1.3)	.037
Diabetics	10 (6.4)	0 (0.0)	.064
Non-diabetics	14 (5.1)	2 (2.0)	.244

iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; MACE, mayor adverse cardiovascular events (all cause-mortality, myocardial infarction, target vessel revascularization).

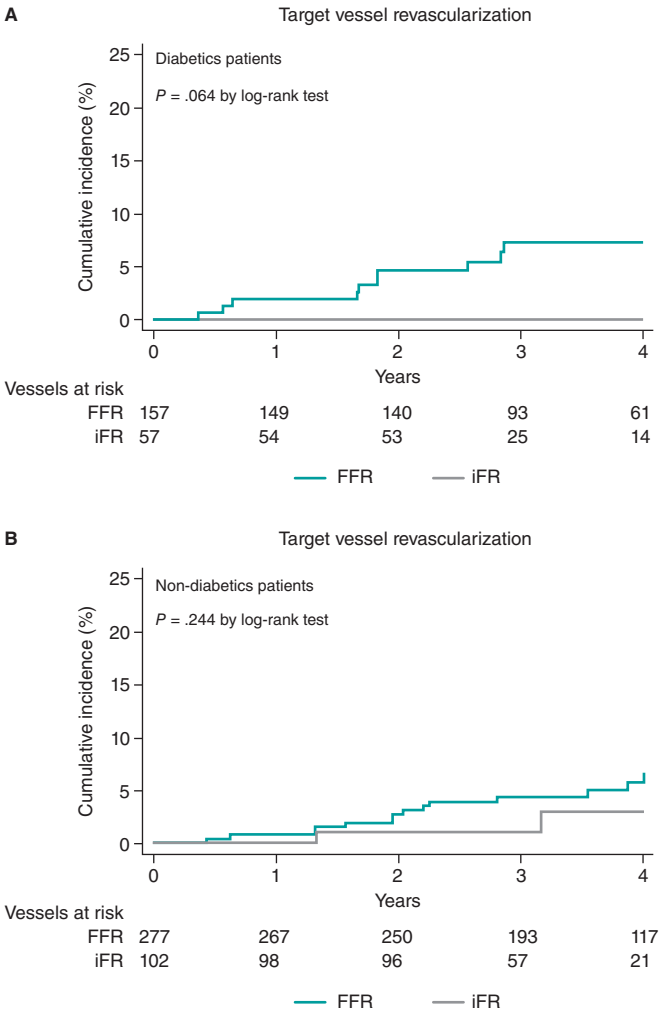

Figure 3. Target vessel revascularization based on the technique used to defer revascularization at the 4-years follow-up. iFR, instantaneous wave-free ratio; FFR, fractional flow reserve.

safely to defer intermediate stenosis in diabetic patients. *c)* there was a trend towards a higher rate of TVR in diabetic patients deffered based on FFR values.

Clinical outcomes based on the presence of diabetes mellitus

The use of coronary physiology to guide revascularization improves patient outcomes compared to angiographic assessment.[3,6,7,13] Currently both the FFR and the iFR have a class IA recommendation in the clinical practice guidelines regarding revascularization for the functional assessment of coronary stenoses.[1]

Diabetic patients are a high-risk population with a more aggressive and accelerated atherosclerosis compared to non-diabetic patients. In the PARADIGM (Progression of atherosclerotic plaque determined by computed tomographic angiography imaging) study, the presence of DM was an independent risk factor for plaque progression.[14] In a pooled analysis of 5 intravascular ultrasound trials, Nicholls SJ et al. found that patients with DM had a greater percent atheroma volume and a more rapid progression.[15]

Around 25% of the patients enrolled in pivotal studies that proved the effectiveness of the FFR and the iFR had DM.[3,4,6,16,17] The safety of physiology-guided revascularization deferral in the DM setting has not been specifically assessed in randomized clinical trials. On the other hand, the results of the few non-randomized studies that have evaluated physiology-guided management in diabetics show conflicting results.[18,19]

Domínguez-Franco et al. analyzed the prognostic safety of the FFR in diabetics. Although, their results are consistent with ours in the sense that no differences were found in the TVR at the long-term follow-up after revascularization deferral in DM vs non-DM patients, the applicability and strength of that study is limited by its small sample size (136 patients, 144 lesions). Also, the use of a FFR cut-off value for the decision-making process was 0.75 while in contemporary practice cut-off values of 0.80 are often used.[18]

Recently, Kennedy et al. analyzed 250 patients (128 DM, and 122 non-DM patients) and found that DM was associated with a higher rate of failed deferred stenoses (18.1% vs 7.5%; $P \leq .01$, Cox regression-adjusted (HR, 3.65; 95%CI, 1.40-9.53; $P < .01$), and target lesion revascularization of the deferred lesion (17.2% vs 7.5%; HR, 3.52; 95%CI, 1.34-9.30; $P = .01$). Nevertheless, and consistent with our results, no significant differences in the rate of target vessel myocardial infarction were seen (6.1% vs 2.0%; HR, 3.34; 95%CI, 0.64-17.30; $P = .15$).[19] The TLR reported in the former study is much higher than the one seen in our population and the one reported by former studies (eg, in the FAME study the 2-year rate of TLR was 3.2% in FFR-negative lesions).[2] These differences can be associated with the characteristics of concomitant medical therapy, which was not specified and may affect the evolution of patients with DM critically. In our study population most patients received optimal medical therapy with over 93% receiving statins while the former study did not specify the medical treatment used. Another important factor can be the percentage of insulin-treated patients with DM (42% in the former study vs 24% in our population). In a different study the same authors found that insulin therapy was a predictive factor of deferred lesion failure in patients with FFR values > 0.80.[20] Differences in the risk profile of the populations may, therefore, explain the different results obtained. Our study, with a larger sample size, proves that compared to non-diabetics deferring the revascularization of intermediate stenoses in diabetic patients is safe, and with no differences in TVR at the follow-up. Another study with similar results was the one conducted by Van Belle et al. who saw that the FFR is an important tool to redefine the severity of stenosis in patients with DM with good results at 1 year in deferred patients (HR, 0.77; 95%CI, 0.47-1.25; $P = .29$; reclassified vs non-reclassified patients with DM).[21]

Clinical outcomes based on the physiological index used to defer revascularization

Our results suggest that both the FFR and the iFR can be used safely to defer intermediate stenoses in patients with DM. Our findings regarding the low rates of MACE at the follow-up are consistent with the sub-analysis of patients with DM from the DEFINE-FLAIR trial compared to the 1-year follow-up.[22] Interestingly enough, we found a trend towards a higher rate of TVR in diabetics deffered with the FFR compared to the iFR. This can be associated with the presence of microvascular dysfunction in diabetic patients, and with the better correlation of iFR with indices that assess microcirculation like coronary flow reserve (CFR). One study evaluated the performance of the iFR and the FFR against invasive CFR in 216 stenoses to find a significantly stronger correlation and a higher diagnostic performance for the iFR (iFR area under the ROC curve, 0.82 vs FFR area under the ROC curve, 0.72; $P < .001$, for a coronary flow velocity reserve of 2).[23] Cook et al. evaluated 567 vessels with sensor-tipped pressure and Doppler ultrasound guidewires and found that with discordant FFR–/iFR+ , the hyperemic flow velocity and the CFR were similar to the FFR+/iFR+ group ($P > .05$). However, with discordant FFR+/iFR–, the hyperemic flow velocity and the CFR were similar to both the FFR–/iFR– and the coronary unobstructed groups ($P > .05$).[24] These findings may potentially explain the lower performance of FFR in the presence of microvascular dysfunction, and the tendency we found towards a higher TVR in diabetic patients deferred with FFR. Interestingly enough, this tendency was not found in non-DM patients, which supports the hypothesis of microvascular compromise as one of the potential causes for the differences observed between the 2 indices.

Limitations

This study has several limitations. First, this is a single-center observational, retrospective, non-randomized study. The results should be analyzed with caution and can only be interpreted as hypothesis-generating given the small sample size that limits the study statistical power. There were more patients evaluated with the FFR compared to the iFR, which may have influenced the results. Neither clinicians nor patients were blinded to the physiological results, which may have influenced future decisions on revascularization. Most patients had a single deferred vessel, meaning that extrapolation of this data to patients with multivessel disease is complex. Finally, microvascular dysfunction was not evaluated in this population, and the actual impact on the results cannot be determined.

CONCLUSIONS

Deferring the revascularization of intermediate stenoses in patients with DM based on the FFR or the iFR is safe regarding the risk of TVR or target vessel myocardial infarction, with a similar rate of these events at the long-term follow-up compared to the rate seen in non-diabetic patients.

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AUTHORS' CONTRIBUTIONS

A.F. Castro-Mejía, and A. Travieso-González contributed to the study idea, design, acquisition, analysis, and interpretation of data, and writing of the article, M.J. Pérez-Vizcayno contributed to both the analysis and interpretation of data, H. Mejía-Rentería, I.J. Núñez-Gil, P. Salinas, L. Nombela-Franco, P. Jiménez-Quevedo, A. Fernández-Ortiz, and C. Macaya contributed to the writing of the article, and made a critical review of its intellectual content. J. Escaned, and N. Gonzalo contributed to the writing of the article, made a critical review of its intellectual content, and gave their final approval to the version that would eventually be published.

CONFLICTS OF INTEREST

I.J Núñez-Gil is a consultant for Aztraseneca. P. Salinas received speaker fees from Boston Scientific, Terumo, Alvinedica, and Biomenco. L. Nombela-Franco has served as a proctor for Abbott, and received speaker fees from Edwards Lifesciences Inc. A. Fernández-Ortiz is a speaker at the educational events of Medtronic, Biotronik, Biosensor, and Bayer. J. Escaned is a speaker and consultant for Abbott, Boston Scientific, and Philips, and received personal fees from Philips Volcano, Boston Scientific, and Abbott/St. Jude Medical outside the submitted work. N. Gonzalo is a speaker at educational events for Abbott, and Boston Scientific. The remaining authors declared no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- The FFR and the iFR have proven to be safe tools to guide revascularization treatment in several clinical scenarios at the long-term follow-up. However, the safety of physiology-based revascularization in diabetics, who have a high-risk of cardiovascular events, has been scarcely investigated.

WHAT DOES THIS STUDY ADD?

– Deferring the revascularization of intermediate stenoses in diabetic patients based on the results of physiological evaluation with pressure guidewires is safe, and has a low rate of secondary events being the deferred vessel similar to those seen in non-diabetic patients at the long-term follow-up.

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Original article

Stent-grafts versus drug-eluting stents in arterial aneurysms, insights from the International Coronary Artery Aneurysm Registry (CAAR)

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ABSTRACT

Introduction and objectives: Coronary artery aneurysms are a complex situation. Our main objective is to describe the frequency of use of covered stents (grafts) for their management, as well as to characterize their long-term results compared to drug-eluting stents.
Methods: Ambispective observational study with data from the International Coronary Artery Aneurysm Registry (CAAR) (NCT-02563626). Only patients who received a stent-graft or a drug-eluting stent where the aneurysm occurred were selected.
Results: A total of 17 patients received, at least, 1 stent-graft while 196 received 1 drug-eluting in the aneurysmal vessel. Male predominance, a higher rate of dyslipidemia, a past medical history of coronary artery disease, previously revascularized coronary artery disease, and giant aneurysms were reported in the stent-graft cohort. The independent predictive variables of the composite endpoint of all-cause mortality, heart failure, unstable angina, reinfarction, stroke, systemic embolism, bleeding or any aneurysmal complications at the median follow-up of 38 months were suggestive of the existence of connective tissue diseases (HR, 5.94;

[◊] Supplementary data: Collaborators from the International Coronary Artery Aneurysm Registry (CAAR)

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95%CI, 1.82-19.37), left ventricular dysfunction ≤ 55% (HR, 1.84; 95%CI, 1.09-3.1), and an acute indication for heart catheterization (HR, 2.98; 95%CI, 1.39-6.3). The use of stent-grafts was not associated with the occurrence of more composite endpoints (23.5% vs 29.6%; *P* = .598).
Conclusions: The use of stent-grafts to treat coronary aneurysms is feasible and safe in the long-term. Randomized clinical trials are needed to decide what the best treatment is for these complex lesions.

Keywords: Coronary aneurysm. Registry. Stent. Stent graft. Angioplasty.

Stents recubiertos o farmacoactivos en aneurismas, resultados del Registro Internacional de Aneurismas Coronarios (CAAR)

RESUMEN

Introducción y objetivos: Los aneurismas coronarios son una situación compleja. Planteamos como objetivo principal describir la frecuencia de utilización de *stents* recubiertos *(grafts)* para su tratamiento y caracterizar sus resultados a largo plazo en comparación con *stents* farmacoactivos.
Métodos: Estudio observacional ambispectivo, con información procedente del Registro Internacional de Aneurismas Coronarios (CAAR) (NCT-02563626). Se seleccionaron los pacientes que recibieron un *stent-graft* o un *stent* farmacoactivo en la zona del aneurisma.
Resultados: Un total de 17 pacientes recibieron al menos un *stent-graft* y 196 un *stent* farmacoactivo en la zona aneurismática. Se observa un predominio del sexo masculino y una mayor frecuencia de dislipemia, antecedentes de coronariopatía, enfermedad coronaria revascularizada previamente y aneurismas gigantes en la cohorte de *stent-graft*. Como variables independientes predictoras del desarrollo del evento combinado (muerte por cualquier causa, insuficiencia cardiaca, angina inestable, reinfarto, ictus, embolia sistémica, sangrado o cualquier complicación en el aneurisma), tras una mediana de seguimiento de 38 meses, destacaron la existencia de conectivopatías (*hazard ratio* [HR] = 5,94; intervalo de confianza del 95% [IC95%], 1,82-19,37), la disfunción del ventrículo izquierdo ≤ 55% (HR = 1,84; IC95%, 1,09-3,1) y la indicación aguda del cateterismo índice (HR = 2,98; IC95%, 1,39-6,3). El uso de *stent-grafts* comparado con el de *stents* farmacoactivos no se asoció al desarrollo de más eventos combinados (23,5 frente a 29,6%; p = 0,598).
Conclusiones: El uso de *stents* recubiertos en aneurismas coronarios es factible y seguro a largo plazo. Se necesitan estudios clínicos aleatorizados para decidir el mejor tratamiento de este tipo de lesiones complejas.

Palabras clave: Aneurismas coronarios. Registro. Resultados. *Stent*. *Stent-graft*. Angioplastia.

Abbreviations

LVEF: Left ventricular ejection fraction.

INTRODUCTION

The first descriptions of a coronary aneurysm were reported by Morgagni back in 1761, and the first series of 21 patients were reported in 1929.[1-4] Since then, a variable incidence rate—between 0.3% and 12%—has been reported in several series following the implementation of imaging modalities and coronary angiography.[5] The overall incidence rate reported in a cohort of over 436 000 contemporary coronary angiographies from an international registry is 0.35%.[5] Same as it happens with the clinical presentation and profile, treatment varies significantly.[5,6] Still, revascularization is often required here.[6] Over the last few years, some of the alternatives available propose the use of stent-grafts for the exclusion of coronary aneurysms.[5-14]

These devices—initially developed for other indications[15] such as coronary perforations—have proven useful and safe in the short-term, and in cases and series previously published.[7-10,12]

The main goal of this paper is to describe the frequency of use of this type of stents for the management of coronary aneurysms and characterize its long-term results using patients with drug-eluting stents as the control group since they have had good results in this context.[5]

METHODS

This paper uses data curated from the International Coronary Artery Aneurysm Registry (CAAR) (NCT-02563626).[16] Using a methodology already published, this ambispective registry included data from adult patients (≥ 18 years) who underwent a coronary angiography for whatever reason in 32 hospitals from 9 different countries.[5] Coronary aneurysm was defined as a focal dilatation (< 1/3 of the vessel) 1.5 times larger compared to the vessel diameter in a healthy adjacent segment; the giant aneurysm was defined as a dilatation 4 times larger compared to the reference diameter.[16] Investigators were advised to collect a consecutive case series in specific closed periods of time. Both the clinical and the procedural variables were collected, as well as the events occurred during the index hospital stay considered as that moment when it was first reported that the patient had, at least, 1 coronary aneurysm. Then, after validating which patients were eligible, the clinical follow-up was performed with information from the health records collected via medical consultations or phone calls. As stated in former reports, the protocol was initially approved by the coordinating center ethics committee and then by the centers that required it. Data were collected anonymously, and patients gave their informed consent to all the study procedures. Clinical decisions were always made by the treating physician of

every patient without any influence from the study protocol whatsoever. The analysis of this study only included patients who received a stent-grafts or drug-eluting stents in an aneurysmal area.

The study primary endpoint was to describe the real-life use of stent-grafts to treat coronary aneurysms. Secondary endpoints were to determine the occurrence of events at the long-term follow-up. Similarly, another secondary endpoint was to conduct a comparison with patients who received drug-eluting stents in the aneurysmal area. If both types of stents were implanted, the patient from the stent-graft group was considered. Similarly, the analyses were conducted individually in each patient.

Statistical analysis

The statistical package SPSS v24.0 (IBM-SPSS, United States) was used to conduct the statistical analysis. Data are expressed as mean ± standard deviation or as median and interquartile range, when appropriate. Categorical variables were expressed as percentages. Inter-group comparisons were made using the chi-square test with qualitative variables. On the other hand, the Student *t* test, Mann-Whitney *U* test or Wilcoxon test were used, when appropriate, with continuous variables. The long-term event-free survival curves for the different analyses and groups were obtained using the Kaplan-Meier method. In them, the inter-group comparisons were performed using the log-rank test.

Based on the principle of parsimony, multivariable models were used in which, to avoid ann excess of variables in the analysis, only those with *P* values ≤ .10 were included in the univariate study that will be further explained later. Both the hazard ratio (HR) and the confidence intervals were estimated at 95% (95%CI) based on a Cox logistic regression model with backward elimination (Wald). Two-tailed *P* values < .05 were considered statistically significant.

RESULTS

Out of a total of 1565 patients eventually considered in the global registry, 250 were referred for coronary artery surgery and 829 to receive some type of percutaneous revascularization.[5] A total of 17 of these patients received, at least, 1 stent-graft to treat their coronary aneurysm. Also, 196 patients received a drug-eluting stent in the aneurysmal area. Therefore, the 17 and 196 patients mentioned before were included in the subsequent analyses of this study. Figure 1 shows the flow of patients.

Approximately, 8% of the patients specifically treated in the aneurysmal area received a stent-graft. Table 1 shows the clinical and angiographic characteristics, and the long-term events of both patients who received stent-grafts and those who received drug-eluting stents. Males were predominant and often showed signs of dyslipidemia, previous coronary arteriopathy, coronary artery disease with previous revascularization, and giant aneurysms in the cohort implanted with stent-grafts. The frequency and type of complications reported at the long-term follow-up with an overall median follow-up of 38 months are shown on table 1. No statistically significant differences were seen at the follow-up regarding the clinical events. A composite event rate of major adverse cardiovascular events (MACE) of 29.6% was reported in patients treated with drug-eluting stents compared to 23.5% in those treated with stent-grafts. Individually, the most common event reported in the group implanted with stent-grafts was unstable angina (11.8%). In the group treated with drug-eluting stents, the most common event was unstable angina (10.2%) and death (10.2%). Every individual event is shown on table 1.

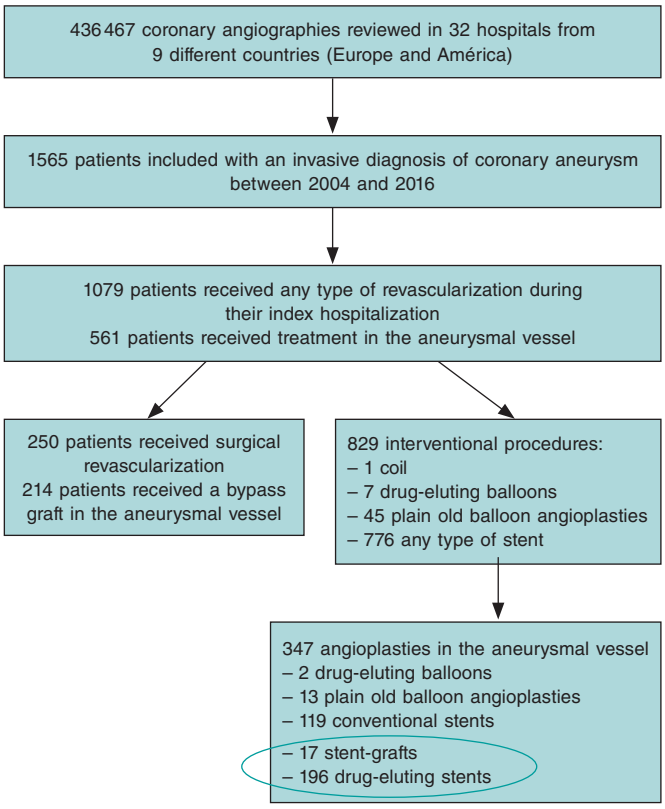

Figure 1. Flow of the registry patients. The devices encircled in an oval were analyzed in this study. In the stent-graft group it was studied whether patients received a device of this type regardless of other devices.

Coronary angiographies at the follow-up became available for 69 patients (32.4%). Eight of them were performed in the group with stent-grafts and only 1 confirmed failed stent implantation due to in-stent restenosis. In the group treated with drug-eluting stents, the aneurysm grew bigger or new aneurysms appeared in over 15% of the patients with follow-up coronary angiographies available. The rate of thrombosis in this selected group reached 9.8%. Table 2 provides an overall comparison between patients with the composite endpoint of MACE and those without it.

The multivariate analysis on the occurrence of MACE included in the model the use of stent-grafts. On the other hand, the univariate analysis included variables with *P* values ≤ .10. All of them are shown on table 2 including the presence or not, of peripheral vasculopathy (on therapy), previous diagnosis of aneurysm (in a territory different from the coronary one), diagnosed connective tissue disease, left ventricular ejection fraction, use of intracoronary imaging modalities (optical coherence tomography or intravascular ultrasound), and acute indication to perform index catheterization.

It was confirmed that the following variables remain in the model as independent predictors of the development of the composite endpoint: the existence of connective tissue disease (HR, 5.94; 95%CI, 1.82-19.37), left ventricular dysfunction—below 55%—(HR, 1.84; 95%CI, 1.09-3.1), and the acute indication for index catheterization (HR, 2.98; 95%CI, 1.39-6.3) (figure 2). The use of intracoronary imaging modalities—more common in the cohort implanted with stent-grafts—reached differences that were not statistically significant in the multivariate analysis. It was not a discriminator either regardless of the use of stent-grafts or drug-eluting stents (table 1, table 2, and figure 2).

Table 1. Overall characteristics of patients treated with stent-grafts compared to those treated with drug-eluting stents as first-line therapy for the management of coronary aneurysms

Patients	Stent-graft (N = 17)	Drug-eluting stent (N = 196)	*P*
Clinical characteristics			
Age, years	61.47 ± 13.8	63.84 ± 12.8	.467
Sex, male	16 (94.1)	146 (74.5)	.069
Arterial hypertension	11 (64.7)	142 (72.4)	.496
Dyslipidemia	15 (88.2)	119 (60.7)	.024
Diabetes	3 (17.6)	58 (29.6)	.296
Smoking habit			.218
Active smoker	10 (58.8)	82 (41.8)	
Former smoker	3 (17.6)	25 (12.8)	
Family history of coronary arteriopathy	7 (41.2)	14 (7.1)	< .001
Kidney disease (CrCl < 30)	1 (5.9)	14 (7.1)	.846
Peripheral vasculopathy	1 (5.9)	18 (9.2)	.647
Aortopathy – aneurysms	1 (5.9)	6 (3.1)	.531
Atrial fibrillation	1 (5.9)	7 (3.6)	.631
Connective tissue disease	0	3 (1.5)	.607
LVEF	56.8 ± 6.1	55.6 ± 11.4	.657
Previous revascularization	8 (47.0)	41 (20.9)	.014
Angiographic characteristics			
Right dominance	14 (82.4)	166 (84.7)	.641
Serious coronary stenoses	15 (88.2)		.132
1 vessel disease	4 (23.5)	62 (31.6)	
2-vessel disease	6 (35.3)	68 (34.7)	
3-vessel disease	5 (29.4)	62 (31.6)	
Location of the aneurysm[a]			
Left main coronary artery	0	3 (1.5)	.607
LAD	7 (41.2)	125 (63.8)	.066
LCX	4 (23.5)	49 (25)	.893
RCA	6 (35.3)	53 (27.0)	.466
Type of aneurysm[b]			.450
Fusiform	5 (29.4)	85 (43.8)	
Saccular	12 (70.6)	107 (55.2)	
Giant aneurysm	3 (17,6)	5 (2,6)	.02
Number of aneurysms per patient			.940
1	15 (88.2)	155 (79.1.2)	
2	2 (6.3)	30 (15.3)	
3	0	6 (3.1)	
4 or more	0	5 (2.5)	
Indication for catheterization, acute	11 (64.7)	144 (73.5)	.436
Indication for catheterization			.179
STEACS	6 (35.3)	49 (25.0)	
NSTEACS	4 (23.5)	91 (46.4)	
Heart failure	1 (5.9)	2 (1)	
Stable angina	6 (35.3)	32 (16.3)	
Other	0	22 (11.2)	
Type of stent			–
Aneugraft	4 (23.5)		
Jostent-graftmaster	11 (64.7)		
Papyrus	1 (5.9)		
Undetermined stent-graft	1 (5.9		
ABSORB		2 (1.0)	
ACTIVE		28 (14.3)	
BIOFREEDOM		1 (0.5)	
BIOMATRIX		4 (2.0)	
COMBO		2 (1.0)	
COROFLEX		1 (0.5)	
CRE8		8 (4.1)	
CYPHER		3 (1.5)	
GENOUS		1 (0.5)	
JANUS		2 (1.0)	
NO ESPECIF		8 (4.1)	
ONYX		1 (0.5)	
ORSIRO		3 (1.5)	
PROMUS		20 (10.2)	
RESOLUTE		23 (11.7)	
STENTYS		6 (3.1)	
SYNERGY		12 (6.1)	
TAXUS		22 (11.2)	
XIENCE		47 (24.0)	
YUKON		2 (1.0)	
Size of the stent-graft, medians			
Diameter	3.5 (3.5-4.0)	3.5 (3.0-3.75)	.336
Length	18.0 (16.0-26.0)	20.0 (15.0-28.0)	.014
Intracoronary imaging modalities			
IVUS	5 (29.4)	19 (9.7)	.014
OCT	1 (5.9)	7 (3.6)	.631
Any or both	6 (35.3)	26 (13.3)	.015

(Continues)

Table 1. Overall characteristics of patients treated with stent-grafts compared to those treated with drug-eluting stents as first-line therapy for the management of coronary aneurysms (*continued*)

Patients	Stent-graft (N = 17)	Drug-eluting stent (N = 196)	*P*
Follow-up			
Median follow-up, months	29.9 (2.33-51.54)	46.95 (11.92-76.75)	.093
Dual antiplatelet therapy at discharge	17 (100)	193 (99.5)	.767
Duration of dual antiplatelet therapy, median	12.0 (11.0-12.0)	12 (12.0-12.0)	.372
Oral anticoagulation/new indication	2/0	9/0	
Adverse events			
Heart failure	0	3 (1.5)	.607
Unstable angina	2 (11.8)	20 (10.2)	.839
Reinfarction	1 (5.9)	16 (8.2)	.739
Clinically relevant bleeding	1 (5.9)	8 (4.1)	.723
Embolism	0	1 (0.5)	.768
Stroke	0	2 (1)	.676
Dead	0	20 (10.2)	.166
All of the above or complicated aneurysm (MACE)	4 (23.5)	58 (29.6)	.598
Coronary angiography at the follow-up	8 (47.0)	61 (31.1)	.187
Control	3 (17.6)	16 (8.2)	
Stable angina	3 (17.6)	6 (3.1)	
NSTEACS	2 (11.8)	25 (12.8)	
STEACS	0	6 (3.1)	
Other	0	8 (4.0)	
Aneurysmal complications on the angiography[c]			
Growth	0	7 (11.5)	.312
New aneurysms	0	3 (4.9)	.521
Thrombosis	0	6 (9.8)	.353
In-stent restenosis	1 (12.5)	0	.005

Cr, creatinine; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NSTEACS, non-ST-segment elevation acute coronary syndrome; OCT, optical coherence tomography; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome. Data are expressed as no. (%) or mean ± standard deviation.

[a] There are more aneurysms than patients because the same patient can have several aneurysms.

[b] Aneurysm was categorized as mixed (fusiform and saccular) in 2 patients.

[c] Statistics is performed on a lower N, only in those with a coronary angiography at the follow-up.

Table 2. Clinical and angiographic characteristics of patients depending on whether they showed, at least, 1 major adverse cardiovascular event at the follow-up[a]

Patients	Without events (N = 151)	Some MACE (N = 62)	*P*
Clinical characteristics			
Age, years	62.99 ± 12.37	65.29 ± 13.93	.234
Sex, make	115 (76.2)	47 (75.8)	.956
Arterial hypertension	107 (70.9)	456 (74.2)	.623
Dyslipidemia	93 (61.6)	41 (66.1)	.533
Diabetes	39 (25.8)	22 (35.5)	.157
Smoking habit			.808
Active smoker	64 (42.4)	28 (30.4)	
Former smoker	19 (12.6)	9 (14.5)	
Family history of coronary arteriopathy	17 (11.3)	4 (6.5)	.285
Kidney disease (CrCl < 30)	8 (5.3)	7 (11.3)	.120
Peripheral vasculopathy	9 (6.0)	10 (16.1)	.018
Aortopathy – aneurysms	3 (2.0)	4 (6.5)	.097
Atrial fibrillation	5 (3.3)	3 (4.8)	.594
Connective tissue disease	0	3 (4.8)	.006
LVEF	56.62 ± 9.74	53.67 ± 13.44	.080
Previous revascularization	36 (23.8)	13 (21.0)	.651
Angiographic characteristics			
Right dominance	127 (84.1)	53 (85.5)	.237
Serious coronary stenoses	147 (97.4)	60 (96.8)	.817
1 vessel disease	47 (31.1)	19 (30.6)	
2-vessel disease	52 (34.4)	22 (35.5)	
3-vessel disease	48 (31.8)	19 (30.6)	
Location of the aneurysm[b]			.429
Left main coronary artery	3 (2.0)	0	
LAD	88 (58.3)	44 (71)	
LCX	41 (27.2)	12 (19.4)	
RCA	41 (27.2)	18 (29.0)	
Type of aneurysm[c]			.676
Fusiform	62 (41.1)	28 (45.2)	
Saccular	86 (57.0)	33 (53.2)	
Giant aneurysm	4 (2.6)	4 (6.5)	.185
Number of aneurysms per patient			
1	122 (80.8)	48 (77.4)	
2	20 (13.2)	12 (19.4)	
3	6 (4.0)	0	
4 or more	3 (2.0)	2 (3.2)	

(Continues)

Table 2. Clinical and angiographic characteristics of patients depending on whether they showed, at least, 1 major adverse cardiovascular event at the follow-up (*continued*)

Patients	Without events (N = 151)	Some MACE (N = 62)	*P*
Indication for catheterization, acute	101 (66.9)	54 (87.1)	.002
Indication for catheterization			.053
STEACS	38 (25.1)	17 (27.4)	
NSTEACS	61 (40.4)	34 (54.8)	
Heart failure	2 (1.3)	1 (1.6)	
Stable angina	33 (21.8)	5 (8.1)	
Other	17 (11.2)	5 (8.1)	
Type of stent			.598
Stent-graft	13 (8.6)	4 (6.5)	
Drug-eluting stent	138 (91.4)	58 (93.5)	
Size of the stent-graft, medians			
Diameter	3.38 (3.0-4.0)	3.28 (3.0-3.5)	.521
Length	22.00 (15.0-28.0)	21.74 (15.0-25.0)	.843
Intracoronary imaging modalities			
IVUS	17 (11.3)	7 (11.3)	.995
OCT	8 (5.3)	0	.065
Median follow-up, months	34.0 (12.0-76.0)	46.93 (18.75-79.75)	.646

CD: coronaria derecha; CX: circunfleja; Cr: creatinina; DA: descendente anterior; FEVI: fracción de eyección del ventrículo izquierdo; IVUS: ecocardiografía intravascular; MACE: eventos adversos cardiovasculares mayores; OCT: tomografía de coherencia óptica; SCACEST: síndrome coronario agudo con elevación del segmento ST; SCASEST: síndrome coronario agudo sin elevación del segmento ST. Los datos se expresan como n (%) o media ± desviación estándar.
[a] Se consideró como MACE el combinado de muerte de cualquier causa, ingreso por insuficiencia cardiaca, angina inestable, reinfarto, ictus, embolia sistémica, sangrado que precisó atención médica o cualquier complicación del aneurisma (crecimiento, nuevo aneurisma, reestenosis o trombosis).
[b] Hay más aneurismas que pacientes, porque cada enfermo puede presentar varios.
[c] En varios pacientes (3 y 1, respectivamente) el aneurisma fue considerado mixto.

DISCUSSION

This analysis is one of the largest series of coronary aneurysms published including data from real-life patients. It compares 2 of the most widely used therapeutic strategies in this context,[5] and its main findings are:

a) The most widely used revascularization method in patients with coronary aneurysms was percutaneous.

b) The exclusion technique, that is, the use of stent-grafts, was used in a relatively lower number of cases (8%).

c) The clinical profile of patients treated with drug-eluting stents was similar compared to patients treated with stent-grafts. However, the presence of giant aneurysms is more common in the latter group. Also, it is probably one of the factors that operators pay most attention to when choosing one stent over the other.

d) An acute indication for the index catheterization and the presence of ventricular dysfunction, at that particular moment, are independent factors of poor prognosis in the study cohort.

e) In the long-term, a similar safety and efficacy profile can be seen in both arms of treatment making stent-grafts a reasonable alternative in selected cases with coronary aneurysms.

The specific treatment of patients with coronary aneurysms has not been well-defined yet to the point that it is not even quoted by the international clinical guidelines on revascularization.[5] Over the last few years, several series and registries have been published trying to shed light on this issue.[5,6,8,11] Generally speaking, coronary aneurysm is a rare coronary comorbidity. Nonetheless, the average interventional cardiologist sees 1 or several cases each year in his cath lab.[7,16] As a matter of fact, in our own experience its estimated that its incidence rate is around 0.35% according to over 430 000 coronary angiographies performed,[5] and around 1% according to a recent Chinese series of a little over 11 000 coronary angiographies.[17] For this reason, it is important to have clinical data available to guide the management of this entity.[7]

Also, the coronary aneurysm is a clear marker of anatomic complexity and in adult patients it is suggestive of extensive coronary artery disease, and possibly, poor prognosis compared to milder forms of coronary arteriopathy.[7] In previous analyses, the use of drug-eluting stents in patients with coronary aneurysms has been proposed as a therapeutic option clearly superior to conventional stents.[5] That is why—as it happens with the rest of patients with ischemic heart disease—this type of platforms is widely recommended for patients with coronary aneurysms. Similarly, the use of an intense and thorough antithrombotic therapy is probably associated with fewer evolutionary complications, which is really reasonable considering the already mentioned high ischemic risk of these patients.[11,18]

The use of stent-grafts has been proposed as an alternative that can restore the anatomy of the blood vessel. Although the early design of these stents originally served other purposes, the data supporting the feasibility of their use with a high rate of success are extensive.[8] In our series, the stent most widely used was the classically designed Jostent Graftmaster coronary stent graft system (Abbott Vascular, United States) (nearly 65%). It is composed of a PTFE layer between 2 stainless-steel stents that may have influenced the results. As a matter of fact, in our setting, Jurado-Román et al.[15] conducted a multicenter registry on a certain state-of-the-art stent-graft. They proved that, in several real-life indications, the rate of events is reasonable (MACE, 7.1% at an average 22 months). However, the rate of stent thrombosis was slightly higher (3%) compared to the rate reported by drug-eluting stents in common uses.

The use of intracoronary imaging modalities to perform angioplasties in patients with coronary aneurysms possibly has prognostic implications as it happens in other complex clinical situations (diagnostic doubts, left main coronary artery, bifurcations). In this series, although they were more widely used in the group with stent-grafts implanted, no statistically significant differences were seen on the development of MACE (figure 2). This possibly has to do with the size of the study sample. Also, a tendency was seen towards fewer events in the group of patients with procedures optimized through intracoronary imaging guidance whether intravascular ultrasound or optical coherence tomography.

Limitations

This study has limitation associated with the particular design of the study. Also, a relatively small number of participants was included,

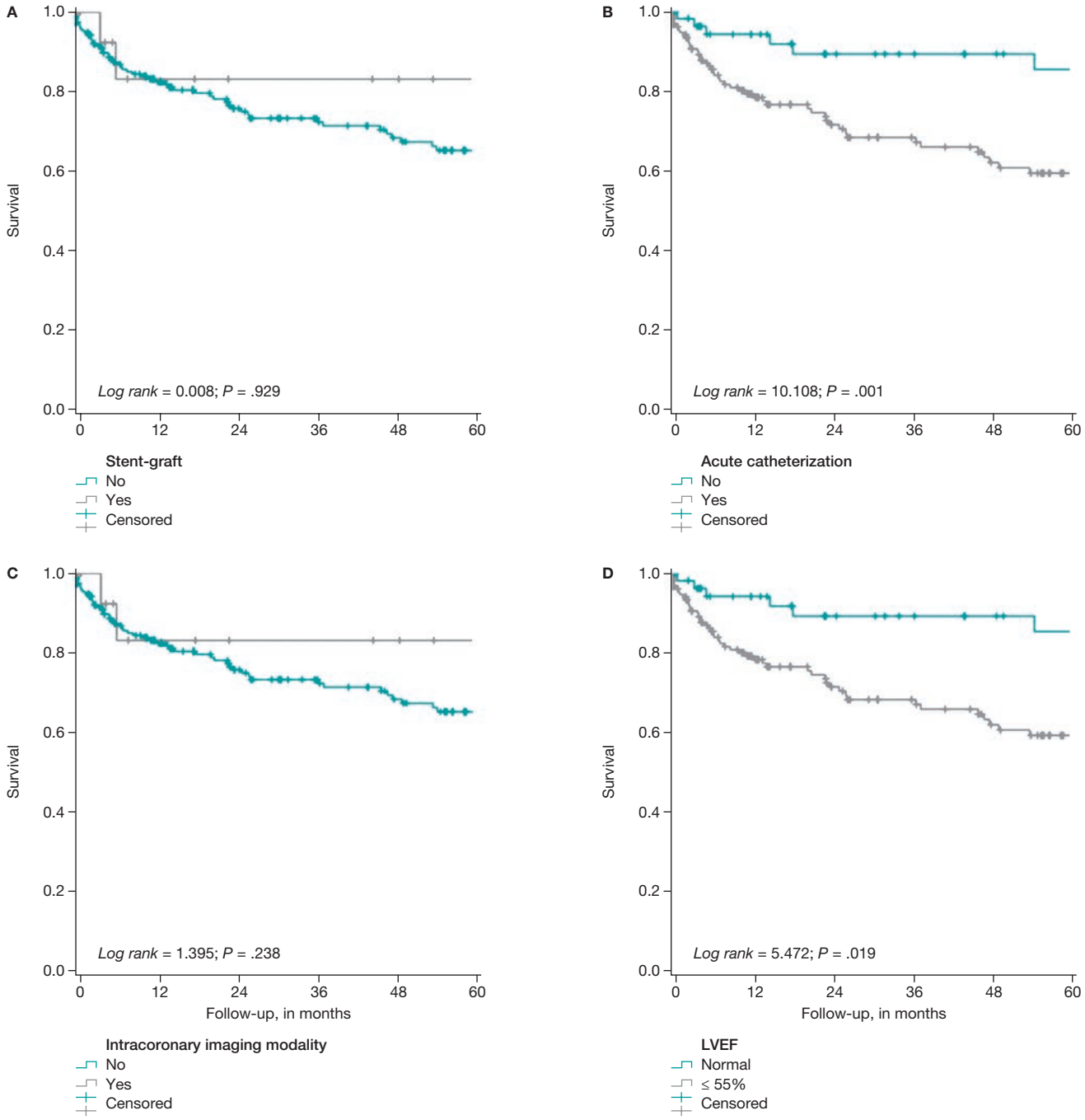

Figure 2. Kaplan Meier survival curves free of the composite MACE event. **A:** on the use, or not of the stent-graft for the management of the aneurysm. **B:** based on whether the indication for index catheterization was acute (acute coronary syndrome, heart failure, etc.). **C:** regarding the use, during the angioplasty, of any of these intracoronary imaging modalities (intravascular ultrasound, optical coherence tomography or both), **D:** stratification based on the left ventricular ejection fraction (LVEF) when the angioplasty was performed.

which may have complicated the detection of differences in the analyses due to the lack of statistical power. The decision to implant stent-grafts or drug-eluting stents was entirely left to each patient's medical team, which may have been associated with a certain degree of heterogeneity in the protocols that could have also been more dynamic in time. At the very complete follow-up from the clinical standpoint, control angiographies became available for a limited number of patients only (32%) who met the criterion set by the treating physicians. This may have underestimated the rate of complications, especially the subclinical ones, or be associated with selection biases in both groups.

However, this study is an approach to real-life clinical practice for a relatively rare heart disease on which there is little information available. It also includes a long-term clinical follow-up.

CONCLUSIONS

Stents-grafts can be used to treat coronary aneurysms and are safe in the long-term. Randomized clinical trials are needed to decide what the best treatment is for this type of complex coronary lesions.

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None.

AUTHORS' CONTRIBUTIONS

I. J. Núñez-Gil, CAAR coordinator: study design, data analysis, and draft writing. E. Cerrato, M. Bollati, L. Nombela-Franco, and A. Fernández-Ortiz: study design. E. Cerrato, M. Bollati, B. Terol, E. Alfonso-Rodríguez, S. J. Camacho-Freire, P. A. Villablanca, I. J. Amat-Santos, J.M. de la Torre-Hernández, I. Pascual, C. Liebetrau, B. Camacho, M. Pavani, R. A. Latini, F.Varbella, V. A. Jiménez Díaz, D. Piraino, MM, F. Alfonso, J. Antonio Linares, J. M. Jiménez-Mazuecos, J. Palazuelos- Molinero, and I. Lozano: data mining and recruitment. E. Cerrato, M. Bollati, B. Terol, L. Nombela-Franco, E. Alfonso-Rodríguez, S. J. Camacho-Freire, P. A. Villablanca, I. J. Amat-Santos J.M. de la Torre-Hernández, I. Pascual, C. Liebetrau, B. Camacho, M. Pavani, R. A. Latini, F.Varbella, V. A. Jiménez Díaz, Davide Piraino, M. Mancone, F. Alfonso, J. A. Linares, J. M. Jiménez-Mazuecos, J. Palazuelos- Molinero, ÍÍ. Lozano, and A. Fernández-Ortiz: reading and critical review of the manuscript.

CONFLICTS OF INTEREST

J. M. de la Torre Hernández is the editor-in-chief of *REC: Interventional Cardiology*, and F. Alfonso is an associate editor of this journal. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. No other conflicts of interest have been declared whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Coronary aneurysms are a complex entity whose incidence rate is between 0.3 and 12% in the different series already published.
- Treatment, like the presentation and the clinical profile, is varied. However, revascularization is often required.
- In this sense, over the last few years, some of the alternatives available propose the use of stent-grafts for the exclusion of coronary aneurysms.

WHAT DOES THIS STUDY ADD?

- The main goal of this paper was to describe the frequency of use of this type of stents to treat coronary aneurysms and then characterize its long-term results.
- From a total of 829 patients with coronary aneurysms treated with some type of percutaneous revascularization, data on the use of stent-grafts and drug-eluting stents was collected in 17 and 196 patients, respectively.
- It seems obvious that patients treated with stent-grafts for the management of coronary aneurysms have a high ischemic load, often complex anatomies, and even more often giant aneurysms.
- The use of stent-grafts for the management of coronary aneurysms is feasible and safe in the long-term. However, randomized clinical trials are still needed to decide what the best therapy is for this type of complex coronary lesions.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000241.

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Original article

Selective serotonin reuptake inhibitors and bleeding risk after PCI. A propensity score matching study

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ABSTRACT

Introduction and objectives: Coronary artery disease and mental health disorders are often coexistent. Selective serotonin reuptake inhibitors (SSRIs) are often used in this context but have been associated with an increased risk of bleeding due to platelet dysfunction. Previous studies have assessed this risk in patients treated with clopidogrel-based dual antiplatelet therapy (DAPT) with contradictory results. However, there is no data regarding the use of SSRIs and potent $P2Y_{12}$ inhibitors or triple antithrombotic therapy after percutaneous coronary intervention (PCI). The purpose of this study was to assess the impact of SSRIs on bleeding outcomes after PCI in patients treated with clopidogrel, prasugrel or ticagrelor-based DAPT or triple antithrombotic therapy.
Methods: Retrospective study including all patients undergoing PCI at a high-volume center during 2018. Patients on SSRIs were propensity-score-matched on a 1:1 ratio with patients naive to SSRIs adjusting for the baseline differences. The primary endpoint was major bleeding (BARC type 3 or 5 bleeding) at the 1-year follow-up. Secondary endpoints were a composite of major/non-major clinically relevant bleeding (BARC type 2, 3 or 5 bleeding), and a composite of major adverse cardiovascular events.
Results: Out of a total of 1063 patients treated with PCI during the study period, 1002 met the selection criteria, and 139 (13.9%) were on SSRIs. The latter had a higher bleeding risk before matching [PRECISE-DAPT, 16 [10-24] vs 13 [9-21]; *P* = .040]. No differences were reported in major bleeding (2.9% vs 2.9%, *P* = .991), major/non-major clinically relevant bleeding (2.9% vs 7.2%, *P* = .120) or in major adverse cardiovascular events (7.9% vs 7.9%, *P* = .979) in patients treated with SSRIs.
Conclusions: The use of SSRIs was frequent in patients treated with PCI, and although it was a marker of a higher bleeding risk at baseline, this was not associated with an additional bleeding liability.

Keywords: Bleeding. Coronary artery disease. Percutaneous coronary intervention. Selective serotonin reuptake inhibitors. Antithrombotic therapy.

Inhibidores selectivos de la recaptación de serotonina y riesgo hemorrágico tras ICP. Un estudio con puntuación de propensión

RESUMEN

Introducción y objetivos: La cardiopatía isquémica y la enfermedad mental coexisten a menudo. Los inhibidores selectivos de la recaptación de serotonina (ISRS) se utilizan con frecuencia en este contexto, pero se han asociado con un incremento en el riesgo hemorrágico. Los estudios previos han evaluado este fenómeno en pacientes tratados con clopidogrel, con resultados contradictorios. No hay datos sobre el uso de ISRS e inhibidores del $P2Y_{12}$ potentes o triple terapia antitrombótica. El objetivo de este estudio fue examinar el impacto de los ISRS en los eventos hemorrágicos en pacientes tratados con doble (incluyendo clopidogrel, prasugrel o ticagrelor) o triple terapia antitrombótica tras una intervención coronaria percutánea (ICP).
Métodos: Estudio retrospectivo en el que se incluyeron todos los pacientes tratados con ICP en un centro de alto volumen durante 2018. Los pacientes en tratamiento con ISRS fueron emparejados mediante puntaje de propensión con pacientes sin ISRS. El objetivo primario fue el sangrado mayor al año de seguimiento (BARC 3 o 5). Los objetivos secundarios fueron un combinado de sangrado mayor o menor clínicamente relevante (BARC 2, 3 o 5) y un combinado de eventos cardiovasculares adversos mayores.

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Resultados: De los 1.063 pacientes tratados con ICP durante el periodo del estudio, 1.002 cumplieron los criterios de selección y 139 (13,9%) recibían ISRS. Los pacientes con ISRS tenían un mayor riesgo de sangrado antes del emparejamiento (PRECISE-DAPT: 16 [10-24] frente a 13 [9-21]; p = 0,040). No hubo diferencias en el objetivo primario (2,9% frente a 2,9%; p = 0,991) ni en los objetivos secundarios de sangrado mayor o menor clínicamente relevante (2,9 frente a 7,2%; p = 0,120) y eventos cardiovasculares adversos mayores (7,9 frente a 7,9%; p = 0,979).
Conclusiones: El uso de ISRS fue frecuente en los pacientes tratados con ICP, y aunque fue un marcador de riesgo hemorrágico basal, no se asoció con un mayor riesgo de sangrado en el seguimiento.

Palabras clave: Sangrado. Enfermedad coronaria. Intervencionismo coronario percutáneo. Inhibidores selectivos de la recaptación de serotonina. Terapia antitrombótica.

Abbreviations

DAPT: dual antiplatelet therapy. **PCI:** percutaneous coronary intervention. **SSRIs:** selective serotonin reuptake inhibitors.

INTRODUCTION

Coronary artery disease and mental health disorders frequently coexist and have a bidirectional relationship.[1,2] Patients with mental health disorders have an increased risk of coronary artery disease and, inversely, it is not rare for patients to experience symptoms of depression or anxiety after a cardiac event.[3] Moreover, depression in patients with CHD is associated with a poor adherence to treatment, unhealthy lifestyle habits, and a poor prognosis.[4-8]

Selective serotonin reuptake inhibitors (SSRIs) are often prescribed as first-line agents to treat depression and anxiety,[9,10] but have a potential for increased bleeding risk due to the concomitant inhibitory effect on the platelet serotonin reuptake transporter (5-HTT).[11] Platelet 5-HTT inhibition has been associated with a reduced platelet activation and aggregation, and with a prolonged bleeding time.[12,13] On the other hand, some studies have linked SSRI-related bleeding risk to older age, comorbidities or polypharmacy.[14,15]

Bleeding risk due to antithrombotic therapy is a major concern following percutaneous coronary intervention (PCI) as hemorrhagic events are prognostically unfavorable as recurrent ischemic events.[16,17] While bleeding risk depends on multiple clinical and laboratory features,[18,19] the identification of potential modifiable factors is key to optimize the balance between ischemic and bleeding risk.[20] Prior studies have evaluated the bleeding risk of patients with a concomitant treatment of SSRIs and dual antiplatelet therapy (DAPT) plus aspirin and clopidogrel with contradictory results.[21-23] However, the impact of SSRIs plus therapy with more potent $P2Y_{12}$ inhibitors (eg, ticagrelor or prasugrel) or triple antithrombotic therapy with DAPT plus an oral anticoagulant (OAC) has never been explored. In this study we tried to compare the 1-year risk of bleeding after PCI and concomitant guideline-recommended antithrombotic therapy (including clopidogrel, ticagrelor or prasugrel-based DAPT and triple antithrombotic therapy) in patients with or without prescribed SSRIs.

METHODS

Study design and setting

Retrospective study including all consecutive patients discharged after PCI performed at a single center during 2018. Those treated with SSRIs were propensity score-matched (PSM) to a control group to compare bleeding outcomes at the 1-year follow-up. Antithrombotic treatment was decided by the clinical cardiologist in accordance with the current clinical practice guidelines.[24] This study was conducted according to the Declaration of Helsinki and was approved by the local clinical research ethics committee. Written informed consent was obtained from all patients before the PCI.

Population

All patients discharged after the PCI performed during the study period were eligible. Those treated at discharge with single antiplatelet therapy, DAPT were excluded—not including acetylsalicylic acid—as well as those anticoagulated with low-molecular-weight heparin for other reasons. Patients with missing information at the follow-up were also excluded. Clinical and procedural data, treatment at discharge, and outcomes during the first year were reviewed through electronic health records. Patients were treated with SSRIs if their list of prescriptions at discharge included one of the following: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline.

Endpoints

The primary safety endpoint was major bleeding at the 1-year follow-up. Secondary endpoints were a composite of major or non-major clinically relevant bleeding, and a composite of major adverse cardiovascular events (MACE). Major bleeding was defined as a bleeding event type 3 or 5 according to the Bleeding Academic Research Consortium (BARC). Major/non-major clinically relevant bleeding was defined as BARC type 2, 3 or 5 bleeding event.[25] MACE was defined as a composite outcome of cardiovascular death, non-fatal myocardial infarction or unplanned revascularization. Events were independently adjudicated by 2 cardiologists who were unaware of the SSRIs group.

Statistical analysis

Categorical variables were expressed as counts (percentages), and the continuous ones as mean ± standard deviation or median [interquartile range] according to their distribution assessed using the Shapiro-Wilk test. *P* values were obtained using the chi-square test or the Mann-Whitney *U* test, as appropriate. PSM was conducted to account for the confounding biases.[26] Logistic regression was used to determine the probability of being treated with SSRIs and included the following confounding variables potentially associated with SSRIs treatment and the primary endpoint:[27] age, sex, prior

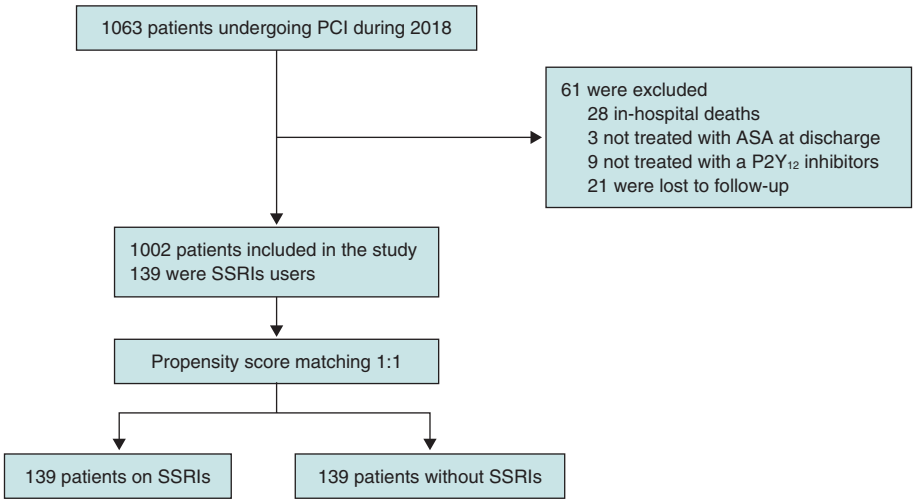

Figure 1. Patient flowchart. PCI, percutaneous coronary intervention; SSRIs, selective serotonin reuptake inhibitors.

relevant bleeding, hypertension, cancer, past medical history of hematologic disease or anemia, liver disease, creatinine clearance, treatment with potent $P2Y_{12}$ inhibitors or concomitant OAC. The nearest neighbor matching method with no replacement, and a caliper width of 0.1 were used in the PSM on a 1:1 ratio. Propensity score histograms and standardized mean differences before and after the PSM were used to evaluate the balance of the groups regarding the covariates.[28] Time-to-event analyses were conducted using the Kaplan-Meier and Cox proportional hazards methods. To determine major bleeding predictors in the unmatched cohort, a multivariate Cox regression model was conducted that used a purposeful selection model and prioritized parsimony. Clinical meaningful variables and those showing P values < 0.2 in the univariate analysis were included. Statistical analyses were performed using SPSS software (version 24; IBM Corp., United States) and R software (version 4.0.3; R Foundation for Statistical Computing, Austria). Matching was performed using the MatchIt R package (Ho, Imai, King, & Stuart, 2011) while covariate balance was assessed using the Cobalt R package (Greifer, 2021).

RESULTS

Baseline clinical characteristics

A total of 1063 patients were treated with PCI during the study period, 1002 of whom met the selection criteria and were included in the analysis. A total of 139 patients (13.9%) were treated with SSRIs at discharge (figure 1). Median age was 66 years (58-75), and 745 patients (74.4%) were male with a median PRECISE-DAPT score of 13 [9-22]. Regarding antithrombotic therapy, 684 patients (68.3%) were treated with potent $P2Y_{12}$ inhibitors and 102 (10.2%) were concomitantly treated with OAC. The baseline clinical characteristics of the overall population and the unmatched groups are shown on table 1. Patients from the SSRIs group were more likely to be women. They also had a more extensive past medical history of hypertension, diabetes mellitus, cancer, significant bleeding, and hematologic disease or anemia. Both the HAS-BLED and the PRECISE-DAPT bleeding risk scores were higher in the SSRIs group.

Unmatched analysis

In the overall population there were a total of 19 major bleeding events at the 1-year follow-up: 4 (2.9%) in the SSRIs group, and 15 (1.7%) in the unmatched non-SSRIs group (P = .350). Of these, 4 (21.1%) were fatal, 10 (52.6%) GI bleedings, 4 (21.1%) intracranial bleedings while the remaining ones occurred in other locations.

The multivariable Cox model identified the following independent predictors for the primary endpoint of major bleeding: PRECISE-DAPT score ≥ 25, and concomitant anticoagulation. Table 2 shows the univariable and multivariable Cox predictors for the primary endpoint.

The major/non-major clinically relevant bleeding endpoint occurred in 4 patients (2.9%) from the SSRIs group, and in 43 patients (4.9%) from the unmatched no-SSRIs group (P = .290). The rate of MACE was similar in both groups: 11 events (7.9%) in the SSRIs group and 50 events (5.8%) in the non-SSRIs group.

The Kaplan-Meier curves and the associated risk tables for each endpoint of the unmatched cohorts are shown on figure 2.

Propensity score matching analysis

The variables used in the PSM, the standardized mean differences, and the Propensity score distributions of the unmatched and matched samples are shown on figure 3. PSM resulted in an excellent balance of covariates with standardized mean differences ≤ 10% in all variables included in the Propensity score. There was also a very good balance across the other baseline characteristics and bleeding risk scores except for diabetes mellitus and hyperlipemia that were more prevalent in the SSRIs group (table 3).

The rate of major bleeding at the 1-year follow-up was 2.9% for both patients on SSRIs and the matched SSRIs non-users (HR, 1.01; 95%CI, 0.25-4.03; P = .991). There were no non-major clinically relevant bleedings in the SSRIs group and 6 (4.3%) among SSRIs non-users (HR, 0.39; 95%CI, 0.16-1.27; P = .120). No differences in MACE were reported between the SSRI and the non-SSRIs groups (HR, 1.01; 95%CI, 0.44-2.33; P = .979) (figure 4).

DISCUSSION

The main findings of this study can be summarized as follows: *a)* the use of SSRIs was frequent among patients undergoing PCI; *b)* patients prescribed with SSRIs had a higher baseline bleeding risk;

Table 1. Baseline clinical characteristics of the overall population, and SSRIs/non-SSRIs users before matching

Variable	Overall (N = 1002)	SSRI (N = 139)	Non-SSRI (N = 863)	*P*
Age, years	66 [58-75]	67 [60-76]	66 [57-75]	.530
Sex, male	745 (74.4)	76 (54.7)	669 (77.5)	.001*
BMI	28.7 [25.9-31.8]	30.0 [25.8-32.0]	28.6 [25.9-31.7]	.067
Hypertension	688 (68.7)	112 (80.6)	576 (66.7)	.001*
Diabetes mellitus	370 (36.9)	64 (46.0)	306 (35.5)	.017*
Hyperlipidemia	525 (52.4)	83 (59.7)	442 (51.2)	.059
Smoking (current or former)	260 (25.9)	34 (24.5)	226 (26.2)	.709
Previous revascularization	248 (24.8)	41 (29.5)	207 (24.0)	.174
COPD	67 (6.7)	10 (7.2)	57 (6.6)	.740
Chronic kidney disease	115 (11.5)	17 (12.2)	98 (11.4)	.774
Cancer	98 (9.8)	20 (14.4)	78 (9.0)	.044*
Liver disease	37 (3.7)	8 (5.8)	29 (3.4)	.166
Hematologic disease or anemia	99 (9.9)	25 (18)	74 (8.6)	.001*
Previous relevant bleeding	31 (3.1)	9 (6.5)	22 (2.5)	.010*
Atrial fibrillation	87 (8.7)	11 (7.9)	76 (8.8)	.871
Oral anticoagulant	102 (10.2)	9 (6.5)	93 (10.8)	.119
Potent $P2Y_{12}$ inhibitors	684 (68.3)	90 (64.7)	594 (68.8)	.323
Ticagrelor, no. (%)	660 (65.9)	86 (61.8)	574 (66.5)	.543
Prasugrel	24 (2.4)	4 (2.9)	20 (2.3)	.543
DAPT duration (months)	8 [6-12]	6 [6-12]	8 [6-12]	.440
PRECISE-DAPT	13 [9-22]	16 [10-24]	13 [9-21]	.040*
PRECISE-DAPT ≥ 25	195 [19.5]	34 [24.5]	161 [18.7]	.109
HAS-BLED	2 (2-3)	3 (2-3)	2 (2-3)	.034*
Creatinine clearance, mL/min/1.73 m^2	100 [82.3-124.1]	94.8 [72.9-125.2]	100 [82.7-124.1]	.154
Clinical presentation				
CCS	441 (44.0)	66 (47.5)	375 (43.5)	.375
ACS	561 (56.0)	73 (52.5)	488 (56.5)	

ACS, acute coronary syndrome; BMI, body mass index (kg/m^2); CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; SSRI, selective serotonin reuptake inhibitors.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].
* Indicates a statistically significant difference with *P* values < .05.

c) despite the imbalance reported in the baseline characteristics, after adjustment SSRIs users were not associated with a significant excess of major or clinically relevant bleeding at the 1-year follow-up.

There is a strict correlation between coronary artery disease and mental health disorders. In our study up to 13.9% of patients treated with PCI were prescribed SSRIs. This group has more comorbidities and bleeding risk factors with the potential to complicate the clinical decision-making process regarding antithrombotic therapy selection. Importantly, whether SSRIs trigger a higher bleeding risk through a biological effect on platelet 5-HTT receptors or are a marker of a higher bleeding risk through concomitant comorbidities has been the matter of discussion in prior studies.

Labos et al.[21] reported an increased risk of bleeding in patients taking both SSRIs and acetylsalicylic acid or clopidogrel-based DAPT after myocardial infarction. On the contrary, Lasella et al.[22] assessed the impact of SSRI therapy on patients on DAPT after PCI finding no excessive bleedings in patients on SSRIs. Interestingly, they reported a lower risk of MACE in patients on SSRIs compared to those on mirtazapine, but a higher risk compared to patients on either one of the 2 antidepressants. This may be explained by a protective effect of SSRIs on MACE[29] that could be exceeded by the unfavorable effect of mental health disorders on cardiovascular events.[30] Another interpretation could be associated with the pharmacokinetics of clopidogrel since it is a prodrug that requires enzymatic conversion into its active metabolite by cytochrome P450

Table 2. Univariable and multivariable Cox predictors for major bleeding

Variable	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age, years	1.06 (1.02-1.11)	.008		
Sex, male	0.47 (0.19-1.18)	.107		
BMI	0.98 (0.89-1.09)	.756		
Hypertension	0.99 (0.38-2.61)	.989		
Diabetes mellitus	1.91 (0.78-4.79)	.160		
Hyperlipidemia	0.82 (0.33-2.01)	.664		
Chronic kidney disease	3.67 (1.39-9.66)	.008		
Cancer	2.47 (0.82-7.46)	.107		
Liver disease	1.48 (0.19-11.05)	.705		
Hematologic disease or anemia	2.47 (0.82-7.46)	.107		
Previous relevant bleeding	3.91 (0.90-16.91)	.068		
Atrial fibrillation	5.45 (2.05-14.53)	.001		
Oral anticoagulant	8.22 (3.34-20.23)	.001	6.99 (2.78-17.64)	.001
Potent $P2Y_{12}$ inhibitors	0.16 (0.06-0.45)	.001		
PRECISE-DAPT ≥ 25	4.77 (1.94-11.75)	.001	3.59 (1.44-8.98)	.006
HAS-BLED	1.69 (1.17-2.43)	.005		
Creatinine clearance	0.98 (0.97-0.99)	.024		
SSRI	1.68 (0.56-5.07)	.356	1.95 (0.64-5.93)	.241

95%CI, 95% confidence interval; BMI, body mass index (kg/m^2); HR, hazard ratio; SSRI, selective serotonin reuptake inhibitors.

(CYP).[31] Bykov et al.[23] reported an increased risk of ischemic events in patients on clopidogrel and a CYP2C19-inhibiting SSRI compared to those on noninhibiting SSRIs. No differences were found regarding major bleeding. The study did not include a group of patients without SSRI treatment.

We should mention that none of the aforementioned studies included patients treated with potent $P2Y_{12}$ inhibitors, which is currently the standard of care of patients with ACS. To our knowledge, this is the first study to assess the impact of SSRIs on a cohort of patients treated with potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor. In our population, two thirds of the patients were treated with potent $P2Y_{12}$ inhibitors, which is more consistent with the antiplatelet strategies recommended by the current clinical practice guidelines.[32,33] In this clinical setting, despite the imbalances reported in the baseline bleeding risk in an unadjusted analysis, we found no differences regarding major or clinically relevant bleeding events among patients on SSRIs and the matched group without a SSRI prescription. Hence, while the prescription of SSRIs can be a marker of a higher risk population with more comorbidities and risk factors, this may not translate into an independent predictor of bleeding events after accounting for the potential confounders. This is consistent with prior evidence in the medical literature. In the study conducted by Labos et al.[21] patients on SSRI had a more significant past medical history of hypertension, renal failure, anemia or other hematologic disease, and non-GI bleeding. Lasella et al.[22] reported that SSRIs users were more likely to have diabetes, hypertension, dyslipidemia, COPD, and chronic kidney disease.

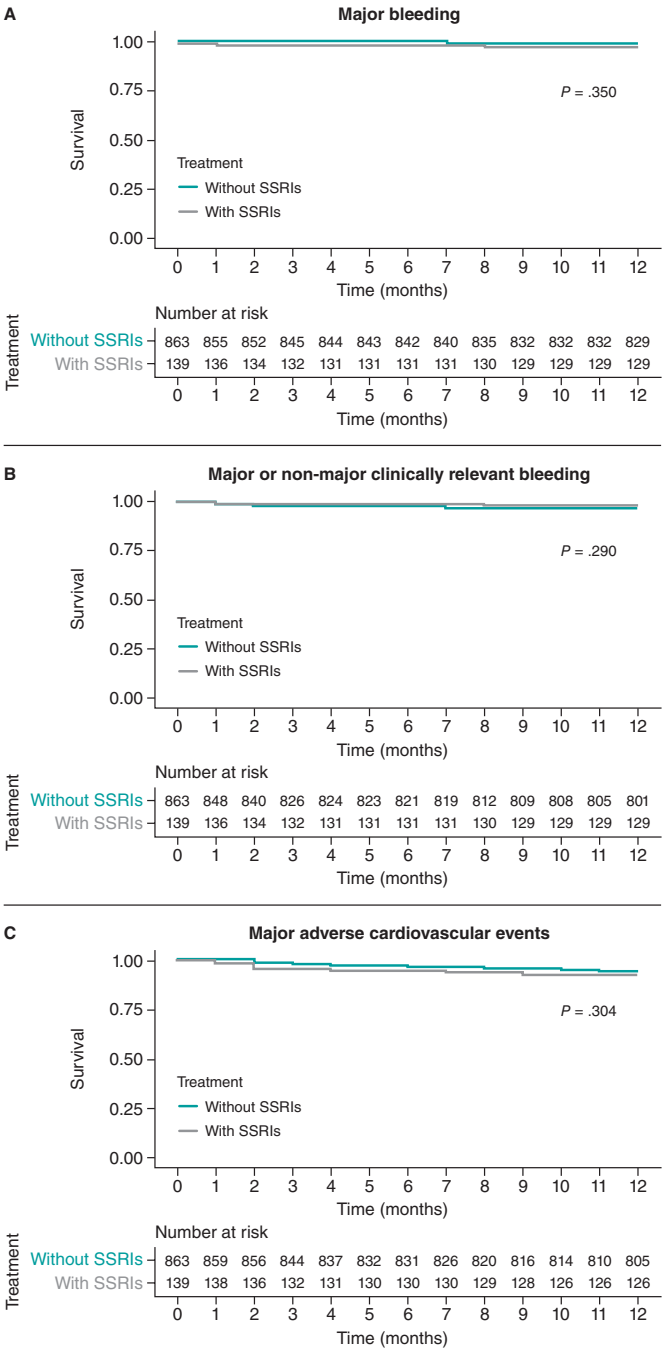

Figure 2. Kaplan-Meier curves for the primary bleeding outcome (A), the secondary composite bleeding (B), and the ischemic outcomes (C). Unmatched cohort. SSRIs, selective serotonin reuptake inhibitors.

Our findings are clinically relevant for different reasons. Although SSRIs have been associated with a potential for an increased bleeding risk, a direct translation into an excess of adverse events has not been confirmed yet. Our data provide reassurance on the relative safety profile of potent antithrombotic therapies in association with SSRIs, which did not substantially increase the risk of bleeding during the first year after PCI when the treatment decision-making process is based on a thorough evaluation of the features of bleeding and ischemic risk.

Our study also included a proportion of patients treated with concomitant antiplatelet and OAC therapy (~10%), which is consistent

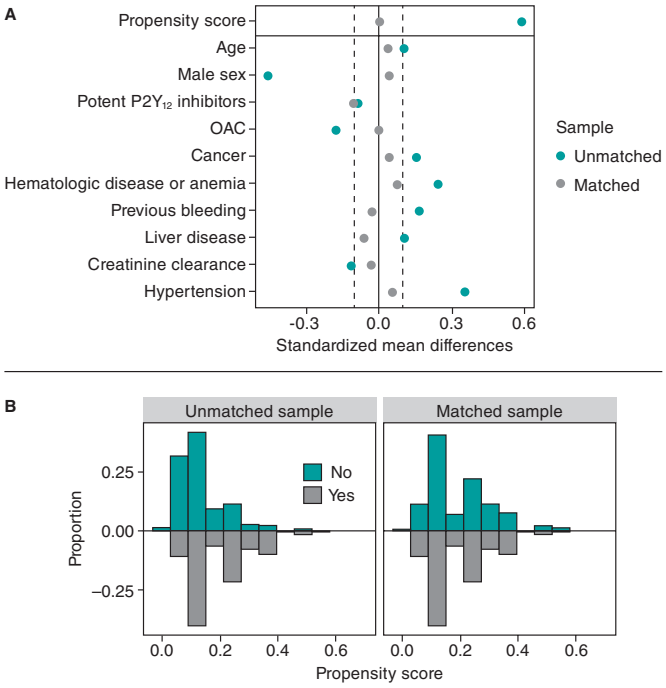

Figure 3. Variables used in the propensity score matching analysis and their standardized differences (A), and the propensity score distributions (B) of the unmatched and matched samples. OAC, oral anticoagulant.

with the current standard practice.[34] The impact of SSRIs on bleeding outcomes in patients with AF treated with OAC has also been examined in the past. Various authors have reported a higher risk of major bleeding in patients concurrently treated with SSRIs and warfarin.[35,36] On the contrary, Quinn et al.[37] did not find a significantly increased risk of bleeding among patients from the ROCKET AF trial assigned to warfarin or rivaroxaban who were also on SSRIs. However, there was a modest but non-statistically significant higher risk of major bleeding in the warfarin group. Since SSRIs are CYP2C9 inhibitors, an increase of warfarin plasma concentrations could explain these findings.[38] This reaffirms the importance of non-vitamin k antagonists to reduce the risk of bleeding also in this population given the need for multiple antithrombotic agents after the PCI and the higher baseline bleeding risk reported.[39]

Limitations

The current study has several limitations. First, its retrospective observational design, and the relatively small size of the sample limits our ability to provide definitive conclusions due to the residual possibility of type-2 errors. Secondly, despite the PSM resulted in a good balance between the selected potential confounders and the other baseline characteristics, the presence of residual confounding factors cannot be completely ruled out. For example, some variables associated with bleeding like the presence of diabetes mellitus or peripheral arterial disease were not included in the propensity score model. Yet similar findings were observed in the adjusted and unadjusted analyses. Thirdly, the classification of SSRI users was based on treatment at discharge without accounting for treatment adherence or discontinuation.

CONCLUSIONS

In this real-world study, a combination of SSRIs and potent antithrombotic therapies was frequently prescribed after PCI. Although the prescription of SSRIs was associated with a higher baseline bleeding risk in the unadjusted analysis this was not the case with an excess of major or clinically relevant bleeding reported at the follow-up.

Table 3. Baseline clinical characteristics of SSRIs/non-SSRIs users after matching

Variable	SSRI (N = 139)	Non-SSRI (N = 139)	*P*
Chronic obstructive pulmonary disease			
Age, years	68 [60-76]	67 [58-75]	.757
Sex, male	76 (54.7)	73 (52.5)	.810
BMI	30.0 [25.8-32.0]	28.4 [25.3-32.4]	.143
Hypertension	112 (80.6)	109 (78.4)	.656
Diabetes mellitus	64 (46.0)	48 (34.5)	.050
Hyperlipidemia	83 (59.7)	67 (48.2)	.045
Smoking (current or former)	34 (24.5)	28 (20.1)	.330
Previous revascularization	41 (29.5)	30 (21.6)	.153
COPD	10 (7.2)	9 (6.5)	.816
Chronic kidney disease	17 (12.2)	19 (13.7)	.721
Cancer	20 (14.4)	18 (12.9)	.727
Liver disease	8 (5.8)	10 (7.2)	.626
Hematologic disease or anemia	25 (18)	21 (15.1)	.519
Previous relevant bleeding	9 (6.5)	10 (7.2)	.812
Atrial fibrillation	11 (7.9)	11 (7.9)	1.000
Oral anticoagulant	9 (6.5)	9 (6.5)	1.000
Potent $P2Y_{12}$ inhibitors	90 (64.7)	97 (69.8)	.371
Ticagrelor	86 (61.8)	91 (65.5)	.749
Prasugrel	4 (2.9)	6 (4.3)	.749
DAPT duration, months	6 [6-12]	6 [6-12]	.810
PRECISE-DAPT	16 [10-24]	15 [10-24]	.863
PRECISE-DAPT ≥ 25	34 (24.5)	32 (23.0)	.778
HAS-BLED	3 [2-3]	3 [2-3]	.560
Creatinine clearance, mL/min/1.73 m^2	94.8 [72.9-125.2]	100 [82.7-114.0]	.747
Clinical presentation			
CCS	66 (47.5)	63 (45.3)	.718
ACS	73 (52.5)	76 (54.7)	

ACS, acute coronary syndrome; BMI, body mass index (kg/m^2); CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; SSRI, selective serotonin reuptake inhibitors.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

FUNDING

None reported.

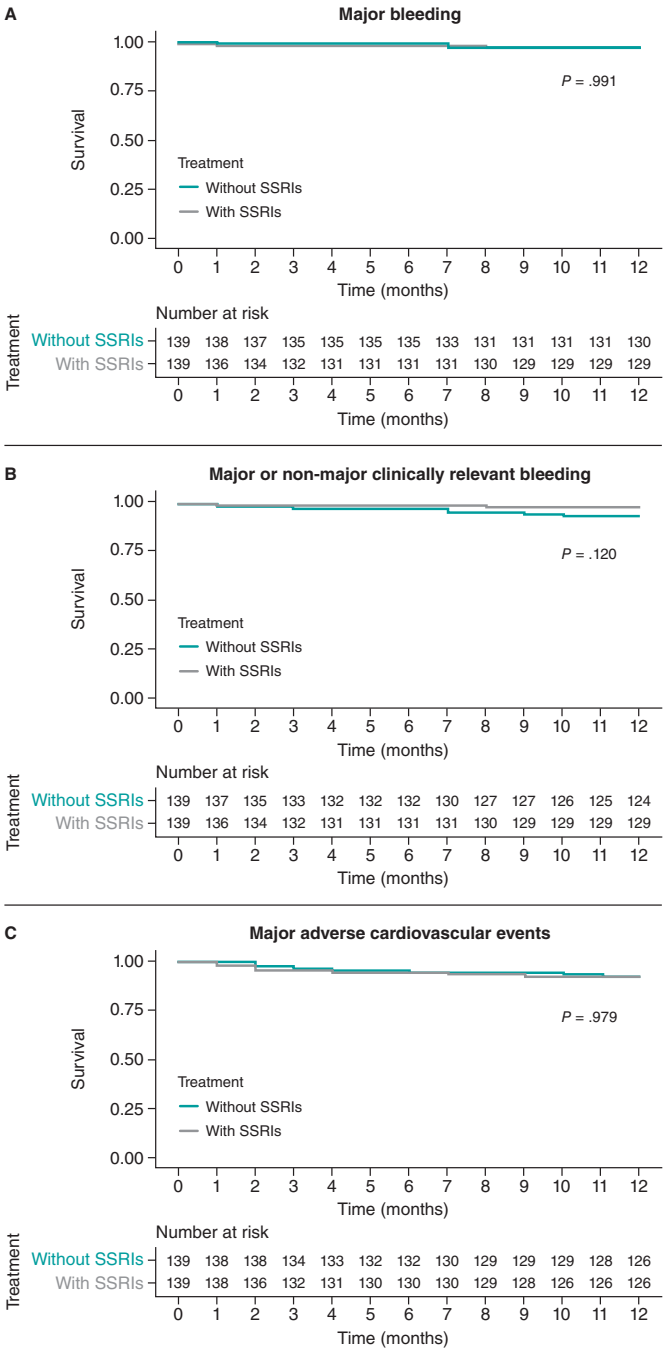

Figure 4. Kaplan-Meier curves for the primary bleeding outcome (A), the secondary composite bleeding (B), and the ischemic outcomes (C). Matched cohorts. SSRIs, selective serotonin reuptake inhibitors.

AUTHORS' CONTRIBUTIONS

R. González-Manzanares, and S. Ojeda conceived and designed the study. R. González-Manzanares, M. Ruiz-Moreno, C. Fernández-Avilés, L. Carmona-Artime, G. Flores-Vergara, and F. Costa collected analyzed data and interpreted the results. R. González-Manzanares, M. Ruiz-Moreno, S. Ojeda, and F. Hidalgo drafted the manuscript and completed the critical revisions. S. Ojeda, F. Hidalgo, G. Flores-Vergara, F. Costa, J. Suárez de Lezo, and M. Pan reviewed and revised the manuscript, and approved its final version before submission. All authors gave their final approval to the version that would eventually be published.

CONFLICTS OF INTEREST

S. Ojeda is an associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. S. Ojeda, and M. Pan declared having received honoraria for lectures given for Abbott, Boston, World Medical, and Terumo. J Suárez de Lezo declared having received honoraria for lectures given for Abbott. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Coronary artery disease and mental health disorders frequently coexist. The combination of SSRIs and potent antithrombotic therapies is common.
- Bleeding events after PCI worsen prognosis same as recurrent ischemic events.
- SSRIs have been potentially associated with an increased risk of bleeding. Data regarding the concomitant use of SSRIs and potent antithrombotic therapies is scarce and inconclusive.

WHAT DOES THIS STUDY ADD?

- This is the first study to assess the impact of SSRIs on the bleeding outcomes in the current PCI practice using potent $P2Y_{12}$ inhibitors or triple antithrombotic therapy.
- SSRIs users have a higher bleeding risk profile.
- The use of SSRIs was not associated with a higher risk of major bleeding after adjusting for the potential confounders.

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Original article

Outcomes of transcatheter aortic valve implantation in Spain through the Activity Registry of Specialized Health Care

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ABSTRACT

Introduction and objectives: Transcatheter aortic valve implantation (TAVI) has become the treatment of choice for the management of symptomatic severe aortic stenosis. As it happens with all procedures, the safety and effectiveness of TAVI must be monitored. To this end, we assessed the data available from the Spanish National Health Service from 2014 through 2017.
Methods: The study included patients aged > 50 years treated with TAVI and registered in the Activity Registry of Specialized Health Care from 2014 through 2017 from public and private hospitals in compliance with the National Health System. Multivariate logistic regression analyses were performed to identify factors associated with mortality and complications, and negative binomial models for the mean hospital length of stay (LoS). Standardized rates were used to discriminate both the effectiveness and safety among regions with higher and lower levels of implementation of the technique using the national median as the threshold, (37 implants x 10^5 habitants) in the 4-year period.
Results: A total of 5454 TAVIs were analyzed. The in-hospital mortality rate dropped from 4.89% in 2014 to 2.7% in 2017. The LoS decreased from 13.1 days in 2014 to 11.3 days in 2017. No differences in mortality were observed among the regions. However, the LoS of regions with a high volume of implants was significantly lower (OR, 0.88; 95%CI, 0.86-0.91; $P < .01$), as well as the risk of infections (OR, 0.54; 95%CI, 0.32-0.9; $P = .02$), and pacemaker implantation (OR, 0.77; 95%CI, 0.65-0.91; $P < .01$).
Conclusions: The use of TAVI in Spain is safe and has grown progressively with improved outcomes regarding morbidity and mortality. Differences among regions have been highlighted regarding patient access to TAVI. This heterogeneity was not associated with mortality but with differences in the morbidity rates.

Keywords: Aortic Stenosis. Surgical aortic valve replacement. Valvular heart disease. Activity Registry of Specialized Health Care. Transcatheter aortic valve implantation. TAVI.

Resultados del implante percutáneo de válvula aórtica en España mediante el Registro de Actividad de Atención Especializada

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica (TAVI) se ha consolidado como tratamiento de la estenosis aórtica grave. Como toda intervención, su seguridad y su efectividad deben monitorizarse en condiciones de práctica real. Para ello, se han analizado los datos del Sistema Nacional de Salud disponibles entre los años 2014 y 2017.
Métodos: Se evaluaron todos los pacientes mayores de 50 años con TAVI por vía transfemoral incluidos en el Registro de Actividad de Atención Especializada entre 2014 y 2017 procedentes de centros públicos o concertados. Se hicieron análisis de regresión logísticos para evaluar los factores asociados con la mortalidad y las complicaciones, y modelos binomiales negativos para la estancia media hospitalaria. Se usaron tasas estandarizadas para ajustar diferencias en las variables de efectividad y seguridad entre las diferentes comunidades autónomas, de acuerdo con el alto y bajo volumen de implantación de la técnica, considerando como referencia la mediana nacional (37 implantes por 10^5 habitantes) durante el periodo de tiempo analizado.

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Resultados: En total se analizaron 5.454 casos de TAVI. La mortalidad intrahospitalaria pasó del 4,89% en 2014 al 2,7% en 2017. La estancia media hospitalaria descendió de 13,1 días en 2014 a 11,3 en 2017. A pesar de no observar diferencias en la mortalidad entre comunidades autónomas, aquellas con mayor volumen de implantes tuvieron una menor estancia media hospitalaria (OR = 0,88; IC95%, 0,86-0,91; p < 0,01), menor riesgo de infecciones (OR = 0,54; IC95%, 0,32-0,9; p = 0,02) y menor necesidad de marcapasos permanente (OR = 0,77; IC95%, 0,65-0,91; p < 0,01).
Conclusiones: El uso de TAVI crece progresivamente en España con resultados cada vez mejores respecto al éxito del implante y la morbimortalidad perioperatoria. La variabilidad interregional en las tasas de implante no se relaciona con la mortalidad observada, pero sí con la morbilidad y la estancia hospitalaria.

Palabras clave: Estenosis aórtica. Reemplazo de la válvula aórtica. Registro de Actividad de Atención Especializada. Enfermedad de las válvulas cardiacas. Implante percutáneo de válvula aórtica. TAVI.

Abbreviations

LoS: length of stay. **PPI:** permanent pacemaker implantation. **RAE-CMBD:** Activity Registry of Specialized Health Care. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Aortic stenosis is the most common acquired valvular heart disease whose prevalence is around 3% in the population ≥ 65 years up to 7.4% in older ages (≥ 85 years).[1] It is also the leading cause of valvular surgery in the adult population.[2] Age and sex are among the risk factors (higher incidence rate in men).[3,4] After symptom onset, mortality rate is high (up to 50%) during the following years.[5,6] Due to the continuing growth of the elderly population in our country,[7] a significant burden of disease associated with aortic stenosis is expected[8] with the corresponding challenge that this poses to the healthcare system.

Until 14-15 years ago the only therapeutic option was surgical aortic valve replacement. In patients considered inoperable due to their age or comorbidities, the therapeutic alternative was only aimed at symptom control. Transcatheter aortic valve implantation (TAVI) created a new option of therapeutic opportunity for inoperable or high-risk patients at the beginning followed by intermediate-risk patients, and eventually for low-risk patients.[9-13] Despite this, the rate of treatment with TAVI in Spain is significantly lower compared to other European countries.[14] Although there are numerous reports and registries in Europe on the clinical results of TAVI, the evidence available in Spain on the local results from public ownership sources is scarce although 10 years have already gone by since the first TAVI was performed back in April 2007.[14]

This study presents the current evidence on the real-world clinical practice available in our country on the use of TAVI including a description of the profile of cases treated, the results obtained in terms of mortality, complications, and length of stay (LoS). Also, the main factors associated are analyzed from the perspective of the Spanish National Health System using the Activity Registry of Specialized Health Care (RAE-CMBD) as the main source of information.

METHODS

Minimum Data Set

This study is based on information included in the RAE-CMBD of the Spanish Ministry of Health, Consumer Affairs, and Social Welfare. It provides detailed information on the demographic characteristics of hospitalized patients, administrative variables, and clinical variables associated with the diagnoses and procedures of both the patient and type of healthcare received. The diagnoses and procedures registered are coded according to the International Classification of Diseases, Ninth Revision – Clinical Modification (ICM-9-CM) for 2014-2015, and the International Classification of Diseases, Tenth Revision – Clinical Modification (ICM-10-CM) for 2016-2017 that is more specific with diagnoses.

This analysis included all episodes registered from 2014 through 2017 of patients > 50 years of age hospitalized in centers of public or public-private partnership after performing the following procedures: "Endovascular replacement of aortic valve" (ICM-9-CM code: 35.05), and "Replacement of aortic valve with zooplastic tissue, percutaneous approach" (ICM-10-CM code: 02RF38Z). Cases treated with extracorporeal circulation were excluded (ICM-9-CM code: 39.61, and ICM-10-CM code: 5A1221Z) for considering that TAVI does not need this technique, which would, therefore, be a coding mistake of the episode. Similarly, episodes of rehospitalization were excluded to complete the patient's recovery.

The safety analysis included all complications coded in chapter 17 of ICM-9-CM, and in particular, with codes from category 996: "Complications peculiar to certain specified procedures" including complications not classified under other concepts, and in the use of artificial substitutes involving internal device implantation, among others. On the other hand, in the most recent ICM-10-CM classification, this type of complications can be found under category T82 "Complications of cardiac and vascular prosthetic devices, implants, and grafts". Also, due to their potential association with TAVI and great interest from the clinical standpoint events such as acute kidney injury, acute myocardial infarction, aortic dissection, stroke, sepsis, and permanent pacemaker implantation (PPI) were considered as well.

Statistical analysis

A descriptive analysis of the study variables was conducted. Continuous variables were expressed as means and standard deviations. The categorical ones as absolute and relative frequencies. The differences between 2 independent groups were compared using the Student *t* test or the *U* Mann-Whitney-Wilcoxon test based on their distribution (parametric or nonparametric, respectively). The chi-square test or Fisher's exact test were used with the categorical variables. Multivariate models were implemented to identify factors

Table 1. Implantation rate per 100 000 inhabitants, mean hospital stay, and in-hospital mortality rate per autonomous community

			Overall IR for the 2014-2017 period			Hospital stay										Mortality
			Adjusted			2014		2015		2016		2017		Overall for the study period		Rate reported during the study period
Autonomous community	TAVI (n)	Seasonal population	Est (x 105 inhabitants)	95%CI LL	95%CI UL	LoS	SD	LoS	SD	LoS	SD	LoS	SD	LoS	SD	
1	945	2,805,282	37	34.6	39	14.8	11.9	13.2	12.7	12.1	10.3	11.7	11.3	12.7	11.5	4.2
2	62	520 240	11	8.2	14	24.6	34.2	14.6	9.9	20.8	20	12.4	6.4	16.3	16.9	1.6
3	238	486 637	45	39.5	51	9.8	7.6	10.9	9.2	11.1	10.3	8.6	5.9	10	8.4	5.5
4	49	357 975	16	11.6	21	14.5	9.5	11.7	10.3	8.2	3.5	12	8.9	11.4	8.4	6.1
5	112	699 707	20	16.3	24	17.9	15.3	20.1	15.7	16.3	19.5	23.2	22.7	20.4	19.5	2.7
6	204	232 793	85	73.5	97	12.7	9.6	11.2	5.7	10.6	6.5	9.1	4	10.7	6.5	1.5
7	114	720 493	14	11.7	17	15.7	9.3	11.2	8.1	15	14	13	10	13.4	10.6	2.6
8	413	1,067,664	32	29.0	35	12	6.5	13.9	14.5	9.7	7.5	11.8	9.7	11.6	9.9	2.9
9	671	2,656,228	25	23.3	27	12.9	11.7	14.2	11.8	15.4	13.5	13.8	13.7	14.2	13.2	3.7
10	251	1,798,755	15	13.1	17	8.6	5.3	9.3	7.8	10.4	9.4	7.2	7.8	8.9	8.1	3.6
11	69	418 558	15	12.0	19	11.4	6.2	15	14.6	12.6	6.8	9.7	5.2	11.7	8.4	7.2
12	673	1,153,586	50	46.6	54	10.6	9.2	10.2	10.4	10.5	11.9	11.1	9.5	10.7	10.2	3.7
13	1126	2,206,886	53	49.9	56	14.8	16.3	12.6	17	12.2	12.8	10.1	7.9	11.9	13	2.9
14	211	456 332	49	42.9	57	8.2	7.1	6	4.9	6.7	6.2	7.8	9.9	7.1	7.5	3.3
15*	91	236 596	37	29.4	45	11	7.1	13.6	12.7	10.9	7.6	9.9	8.1	11	8.7	5.5
16*	225	890 671	25	21.5	28	13.7	14.8	9.6	6.1	11.1	7.2	10.2	8.2	10.9	9.2	3.1
National	5454	16,708,405	33	31.8	34	13.1	12.5	12.1	12.6	11.9	11.3	11.3	10.6	11.9	11.5	3.6

95%CI, 95% confidence interval; IR, implantation rate; LL, lower limit; LoS, length of stay (days); SD, standard deviation; TAVI, transcatheter aortic valve implantation; UL, upper limit.
* Due to the peculiarities described in the rendering of the service in these regions, the implantation rate could take a detour with respect to the routine clinical practice in these regions.
The highest mortality rates are due to the negative results reported within the first years (eg, in autonomous community #3, the mortality rate in 2014 was 16.7% but dropped to 3.3% in 2017; in autonomous community #4, the rate in 2014 was 25% but dropped to 7.4% in 2017; in autonomous community #11, the rate in 2014 was 14.3% but dropped to 6.7% in 2017). In all cases, a clearly positive tendency towards a lower procedural mortality rate was reported.

associated with the risk of in-hospital mortality, significant complications (logistic regression), and LoS (negative binomial regression). Demographic and clinical variables were examined as explanatory variables: age, sex, rate of implantation in the autonomous community where the procedure was performed, complications, and level of severity of each case based on the RAE-CMBD classification (stratified depending on the characteristics of each patient, diagnoses, and procedures) and categorized into a 4-level scale:[15,16] mild, moderate, major or extreme according to the severity-adjusted Diagnosis Related Groups (DRG).

To analyze the possible differences among autonomous communities in the volume of TAVIs performed, the rates of implantation standardized per 100 000 inhabitants ($\times 10^5$) were estimated. The seasonal population of each region in the period adjusted by age group (50-74, 75-84, ≥ 85), and sex was taken as the reference point.[17] Discrimination between high- and low-volume regions was made by categorizing the rates of implantation. Rates above the national average during the study period were considered high-volume regions (37 procedures × 10^5 inhabitants). Differences in the baseline characteristics of patients treated in high- and low-volume autonomous communities were taken into consideration during the adjustment of multivariate models.

The independent variables of all logistic regression and negative binomial models were reviewed by clinical experts to guarantee their clinical sense and then selected in such a way that the resulting model would minimize the Akaike information criterion.[18] Once the best model was determined in each case, the odds ratios (OR) and their 95% confidence intervals (95%CI) were estimated to determine whether a certain factor was associated with a higher risk (OR > 1) in the presence of a given result and then compare the size of several factors.

Regarding the multivariate analysis of complications, when the number of cases registered was low and statistical power of contrast was limited, all major complications were grouped following the clinical criterion once again. This is how factors associated with the risk of bleeding and accidental puncture or laceration (ICM-9-CM: 998.11, and 998.2 | ICM-10-CM: I97.4, I97.6, and I97.5*), acute myocardial infarction (ICM-9-CM: 410.*1 | ICM-10-CM: I21*), PPI (ICM-9-CM: 37.8 | ICM-10-CM: 5A1223Z), sepsis, and infections (ICM-9-CM: 995.91, 995.92, and 998.5 | ICM-10-CM: T81.4XXA, and A41*); acute kidney injury (ICM-9-CM: 584 | ICM-10-CM: N17*); and stroke (ICM-9-CM: 997.02, 434, and 435 | ICM-10-CM: I97.8*0, I66, I63.3, I63.4, I63.5, G45*, and I67.82) were identified and assessed.

Table 2. Complications associated with TAVI

Complication	Total		ICM-9-CM	2014		2015		ICM-10-CM	2016		2017	
	N	%		N	%	N	%		N	%	N	%
Mechanical heart valve prosthesis complication	218	4	996.02	56	7.3	47	4	T82.0*XA	49	3.3	66	3.2
Other complication of heart valve implantation	143	2.6	996.71	13	1.7	27	2.3	T82.8*7A, T82.9XXA	39	2.6	64	3.1
Dissection of aorta	15	0.3	441	2	0.3	3	0.3	I71.0*	3	0.2	7	0.3
Bleeding or iatrogenic stroke	40	0.7	997.02	4	0.5	9	0.8	I97.8*0	11	0.7	16	0.8
Cerebral artery occlusion	46	0.8	434	8	1	11	0.9	I66, I63.3, I63.4, I63.5	11	0.7	16	0.8
Transient cerebral ischemia	27	0.5	435	3	0.4	6	0.5	G45*, I67.82	9	0.6	9	0.4
Acute myocardial infarction	87	1.6	410.*1	14	1.8	14	1.2	I21*	25	1.7	34	1.7
Permanent pacemaker implantation	663	12.2	37.8	146	19.1	149	12.7	5A1223Z	155	10.5	213	10.4
Acute kidney injury	441	8.1	584	74	9.7	90	7.7	N17*	119	8.1	158	7.7
Postoperative shock	55	1	998	10	1.3	14	1.2	T81.1*XA	16	1.1	15	0.7
Bleeding complicating the procedure	314	5.8	998.11	54	7.1	63	5.4	I97.4*, I97.6*	90	6.1	107	5.2
Accidental puncture or laceration during the procedure	156	2.9	998.2	31	4.1	45	3.8	I97.5*	36	2.4	44	2.2
Infection following a procedure	45	0.8	998.5	11	1.4	13	1.1	T81.4XXA	12	0.8	9	0.4
Sepsis	28	0.5	995.91, 995.92	6	0.8	6	0.5	A41*	8	0.5	8	0.4

TAVI transcatheter aortic valve implantation.
Codes (ICM-10-CM), T82.0*XA, Other mechanical complication of heart valve prosthesis (initial encounter); T82.8*7A, Other specified complications of cardiac and vascular prosthetic devices, implants and grafts (initial encounter); T82.9XXA, Unspecified complication of cardiac and vascular prosthetic device, implant and graft (initial encounter); I71.0*, Dissection of aorta; I97.8*0, Intraoperative and postprocedural complications and disorders of circulatory system (cardiac surgery); I66, Occlusion and stenosis of cerebral arteries; I63.3, Cerebral infarction due to thrombosis of cerebral arteries; I63.4, Cerebral infarction due to embolism of cerebral arteries; I63.5, Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries; G45, Transient cerebral ischemic attacks and related syndromes; I67.82, Cerebral ischemia; I21, Acute myocardial infarction; 5A1223Z, Performance of cardiac pacing; N17, Acute kidney failure; T81.1*XA, Shock during or resulting from a procedure (initial encounter); I97.4*, Intraoperative hemorrhage and hematoma of a circulatory system organ or structure complicating a procedure; I97.6*, Postprocedural hemorrhage and hematoma of a circulatory system organ or structure following a procedure; I97.5*, Accidental puncture and laceration of a circulatory system organ or structure during a procedure; T81.4XXA, Infection following a procedure, initial encounter; A41, Sepsis.

All statistical contrasts were bilateral, and differences with P values > .05 were considered statistically significant. Statistical analysis was conducted using the statistical software package *R* (version 3.6.1).

RESULTS

A total of 5454 cases with transcatheter aortic valve implantation via transfemoral access were accounted for: 763 cases reported in 2014, 1171 in 2015, 1477 in 2016, and 2043 back in 2017. Implantation was more common in women (52.2%), mostly in patients between 81 and 85 years of age, both men (37%) and women (44%). Mean age was 81.12 ± 6.43 years during the entire period. Overall, the most common diagnoses that triggered the patients' hospitalization were aortic valve disease (79.7%, ICM-9-CM, and ICM-10-CM codes: 424.1, and I35, respectively) followed by mitral valve regurgitation, and rheumatic stenosis (3.1%, ICM-9-CM, and ICM-10-CM codes: 396.2, and T82.0*XA, respectively), and congestive heart failure (2.9%, ICM-9-CM, and ICM-10-CM codes: 428.0, and I08.0, respectively).

Rates of transfemoral TAVI, mortality, and hospital stay

The number of TAVIs performed remained variable across the years, and grew gradually with significant increases reported between 2014 and 2017 both in the number of centers where this procedure was conducted and in the overall number of TAVIs performed. Therefore, the national implantation rate ($\times 10^5$ inhabitants) doubled, and the mean during the study period was 33 procedures $\times 10^5$ inhabitants (table 1).

The overall mortality rate during the entire period was 3.6% with an obvious decrease from 2014 (4.8%) through 2017 (2.7%) despite the fact that the severity profile assigned to the patients remained constant across the 4 years studied (in 70% of the patients the severity-adjusted DRG score was extreme).

Regarding the length of hospital stay associated with the procedure, the LoS reported in 2014 was 13.1 ± 12.5 days dropping gradually down to 11.3 ± 10.6 days in 2017 with great variability among the different autonomous communities (table 1). When extreme cases were eliminated (defined as cases with stays > 2 standard deviations with respect to the mean), the mean national hospital stay was 8.9 ± 4.69 days, and differences among autonomous communities were reduced from 6.07 ± 4.8 to 11.35 ± 4.31 days; see table 1.

Complications associated with TAVI

Table 2 describes the complications associated with TAVI. Same as it happened with mortality, a gradual reduction in the rate of the most significant complications was reported from 2014 through 2017. The need for PPI was 12.2%, also with great variability of this complication among the different autonomous communities.

Factors associated with mortality risk, hospital stay, and complications associated with TAVI

Table 3 describes the profile of cases treated, and the results of the procedures performed in high- and low-volume regions.

Table 3. Comparative analysis between high- and low-volume autonomous communities regarding TAVI

	Low-volume (N = 3002)		High-volume (N = 2452)		*P*
Characteristics of the patient					
Age; mean (SD)	80.47	6.48	81.91	6.29	< .001*
Age group; n (%)					
50-74	455	15.2	275	11.2	< .001*
75-84	1749	58.3	1228	50.1	
≥ 85	798	26.6	949	38.7	
Sex (% women), n (%)	1520	50.6	1327	54.1	.011*
Level of severity, n (%)					
Mild	13	0.4	20	0.8	.013*
Moderate	44	1.5	18	0.7	
Major	835	27.8	768	31.3	
Extreme	2110	70.3	1646	67.1	
Diabetes mellitus; n (%)	1059	35.3	706	28.8	< .001*
Hypercholesterolemia; n (%)	1365	45.5	1070	43.6	.185
Obesity; n (%)	381	12.7	273	11.1	.085
Arterial hypertension; n (%)	1742	58.0	1234	50.3	< .001*
Atrial fibrillation; n (%)	1037	34.5	904	36.9	.079
Heart failure; n (%)	611	20.4	357	14.6	< .001*
COPD; n (%)	330	11.0	207	8.4	.002*
Chronic kidney injury; n (%)	634	21.1	482	19.7	.194*
Smoking; n (%)	450	15.0	283	11.5	< .001*
Use of anticoagulants; n (%)	511	17.0	485	19.8	.01*
Procedural results					
Death; n (%)	113	3.8	81	3.3	.401
Hospital stay (days); mean (SD)	12.72	11.82	10.85	11.08	< .001*
Puncture/laceration; n (%)	89	3.0	67	2.7	.667
Hemorrhage complicating the procedure; n (%)	156	5.2	158	6.4	.056
AMI; n (%)	56	1.9	31	1.3	.098
Permanent pacemaker implantation; n (%)	400	13.3	263	10.7	.004*
Sepsis and infectious events; n (%)	47	1.6	21	0.9	.026
Acute kidney injury; n (%)	215	7.2	226	9.2	.007
Stroke; n (%)	54	1.8	41	1.7	.801

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
* Statistically significant differences between high- and low-income autonomous communities.
High-volume of implants defined as regions with implantation rates > national mean of 37 procedures × 10^5 inhabitants. Level of severity according to the RAE-CMBD case classification.

The rate of PPI found was similar to the one reported by other authors in our country.[22] In this case, coding the severity of the cases treated was actually associated with a higher risk. The need for PPI after TAVI has been associated, above all, with the type of valve used (this need is greater with self-expanding valves).[25] In our analysis, it is impossible to distinguish the type of valve used because this information is not on the data provided by the RAE-CMBD. Both the need for postoperative PPI and the appearance of infectious processes and sepsis after the procedure were inversely associated with a higher number of procedures being

High-volume autonomous communities treated older patients (80.47 vs 81.91, $P < .001$) with a rate of extreme risk that was slightly lower (70.3% in low-volume autonomous communities vs 67.1% in high-volume autonomous communities; $P = .013$). In these autonomous communities, it was reported that the population treated had a lower rate of comorbidities such as diabetes, arterial hypertension, heart failure, chronic obstructive pulmonary disease or smoking (table 3).

Procedural results also varied between high- and low-volume autonomous communities: in high-volume regions, the duration of the LoS was shorter and the risk of certain complications like need for PPI, sepsis or infections was lower too. However, these regions reported a higher risk of acute kidney injury in the bivariate analysis (table 3).

Due to these differences, age, sex, and the level of severity of each case were included in the programmed multivariate models to adjust the analyses of the explanatory variables associated with the in-hospital mortality rate. Figure 1 shows that aortic dissection (OR, 20.58; 95%CI, 6.27-62.40; $P < .01$), and postoperative shock (OR, 18.16; 95%CI, 9.43-35.16; $P < .01$) were significantly associated with the postoperative mortality rate. The explanatory weight of other complications like acute myocardial infarction, acute kidney injury, cerebral artery occlusion or heart complications was significantly lower. Mortality differences between high- and low-risk autonomous communities did not reach statistical significance in the overall period studied (figure 1).

On the other hand, the higher severity of the cases, and the appearance of some complications contributed to a significant increase in the duration of the LoS (figure 1). The level of severity was also the factor that kept a stronger correlation with the occurrence of complications such as bleeding and accidental puncture or laceration, acute myocardial infarction, PPI, acute kidney injury, and stroke (figure 2). In high-volume autonomous communities, the risk of sepsis or infections and need for PPI was significantly lower compared to low-volume autonomous communities (OR, 0.77; 95%CI, 0.65-0.91; $P < .01$, and OR, 0.54; 95%CI, 0.32-0.9; $P = .02$, respectively). Finally, we should mention that high-volume autonomous communities also had a significantly shorter LoS that was 12% shorter compared to low-volume autonomous communities (OR, 0.88; 95%CI, 0.86-0.91; $P < .01$) as shown on figure 1.

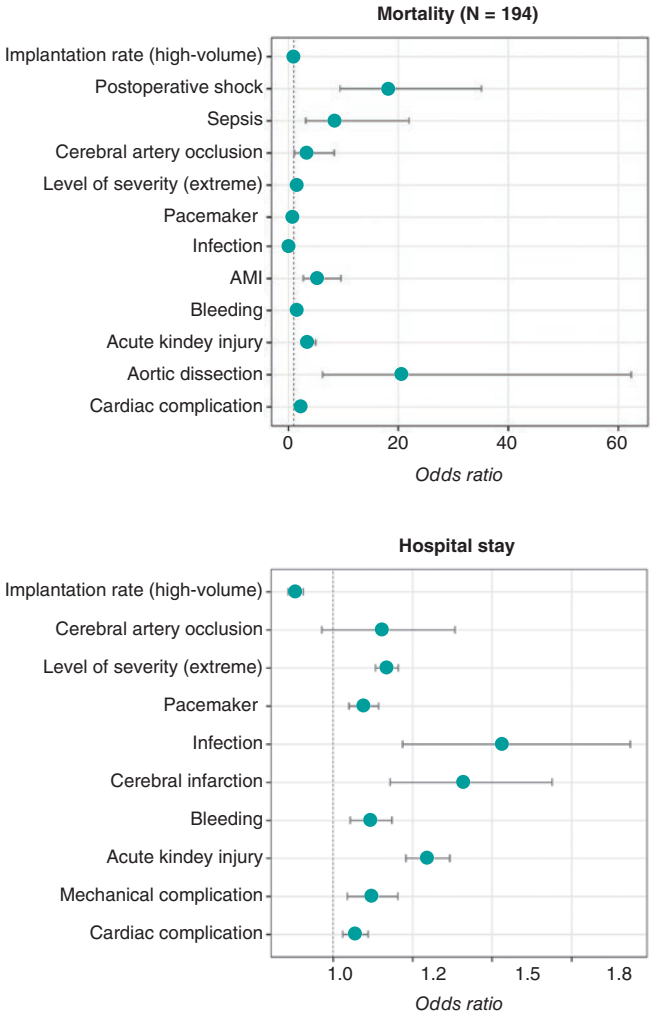

Figure 1. Mortality and hospital stay registered based on the rate of implantation and occurrence of procedural complications. Figures represent the impact that the independent variables selected in the logistic multivariate (mortality) or negative binomial models (hospital stay) have on every complication. The following were always among the candidate variables considered: sex, age, region-adjusted volume of TAVIs performed, and level of severity (RAE-CMBD). Axes in the coordinate plane vary based on the sizes of the odds ratio presented. AMI, acute myocardial infarction.

DISCUSSION

Our study main finding was that transcatheter aortic valve implantation via transfemoral access is safe and effective in Spain. Secondly, with the growing number of procedures performed each year and the experience gained, the rates of non-lethal complications, and mortality (2.7% over the last year studied) have reduced gradually.

It is undeniable that TAVI is a safe and effective procedure according to the scientific evidence available from clinical trials,[12,13,19] and meta-analyses.[20,21] That is why its indication has probably widened from inoperable high-risk patients to intermediate and low-risk patients. This study includes evidence from sources from the Spanish Ministry of Health, Consumer Affairs, and Social Welfare including data from the real-world routine clinical practice in our country.

In Spain, data from the National Registry of Activities in Interventional Cardiology of the Spanish Society of Cardiology Working Group on Hemodynamics and Interventional Cardiology[22] and from RAE-CMBD show a considerable increase in the number of cases treated in the 2014-2017 period[22] in all autonomous communities. Even so, in our country, the rate of TAVI is still significantly lower compared to other countries.[14] We should mention the ongoing improvement reported in the rates of mortality (56.25% reduction in the study period), non-lethal complications, and LoS despite the high rates (around 70%) of cases reported of extreme severity according to the codification of cases in the RAE-CMBD.

Unlike previous studies that showed a worse prognosis in men after implantation data do not show any significant differences based on sex.[23] Indeed, the factors that seem to be associated with a higher mortality rate are postoperative shock, sepsis, aortic dissection, and myocardial infarction. In this case, the patient's risk ratio and the volume of implantation are clearly associated with a different mortality rate, which may have to do with the fact that more experience has been gained with this procedure in the entire country. Consistent with this, data from the CMBD have shown a better mortality rate after conventional surgical aortic valve replacement of 3.3% in 2017 (3.6% in patients between 70 and 80 years of age, and 4.3% in patients > 80 years of age).[24]

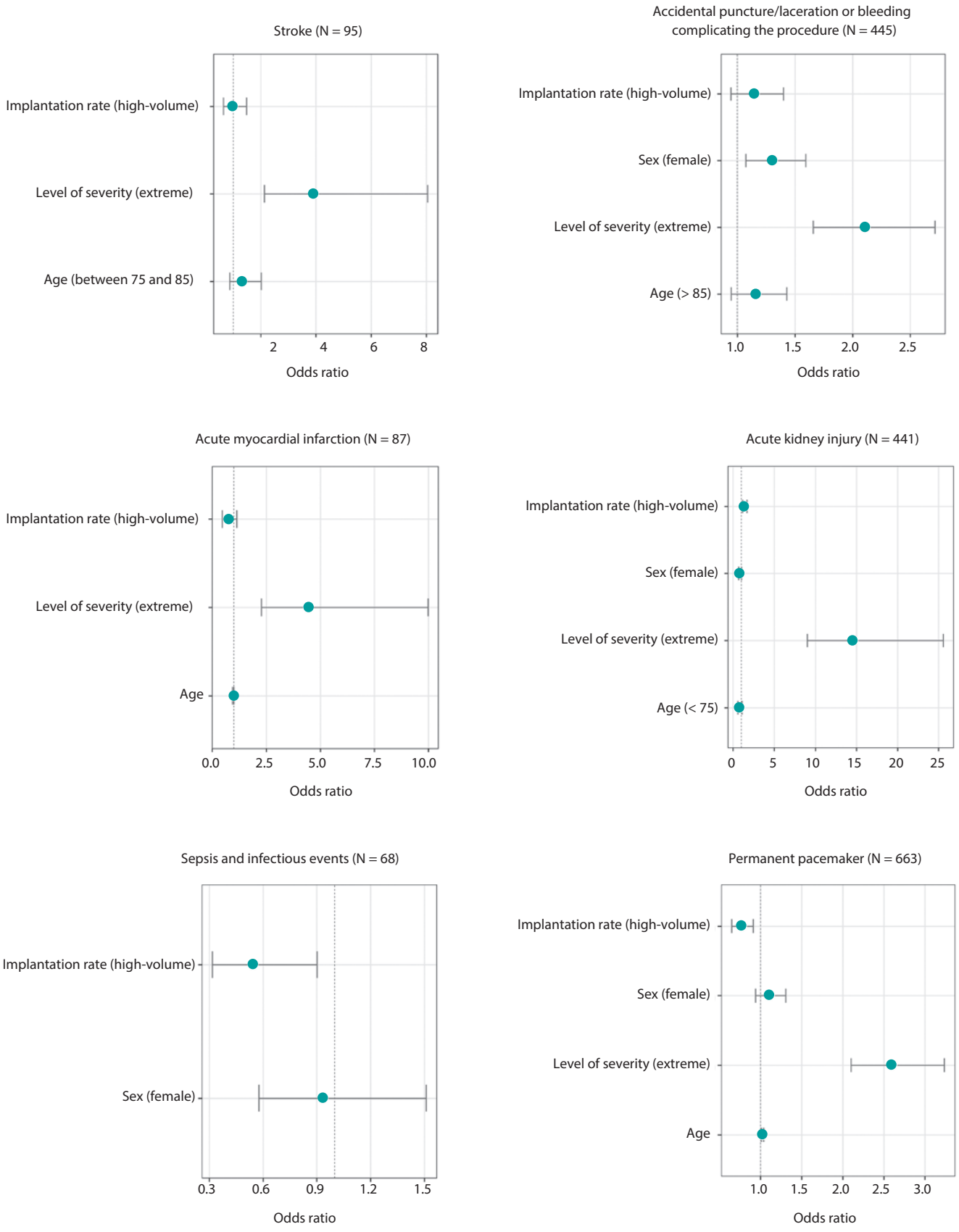

Figure 2. Results of the logistic regression analysis on the risk of clinical complications. Figures represent the impact that the independent variables selected in the multivariate models (genetic algorithm selection following the Akaike information criterion) have on every complication. The following were always among the candidate variables considered: sex, age, region-adjusted volume of TAVIs performed, and level of severity (RAE-CMBD). Axes in the coordinate plane vary based on the sizes of the odds ratio presented.

performed. This association between the volume of procedures performed and fewer complications has already been described in different settings such as after coronary revascularization[26] or after conventional surgical aortic valve replacement,[24] among others.

Added to its clinical benefits, TAVI has consolidated as a cost-effective alternative to conventional surgical aortic valve replacement. The fact that the procedural results of TAVI have become safer and more effective gradually with lower mortality and morbidity rates and shorter LOSs is probably associated with the experience gained by the surgeons, the volume of procedures performed, and the technical and technological advances made.[24]

The growing elderly population in our country and the growing number of indications are the reason why the number of TAVI-eligible patients has been growing.[1,11] In this sense, it is important to add new evidence to contribute to the assessment of the health outcomes of these procedures[27] to guarantee homogeneous quality services in our National Health System. Also, to provide assessment mechanisms to the strategic lines defined in cardiovascular health[28] since TAVI has consolidated a cost-effective option compared to conventional surgical aortic valve replacement.[29,30]

Limitations

The use of an administrative database to obtain information has obvious pros and cons. On the one hand, it allows us to draw a great deal of information from the national census thanks to the obligatory nature of this registry. Also one of its strengths is the high data standardization.[27] However, the administrative nature of the RAE-CMBD whose clinical variables are based on the discharge summary, the thoroughness of coding, and the possible inconsistencies among centers when implementing the codes can impact the accuracy of the results. However, since the period analyzed is a 4-year period, we could say that there are no substantial changes in coding capable of impacting the results significantly. Still, we should mention that the specific codes of complications of ICM-9-CM may not include all the complications that can occur during TAVI. Despite of this, all major clinical complications for the analysis of procedural results were studied. On the other hand, the analysis conducted took into consideration data from the RAE-CMBD until 2017, the most recent ones collected to this date. Also, it would be good to analyze data collected over the last years to see how results evolved. We should expect these results to be even better given the increased number of TAVIs performed, the surgeons' greater experience, and the improved technology available. This should be analyzed by future studies.

Added to this, we should mention that the information collected in this analysis comes from procedures registered in public or public centers with shared activity. Therefore, discrepancies can be found with the data published by the National Registry of Activities in Interventional Cardiology of the Spanish Society of Cardiology Working Group on Hemodynamics and Interventional Cardiology in absolute terms.[22] Still, both sources barely differ in the percentage of cases seen that require PPI (overall difference of 2% in 2016, and 0.1% in 2017 being the data from the Registry of the Spanish Society of Cardiology Working Group on Hemodynamics and Interventional Cardiology) greater.

One of the last limitations of this study is that only the episode that triggered the implantation was analyzed, and no long-term results were obtained, which would provide quality information to assess the extent and cost of healthcare. However, the results from this study are interesting to the extent that they provide key information on aspects to go deeper in the generation of arguments for quality healthcare management.

CONCLUSIONS

TAVI is a safe and effective procedure whose implantation rate is on the rise. Still, there is a huge variability between different autonomous communities and hospitals in Spain. This procedure is mostly performed in patients > 75 years of age with low morbidity and mortality rates that can be compared absolutely to those of conventional surgery. Rates have been going down over the 4 years studied (2014-2017) with gradual reductions in the postoperative LoS, especially in autonomous communities with higher implantation rates.

FUNDING

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AUTHORS' CONTRIBUTIONS

M. Álvarez-Bartolomé, and J. Cuervo conducted both the validation and statistical management of data. All authors contributed to the study design, conducted the critical review of the manuscript, and gave their final approval. Also, they take full responsibility in all aspects of the study by guaranteeing its integrity and accuracy.

CONFLICT OF INTERESTS

B. Martí-Sánchez is a member of Edwards Lifesciences S.L., the sponsor of this study. J. Cuervo is a member of Axentiva Solutions and received fees for his scientific consulting work for Edwards Lifesciences S.L.

WHAT IS KNOWN ABOUT THE TOPIC?

- The rate of TAVI via transfemoral access is significantly lower in Spain compared to other European countries. Also, even though a decade has passed since the first implantation was performed, there is still scarce evidence on the use and results of this procedure in our country.

WHAT DOES THIS STUDY ADD?

- The study provides solid and precise information on the safety, effectiveness, and results of the use of TAVI in the Spanish population.
- There is inter-territory variability in the use of TAVI. Still, the results show low mortality and morbidity rates and a gradual reduction of the mean hospital stay in the study period.
- The rate of complications and mortality seems to go down as more and more TAVIs are performed.
- Higher implantation rates were associated with shorter hospital stays, and a lower risk of permanent pacemaker implantation and infections during the hospital stay.

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Review article

Interventional heart failure therapies: an emerging field in interventional cardiology

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ABSTRACT

Heart failure (HF) is the leading cause of hospitalization in the Western world. Despite improvements in diagnostic tools and therapies, a substantial number of patients with HF still remain highly symptomatic, with a poor quality of life. Most of these patients are ineligible for heart transplantation or left ventricular assist device placement, which underscores an unmet clinical need in this population. Novel device-based HF therapies represent therapeutic options for these patients to improve their symptoms and quality of life. First-in-man studies showed promising results in terms of feasibility, and device performances. However, there is still scarce data regarding efficacy. In this review, we focus on the pathophysiological rationale, emerging data, concerns, and future perspective behind the 3 most studied type of device-based HF therapy: interatrial shunt devices, designed to decompress the left atrium and prevent pulmonary edema; ventriculoplasty devices, designed to physically restore the left ventricle in patients with maladaptive left ventricular remodeling; and cardiorenal flow modulator devices, designed to improve diuresis and renal function in acute decompensated heart failure with cardiorenal syndrome.

Keywords: Heart failure. Novel devices. Interventional cardiology.

Terapéutica intervencionista en insuficiencia cardiaca: un ámbito emergente en cardiología intervencionista

RESUMEN

La insuficiencia cardiaca (IC) es la principal causa de hospitalización en los países desarrollados. A pesar de las mejoras en el diagnóstico y las terapias, una proporción importante de pacientes con IC aún persisten muy sintomáticos o con pobre calidad de vida. La mayoría de estos pacientes, además, no son candidatos a trasplante cardiaco ni a asistencia ventricular de destino. Así pues, existe una necesidad clínica no cubierta de tratar a este creciente subgrupo de pacientes. Los nuevos dispositivos percutáneos para IC son una opción de tratamiento para mejorar los síntomas y la calidad de vida de estos pacientes. Los primeros estudios en humanos con estos dispositivos han mostrado unos resultados prometedores en términos de factibilidad, seguridad e integridad de los dispositivos. No obstante, todavía hay pocos datos sobre su eficacia. En esta revisión nos centramos en describir las características, las ventajas y los inconvenientes, así como las evidencias, de los 3 tipos principales de dispositivos percutáneos para la IC, con especial énfasis en la base fisiopatológica subyacente que justifica su diseño: los dispositivos de derivación interauriculares, que pretenden descomprimir la presión de la aurícula izquierda y así evitar el edema pulmonar; los dispositivos de ventriculoplastia, que restauran físicamente el ventrículo izquierdo en situaciones de mal remodelado ventricular; y los dispositivos de modulación del flujo cardiorrenal, diseñados para mejorar la diuresis en situación de IC aguda descompensada con síndrome cardiorrenal asociado.

Palabras clave: Insuficiencia cardiaca. Nuevas terapias. Cardiología intervencionista.

Abbreviations

ADHF: acute decompensated heart failure. **GDMT**: guideline-directed medical therapies. **HF**: heart failure. **HFrEF**: heart failure with reduced ejection fraction. **IASD**: interatrial shunt device. **LV**: left ventricle. **RV**: right ventricle.

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INTRODUCTION

Heart failure (HF) is the leading cause of hospitalization in the Western world, and a major issue for public health. The estimated prevalence of HF is between 1% and 2% in the adult population in developed countries, and up to 10% among patients aged > 70 years.[1] Despite improvements in diagnostic tools and guideline-directed medical therapies (GDMT) such as continuous monitoring of pulmonary artery pressures, sacubitril, and selective sodium–glucose cotransporter 2 inhibitors, a significant proportion of patients with HF remain symptomatic and with a poor quality of life.[2-4] According to the latest European data, the annual mortality and re-hospitalization rates in patients with HF are between 7%-17%, and 34%-44% respectively.[4] Most of these individuals are ineligible for heart transplantation or left ventricular assist device placement, which underscores an unmet clinical need in this ever growing population. Consequently, novel applications of minimally invasive, device-based therapies are being developed to bridge this treatment gap, that is now starting to fall into an emerging sub-specialty called «interventional heart failure». Novel device-based HF therapies may represent an option to improve the quality of life and reduce the rates of hospitalization or even mortality of these patients who are GDMT-optimized, yet with residual morbidity and suboptimal quality of life.

This article will focus on the pathophysiological rationale and emerging data and concerns behind some of these device-based HF therapies that have been designed to target a range of mechanisms involved in the HF syndrome.

INTERATRIAL SHUNT DEVICES

An early sign of left ventricular (LV) failure (involving both preserved or reduced ejection fraction) is an increased LV end-diastolic pressure, retrogradely transmitted to the left atrium and pulmonary capillaries causing dyspnea and ultimately pulmonary edema if left untreated.[5] Interatrial shunt devices (IASD) create a permanent interatrial communication using a conventional percutaneous transseptal approach. It is intended to dynamically decompress left atrial pressure, and thus, attenuate or even reverse the underlying mechanism of pulmonary edema.[6] However, left-to-right interatrial shunt may increase right ventricular (RV) preload and eventually RV dilatation. Prior studies suggest that the size of the shunt plays a key role in the final outcomes. Indeed, the ideal size of the shunt should allow the reduction of left atrial pressure without hampering right heart function: too large IASDs may increase the Qp/Qs ratio enough to cause RV failure while too small IASDs may have negligible hemodynamic and clinical effects. Data from first-in-man studies indicate that devices < 10 mm are unlikely to cause hemodynamically significant shunting (ie, Qp/Qs ratio > 1.5) or RV size/functional compromise.[7] The 2 shunt devices most studied to date are the 5 mm- (V-Wave device, V-Wave Ltd., Israel) and 8 mm-long (Interatrial Shunt Device, Corvia Medical, United States) in diameter apertures (figure 1A, figure 1B and table 1).[8] Another concern is related to patients with stiff or fibrotic atria or RV. In this scenario the right atrium or RV may not be able to accept an increased preload. For all these reasons, patients with restrictive cardiomyopathy, pulmonary hypertension (pulmonary vascular resistance > 4 Wood units) or RV dysfunction have been excluded from shunt studies. Finally, paradoxically, strokes due to transient flow reversal are another potential concern when using this technology.

The first-in-man experience with both the V-wave and the Corvia Medical devices showed significant improvements in quality of life, HF symptom relief, and exercise capacity.[6,8-9] There are currently several ongoing studies, and randomized clinical trials assessing IASD in patients with symptomatic HF despite GDMT including both HF with reduced or preserved LV function patients (table 1, REDUCE LAP-HFREF trial [NCT03093961], REDUCE LAP-HF trial II [NCT03088033], and REDUCE LAP-HF IV [NCT04632160]).

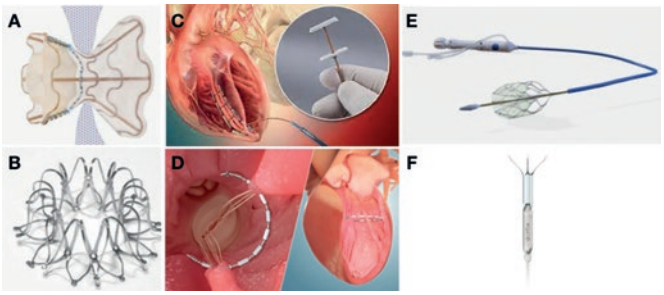

Figure 1. Interventional heart failure therapy devices. **A:** V-Wave (V-Wave Ltd., Israel) is an interatrial shunt device with an hourglass-shaped self-expandable nitinol frame and expanded PTFE skirt with 5 mm central hole. **B:** Interatrial Shunt Device (Corvia Medical, United States) provides 8 mm of central hole. **C:** AccuCinch ventricular restoration system (Ancora Heart, United States) is a fully percutaneous left ventriculoplasty device. **D:** Revivent TC System (BioVentrix Inc., United States) is a left ventriculoplasty device that uses micro-anchors to exclude a scar via hybrid approach (jugular plus mini lateral thoracotomy). **E:** Doraya catheter (Revamp Medical, Israel) reduces both the venous renal hypertension and preload to improve diuresis in acute decompensated heart failure (ADHF) with cardiorenal syndrome (CRS). **F:** Aortix (Procyrion Inc., United States) device is a pump that improves the renal arterial perfusion pressure and reduces the left ventricular afterload. Aortix is intended to improve diuresis in ADHF with CRS.

VENTRICULOPLASTY (LEFT VENTRICULAR RESTORATION)

The LV has a unique architecture with 3 different myofiber orientations and an elongated ellipsoid shape that are essential for its optimal function. Different pathological states cause molecular and cellular changes that alter the obliquity of the myofibers, which become more horizontal, and macroscopically result in chamber dilatation and increased sphericity. This early adaptive response is ultimately detrimental and self-propagating, resulting in a loss of ventricular function (maladaptive remodeling). Maladaptive LV remodeling is clearly associated with poor prognosis.[10]

Ventriculoplasty refers to a physical intervention aimed to anatomically modify the LV geometry. The rationale is based on Laplace's Law, according to which wall tension and LV wall stress are decreased by reductions in the LV radius, thus reversing or attenuating maladaptive LV remodeling. Compared to the ejection fraction, LV volume reduction is likely to be equally important in improving symptoms and possibly clinical outcomes. Prior surgical attempts of this concept showed disappointing results due to protocol deviations, and poor patient selection, thus contributing to less than anticipated LV volume reductions compared to the control arm. However, a post-hoc analysis demonstrated promising results (significant and sustained mortality reductions out to 6 years) in patients with an achieved LV end-systolic volume index < 70 mL/m^2 with strong trends in survival advantage in patients who achieved a 30% threshold in LV end-systolic volume index reduction.[11] Despite the controversial results of surgical LV reconstruction, there is considerable interest in percutaneous reverse LV remodeling, specifically in patients with HF with reduced ejection fraction (HFrEF). Several methods have been developed to perform percutaneous left ventriculoplasties. However, we will be focusing on the 3 methods that showed promising results in early feasibility studies: the Revivent TC system (BioVentrix Inc., United States),

Table 1. Device mechanism, features and, evidence of interventional heart failure devices

Device	Device mechanism & features	Trial	Study design	Main inclusion criteria	N	Main results
V-Wave	– Interatrial shunt (transseptal approach). – Fully percutaneous (via femoral vein using a 12-Fr delivery system). – Hourglass-shaped device on a nitinol frame with an expanded PTFE skirt. – Lumen diameter: 5 mm. – Second generation has no unidirectional valve to ensure left-to-right shunt	VW-SP-1 + Canadian cohort[8]	Multicenter, single-arm, open-label, phase I trial with a 12-month follow-up	– NYHA class III-IV; ≥ 1 HF hospitalization within the last year or ↑ BNP	38 (30 with HFrEF)	– 1-year rate of MACE: 2.6% (1 tamponade) – Significant improvements in NYHA class, QoL, KCCQ – Significant increase in the Qp/Qs ratio
		RELIEVE-HF NCT03499236	Multicenter, sham-controlled, blinded RCT with a 1:1 allocation ratio, and a 1-to-2-year follow-up	– NYHA class II-IV; ≥ 1 HF hospitalization within the last year or ↑ BNP PCWP > RAP; PVR < 4 WU; transseptal eilgible	500 (ongoing)	Enrolling (estimated completion by 2022) – Endpoints: device MDAE, MACE, NYHA, KCCQ, and 6MWT
Interatrial Shunt Device	– Interatrial shunt (transseptal approach) – Fully percutaneous (femoral vein) – Nitinol, self-expanding metal cage with a double-disc design and an opening (barrel) in the center – Central hole of 8 mm	REDUCE LAP-HF NCT01913613	Multicenter, open-label, single-arm with a 6-month follow-up	– NYHA class II-IV; LVEF > 40%; PCWP ≥ 15 mmHg (or 25 mmHg exercise)	64	– No MACE; 52% had a reduction in resting PCWP; 54% had a reduction in PCWP during exertion; improvement in NYHA class; QoL, and 6MWT
		REDUCE LAP-HF I NCT02600234	Multicenter, double-blind, sham-controlled RCT with a 1:1 allocation ratio, and a 1-year follow-up	– NYHA class III-IV; LVEF > 40%; Exercise PCWP ≥ 25 mmHg; PCWP-RAP ≥ 5 mmHg; prior HF hospitalization or ↑BNP	44	– Reduction in PCWP on exercise; similar rate of MACCE, and no strokes in either one of the 2 arms. – Trends of reduction of HF-related hospitalizations; improvement in QoL, and RV size in the device arm
Revivent TC System	– Ventriculoplasty – Hybrid (jugular vein + mini lateral thoracotomy) – Anchors and external locking on the LV epicardial surface	REVIVE-HF NCT03845127	Multicenter prospective RCT with a 6-month follow-up (2:1 allocation ratio; device vs guide-line-directed medical therapy)	– HF symptoms with previous myocardial infarctio, increased LV systolic volume, and contiguous scar located in the anterior/ apical LV	180 (ongoing)	Enrolling (estimated completion by 2022). – Endpoints: 6MWT distance at 6 months; QoL at 6 months; change in NYHA class at 6 months; LVESVI at 6 months; LVEF at 6 months
AccuCinch Ventricular Restoration System	– Ventriculoplasty – Fully percutaneous; femoral artery access, retrograde aortic approach; initially designed for mitral regurgitation – Cinching anchors attached to the mitral subvalvular apparatus	CORCINCH-HF NCT04331769	Multicenter, open-label, RCT with a 5-year follow-up.	– NYHA class II-IV; LVEF, 20% to 40%; and LVEDD > 55 mm; 6MWT distance, 100 m to 450 m	400 (ongoing)	Enrolling (estimated completion by 2025) – Endpoints: MAEs at 6 months, and 1 year; changes in the KCCQ score; change in the 6MWT; composite of all-cause mortality, LVAD implant or heart transplantation, HF hospitalizations, and changes in the KCCQ score
Papillary muscle sling	– Ventriculoplasty – Femoral artery access, retrograde aortic approach – 4 mm PFTE graft implanted around the base of the papil-lary muscles and then tightened	NCT04475315	Single-center, open-label RCT (1:1 allocation ratio; CABG vs CABG + sling) with a 5-year follow-up	– NYHA class II-IV; LVEDD ≥ 55; LVEF 20% to 40%; FMR ≤ 2+; end-systolic interpapillary muscle distance ≥ 20 mm; ischemic or nonischemic cardiomyopathy	40 (ongoing)	Enrolling (estimated completion by 2026) – Endpoints: changes of LVEF and LV volume, mortality, MACE, functional mitral regurgitation severity, change in QoL and the 6MWT, all-cause readmission, HF readmission, and in the rate of mitral leaflet tenting area
Doraya catheter	– Venous renal flow modulator via femoral vein (12-Fr delivery system) – Decreased renal hyperten-sion and RV preload	NCT03234647	Multicenter, first-in-man, single-group study of feasi-bility, and safety	– ADHF with poor diuretic response	9	Enrolling ended back in May 2021. – Device-related or procedural serious adverse events at 60 days
Aortix	– Arterial renal flow modulator via femoral artery (18-Fr delivery system) – Pump that increases aortic flow (up to 5 L/min), and renal perfusion pressure, and reduces the LV afterload	NCT04145635	Multicenter, prospective non-RCT of feasibility and safety	– ADHF with HFrEF or HFpEF – Worsening renal function after 48 hours of IV diuretics (increase of 0.3 mg/dL) – Persistent congestion (PCWP ≥ 20 or central venous pressure ≥ 12mmHg)	60 (ongoing)	Enrolling (estimated completion by 2022) – Endpoints: 30-day serious adverse events, serious procedural adverse events, device performance, 7-day decrease of central venous pressure or PCWP > 20%, changes in urine output, and lower BNP levels by 20%

6MWT, 6-minute walk test; ADHF, acute decompensated heart failure; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricle; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MACE, major adverse cardiovascular event; MACCE, major adverse cardiovascular and cerebrovascular event; MAE, major adverse event; MDAE, medical device adverse event; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVP, pulmonary vascular resistance; QoL, quality of life; RAP, right atrial pressure; RCT, randomized clinical trial; RV, right ventricle.

the AccuCinch (Ancora Heart, United States), and the papillary muscle sling.

The BioVentrix Revivent TC system is a hybrid transcatheter procedure via mini lateral thoracotomy and transcatheter jugular access. The system is designed to exclude an aneurysm or scar located in the anterior or apical LV wall. A hinged anchor is deployed inside the RV side of the distal interventricular septum (via jugular access) and 1 external locking anchor on the LV epicardial surface (via minithoracotomy). A tether is used to draw the 2 anchors towards each other until enough contact between the 2 opposing walls has been achieved. This action is repeated along the long axis of the LV, resulting in the exclusion of the dysfunctional scar tissue from a healthy and functional myocardium (figure 1C). Data from a study of 86 patients demonstrated improvements in the LV ejection fraction, LV volumes, quality of life, and functional status.[12] Currently, there are 2 pivotal trials assessing this therapy (the REVIVE-HF [NCT03845127], and the ALIVE [NCT02931240]) (table 1).

The AccuCinch ventricular restoration system consists of a predesigned tracking catheter that, via retrograde aortic access, is positioned to encircle the basal aspect of the LV, which is used to position a band anchored to the basal LV myocardium. Tension is applied to a cable reducing the basal wall diameters and the LV volumes[13] (figure 1D). Although this device was initially designed to treat functional mitral regurgitation, the current focus remains on patients with HFrEF. There is currently an ongoing pivotal randomized clinical trial assessing this device in individuals with HFrEF vs GDMT (table 1, CORCINCH-HF [NCT04331769]).

The papillary muscle sling procedure, based on an existing surgical sling procedure, is aimed at reducing the lateral interpapillary muscle separation distance. A sling is used to draw together the LV via retrograde aortic access. Currently, there is 1 clinical trial assessing this technique in a surgical cohort (table 1, NCT04475315).

CARDIORENAL FLOW MODULATION

Acute decompensated HF (ADHF) in patients with prior renal injury and/or cardiorenal syndrome is an extremely challenging scenario for medical management. The pathophysiology of cardiorenal syndrome is complex, dynamic, and multifactorial, including hemodynamic and neurohumoral axis alterations.[14] Data from previous studies suggest that the difference between renal arterial driving pressure and venous outflow pressures must remain sufficiently large for the proper renal blood flow and glomerular filtration. Maintenance of this homeostatic mechanism is especially important in patients with preexisting renal injuries. In patients with ADHF and cardiorenal syndrome, both pre-renal perfusion reduction, and renal venous hypertension are present. Renal venous hypertension increases renal resistance, which in turn impairs intrarenal blood flow. The decrease in renal perfusion is aggravated by the preglomerular vasoconstriction caused by the neurohumoral activation of the renin-angiotensin-aldosterone axis, which results in increased proximal tubular sodium and water reabsorption to maintain an effective plasma volume. This results in oliguria, worsening congestion symptoms, and diuretic resistance. The relationship between diuretic resistance and poor outcomes in this scenario is well established.[14]

There are 2 main types of devices designed to interrupt the vicious circle of cardiorenal syndrome in ADHF: those aimed at reducing renal venous hypertension such as the Doraya catheter (Revamp Medical, Israel); and those aimed at increasing arterial renal perfusion pressure such as the Aortix (Procyrion Inc., United States) and the Second Heart Assist (Second Heart LLC, United States) devices.

The Doraya catheter is a self-expanding flexible nitinol frame covered in its distal portion to restrict blood flow. It is placed in the inferior vena cava below the renal vein via femoral vein access using a 12-Fr delivery system. It serves as a temporary flow regulator for up to 24 hours. Doraya causes a temporal decrease in central venous pressure at the renal vein level, thus reducing cardiac preload, and contributing to LV unloading[15] (figure 1E). A first-in-man clinical study to assess the safety, feasibility, and hemodynamic effects of this device in patients with ADHF, congestion, and an inadequate response to diuretics completed enrollment back in May 2021 (table 1, NCT03234647).

Aortix is a percutaneous axial pump positioned in the suprarenal descending aorta via transfemoral approach using an 18-Fr delivery system. This device increases aortic flow, decreases afterload, and can provide up to 5 L/min (figure 1F). A study performed in the percutaneous coronary intervention setting demonstrated a 10-fold increase in urine output.[16] There is an ongoing study aimed at evaluating the feasibility, safety, and efficacy profile of Aortix in patients with ADHF (HF with preserved ejection fraction, and HRrEF), and cardiorenal syndrome (table 1, NCT04145635).

Despite improvements made in the management of HF, a substantial proportion of patients still remain severely symptomatic, and with a poor quality of life. Interventional HF is a promising new field within interventional cardiology to provide a percutaneous device-based therapeutic response to these patients. Interatrial shunts, percutaneous ventriculoplasties, and cardiorenal flow modulators are some of the most remarkable devices in this emerging field.

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AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

None declared.

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Debate: Severe bicuspid aortic valve stenosis in non-high-risk surgical patients. In favor of TAVI

A debate: Estenosis aórtica grave bicúspide en el paciente sin riesgo elevado para cirugía. A favor del TAVI

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Question: What is the prevalence of bicuspid aortic valve (BAV) in your case series of transcatheter aortic valve implantation (TAVI) to this date? And what's the patients' surgical risk?

Answer: Over 1000 TAVIs have already been performed at our center, and the prevalence of BAV stands at around 4.4%. It is greater compared to the Spanish TAVI registry where nearly 2% of the patients treated with TAVI have BAV.[1] Thanks to the use of computed tomography scan as a systematic imaging modality to plan TAVI, its diagnosis has gone up. As a matter of fact, our group included the number of patients treated with TAVI or surgery in 2019 in 17 Spanish centers being the prevalence of BAV around 4.6%, and 16%, respectively. At times, the diagnosis of BAV is not an easy one, and when the heart valve is highly unstructured and calcified, it can go unnoticed. Therefore, it can be underdiagnosed in our series of TAVI. However, an «active» search can increase the number of diagnoses.

In our series the risk profile of these patients is intermediate-high. The mean age is 80 years old with a similar distribution by sex. The risk scores measured were the logistic EuroSCORE (14.8%), the EuroSCORE II (5.8%), and the STS (5.7%). However, these scores are influenced by the ones obtained in younger patients (< 75 years) that, although with lower scores, have proven inoperable or are very high-risk surgical patients (mainly due to a respiratory condition or hemodynamic instability).

Q.: What evidence do we have for TAVI to treat bicuspid aortic valve stenosis? Are the actual results equivalent to the ones reported for the non-bicuspid aortic valve?

A.: In short, I would say that although scarce (mainly from retrospective registries), evidence is mounting. The results coming from the oldest series were worse. However, they are currently similar with certain differences.

The evidence available on TAVI in the BAV aortic stenosis fall into 3 categories: *a)* TAVI in the BAV vs TAVI in the tricuspid valve; *b)* different types of TAVI in the BAV (TAVI vs TAVI), and *c)* TAVI vs surgery in the BAV.

The early studies showed that TAVI performed in the BAV had higher rates of paravalvular leak, embolization, need for second valve implantation, and a lower rate of successful device implantation. Thanks to the technical advances made and second and third-generation valves, these results have equalized. However, there is still a significant rate of stroke (2.5%) that is even higher compared to tricuspid valves.[2] A meta-analysis demonstrated that the rate of paravalvular leak is still a little higher in self-expanding valves, as well as the rate of mechanical complications in balloon-expandable valves.[3] No all valves are the same for the different anatomical and clinical settings. In the BAV only 1 retrospective registry has been published comparing the Edwards SAPIEN 3 valve (Edwards Lifesciences LLC, United States) to the Evolut R/Pro (Medtronic, United States). The outcomes were similar regarding mortality and stroke, but with higher rates of paravalvular leak and device embolization, and fewer overall events of successful implantation in the self-expanding valve group vs higher gradients (approximately 2 mmHg) in the balloon-expandable valve group.[4] In the most recent series published on the SAPIEN 3 valve in the context of the Partner-3 trial, a group of patients with BAV was compared—after propensity score-based risk adjustment—to another group of patients with tricuspid valve. It turned out that the clinical outcomes overlapped in both (mortality and stroke rates of 0% and 1.4%, respectively at 30 days). We should mention that the CoreValve Evolut device achieved an indication in patients with BAV (based on the TVT registry[5]) while the SAPIEN 3 valve does not have a specific contraindication in this context in its instructions for use. However, the remaining valves available today are specifically contraindicated for BAV in the instructions for use. Finally, the outcomes of TAVI vs surgery in the BAV were published in 2 studies,

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one with in-hospital outcomes and the other with the outcomes reported at the 2-year median follow-up.[6,7] Patients treated with TAVI had a higher rate of pacemaker implantation, and better data regarding bleeding, vascular complications, and lengths of stay with similar rates of in-hospital mortality and stroke at the 2-year follow-up. Therefore, although we still don't have robust evidence that TAVI is superior to surgery regarding the BAV, there is no single piece of evidence that says that TAVI fares worse compared to surgery.

Q.: What special considerations should be made with TAVI when performed on the bicuspid aortic valve? Are there any anatomical variants with specific technical implications?

A.: The first consideration should be to know whether we are really talking about a BAV or not. Like I said, in heavily calcified and unstructured valves it can go unnoticed. For procedural planning purposes, it is essential to make a thorough assessment of the baseline computed tomography scan. It should provide us with detailed information on the valve and the ascending aorta to obtain optimal results. In the first place, we should know both the type of BAV (type 0, I or II) and its morphology. In highly asymmetrical type 0 valves with a heavily calcified raphe, the expansion of the valve can be inadequate (very elliptical) and affect the hemodynamic outcomes (due to gradients and paravalvular regurgitation). Also, both the location of the raphe and calcification *per se* can have an impact on the position of the valve that can move towards either one of the sinuses (with greater risk of coronary obstruction in case of displacement towards the left or the right sinus). We should mention that the presence of a calcified raphe plus excessive leaflet calcification has been associated with a higher mortality rate.[8] The computed tomography scan can also be used to measure the right size of the valve both at annular and supra-annular level (intercommissural distance) always remembering that minimal valve oversizing is often necessary.

Once the right procedural planning is in place, the technical considerations on the day of the surgery should be:

- Avoid brain damage as much as possible and, if possible, always use cerebral protection devices.

- Use high support guidewires like Lunderquist (Cook Medical, United States) or Back-up Meier (Boston Scientific, United States) when treating tortuous aortas.

- Use the necessary time to locate the angiographic plane for implantation since it is often more complex compared to tricuspid valve cases.

- Always predilate (in most cases with the minimum diameter and without exceeding the medium) and watch the degree of balloon opening and calcium displacements from the leaflets towards the coronary arteries. The strategy of performing a simultaneous injection during predilation provides us with valuable information to analyze the risk of coronary occlusion and select the size of the valve.

- Select the right type of TAVI based on the patient's characteristics. Self-expanding valves with less radial strength can remain underexpanded so before their implantation we should always acquire several projections to confirm their correct expansion. If there is a high risk of rupture in the annulus with an aggressive expansion, the Evolut Pro+ valve can be used. However, if the risk of aortic regurgitation is high, the SAPIEN 3 Ultra valve should rather be used. We should mention that these risks happen together and the trade-off is complex. The tortuosity of the aortic arch and the horizontally of the ascending aorta (very common in the BAV) can also help us select a flexible valve or with a deflectable catheter. Another significant aspect to select the type of valve is the operator's experience.

- If postdilation is required (needed in over 50% of the cases with self-expanding valves), the balance between the rupture of the annulus and the leak should be observed when selecting the balloon size. On many occasions, the annuli of BAVs are large meaning that large balloons will also be needed (26 mm, 28 mm or 30 mm). Still, balloons this big are not always available at the cath lab.

Q.: Which cases with BAV do you think are clearly eligible for TAVI and which are not?

A.: This is a very relevant question because, like I said, evidence is scarce and barely any randomized trials have been published on this regard (at least in the short and mid-term) comparing TAVI to surgery in the BAV setting. Therefore, decisions should be made based on the operator's experience and the local outcomes. When examining a patient with BAV for TAVI a series of clinical, and anatomical (or technical) aspects should be taken into consideration. The clinical features in favor of TAVI are the same as for tricuspid valves, that is, old, frail, and female patients (> 75 years) with comorbidities and lack of coronary artery disease or other concomitant valvular heart disease. The favorable anatomical aspects would be a suitable femoral access, type 1 bicuspid anatomy (versus type 0 and 2), small annuli, mild or moderate calcification, no dilatation of the ascending aorta, no calcification of the raphe, and no risk of coronary artery occlusion. I would use TAVI as the first-line therapy for high-risk frail or elderly patients. However, I would use surgery for young low-risk patients (< 70 years). It should be the job of the heart team to know how to deal with intermediate settings in each case like young patients with comorbidities and intermediate risk but with a favorable anatomy for TAVI or high-risk older patients with an unfavorable anatomy for TAVI. Something that should be studied based on the patients' clinical and anatomical features is whether the long-term results of surgery are predominant compared to its immediate risks or if, on the contrary, TAVI less invasive approach is preferred in this balance even after obtaining suboptimal outcomes in highly unfavorable anatomies. Thanks to the technical advances made, the new valves available, and the experience gained with TAVI with careful procedural planning good results can be achieved even in complex settings. However, since a proportion of patients with BAV are young, we interventional cardiologists need to be aware of the heterogeneity of this disease, refine the technical details of implantation, and the selection of patients and devices to optimize results.

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Debate: Severe bicuspid aortic valve stenosis in non-high-risk surgical patients. In favor of surgery

A debate: Estenosis aórtica grave bicúspide en el paciente sin riesgo elevado para cirugía. A favor de la cirugía

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Question: What is the prevalence of bicuspid aortic valve in the population currently eligible for surgical aortic valve replacement?

Answer: The prevalence of bicuspid aortic valve is around 1% to 2% of the population. Somewhere between 27% and 35% of the population will eventually require surgery at the 20-year follow-up.[1] On the other hand, the associated dilatation of the ascending aorta, with conflicting results regarding its prevalence, stands at around 50% to 80%.[1] At our center, 30% of all aortic valve replacements or repairs—with or without replacement of the ascending aorta—are performed on the bicuspid aortic valve. Also, this is a group of predominantly male patients with a mean age of 55 years, and different clinical features compared to the aortic stenosis described in elderly patients. Many of these patients are repaired when regurgitation is predominant with excellent clinical outcomes.

Q.: What special considerations should be made with surgery when performed on the bicuspid aortic valve?

A.: There are 3 special considerations that should be observed. In the first place, this condition affects a group of younger patients. Also, these valves have severe calcification posing great technical difficulties regarding decalcification for correct implantation under direct vison. On many occasions, eventually, the ascending aorta needs to be replaced. According to the clinical practice guidelines from the European medical societies on cardiology and thoracic surgery, the ascending aorta needs to be replaced if it is longer than 45 mm in the presence of associated valve replacement. The indication for isolated aneurysm without valvular lesion is 50 mm in the presence of associated risk factors (arterial hypertension, past medical history of dissection or aortic syndrome).[2]

Q.: Do you think that severe aortic stenosis in the bicuspid aortic valve is an indication for surgery *per se* regardless of the surgical risk?

A.: I do for the reasons I already gave you on the special characteristics of this condition that, in most cases, require surgery. The main reason is that it affects younger patients in whom other therapeutic options have not been validate with 10+year follow-ups. Other less important reasons are severe calcification, repair possibilities in the presence of double valvular lesion, and quite often, the need to replace the ascending aorta.

Q.: In your opinion, which are the cases of severe bicuspid aortic stenosis clearly eligible for surgery and which are ineligible?

A.: In principle, preferably, all cases should be treated surgically. Other options can be considered only in patients in whom surgery is contraindicated, although the evidence available on this matter is still weak. Studies on transcatheter aortic valve implantation include elderly patients with aortic stenosis. According to the European clinical practice guidelines, patients over 75 with comorbidities can be treated percutaneously. However, the severe associated calcification, and lack of scientific evidence should always be taken into consideration.[3]

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CONFLICTS OF INTEREST

None whatsoever.

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Invasively managed acute and chronic coronary syndromes during the first wave of the COVID-19 pandemic: one-year outcomes

Síndromes coronarios agudos y crónicos tratados de forma invasiva durante la primera ola de la pandemia de COVID-19: resultados a 1 año

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To the Editor,

Acute SARS-CoV-2 infections (COVID-19) have caused a global pandemic since the first cases were described in Wuhan, China, back in December 2019. The first wave of COVID-19 cases in Western Europe led to substantial healthcare disruption and population lockdowns from March 2020 through May 2020. Regarding the cardiovascular implications, COVID-19 has been associated with higher in-hospital mortality rates in patients with coronary syndromes.[1] Among others, a higher thrombogenic risk has been proposed as the underlying mechanism of this increased rate of adverse events.[2] Subsequently, observational studies have suggested an increased number of stent thrombosis during acute COVID-19 infections.[3] The underlying mechanisms of this stent thrombosis are endotheliitis, platelet activation, and coagulopathy. It is unknown whether these mechanisms could also lead to late adverse cardiovascular events or stent failure.

We previously reported on an increased 30-day mortality rate in patients with acute coronary syndrome and COVID-19 compared to non-COVID-19 patients.[4] Later studies confirmed similar rates of death after myocardial infarction.[5]

This study aimed to analyze the 1-year rate of adverse cardiovascular events and stent failure in consecutive patients referred for coronary angiography from March through April 2020. All the participant patients gave their informed consent and the project was approved by the local ethics committee.

Out of a total of 134 patients, 117 had coronary artery disease (either acute coronary syndrome or stable coronary artery disease). Patients (n = 17) with alternative diagnoses (MINOCA, tako-tsubo, myocarditis, others) were excluded. A total of 10 (8.5%) of these 117 patients tested positive on the polymerase chain reaction (PCR) test for SARS-CoV-2 (CoV+) while the PCR of 107 patients tested negative or were never tested due to the lack of clinical data suggestive of acute COVID-19 (universal testing for COVID-19 was unavailable at this early stage of the pandemic). The primary event was a patient-oriented combined endpoint (POCE) of all-cause mortality, any myocardial infarctions or any revascularizations. The device-oriented composite endpoint (DOCE) was defined as a composite of cardiac death, target vessel revascularization or stent thrombosis. Both the patient selection and the study flowchart are shown on figure 1.

The baseline and clinical characteristics of both CoV- and CoV+ patients are shown on table 1. Patients who were CoV+ had been revascularized slightly less frequently (60.0% vs 74.7%). Also, complete revascularization was less likely (30.0% vs 56.2%) although both were non-significant differences (P = .312, and P = .183, respectively).

At the 1-year follow-up, the rate of MACE was similar in CoV+ and CoV- patients (20.0% vs 13.9%, respectively, P = .635) as shown on figure 2A. Two deaths were reported among CoV+ individuals (20.0% vs 6.9% in CoV-). These deaths occurred shortly after performing a coronary angiography due to COVID-19-related severe respiratory failure. Interesting enough, none of the other CoV+ patients experienced any adverse cardiovascular events at the 1-year follow-up (figure 2B). Among stent-revascularized patients (5 in the CoV+ group; 573 in the CoV- group, the rate of DOCE was 0%, and 10.0%, respectively). One stent thrombosis was reported in the CoV- group, and neither definitive nor suspected thrombosis were reported in CoV+ patients who underwent stent implantation.

Although these results should be interpreted while understanding the inherent biases of observational reports, this small series suggests that CoV+ patients may be at a higher risk of death, but not precisely at a higher risk of cardiovascular events. We did not find a significant or numerical trend towards more myocardial infarctions, target vessel failures or stent thromboses. The low rate of adverse cardiovascular events reported in our cohort of CoV+ patients suggests that, in clinically indicated cases, the invasive management of coronary artery disease should not be different from that of non-COVID-19 patients. We acknowledge the limitation of the small number of patients. However, as far as we know, this is the first series to report on the 1-year outcomes of coronary syndromes treated during the COVID-19 pandemic. Certain rare events such as stent thrombosis may need a much larger series to be properly examined, but conversely, the global pandemic may have led to an unsought positive publication bias of COVID-19-related complications. The reporting of consecutive patient data like our cohort, rather than selected case series, will refine our knowledge on the actual cardiovascular outcomes in patients recovered from COVID-19.

We conclude that the invasive management of coronary artery disease in COVID-19 positive patients did not convey a higher risk

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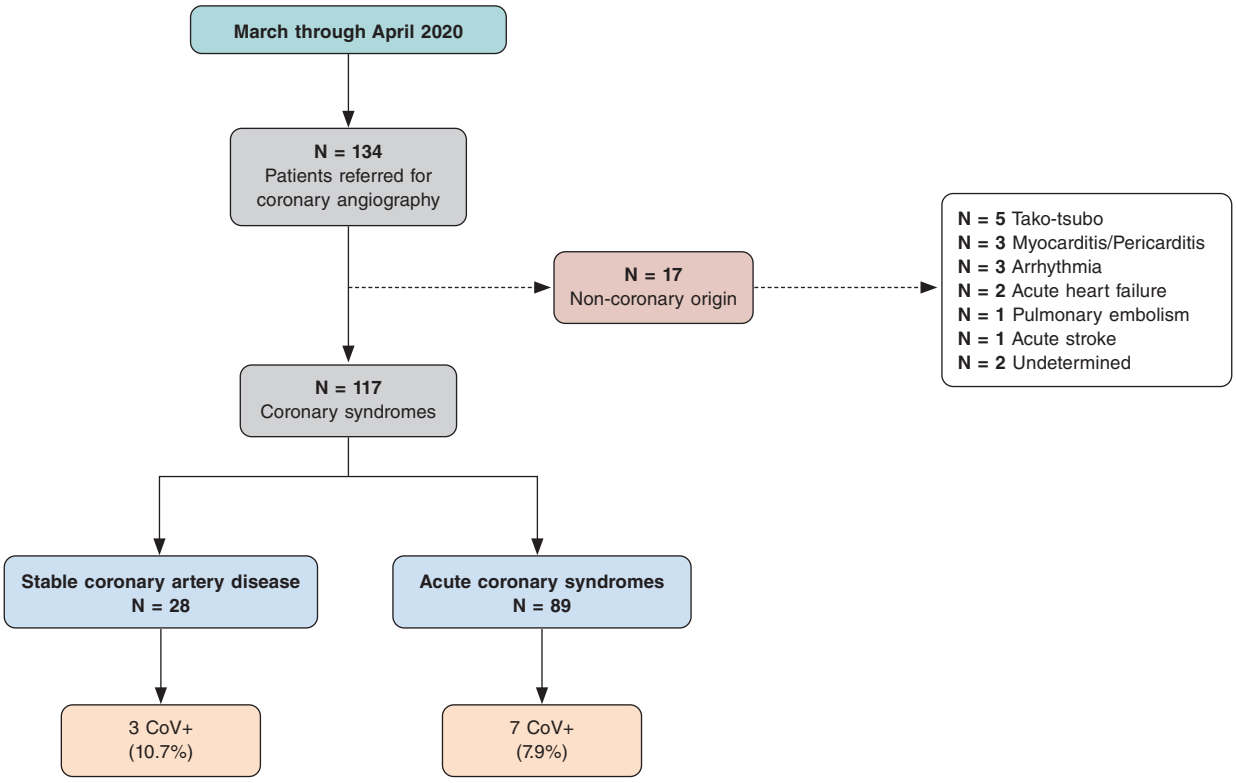

Figure 1. Study flowchart.

Table 1. Clinical characteristics and angiographic findings

	CoV–	CoV+	*P*		CoV–	CoV+	*P*
N	107	10		*Left main coronary artery disease*	5 (4.67)	2 (20.0)	.110
Age (years)	64.8 (16.9)	66.8 (25.0)	.730	*Revascularization*			.312
Female sex	30 (28.04)	2 (20.0)	.726	No	27 (25.23)	4 (40.0)	
Hypertension	72 (69.23)	7 (70.0)	.721	PCI	73 (68.22)	5 (50.0)	
Hyperlipidemia	58 (55.24)	4 (44.0)	.533	CABG	7 (6.54)	1 (10.0)	
Diabetes	33 (31.43)	2 (20.0)	.719	*Complete revascularization*	59 (56.19)	3 (30.0)	.183
Tobacco use (former or active smoker)	54 (51.43)	6 (60.0)	.496	*PCI patients (n)*	73	5	
Chronic kidney disease	17 (16.5)	1 (10.0)	1.000	*Stent implantation*	66 (90.4)	5 (100)	.438
LVEF	52.2 (12.5)	48.8 (19.3)	.611	*Procedural success*	69 (94.5)	5 (100)	.548
Clinical presentation			.701	*Successfully treated lesions*			.602
SA/UA	25 (23.36)	3 (30.0)		0	4 (5.5)	1 (20.0)	
MI (STEMI, NSTEMI)	82 (76.64)	7 (70.0)		1	52 (71.2)	3 (60.0	
Vessels with > 70 stenosis			.549	2	13 (17.8)	1 (20.0)	
0	19 (17.76)	1 (10.0)		3	4 (5.5)	0 (0)	
1	48 (44.86)	3 (30.0)		*Procedural time (min)*	63.5 (44.3)	55.56 (32.0)	.599
2	22 (20.56)	3 (30.0)		*Fluoroscopy time (min)*	13.2 (10.7)	10.8 (7.1)	.502
3	18 (16.82)	3 (30.0)		*Contrast volume (ml)*	136.3 (77.5)	148.8 (120.5)	.681

CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation acute myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.
Data are expressed as mean (± standard deviation) or no. (%) for categorical variables.

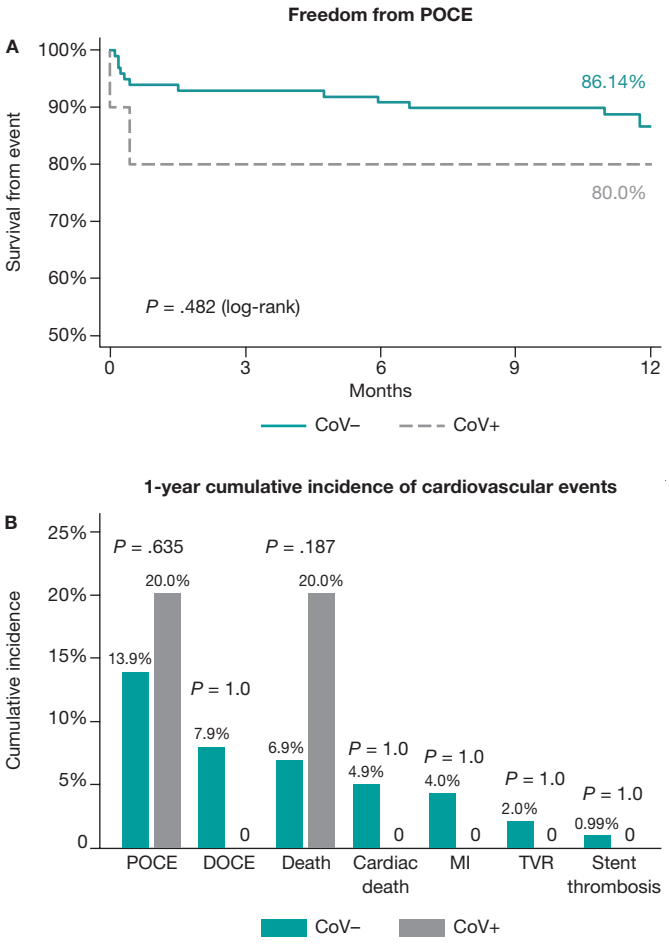

Figure 2. **A:** Kaplan-Meier survival curves of the patient-oriented composite endpoint for CoV- and CoV+ patients. **B:** cumulative incidence at the 1-year follow-up of patient-oriented and device-oriented composite endpoints and their components in both CoV– and CoV+ patients. DOCE, device-oriented composite endpoint; MI, myocardial infarction; POCE, patient-oriented composite endpoint; TVR, target vessel revascularization.

of adverse events at the 1-year follow-up. Therefore, management should not be different when dealing with acute SARS-CoV-2 infections.

FUNDING

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AUTHORS' CONTRIBUTIONS

A. Travieso: manuscript writing, data curation, data analysis, and project design. C. E. Vergara-Uzcategui: data curation, and manuscript corrections. I. J. Núñez-Gil: data curation, and manuscript corrections. A. Fernández-Ortiz: project organization, and manuscript corrections. P. Salinas: manuscript writing, data curation, project design, and study direction.

CONFLICTS OF INTEREST

None.

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Transfemoral TAVI with balloon-expandable valve for failing aortic root homografts

TAVI transfemoral con prótesis de balón expandible en homoinjertos aórticos degenerados

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To the Editor,

The use of cryopreserved homografts as complete aortic root replacements was introduced for the first time over 3 decades ago with considerable advantages with respect to biological heart valves such as greater durability, lower risk of endocarditis, and better hemodynamic profile with a much greater preservation of the ventricular function in the long run.[1] However, most of these grafts start degenerating 10 years after being implanted, and they often present with massive calcification of the homograft wall, and valvular dysfunction.[2]

In this context, surgical reintervention is associated with a very high risk given the need to operate on a heavily calcified aorta that often requires a new and total replacement of the aortic root,[3,4] which is why transcatheter aortic valve implantation (TAVI) seems especially appealing. Homograft valves often degenerate presenting with clinically pure aortic regurgitation. Also, the aortic root often shows very extensive calcification at sinus and sinotubular junction level; paradoxically, however, annular calcification is sometimes a rare phenomenon.[3,4] This can jeopardize the stability of the balloon-expandable valve. However, to this point, there is scarce scientific evidence on the role it plays in this specific anatomical context.

These are the cases of 5 consecutive patients (mean age: 68.4 ± 10.4 years) with degenerated aortic root homograft presenting with isolated aortic regurgitation (video 1 of the supplementary data) or double aortic lesion treated with transfemoral TAVI with a balloon-expandable valve between 2017 and 2021 in 1 center (table 1). A new surgical aortic valve replacement was discarded in all the cases because of the high risk associated with the procedure due to the massive and circumferential calcification of the homograft. Procedures were performed after obtaining the patients' informed consent under deep sedation (patients #2, #3, and #4) or general anesthesia (patients #1, and #5, to improve tolerance to the transesophageal echocardiogram and achieve greater accuracy when placing the heart valve). Also, the procedures were transesophageal echocardiography-guided plus a computed tomography scan was performed prior to the procedure to assess the degree of calcification and the diameters of the graft. Direct implantation was performed with slow and prolonged inflation of the valve in all the cases except for patient #5 who underwent a first incomplete inflation followed by complete postdilatation (figure 1 and video 2 of the supplementary data) for showing significant resistance to the expansion during the initial inflation. In an female patient (patient #2 of table 1) a guidewire was advanced to protect the left main coronary artery during valve implantation (video 3 of the supplementary data).

Implantation was successful in all the patients, and nobody showed significant paravalvular aortic regurgitation or atrioventricular block after the procedure. Only 1 complication was reported: the presence of a contralateral femoral artery pseudoaneurysm that was treated with ultrasound-guided compression (patient #3 of table 1). The mean hospital stay was 5.2 days. After a median follow-up of 20.2 ± 15.2 months all patients remained free of events, and all the valves were working properly.

To this date, most of the experienced published on degenerated aortic homografts treated percutaneously has been limited to the use of self-expanding valves[5,6] possibly for their capacity to be retrieved and repositioned given the fear of valve embolization due to the lack of calcium in the valve annulus. However, the use of balloon-expandable valves can also bring additional advantages: *a)* it guarantees the proper expansion of the valve, *b)* there is less interference of metal material in the calcified homograft wall, and *c)* it preserves access to coronary arteries at the follow-up of patients whose mean age is often lower compared to that of most patients treated with TAVI.

Degenerated aortic root homograft is a complex scenario on which there is scarce scientific evidence available. Our series of homografts treated with balloon-expandable valve shows that it is a feasible and safe option for this type of patients.

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Table 1. Patients with degenerated aortic homograft treated with transfemoral TAVI

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Baseline characteristics					
Age, years	84	70	63	69	56
Sex	Woman	Woman	Woman	Man	Man
EuroSCORE II (%)	23%	7%	4%	10%	5%
STS (%)	17%	5%	3%	7%	3%
Indication for homograft	BAV-AAA	BAV-AAA	IE	IE	BAV-AAA
Age of homograft, years	12	12	15	14	17
Type of dysfunction	Severe AR	Severe AR	Double lesion	Severe AR	Double lesion
Transprosthetic pressure gradient (mmHg)	NA	NA	80	NA	54
Agatston score of the valve	3824	1936	1873	1650	5555
Agatston score of the homograft	9100	9037	10 456	11 456	17 400
Homograft calcification	Severe	Severe	Severe	Severe	Severe
Diameter derived from the annulus (mm)	24.8	24.2	23.2	25.7	28.02
Perimeter of the annulus (mm)	78	76	73	81	88
Maximum diameter (mm)	24	24	22	25	26
Procedure					
Anesthesia	General	Sedation	Sedation	Sedation	General
Measure of the annulus (TEE, mm)	25	25	22	24	24
Edwards valve	SAPIEN XT 26	SAPIEN 3 26	SAPIEN 3 23	SAPIEN 3 26	SAPIEN 3 Ultra 26
Access	Transfemoral	Transfemoral	Transfemoral	Transfemoral	Transfemoral
Paravalvular regurgitation	0	0	0	0	0
Pacemaker	No	No	No	No	No
X-ray image time (min)	19	23	36	29	21
Contrast (mL)	60	100	80	60	60
Complications according to the VARC-3	No	No	No	No	No
Follow-up					
Follow-up time (months)	41	35	14	10	1
Death after 1 year	None	None	None	None	NA
Heart failure after 1 year	None	None	None	None	NA
Stroke after 1 year	None	None	None	None	NA
Pacemaker after 1 year	None	None	None	None	NA
Transaortic gradient (mmHg)	24	15	35	20	NA
Aortic regurgitation	No	No	No	No	NA
Events at the follow-up	None	None	None	None	NA

AAA, ascending aortic aneurysm; AR, aortic regurgitation; BAV, bicuspid aortic valve; IE, infectious endocarditis; NA, not applicable; TEE, transesophageal echocardiography; VARC-3: Valvular Academic Research Consortium-3.

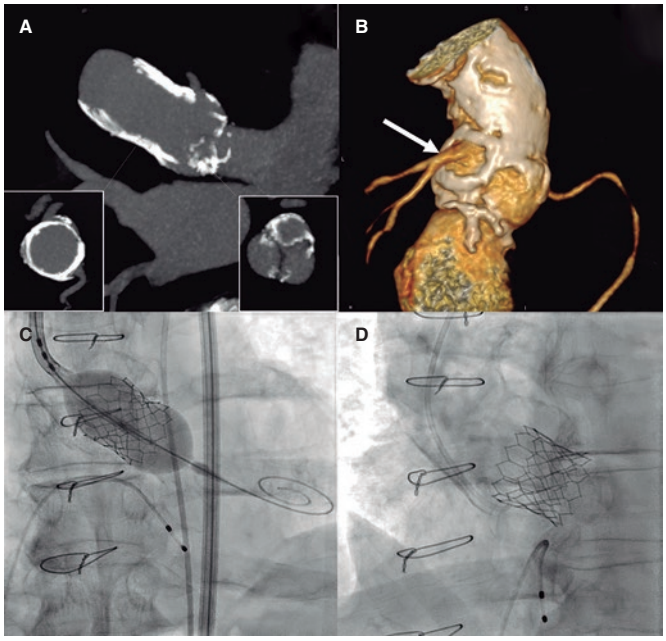

Figure 1. A: multiplanar reconstructed computed tomography images showing the calcified homograft (cross-sectional view in the left lower quadrant) with less calcification in the aortic valve (cross-sectional view in the right lower quadrant. **B:** 3D reconstruction of the aortic root through computed tomography scan with posterior view showing severe calcification of the homograft that preserves the left main coronary artery neo-ostium (arrow). **C:** implantation of a SAPIEN 3 Ultra 26 mm aortic valve (Edwards Lifesciences, United States) with incomplete expansion that is completed in a second inflation. **D:** final angiographic image showing severe calcification of the homograft with a properly expanded valve.

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None reported.

AUTHORS' CONTRIBUTIONS

All authors have contributed to the preparation, writing, and review this letter.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000254.

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State of the STEMI Care Network after the early phase of the COVID-19 pandemic. The experience of a high-volume centre

Situación del Código Infarto tras la fase inicial de la pandemia de COVID-19. Experiencia en un centro de alto volumen

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To the Editor,

The outbreak of the COVID-19 pandemic had enormous repercussions for the management of ST-segment elevation myocardial infarction (STEMI) worldwide.[1,2] Overall, the number of patients treated with primary angioplasty in Spain dropped while ischemia time increased from symptom onset until reperfusion.[3] The early phase of the pandemic gave rise to a period of consecutive outbreaks during which the management of STEMI seems to have improved thanks to a less saturated healthcare system and the implementation of proper healthcare protocols.[4] However, data on the possible side effects associated with the functioning of the healthcare systems in the STEMI Care Network after the first phase of the pandemic are scarce. In the Madrid area, our hospital is one of the highest-volume centers regarding primary angioplasty as it takes over nearly 20% of all activations in the region.[5] We present our experience with the STEMI Care Network in the months that followed the de-escalation of June 2020 when the early phase of the COVID-19 pandemic ended in Spain.

Our center STEMI Care Network activation times were analyzed during the first phase of the pandemic (March 14 through June 21, 2020), as well as in the previous and following 12 months. Also, consistent with the data published to this date,[3] during the early phase of the pandemic, ischemia time increased in patients from our series. It fluctuated during the following months, with median ischemia times during the second and third waves similar to those reached during the first wave (figure 1). During 2021, equivalent to 2020 when the early phase of the pandemic occurred, the fourth wave of the pandemic broke out. The intensity of this wave was lower compared to the previous ones, and although the median ischemia time was closer to the one described before the pandemic, the number of patients with prolonged ischemia time remained higher than usual (figure 2).

Table 1 shows a comparison of the STEMI Care Network activation times during the 12 previous and following months compared to the first phase of the pandemic. The percentage of patients with late onsets (ischemia time >12 hours) was significantly higher during the months that followed the first phase and almost double compared to the time before the pandemic (9.2% vs 4.3%; $P = .004$).

When times were analyzed based on the patients' clinical presentation it was found that, during the period that followed the pandemic early phase, ischemia time was higher than usual in the group of patients who went directly to the health center (including PCI- and non-PCI-capable centers, and primary care centers). In these patients the median ischemia time after the first wave was 36 minutes longer compared to pre-pandemic time (252 [165-412] vs 216 [150-336] minutes; $P = .011$) basically at the expense of prolonged time from symptom onset until diagnosis. However, it is surprising to see that ischemia time did no go up in patients assisted by the medical emergency services. On the other hand, after the start of the pandemic we saw a change in the pattern of clinical presentation with fewer patients going directly to the health center. This lower percentage of patients who went directly to the health center and the persistently prolonged ischemia time reported in this group of patients due to late diagnosis can be indicative that, at least, part of the population is still afraid that they will get coronavirus at the hospital.

Our analysis suggests that, once the early phase of the pandemic was over, the percentage of patients with an evolving STEMI referred for primary angioplasty remained high. Also, that the STEMI Care Network activation times never went back to normal in patients who went directly to the health center. Therefore, it seems essential to raise awareness among the population of the importance of seeking medical attention at the first sign of chest pain, check the action protocols available in the ERs of health centers, and try to prioritize the care of these patients to return to similar ischemia times to the pre-COVID-19 era.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, draft, and process of critical revision of the final manuscript.

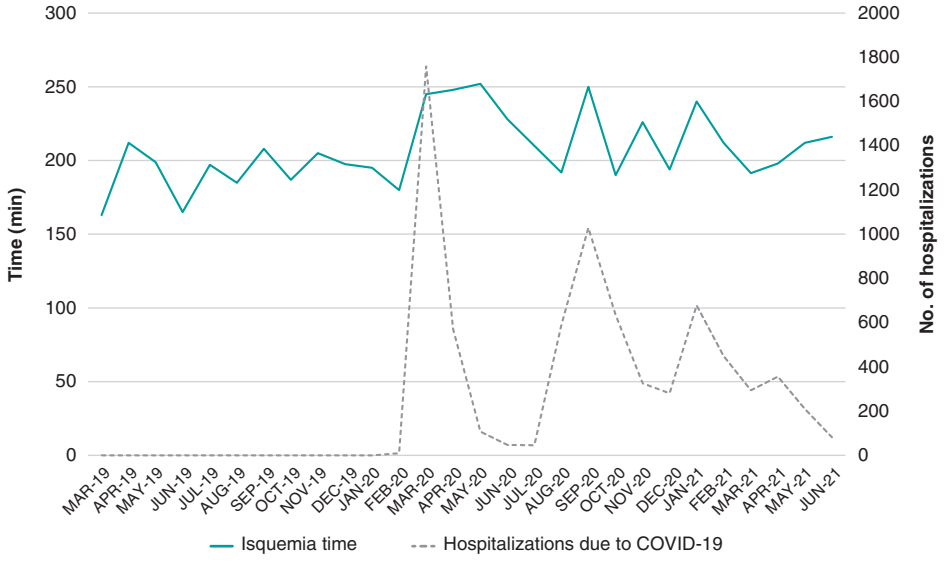

Figure 1. Median ischemia time of patients referred for primary angioplasty, and number of patients hospitalized in our center with COVID-19.

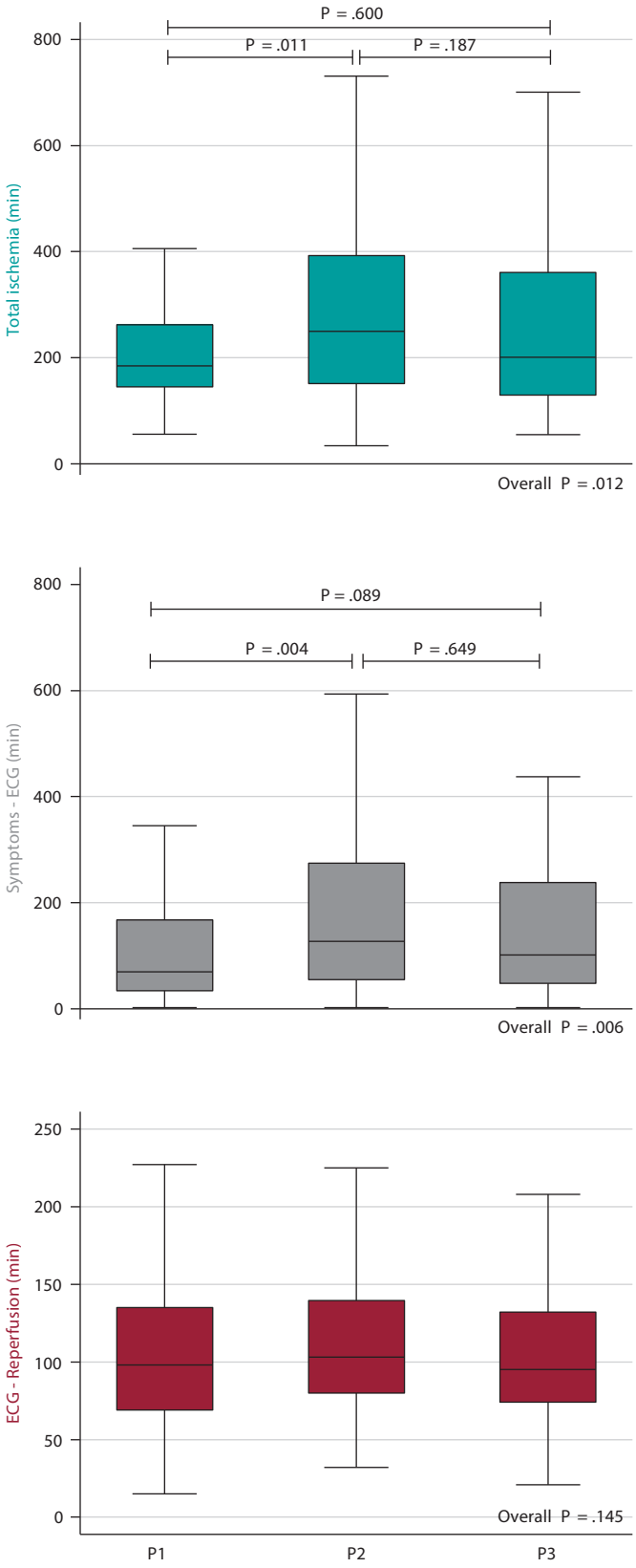

Figure 2. Times during the early phase of the pandemic and within the same period of 2019 and 2021. P1, March/14/2019 through June/21/2019; P2, March/14/2020 through June/21/2020; P3, March/14/2021 through June/21/2021; number of STEMI Care Network activations in each period: 111, 144, and 140 respectively. Bonferroni correction for multiple comparisons. ECG, electrocardiogram.

Table 1. Times and clinical presentation of patients from the STEMI Care Network during the previous and following 12 months with respect to the first phase of the pandemic

	Previous period (03/14/2019 through 03/13/2020)	Later period (06/22/2020 through 06/21/2021)	*P*
N	438	434	
Age, years	64.1 ± 14.2	63.9 ± 13.9	.982
Sex (male)	317 (72.4)	319 (73.5)	.708
Clinical presentation			
Healthcare centers	296 (67.6)	251 (57.8)	.003
Emergency medical services	142 (32.4)	183 (42.2)	
Overall times			
Total ischemia, min	191 [135-280]	207 [135-353]	.048
Symptoms – ECG, min	80 [37-163]	100 [50-244]	.001
ECG – reperfusion, min	96 [71-134]	92 [72-127]	.402
Infarctions with ischemia times > 12 hours	19 (4.3)	40 (9.2)	.004
Times based on the clinical presentation			
Health centers	296	251	
Total ischemia, min	216 [150-336]	252 [165-412]	.011
Symptoms – ECG, min	95 [42-185]	124 [63-290]	< .001
ECG – reperfusion, min	106 [80-155]	106 [79-154]	.840
Emergency medical services	142	183	
Total ischemia, min	154 [121-205]	155 [120-240]	.230
Symptoms – ECG, min	65 [31-11]	70 [45-157]	.024
ECG – reperfusion, min	75 [64-100]	79 [65-97]	.926

ECG, electrocardiogram.
Data are expressed as no. (%) or mean ± standard deviation or median [interquartile range].

CONFLICT OF INTERESTS

None reported.

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Implementing a fast-track TAVI pathway in times of COVID-19: necessity or opportunity?

Implementación de un programa de alta precoz tras TAVI en tiempos de la COVID-19: ¿necesidad u oportunidad?

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To the Editor,

Despite the expansion of transcatheter aortic valve implantation (TAVI) to lower-risk patients, the length of stay after TAVI remains high for an average 8 days according to the Spanish TAVI registry.[1] Recently published studies have demonstrated that early discharge following balloon-expandable transfemoral TAVI is feasible and safe.[2,3] The unprecedented demand sustained by the healthcare services during the current COVID-19 pandemic has led to redirecting assets and restricting many cardiovascular procedures to protect the limited resources available like anesthesia support, ventilators, and critical care infrastructures. The present fast-track protocol was developed in response to the COVID-19 pandemic to assess the safety and feasibility of early discharge after minimalist TAVI with either balloon-expandable or self-expanding valves in our setting.

Patients undergoing transfemoral TAVI were prospectively recruited. The inclusion criteria in the fast-track pathway were based on the 3M TAVI study: femoral access eligible for percutaneous closure, body mass index < 35, low-risk aortic annulus anatomy (coronary height > 10 mm, tricuspid valve, non-severe left ventricular outflow tract calcification), ejection fraction ≥ 30%, low anticipated risk of advanced conduction disturbances (PR interval < 240 ms, absence of right bundle branch block), familial support within the first 24-48 hours. All procedures were performed under local anaesthesia and conscious sedation. Pre-closure of the access site was performed using the double ProGlide technique (Abbott Vascular, United States), and in general patients received unfractionated heparin (70 U/kg) without a reversal agent. The implantation technique included a coplanar view of the balloon-expandable valves and a cusp overlap view of the self-expanding valves. In the absence of procedural complications (major vascular

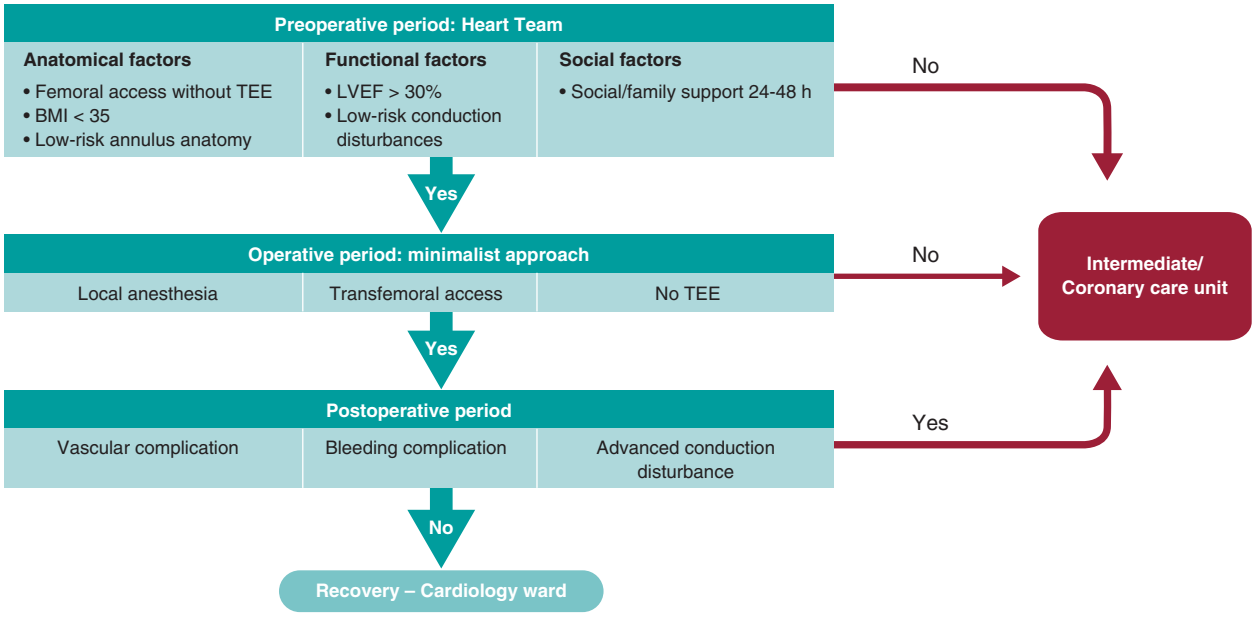

Figure 1. Fast-track TAVI pathway. BMI, body mass index; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography.

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complications, major bleeding or high-degree atrioventricular block), and after 2 hours at the cath lab recovery room, patients were transferred to the cardiology ward under cardiac telemetry monitoring (figure 1). Conduction disturbances were managed as described in the 2019 expert consensus document.[4] The study was approved by Hospital de la Santa Creu i Sant Pau local ethics committee, and patients gave their informed consent to the procedures.

A total of 38 out of the 93 patients (40.9%) treated with TAVI at our centre between October 2020 through July 2021 met the fast-track inclusion criteria. The mean age was 84 years (63.2%, women) with a mean STS-score of 3.7%. One third of the patients (29.0%) had atrial fibrillation, and chronic obstructive pulmonary disease while 16 patients (42.1%) had coronary artery disease. Further baseline characteristics are shown on table 1.

The minimalist approach was suggested in most patients: ultrasound-guided percutaneous primary access (100%), transradial secondary access (100%) while the simplified crossover technique via radial artery was required in 6 patients (15.8%) only (upfront guidewire protection was used in 4 obese patients, bailout balloon inflation in 2 patients to achieve femoral hemostasis). Also, pacing over stiff guidewire was used in all but 1 patient (with incomplete right bundle branch block). A balloon-expandable valve was used in 23 patients (60.5%) and a self-expanding valve in 15 patients (39.5%). Procedural success was achieved in all patients. There were no cases of valve embolization, coronary occlusion, annulus rupture or procedural death. A total of 3 patients (7.9%) were transferred to the intermediate or coronary care unit following vascular complications (n = 1) or high-degree atrioventricular block (n = 2). Next-day discharge was achieved in 6 patients (15.8%), and in nearly 80% within 72 hours for a median length of stay of 2 days (2-3). One patient experienced 2 adverse events (major bleeding and vascular failure that required covered stent graft implantation). A permanent pacemaker (PPM) was implanted in 5 patients (13.2%, 3 after balloon-expandable valve implantation, 2 after self-expanding valve implantation). Thirty-day readmission occurred in 2 patients (5.3%) with heart failure (n = 1) and transient ischemic attack (n = 1), the latter patient being discharged from the emergency room on the same day. No cases of mortality or late heart block requiring PPM after hospital discharge were reported. With the experience gained, the rate of patients discharged within the first 24 hours increased from 9% within the first trimester to 33% during the third.

Our study main findings are: *a)* a pre-defined accelerated pathway after minimalist TAVI using either balloon-expandable or self-expanding valves was safe and feasible with a high rate of procedural success, and a low rate of adverse events; *b)* direct transfer to the cardiology ward was achieved in most patients (92%); *c)* it enabled early discharges within the first 72 hours in 80% of patients and next-day discharges in nearly a fifth of the patients.

To our knowledge this study is the first experience of an accelerated pathway after TAVI in our country. Its objective was to pursue the TAVI program during the pandemic without collapsing the limited resources available. In recent years, 2 studies have shown the safety of early discharge after TAVI in selected patients who received a balloon-expandable transcatheter aortic heart valve. Of note, nearly 40% of the patients received a self-expanding valve in our study. In the 3M TAVI study that included 55% of the screened patients, 89% of the patients were discharged within 48 hours with a good safety and efficacy profile (mortality, stroke, major vascular complication, PPM implantation, and readmission 30-day rates of 1.5%, 1.5%, 2.4%, 5.7%, and 9.2%, respectively).[2] Similarly, in the FAST-TAVI trial, most patients (72%) were early discharged within 72

Table 1. Baseline, in-hospital, and 30-day outcomes

Baseline characteristics	N = 38
Age, years	84.4 ± 3.9
Female	24 (63.2)
Diabetes mellitus	9 (23.7)
Hypertension	31 (81.6)
Atrial fibrillation	11 (29.0)
COPD	11 (29.0)
Previous coronary artery disease	16 (42.1)
Previous stroke	4 (10.5)
LVEF, %	59.1 ± 11.9
Aortic valve gradient, mean, mmHg	48.1 ± 10.3
Aortic valve area, cm^2	0.7 ± 0.2
STS-PROM, %	3.7 ± 1.4
EuroSCORE II, %	3.7 ± 2.2
Procedural characteristics	
Transfemoral approach	38 (100)
Local anesthesia	38 (100)
Transradial secondary access	38 (100)
Crossover technique	6 (15.8)
Pacing over guidewire	37 (97.4)
Prosthesis type	
SAPIEN 3/Ultra	23 (60.5)
Portico	13 (34.2)
Evolut R/Pro	2 (5.3)
Procedural success	38 (100)
Valve embolization	0 (0)
Coronary occlusion	0 (0)
Conversion to surgery	0 (0)
Procedural death	0 (0)
In-hospital, and 30-day outcomes	
Length of stay	2 (2-3)
< 24 h	6 (15.8)
< 48 h	23 (60.5)
< 72 h	30 (78.9)
Intensive/intermediate care unit	3 (7.9)
Mortality	0 (0)
Stroke/TIA	1 (2.6)
Major vascular complication	1 (2.6)
Major bleeding	1 (2.6)
Permanent pacemaker implantation	5 (13.2)
Readmission at 30 days	2 (5.3)
Pacemaker implantation after discharge	0 (0)

COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TIA, transient ischemic attack.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

hours with low mortality (1.1%), stroke (1.7%), PPM implantation (7.3%), and rehospitalization (3.7%) 30-day rates.[3] Despite the limited size of the sample, our results are consistent with both studies with a remarkable 0% mortality rate at 30 days, but with a higher rate of PPM implantation, which may be explained by the inclusion of self-expanding valves in the present study.

While the volume of TAVI will continue to grow, there is an urgent need to optimize the patient care pathway and reduce the length of stay. The widely used minimalist approach plus the challenges posed by the COVID-19 pandemic pave the way for more efficient clinical pathways that guarantee safe early discharges using minimal resources and critical care infrastructure.

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AUTHORS' CONTRIBUTIONS

All authors participated in the collection of data, analysis, drafting, and review of the manuscript.

CONFLICTS OF INTERESTS

D. Arzamendi has received proctoring, and speaker fees from Abbott and Edwards. L. Asmarats is a proctor for Abbott, and received speaking fees from Edwards. X. Millán received proctoring and speaking fees from Abbott. The remaining authors have no relationships to disclose relevant to the content of this paper.

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Clinical case

Rotational angiography and the contribution of roadmapping to the occlusion of arteriovenous malformations

Angiografía rotacional y contribución del roadmapping *a la oclusión de malformaciones arteriovenosas*

Domingo López Vázquez,[a,*] Isaac Martínez Bendayan,[a] Ariana Varela Cancelo,[a] Martín Quintas Guzmán,[a] Jorge Salgado Fernández,[a] and Fernando Rueda Núñez[b]

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CASE PRESENTATION

Among other causes, arteriovenous malformations (AVMs) can be congenital and associated with Rendu-Osler-Weber disease. It is a conglomerate of anomalous vessels of variable size and number characterized by the lack of an intermediate normal capillary network between the arterial and the venous circuits. Its prevalence is of approximately 1 AVM for every 2600 individuals, and it is a significant cause of morbidity and mortality. The percutaneous closure of AVMs is the standard of care established. However, there is a significant rate of recanalization of AVMs at the long-term follow-up due to the recanalization of the main occluded vessel and the formation of collateral circulation towards the vascular tangle. A few articles already published support sequential embolization to reduce the risk of the latter.

This article describes the percutaneous closure of 1 AMV in a pediatric patient using a technique of sequential embolization through rotational angiography, 3D analysis, and roadmapping (technique based on merging the 3D reconstruction acquired through rotational angiography and x-ray images in such a way that reconstruction acts as a «map» or «flight plan» during the procedure). In our opinion this experience is very interesting because, as far as we know, its use has not been described regarding the closure of pulmonary AVMs in the pediatric age (only regarding the closure of cerebral AVMs in the adult population).

This is the case of a 10-year-old girl with a familial history of Rendu-Osler-Weber disease. She was examined in a pediatric office in her hometown of Santiago de Compostela, Spain due to cyanosis, polyglobulia, and baseline oxygen saturation levels of 85%. The patient remained asymptomatic. The echocardiogram revealed no intracardiac disorders. However, due to the patient's past medical history, a thoracic x-ray and a thoracic computed tomography scan were performed. Both revealed an image compatible with an AVM (figure 1, and figure 2). An easy way to achieve the diagnosis of suspected shunt would be to perform an echo bubble study where the passage of these to the left chambers of the heart would occur from the third cardiac cycle (late compared to the intracardiac shunt). The study was completed at our center with a rotational angiography that revealed the presence of a high output pulmonary AVM with 3 afferent arterial vessels, and a 12 mm pulmonary venous drainage (video 1 of the supplementary data).

The patient's family signed the written informed consent authorizing the use of the girl's personal data for this article.

FUNDING

All authors declared that no funding of any sort was received to publish this manuscript.

AUTHORS' CONTRIBUTIONS

I. Martínez Bendayan, J. Salgado Fernández, and F. Rueda Núñez all contributed to the processes of image selection, image acquisition from the rotational angiography, and technical specifications on how to perform the procedure. D. López Vázquez, A. Varela Cancelo, and M. Quintas Guzmán all drafted and prepared this manuscript.

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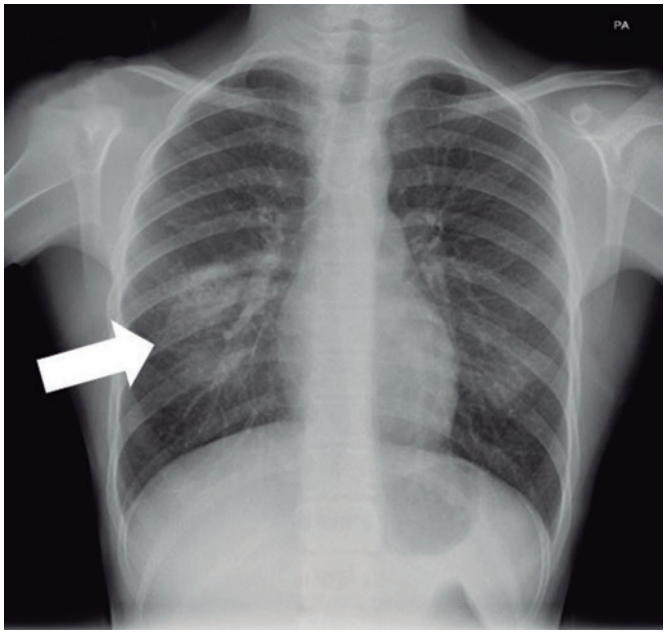

Figure 1. Pulmonary arteriovenous malformation seen on the x-ray (arrow).

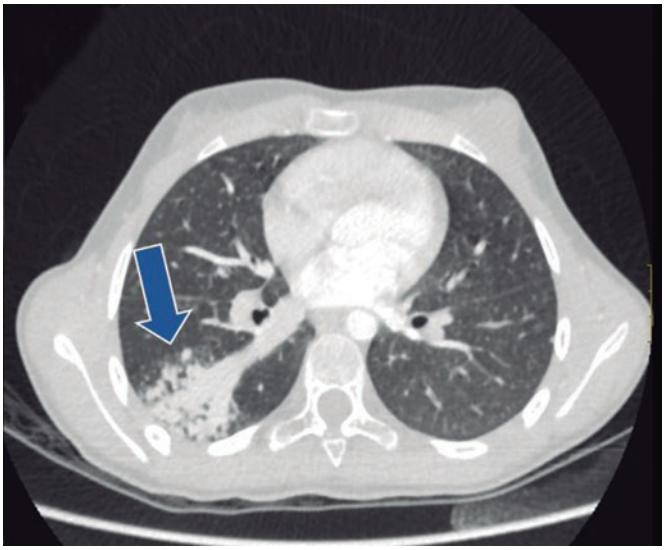

Figure 2. Pulmonary arteriovenous malformation seen on the thoracic computed tomography scan (arrow).

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000265.

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Rotational angiography and the contribution of roadmapping to the occlusion of arteriovenous malformations. How would I approach it?

Angiografía rotacional y contribución del roadmapping *a la oclusión de malformaciones arteriovenosas. ¿Cómo lo haría?*

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Online: 11-02-2022.

HOW WOULD I APPROACH IT?

Authors present an interesting case of a 10-year-old with a familial history of Rendu-Osler-Weber disease. The patient shows signs of cyanosis, polyglobulia, and baseline oxygen saturation levels of 85% due to a large and complex pulmonary arteriovenous malformation (PAVM) that is causing systemic desaturation due to the existence of a significant right-to-left shunt.

PAVMs are direct connections between arterial branches—often the pulmonary artery—and pulmonary veins without a normal capillary bed connected through an aneurysmal sac that can be partially septated in the inside. PAVMs can be categorized into simple, when they receive blood from a single afferent arterial vessel, and complex, when afference is multiple.

Most of them are congenital and in over 70% of the cases they are associated with Rendu-Osler-Weber disease or hereditary hemorrhagic telangiectasia. Although it is a dominant autosomal disease that can be diagnosed through a genetic study the so-called Curaçao diagnostic criteria[1] are often used to achieve diagnosis:

- Recurrent epistaxis.
- Multiple telangiectasias in typical locations: lips, oral cavity, fingers, and nose.
- Visceral vascular malformations: gastrointestinal, pulmonary, hepatic, cerebral or spinal.
- First-degree relative who is a disease carrier.

With 3 or more criteria, the diagnosis becomes conclusive. With just 2 the diagnosis is possible.

Most of the times this disease is asymptomatic, and the presence of clinical signs depends on the size and number of these signs. The symptoms surrounding PAVMs are:

- Associated with desaturation—due to the right-to-left shunt—with peripheral oxygen saturation levels < 90% that lead to cyanosis, acropachies, and reactive polycythemia.
- Due to the frailty of the PAVM walls that can rupture towards the bronchial bed causing hemoptysis or towards the pleural space causing hemothorax.
- Due to the lack of pulmonary capillary filtration, paradoxical embolisms can occur and, sometimes, be followed by the formation of cerebral abscesses, which is not rare.

Diagnosis is based on the existence of suggestive clinical signs. Thoracic x-rays show disturbances in over 95% of the patients. The agitated saline contrast echocardiography reveals the presence of bubbles passing through after 3-5 seconds (3 to 8 cardiac cycles). Currently, the computed tomography scan is the reference imaging modality; it allows accurate anatomical studies, and is used to plan embolization, as well as for evolutionary follow-up purposes.

Although, initially, surgical resection was indicated, the treatment of choice is endovascular embolization. It is indicated[2] when the afferent arterial vessel is ≥ 3 mm because with this size the risk of paradoxical embolism is higher compared to the annual 1.5% reported. Thanks to state-of-the-art materials the procedure can be performed safely in afferent arterial vessels < 2 mm, which is why each patient should be assessed individually when the size of the arterial vessels is between 2 mm and 3 mm.

Embolization can be performed using metallic coils as described by Gianturco et al.[3] in 1975. In our case we used the MReye Flipper Detachable Embolization Coil and Delivery System (Cook, United States). To start embolization with the right controlled delivery coil, the size of the coil should be, at least, 30% larger compared to the target vessel diameter. Also, it should be released into the afferent arterial vessel as distal as possible. Other coils are deployed following the first coil until the occlusion is complete. Another option is to use nitinol vascular plugs for embolization purposes. In our case we used devices from the Amplatzer Family of Vascular Plugs (Abbott, United States). The size selected was 30% to 50% larger compared to the diameter of the target vessel, and the plug was deployed into the afferent arterial vessel as distal as possible to not interfere with other branches leading towards the healthy parenchyma. Choosing one material over the other often depends on the operator's experience and preferences.

In the case presented here, the indication for closure is a consequence of the significance of the shunt that is causing desaturation. It is also associated with the complications occurred due to the size of the malformation, the paradoxical embolism, and eventual rupture.

In our own experience, analyzing the computed tomography scan beforehand allows us to study embolization-eligible regions, choose the devices that will be used, and the most favorable angles to work with. It also allows us to keep an eye on the presence of branches perfusing healthy tissue so they don't interfere with the devices.

The procedure should be performed under general anesthesia via right femoral venous access using a 6-Fr introducer sheath to advance a Wedge catheter (Teleflex, United States) towards the right pulmonary branch. From that position, it should be advanced selectively towards the afferent arterial vessels while supported by 4- or 5-Fr Judkins Right 4.0, Cobra or Vertebral multipurpose diagnostic catheters mounted over 0.018 to 0.035 in hydrophilic guidewires (Radiofocus Guide Wire, Terumo, Japan) or 0.014 in workhorse coronary guidewires. Selective angiographies are performed in each afferent arterial vessel to confirm the characteristics of the embolization target vessel. Once it reaches the niche of the malformation, the transporter sheath is exchanged. In this context, my preference is to use nitinol self-expanding

devices like the Amplatzer Vascular Plug (AVP), the Amplatzer Vascular Plug II (AVP II) or the Amplatzer Vascular Plug IV (AVP 4) (Abbott, United States). There are times that we use coils and plugs in the same patient based on the anatomical characteristics of each afferent arterial vessel. In this case I would approach the 3 afferent arterial vessels one by one within the same procedure. Then, I would deploy the devices after confirming their correct position, and stability. Given the lack of a limiting capillary bed, device migration to the left cavities can occur. Therefore, all devices should be properly sized. If this complication occurs the device can be reached via arterial access, often femoral, captured with a snare, and then removed with a larger 2-Fr sheath compared to the one used for release.

After the occlusion—during the evolutionary follow-up—it is advisable to perform a computed tomography scan after 6 months to confirm the effective closure and discard the recanalization of embolized arteries or the appearance of new malformations. Similarly, periodic controls are advised.

FUNDING

None.

CONFLICTS OF INTEREST

None whatsoever.

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Rotational angiography and the contribution of roadmapping to the occlusion of arteriovenous malformations. Case resolution

Angiografía rotacional y contribución del roadmapping *a la oclusión de malformaciones arteriovenosas. Resolución*

Domingo López Vázquez,[a,*] Isaac Martínez Bendayan,[a] Ariana Varela Cancelo,[a] Martín Quintas Guzmán,[a] Jorge Salgado Fernández,[a] and Fernando Rueda Núñez[b]

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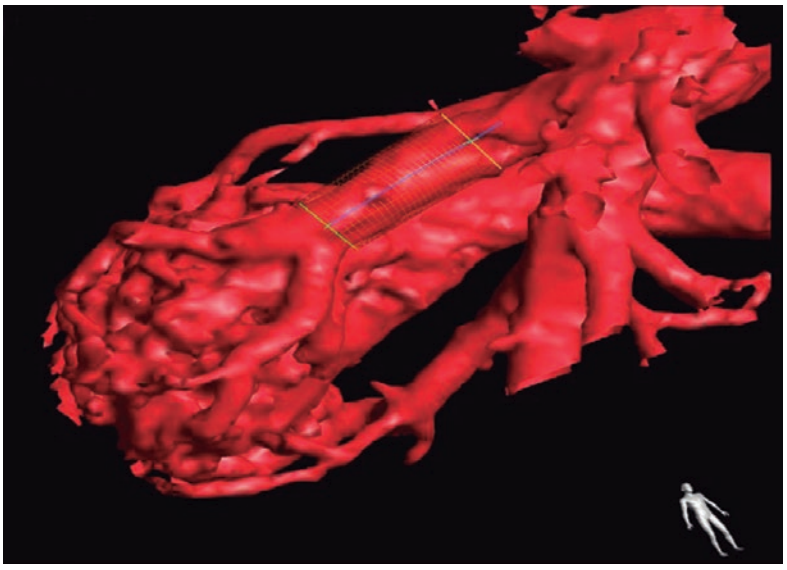

Figure 1. 3D reconstruction of a pulmonary arteriovenous malformation from data obtained from the rotational angiography performed.

CASE RESOLUTION

The procedure was performed under general anesthesia and with the administration of the standard dose of sodium heparin to prevent thrombosis or systemic embolisms (high risk considering the patient's condition) via venous femoral access.

This procedure was planned using 3D reconstruction through rotational angiography (figure 1 and video 1 of the supplementyary data). Embolization was guided using the roadmapping technique that merges the 3D reconstruction simultaneously while overlapped to the 2D reconstruction in the x-ray image projection required during multiple occlusion device implantations.

The medical equipment used during the procedure included 4-Fr guide-catheters (using JR4 or MP catheters based on the anatomical needs of each patient), coils (Concerto Coil System 5/20 mm; Medtronic, United States), and vascular occluder devices (4 mm to 8 mm Amplatzer Vascular Plug from; Abbott, United States). A staged occlusion strategy was planned that started with the peripheral closure of the arteriovenous malformations (AVMs) using coils followed by the closure of nutrient vessels with coils and vascular plugs. Indeed, according to former studies, both devices combined are associated with a low rate of recanalization after embolization.[1] This is the approach that has been systematically used at our center for quite some time to avoid possible spontaneous recanalizations due to collateral circulation towards the nonembolized vascular sac. The AVMs were embolized in a 2-stage procedure, 2 months apart, and without any complications being reported.

The procedure final outcomes were satisfactory with total occlusion criteria for the AVMs (video 2 of the supplementyary data). It was decided to keep the patient on low-molecular weight heparin (40 mg/24 h) for 3 months. Afterwards, anticoagulation was withdrawn. No thromboembolic (vascular or systemic) or hemorrhagic complications or associated with device embolizations were reported in any of the procedures performed. The patient's current clinical situation (2 years after the procedure) is satisfactory. She remains asymptomatic without clinical signs of cyanosis, and peripheral arterial blood oxygen saturation levels close to 98%.

The patient's family signed the written informed consent authorizing the use of the girl's personal data for this article.

Although data among the pediatric population is limited, the medical literature available demonstrates that the presence of AVMs is associated with the occurrence of adverse events.[2] Additionally, the use of roadmapping has proven useful for the closure of cerebral AVMs in the adult population.[3] Based on our own experience, the addition of rotational angiography with 3D reconstruction and roadmapping to the embolization technique is an added value to plan this technique with greater technical accuracy. Also, it facilitates the staged occlusion strategy, which happens to be a safe technique with low rates of relapse.

FUNDING

All authors declared that no funding of any sort was received to publish this manuscript.

AUTHORS' CONTRIBUTIONS

I. Martínez Bendayan, J. Salgado Fernández, and F. Rueda Núñez all contributed to the processes of image selection, image acquisition from the rotational angiography, and technical specifications on how to perform the procedure. The authors D. López Vázquez, A. Varela Cancelo, and M. Quintas Guzmán all contributed to the bibliographic search, drafted, and prepared this manuscript.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000267.

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Percutaneous approach to treat aortic coarctation and pseudoaneurysm

Abordaje percutáneo de recoartación aórtica y seudoaneurisma

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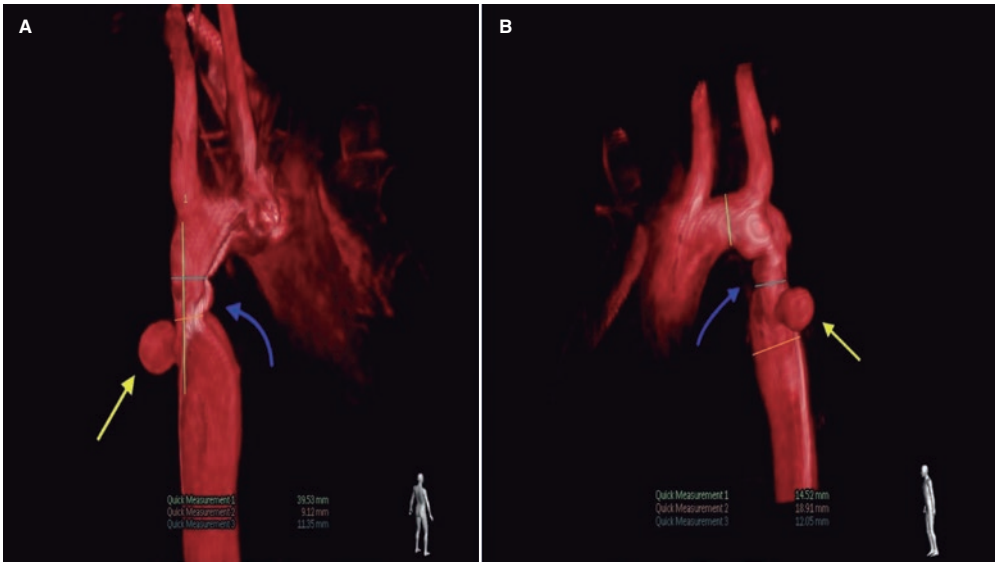

Figure 1.

This is the case of a 34-year-old woman treated percutaneously for aortic coarctation repair. The patient's past medical history included muscular ventricular septal defects with spontaneous closure, bicuspid aortic valve with asymptomatic moderate regurgitation with normal ventricular volume and function, and juxtaductal coarctation of the aorta treated with patch aortoplasty at 2 months old.

The data of progressive recoarctation were obtained from the echocardiography and magnetic resonance imaging at the outpatient follow-up, and the hypertensive response from the ergometric work. The case was brought to the heart team that decided to perform endovascular treatment. The aortography performed via right femoral access confirmed the presence of recoarctation at the junction between the aortic arch and the descending thoracic aorta (figure 1A,B, blue arrow) with a minimum diameter of 9 mm, and a peak-to-peak gradient of 20 mmHg. Similarly, a saccular-shaped pseudoaneurysm was found adjacent to the stenosed region (figure 1A,B; figure 2A, yellow arrow; video 1 of the supplementary data) with internal diameters of 8 mm x 10 mm (figure 2B). Therefore, it was decided to implant a 45 mm long covered stent (Covered CP Stent, NuMED Canada) (figure 3) with good angiographic results (videos 2 and 3 of the supplementary data), no evidence of residual gradient, and successful and complete exclusion of the pseudoaneurysm.

The use of imaging modalities with 3D analysis including traditional fluoroscopy is a very useful tool to diagnosis of complex anatomies and plan therapeutic alternatives. Also, it allows us to shorten the duration of the procedure, reduce the dose of contrast used, and minimize radiation exposure time.

The patient's written informed consent was obtained before publishing this clinical case.

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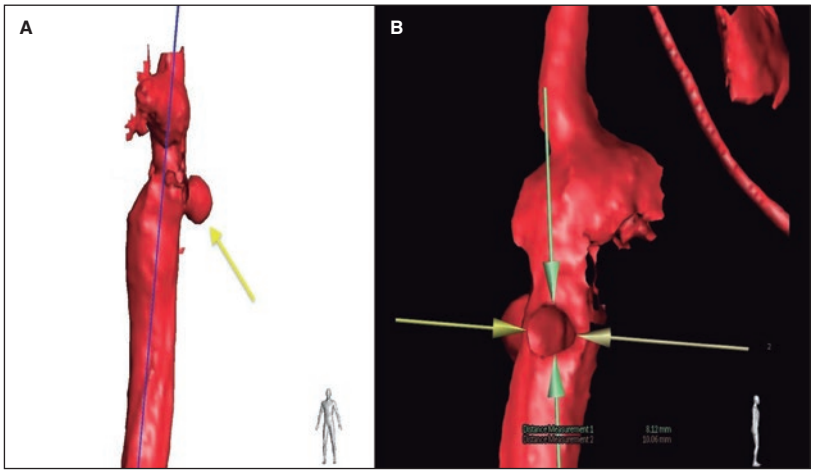

Figure 2.

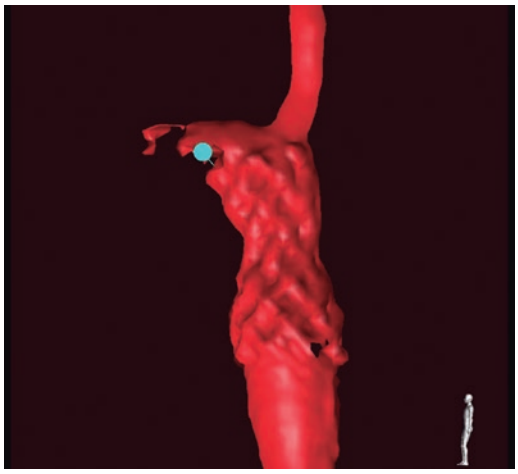

Figure 3.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

N. Barja González wrote the manuscript first draft as well as its final version. F. Rueda Núñez, and I. Martínez Bendayán provided the supplementary data and reviewed the manuscript draft and final version.

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000247.

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Pulmonary valve-in-valve procedure after fractured biological prosthetic valve

Valve-in-valve *pulmonar tras rotura de prótesis valvular biológica*

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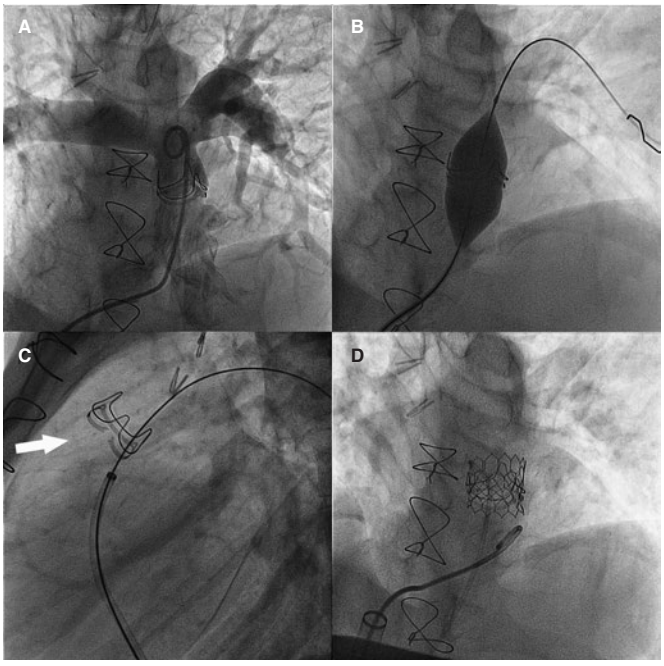

Figure 1.

While performing aortic valve-in-valve procedures the fracture of certain surgical biological valve annuli has been widely reported regarding the implantation of a larger percutaneous valve with a better hemodynamic profile. The pulmonary valve-in-valve technique has not been around that much, but its role is more important because it allows «small» valve implantation in pediatric patients who later progress into significant somatic growths. We present 2 cases after obtaining the express consent of the patients or, if minors, of their legal tutorss.

Case #1 is a 15-year-old patient with Fallot's tetralogy, and previous surgical implantation of a 19 mm Carpentier Magna Ease valve (Edwards Lifesciences Corp., United States) (internal lumen of 17 mm) at 11 years old. Severe stenosis and moderate regurgitation. The annulus ruptured with a 20 mm x 20 mm Atlas Gold balloon (Becton, Dickinson and Company Franklin Lakes, United States) inflated at 22 atm, and a 23 mm Edwards S3 valve was implanted (figure 1A, angiography of pulmonary artery; figure 1B, rupture with balloon; figure 1C, previous ruptured valve [arrow]; figure 1D, new valve; and videos 1-4 of the supplementary data).

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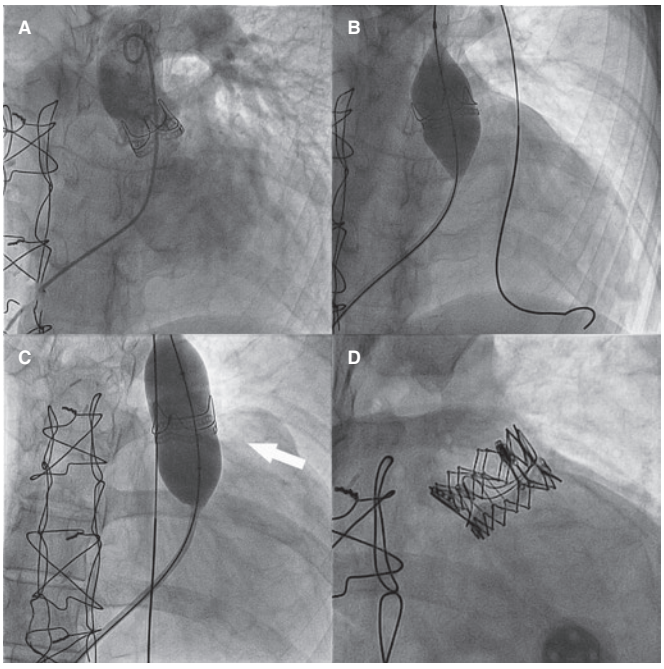

Figure 2.

Case #2 is a 24-year-old patient with Fallot's tetralogy and previous surgical implantation of a 21 mm Carpentier Edwards valve (internal lumen of 19 mm) at 14 years old. Moderate doble lesion. The valve ruptured with a 24 mm x 20 mm Atlas Gold balloon inflated at 20 atm, and a 26 mm Edwards XT valve was implanted (figure 2A, angiography of pulmonary artery; figure 2B, rupture with balloon; figure 2C, previous ruptured valved distended with a 25 mm Cristal balloon (Balt, France) [arrow]; figure 2D, new valve; and videos 5-8 of the supplementary data).

The rupture of a biological prosthetic valve annulus in pulmonary position facilitates the implantation of another larger valve to match the growth of each patient, and makes valve-in-valve procedures possible in the future. This procedure can be unnecessary if the first prosthetic valve implantation is performed with long-term thinking and the largest possible valve is used.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

The 3 authors participated in the idea, writing, and review of this article.

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

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Orbital atherectomy for calcified nodule: optical coherence tomography assessment

Aterectomía orbitacional de nódulo de calcio: valoración con tomografía de coherencia óptica

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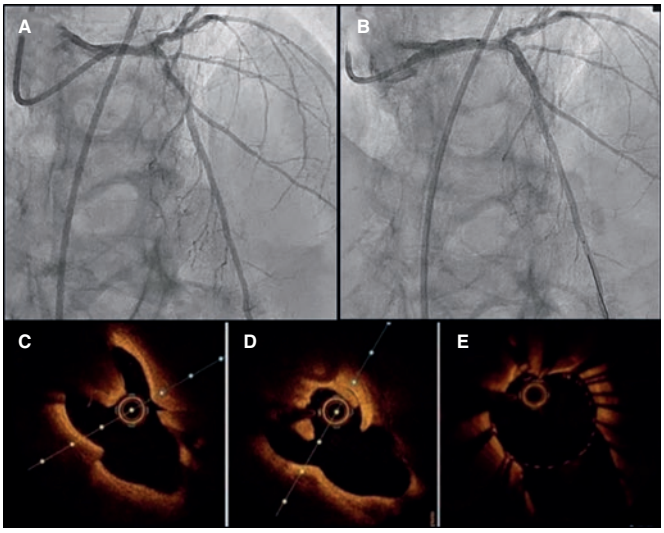

Figure 1.

We present the case of a 91-year-old man with a past medical history of moderate-to-severe aortic stenosis referred due to breathlessness. The routine invasive coronary angiography performed before transcatheter aortic valve replacement confirmed the presence of a severely calcified left anterior descending coronary artery proximal segment (figure 1A; video 1 of the supplementary data). The functional assessment performed showed a fractional flow reserve of 0.79. The optical coherence tomography (OCT) interrogation revealed an arc of calcium > 180°, thickness of 0.6 mm, and length > 5 mm with a calcified nodule with a minimum lumen area of 3.49 mm^2 (figure 1C; video 2 of the supplementary data). Orbital atherectomy with the Diamondback 360 Coronary OAS (Cardiovascular Systems, Inc., United States) was selected to prepare the lesion. After 5 runs at low speed (80 000 rpm), a new OCT was performed that confirmed the fracture of the calcified nodule achieving a minimum lumen area of 7.5 mm^2 (figure 1D; video 3 of the supplementary data). Consecutively, a 2.5 mm x 15 mm SC balloon (OrbusNeich, China) plus a 3.0 mm x 10 mm NC balloon (Medtronic, United States) were advanced through the lesion and inflated twice. Finally, a Megatron 3.5 mm x 20 mm drug-eluting stent (Boston Scientific, United States) was implanted at 20 atm. Both the post-stenting final coronary angiogram (figure 1B; video 4 of the supplementary data) and the OCT pullbacks confirmed the homogeneous expansion and correct apposition of the stent (figure 1E; video 5 of the supplementary data). All the pertinent informed consents were obtained.

We presented one of the first cases of orbital atherectomy as an effective tool to treat calcified nodules, and the first case of revascularization supported not only by angiography, but also by intracoronary imaging.

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AUTHORS' CONTRIBUTIONS

All authors participated in the process of drafting this manuscript. Also, all the authors approved its final version.

CONFLICTS OF INTEREST

None of the authors declared any conflicts of interest in association with this manuscript.

SUPPLEMENTARY DATA

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