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Pulmonary artery perforation due to off-label stent
Alejandro Rasines-Rodríguez, César Abelleira Pardeiro, and Enrique José Balbaidic Domingo
The use of drug-coated balloons (DCB) to treat stenotic coronary artery lesions is a treatment strategy whose main asset is to avoid leaving a permanent intracoronary stent device. Although highly effective in the percutaneous coronary intervention setting, it is associated with a risk of acute thrombosis, future events like restenosis, and late thrombosis following processes known as neointimal proliferation, neoatherosclerosis or fractures of material. This could be even more relevant in younger patients with a long trajectory of possible coronary events ahead of them.

The use of DCB is widely accepted to treat in-stent restenosis and de novo lesions in small vessels, and it is considered an interesting option in patients with high risk of bleeding. Another possible indication currently under scrutiny due to its possible potential is the management of bifurcations—one of the most interesting indications of all. However, clearly defined recommendations have not been established yet.

Over the last few years, small clinical trials have been published on the use of DCB in this indication; although they have not proven definitive for a strong guideline recommendation, they provide valuable data. In general, trials have grouped into those looking into the safety and efficacy profile of DCB—without comparison group—and trials that compared strategies with DCBs or conventional balloons (CB).

**PROSPECTIVE NON-RANDOMIZED TRIALS WITHOUT COMPARISON CONTROL GROUP**

Table 1 shows 5 small trials (between 28 and 50 patients) including this type of different strategies with acceptable results regarding late lumen loss and safety.

**TRIALS COMPARING THE RESULTS TO DIFFERENT STRATEGIES AND 2 COMPARISON GROUPS, MOST OF THEM RANDOMIZED**

Table 2 shows the 6 landmark trials comparing different strategies, 5 of them randomized, and 1 non-randomized.

**CONCLUSIONS FROM TRIAL RESULTS**

1. The use of bare metal stents (now in disuse) neutralizes all positive effects from the DCB in the main or side branch (DEBIUT and BABILON trials).

2. In lesions without proximal damage to the bifurcation, an early strategy of DCB can only be considered in 1 or in both branches (PEPCAD-BIF). Also, non-flow-limiting dissections have good prognosis at follow-up.

3. The use of DCB alone into the main branch can also have positive effects on the side branch ostium. Even using a limus-eluting stent in the main branch can only have a positive remodeling effect on the side branch ostium (aside from the study conducted by Her et al., the BABILON trial already suggested it). In any case, the use of a DCB as a single stentless strategy (unless results are poor or in the presence of flow-limiting dissections) seems like a reasonable option with a favorable long-term remodeling both in the main and side branches.

4. The use of a limus-eluting stent in the main branch with a DCB implanted in the side branch (currently the most widely used strategy) can improve angiographic intraluminal parameters like late lumen loss or minimum lumen diameter without any significant clinical repercussions on the long-term events (the BEYOND trial). This is probably so because, in the other group, late lumen loss in the side branch is also small since events are more conditioned by the main compared to the side branch (BABILON), and also because there are barely any myocardial infarctions or target lesion revascularizations associated with the side branch in any of the 2 groups.

5. The results obtained with different balloons could also be different.

However, we should mention other aspects like vessel length, and not only vessel diameter since some studies demonstrate that length—and not diameter—can be a more important predictor of the impact side branch occlusion. Moreover, almost all these trials...
included side branch lesions < 10 mm in length, which is a well-known favorable predictor for the provisional stenting technique. Side branch lesions > 10 mm plus other signs of complexity like calcium, etc. can require the double stenting strategy, especially in left main coronary artery bifurcation lesions.\(^\text{10}\)

Its role in more complex settings like left main coronary artery bifurcations or in-stent restenosis in bifurcations has also been studied, with reasonably good results.\(^\text{17,14}\)

The article by Valencia et al.\(^\text{6}\) recently published in REC: Interventional Cardiology falls within the category of observational studies without control group that do not include angiographic measurements to allow, at least, a rough result comparison with other studies. This article combines treatment strategies like drug-eluting stent implantation into the main vessel in 71% of the cases or DCB alone into the side branch in 29% of the cases followed by DCB implantation into the side branch or DCB alone into the side branch, since 18% of the lesions were Medina 0,0,1 while, overall, 37.5% had no proximal damage. However, the study shows what precisely in the most unfavorable cases of all, patients with in-stent restenosis.

According to the authors, this article contribution is the presentation of the clinical results of a small series of 54 patients with 55 lesions and the authors’ management of this type of lesions without excluding patients with higher risk of restenosis, as 32.1% of the patients with in-stent restenosis in the bifurcation and 8.9% with left main coronary artery lesions showed. Nevertheless the clinical outcomes are good with a median follow-up of 12 months. The rates of all-cause mortality, lesion thrombosis or infarction, and target lesion revascularization were 3.7%, 0%, and 3.6%, respectively, precisely in the most unfavorable cases of all, patients with in-stent restenosis.

The study limitations are obvious and well-established by the authors in the corresponding section. In brief, a small number of patients, no control group or angiographic follow-up, and the assumption that asymptomatic patients had no side branch restenosis. Also, since follow-up was not conducted on-site, possible developments of new Q waves associated with the side branch segment could not be detected. However, the study shows what many interventional cardiologists currently do in their cath labs and maintains interest for this strategy that should undoubtedly be taken into consideration when treating bifurcations. The most recent trials on drug-eluting stent and DCB implantation into the main and side branch, respectively, show good results in both branches, though with small differences in the repercussion of clinical events. Randomized clinical trials with a large cohort of patients are needed so that all possible trends favorable to the side branch become significant. Despite the presence of complex patients, the results from the trial conducted by Valencia et al.\(^\text{6}\) are good, promising, and their data welcome.

**FUNDING**

None whatsoever.

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**Table 1.** Non-randomized, prospective clinical trials without comparison control group

<table>
<thead>
<tr>
<th>Trial</th>
<th>Name or author and DCB</th>
<th>No. of patients</th>
<th>LLL, TLR events, and restenosis</th>
<th>Restenosis, and MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD-V(^1) (Sequent Please B. Braun, Germany)</td>
<td>28</td>
<td>0.21 ± 0.46 in the SB 0.38 ± 0.46 mm in the MB Only 1 TLR (3.57%) and 3 restenoses (10.1%)</td>
<td>2 patients (7.14%) had late thrombosis at 6 and 8 months</td>
<td></td>
</tr>
<tr>
<td>DEBSIDE (NCT01465501) (Danubio, France)</td>
<td>50</td>
<td>LLL in the SB: -0.04 ± 0.34 mm and in the MB: 0.54 ± 0.60 mm TLR in 1 patient (2%) Restenosis, 7.5.</td>
<td>1 AMI (2%) without cardiac deaths</td>
<td></td>
</tr>
<tr>
<td>BIOLUX-A (<a href="http://www.anzctr.org.au">www.anzctr.org.au</a>, ID 335843) (Pantera Lux, Biotronik AG, Switzerland)</td>
<td>35</td>
<td>LLL in the SB: 0.1 ± 0.43 mm 1 TLR (2.85%) No restenosis</td>
<td>1 patient died, and 3 AMIs were reported in different vessels</td>
<td></td>
</tr>
<tr>
<td>SARPEDON(^3) (Pantera Lux, BIOTRONIK AG, Bülach, Switzerland)</td>
<td>50</td>
<td>TLR, 5.2% at 1 year 4% of restenosis in the MB, and 6% in the SB</td>
<td>Stent thrombosis, 0%</td>
<td></td>
</tr>
<tr>
<td>Estudio de Valencia et al.(^5) (Sequent Please)</td>
<td>54</td>
<td>TLR, 3.6%</td>
<td>Overall mortality, 3.7%</td>
<td></td>
</tr>
<tr>
<td>Schulz et al.(^7) (Sequent Please)</td>
<td>39</td>
<td>10% restenosis, and all in the left main coronary artery bifurcation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruch et al.(^8) (Sequent Please)</td>
<td>127</td>
<td>TLR, 4.5</td>
<td>MACE, 0.1% Use of bailout stent in 45%</td>
<td></td>
</tr>
<tr>
<td>Her et al.(^9) (Sequent Please) (Only in the MB)</td>
<td>16</td>
<td>There was a significant increase in the SB luminal area at 9 months, 0.37 mm² = 0.64 mm² (P = .013), with a similar increase in the MB luminal area</td>
<td>The use of DCB alone in the MB also had a favorable impact on an area gain of 52% in the SB ostium</td>
<td></td>
</tr>
<tr>
<td>Vaquerizo et al. (NCT01375465) (Eurocor GmbH, Germany) (Only in the SB and 001 lesions)</td>
<td>31</td>
<td>LLL in the SB, 0.32 mm² ± 0.73 mm², and binary restenosis, and TLR of 22.5%</td>
<td>High need for bailout BMS (14%) 1 AMI (3.2%)</td>
<td></td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; BMS, bare metal stent; CB, conventional balloon; DCB, drug-coated balloon; DES, drug-eluting stent; LLL, late lumen loss; MACE, major adverse cardiovascular events; MB, main branch; SB, side branch; TLR, target lesion revascularization.
**Table 2. Trials that compared the results with different strategies in 2 randomized comparison groups (except for the one conducted by Li et al.)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Name and no. of patients</th>
<th>LLL</th>
<th>Restenosis and MACE, TLR events</th>
<th>Takeaway</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCB alone vs CB as a first-line therapy in lesions without damage to the proximal segment</td>
<td>PEPCAD-BIF10 (Sequent Please) 64 patients</td>
<td>LLL in the DCB group, 0.08 mm ± 0.31 mm vs 0.47 ± 0.61 mm in the CB group (P = .008).</td>
<td>Rates of restenosis of 26% vs 6% Rates of TLR of 9% vs 3% Favorable to DCB</td>
<td>In this type of lesions, stents were required in &lt; 10% of the cases only</td>
</tr>
<tr>
<td>DCCB vs CB in the SB with the use of BMS in the MB</td>
<td>DEBIUT11 (Dior-I, Eurocor GmbH, Germany) 117 patients A) DCB in both branches and BMS in the MB B) BMS in the MB, and CB in the SB C) Paclitaxel DES in the MB, and CB in the SB</td>
<td>LLL in the SB was 0.19 mm ± 0.66 mm in group A, 0.21 mm ± 0.57 mm in group B, and 0.11 mm ± 0.43 mm in group C (P = .001)</td>
<td>The rates of binary restenosis were 24.2%, 26.8%, and 15%, (P = .45), and the rates of MACE were 20%, 29.7%, and 17.5%, (P = .40) in groups A, B, and C, respectively</td>
<td>With this strategy, pretreatment of both branches with DCCB was not superior to conventional BMS with the provisional stenting technique. Also, the use of DES was superior to DCB plus BMS</td>
</tr>
<tr>
<td>Paclitaxel DES in the MB with CB vs DCB in the SB</td>
<td>Herrador et al.13 (Sequent Please) 90 patients</td>
<td>LLL: 0.40 mm ± 0.50 mm vs 0.09 mm ± 0.40 mm, (P = .01) favorable to the DCB group</td>
<td>The rates of DB restenosis were 20% vs 7%, (P = .08), and the rates of TLR, 22% vs 12% (P = .16)</td>
<td>The rates of MACE at 12 months were 24% vs 11% (P = .11)</td>
</tr>
<tr>
<td>-imus DES in the MB with CB vs DCB in the SB</td>
<td>BEYOND14 (Bingo, Yinyi Biotech, China) 222 patients with coronary bifurcation lesions excluding the left main coronary artery</td>
<td>Significantly lower LLL in the DCB compared to the CB group (~0.06 mm vs 0.32 mm vs 0.18 mm ± 0.34 mm; P &lt; .0001)</td>
<td>The rates of restenosis were 28.7% vs 40% (P &lt; .0001)</td>
<td>No differences regarding MACE (0.9% vs 3.7%, P = .16) or non-fatal AMI were found (0% vs 0.9%, P = .49)</td>
</tr>
<tr>
<td>Li et al.15 (Sequent Please) NON-randomized</td>
<td>Li et al.15 (Sequent Please) NON-randomized</td>
<td>LLL of SB in the DCB group was lower compared to the CB group (0.11 mm ± 0.18 mm vs 0.19 mm ± 0.25 mm; P = .024) at 12-month follow-up</td>
<td>Multivariate Cox analysis indicated that the DCB group had less MACE (23.9% vs 12.8%; P = .03)</td>
<td>Better results in the SB with DCB and fewer composite endpoints, but basically at the expense of unstable angiography</td>
</tr>
</tbody>
</table>

**REFERENCES**


Ischemic postconditioning and duration of previous ischemia

José A. Barrabés

Ischemic postconditioning (iPost) was first described in 2003 as a strategy capable of reducing the size of infarction after prolonged coronary occlusion in dogs through the immediate application of reperfusion after 3 cycles of 30 seconds of coronary reocclusion followed by 30 seconds of reperfusion. These results were soon confirmed independently, and the potential mechanisms involved described including, among others, a delayed normalization of pH levels, less accumulation of intracellular calcium, inhibition of the mitochondrial permeability transition pore, and less oxidative stress. Compared to the robust protective effect of ischemic preconditioning, it was confirmed that iPost was only beneficial if the procedure started right after reperfusion. However, it was attenuated in elderly subjects or in the presence of comorbidities or certain drug therapies.

Despite these limitations, iPost soon called the attention of interventional cardiologists because it was easy to apply during primary percutaneous coronary intervention. Back in 2005 the very first study ever conducted in humans was published. In this study, iPost reduced the size of creatine kinase release compared to the control group in patients with ST-segment elevation myocardial infarction (STEMI). However, successive trials that estimated the size of infarction using similar methods or was more reliably measured by contrast-enhanced cardiac magnetic resonance imaging showed contradictory results. Some of these confirmed iPost protective effect while others revealed the opposite or even less myocardial salvage in patients treated with iPost compared to those who were iPost-naïve. So far, no clinical trial has been able to demonstrate that iPost reduces clinical events. The largest trial ever conducted is the DANAMI-3-iPOST that included 1234 patients with STEMI. Authors conclude that iPost did not reduce the size of infarction in animals with 30-min coronary occlusion (0.3% [0.0-3.9] vs 0.9 [0.0-2.6] of left ventricular mass in animals treated with iPost or in the control group, respectively) or 40-min coronary occlusion (31.1% [27.3-32.8] vs 27.3 [25.1-27.5], respectively; both with non-significant P values). Overall, T1 relaxation times—a marker of interstitial fibrosis—in animals with previous ischemia was measured on the contrast-enhanced multidetector computed tomography scan with contrast during ischemia while the size of infarction was measured on the contrast-enhanced cardiac magnetic resonance imaging at 7 days.

Given these results, clinicians have consequently lost interest in this strategy. Therefore, iPost has not joined the therapeutic arsenal for the management of patients with STEMI. However, the reason behind the contradictory results of the mentioned trials is worth analyzing to identify, if any, subgroups of patients who could benefit from the protective effect of iPost. A possible explanation could be that the benefit of iPost depends on the duration of previous ischemia.

In an article recently published in REC: Interventional Cardiology, Nuche et al. put this hypothesis to the test by comparing the effect of iPost on the size of infarction in a series of pigs undergoing left anterior descending coronary artery occlusion through 30-min balloon inflation [N = 19] to a different series from a previous report where occlusion went on for 40 min [N = 10]. Except for the duration of ischemia, the experimental protocol was identical. iPost consisted of 4 cycles of balloon reinflation and deflation (1 min each) started 1 min after reperfusion. The area at risk was measured on the contrast-enhanced multidetector computed tomography scan with contrast during ischemia while the size of infarction was measured on the contrast-enhanced cardiac magnetic resonance imaging at 7 days.

meta-analysis confirmed the lack of tangible clinical benefits in iPost in an aggregate population of 3619 patients with STEMI. Given these results, clinicians have consequently lost interest in this strategy. Therefore, iPost has not joined the therapeutic arsenal for the management of patients with STEMI. However, the reason behind the contradictory results of the mentioned trials is worth analyzing to identify, if any, subgroups of patients who could benefit from the protective effect of iPost. A possible explanation could be that the benefit of iPost depends on the duration of previous ischemia.

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should be credited. Results go against an interaction between the benefit of iPost and the duration of previous ischemia. However, before this becomes the definitive conclusion, some methodological considerations should be made. In the first place, to assess the effect of any protective procedures, the size of infarction in the control group should have certain variability and, on average, should not be too large or too small. However, in this trial, after 30 min of ischemia barely any infarction was reported [3.8% (0.0-8.5%)] of the area at risk) while after 40 min infarctions were massive [98.2% (97.7-98.8% of the area at risk). Although these ischemia times were selected because they had caused medium-sized infarctions in former trials, homogeneity of the infarction size seen in both series and the almost non-existent infarctions in the 30 min series complicate discounting a possible beneficial effect of iPost in the results reported. Secondly, and on this regard too, it was surprising to see that by increasing ischemia time in just 10 min we went from almost non-existent infarctions to infarctions that occupy the entire area at risk. Although the experimental protocol was the same, as both series were conducted in different moments in time, variations in the conditions of the experiment such as animal breed, room temperature, materials used, etc, may have impacted the results and, therefore, cannot be ruled out. In this sense, results stress out the possible setback associated with the use of historic series. Finally, for the lack of a targeted anatomo-pathological study, a possible explanation for the massive infarctions reported in the 40 min series is that maybe some animals had coronary reocclusions between the end of the experiment and when the size of infarction was estimated 7 days later. Reocclusion is a common occurrence in this experimental model, especially when ischemia has been prolonged, and although the risk of ischemia drops with antiplatelet therapy (3 doses of clopidogrel were used in this trial) it does not go away completely.

Despite these considerations, the truth is that the results of this study do not offer any signs of a potential cardioprotective effect of iPost by changing the ischemia times in this experimental model. This, added to the lack of clinical benefits reported in the previously mentioned trials confirms that, currently, iPost should not be used in patients with STEMI. This anticipates that it will be difficult to find a population of target patients in whom this procedure might be beneficial.

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CONFLICTS OF INTEREST

None reported.

REFERENCES

Long-term effectiveness of drug-coated balloon in the side branch treatment of bifurcation lesions

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ABSTRACT

Introduction and objectives: There are few data on the utility of drug-coated balloons (DCB) for the side branch treatment of bifurcated lesions. Our objective was to determine the long-term effectiveness of such device in this scenario.

Methods: Retrospective-prospective registry of all such lesions treated with DCB (paclitaxel coating) at our unit from 2018 until present day with clinical follow-up including a record of adverse events.

Results: A total of 56 lesions from 55 patients were included. The main demographic characteristics were mean age, 66.2 ± 11.3; and/or women, 27.3%; hypertension, 67.3%; dyslipidemia, 83.6%, and diabetes, 32.7%. The most common causes according to the coronary angiography were non-ST segment elevation acute coronary syndrome and stable angina. The main characteristics of the lesions were the location (circumflex-obtuse marginal, 19.6%; left anterior descending-diagonal, 64.3%; left main-circumflex, 8.9%; posterior descending-posterolateral trunk, 7.1%). The Medina classification was 1-1-1 37.5% of the times, and 1-1-0, 19.6% of the times. The rate of in-stent restenotic lesions was 32.1%. Procedural characteristics: radial access, 100%; side branch (SB) and main branch (MB) predilatation, 83.9% and 58.9%, respectively; MB stenting, 71.4%; POT technique, 35.7%; final kissing, 48.2%; optical coherence tomography/intravascular ultrasound, 7.1%. Procedural success was achieved in 98.2% of the cases. The median follow-up he all-cause mortality, myocardial infarction and lesion thrombosis, and target lesion revascularization rates were .7%, 0%, and 3.6%, respectively.

Conclusions: SB treatment with DCB in selected bifurcation lesions is safe and highly effective with a long-term success rate of 96.4%. Very large studies are still required to compare this strategy to SB conservative approach, and determine its optimal treatment.

Keywords: Drug-coated balloon. Bifurcation lesions. Follow-up study. Side branch.

Efectividad a largo plazo del balón farmacoactivo en el tratamiento de la rama lateral de lesiones en bifurcación

RESUMEN

Introducción y objetivos: Hay pocos datos acerca de la utilidad del balón farmacoactivo (BFA) para el tratamiento de la rama lateral de las lesiones en bifurcación. El objetivo fue determinar la efectividad a largo plazo de dicho dispositivo en este escenario.

Métodos: Registro retrospectivo-prospectivo de todas las lesiones de este tipo tratadas con BFA recubierto de paclitaxel en nuestra unidad desde 2018 hasta la actualidad. Se realizó un seguimiento clínico con registro de eventos adversos.

Resultados: Se incluyeron 56 lesiones de 55 pacientes. Principales características demográficas: edad media 66,2 ± 11,3 años, 27,3% mujeres, 67,3% hipertensión arterial, 83,6% dislipemia y 32,7% diabetes. Las indicaciones más frecuentes para el cateterismo fueron síndrome coronario agudo sin elevación del ST y angina estable. Características de las lesiones tratadas: localización circumflexia-obtusa marginal 19,6%, descendente anterior-diagonal 64,3%, tronco común-circumflexa 8,9% y descendente posterior-tronco posterolateral 7,1%. Según la clasificación de Medina, el tipo más frecuente fue el 1,1,1 con el 37,3%, seguido del 1,1,0 con el 19,6%. Las lesiones tipo reestenosis en el interior del stent fueron del 32,1%. Características principales del procedimiento: acceso radial 100%, predilatación de rama lateral 83,9% y de rama principal 58,9%, stent en rama principal 71,4%, técnica POT 35,7%, kissing final 48,2% y tomografía de coherencia óptica/ecocardiografía intravascular 7,1%. Se logró el éxito del procedimiento en el 98,2%. Con un seguimiento medio de 12 meses, se registraron una incidencia de muerte por cualquier causa del 3,7%, trombosis lesional o infarto 0%, y revascularización de la lesión diana del 3,6%.

Conclusiones: El tratamiento con BFA de la rama lateral en lesiones bifurcadas seleccionadas es seguro y presenta una alta efectividad, con una tasa de éxito a largo plazo del 96,4%. Serían necesarios estudios muy amplios que permitieran comparar dicha estrategia con el abordaje conservador de la rama lateral y determinar cuál es su tratamiento óptimo.
INTRODUCTION

Coronary bifurcation lesions are still challenging for interventional cardiologists. The complexity surrounding such lesions regarding their anatomical, functional, and even clinical aspects truly complicate the management of this entity despite its high incidence rate that can be up to 20% of all the lesions that are treated at a cath lab on a routine basis. The relentless publication of articles on such lesions over the last few decades, the creation of specific study groups like the European Bifurcation Club, and the periodic publication of consensus documents for the management of this entity shows, without a doubt, that this scenario is in constant change and has not been solved today yet. One of the most controversial aspects is the importance of the side branch (SB) regarding the long-term prognosis of such lesions. Drug-coated balloon (DCB) is part of the therapeutic armamentarium of interventional cardiologists to treat coronary bifurcation lesions. Its utility for the management of certain anatomical settings like in-stent restenosis (ISR) type of lesions has already been demonstrated. However, its effectiveness to treat the SB is much less evident with scarce studies available in the medical literature. The theoretical advances posed by this device to treat the SB would be the administration of antiproliferative drugs into the ostium mainly, the lack of distortion of its original anatomy, and the minimization of strut deformation at carina level. This article presents a registry with the results obtained in our unit with the management of SB with DCB with a longer than usual clinical follow-up in this type of studies.

METHODS

This was a single-center, prospective-retrospective registry started back in 2019 of all coronary bifurcation lesions where the SB was treated with paclitaxel-coated DCB from October 2018 through March 2022. The device used was the SeQuent Please NEO (Braun, Germany), a paclitaxel-iodopromide coated polymer-free balloon using Paccocath technology. Inclusion criteria were the presence of coronary bifurcation lesions with 1 compromised SB of, at least, 2 mm in diameter through visual angiographic estimate regardless of the aprioristic presence of a diseased SB or the appearance of carina displacement or slow flow after treating the main branch (MB). Also, the operator should consider the DCB approach of clinical and prognostic interest. Patient recruitment in the registry was on the rise: 4 patients in 2018, another 4 in 2019, 9 patients in 2020, 31 in 2021, and finally 7 within the first 3 months of 2022. No exclusion criteria were established. Approach strategy consisted of an early provisional stenting or DCB technique to treat the MB when damaged. Further management of SB with DCB was left to the operator’s criterion if, after treating the MB, significant damage done to the SB would require stenting in such branch. In that case, the patient would not be included, and the SB would not be eligible for treatment with a DCB. If, after preparing the lesion, the operator would actually consider using the DCB option, that would be the time to include the patient in the study. The rate of procedural failure—defined as the impossibility to cross the lesion with the DCB once it was used or unsatisfactory angiographic outcomes after balloon inflation involving SB stenting. The protocol for using the DCB—based on the recommendations established on the use of such devices—consisted of SB predilatation with non-compliant or scoring balloons in a 0.8-1 vessel/balloon diameter ratio, use of the device if an acceptable angiographic result with TIMI grade-3 flow was achieved, lack of significant dissection, and residual stenosis < 30%. If other lesions different from the one that triggered the inclusion in the registry needed revascularization, this was scheduled for a second surgical act. The study design followed a per protocol analysis to estimate the benefits of the technique described compared to the routine clinical practice including cases with successful DCB treatment at the follow-up and excluding those with acute device failure or impossibility to use the device once opened for being unable to cross the lesion. The lack of dissection after DCB that required stenting with residual stenosis < 50%, and final TIMI grade-3 flow was considered as procedural success. Device failure, on the other hand, was considered as an impossible DCB inflation once used or the need for stenting the SB with unsatisfactory DCB results. Different clinical variables from the patient were analyzed, as well as the lesion anatomy, and the procedural intervention per se. Retrospective clinical follow-up of patients successfully treated with the DCB was conducted. Follow-up went on for a maximum of 2 years after the procedure, and prospectively since the registry started back in 2019 until present time. This follow-up was conducted through phone calls or by checking the patients’ electronic health records. The ARC-2 definitions2 were used to collect the adverse clinical events including a composite endpoint of all-cause mortality, cardiac death, myocardial infarction, device thrombosis, clinically driven target lesion failure and revascularization, target vessel failure outside the target lesion, and revascularization of other lesions occurred at follow-up. All patients signed their written informed consent forms, and the study was approved by our center research ethics committee.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequency and percentage. Also, actuarial curves of adverse event-free survival using the Kaplan-Meier method were built, specifically target lesion failure-free and adverse event-free curves (all-cause mortality, target lesion revascularization, target vessel failure, and revascularization of other lesions).

RESULTS

A total of 55 patients and 56 lesions were included since 2 different bifurcations found in 1 of the patients were treated in the same procedure. The patient/lesion flowchart included in the study is shown on figure 1. The patients’ clinical characteristics are shown on table 1. Vascular access was radial in 100% of the cases using a 6-Fr introducer sheath also in all of them. Table 2 shows the anatomical characteristics of target lesions. Figure 2 shows a schematic representation of the type of lesion according to the Medina
Table 3 shows the variables associated with the classification. The rate of adverse events at follow-up is shown on Table 4. After a median follow-up of 12 months (377 ± 11.3 years [range, 45-91]) was also remarkable.

Both cases were treated with drug-eluting stent implantation. Two deaths were reported: 1 cardiac death due to advanced left ventricular dysfunction in an 80-year-old woman who, after percutaneous coronary intervention, was implanted with a transfemoral aortic valve and a definitive pacemaker, with poor disease progression that eventually led to her death. The other death was septic shock related. No admissions due to acute myocardial infarction or episodes of target lesion thrombosis (both probable and definitive) were reported. No cases of target vessel failure outside the target lesion were reported either. A total of 5 revascularizations of other lesions (9.3%) were performed—all of them scheduled—but none due to acute coronary syndrome. The Kaplan-Meier curves showing target lesion revascularization-free and adverse event-free survival are shown on Figure 6.

**DISCUSSION**

The latest document of the European Bifurcation Club on the utility of DCBs to treat SBs in coronary bifurcation lesions pays little attention to it due to the lack of large enough clinical trials to be conclusive. Despite the huge amount of medical literature available on the management of coronary bifurcation lesions, the actual significance of the SB and its involvement in target lesion failure has not been properly explained to this date. A study conducted by Oh et al.2 conclude that treating the SB in 1089 patients with bifurcation lesions at left anterior descending coronary artery-diagonal branch level was associated with a lower—yet not statistically significant—rate of target vessel failure. However, this difference was statistically significant when the subgroup studied included low-risk patients. On the other hand, a different clinical trial that studied factors associated with failed recanalizations of the left main coronary artery bifurcation found that the presence of MB stent struts inside the SB ostium was one of them5 suggestive that the use of intracoronary imaging modalities like intracoronary ultrasound or optical coherence tomography could improve results, at least, on such location, by telling us what patients would benefit from specifically treating the SB.

The strongest evidence available to this date leans towards the utility of DCB to treat ISR-type of lesions without a word dedicated
Very few studies have focused on the effectiveness of DCB to treat the SB. Such document advocates for treating coronary bifurcation lesions with the provisional stenting strategy according to the latest clinical practice guidelines drafted by the European Cardiology Society followed by treating the SB with a DCB. The first clinical trials on this regard were published back in 2011 like the DEBIUT,\textsuperscript{6} BABILON,\textsuperscript{7} DEBSIDE,\textsuperscript{8} the study conducted by Herrador et al.,\textsuperscript{9} the PEPCAD V,\textsuperscript{10} and the PEPCAD-BIF\textsuperscript{11} clinical trials. These studies showed contradictory—yet overall satisfactory—data regarding the effectiveness of DCB. These studies presented better quantitative angiographic parameters regarding restenosis or late lumen loss. However, not in every one of them this was associated with a lower rate of revascularization. As a matter of fact, there were doubts around the possibility of a higher rate of late thrombosis suggested by some of these trials. The recently published BEYOND clinical trial conducted by Jing et al.\textsuperscript{12} compared the use of a conventional balloon vs DCB to treat the SB with a 9-month angiographic follow-up. This trial found that the DCB was associated with better results regarding less late lumen loss. However, such an improvement did not translate into a lower rate of clinical adverse events since surprisingly enough no new revascularizations were reported in any of the 2 groups. A recent meta-analysis\textsuperscript{13} that included 10 studies on the effect of DCB on the SB concluded that such technique improved the angiographic outcomes significantly. However, this did not translate either into statistically significant clinical outcomes (target lesion failure mainly) basically due, according to the authors, to the low rate of this adverse event reported, and the fact that the study was statistically underpowered due to its small sample size. In a different study published in 2022,\textsuperscript{14} the management of coronary bifurcation lesions of left main coronary artery using 2 strategies was compared: double stenting for the MB and the SB vs 1 stent into the MB, and 1 DCB into the SB. They found controversial results at follow-up.

Table 3. Procedural characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dilatation</td>
<td></td>
</tr>
<tr>
<td>SB</td>
<td>47 (83.9%)</td>
</tr>
<tr>
<td>MB</td>
<td>33 (58.9%)</td>
</tr>
<tr>
<td>MB treatment</td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>40 (71.4%)</td>
</tr>
<tr>
<td>DCB</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>DCB diameter for the SB (mm)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20 (35.7%)</td>
</tr>
<tr>
<td>2.25</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>2.5</td>
<td>23 (41.1%)</td>
</tr>
<tr>
<td>3</td>
<td>8 (14.3%)</td>
</tr>
<tr>
<td>3.5</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Post-dilatation</td>
<td></td>
</tr>
<tr>
<td>MB</td>
<td>36 (64.3%)</td>
</tr>
<tr>
<td>POT</td>
<td>20 (35.7%)</td>
</tr>
<tr>
<td>SB</td>
<td>17 (30.4%)</td>
</tr>
<tr>
<td>Final kissing balloon</td>
<td>27 (48.2%)</td>
</tr>
<tr>
<td>OCT/IVUS</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>Procedural success</td>
<td>55 (98.2%)</td>
</tr>
</tbody>
</table>

DCB, drug-coated balloon; IVUS, intravascular ultrasound; MB, main branch; OCT, optical coherence tomography; POT, proximal optimization technique; SB, side branch.

Table 4. Rate of adverse cardiovascular events at follow-up

<table>
<thead>
<tr>
<th>N</th>
<th>54/55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up days</td>
<td>377 ± 244 [range, 79-734]</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2/54 (3.7%)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1/54 (1.8%)</td>
</tr>
<tr>
<td>Myocardial infarction/target lesion device thrombosis</td>
<td>0/55 (0%)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>2/55 (3.6%)</td>
</tr>
<tr>
<td>Target vessel failure outside the target lesion</td>
<td>0/55 (0%)</td>
</tr>
<tr>
<td>Revascularization of other lesions outside the target vessel</td>
<td>5/54 (9.3%)</td>
</tr>
</tbody>
</table>

The DEBIUT,\textsuperscript{6} BABILON,\textsuperscript{7} DEBSIDE,\textsuperscript{8} the study conducted by Herrador et al.,\textsuperscript{9} the PEPCAD V,\textsuperscript{10} and the PEPCAD-BIF\textsuperscript{11} clinical trials. These studies showed contradictory—yet overall satisfactory—data regarding the effectiveness of DCB. These studies presented better quantitative angiographic parameters regarding restenosis or late lumen loss. However, not in every one of them this was associated with a lower rate of revascularization. As a matter of fact, there were doubts around the possibility of a higher rate of late thrombosis suggested by some of these trials. The recently published BEYOND clinical trial conducted by Jing et al.\textsuperscript{12} compared the use of a conventional balloon vs DCB to treat the SB with a 9-month angiographic follow-up. This trial found that the DCB was associated with better results regarding less late lumen loss. However, such an improvement did not translate into a lower rate of clinical adverse events since surprisingly enough no new revascularizations were reported in any of the 2 groups. A recent meta-analysis\textsuperscript{13} that included 10 studies on the effect of DCB on the SB concluded that such technique improved the angiographic outcomes significantly. However, this did not translate either into statistically significant clinical outcomes (target lesion failure mainly) basically due, according to the authors, to the low rate of this adverse event reported, and the fact that the study was statistically underpowered due to its small sample size. In a different study published in 2022,\textsuperscript{14} the management of coronary bifurcation lesions of left main coronary artery using 2 strategies was compared: double stenting for the MB and the SB vs 1 stent into the MB, and 1 DCB into the SB. They found controversial results at follow-up.
the range found goes from a surprising 0% up to a whopping 22%. However, we should mention the truly unfavorable clinical and anatomical profile of our sample since in most clinical trials, ISR-type of lesions, left main coronary artery disease or ST-segment elevation acute coronary syndrome—all allowed in our registry—were considered exclusion criteria regarding.

Out of the only 2 cases reported of target lesion failure requiring new revascularization, 1 occurred in a patient with an ISR-type of lesion. This occurred precisely in the SB while in former studies—as already explained—the main incidence rate of failure occurred in the MB, not in the SB. The exclusion of patients with ISR would account for this difference. In our sample this type of lesions were 32.7% of all the lesions included. This added to the high rate (30.6%) of Medina 1,1,1 coronary bifurcation lesions (the one with the greatest complexity of all bifurcations) demonstrates the truly unfavorable profile of our sample. As a matter of fact, the rate of lesions included with damage to, at least, 2 segments of 1 bifurcation according to the Medina classification reached 71.4%. Very few studies have been conducted on this subgroup of patients. One of the most significant ones is the one conducted by Harada et al. that included 177 patients with ISR-type of lesions both in the MB and the SB treated with DCB. The latter was used in 80.6% of the SBs. The rate of binary restenosis was 24% at 6-to-8-month angiographic follow-up while the 1-year rate of new target lesion revascularization was 22%.

between both groups in different angiographic parameters with similar rates of restenosis and adverse events. However, the group treated with DCB significantly improved all the parameters associated with the SB [left circumflex artery, in this study]—as opposed to those associated with the MB [left main coronary artery-left anterior descending coronary artery]—with less late lumen loss (0.43 vs -0.17; \(P < .001\)), less luminal narrowing (16.7 vs 32.1; \(P = .002\)), and greater minimal lumen diameter (2.4 vs 1.8; \(P = .0031\)). Still, the rate of restenosis in the left circumflex artery [SB in this study] was 4 times higher in the double stenting group compared to the DCB group (30.4% vs 7.7%) although this difference was not statistically significant (\(P = .09\)). This could be indicative of greater superiority of the DCB if studies with larger samples would be conducted. Another recent study published in 2021 randomized 219 true de novo coronary bifurcation lesions where the SB was treated with conventional balloon vs DCB. At 12-month clinical and angiographic follow-up, significant improvements were reported in both the angiographic (less late lumen loss and greater minimal lumen diameter) and clinical parameters with a lower rate of major adverse cardiovascular events being reported. This improvement, however, did not translate into significant reductions regarding new revascularizations or target vessel failure.

The rate of target lesion failure requiring new revascularization was 3.6%, a figure that is consistent with most former studies. However, the rate found goes from a surprising 0% up to a whopping 22%.

Out of the only 2 cases reported of target lesion failure requiring new revascularization, 1 occurred in a patient with an ISR-type of lesion. This occurred precisely in the SB while in former studies—as already explained—the main incidence rate of failure occurred in the MB, not in the SB. The exclusion of patients with ISR would account for this difference. In our sample this type of lesions were 32.7% of all the lesions included. This added to the high rate (30.6%) of Medina 1,1,1 coronary bifurcation lesions (the one with the greatest complexity of all bifurcations) demonstrates the truly unfavorable profile of our sample. As a matter of fact, the rate of lesions included with damage to, at least, 2 segments of 1 bifurcation according to the Medina classification reached 71.4%. Very few studies have been conducted on this subgroup of patients. One of the most significant ones is the one conducted by Harada et al. that included 177 patients with ISR-type of lesions both in the MB and the SB treated with DCB. The latter was used in 80.6% of the SBs. The rate of binary restenosis was 24% at 6-to-8-month angiographic follow-up while the 1-year rate of new target lesion revascularization was 22%.
Limitations

Our study main limitation is the lack of a control group with lesions of similar characteristics, which would have allowed us to compare both groups and determine exactly the impact DCB has on the prognosis of patients. Similarly, the lack of angiographic follow-up does not discard the possibility of device failure. However, this would probably occur in the SB, not the MB, since it is in the latter where target lesion failure occurs according to the BABILON clinical trial. Another study limitation we should take into consideration is the elevated presence of small SB with a rate of use, in our sample, of DCB sizes < 2.25 mm of 43.7%. This would make target lesion failure go clinically inadvertently in some of these cases. Finally, we should mention that this study is limited by the relatively small number of patients included. Also, because due to its observational nature, no selection biases can be excluded.

CONCLUSIONS

The findings presented here show the experience of a single center with a very low rate of acute procedural complications, and a low rate of long-term adverse events despite dealing very high-risk profile lesions and patients with a 3.6% rate of target lesion failure reported. It is crucial to select the right type of lesions that can benefit from such therapy (basically the lack of a large plaque burden in the SB), a very refined technique of lesion preparation, and a greater use of tools to guide the angioplasty like intracoronary ultrasound or optical coherence tomography, preferably in ISR-type of lesions whose clinical progression is more unfavorable compared to that of de novo lesions. Despite the low rate of adverse events reported since no comparison with a control group was made, no definitive conclusions can be drawn on the advantages of DCBs in this clinical setting. We can only say that both in the «real-world» and the routine clinical practice described here, such strategy yields good long-term results.
without prejudice to other strategies may have given better or worse results regarding effectiveness. Randomized clinical trials are needed with enough statistical power and large enough samples to corroborate the promising data obtained from former studies to confirm or discard the superiority of DCB in the management of the SB in coronary bifurcation lesions. Until that time, the DCB can be considered a therapeutic tool that can be tremendously useful to improve the long-term results obtained in this type of complex lesions.

**CONFLICTS OF INTEREST**

None reported.

**AUTHORS’ CONTRIBUTIONS**

J. Valencia drafted the manuscript. J. Valencia, F. Torres-Mezcua, and M. Herrero-Brocal participated in data curation, and in the clinical follow-up of the patients. J. Valencia, J. Pineda, P. Bordes, F. Torres-Saura, and J.M. Ruiz-Nodar participated in patient recruitment and in the manuscript critical review process. All the authors gave their final approval to the manuscript.

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None whatsoever.

**REFERENCES**

Impact of time of intervention in patients with NSTEMI.

The IMPACT-TIMING-GO trial design


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ABSTRACT

Introduction and objectives: The optimal time to perform a diagnostic coronary angiography in patients admitted due to non-ST-segment elevation acute coronary syndrome (NSTEMACS) and start pretreatment with dual antiplatelet therapy is controversial. Our study aims to identify the current diagnostic and therapeutic approach, and clinical progression of patients with NSTEMACS in our country.

Methods: The IMPACT-TIMING-GO trial [Impact of time of intervention in patients with myocardial infarction with non-ST segment elevation. Management and outcomes] is a national, observational, prospective, and multicenter registry that will include consecutive patients from 24 Spanish centers with a clinical diagnosis of NSTEMACS treated with diagnostic coronary angiography and with present unstable or causal atherosclerotic coronary artery disease. The study primary endpoint is to assess the level of compliance to clinical practice guidelines in patients admitted due to NSTEMACS undergoing coronary angiography in Spain, describe the use of antithrombotic treatment prior to cardiac catheterization, and register the time elapsed until it is performed. Major adverse cardiovascular events will also be described like all-cause mortality, non-fatal myocardial infarction and non-fatal stroke, and the rate of major bleeding according to the BARC [Bleeding Academic Research Consortium] scale at 1- and 3-year follow-up.

Results: This study will provide more information on the impact of different early management strategies in patients admitted with NSTEMACS in Spain, and the degree of implementation of current recommendations into the routine clinical practice. It will also provide information on these patients’ baseline and clinical characteristics.
Impacto del tiempo de intervención en pacientes con IAMSEST: diseño del estudio IMPACT-TIMING-GO

RESUMEN

Introduction y objetivos: El momento óptimo para la realización de un cateterismo diagnóstico en pacientes con síndrome coronario agudo sin elevación del segmento ST (SCASEST) y la necesidad de pretratamiento con doble antiagregación son motivo de controversia. Este estudio pretende conocer el abordaje diagnóstico y terapéutico actual, así como la evolución clínica de los pacientes con SCASEST en España.

Métodos: El estudio IMPACT of Time of Intervention in patients with Myocardial Infarction with Non-ST segment elevation. Management and Outcomes (IMPACT-TIMING-GO) es un registro nacional observacional, prospectivo y multicéntrico, que incluirá pacientes consecutivos con diagnóstico de SCASEST tratados con coronariografía diagnóstica y que presenten enfermedad coronaria aterosclerótica inestable o causal en 24 centros españoles. El objetivo primario del estudio es conocer el grado de cumplimiento de las recomendaciones de las guías de práctica clínica en pacientes que ingresan por SCASEST tratados con coronariografía en España, describir el uso del tratamiento antitrombótico antes del cateterismo y determinar el tiempo hasta este en la práctica clínica real. Se describirán también los eventos adversos cardiovasculares mayores: mortalidad por cualquier causa, infarto no fatal e ictus no fatal, y también la incidencia de hemorragia mayor según la escala BARC (Bleeding Academic Research Consortium) durante el seguimiento a 1 y 3 años.

Resultados: Este registro permitirá mejorar el conocimiento en relación con el abordaje terapéutico inicial en pacientes que ingresan por SCASEST en España. Contribuirá a conocer sus características basales y su evolución clínica, así como el grado de adherencia y cumplimiento de las recomendaciones de las que se dispone actualmente.

Conclusiones: Se trata del primer estudio prospectivo realizado en España que permitirá conocer las estrategias terapéuticas iniciales, tanto farmacológicas como intervencionistas, que se realizan en nuestro país en pacientes con SCASEST tras la publicación de las guías europeas de 2020, y la evolución clínica de estos pacientes a corto y largo plazo.


INTRODUCTION

Ischemic heart disease is the leading cause of mortality in developed countries.1 The rate of acute coronary syndrome (ACS), specially non-ST-segment elevation ACS (NSTEACS), has increased over the last few years, in part, due to the ageing of the population.2,3 Given the underlying pathophysiology4 patients receive specific antithrombotic treatment, and invasive approach is used in most of the cases.1,2 The new guidelines published by the European Society of Cardiology (ESC) on the management of NSTEACS3 include changes compared to the guidelines published back in 2016. The most significant ones include antithrombotic treatment, the revascularization strategy, and several controversial innovations.

In the guidelines published in 2020, early cardiac catheterization within the first 24 hours after admission was advised (level of evidence IA) in patients diagnosed with acute myocardial infarction with GRACE scores [Global Registry of Acute Coronary Events] > 140 or dynamic electrocardiographic changes suggestive of ischemia.1 Also, the previous window of recommendation of 0 to 72 hours for moderate risk patients is now gone.4 On the other hand, the systematic use of pretreatment at admission with an P2Y12 inhibitor antiplatelet drug (ticagrelor, prasugrel or clopidogrel) in patients to be treated with an early invasive strategy is now ill-advised.1

The objective of the IMPACT registry [Time of intervention in patients with myocardial infarction with non-ST segment elevation, management and outcomes [IMPACT-TIMING-GO]] is to get the big picture on the current treatment of NSTEACS, in Spain, in association with catheterization times, use of pretreatment in these patients, and describe the possible prognostic implications of the different strategies used in real life.

METHODS

Study design and population

This is an observational, prospective, multicenter, and nationwide registry that will include all consecutive patients admitted with a diagnosis of NSTEACS to the different participant centers, treated with diagnostic coronary angiography, and with unstable or causal.
atherosclerotic disease regardless of further treatment administered by the heart team. The baseline characteristics of the patients included, and their clinical progression regarding in-hospital events will be studied. Patients will undergo a 1-and-3-year clinical follow-up period.

This registry has been promoted by the Spanish Society of Cardiology Young Cardiologists Working Group with scientific support from the Spanish Society of Cardiology Research Agency. Also, it has been approved by different Research Ethics Committees with drugs from all the participant hospitals. Finally, it has been designed according to the STROBE checklist for observational studies.

The list of centers that will eventually participate in the registry is shown on figure 1. Inclusion and exclusion criteria are shown on table 1. The presence of elevated markers of myocardial damage or electrocardiographic changes is not mandatory. Patients with a clinical diagnosis of unstable angina can be included as long as coronary angiography confirms the clinical diagnosis.

Endpoints

The study primary endpoint is to know the degree of compliance of the recommendations included in the clinical practice guidelines in patients admitted due to NSTEACS treated with coronary angiography, in Spain, describe the use of antithrombotic treatment before cardiac catheterization, and the time elapsed until it is performed in the real-world clinical practice.

The secondary endpoints are:

- To describe the baseline, clinical, and epidemiological characteristics of the study population.
- To study the rates of cardiovascular mortality, new revascularization, stent thrombosis, and hospitalizations due to heart failure during admission and at the 1-and-3-year follow-up.
- To describe major cardiovascular adverse events of all-cause mortality, non-fatal stroke, non-fatal infarction, and the rate of major bleeding grades 3, 4, and 5 according to the BARC scale (Bleeding Academic Research consortium). Data will be analyzed during admission and at the 1-and-3-year follow-up.
- To know the medical treatment at discharge and at follow-up of patients discharged in Spain after NSTEACS.
- To know the degree of control of the different cardiovascular risk factors associated with the endpoints defined in the ESC guidelines 2021 on prevention of cardiovascular disease in the routine clinical practice.
Clinical follow-up to detect events will be conducted by medical investigators through on-site visits, health record reviews or phone calls with the patient, family members or treating physician at 1 and 3 years. Clinical variables, functional class, and additional variables (analytical, electrocardiographic, and echocardiographic, and treatment received) will be included. The overall mortality rate and its causes, need of emergency hospitalization (duration > 24 hours) and its causes, and the rates of non-fatal infarction and stroke will be collected as well. All deaths due to myocardial infarction, sudden death or heart failure will be considered cardiovascular deaths.

Table 2. Definitions of target variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>All deaths regardless of their cause.</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>All deaths of vascular causes both cardiac (heart failure/shock; malignant arrhythmias; myocardial infarction) and non-coronary vascular including cerebrovascular disease, pulmonary embolism, aneurysms/aortic dissections, acute ischemia of lower limbs, etc. All sudden deaths of unknown causes will be adjudicated as cardiovascular death.</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>All deaths that do not meet the previous definition like deaths due to infections, cancer, pulmonary diseases, accidents, suicide or trauma.</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>It is defined based on the criteria established in the 4th and current Universal definition. Therefore, patients with type 2 infarction, extracardiac causes or without elevated markers of myocardial damage were excluded.</td>
</tr>
<tr>
<td>Stroke/Transient ischemic attack</td>
<td>New-onset neurological, focal or global deficit due to ischemia or hemorrhage, and as long as it is part of diagnostic judgement at hospital discharge.</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>Defined based on the Academic Research Consortium of randomized clinical trials with stents.</td>
</tr>
<tr>
<td>New revascularization</td>
<td>All unscheduled revascularizations performed after hospital discharge, whether surgical or percutaneous, including target vessel failure and target lesion failure.</td>
</tr>
<tr>
<td>Admission due to heart failure</td>
<td>Unscheduled hospital admission &gt; 24 hours with a primary diagnosis of heart failure based on the current definition.</td>
</tr>
</tbody>
</table>

Sample size estimate

Taking the events seen in previous studies with a population of similar characteristics as the reference, a sample size of 800 patients will be enough to know the baseline characteristics of the study population, and the therapeutic approach currently used in Spain in our routine clinical practice. Patients lost to follow-up will be handled by multiple imputation.

Statistical analysis

Categorical variables will be expressed as number and percentage. Quantitative variables will be expressed as mean ± standard deviation. Quantitative variables with normal distribution will be expressed as median and interquartile range [25%-75%]. The normal distribution of quantitative variables will be assessed using the Kolmogorov-Smirnoff test. Regarding the reference variables, Student t test will be used to compare quantitative variables, and the chi-square test or Fisher’s exact test, if applicable, to compare categorical variables. Statistical analysis will be performed using the SPSS statistical software version 22.0 (IBM Corp., Armonk, United States).

Specific studies on subgroups of special interest will be conducted: feminine sex, patients ≥ 75 years, those with GRACE scores > 140, diabetic patients, those with a past medical history of renal failure, with an indication for chronic oral anticoagulation, with multivessel disease, acute myocardial infarction, ventricular dysfunction...
Ethical principles

Inclusion in the study will not imply changes to the patients’ treatment. Instead, it will follow the routine clinical practice and the recommendations set forth by the current clinical practice guidelines. Therefore, antithrombotic treatment and additional examinations including the need for a coronary angiography and the time it is performed will all be decided by the heart team based on the routine clinical practice. Coronary angiography, vascular access, antithrombotic treatment during the procedure, and the material and devices used will all be decided by the treating operator in charge of the case. All patients will sign a written informed consent form before being included in the study that will be conducted in full compliance with the Declaration of Helsinki. This study will also observe all legal regulations applicable to this type of studies and follow the good clinical practice rules while being conducted.

DISCUSSION

The IMPACT-TIMING-GO registry will give us information on the current real-world management of patients with NSTEACS with invasive treatment and causal coronary artery disease, which will allow us to assess the degree of implementation of the current recommendations of ESC guidelines 2020 on cardiac catheterizations performed within the first 24 hours and no pretreatment with P2Y12 inhibitors. Similarly, different prognostic differences that early invasive treatment and no pretreatment could have in the real life of patients diagnosed with NSTEACS could be suggested.

Despite the clinical practice guidelines recommendations on the invasive treatment of patients with NSTEACS, the main clinical trials published to this date have been unable to demonstrate any clear benefits from systematic early invasive treatment. The VERDICT trial, published in 2018, randomized 2147 patients with NSTEACS on a 1:1 ratio to receive early (<12 hours) or delayed (48 to 72 hours) cardiac catheterization. No significant differences were found in the composite endpoint of major cardiovascular events at 4-year follow-up. However, in the subgroup of patients with GRACE scores > 140 statistically significant differences were seen favorable to the early strategy regarding major adverse cardiovascular events (hazard ratio, 0.81; 95% confidence interval, 0.67-1.01; P = .023). Consistent with this, the TIMACS clinical trial published in 2008 of 3031 patients with NSTEACS found no differences in the primary endpoint when early invasive strategy (<24 hours) and delayed approach (>36 hours) were compared, except for, once again, in patients with GRACE scores > 140. Other randomized clinical trials with fewer patients show contradictory results some without significant differences. Also, in many cases, the results favorable to the early strategy are associated with refractory ischemia, not with hard endpoints like cardiovascular mortality or non-fatal myocardial infarction. In Spain, evidence on the management of NSTEACS is prior to the current clinical practice guidelines, and the most recent registry is retrospective, which is suggestive of a possible mortality benefit in patients with GRACE scores > 140. Over the last 2 decades, in our country, the use of an invasive strategy in patients with NSTEACS has increased significantly from 20% in the MASCARA registry in 2005 to up to 80% in the DIOCLES study from 2012. However, evidence is scarce on catheterization times, our capacity to adapt to current recommendations the median time of the DIOCLES trial was 3 days), the possible impact this time reduction can have, and on the consequences from not starting antiplatelet pretreatment in patients who don’t meet the times recommended.

On the other hand, the current formal recommendation from the clinical practice guidelines of not pretreating systematically with a P2Y12 inhibitor in patients on early invasive treatment is mainly based on 3 clinical trials and their meta-analysis. In the ACCOAST trial, pretreatment with prasugrel did not reduce thrombotic events in patients with NSTEMI. However, cardiac surgery-related and potentially fatal hemorrhages increased. We should mention that the median time elapsed since the prasugrel loading dose was received in the non-pretreatment group was 60 minutes. Finally, the first study that compared 2 different pretreatment strategies vs the intraoperative administration of ticagrelor did not show any clear benefits regarding thrombosis or a deleterious effect of pretreatment regarding bleeding. Once again, the median time elapsed until the cardiac catheterization was performed was <24 hours since hospital admission (23 hours). Surprisingly, clinical practice guidelines leave the door opened to a weak level of recommendation (IIbC) regarding pretreatment of patients in whom early catheterization < 24 hours is not possible.

In conclusion, current recommendations on early invasive treatment and no antiplatelet pretreatment in patients with NSTEACS are controversial and can also be difficult to implement in the routine clinical practice in our setting. The ultimate objective of the IMPACT-TIMING-GO registry is to shed light on the current management of NSTEACS in Spain. After the impact that the COVID-19 pandemic has had on the general structure of the healthcare system and the drop in the number of interventional procedures performed in 2020, we should expect to see pre-pandemic numbers in 2022 and cath labs and cardiac surgery intensive care units going back to normal. Therefore, moment seems ripe to conduct a real-world registry.

CONCLUSIONS

The IMPACT-TIMING-GO registry is the first prospective study ever conducted in Spain that will be giving us information on the early therapeutic strategies—both pharmacological and interventional—performed in our country in patients with NSTEACS after the publication of the ESC guidelines 2020, and the impact of these and other measures indicated in these patients at follow-up.

FUNDING

This unfunded study has been promoted by the Spanish Society of Cardiology Young Cardiologists Working Group with scientific endorsement from the Spanish Society of Cardiology.

AUTHORS’ CONTRIBUTIONS

Study design, data curation and review, statistical analysis, and manuscript drafting: F. Díez-Delhoyo, F. Díez-Villanueva, F. Díez-Delhoyo, and M.T. López-Lluva. All the authors participated in the manuscript review and approval process.
CONFLICTS OF INTEREST

None reported.

ACKNOWLEDGEMENTS

We wish to thank the Spanish Society of Cardiology Young Cardiologists Working Group for their drive to engage the youth in medical research.

WHAT IS KNOWN ABOUT THE TOPIC?

– The management of patients with NSTEACS includes dual antiplatelet therapy with a P2Y₁₂ inhibitor and, in most cases, invasive approach through cardiac catheterization for further revascularization. The current ESC clinical practice guidelines recommend early invasive approach (<24 hours) and no pretreatment systemically though both aspects are still controversial.
– The degree of implementation of such recommendations in the routine clinical practice, in Spain, is still unknown.

WHAT DOES THIS STUDY ADD?

– This study will improve our knowledge on early therapeutic approach, and its prognostic impact in patients admitted due to NSTEACS in Spain.
– Also, it will bring us information on the characteristics and clinical evolution of these patients in association with the recommendations and therapeutic targets we have today.

REFERENCES

High rate of uncovered struts in latest generation drug-eluting stents with durable, biodegradable polymer or lack of it 1 month after implantation

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ABSTRACT

Introduction and objectives: Delayed vascular healing may induce late stent thrombosis. Optical coherence tomography (OCT) is useful to evaluate endothelial coverage. The objective of this study was to compare stent coverage and apposition in non-complex coronary artery lesions treated with durable polymer-coated everolimus-eluting stents (durable-polymer EES) vs biodegradable polymer-coated everolimus-eluting stents (biodegradable-polymer EES) vs polymer-free biolimus-eluting stents (BES) 1 and 6 months after stent implantation.

Methods: Prospective, multicenter, non-randomized study that compared the 3 types of DES. Follow-up angiography and OCT were performed 1 and 6 months later. The primary endpoint was the rate of uncovered struts as assessed by the OCT at 1 month.

Results: A total of 104 patients with de novo non-complex coronary artery lesions were enrolled. A total of 44 patients were treated with polymer-free BES, 35 with biodegradable-polymer EES, and 25 with durable-polymer EES. A high rate of uncovered struts was found at 1 month with no significant differences reported among the stents (80.2%, polymer-free BES; 88.1%, biodegradable-polymer EES; 82.5%, durable-polymer EES; \( P = .209 \)). Coverage improved after 6 months in the 3 groups without significant differences being reported (97%, 95%, and 93.7%, respectively; \( P = .172 \)).

Conclusions: In patients with de novo non-complex coronary artery lesions treated with durable vs biodegradable vs polymer-free DES, strut coverage and apposition were suboptimal at 1 month with significant improvement at 6 months.

Keywords: Optical coherence tomography. Drug-eluting stents. Endothelization. Apposition. Restenosis.

Alta tasa de struts no cubiertos en stents de última generación con polímero persistente, absorbible o sin polímero a un mes del implante

RESUMEN

Introducción y objetivos: A pesar del desarrollo de los stents farmacoactivos, el retraso en la endotelización puede causar trombosis tardía. La tomografía de coherencia óptica puede evaluar la cobertura intimal. El objetivo de este estudio fue comparar la cobertura y la aposición en lesiones coronarias no complejas de 3 tipos de stent: stent de everolimus con polímero persistente, stent de everolimus con polímero bioabsorbible y stent de biolimus sin polímero, a 1 y 6 meses del implante.

Métodos: Se diseñó un estudio prospectivo, multicéntrico, no aleatorizado, que comparó 3 stents farmacoactivos. Se realizaron angiografía y tomografía de coherencia óptica a 1 o 6 meses. El objetivo primario fue comparar la cobertura.

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INTRODUCTION

Uncovered stent struts is one of the key predictors of stent thrombosis, and dual antiplatelet therapy (DAPT) has shown to reduce its risk. However, DAPT increases the risk of hemorrhage, and nearly one third of the patients treated with percutaneous coronary intervention (PCI) are considered at high bleeding risk. Given the desire for earlier discontinuation of DAPT to reduce the risk of bleeding complications, healing of the stents at earlier time points is desirable.

Drug-eluting stents (DES) significantly reduce neointimal hyperplasia and restenosis compared to bare-metal stents (BMS). However, the main concern regarding first-generation DES was late stent thrombosis due to lack of endothelialization of stent struts. Therefore, a new generation of DES was developed based on improved thinner metal platforms, new drugs (alternative antiproliferative –limus analogues), and more biocompatible polymers. The evolution of DES moved towards DES with biodegradable polymers. The comparative studies between DES with biodegradable polymers and BMS showed a lower rate of cardiac death, target vessel-related myocardial infarction, and revascularization at 1 year. Compared to biodegradable polymer DES, those with durable polymer were noninferior regarding acute coronary syndromes with respect to all-cause mortality, nonfatal myocardial infarction, and revascularization. Furthermore, the most recent advance to overcome stent thrombosis has been the polymer-free DES. This type of DES was initially designed to reduce the risk of stent thrombosis in patients with high bleeding risk who could only take short courses of DAPT. It was compared to BMS showing a better efficacy and safety profile. It has recently been compared to DES in large clinical trials, especially in patients with high bleeding risk and need for shorter DAPT courses. In these studies, the use of polymer-based zotarolimus-eluting stent was noninferior to polymer-free DES, and non-measurable differences in device-oriented composite primary endpoints were found.

However, despite these large clinical trials, there is scarce information on the difference between the characteristics of arterial healing among different types of latest generation DES. Optical coherence tomography (OCT) is a widely used high-resolution intracoronary imaging modality to assess vascular response after stent implantation, thus detecting stent strut coverage and its apposition to the vessel wall. Stent strut coverage as studied by the OCT is considered a valuable surrogate marker for vessel healing after DES implantation.

The objective of this study was to compare durable polymer-coated everolimus-eluting stents (durable-polymer EES) vs biodegradable polymer-coated everolimus-eluting stents (biodegradable-polymer EES) vs polymer-free BES using stent strut coverage as assessed by the optical coherence tomography (OCT) as a surrogate marker to evaluate short-term arterial healing.

METHODS

Patient population and data collection

This was a prospective, multicenter, non-randomized study that compared 3 different types of DES: a) the durable polymer-coated everolimus-eluting stent Xience DES (Abbott, United States); b) the biodegradable polymer-coated everolimus-eluting stent Synergy DES (Boston Scientific, United States), and c) the polymer-free BES Biofreedom DES (Biosensors International Ltd, Singapore). The study was conducted at 4 Spanish teaching hospitals.

A total of 144 patients were consecutively recruited from January 2018 through December 2019. Patients were eligible if they had been admitted due to stable coronary artery disease or acute coronary syndrome without cardiogenic shock. The medical team selected the type of stent that should be implanted. The detailed study flowchart is shown on figure 1. Inclusion criteria were a) de novo lesions; b) ≥ 1 target lesions in the same or different coronary artery; c) no need for stent overlapping, and a 10 mm minimal distance between the stents; d) stent length between 8 mm and 30 mm; e) use of stents with diameters ≥ 2.5 mm. Exclusion criteria were a) complex lesions including ostial lesions, chronic total coronary occlusions, calcified lesions requiring calcium modification techniques, and bifurcations requiring the kissing balloon technique; b) target lesions in small vessels (< 2.5 mm) and long lesions (> 30 mm) requiring small diameter stents [2.25 mm] or overlapping stents; c) diabetic patients; d) very tortuous arteries that anticipated the impossibility of access with the OCT catheter for follow-up purposes; and e) complications during index procedure. Patients with diabetes mellitus were excluded from the study because of their pro-inflammatory status that facilitates both stent thrombosis and restenosis.
Once recruited, patients were consecutively assigned to a 1- or 6-month OCT follow-up group. The baseline characteristics, angiographic and procedural data, follow-up data, and outcome data were prospectively collected by the study coordinators. Clinical data at follow-up were obtained from the clinical records. This study was performed following the principles established by the Declaration of Helsinki, ISO14155, and the clinical practice guidelines. The study protocol was approved by the Institutional Ethics Committee (IEC) and the hospital research committee. Informed consent was obtained from all the patients.

Percutaneous coronary intervention, angiographic analysis, and optical coherence tomography

In the index procedure stents were implanted according to the standard approach. Patients were medically treated following the European guidelines on the management of chronic ischemic heart disease or acute coronary syndrome.

Regarding the initial angiographic analysis, 2 orthogonal projections without coronary guidewire were obtained after finishing the index procedure. These same projections were acquired at follow-up. The off-line analysis of the angiographic images (quantitative coronary angiography [QCA], [Barcelona Cardiac Imaging Core-Lab [BARCICORElab]], following their standard protocol. They used a dedicated software (CAAS, version 5.9; Pie Medical BV, The Netherlands). Methods used in this core lab have been previously reported.

The follow-up angiography was performed at 1-or-6-month follow-up. Angiographic and OCT images were obtained from each patient. The Dragonfly frequency domain OCT C7-XR system (St. Jude Medical, United States) was used. This analysis was performed at the same independent core lab with a dedicated software (St. Jude Medical). Further information can be found on the supplementary data. The struts were classified as non-covered if their surface was totally or partially exposed to the lumen, and without any tissue coverage above its high-density scaffold. Stent strut apposition was defined as the perpendicular distance between the luminal edge of the strut and the vascular wall. Incomplete apposition was considered when distance was higher compared to the total strut thickness considering the addition of strut plus polymer. Intimal hyperplasia was measured as the perpendicular distance between the luminal surface of the stent strut and the luminal surface of the neointima.

Endpoints

The study primary endpoint was the percentage of uncovered struts among durable-polymer EES vs biodegradable-polymer EES vs polymer-free BES as seen on the OCT at 1 month.

The study secondary endpoint was to compare the coverage and apposition of these 3 different types of DES on the OCT 1 vs 6 months after implantation. In addition, we evaluated the intimal hyperplasia in the 3 stent groups over time.

Statistical analysis

Continuous variables were expressed as mean and standard deviation except when they did not follow normal distribution, in which case they were expressed as median and 25th-75th percentile. Categorical variables were expressed as frequency and percentage. The analysis of the clinical differences was performed using the chi-square test or Fisher’s exact test for qualitative variables. Comparison among quantitative variables was performed using the 1-way ANOVA test. Generalized estimating equations, considering the clustering nature of the OCT data, were used to conduct analyses at strut level. All probability values were two-sided, $P$ values < .05 were considered statistically significant. Statistical analysis was performed using the SPSS software package, version 22.0 [SPSS, United States]. The sample size estimate is shown on the supplementary data.

RESULTS

Baseline clinical characteristics

A total of 104 patients from 4 different hospitals were included in the study: 44 patients were treated with a polymer-free BES, 35 with a biodegradable-polymer EES, and 25 patients with a durable-polymer EES. Of these, 37 patients underwent follow-up angiography and OCT 1 month after DES implantation, and 67 patients after 6 months. Mean age was 57 years; most patients were men [11% women]. The inter-group baseline clinical characteristics are shown on table 1 according to the type of stent implanted. We observed a statistically significant difference in the left ventricular ejection fraction that was slightly lower in patients who received a polymer-free BES [54% vs 60%]. The number of patients who needed postdilation was higher in the durable-polymer EES group [68%] especially compared to the polymer-free BES group [38%].
Procedural and lesion characteristics

Procedural characteristics based on the type of stent implanted are shown on Table 1. We found no significant differences in stent diameter or length in the 3 stent groups. The left anterior descending coronary artery was the most treated of all whereas secondary arteries were scarcely included in this study.

Angiographic analysis

The lesion angiographic characteristics are shown on Table 2 and Table 1 of the supplementary data. There were 2 patients with angiographic images with insufficient quality for analysis, 2 from the polymer-free BES, 3 from the biodegradable-polymer EES group, and 1 from the durable-polymer EES group. Stent strut coverage and apposition were analyzed, as well as neointimal hyperplasia. Overall, 15,906 struts were examined. Of these, 4380 struts were from durable-polymer EES; 5122 from biodegradable-polymer EES; and 6404 from polymer-free BES; 6184 and 9722 struts were analyzed at 1 and 6 months, respectively.

A high rate of uncovered struts was found among stents 1 month after implantation, with no significant differences ($P = .209$). We observed ≥ 5% of uncovered struts in > 80% of the patients. There was better coverage in the 3 stent groups at 6 months compared to 1 month ($P < .001$ polymer-free BES; $P = .007$ biodegradable-polymer EES; $P = .001$ durable-polymer EES). No statistically significant differences were reported in strut coverage at 6 months among the different stents ($P = .172$) (Figure 2, Figure 3A).

Regarding strut apposition to the artery walls, no significant differences were reported among the 3 stents after 1 month ($P = .497$). We observed ≥ 5% of malapposed struts in 29% to 30% of the patients with no differences among stents. No significant differences were reported among the stents after 6 months either. The rate of apposition was higher at 6 months compared to 1 month in all stent groups ($P < .001$ polymer-free BES; $P = .001$ biodegradable-polymer EES; $P = .029$ durable-polymer EES) (Figure 2, Figure 3B).

OCT outcomes

OCT results are shown on Table 3, and Table 2 in the supplementary data. There were 6 patients with OCT images with insufficient quality for analysis, 2 from the polymer-free BES, 3 from the biodegradable-polymer EES group, and 1 from the durable-polymer EES group. Stent strut coverage and apposition were analyzed, as well as neointimal hyperplasia. Overall, 15,906 struts were examined. Of these, 4380 struts were from durable-polymer EES; 5122 from biodegradable-polymer EES; and 6404 from polymer-free BES; 6184 and 9722 struts were analyzed at 1 and 6 months, respectively.

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**Table 1. Baseline clinical, lesion, and procedural characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Polymer-free BES (N = 44)</th>
<th>Biodegradable-polymer EES (N = 35)</th>
<th>Durable-polymer EES (N = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 ± 8</td>
<td>61 ± 9</td>
<td>59 ± 10</td>
<td>.094</td>
</tr>
<tr>
<td>Women</td>
<td>3 (7)</td>
<td>4 (11)</td>
<td>4 (16)</td>
<td>.462</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>24 (55)</td>
<td>19 (54)</td>
<td>14 (56)</td>
<td>.990</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (39)</td>
<td>14 (40)</td>
<td>13 (52)</td>
<td>.527</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>10 (23)</td>
<td>4 (11)</td>
<td>6 (24)</td>
<td>.353</td>
</tr>
<tr>
<td>Smoker</td>
<td>26 (59)</td>
<td>13 (37)</td>
<td>9 (38)</td>
<td>.076</td>
</tr>
<tr>
<td>LVEF %</td>
<td>54 ± 9</td>
<td>60 ± 9</td>
<td>60 ± 8</td>
<td>.006</td>
</tr>
<tr>
<td>Chronic kidney disease (creatinine &gt; 1.5 mg/dL)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>.370</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2 (5)</td>
<td>7 (20)</td>
<td>4 (12)</td>
<td>.102</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2 (5)</td>
<td>6 (17)</td>
<td>4 (16)</td>
<td>.159</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>.526</td>
</tr>
</tbody>
</table>

Target lesion location

<table>
<thead>
<tr>
<th></th>
<th>Polymer-free BES (N = 44)</th>
<th>Biodegradable-polymer EES (N = 35)</th>
<th>Durable-polymer EES (N = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending coronary artery</td>
<td>18 (41)</td>
<td>10 (29)</td>
<td>11 (44)</td>
<td>.101</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>10 (23)</td>
<td>8 (23)</td>
<td>19 (40)</td>
<td>.527</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>15 (34)</td>
<td>13 (37)</td>
<td>4 (16)</td>
<td>.006</td>
</tr>
<tr>
<td>Secondary artery (diagonal, posterolateral, posterior descending)</td>
<td>1 (2)</td>
<td>4 (11)</td>
<td>0 (0)</td>
<td>.006</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>18.6 ± 5</td>
<td>18.8 ± 6</td>
<td>19.5 ± 6</td>
<td>.769</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.4 ± 0.8</td>
<td>3.1 ± 0.5</td>
<td>3.1 ± 0.4</td>
<td>.053</td>
</tr>
<tr>
<td>Predilatation, %</td>
<td>19 (43)</td>
<td>16 (73)</td>
<td>13 (53)</td>
<td>.076</td>
</tr>
<tr>
<td>Postdilatation, %</td>
<td>16 (38)</td>
<td>12 (57)</td>
<td>17 (68)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Data are expressed as no. (%) or mean ± standard deviation.

BES, biolimus-eluting stent; CABG, coronary artery bypass grafting; EES, everolimus-eluting stent; LVEF, left ventricle ejection fraction; MI, myocardial infarction; PCI, percutaneous intracoronary intervention; SD, standard deviation.
Table 2. Angiographic analysis

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Polymer-free BES (N = 44)</th>
<th>Biodegradable-polymer EES (N = 35)</th>
<th>Durable-polymer EES (N = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month follow-up</td>
<td>(N = 7)</td>
<td>(N = 16)</td>
<td>(N = 12)</td>
<td></td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>17.85 ± 4.32</td>
<td>19.24 ± 5.63</td>
<td>19.39 ± 4.41</td>
<td>.788</td>
</tr>
<tr>
<td>Reference lumen diameter, mm</td>
<td>2.93 ± 0.60</td>
<td>2.80 ± 0.53</td>
<td>2.77 ± 0.55</td>
<td>.827</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.75 ± 0.46</td>
<td>2.65 ± 0.50</td>
<td>2.51 ± 0.49</td>
<td>.586</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>0.03 ± 0.09</td>
<td>0.04 ± 0.10</td>
<td>0.03 ± 0.08</td>
<td>.985</td>
</tr>
<tr>
<td>Percentage diameter stenosis, %</td>
<td>5.57 ± 6.27</td>
<td>6.50 ± 7.14</td>
<td>8.67 ± 9.27</td>
<td>.658</td>
</tr>
</tbody>
</table>

Table 3. Optical coherence tomography analysis

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Polymer-free BES</th>
<th>Biodegradable-polymer EES</th>
<th>Durable-polymer EES</th>
<th>P*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-month (N = 7)</td>
<td>6-months (N = 35)</td>
<td>1-month (N = 17)</td>
<td>6-months (N = 15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N = 1242)</td>
<td>(N = 5162)</td>
<td>(N = 2673)</td>
<td>(N = 2449)</td>
<td></td>
</tr>
<tr>
<td>Strut level analysis</td>
<td>&lt; .001</td>
<td></td>
<td>&lt; .007</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Uncovered struts, n</td>
<td>238 (19.2)</td>
<td>154 (3.0)</td>
<td>318 (11.9)</td>
<td>123 (5.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Malapposed struts, n</td>
<td>66 (5.3)</td>
<td>13 (0.3)</td>
<td>101 (3.8)</td>
<td>21 (0.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Neointimal thickness, µm</td>
<td>50.7 ± 41.9</td>
<td>138.1 ± 102.9</td>
<td>59.9 ± 45.1</td>
<td>80.3 ± 83.9</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Data are expressed as no. (%) or mean ± standard deviation. BES, biolimus-eluting stent; EES, everolimus-eluting stent.

DISCUSSION

The main findings of this prospective multicenter registry are: a) in non-diabetic patients with de novo non-complex coronary lesions treated with durable vs biodegradable vs polymer-free DES, strut coverage was similar and low (> 5% of uncovered struts in > 80% of patients) at 1 month; b) there was a similar high rate of malapposed struts (4% to 6%) at 1 month; c) intimal coverage and apposition improved significantly at 6 months; d) polymer-free BES had higher intimal hyperplasia at 6 months.

When we analyzed neointimal hyperplasia, no significant differences were found at 1 month among the 3 stent groups (P = .083). At 6 months, we found higher hyperplasia in the polymer-free BES compared to the durable-polymer EES (P < .001). We found more hyperplasia at 6 months compared to 1 month in all groups (P < .001 polymer-free BES; P < .001 biodegradable-polymer EES; P = .005 durable-polymer EES; figure 2).

Several small-scale OCT studies have been performed to compare the coverage and apposition of stents with permanent and absorbable polymers. Conclusions of these studies differ with most of them stating that the absorbable polymer stent has better coverage than the permanent polymer, and 1 of them concluding the opposite. One of the studies found coverage to be sufficient after 3 months, whereas another stated that coverage improved at 12 months. In this study, we found no significant differences in stent strut coverage or apposition between permanent and absorbable polymer at 1 or 6 months on the OCT analysis (figure 2). Differences in stent strut coverage at follow-up may in part be explained by the stent platform, the polymers used to control drug release, and the antiproliferative drug itself. The stents of the study had a similar drug- (limus analogue) but different polymeric features (durable vs biodegradable vs polymer-free), and different platform thickness (the polymer-free BES had a thicker platform). Probably within the first month the drug effect is most important, and it was
neointimal hyperplasia at 6 months among stents. 

Accordingly, other studies have analyzed other types of polymer-free stents different to the one from our study. They found that coverage was achieved in a high percentage at 3 to 9 months, reaching conclusions that were similar to our study. One of the studies performed an OCT at 1, 3, and 9 months, demonstrating higher strut coverage over time, which is consistent with our results. Only 1 study analyzed the Biolimus A9 polymer-free stent with OCT without comparing it to other stents. It was a prospective single-center single-armed study that examined strut coverage of the Biolimus A9 polymer-free stent at 1, 2, 3, 4, 5, and 9 months. Researchers found that coverage was fast and improved over time with the stent remaining safe and effective. These results are similar to ours in the sense that coverage was significantly better at 6 months. However, we also compared polymer-free stents to other polymer-based stents, something that, to the best of our knowledge, has not been tested before.

One of the limitations of extrapolating the clinical safety of the stents and the degree of intimal coverage as seen on the OCT is that there is no consensus on the cut-off value of coverage that would allow safe discontinuation of DAPT. Few studies have tried to decide on a percentage of coverage, with the only in-vivo study estimating that > 5.9% of uncovered struts was an independent risk factor for stent thrombosis. However, these studies were limited in the number of patients included, and only some stents were tested. Larger studies are needed to decide on a security threshold for strut coverage that would make it safe to stop DAPT without increasing the risk of stent thrombosis. Therefore, the rate of coverage at 1 month (80% to 88%) in our study seems insufficient, reaching a very high percentage after 6 months (94% to 97%) in the 3 types of stents.

Finally, our study shows that intimal hyperplasia was significantly higher in polymer-free stents at 6 months. Polymer-free Biolimus A9 has a stainless steel and thicker platform, which has been associated with more intimal hyperplasia and in-stent restenosis in previous studies. The other 2 types of DES have a cobalt-chromium platform which has largely substituted stainless steel to provide sufficient strength and visibility with thinner struts of around 70-90 μm, resulting in lower rates of angiographic and clinical restenosis. Thus, inflammatory response to this thicker stent platform (130-140 μm) could be in part responsible for this finding.

Study limitations

This was an OCT-based study; unfortunately, it was not powered to assess clinical outcomes. Our study was non-randomized. However, we minimized the confounding factors through selected inclusion/exclusion criteria for patients and lesions (non-diabetic patients with non-complex coronary lesions). We analyzed the differences among the groups and no significant differences were found, except in the left ventricular ejection fraction, which was significantly lower in the group of polymer-free stents. It has not been described in the medical literature whether a lower left ventricular ejection fraction has any correlation with stent thrombosis. This study included selected non-diabetic patients with simple coronary artery lesions. Therefore, the conclusions cannot be extrapolated to other groups with different characteristics.

The distribution of patients who underwent the follow-up angiography in the polymer-free DES group at 1 or 6 months was uneven.
More patients rejected the follow-up angiography at 1 month in the polymer-free DES group, which may account for this difference. Finally, the complexity of the analysis of 3 different groups in 2 different moments of time caused a disgregation of cases. This led to a small N in each group, with the potential biases associated.

CONCLUSIONS

In non-diabetic patients, a significantly high percentage of uncovered struts was detected at 1 month with OCT in latest generation DES regardless of the polymeric features of the stent (durable vs biodegradable vs polymer-free stent) in the non-complex coronary artery lesion setting. Our OCT findings do not support improved short-term healing characteristics of stents with biodegradable polymer or polymer-free based -imus elution compared to current generation of durable polymer DES.

FUNDING

This study received funding from Abbott Vascular and Biosensors International. Funders were not involved in the study design, collection, analysis, interpretation of data, drafting of this article or decision to submit it for publication.

AUTHORS’ CONTRIBUTIONS

A. Calvo-Fernández, R. Elosua, and B. Vaquerizo designed the study. J. Gómez-Lara, Héctor Cubero-Gallego, Helena Tizón-Marcos,
WHAT IS KNOWN ABOUT THE TOPIC?

- Current DES with biodegradable polymer coating or the new polymer-free bioresorbable stent have been proposed as the optimal solution to the problem of delayed coronary artery healing characteristics seen with first-generation durable polymer-coated DES.

WHAT DOES THIS STUDY ADD?

- This multicenter registry compared 3 types of DES with similar drug elution (−limus analogue), but different stent polymeric features (durable vs biodegradable vs polymer free).

- Using the percentage of uncovered struts at short term assessed by optical coherence tomography as a surrogate endpoint, healing characteristics at 1 month were similar among stents and insufficient after 1 month.

- Our findings do not support a preferential use of stents with biodegradable polymer-based or polymer-free stents to reduce the time of dual antiplatelet therapy at 1 month.

CONFLICTS OF INTEREST

J.M. de la Torre Hernandez is an associate editor of REC: Interventional Cardiology; the journal’s editorial procedure to ensure impartial handling of the manuscript has been followed; he has received grants and research support from Abbott Medical, Biosensors, Bristol Myers Squibb, Amgen; honoraria or consultation fees from Boston Scientific, Medtronic, Biotronik, Astra Zeneca, Daiichi-Sankyo. N. Salvatella has received teaching honoraria from Abbott Vascular, and consultation fees from Boston Scientific. The remaining authors declared no other competing interests.


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REFERENCES


Ischemic postconditioning fails to reduce infarct size in pig models of intermediate and prolonged ischemia

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ABSTRACT

Introduction and objectives: Ischemic postconditioning (iPost, coronary intermittent re-occlusion maneuvers immediately after PCI-mediated reperfusion) has been proposed to limit infarct size (IS). However, a few experimental and clinical contradictory results have been reported. We hypothesized that iPost cardioprotection is affected by the duration of ischemia. Our objective was to assess IS in the presence/absence of iPost in a pig model of myocardial infarction of variable ischemia duration.

Methods: Large white pigs (n = 38) underwent angioplasty balloon-induced coronary ischemia followed by reperfusion. Two set of experiments were carried out: intermediate [30 min] and prolonged [40 min] ischemia. In both, pigs were allocated on a 1:1 ratio to receive iPost (4 cycles of “1 min balloon inflation followed by 1 min deflation” upon reperfusion) or control. Animals underwent contrast-enhanced multiparametric cardiac magnetic resonance scan on day 7. Primary outcome measure was cardiac magnetic resonance-based IS (% of left ventricular mass). The interaction between treatment allocation and ischemia duration was assessed using a 2-way ANOVA test.

Results: iPost was not associated with smaller IS in any of the ischemia duration protocols [intermediate ischemia: 0.3% [0.0–3.9] vs 0.9% [0.0–2.6] in iPost and control, respectively; P = .378; long ischemia: 31.1% [27.3–32.8] vs 27.3% [25.1–27.5]; P = .248]. When both ischemia-duration protocols were combined, iPost was not associated with smaller IS (3.9% [0.0–30.9] vs 4.6% [0.2–25.1]; P = .672). T1 relaxation times were longer in animals undergoing iPost compared to controls (1306.2 ms [1190.7–1492.7] vs 1240.7 ms [1167.1–1304.5]; P = .024).

Conclusions: In a pig model of reperfused myocardial infarction of variable ischemia duration, iPost failed to reduce IS. T1 relaxation times were longer in animals undergoing iPost indicative of the potential harm involved in this procedure.

Keywords: Reperfusion injury. Ischemic postconditioning. Cardioprotection. Myocardial infarction.

El poscondicionamiento local no reduce el tamaño de infarto en modelos porcinos de infarto agudo de miocardio de intermedia y larga duración

RESUMEN

Introducción y objetivos: Existen resultados contradictorios sobre la eficacia del poscondicionamiento isquémico local [iPost] como intervención para reducir el tamaño del infarto [TI]. Pretendemos evaluar si el efecto del iPost se ve alterado por el tiempo de isquemia en un modelo porcino de infarto de miocardio.

Métodos: Se sometió a 38 cerdos Large-White a isquemia-reperfusion coronaria con balón de angioplastia. Se realizaron dos series de experimentos: isquemia de intermedia [30 minutos] y larga [40 minutos] duración. Los animales se asignaron 1:1 a iPost [4 ciclos de 1 minuto inflado/1 minuto desinflado, comenzando 1 minuto tras la reperfusión] o control. Se realizó una resonancia magnética...
INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a life-threatening condition that affects more than 7 million people worldwide each year.\(^1\) Despite the improved short-term survival and reduced need for repeat revascularization achieved with primary percutaneous coronary intervention (PCI), long-term survival, and the rate of heart failure (HF) have barely improved over the last few years.\(^2\)

Infarct size (IS), the extent of irreversible injury after MI, is a main contributor to long-term mortality and HF in STEMI survivors.\(^3,4\) Therefore, there is a strong need for identifying interventional (invasive) and/or pharmacological strategies than can limit the extent of MI. Upon coronary occlusion, there is a time-dependent progression of irreversible injury.\(^6\) Therefore, timely restoration of blood flow (reperfusion) in the ischemic region is of paramount importance to reduce IS and improve the left ventricular ejection fraction (LVEF).\(^7\) However, reperfusion per se causes additional damage to the myocardium and microcirculation that contributes to the final IS,\(^9\) the so-called ischemia/reperfusion injury (IRI).\(^9\)

Ischemic postconditioning (iPost) is an interventional cardiology procedure that tested extensively in experimental\(^10\) and clinical trials.\(^11-14\) IPost is based on the idea that after index ischemia, gentle reperfusion results in less damage than abrupt straight reperfusion.\(^14\) This procedure has the great advantage of its easy implementation during primary percutaneous intervention (PCI). It consists of intermittent 1-min brief episodes of coronary flow reocclusion (ie, angioplasty balloon reinflation).

There is controversy though with some studies showing strong cardioprotection through iPost,\(^11\) while others disagree.\(^12\) One potential explanation for these controversial results is that iPost is only protective in cases where previous ischemic time has not been very prolonged.

To address whether iPost has variable cardioprotective effects depending on ischemic time, we performed a controlled experimental study in which pigs undergoing different times of coronary ischemia are allocated to iPost or control. We used state-of-the-art technology (ie, cardiac magnetic resonance [CMR]) to accurately assess the effect of the procedure on cardioprotection.

METHODS

Studies were approved by Institutional and Regional Animal Research Committees.

Study design

The cardioprotection provided by iPost was tested in 2 different sets of experiment groups: intermediate ischemia duration (30 min) followed by reperfusion, and prolonged ischemia (40 min) followed by reperfusion. All animals underwent a multiparametric CMR scan 1 week after MI. This timing regarding the assessment of the effect of the intervention was chosen since it is the recommended one by international expert consensus.\(^5\) Selecting between the intermediate or prolonged ischemic time was based on our previous experiments where we saw that ischemia durations of < 30 min lead to very small IS (< 20% of the area at risk [AAR]) yielding no window for cardioprotection of established pharmacological interventions (eg, metoprolol).\(^12\) Similarly, in our experimental setting, ischemia durations > 40 min result in very large IS (> 80% of the AAR) thus reducing the window for cardioprotection.\(^15\)

Following the 3Rs principle to reduce the use of animals, those on prolonged ischemia (40 min) with/without iPost (as well as the CMR data) were the ones already used in a former article with a different objective.\(^24\) In this study, the group of animals undergoing intermediate ischemia duration (30 min) with/without iPost (n = 28) were used ad hoc.

Apart from ischemia duration, the study protocol was equal for both ischemia–duration groups. For these experiments, we employed 3-month-old castrated male large white pigs weighing 30 to 40 Kg. Pigs were allocated to iPost or control before MI was induced. Myocardial AAR was assessed through multidetector computed tomography immediately after vessel occlusion following a previously published methodology.\(^25\) Seven days after the MI, all
animals underwent a multiparametric CMR scan to assess IS (primary outcome measure), LVEF, and T2 and T1 relaxation times both in the AAR and in the remote area [figure 1].

**Anesthesia and animal care protocol**

Every test or experiment was performed under deep sedation. Sedation was induced through the intramuscular injection of ketamine (20 mg/Kg), xylazine (2 mg/Kg), and midazolam (0.5 mg/Kg); and maintained through the continuous infusion of ketamine (2 mg/Kg/h), xylazine (0.2 mg/Kg/h), and midazolam (0.2 mg/Kg/h). Buprenorphine (0.03 mg/Kg) was administered immediately before the MI experiment.

Animals were intubated and received mechanical ventilatory support with volume-control synchronized intermittent mandatory ventilation (fraction of inspired oxygen = 28%).

To avoid coronary thrombosis following balloon-induced MI induction, animals received 150 mg of clopidogrel orally on the day of the procedure and 75 mg 24 and 48 hours later. All animals were euthanized immediately after the day-7 CMR scan.

**Myocardial infarction and ischemic postconditioning protocol**

All animals underwent the same closed-chest ischemia-reperfusion protocol consisting of 30-min or 40-minute left anterior descending coronary artery occlusion with a monorail angioplasty balloon inserted percutaneously through the femoral artery. Balloon was inflated at 8 atm immediately distal to the first diagonal branch. Both the location of the balloon and the status of inflation were monitored on the angiography. A single intra-arterial bolus of 300 IU/Kg of unfractionated heparin was administered right before coronary occlusion. Furthermore, to reduce the rate of fatal ventricular arrhythmias, continuous infusion of amiodarone (300 mg/h, no bolus) was initiated immediately after coronary occlusion and maintained until catheters were removed.

Pigs were allocated on a 1:1 ratio to iPost or control before MI induction. After index ischemia duration [30 min or 40 min according to the protocol], animals allocated to control underwent straight chronic reperfusion [balloon deflation] while animals allocated to iPost underwent balloon deflation but 1 min after balloon was reinfated for 1 min. iPost was induced by repeating the 1 min inflation-1 min deflation cycle 4 times. Artery patency was assessed after every inflation/deflation cycle.
Arterial enhanced multidetector computed tomography protocol and analysis

Multidetector computed tomography (MDCT) arterial phase studies were performed during ongoing ischemia on a 64-slice computed tomography scanner (Brilliance CT 64; Philips Healthcare, Cleveland, OH, United States) after the IV administration of iodinated contrast media. Since the MDCT scan was performed during ongoing ischemia (ie, while the balloon was inflated), non-enhanced regions accurately represent the ischemic region (ie, the AAR). MDCT images were analyzed using dedicated software (Extended MR Workspace 2.6; Philips Healthcare, The Netherlands) by 2 observers who remained blind to group allocation. Short axes orientation was obtained from volumetric computed tomography images through multiplanar reconstruction. AAR and remote areas were visually identified based on contrast enhancement differences, manually delineated, and expressed as a percentage of left ventricular (LV) area.15,16

Cardiac magnetic resonance protocol

CMR scans were performed 7 days after the MI on a Philips 3-Tesla Achieva Tx whole-body scanner (Philips Healthcare, The Netherlands) equipped with a 32-element phased-array cardiac coil. The imaging protocol included a standard segmented cine imaging with a steady-state free-precession sequence to provide high-quality anatomic references and assessment of the left ventricular mass, wall thickness, and LVEF, a T1-mapping sequence (modified Look-Locker inversion recovery) to assess T1 native relaxation time, a T2 mapping based on gradient-spin-echo imaging to provide precise myocardial T2 relaxation time,17 and a T1-weighted inversion relaxation turbo field echo sequence acquired 10 min to 15 min after the administration of gadolinium contrast (late gadolinium enhancement, LGE) to assess IS. CMR images were analyzed using dedicated software (MR Extended Workspace 2.6; QMassMR 7.6; Medis, The Netherlands and IntelliSpace Portal, Philips Healthcare, The Netherlands) by 2 experienced observers in CMR analysis and blinded to group allocation.

Statistical analysis

Normal distribution of data was assessed using the Shapiro-Wilk test. Quantitative variables were expressed as median [interquartile range]. Categorical variables were expressed as numbers and percentage and rounded to the nearest integer. A 2-way ANOVA test was run on the overall sample with CMR performed on day 7 (29 pigs) to examine the effect of ischemia time and iPost on primary and secondary outcomes (IS, % LV mass), IS indexed to the AAR, LVEF, T2 relaxation time, and native T1 relaxation time). Regarding variables where we found a significant interaction between the duration of ischemia and iPost, we performed a post hoc analysis (Tukey’s method) to confirm the differences seen. We estimated the sample size based on our previous experiments on cardioprotection with metoprolol.15 Lost animals were replaced to achieve the required sample size.

RESULTS

Study groups

Intermediate-ischemia protocol (30 min)

As shown on figure 1, 28 animals underwent MI induction after replacing the lost subjects. From the 16 pigs allocated to control, 3 [19%] died during ischemia induction, and 3 [19%] suddenly died before the day-7 CMR scan. One (10%) out of the 10 animals that completed the day-7 CMR protocol was excluded from the analysis due to poor image quality.

Zero out of the 12 pigs allocated to iPost died during MI induction [0%] while 1 (8%) suddenly died before the CMR scan. One [9%] out the 11 animals that completed the day-7 CMR was excluded from the analysis due to poor image quality.

Therefore, the final population available for outcome assessment was 19 [9 controls, and 10 iPost, figure 1].

Prolonged ischemia protocol (40 min)

As shown on figure 1, 10 animals that completed the protocol in a previously published study were included.

Baseline characteristics

Both control and iPost groups were similar in body weight and baseline CMR-based characteristics except for the indexed left ventricular mass that was larger in the control group of animals with 40 min ischemia times (table 1). A non-significant trend towards larger MDCT-based AAR (% left ventricle mass) was observed in the iPost group (table 1).

Cardiac magnetic resonance results

Effect of iPost in a model of intermediate ischemia protocol

In the intermediate-duration ischemia group, iPost did not have any effects on any of the CMR-based variables (table 2; figure 2, figure 3 and figure 4). Both iPost and control animals present small IS with no differences being reported between the intervention groups [0.3% of LV mass [0.0 – 3.9] vs 0.9% [0.0 – 2.6] %LV in iPost and control, respectively, P = .378). We did not find any differences regarding the indexed IS (IS/AAR) either (table 2).

Effect of iPost on a model of prolonged ischemia protocol

The results of this experiment have already been published.16 In conclusion, iPost did not show any cardioprotective effects in terms of IS reduction [31.1% of LV mass [27.3–32.8] LV vs 27.3% [25.1– 27.5] in iPost and control respectively; P = .248). Regarding the previous group, we did not find any differences in indexed IS (IS/AAR). Differences in other CMR-based parameters were not observed except for a significantly longer AAR T1-relaxation time in the iPost group (1590.3 ms [1441.6 – 1591.4] vs 1309.7 ms [1248.1–1310.8] in iPost and control, respectively; P = .002) (table 3 and figure 2, figure 3 and figure 4).

Interaction between duration of ischemia and iPost benefits

We did not find a significant interaction between duration of ischemia time and the effect of iPost, CMR-based IS [3.9% of LV mass [0.0–30.9] vs 4.6% [0.2 – 25.1]] in iPost and control, respectively, F [1.25] = 0.18; P = .672). Therefore, iPost was not associated with smaller IS regardless of ischemia duration (table 4 and figure 2). We did not find any differences in indexed IS (IS/AAR), LVEF, LV end-diastolic or end-systolic volumes either (table 4, and figure 3).
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 29)</th>
<th>Intermediate ischemia (30 min) (N = 19)</th>
<th>Prolonged ischemia (40 min) (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (N = 14)</td>
<td>iPost (N = 15)</td>
<td>Control (N = 9)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>36.2 (34.0-38.5)</td>
<td>33.5 (31.0-40.0)</td>
<td>36.0 (34.5-38.5)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57.6 (55.2-63.0)</td>
<td>55.9 (52.3-59.5)</td>
<td>57.7 (55.9-61.3)</td>
</tr>
<tr>
<td>iLVEDV, mL/m²</td>
<td>104.2 (93.5-105.8)</td>
<td>105.9 (96.1-123.6)</td>
<td>95.8 (87.5-105.3)</td>
</tr>
<tr>
<td>iLVESV, mL/m²</td>
<td>43.0 (37.0-48.6)</td>
<td>45.6 (38.0-54.5)</td>
<td>40.7 (35.8-46.6)</td>
</tr>
<tr>
<td>Area at risk (% LV)</td>
<td>27.8 (26.2-27.2)</td>
<td>31.7 (29.2-32.3)</td>
<td>24.6 (22.3-27.6)</td>
</tr>
</tbody>
</table>

ilVEDV, indexed left ventricular end-diastolic volume; ilVESV, indexed left ventricular end-systolic volume; iPost, ischemic postconditioning; LV, left ventricle; LVEF, left ventricular ejection fraction.

Table 2. CMR-based parameters for intermediate ischemia group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intermediate ischemia duration (N = 19)</th>
<th>Control (N = 9)</th>
<th>iPost (N = 10)</th>
<th>P (post hoc analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS, %LV mass</td>
<td>0.9 (0.0-2.6)</td>
<td>0.3 (0.0-3.9)</td>
<td>.378</td>
<td></td>
</tr>
<tr>
<td>Indexed IS, IS/AAR (%)</td>
<td>3.8 (0.0-8.5)</td>
<td>0.9 (0.0-15.1)</td>
<td>.474</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.0 (50.2-55.9)</td>
<td>52.9 (47.1-56.0)</td>
<td>.521</td>
<td></td>
</tr>
<tr>
<td>iLVEDV, mL/m²</td>
<td>98.7 (92.3-104.1)</td>
<td>107.3 (90.0-118.6)</td>
<td>.438</td>
<td></td>
</tr>
<tr>
<td>iLVESV, mL/m²</td>
<td>45.9 (40.4-52.4)</td>
<td>48.5 (41.0-55.2)</td>
<td>.355</td>
<td></td>
</tr>
<tr>
<td>T2 relaxation time AAR, ms</td>
<td>51.3 (48.3-54.8)</td>
<td>57.0 (53.2-58.5)</td>
<td>.583</td>
<td></td>
</tr>
<tr>
<td>T2 relaxation time REM, ms</td>
<td>45.6 (42.2-46.1)</td>
<td>44.7 (43.7-47.4)</td>
<td>.881</td>
<td></td>
</tr>
<tr>
<td>Native T1 relaxation time AAR, ms</td>
<td>1179.2 (1167.1-1266.4)</td>
<td>1225.9 (1170.2-1306.2)</td>
<td>.584</td>
<td></td>
</tr>
<tr>
<td>Native T1 relaxation time REM, ms</td>
<td>1087.8 (1075.1-1109.7)</td>
<td>1078.4 (1051.2-1134.8)</td>
<td>.925</td>
<td></td>
</tr>
</tbody>
</table>

AAR, area at risk; ilVEDV, indexed left ventricular end-diastolic volume; ilVESV, indexed left ventricular end-systolic volume; iPost, ischemic postconditioning; IS, infarct size; LV, left ventricle; LVEF, left ventricular ejection fraction; REM, remote area.

Figure 2. Differences in cardiac magnetic resonance-based infarct size (% of left ventricular mass) between control and iPost groups, in the overall population and based on ischemia duration.

Figure 3. Differences in cardiac magnetic resonance-based LVEF (%) between control and iPost groups in the overall population and based on ischemia duration.
iPost is a very attractive intervention to reduce IRI since it can be applied in the cath lab at the time of reperfusion. Technically, it is a straightforward intervention that does not require any additional material to that already used during primary PCI.

Local ischemic preconditioning (repetitive cycles of brief coronary artery occlusion/blood flow restoration before prolonged ischemia) has consistently shown to be a very strong cardioprotective intervention to reduce IRI. In most (if not all) experimental settings this strategy is consistently associated with a massive reduction of IS. However, local ischemic preconditioning is not feasible to be applied at the centers where patients already have initiated coronary artery occlusion. To overcome this limitation, Vinten-Johansen’s group tested whether the same ischemic conditioning maneuver started right after reperfusion (iPost) could also be associated with smaller IS. This group reported, in the dog model of IRI (60 min ischemia followed by blood flow restoration), that 3 cycles of “30 sec re-occlusion/30 sec reperfusion” applied 1 min after reperfusion were associated with a significant reduction of IS. Due to its easiness of implementation, iPost was translated very fast to a pilot clinical trial. Ovize’s group reported that in a small group of patients with STEMI, iPost [in this case 4 cycles of 1 min occlusion/1 min reperfusion] started right after PCI-mediated reperfusion was associated with smaller IS. In another small trial of 79 patients with STEMI, Freixa et al. reported that iPost not only did not reduce IS, but was associated with significantly less myocardial salvage. Two larger clinical trials, POST20 (N = 700), and DANAMI-3–iPOST21 (N = 1234) failed to prove the benefits of iPost.

There are some potential explanations for the divergent results. It has been speculated that there can be an interaction between the cardioprotection provided by iPost and the duration of preceding ischemia. However, this has not been tested in an ad hoc designed study. With this in mind, we conducted this study, where we did not find any cardioprotection provided by iPost regardless of the ischemia duration.

Although it seems that 30 min and 40 min of ischemia duration are not very different, we have previous reported in the pig model that occlusion times < 30 min are associated with a very small IS while occlusions > 40 min are associated with transmural infarction. Overall, in our study, 4 cycles of iPost [1 minute occlusion/1 minute reperfusion] did not have any cardioprotective effects regarding IS reduction neither expressed as % of LV mass nor as % of AAR. This was the case in both ischemia duration protocols. Although no formal interaction between ischemia duration and iPost effects on IS was found some findings suggest a possible deleterious effect of iPost in the longer ischemia duration protocol (trend towards a higher IS and a lower LVEF and, especially a significantly longer T1 relaxation time in the AAR). In addition, even in the absence of any significant differences in the intermediate ischemia group, when visualizing individual data [figure 2], asymmetry towards larger IS is seen in the iPost group including the 2 subjects with the highest IS of the entire 30 minute occlusion cohort. Furthermore, differences in secondary CMR-based outcomes suggest a potential deleterious effect of iPost in our ischemia-reperfusion model: pigs in the iPost group had significantly longer native T1 relaxation times, a surrogate marker of increased interstitial fibrosis. In addition, we found a non-significant trend towards poorer LVEF in animals undergoing iPost both in the intermediate and prolonged ischemia groups. Nevertheless, this finding can be due to the non-significant trend towards larger AAR in the iPost group.

One possible explanation for these results is the delayed start of the iPost protocol since animal experiments have shown that the

**DISCUSSION**

In this study, we tested the potential cardioprotective effect of iPost in a large animal model of reperfused MI with intermediate [30 min] and prolonged [40 min] ischemia times. In our pig model of ischemia/reperfusion, iPost failed to reduce IS in any of the ischemia duration protocols as seen on the state-of-the-art CMR 7 days after MI. A non-significant sign of damage (trend towards larger IS and lower LVEF, as well as significantly longer T1 relaxation times in the ischemic region) associated with iPost was observed in animals in the prolonged ischemia protocol. Our data do not support iPost as an intervention capable of improving outcomes in the IRI setting.

Conversely, animals treated with iPost presented longer native-T1 relaxation times in the AAR (1306.2 ms [1190.7–1492.7] vs 1240.7 ms [1167.1–1304.5] in iPost and control, respectively (F[1.25] = 5.79, \(P = .024\)) without any differences being reported in the remote area or in T2 relaxation time (figure 4).

**Figure 4.** Differences in cardiac magnetic resonance native T1 and T2 relaxation time (ms) between control and iPost groups, in the overall population and based on ischemia duration. A: native T1 relaxation time at the area at risk. B: native T1 relaxation time at remote area. C: native T2 relaxation time at the area at risk. D: native T2 relaxation time at remote area. AAR, area at risk.

**Overall Intermediate ischemia Prolonged ischemia**

**Overall Intermediate ischemia Prolonged ischemia**

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**DISCUSSION**

In this study, we tested the potential cardioprotective effect of iPost in a large animal model of reperfused MI with intermediate [30 min] and prolonged [40 min] ischemia times. In our pig model of ischemia/reperfusion, iPost failed to reduce IS in any of the ischemia duration protocols as seen on the state-of-the-art CMR 7 days after MI. A non-significant sign of damage (trend towards larger IS and lower LVEF, as well as significantly longer T1 relaxation times in the ischemic region) associated with iPost was observed in animals in the prolonged ischemia protocol. Our data do not support iPost as an intervention capable of improving outcomes in the IRI setting.
The cardioprotective effect of iPost is restricted to the first minute after reperfusion with no effect observed if the maneuver delays for another 60 seconds. In fact, in clinical trials in which iPost proved to be effective, the inflation/deflation protocol was started immediately after reperfusion.

Study limitations

This study has some limitations that must be acknowledged. Despite being one of the most translatable, the present pig model has some differences with human IRI: tolerance to ischemia is species-dependent, and duration of ischemia in pigs is not equivalent to humans; similarly, the time-dependent progression of irreversible injury is much faster in pigs compared to humans as seen by the transmural progression of infarction between 30 min and 40 min of ischemia. Another limitation of the study is that animal allocation to iPost or control was not entirely random, but rather based on an alternative assignment; however, the person responsible for the CMR analysis validation was blind to the subjects’ allocation group. In addition, as previously presented, data on the prolonged ischemia group correspond to experiments previously conducted at our center by a different operator and published elsewhere. The use of animals of different breeds, different anesthesia protocols, different material or any other environmental factors could explain, at least partially, the great differences seen on IS between the intermediate and the prolonged ischemia groups. Nevertheless, the decision to use these previously reported data was based on the principle of reducing animal use in animal research.

CONCLUSIONS

In a pig model of ischemia/reperfusion, iPost (4 cycles of 1 min balloon inflation/deflation) initiated immediately after reperfusion ineffectively reduced IS. The lack of benefits was consistent across different ischemia duration protocols, which ruled out an interaction between duration of coronary occlusion and iPost benefits.
Overall, we observed a sign of harm due to iPst (significantly longer T1 relaxation times) mainly driven by an effect in the prolonged ischemia protocol.

**FUNDING**

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**AUTHORS’ CONTRIBUTION**

J. Nuche was responsible for conducting experiments and CMR analysis; also, for data analysis and manuscript drafting. C. Galán-Arriola was responsible for the blind CMR analysis and offered support for statistical analysis and figure design. R. Fernández-Jiménez was responsible for the experiments and analysis of the prolonged ischemia group. M. I. Higuero Verdejo, R. Vazirani, M. Anguita-Gámez, and A. Lanasa gave support in the experimental setting. G. J. López Martín was responsible for CT and CMR acquisition. J. Sánchez-González designed the CMR protocol. B. Ibáñez was responsible for the project design, results supervision, and final approval of the manuscript draft.

**CONFLICTS OF INTEREST**

J. Sánchez-González is an employee of Philips Healthcare. The authors have no conflicts of interest to declare. All co-authors have seen and agreed on the contents of the manuscript and there is no financial interest to report.

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**WHAT IS KNOWN ABOUT THE TOPIC?**

- There is a strong need to identify interventional or pharmacological interventions that can reduce infarct size (IS), a main contributor to long-term heart failure in STEMI survivors.
- There is controversy surrounding the cardioprotection associated with local iPst in experimental models and clinical trials.
- A possible explanation to this controversy is the potential interaction between the duration of ischemia and the benefits of iPst.

**WHAT DOES THIS STUDY ADD?**

- It shows that iPst is not associated with IS reduction.
- The lack of benefits is consistent across different ischemia duration protocols, which rules out a possible interaction between duration of coronary occlusion and iPst benefits.
- iPst can be associated with damage especially when applied after long ischemia duration.

**REFERENCES**


Cost-effectiveness of SAPIEN 3 transcatheter aortic valve implantation in low surgical mortality risk patients in Spain

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ABSTRACT

Introduction and objectives: Transcatheter aortic valve implantation (TAVI) was first introduced in 2007 as an alternative to open heart surgery to treat patients with severe symptomatic aortic stenosis (sSAS) with various indication expansions since that date. Recently, the PARTNER 3 study (Placement of aortic transcatheter valve) demonstrated clinical benefits with TAVI with the SAPIEN 3 valve vs surgical aortic valve replacement (SAVR) in selected low surgical mortality risk patients. We reviewed data from the PARTNER 3 and economic data from Spain to assess the cost-effectiveness ratio of TAVI vs SAVR in patients with sSAS and low surgical mortality risk.

Methods: A 2-stage model was used to estimate direct healthcare costs and health-related quality of life data regarding TAVI with the SAPIEN 3 valve and SAVR. Early adverse events associated with TAVI from the PARTNER 3 were fed into a Markov model that captured longer-term outcomes after TAVI or SAVR.

Results: TAVI with SAPIEN 3 improved quality-adjusted life years per patient (+ 1.00) with an increase in costs vs SAVR (€6971 per patient). This meant an incremental cost-effectiveness ratio of TAVI vs SAVR (€6952 per patient). The results were robust with TAVI with the SAPIEN 3 valve remaining cost-effective across several sensitivity analyses.

Conclusions: TAVI with the SAPIEN 3 valve is cost effective compared to SAVR in patients with sSAS and low surgical mortality risk. These findings can inform policymakers to facilitate policy development in Spain on intervention selection in this patient population.


Coste-efectividad del implante percutáneo de válvula aórtica con SAPIEN 3 en pacientes con bajo riesgo de mortality quirúrgica en España

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica (TAVI) se introdujo en 2007 como una alternativa a la cirugía a corazón abierto para tratar a pacientes con estenosis aórtica grave sintomática, y desde entonces han aumentado las indicaciones autorizadas. Recientemente, el Placement of Aortic Transcatheter Valve Study (PARTNER 3) ha demostrado beneficios clínicos con el TAVI con la válvula SAPIEN 3 frente al reemplazo quirúrgico de válvula aórtica (RVAo) en pacientes seleccionados con bajo riesgo de mortalidad quirúrgica. Utilizando los datos del PARTNER 3 junto con datos económicos de España, se evaluó la relación coste-efectividad del TAVI en comparación con el RV Ao en pacientes con estenosis aórtica grave sintomática con bajo riesgo de mortalidad quirúrgica.

INTRODUCCIÓN

La estenosis aórtica afecta a cerca de 3% de adultos mayores de 65 años.1 A menudo tiene un período latente asintomático inicial, pero a medida que la enfermedad se vuelve más severa, los síntomas pueden comenzar a aparecer, como fatiga, angina, o síntomas neurológicos.1,2 La colocación percutánea de válvulas aórticas es recomendada como una opción terapéutica para pacientes con estenosis aórtica severa que no son candidatos para el tratamiento cirugónico.3 En el año 2013, TAVI se convirtió en la opción terapéutica de elección para pacientes inoperables con estenosis aórtica severa, y la evidencia clínica ha estado creciendo y ha validado la implantación de esta tecnología en varios estudios.3,4,5

Desde el primer implante transcatheter de válvula aórtica (TAVI) se ha utilizado como una opción terapéutica para pacientes con estenosis aórtica severa (sSAS) hace más de 20 años, la evidencia clínica ha aumentado y ha continuado con el tiempo.6,7 En 2013, TAVI se convirtió en el tratamiento de primera línea para pacientes inoperables con estenosis aórtica severa, y los pacientes con enfermedad avanzada o alto riesgo. More recently, this treatment choice has expanded to include patients of intermediate/low surgical mortality risk.6,8,9

El very recent Placement of aortic transcatheter valve study (PARTNER 3) is among the growing body of robust clinical trial evidence. This is a pivotal, multicenter, randomized, and controlled study in patients with sSAS of low surgical mortality risk.5,10 In PARTNER 3, treatment outcomes with surgical aortic valve replacement (SAVR) were compared to TAVI with the SAPIEN 3 transcatheter heart valve via transfemoral access.6,7 Compared to SAVR, TAVI with the SAPIEN 3 valve reduced the composite endpoint of death, stroke or rehospitalization after 1 and 2 years.6,7 In view of these positive clinical developments, the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines now recommend SAVR in younger, low-risk patients, while TAVI is now considered the treatment of choice in older patients. Also, it can be considered in all other patients with sSAS following careful evaluation of individual clinical, anatomical, and procedural characteristics by the heart team.5

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There are no treatment guidelines specific to Spain describing the use of TAVI, but the Spanish Society of Cardiology, as a member of the ESC, endorses the ESC guidelines, and healthcare professionals in Spain follow these ESC guidelines.7 Irrespective of these guidelines, TAVI adoption in Spain remains low compared to other European countries. Despite a higher level of infrastructure available,7 defined as the number of TAVI centers available per million population, there is still significant variability among regions regarding TAVI implantation rates in Spain.9 In 2021, nearly 5000 patients benefited from this transformative minimally invasive technology in Spain. In a recent publication,10 the annual number of TAVI candidates for Spain was estimated at 15 783 patients including low-risk patients. Considering this together with the increasing evidence of clinical benefits of TAVI in patients with sSAS, it is important to evaluate the cost-effectiveness ratio of using TAVI vs SAVR in patients with sSAS.11 Since the first transcatheter aortic valve implantation (TAVI) was used as a treatment option for severe symptomatic aortic stenosis (sSAS) almost 20 years ago, clinical trial evidence has further increased and has continued to validate its use.5,12

METHODS

A cost-utility analysis was developed using methodology validated for the French12 and Italian13 population to estimate changes in both direct healthcare costs and health-related quality of life with the use of TAVI with the SAPIEN 3 valve compared to SAVR in patients with sSAS and low surgical mortality risk (75% of Thoracic Surgeons < 4%; from the perspective of the Spanish National Health System. Costs were measured in 2021 euros and benefits in quality-adjusted life years (QALYs) gained. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs between the 2 treatment groups by the difference in QALYs. Consistent with previous studies,12,13 an incremental cost-effectiveness ratio of < €30 000 per QALY gained was used as the willingness-to-pay (WTP) threshold of acceptable cost-effectiveness.

Model structure

Details of the 2-stage model structure have been previously described for the French population.12 In brief, early adverse events associated with TAVI were first captured using the 30-day early adverse events dataset from the PARTNER 3 study2 in a decision tree (figure 1A); subsequently, these data were fed into a Markov...
model that included 4 distinct health states (‘alive and well’, ‘treated atrial fibrillation [AF]’, ‘disabling stroke’, and ‘dead’) to capture long-term outcomes of patients after TAVI or SAVR (figure 1B). The model was considered appropriate for the Spanish setting by all authors based on their clinical and health-economic expertise.

Given that sSAS requires life-long valve replacement, a lifetime timespan of 50 years was selected for the cost-utility analysis with a discounting factor per year of 3% applied for both future costs and benefits following the recommendations set for Spain. This timespan was chosen to reflect all potential consequences to individuals with sSAS over their lifetime. Healthcare costs and health-related quality of life was measured using QALYs.

Model inputs

Study overview

The model was informed by the PARTNER 3 study population, which excluded patients with clinical frailty, bicuspid aortic valves or other anatomical features that increased the risk of complications associated with either surgery or TAVI. In the PARTNER 3, 1000 patients were enrolled, 503 of whom were randomized to TAVI and 497 to SAVR, with ‘as treated’ groups of 496 and 454 patients, respectively. The primary endpoint was a composite of all-cause mortality, stroke or rehospitalization 1 year after the procedure.

Clinical events

Probabilities of clinical events used in the model (table 1 of the supplementary data) were based on a decision tree that captured all early adverse events experienced up to 30 days after the procedure as reported in the PARTNER 3. Monthly transition probabilities among the Markov model health states were estimated. Regarding the transition from ‘alive and well’ to ‘treated AF’, data from the PARTNER 3 on new-onset treated AF between 30 days and 1 year were used. Other literature sources provided a more realistic estimate of the remaining 2 transitions due to the scarcity of these events reported in the PARTNER 3. Burden of stroke data in Spain (Stroke Alliance for Europe) were used for the transition from ‘alive and well’ to ‘disabling stroke’, and data from a systematic review/meta-analysis involving 104 eligible cohort studies were used for the transition from ‘treated AF’ to ‘disabling stroke’. Myocardial infarction, transient ischemic attack, and severe or life-threatening bleeding were captured as intercurrent events between 30 days and 1 year from PARTNER 3 data. Other relevant events like rehospitalization rates using data from the PARTNER 3, and reintervention rates due to valve deterioration (data up to 2 years from the PARTNER 3) and from 3 years onwards from a study on 20-year outcomes of pericardial aortic tissue valve bioprosthesis were also considered (table 1 of the supplementary data). In the base case, the same reintervention rate was used for both the TAVI and SAVR arms; this simplifying assumption allowed better use of the available data. In scenario #1, higher reintervention rates were assumed for TAVI with the SAPIEN 3 valve compared to SAVR based on data from the PARTNER 2 at 5 years while in scenario #2, an increased risk of stroke was assumed, which was consistent with the PARTNER 3 outcomes.

Survival extrapolation

There were 2 options regarding survival extrapolation. In option #1, transition probabilities were taken from the literature (relative risk of death with AF of 1.517; and relative risk of death with disabling stroke of 2.0520). In option #2, parametric survival fitting was performed based on Kaplan-Meier data from the PARTNER 3. A total of 3 parametric distributions were used (Weibull, Exponential, Gompertz) and adjusted to the survival of the overall Spanish population. Therefore, in the base case, survival estimates were based on transition probabilities due to immaturity of survival data from the trial. Annual mortality risk for ‘alive and well’, and other relative risks for other health states are shown on table 2 of the supplementary data. Option #2 (parametric survival analysis) was
explored using alternative hazard ratios (HR) in scenario #3: HR, 0.75 from the PARTNER 3 at 2 years adjusted to Spanish population overall mortality. An additional scenario #4 removed any survival benefit with the SAPIEN 3 valve [HR, 1].

Health utilities

There were 2 options for determining utility decrement: option #1 used utility decrements by health state from the literature adjusted by age and Spanish population standards. This was the preferred option because there were very few corresponding events in the PARTNER 3, and estimates from the literature were deemed realistic. The age and population standards adjusted utility decrements were 0.16 for AF and 0.42 for disabling stroke. Option #2 used treatment options from the PARTNER 3 and was explored within scenario #5. The utility decrement for option #2 was individually extracted from the PARTNER 3 at baseline, after 30 days, 6 months and 1 year, and then converted to Spanish health utilities.

Cost inputs

Costs associated with TAVI and SAVR (procedure, complications, and long-term) are shown on Table 3 of the supplementary data. Base case procedure cost information was drawn from the SERGAS. We should mention that the SERGAS fee includes market valve and ancillary material price. Also, personnel costs were additionally estimated on a per hour price basis for different professionals. Costs corresponding to complications and health states were drawn from the literature and diagnosis-related groups (DRG). The breakdown of TAVI and SAVR procedure costs are shown on Table 4 of the supplementary data. The micro-cost elements are informed from the study conducted by Bayón et al. and updated to reflect current TAVI practice in Spanish low-risk patients with sSAS. As costs vary depending on the Spanish region at stake, 3 additional scenarios: 6A, 6B, and 6C were explored using cost information adjusted to reflect current clinical practice in Murcia, Huelva, and Basque regions. Furthermore, a scenario #7 was included to account for early adverse events costs at 30 days.

Model outputs

Key outputs of the model were the overall per-patient costs and QALYs in each arm and ICER.

Sensitivity analyses

To evaluate uncertainty, 1-way deterministic sensitivity analyses were performed by varying inputs using confidence intervals and ranges from the literature when available, and plausible ranges when data were unavailable (Table 5 of the supplementary data). Multiple parameters were changed and the impact on the results explored. Overall parameter uncertainty was addressed using a probabilistic sensitivity analysis (PSA) (Table 6 of the supplementary data). Several scenario analyses were conducted to explore the impact of major structural assumptions as shown on Table 7 of the supplementary data. All analyses were performed using Microsoft Excel [Microsoft Corporation, United States].

RESULTS

Base case

TAVI with SAPIEN 3 improved QALYs per patient (+ 1.0) with higher costs compared to SAVR of approximately €6971 per patient.

Table 1. Base case results with acute and lifetime costs

<table>
<thead>
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<th>Summary results</th>
<th>TAVI with SAPIEN 3</th>
<th>SAVR</th>
<th>Incremental</th>
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<td>Cost per patient</td>
<td>€ 39 052</td>
<td>€ 32 081</td>
<td>€ 6971</td>
</tr>
<tr>
<td>Life year gained (undiscounted)</td>
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<td>13.22</td>
<td>0.86</td>
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<tr>
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<td>QALYs per patient</td>
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<td>7.66</td>
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<td>Incremental net monetary benefit (NMB)</td>
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<td>Incremental net health benefit (NHB)</td>
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<td>Pacemaker implantation</td>
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<td>€ 311</td>
<td>€ 195</td>
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<td>MI</td>
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<tr>
<td>Death costs</td>
<td>€ 0</td>
<td>€ 0</td>
<td>€ 0</td>
</tr>
<tr>
<td>Overall cost at 1 year</td>
<td>€ 27 267</td>
<td>€ 16 570</td>
<td>€ 10 098</td>
</tr>
<tr>
<td>MI</td>
<td>€ 181</td>
<td>€ 92</td>
<td>€ 89</td>
</tr>
<tr>
<td>Pacemaker implantation complication costs</td>
<td>€ 38</td>
<td>€ 23</td>
<td>€ 15</td>
</tr>
<tr>
<td>Hospitalization costs</td>
<td>€ 212</td>
<td>€ 316</td>
<td>-€ 104</td>
</tr>
<tr>
<td>Reintervention costs</td>
<td>€ 117</td>
<td>€ 147</td>
<td>-€ 30</td>
</tr>
<tr>
<td>Alive &amp; well health state costs</td>
<td>€ 1 258</td>
<td>€ 844</td>
<td>€ 415</td>
</tr>
<tr>
<td>Treated AF health state costs</td>
<td>€ 48</td>
<td>€ 376</td>
<td>-€ 328</td>
</tr>
<tr>
<td>Disabling stroke costs</td>
<td>€ 11</td>
<td>€ 221</td>
<td>-€ 210</td>
</tr>
<tr>
<td>Death costs</td>
<td>€ 0</td>
<td>€ 0</td>
<td>€ 0</td>
</tr>
<tr>
<td>Overall lifetime costs</td>
<td>€ 39 052</td>
<td>€ 32 081</td>
<td>€ 6971</td>
</tr>
<tr>
<td>Pacemaker implantation complication costs</td>
<td>€ 433</td>
<td>€ 251</td>
<td>€ 182</td>
</tr>
<tr>
<td>Hospitalization costs</td>
<td>€ 374</td>
<td>€ 353</td>
<td>€ 21</td>
</tr>
<tr>
<td>Reintervention costs</td>
<td>€ 4464</td>
<td>€ 4941</td>
<td>-€ 477</td>
</tr>
<tr>
<td>Alive &amp; well health state costs</td>
<td>€ 4120</td>
<td>€ 2590</td>
<td>€ 1530</td>
</tr>
<tr>
<td>Treated AF health state costs</td>
<td>€ 970</td>
<td>€ 3963</td>
<td>-€ 2993</td>
</tr>
<tr>
<td>Disabling stroke costs</td>
<td>€ 1424</td>
<td>€ 3414</td>
<td>-€ 1990</td>
</tr>
<tr>
<td>Additional lifetime costs</td>
<td>€ 11 785</td>
<td>€ 15 512</td>
<td>-€ 3727</td>
</tr>
<tr>
<td>Total lifetime costs</td>
<td>€ 39 052</td>
<td>€ 32 081</td>
<td>€ 6971</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; MI, myocardial infarction; QALY, quality-adjusted life-year.

This represented an ICER of €6952 per QALY, which is lower compared to the WTP threshold of €30 000/QALY that is commonly referenced in the Spanish setting. Base case results over a 50-year timespan are shown on Table 1. Further examination of the breakdown of costs for TAVI vs SAVR revealed that although initial procedural costs in the model were higher with TAVI, costs associated with ‘disabling stroke’ and ‘treated AF’ were somehow lower [Table 1, and figure 1 of the supplementary data].
Deterministic sensitivity analyses

Univariate sensitivity analyses are displayed in the Tornado diagram (figure 2). SAPIEN 3 TAVI remained cost-effective regardless of any plausible changes to individual model parameters [note: the 20 parameters with the greatest influence on the model are shown on the diagram]. The model was most sensitive to age, SAVR procedural costs, and risk of disabling stroke at 30 days with TAVI.

Probabilistic sensitivity analysis

The results of the PSAs confirm the results of the base case analysis. At the conventional WTP threshold of €30 000/QALY, TAVI with SAPIEN 3 remains cost-effective compared to SAVR in 100% of the simulations run in the model (figure 3A). In addition, the cost-effectiveness acceptability curve indicates that SAPIEN 3 TAVI has a 99.9% probability of treatment being cost-effective with a €30 000/QALY WTP threshold (figure 3B). PSA assumptions are shown on table 5 of the supplementary data.

Scenario analysis

A series of different scenario analyses were conducted to assess the impact of changing various assumptions on the results of the model and the model robustness. TAVI with the SAPIEN 3 valve remains cost-effective compared to SAVR across most of the tested scenarios (table 6 of the supplementary data) including those with different timespans (10, 15, 20, and 30 years). The results from the scenario analyses demonstrate the comparative robustness of the model reported.

DISCUSSION

This analysis suggests that TAVI with the SAPIEN 3 valve is likely to be a cost-effective valve replacement option for patients with sSAS and low surgical mortality risk in Spain. TAVI with the SAPIEN 3 valve showed an improvement in QALYs (+1.0) associated with slightly increased costs compared to SAVR (approximately €6971 per patient). The ICER benefits for TAVI with the SAPIEN 3 shown in this model represent a highly cost-effective intervention [ICER/QALY €6 952] in the Spanish system with a WTP threshold of €30 000/QALY. Uncertainty was assessed using various sensitivity analyses, and the results appeared robust.

The findings of the current study are supported by other cost-effectiveness studies that show that TAVI with SAPIEN 3 is either dominant or cost-effective in patients of low risk surgical mortality risk.27-31 The Spanish findings are also consistent with cost-effectiveness analyses of TAVI with SAPIEN 3 vs SAVR in France12 and Italy13 using the same model structure.

The current analysis is important because TAVI provides patients with a minimally invasive treatment option and a lower risk of complications and/or rehospitalization plus improved recovery rates and quality of life gains. From a provider perspective, TAVI also brings efficiencies by limiting healthcare resource use, reducing postoperative complications, and shortening hospital stays (including Intensive care unit [ICU] beds).32 Shortening the hospital stay allows more patients to be treated in the same hospital, an important element for a health system in high demand and with long waiting lists. These efficiencies also lead to a reduced risk of infections and contamination,33 which was much welcomed during the recent COVID-19 pandemic. Finally, TAVI reduces the recovery period to normal activity that may not be accounted for in this analysis. Indirect benefits like volunteering, grandchild support or less caregiving support most likely would increase even further the overall benefits of this technology.34

The results of this analysis could also enable greater access to TAVI for Spanish patients with sSAS. Recent studies demonstrate the efficacy and safety profile of transfemoral TAVI in Spain.9 This together with the recent European guidelines suggests that the number of TAVIs will increase, thus rendering many low surgical
risk patients with sSAS eligible for TAVI. Moreover, with time, TAVI will likely become simplified even further with shorter admission times,\textsuperscript{35} this should lead to lower TAVI costs in the future. In this regard, the results of this study could inform policymakers on the management of patients with sSAS in Spain.

Limitations

This study comes with certain limitations. The first pertains to certain model inputs and assumptions made. In this model, hospitalization data were based on 1- and 2-year data from the PARTNER 3 study with the assumption that this rate remained constant over the model timespan after 2 years. The impact of this assumption is unknown because individuals from both treatment arms in the model remained at risk of hospitalization. The rate of reinterventions was assumed to remain constant after 22 years; the impact of this assumption on modelled outcomes was deemed minimal based on the expectation that nearly 11% of patients would still be alive in the model after this point in time with limited need for reintervention. Despite of this, uncertainty on the longer-term durability of the TAVI device and subsequent reintervention rates in younger patients cannot be disregarded. Disutilities were not included for any intercurrent events because you can run the risk of counting them twice with the health state utilities being applied to patients in the ‘treated AF’ and ‘disabling stroke’ states. This was a conservative assumption because, apart from pacemaker complications, the rates of intercurrent events are generally lower for TAVI with SAPIEN 3 compared to SAVR.\textsuperscript{6}

A second limitation of this study is the generalizability of the results. Conclusions cannot be generalised to the overall population with aortic stenosis because, among others, patients with unfavourable coronary anatomy were excluded from the PARTNER 3 study. Moreover, caution should be observed when trying to generalize any findings from this model to populations outside Spain.

Finally, we should mention that procedural costs across different regions of Spain are heterogenous. In this study, we use publicly available cost data from a region in Spain and our approach is conservative as we additionally account for current practice. We also conducted multiple scenario analyses with other available cost data sets.

CONCLUSIONS

Data from the PARTNER 3 suggested that the use of TAVI with the SAPIEN 3 valve was more favorable, on the clinical level,
compared to SAVR in patients with sSAS and low surgical mortality risk. The results of this cost-effectiveness model indicate that, in Spain, TAVI could provide a cost-effective option over SAVR for this population with an estimated ICER/QALY value well below the national threshold. The model appeared to be robust with uncertainty assessed by various sensitivity analyses. The results of this cost-effectiveness analysis can support policy makers and healthcare budget holders to optimize the management of Spanish patients with sSAS.

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Edwards Lifesciences SA, Switzerland provided funding for the economic assessment and was involved in the analysis as well as in the drafting of this manuscript.

AUTHORS’ CONTRIBUTIONS
J.M. Vázquez participated in economic data mining, model validation, and manuscript review. E. Pinar in economic data mining, and model validation. J. Zamorano participated in data mining, and model validation. J. Burgos participated in data mining and model validation. J. Díaz participated in data mining, and model validation. B. García del Blanco participated in data mining, and model validation. A. Sarmah in data collection and analysis, result preparation, and manuscript drafting and review. P. Candolfi participated in cost analysis and manuscript drafting. J. Shore was involved in model development and manuscript review. M. Green participated in model development, and manuscript drafting.

CONFLICTS OF INTEREST
J.M. Vázquez Rodríguez declared department research or training grants from Edwards Lifesciences, Medtronic, and Boston Scientific, and personal advisory fees from Medtronic, and Boston Scientific. J.L. Zamorano declared research grants from Abbott, and Medtronic to the Institution, and speaker fees from Edwards Lifesciences, Bayer, Novo Nordisk, and Daiichi Sankyo. J. Moreu Burgos declared having received fees from Biosensors, Boston Scientific, Cardiva, Edwards Lifesciences, and Medtronic. A. Sarmah declared to be an employee of Edwards Lifesciences and hold stock options. P. Candolfi declared to be an employee of Edwards Lifesciences and hold stock option. J. Shore declared consultancy fees to the employer for developing the economic model. M. Green declared consultancy fees to the employer for developing the economic model. E. Pinar, J.F. Díaz-Fernández, and B. García del Blanco declared no conflicts of interest whatsoever.

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WHAT IS KNOWN ABOUT THE TOPIC?
– Recent clinical trial evidence confirms the clinical benefits of TAVI with the SAPIEN 3 valve for a low surgical risk population compared to SAVR. Furthermore, following favorable recent updates in the American and European guidelines, TAVI can now be considered as a treatment option in low surgical risk patients with sSAS. Regarding the economic evidence, however, TAVI with the SAPIEN 3 valve has proven cost-effective compared to SAVR only in high and intermediate risk patients with sSAS in Spain.

WHAT DOES THIS STUDY ADD?
– Data from the PARTNER 3 suggested that the use of TAVI with the SAPIEN 3 valve was more clinically favorable compared to SAVR in patients with sSAS and low surgical mortality risk. The results of this robust, cost-effectiveness analysis indicate that, in Spain, TAVI could provide a cost-effective option over SAVR for this population with an estimated ICER/QALY value well below the national threshold. Data from the PARTNER 3 together with data from this cost-effectiveness analysis can support policy makers and healthcare budget holders to optimize the management of Spanish patients with sSAS.

SUPPLEMENTARY DATA
Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000340.

REFERENCES


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Plaque modification techniques to treat calcified coronary lesions. Position paper from the ACI-SEC

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ABSTRACT

Coronary artery calcification is probably the main determinant of the poor outcome of percutaneous coronary interventions and is associated with higher rates of adverse events. There are currently different balloon or specific device-based plaque modification techniques available. Knowing their characteristics and proper use is key for the optimal treatment of calcified lesions. This position paper—promoted by the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC)—describes existing plaque modification techniques currently available and proposes an algorithm for the management of calcified lesions.

Keywords: Calcified coronary lesions. Plaque modification techniques. Intracoronary imaging modalities.

Documento de posicionamiento de la ACI-SEC sobre la modificación de placa en el tratamiento de las lesiones calcificadas

RESUMEN

La calcificación coronaria es probablemente el mayor determinante de un mal resultado de la angioplastia y se asocia a mayores tasas de eventos adversos. En la actualidad existen distintas técnicas de modificación de la placa basadas en balones o en dispositivos específicos. El conocimiento de sus características y su uso adecuado son aspectos clave para el tratamiento óptimo de las lesiones calcificadas. Este artículo de posicionamiento, promovido desde la Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC), describe las técnicas de modificación de la placa existentes en la actualidad y propone un algoritmo para el tratamiento de la lesión calcificada.

Palabras clave: Lesiones coronarias calcificadas. Técnicas de modificación de la placa. Imagen intracoronaria.

Abbreviations


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IMPLICATIONS OF CALCIFICATION IN PERCUTANEOUS CORONARY INTERVENTIONS

Vascular calcification is a process closely associated with atherosclerosis. It can occur in the media (in peripheral arteries mainly) or intima layers (in coronary arteries). In the context of coronary atherosclerosis, it debuts in intermediate or advanced stages in plaque evolution due to conversion of smooth muscle cells into osteoblast phenotypes and infiltration of atheromatous plaque due to macrophages that clear out apoptotic smooth muscle cells and contain calcified vesicles.1 Atheromatous plaque calcification can take different shapes that probably correspond to different stages of the same disease like microcalcifications (< 15 μm), punctiform calcifications (circular arc < 90º), leaves or thin calcium layers (circular arc > 90º or > 3 mm in length), and calcium nodules.1

The main risk factors associated with coronary artery calcification are age, Caucasian race, diabetes mellitus, and chronic kidney disease.1

Table 1. Intracoronary imaging modalities for calcified coronary artery lesion classification

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Calcium pattern</th>
<th>Calcium arc</th>
<th>Calcium thickness</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT</td>
<td>++++</td>
<td>++++</td>
<td>Parietal calcium: low reflectivity structure with demarcated borders and without posterior shadowing (figure 1A)</td>
<td>Allows quantification</td>
<td>Allows quantification</td>
<td>Can be measured</td>
</tr>
<tr>
<td>IVUS</td>
<td>++++</td>
<td>++++</td>
<td>Parietal calcium: hyperechogenic structure with posterior shadowing (figure 1B)</td>
<td>Allows quantification</td>
<td>Allows quantification</td>
<td>Cannot be measured due to posterior shadowing. Reverberations are a marker of thin calcium (&lt; 0.5 mm)</td>
</tr>
</tbody>
</table>

Calcification complicates percutaneous coronary interventions (PCI) for various reasons: a) resistance to the advance of different devices especially in the presence of tortuosity (eventually, ‘non-crossable’ lesions); b) reduced plaque compliance that will eventually require higher pressure in dilatation balloons or plaque modification devices (‘non-dilatable’ lesions); and c) difficulties advancing the stent and expanding it.5 Other issues would be malapposition and polymer damage that can lead to a non-homogeneous release of antiproliferative drugs. Everything combined makes calcification one of the major determinants of the SYNTAX score,6 and associated with worse PCI outcomes and higher rates of adverse events at follow-up including mortality in patients with extremely calcified coronary artery lesions.7 In addition, it increases the rate of procedural complications associated with calcification per se and with the tools necessary for treatment: coronary artery dissection, loss of side branches, PCI material entrapment, stent distortion or even stent loss, and the dreaded coronary artery perforation that is particularly severe since it is very difficult to advance any kind of sealing materials.8

To stop these issues and their prognostic implications from happening numerous plaque modification devices have been developed. The appropriate use of these devices is essential to perform safe and effective PCIs on calcified coronary artery lesions.

This position paper has been promoted by the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) with contributions from different expert professionals in this setting. It describes the plaque modification techniques currently available in our field and proposes an algorithm for the management of calcified coronary artery lesions.

INTRACORONARY IMAGING MODALITIES FOR CALCIFIED LESION ASSESSMENT

Intracoronary imaging modalities play a key role in the assessment of calcified coronary artery lesions. The use of optical coherence tomography (OCT) or intravascular ultrasound (IVUS) can be very useful to improve the detection and assessment of coronary artery calcium, select the plaque modification technique, and optimize results especially in association with stent expansion.

Calcification detection and assessment

Angiography is a limited sensitivity tool to detect coronary artery calcium. Unlike angiography both the IVUS and the OCT have higher sensitivity and specificity to assess the characteristics and degree of calcification, which are basic aspects to determine the therapeutic options.2,9 Table 1 shows the differences of these 2 intracoronary imaging modalities regarding calcium detection. The main difference between the 2 is that, since calcium creates posterior acoustic shadowing on the IVUS, calcium thickness cannot be properly assessed. As alternative marker, the presence of reverberations on the IVUS has been associated with the presence of thinner calcium layers (< 0.5 mm). On the OCT, parietal calcium

IVUS, intravascular ultrasound; OCT, optical coherence tomography.
risks of stent underexpansion if proper plaque preparation is lacking. If calcium arc > 360º (score = 2), length > 5 mm in length (score = 1), and thickness > 0.5 mm (score = 1). Lesions with scores > 2 have a higher risk of stent underexpansion if proper plaque preparation is lacking. A similar scale has been developed for IVUS using 4 different criteria: calcium arc > 180º (score = 2), length > 5 mm (score = 1), and thickness > 0.5 mm (score = 1). Lesions with scores > 2 are indicative of the need for plaque modification prior to stenting. 

**Table 2. Intracoronary calcium scores based on optical coherence tomography and intravascular ultrasound**

<table>
<thead>
<tr>
<th>OCT/IVUS</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Máximo arco de calcio</td>
<td>≤ 180°: 0, &gt; 180° (&gt; 50%* of arc circumference): 2, 270° and &gt; 5 mm in length: 1, 360°: 1</td>
</tr>
<tr>
<td>Máximo grosor de calcio</td>
<td>≤ 0.5 mm: 0, &gt; 0.5° mm: 1</td>
</tr>
<tr>
<td>Longitud de calcio</td>
<td>≤ 5 mm: 0, &gt; 5° mm: 1</td>
</tr>
</tbody>
</table>

* Rule of 5: Lesions where calcium occupies > 50% of the arc circumference extend longitudinally > 5 mm and have > 0.5 mm of thickness require advanced calcium modification techniques.

**Ballooon-free techniques**

**Rotational atherectomy**

The rotational atherectomy (RA) technique uses a metal olive-shaped burr covered with diamond crystals in its distal third that rotates at high speed and performs a differential cut when advancing through the vessel (figure 2A) while pulverizing calcified tissue and preserving the adjacent elastic tissue. It appeared over 30 years ago to facilitate the management of coronary artery lesions by reducing plaque burden. Early enthusiasm turned into an elevated use of RA in different settings without the proper scientific back-up. This triggered suboptimal results that reduced its use to highly selected cases only. Through all these years, RA has evolved with technological improvements, and also of the technique itself, as well as the selection of patients.

Currently, the ROTAPRO system (Boston Scientific, United States) is available. It has made the technique easier because it has replaced the pedal of the early version for a button placed on top of the olive-shaped burr advancer. There is another button on the side of the advancer to change to the Dynaglide mode (rotation at low revolutions is advised to introduce and remove the burr). Console is smaller and comes with a digital screen. Size of the burrs is between 1.25 mm and 2.5 mm, and they are compatible with...
6-Fr-to-8-Fr catheters based on the size of the olive-shaped burr that advances on a 0.009 in specific guidewire (0.014 in the radiopaque side) of which 2 different versions exist (RotaWire Floppy and RotaWire Extra-Support) that should be used depending on the characteristics of the plaque and support needed. 13

The main indication is to treat extremely calcified non-crossable or non-dilatable coronary artery lesions with balloon. Probably, the optimal scenario is a concentric calcified lesion with a smaller luminal area compared to the olive-shaped burr. Eccentric angled lesions are less favorable since they are associated with a higher risk of complications. 13,15 It can be used as a primary or a bailout strategy after ‘balloon failure’. The primary strategy has been associated with shorter procedures, less radiation and contrast, and probably lower cost regarding the material used. 15

The target of RA has also changed from the old idea of removing as much plaque as possible (debulking) to the modern approach of modifying plaque to “facilitate” the PCI. Technical recommendations to perform RA have evolved too. Current recommendations are shown on table 3. 16

The most common complication is slow/no-flow although its rate has dropped down to 2.6%. 17 It is due to debris embolization towards microcirculation and there is higher risk in long lesions where multiple and prolonged passes with large olive-shaped burrs are performed without proper pauses among them and in the presence of a poor distal vessel. The management of dominant right coronary or left circumflex coronary arteries can be associated with transient conduction disorders. Severe complications like burr entrapment, perforation, and coronary dissection are rare. 13 Factors predisposing burr entrapment are lesion severity, steep angulations, and the use of very small burrs. Tortuosity and the lack of guide catheter coaxiality in the management of ostial lesions can trigger dissections and coronary perforations.

Although RA has demonstrated that it facilitates PCI with higher rates of success compared to balloon angioplasty, No clinical benefit has been yet confirmed.18-21

To analyze its results we should mention that RA has been used in patients of higher clinical risk with more complex coronary artery lesions.22 Another aspect we should take into consideration is the high percentage of cases where this technique was used as a bailout strategy (12% to 50%) 20,21,23 meaning that without RA these cases would not have been performed or had had worse results. Although ongoing trials are studying the advantages of elective or bailout RA, proper patient and lesion assessment should lean towards increasing its elective or earlier use with a potential beneficial impact on clinical outcomes. 24

In conclusion, when performed under the current recommendations RA is a safe and effective procedure. It should become part of our therapeutic arsenal in our cath labs with trained personnel for proper use.

Orbital atherectomy

The Diamonback-360 [OAS] device [Cardiovascular Systems, United States] is a diamond-coated bidirectional orbital crown that uses a combination of centrifugal force [by creating elliptical orbits] and friction to the surface to modify the calcified plaque and increase compliance (figure 2B). Also, with the pulsatile impact of the crown after speeding up, microfractures can occur that eventually modify deep calcium layers (figure 2B and figure 3). That is why a single 1.25 mm crown can treat vessels from 2.5 mm up to 4 mm.

Compared to the remaining plaque modification techniques, this orbital atherectomy [OA] has arrived late to our country and our experience is still scarce.
its main indication is to treat no-dilatable calcified coronary artery lesions.26

Preparation is very similar to RA, but here a specific guidewire is needed, the Viper-Wire. Crown advances with the Glide-Assist system (rotation at low revolutions) until coming close to the lesion. Another distinctive feature of this device is its antegrade and retrograde ablation functionalities. Unlike RA, the speed at which the device moves forward needs to be very slow (between 1 mm and 3 mm per second) to guarantee good procedural results and reduce complications.17,26 The mechanism of action of OA consists of the crown elliptical rotation that achieves a gradual increase of orbital diameter as rotation speed increases from 80 000 rpm up to 120 000 rpm. Cycles ≤ 30 seconds are advised (it comes with a sound warning signal to end the cycle) with pauses needed, the Viper-Wire. Crown advances with the Glide-Assist system (rotation at low revolutions) until coming close to the lesion. Another distinctive feature of this device is its antegrade and retrograde ablation functionalities. Unlike RA, the speed at which the device moves forward needs to be very slow (between 1 mm and 3 mm per second) to guarantee good procedural results and reduce complications.17,26 The mechanism of action of OA consists of the crown elliptical rotation that achieves a gradual increase of orbital diameter as rotation speed increases from 80 000 rpm up to 120 000 rpm. Cycles ≤ 30 seconds are advised (it comes with a sound warning signal to end the cycle) with pauses between 20 and 30 seconds among them that can duplicate in cases of poor hemodynamic tolerance.26 The continuous infusion of a lubricant solution is necessary to minimize thermal lesions during OA. Also, 18 mL/min are administered to cool the device down and get rid of debris, thus reducing the chances of ischemia and distal embolization.13,26,27

Complications are similar to those of RA. However, the possibility of retrograde application reduces the chances of crown entrapment and the risk of dissection or perforation in angulated or ostial lesions. The rate of perforation is between 0.7% and 2%.25,26 Theoretically speaking, the debris created by OA is smaller compared to the debris created by RA. This added to the fact that the crown does not stop coronary flow during atherectomy reduces the risk of slow/no-reflow and endothelial thermal lesion.27 However, transient conduction disorders are not rare when dominant right coronary or left circumflex arteries are treated. Current evidence available is based on the ORBIT I28 and ORBIT II28 clinical trials where OA obtained good results regarding procedural success (94% and 89%, respectively) with higher rates of major adverse cardiovascular events (MACE), and target lesion failure of 23.5% and 7.8%, respectively, at 3 years.31 Afterwards, the COAST trial32 was conducted where the new MicroCrown system was used. A total of 100 patients were included with rates of procedural success and MACE of 85% and 22.2%, respectively, at 1-year follow-up. We are waiting to see the results from the ECLIPSE trial that will randomize a total of 2000 patients with severe calcifications to receive OA or balloon predilatation prior to by drug-eluting stent implantation.

In conclusion, OA is another calcium plaque modification technique with potential technical advantages like having only 1 size of crown compatible with 6-Fr to treat all lesions and with pull-back capabilities. Although there are insufficient data from comparative studies, choosing this technique will depend on the profile of the patient and the lesion to be treated, the intracoronary being an essential aspect.

**Excimer laser**

Excimer laser coronary angioplasty (ELCA) is based on a xenon chloride laser that generates short ultraviolet pulses of 308 nm that only penetrate 50 µm in depth, which makes it safer compared to old continuous-wave-near-infrared lasers. It modifies the plaque through a triple mechanism: photochemical (by breaking molecular bonds), photothermal (through tissue vaporization), and photokinetic (through the expansion and collapse of the bubble of the catheter tip as it moves forward). Fragments released are <10 µm, which minimizes microvascular damage after being absorbed by the reticuloendothelial system.

The system currently used is the CVX-300 Laser System (Philips) although there is already a new generation one, the LAS-100 Laser System (Philips) that will be replacing it shortly (figure 2C). There are different sizes of catheters available [0.9 mm, 1.4 mm, 1.7 mm, and 2.0 mm] [table 4]. The selection of the catheter depends on the type of lesion and size of the vessel (catheter to vessel diameter ratio, 0.5–0.6) being the 0.9 mm catheter the most widely used for its lower profile and because it can reach higher fluency [80 mJ/mm²], pulse repetition rate (80 Hz), and longer application durations [10 seconds with 5-second rests], which increases the chances of success in fibrous calcific plaques.32,33

Before being used, it is necessary to calibrate the console and then the catheter. In both cases, health professionals and patients should use protective glasses to prevent eye damage. Afterwards, a 0.014 in intracoronary guidewire is inserted until it reaches the lesion. There is a monorail system to facilitate moving forward. Energy is released through the catheter distal border as it slowly advances (0.5 mm/second) to modify the plaque. Catheter withdrawing can also be applied. It is important to optimize support to ensure that the catheter advances. There is no limit in the number of pulses that can be administered since the more it is used, the stronger the effect. However, there is also a higher risk of complications involved. Some authors suggest a maximum of 12 applications.31 The state of the vessel should be assessed after each application. Regarding the selection of parameters, traditionally it started at 45 mJ/mm², and 25 Hz. However, more and more operators prefer higher energies and initial frequencies especially to treat resistant or calcified lesions.31
Before and during the applications, the blood vessel should be washed, and contrast administered through the infusion of a physiological saline solution (1 mL/s to 3 mL/s). In resistant lesions with severe calcification or underexpanded stents, more energy may be needed. This can be reached by not washing the blood with the physiological saline solution or even administering contrast during applications (the so-called “explosion technique”). This technique reaches maximum power although it increases the chances of complications. Some authors recommend it as the first option to treat non-thrombotic lesions, although it seems reasonable to spare it for ELCA-resistant lesions with saline infusion.

Traditionally, the indications for ELCA have been categorized into two different groups: “thrombotic” [not discussed in this document] and “calcified” lesions [non-thrombotic like in-stent restenosis, chronic total coronary occlusions, calcified lesions, etc.]. The latter can be categorized into non-crossable or non-dilatable lesions:

**Non-crossable lesions**

The laser main advantage is that it is compatible with all intracoronary guidewires. Therefore, non-crossable lesions with balloon/microcatheter are its main indication. In a multicenter registry of non-crossable lesions, the rate of procedural success was 87.3% with 0.8% of dissections showing an impaired flow and no perforations. Severe calcification has been associated with a higher probability of technique failure since ablation is primarily performed in the tissues between calcium. However, the use of ELCA with contrast can increase its chances of success in these lesions.

**Non-dilatable lesions**

Although the success of ELCA in non-dilatable lesions is high, it has never been the first-line therapy. Among these lesions, an interesting scenario is in-stent lesions (restenosis or underexpansion). In acute underexpansion, ELCA could be the treatment of choice. It allows the modification of resistant tissue located behind the stent without changing its architecture. Its use with contrast can be safer thanks to the stent “protective” effect. Isolated cases and small case series with success rates > 95% and few complications have been published.

It is a safe technique when the recommendations given are observed. Coronary artery dissection is the most common complication, although it is rarely flow-limiting (1%). The rate of coronary artery perforation is < 1%, and distal embolizations and ventricular arrhythmias are exceptional.

In conclusion, ELCA is especially useful to treat non-crossable lesions thanks to its compatibility with all kinds of angioplasty guidewires. It has also proven effective to treat non-dilatable lesions including in-stent lesions. However, there is still scarce information on its efficacy in calcified coronary artery lesions.

**Table 4. Characteristics of Excimer laser coronary angioplasty catheters**

<table>
<thead>
<tr>
<th></th>
<th>0.9 mm-X 80</th>
<th>1.4 mm</th>
<th>1.7 mm</th>
<th>2 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compatible guide catheter</td>
<td>6-Fr</td>
<td>6-Fr/7-Fr</td>
<td>7-Fr</td>
<td>8-Fr</td>
</tr>
<tr>
<td>Minimum vessel diameter (mm)</td>
<td>2</td>
<td>2.2</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Energy (mJ/mm²)</td>
<td>30-80</td>
<td>30-60</td>
<td>30-60</td>
<td>30-60</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>25-80</td>
<td>25-40</td>
<td>25-40</td>
<td>25-40</td>
</tr>
<tr>
<td>Application/pause time (seconds)</td>
<td>10/5</td>
<td>5/10</td>
<td>5/10</td>
<td>5/10</td>
</tr>
</tbody>
</table>

**Figure 3. Characteristics of orbital atherectomy catheter and its effects. (Modified with permission from Cardiovascular Systems.)**

**Figure 4.** Characteristics of Excimer laser coronary angioplasty catheters

**BALLOON-BASED TECHNIQUES**

**Cutting and scoring balloons**

Cutting balloons (CB) are plaque modification devices that appeared as an alternative to old coronary angioplasty balloons. Their objective is to achieve controlled ruptures of the plaque (through incisions in fibrocalcific tissue) (figure 4), thus facilitating balloon expansion, minimizing damage to the intima layer, and reducing stenosis.
There are 2 different types: CB and scoring balloon (BS). Their use has been described in different settings like in-stent restenosis, aorto-ostial lesions, bifurcations, and small vessels associated with the use of drug-eluting stents.\(^\text{42}\) The main limitations of CBs are their worst navigability and crossing profile compared to conventional balloons. However, over the past few years, both aspects have improved. SBs are associated with better navigability compared to old CBs.

The most dreaded complication is the rupture of coronary artery, although it has significantly increased following its use.

The main difference among the different devices lies in their different external atherotomy elements as described herein (figure 5).

**Cutting Balloon Flextome**

Cutting Balloon Flextome (Boston Scientific, United States) consists of a noncompliant (NC) balloon with 3 microrazors longitudinally mounted on the surface. Its superiority over conventional balloons in A/B lesions has not been confirmed yet, which is why, so far, its use is limited to complex and calcified lesions only.\(^\text{43}\)

**WOLVERINE**

Wolverine (Boston Scientific, United States) is an evolution of the former one with a better crossing profile, greater flexibility, and a more visible tip.

**AngioSculpt**

AngioSculpt (Spectranetics, United States) is a semicompliant balloon with low crossing profile surrounded by 3 nitinol filaments arranged in a helical cage to secure balloon anchorage. There is a lower risk of dissection or perforation associated with this device.\(^\text{17}\) It provides more flexibility and better navigability compared to old CBs,\(^\text{44}\) as well as good results compared to dilatation with semicompliant balloons.\(^\text{45}\)

**Scoreflex**

Scoreflex (OrbusNeich, Hong Kong) is a NC consisting of a NC balloon with a nitinol dual-wire system to facilitate the controlled modification of the plaque at low pressures. It has a low profile and a combination of hydrophilic and hydrophobic coating that minimizes friction during lesion crossing.

**Grip**

Grip (Acrostan, Switzerland) is a high-pressure balloon with 4 rows of 3 or 4 knobs in each row. It allows dilatations of up to 22 atm. It comes with a cone-shaped tip in 2 different versions: Grip with a short 2 mm tip, and Grip TT with a long 4 mm tip for greater navigability in tortuous anatomies. It comes with a hydrolubricated coating on its tip and the catheter, which facilitates both its anchorage to the lesion and navigability across lesions.

**NSE Alpha**

NSE Alpha (B. Braun, Germany) is a SB with 3 nylon scoring elements and 1 triangular cutting section connected in both borders of the balloon and arranged in a 120º disposition. We should mention its flexibility and navigability with good results in de novo lesions and in-stent restenosis.\(^\text{18}\)

**NaviscoreTM (iVascular, Spain)**

NaviscoreTM (iVascular, Spain) is a SB with a design that combines the benefits of SB plus CB. It consists of a high-pressure balloon with 125 μm nitinol filaments. These have an axial orientation for greater crossing abilities and flexibility, and plaque modification in a 90º angle, which is associated with lower chances of perforation. The catheter hydrophilic coating improves its navigability.

In conclusion CBs and SBs are useful plaque modification devices to treat non-dilatable lesions when calcification is not very severe. Their main advantage is how easy they are to use since it is a balloon-based technique compatible with conventional angioplasty guidewires.

**Very high-pressure balloons**

The NC very high-pressure balloon (VHPB) OPN (SIS medical, Switzerland) is a double-layer balloon for homogeneous expansion at
extremely high pressures without increasing its diameter (from 2 mm to 4 mm) with a rated burst pressure of 35 atm, although the manufacturer’s testing rated burst pressure limit is 45 atm [table 5].

The VHPB has been used for over 10 years now and it has proven safe and effective in up to 40 atm in extremely calcified coronary artery lesions where other devices have failed or in stent underexpansion. Success rates are as high as 75% to 100% without evidence of dissection, perforation or balloon bursts in small case series. Compared to conventional NC balloon, it can achieve minimum luminal diameters and major acute gains with less residual stenosis in non-dilatable lesions.

The largest registry ever conducted to this date included 326 patients with non-dilatable lesions treated with VHPB after failed NC balloon. Patients were categorized into 2 groups: those who responded to pressures between 30 atm and 40 atm, and those who responded with pressures > 40 atm. Procedural success was reached in up to 96.6% of the patients. A total of 53% of the patients responded to pressures between 30 atm and 40 atm while the remaining 47% did so to pressures > 40 atm. A total of 180 patients were treated with intracoronary imaging modalities and 106 of these showed calcifications > 270°. In this subgroup of patients, the pressured needed for optimal expansion was > 40 atm in 78.3% of the cases. Three patients (0.9%) showed coronary artery ruptures that resolved with prolonged inflation or covered stent implantation. In the 3 cases, the ruptures occurred during predilatation and were associated with balloon bursts with pressures between 30 atm and 40 atm. This is suggestive that perforations don’t seem to be associated with inflation pressure but with the characteristics of the plaque or the vessel size estimate that was angiographic in the 3 cases reported.

The ISAR-CAL trial was published back in 2021. It randomized 70 patients with extremely calcified coronary artery lesions and failed predilatation with NC balloon to receive a SB or a VHPB. The study primary endpoint was to compare stent expansion on the OCT. No differences were reported in the percentage of stent expansion. However, differences were seen in angiographic secondary endpoints like improved minimum luminal diameters and residual stenoses favorable to VHPB.

Finally, chronic total coronary occlusions are the pinnacle of calcified complex lesions. In the PLACCTON trial the use of the VHPB both...
alone and with other plaque modification techniques was safe and effective in selected cases with chronic total coronary occlusions.\textsuperscript{53}

In conclusion, the VHPB is a safe and effective alternative to treat non-dilatable calcified coronary artery lesions. Randomized clinical trials better defining this device strategy of use and the remaining plaque modification techniques are lacking.

**Intracoronary lithotripsy**

Intracoronary lithotripsy (ICL) system consists of a specific balloon catheter (Shockwave Medical, United States) connected to a rechargeable portable generator (figure 2D). The generator produces energy pulses that are transmitted to emitters placed inside the balloon. Pulses are emitted at a frequency of 1 per second up to a maximum of 10 pulses per application. Each balloon catheter can administer a maximum of 80 pulses. The catheter consists of a rapid-exchange semicompliant balloon with a 0.042 in crossing profile compatible with any 0.014 guidewires and 6-Fr guide catheters.

Its main indication is to treat calcified non-dilatable coronary artery lesions.

A 1:1: ratio between the vessel and balloon diameters is advised. Once it has been placed inside the lesion, the balloon inflates up to 4 atm to secure proper contact between the balloon surface and the vascular wall to allow energy transfer. The balloon includes 2 emitters that receive an electric discharge from the generator that vaporizes the fluid inside generating sound waves that have a local effect. Each pulse releases the equivalent of 50 atm.

These waves run across soft tissues causing selective calcium microfractures at intima and media layer level. After pulse emission and the corresponding modification of calcium, the balloon inflates up to 6 atm to maximize luminal gain. Balloon catheter is only available at a length of 12 mm and comes in diameters of 2.5 mm, 30 mm, 3.5 mm, and 4.0 mm.\textsuperscript{54}

The greatest evidence available comes from the Disrupt-CAD III trial, a prospective registry that assessed the efficacy and safety profile of ICL in 431 patients with calcified lesions. The 30-day rate of MACE (death, infarction or target lesion revascularization) was 7.8% while the rate of effectiveness (procedural success with complete plaque modification) was 92.4%. No patients with acute myocardial infarction or complex lesions were included in this study.\textsuperscript{53}

Recently, 12-month follow-up results have been published confirming rates of MACE and stent thrombosis of 13.8% and 1.1%, respectively.\textsuperscript{54}

Controlled break down of coronary calcium is the basis of treatment of ICL balloons. In an OCT substudy of the Disrupt-CAD II trial after ICL calcium fractures were seen in 79% of the lesions\textsuperscript{50} compared to 67% of the lesions of the Disrupt-CAD III trial.\textsuperscript{53}

Although the use of ICL balloons has become very popular worldwide, information on its safety and efficacy profile regarding its use in complex settings is still scarce (acute coronary syndrome, chronic total coronary occlusions, bifurcations or aorto-ostial lesions). As a matter of fact, its use is often limited to isolated cases or short series.\textsuperscript{52} The main limitations of this system are its reduced crossing profile in extremely calcified or tortuous stenoses and difficult use in diffuse or multivessel lesions (due to the limited number of pulses per catheter and the different caliber of target vessels).

A recent trial assessed the use of underexpanded stents due to severe coronary artery calcification and confirmed angiographic success rates of up to 73%, which is lower compared to the 75% seen in native lesions\textsuperscript{56} probably because it is more difficult to expand a calcified lesion when the stent has already been deployed. Therefore, regardless of the technique used, stenting is ill-advised until the lesion has been properly prepared. Also, the application of lithotripsy in this context, especially on freshly implanted stents, can cause structural damage to the polymer.\textsuperscript{57} Another multicenter registry proved the device was successful 92.3% of the times in this type of lesions.\textsuperscript{53} Mid- and short-term data on the safety profile of this technique are still lacking.

The combined use of ICL balloon and other plaque modification devices like RA,\textsuperscript{59} OA\textsuperscript{60} or ELCA\textsuperscript{61} has been described, and it seems like a very attractive strategy in cases where the ICL balloon cannot reach the target lesion.

In conclusion, ICL has grown exponentially in the management of non-dilatable calcified coronary artery lesions thanks to its safety and efficacy profile, and short learning curve. However, information on its use in complex scenarios and comparative results with other plaque modification techniques are still lacking.

**COMBINED TECHNIQUES**

There is not much evidence on the combination of devices or plaque modification techniques in extremely calcified coronary artery lesions.

The use of RA followed by CB (RotaCutting) [figure 4] or lithotripsy (RotaTripsy) [figure 6] has been described as an additional, safe, and effective technique.\textsuperscript{52-64} In both cases the concept is similar. Primarily, RA damages superficial calcium, but not the deepest calcium layers, and there are times when it is not enough for proper plaque preparation. On the other hand, CB or lithotripsy can complement the plaque modification provided by RA. However, when calcified lesions progress into very severe aortic stenosis, the target lesion can be difficult to reach with these balloons. In a combined use, RA modifies superficial calcium by creating a tunnel that the CB or lithotripsy balloon can use to move forward and, when in position, complete plaque modification. One of the differences between both techniques is that CB can contribute to breaking down the calcium layer in the absence of very severe calcification. The RotaTripsy technique\textsuperscript{59,63} can be more effective to treat extremely calcified coronary artery lesions with thick calcium layers. However, its cost is also higher. Based on a similar concept, the combination of OA plus lithotripsy has been recently described with good results.\textsuperscript{60}

RA has also teamed up with ELCA (the RASER technique).\textsuperscript{65} Laser can be the only option in truly non-curable lesions to facilitate the advancement of a microcatheter, perform the Rotawire exchange, and complete the PCI. This can also be used similarly by combining laser plus OA.

The combination of ELCA plus lithotripsy (the ELCATripsy technique) has been described for cases where RA or OA are ill-advised like nearby lesions or at freshly implanted stent level. In these cases, laser can create a tunnel through which the lithotripsy balloon can advance without the risk or damaging the freshly implanted stent.\textsuperscript{61}

**ALGORITHM FOR THE OPTIMAL MANAGEMENT OF CALCIFIED CORONARY ARTERY LESIONS**

To select the most suitable plaque modification technique we need to become familiar with the characteristics of the different
techniques available, their indications, and risks (Table 6). Also, the patient’s clinical profile should be taken into consideration, as well as the characteristics of the lesion, the resources available, and the operator’s skills. In some complex cases, it can be reasonable to perform an ad hoc PCI for proper planning and even an angioplasty between 2 expert operators.

Current evidence available from comparative or clinical trials allowing us to select among the different plaque modification techniques available is very limited (Table 7). Therefore, although several algorithms have been proposed on the type of calcium and the plaque modification technique that should be used, there are no clear indications in the routine clinical practice guidelines. Currently ongoing studies may bring us more in-depth information in the future.

In cases of mild angiographic calcification and proper balloon expansion, further plaque preparation prior to stenting may not be required. However, when angiographic calcification is moderate or severe, the use of intracoronary imaging modalities is advised for their great utility to plan the procedure and optimize results (Figure 7).

Overall, it is useful to apply the “rule of 5”: lesions where calcium occupies < 50% of arc circumference, does not extend longitudinally > 5 mm, and thickness is not > 0.5 mm can be properly treated with high-pressure or modified balloons (CB or SB).

If these criteria are met or calcium nodules are spotted further advanced plaque modification techniques should be used. In addition to circumferential and longitudinal spread, and thickness, calcium depth is important as well since some techniques like RA act basically on the superficial—and not on the deep—portion of calcium plaque.

Lesions with extremely severe calcifications so stenotic that cannot be crossed with the IVUS or OCT probe probably need RA/OA or laser (that can be of choice if the lesion is non-crossable not even with a microcatheter to allow specific RA/OA guidewire exchange). Another alternative is to try predilatation with low-profile balloons that often allow early assessments with intravascular coronary imaging to guide the decision-making process as already described.

Balloon expansion after using these techniques will guide us on proper plaque preparation. Also, intracoronary images are very useful to confirm proper calcium modification to allow stent expansion. The effects of different techniques like the presence of fractures (with balloon or lithotripsy), superficial calcium sanding (with RA) or both effects (with OA) can be visible when intracoronary imaging modalities are used (Figure 6). After the use of ELCA, superficial and deep fractures have been described. However, effects may not be visible on the OCT and, same as it happens with ICL, that does not mean that the plaque has not been modified.

Based on the type of lesion and effects caused by these techniques, the combination of 1 or more of these techniques can be necessary to secure optimal stenting and favorable clinical outcomes.

**CONCLUSIONS**

Coronary artery calcification is probably the greatest determinant of poor PCI outcomes and incomplete percutaneous revascularizations,
Table 6. Comparison of the different plaque modification techniques available

<table>
<thead>
<tr>
<th>Techniques non derived from balloon technology</th>
<th>Techniques derived from balloon technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>OA</td>
</tr>
<tr>
<td>ELCA</td>
<td>CB</td>
</tr>
<tr>
<td>SB</td>
<td>VHPB</td>
</tr>
<tr>
<td>ICL</td>
<td></td>
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### Technical characteristics

<table>
<thead>
<tr>
<th>Description of the technology involved</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamond-coated olive-shaped burr rotating at high speed</td>
<td>Diamond-coated crown with elliptical rotation</td>
<td>Ultraviolet energy with photochemical, photothermal, and photokinetic effects</td>
<td></td>
</tr>
<tr>
<td>Diamond-coated crown with elliptical rotation</td>
<td>Ultraviolet energy with photochemical, photothermal, and photokinetic effects</td>
<td>NC balloon with longitudinal microrazors</td>
<td></td>
</tr>
<tr>
<td>Ultraviolet energy with photochemical, photothermal, and photokinetic effects</td>
<td>SC balloon with scoring elements on its surface</td>
<td>Double-layer NC balloon to allow very high-pressures</td>
<td></td>
</tr>
<tr>
<td>Double-layer NC balloon to allow very high-pressures</td>
<td>SC balloon emitting pulsatile mechanical energy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential cut/ Antegrade abrasion. Additional effect from crown vibration (+)</td>
<td>Differential sanding/ Antegrade and retrograde abrasion. Additional effect from crown vibration (+++)</td>
<td>Photoablation/vaporization</td>
<td></td>
</tr>
<tr>
<td>Photoablation/vaporization</td>
<td>Superficial cut of the plaque</td>
<td>Inflation at 35 atm to 40 atm</td>
<td></td>
</tr>
<tr>
<td>Superficial cut of the plaque</td>
<td>Lithotripsy/Calcium fragmentation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of devices</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 mm to 2.5 mm burr</td>
<td>1.25 mm crown</td>
<td>0.9 mm to 2 mm catheters</td>
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</tr>
<tr>
<td>2 mm to 4 mm</td>
<td>1.47 mm to 4 mm</td>
<td>1.5 mm to 4 mm</td>
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<tr>
<td>2.5 mm to 4 mm</td>
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<table>
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<tr>
<th>Compatible GC*</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
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</thead>
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<tr>
<td>6-Fr; 1.25 mm and 1.5 mm</td>
<td>6-Fr; 0.9 mm and 1.4 mm</td>
<td>6-Fr</td>
<td></td>
</tr>
<tr>
<td>7-Fr; 1.75 mm</td>
<td>7-Fr; 1.7 mm</td>
<td>6-Fr (some with 5-Fr)</td>
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</tr>
<tr>
<td>8-Fr; 2.0 mm and 2.15 mm</td>
<td>8-Fr; 2.0 mm</td>
<td>6-Fr</td>
<td></td>
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<tr>
<td>9-Fr; 2.25 mm and 2.38 mm</td>
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<td>6-Fr</td>
<td></td>
</tr>
<tr>
<td>10-Fr; 2.50 mm</td>
<td>6-Fr</td>
<td>6-Fr</td>
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<table>
<thead>
<tr>
<th>Type of compatible guidewire</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.009 in RotaWire (0.014 in the radiopaque part)</td>
<td>0.012 in ViperWire (0.014 in the radiopaque part)</td>
<td>Any 0.014 in guidewire</td>
<td></td>
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<tr>
<td>Any 0.014 in guidewire</td>
<td>Any 0.014 in guidewire</td>
<td>Any 0.014 in guidewire</td>
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<tr>
<td>Any 0.014 in guidewire</td>
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</table>

<table>
<thead>
<tr>
<th>Type of Console/System</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small without pedal (RotaPro)</td>
<td>Small without pedal</td>
<td>Large with pedal</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>Small without pedal</td>
<td></td>
</tr>
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### Indications and effects

<table>
<thead>
<tr>
<th>Main indication</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
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<tbody>
<tr>
<td>Plaque modification (non-dilatable calcified coronary lesions or only crossable through microcatheter)</td>
<td>Plaque modification (non-dilatable calcified coronary lesions or only crossable through microcatheter)</td>
<td>Plaque modification (non-crossable lesion, in-stent non-dilatable coronary lesions)</td>
<td></td>
</tr>
<tr>
<td>Plaque modification (non-crossable lesion, in-stent non-dilatable coronary lesions)</td>
<td>ISR</td>
<td>ISR</td>
<td></td>
</tr>
<tr>
<td>ISR</td>
<td>Optimization of stent expansion</td>
<td>Calcified plaque modification</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect on intimal or deep calcium layers</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal</td>
<td>Intimal and deep</td>
<td>Intimal and deep</td>
<td>Intimal</td>
</tr>
<tr>
<td>Intimal</td>
<td>Intimal</td>
<td>Intimal</td>
<td>Intimal and deep</td>
</tr>
</tbody>
</table>

| ISR | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Stent underexpansion | Chronic only | Chronic only | Acute or chronic | – | – | Acute or chronic | Recommended in chronic only |

<table>
<thead>
<tr>
<th>Advantages</th>
<th>RA</th>
<th>OA</th>
<th>ELCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usefulness in non-crossable lesion with balloon</td>
<td>Possibility of retrograde application (useful in angulated/ostial lesions)</td>
<td>No need for specific guidewire. 0.9 mm catheter (the most common one) compatible with 6-Fr</td>
<td></td>
</tr>
<tr>
<td>Greater availability compared to OA/ELCA</td>
<td>1 crown only for all cases (compatible with 6-Fr)</td>
<td>No need for specific guidewire. 0.9 mm catheter (the most common one) compatible with 6-Fr</td>
<td></td>
</tr>
<tr>
<td>It allows the use of guidewires in the side branches</td>
<td>Short learning curve. Compatible with 0.014 in and 6-Fr guidewires</td>
<td>Short learning curve. Compatible with 0.014 in and 6-Fr guidewires</td>
<td></td>
</tr>
<tr>
<td>It allows the use of guidewires in the side branches, Lower cost</td>
<td>Short learning curve. Compatible with 0.014 in and 6-Fr guidewires</td>
<td>Short learning curve. Compatible with 0.014 in and 6-Fr guidewires</td>
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</tr>
</tbody>
</table>

(Continues)
Table 6. Comparison of the different plaque modification techniques available (continued)

<table>
<thead>
<tr>
<th>Techniques non derived from balloon technology</th>
<th>Techniques derived from balloon technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>OA</td>
</tr>
<tr>
<td>Disadvantages</td>
<td></td>
</tr>
<tr>
<td>Long learning curve</td>
<td>Long learning curve</td>
</tr>
<tr>
<td>Need for specific guidewire</td>
<td>Need for specific guidewire</td>
</tr>
<tr>
<td>Need for large French sizes for large burrs</td>
<td>Worse crossing ability in non-crossable lesions with balloon</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>Major perforation/dissection</td>
<td>Moderate</td>
</tr>
<tr>
<td>Slow/No-Flow</td>
<td>Moderate</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>Moderate in dominant RCA/LCx</td>
</tr>
<tr>
<td>Entrapment</td>
<td>Moderate (greater with 1.25 mm burrs and severe angulated lesions)</td>
</tr>
<tr>
<td>Technical recommendations</td>
<td></td>
</tr>
<tr>
<td>Speeds of 135 000 rpm to 180 000 rpm</td>
<td>Speeds of 80 000 rpm to 120 000 rpm</td>
</tr>
<tr>
<td>Device/vessel ratio ≤ 0.6</td>
<td>Slow continuous forward and backward motion (useful in angulated/ostial lesions)</td>
</tr>
<tr>
<td>Pecking motion</td>
<td>Short cycles with pauses among them. Avoid angulated lesions</td>
</tr>
</tbody>
</table>

CB, cutting balloon; ELCA, Excimer laser coronary angioplasty; GC, guide catheter; ICL, intracoronary lithotripsy; ISR, in-stent restenosis; LCx, left circumflex artery; MC, microcatheter; NC, noncompliant; OA, orbital atherectomy; RA, rotational atherectomy; RCA, right coronary artery; SB, scoring balloon; SC, semicompliant; VHPB, very high-pressure balloon.

* The 1.75 olive-shaped burr is compatible with some 6-Fr guide catheter models although with some level of friction (it is 0.069 in thick and requires a 0.073 in internal catheter diameter).

and is associated with higher rates of adverse events. Intracoronary imaging modalities play a key role in the understanding of calcified coronary artery lesions, help us select the plaque modification technique we’ll eventually use, and optimize the PCI results. Knowing the different plaque modification techniques available is essential for the optimal management of calcified coronary artery lesions. Until comparative trials among techniques are conducted, it seems reasonable to combine them depending on the type of lesion. In addition, there are situations in which techniques should be combined to secure optimal stenting and the most favorable clinical outcomes.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

Table 7. Main clinical trials on plaque modification techniques

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Design and sample size</th>
<th>Type of lesion</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotational atherectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ROTAXUS\(^{14,34}\) (2013) | RCA of 240 p. (120 RA: 120 ST) | Moderate to severe calcification | – Successful strategy: RA, 92.5% vs ST, 83.3%; \( P = .03 \)  
– Acute luminal gain: RA, 1.58 mm vs ST, 1.44 mm; \( P < .01 \)  
– No significant differences regarding dissections, perforations or slow/no-reflow  
– Stent luminal loss at 9 months: RA, 0.44 mm vs ST, 0.31 mm; \( P = .04 \)  
– MACE at 9 months: RA, 24.2% vs ST, 28.3%; \( P = .46 \)  
– MACE at 2 years: RA, 29.4% vs ST, 34.3%; \( P = .47 \)  |
| PREPARE CALC\(^{21}\) (2018) | RCA of 200 p. AR vs MB (cutting or scoring) | Severe calcification | – Successful strategy: RA, 98% vs MB, 81%; \( P = .0001 \)  
– No significant differences regarding dissections, perforations or slow/no-reflow  
– Luminal loss at 9 months: RA, 0.22 mm vs MB, 0.16 mm; \( P = .21 \)  
– TLR at 9 months: RA, 2% vs MB, 7%; \( P = .17 \)  |
| **Orbital atherectomy** | | | |
| ORBIT I\(^{12}\) (2013) | NRPT of 50 p | Calcification (mild to severe) | – Procedural success (residual stenosis <20% after stenting): 94%  
– Rate of MACE at 6 months: 8%  
– Dissection: 12%  
– Perforation: 2%  |
| ORBIT II\(^{20,21}\) (2014) | NRPT of 443 p | Severe calcification | – Procedural success (stenosis < 50% after stenting without in-hospital MACE): 98.6%  
– Severe dissection: 2.3%  
– Perforation: 0.9%  
– Slow/no-reflow: 0.2%  
– MACE at 30 days and 3 years: 10.4% and 23.5%, respectively  |
| COAST\(^{29}\) (2020) | NRPT of 100 p | Severe calcification | – Procedural success (stenosis < 50% after stenting without in-hospital MACE): 85%  
– Dissection: 2%  
– Perforation: 2%  
– Slow/no-reflow: 2%  
– MACE at 30 days and 1 year: 15% and 22.2%, respectively  |
| **ELCA** | | | |
| Fernandez et al.\(^{28}\) (2013) | Observational trial of 58 p | – Balloon failure (non-crossable or non-dilatable lesions) treated with ELCA ± RA  
– Calcification > moderate: 82.1% | – Procedural success (stenosis < 20% after stenting without flow-limiting dissection or type II or III perforations): 91%  
– ELCA success isolated in 76.1%; ELCA after failed RA, 6.8% and ELCA + RA, 8.6%  
– Only 1 successful case of RA when ELCA failed  
– 4 procedural complications reported (1 transient slow flow, 1 side branch occlusion, and 2 perforations)  |
| ELEMENT\(^{37}\) (2014) | Observational trial of 28 p | – Stent underexpansion treated with high-energy ELCA with contrast after NC balloon failure  
– Calcification: 89.3% | – Laser success (increase ≥ 1 mm\(^2\) in SMA with IVUS or ≥ 20% MLD on the quantitative coronary angiography after predilatation with the NC balloon that failed before ELCA): 96.4%  
– Perioperative infarction: 7.1%  
– Transient slow flow: 3.6%  |
| LEONARDO\(^{58}\) (2015) | Observational trial of 100 p | – Balloon failure in complex lesions  
– Calcification: 57%  | – Procedural success (stenosis <50% after stenting): 91.7%  
– No perforations, dissections, significant side branch occlusions, spasms or lack of flow  |
| LAVA\(^{58}\) (2018) | Observational trial of 130 lesions | – Non-crossable lesions with balloon: 43.8%  
– Non-dilatable lesions with balloon: 40.8%  
– Moderate or severe calcification: 62%  
– ISR: 37%  | – Procedural success: 88.8% (93.8% in non-dilatable lesions and 83.7% in non-crossable lesions)  
– Perforation: 1.78%  
– Perioperative infarction: 0.86%  |
| Ojeda et al.\(^{34}\) (2020) | Observational trial of 126 lesions | – Non-crossable lesions with balloon  
– Calcification ≥ moderate: 62.7%  
– Chronic total coronary occlusion: 46%  | – Technical success (residual stenosis < 30% and TIMI grade-3 flow): 90.5%  
– Procedural success (technical success without in-hospital adverse events): 87.3%  
– Severe calcification associated with failed ELCA  |

(Continues)
### Table 7. Main clinical trials on plaque modification techniques (continued)

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Design and sample size</th>
<th>Type of lesion</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified balloons (cutting or scoring balloons), and VHPB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR-CALC&lt;sup&gt;50&lt;/sup&gt;</td>
<td>RCA of 74 p (VHPB vs SB)</td>
<td>Extremely calcified non-dilatable lesions with balloon</td>
<td>Stent expansion on the CTO similar compared to VHPB and SB (0.72 ± 0.12 vs 0.68 ± 0.13, P = .22) — VHPB: higher increase of MLD (2.83 mm ± 0.34 mm vs 2.65 mm ± 0.36 mm; P = .03) and less stenosis (11.6% ± 4.8% vs 14.4% ± 5.6%; P = .02) — No differences associated with procedural success</td>
</tr>
</tbody>
</table>

**Intracoronary lithotripsy**

| DISRUPT CAD III<sup>53,54</sup> | NRPT of 431 p | Severe calcification | Procedural success (residual stenosis < 50% without in-hospital MACE): 92.4% — Perioperative infarction: 6.8% — Severe dissection: 0.3% — Perforation: 0.3% — Slow or no-reflow: 0% — TLR at 30 days: 1.3% — Stent thrombosis: 0.8% — MACE at 1 year: 13.8% |

ELCA, Excimer laser coronary angioplasty; ISR, in-stent restenosis; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MB, modified balloon; MLD, minimum luminal diameter; NC, noncompliant; NRPT, non-randomized prospective trial; OCT, optical coherence tomography; p, patients; QCA, quantitative coronary angiography; RA, rotational atherectomy; RCA, randomized clinical trial; SB, scoring balloon; SMA, stent minimal area; ST, standard therapy; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; VHPB, very high-pressure balloon.

---

**Figure 7.** Central figure. Calcified plaque modification algorithm. ELCA, Excimer laser coronary angioplasty; NC, noncompliant; OA, orbital atherectomy; RA, rotational atherectomy; SC, semicompliant; VHPB, very high-pressure balloon.

0 Predilatation with low-profile balloons can be attempted. At times, this allows early assessment with intravascular imaging tools.

1 Of choice if microcatheter is unable to cross.

2 If lithotripsy balloon is unable to cross, predilatation can be attempted with balloon or combination of other techniques (Rotatripsy, Elcatripsy, Orbital-tripsy).

3 Currently, lithotripsy is preferred in the presence of acute stent underexpansion.

4 In addition to NC balloon final angiographic expansion, intracoronary imaging are useful to confirm the effect of the techniques used on plaque modification.


Debate. Drug-coated balloons for de novo coronary artery lesions. Still not enough evidence, and the new drug-eluting stents are still better

A debate. Balones liberadores de fármaco para lesiones coronarias de novo. Todavía no hay suficiente evidencia y lo mejor son los nuevos stents farmacoactivos

Manel Sabaté*

Sección de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Instituto Cardiovascular, Hospital Clínico, IDIBAPS, Barcelona, Spain

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https://doi.org/10.24875/RECICE.M22000346
which this indication should stand are those where the comparison stent should be a latest generation stent. Therefore, evidence from trials that compared the use of DCB vs conventional stents or first-generation DES should not be extrapolated to the current situation. Secondly, when the DCB strategy is analyzed in the de novo lesion setting, optimal lesion preparation should precede without flow-limiting dissections and residual stenosis of 30% at most. Only then the use of DCB is advised. We should remember that stents were designed to solve the potential risk of acute vessel occlusion after balloon predilation and that, incidentally, it also reduced the rate of restenosis. In this sense, like we have already seen in former studies, there will always be a percentage of lesions that will eventually need stenting as a bailout strategy after predilation. Thirdly, the type of balloon, type of drug used, formulation, and release are much more relevant when treatment with DCB is planned. Obviously, not all DCBs are the same in this setting, which means that the results from 1 study with a certain type of DCB shouldn’t be extrapolated to another DCB with a different formulation or drug release system. Finally, when dealing with de novo lesions the characteristics of these should be known such as calcifications, thrombus, size of the vessel, length, clinical syndrome, etc.

Therefore, while we await the results of the ongoing clinical trials we can use iopromide-based paclitaxel-coated balloons to treat de novo stenoses in small vessels after optimal lesion preparation for the lack of significant traits of risk of acute vessel thrombosis [lack of significant residual dissection, flow-limiting, etc.).

Q.: Do you think that there are differences in the results obtained from the studies and in the level of evidence according to the size of the target vessel?

A.: To know the exact role of sirolimus-based DCBs in the management of de novo coronary lesions is still premature. In such a hydrophilic drug, dose, formulation, and release are crucial to define its potential. Therefore, results can vary tremendously based on whether we’re dealing with phospholipid encapsulated sirolimus or a crystalline coating, for instance. Regarding the size of the vessel, the use of the DCB is spared for small caliber vessels (< 3 mm), and, among them, it seems like very small caliber vessels (< 2.5 mm) are the ones that can benefit the most from its use.7

Q.: In which cases would you consider using DCBs to treat de novo coronary artery lesions?

A.: Like I said before, the current evidence available supports its use to treat small caliber coronary vessels, and with a certain type of DCB only (iopromide-based paclitaxel-coated balloons, 3 μg/mm²).

Q.: What is the predilatation protocol, cross-over criteria, and specific DCB treatment technique in this setting?

A.: I use the DCB-only strategy, which involves good target vessel preparation, obtaining good angiographic results without clinically relevant residual dissections, and residual stenosis < 30%. It is in this setting where the bailout stent is not necessary that I use the DCB.

**FUNDING**

None whatsoever.

**CONFLICTS OF INTEREST**

M. Sabaté is a consultant for Abbott Vascular and iVascular.

**REFERENCES**

Debate. Drug-coated balloons for de novo coronary artery lesions. Evidence available and potential superiority in some settings

A debate. Balones liberadores de fármaco para lesiones coronarias de novo. Evidencia disponible y posible superioridad en determinados contextos

Bernardo Cortese*

Cardiovascular Research Group, Fondazione Ricerca e Innovazione Cardiovascolare, Milan, Italy

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https://doi.org/10.24875/RECICE.M22000347

QUESTION: What is the evidence available on the use of drug-coated balloons (DCB) in the de novo lesion setting?

ANSWER: The use of DCB to treat de novo lesions is the most compelling argument regarding this technology, an area that has advanced significantly over the last 5 years. Only recently, investigators and companies have begun to understand that this area also needed strong and reliable scientific evidence similar to the one provided for stent platforms, to understand the real safety and efficacy profile of DCB in the de novo lesion setting. Argument here is currently quite strong: the BASKET-SMALL 2 trial (700 patients) showed no differences at 3 years between paclitaxel-coated balloon and drug-eluting stents (DES), the EASTBOURNE (2100 patients) showed the 1-year safety and efficacy profile of the first sirolimus-coated balloon (target lesion revascularization, 5%), the PICCOLETO II trial showed fewer major adverse cardiovascular events with another paclitaxel-coated balloon compared to an everolimus-eluting stent in the small vessel setting at 3-year follow-up. Finally, the RESTORE SVD trial showed similar results with another paclitaxel-coated balloon at the long-term follow up and similar data vs DES. Interestingly enough, the long-term follow-up of the 2 latter trials was presented in September 2022 at the TCT Conference (late breaking clinical science session) confirming that this field is currently highly active.

Q: Do you think there is enough evidence to recommend their use in the routine clinical practice?

A: Evidence is compelling enough to recommend DCB in this setting. However, some simple rules should be applied: (1) we recommend using these devices in the in-stent restenosis setting under imaging guidance for proper lesion assessment. Therefore, treatment of small coronary vessels (< 2.5 mm) can be adopted. Afterwards, larger vessels should also be treated with DCB. The important thing here is to “have a good eye” to treat coronary artery dissections left after treatment [please see below]; (2) class effect does not exist for DCB. Therefore, only devices with robust clinical data should be used in this setting. Angiographic monitoring is often unnecessary unless DCB is used in a complex lesion setting without prior reliable experience or scientific evidence.

Q: Do you think that there are differences in the results obtained from the studies and in the level of evidence according to the size of the target vessel?

A: We believe that most DCBs can also be used for larger vessels (> 3 mm), but a wide use in this setting can be suggested in selected cases only where the stent is not seen as a safe enough solution (highly complex calcified lesions, trifurcations...). Also, the broader use of DCB requires more clinical data—that are still pending—which will hopefully be provided within the next 2 to 3 years. Unfortunately, direct comparisons among DCBs are not available yet except for a small, sponsored trial. A couple of years ago we “indirectly” compared a paclitaxel- and a sirolimus-coated balloon in the SIRPAC trial (1100 patients) showing no differences at 1 year regarding hard endpoints. The ongoing TRANSFORM I trial, which has recently completed the enrollment, is comparing paclitaxel- and sirolimus-based DCBs on mid-term angiographic and optical coherence tomography outcomes. This mechanistic study is important because it will shed light on the current effect of these drugs on the vessel wall, and on the role paclitaxel plays determining late lumen enlargement for a direct effect in the adventitia, something that is still to be proven by sirolimus. Finally, the ongoing TRANSFORM II trial that is comparing a sirolimus-based DCB to a DES will shed light on the long-term role of this technology. In this study, whose primary endpoint is TLF, patients with native vessel disease will be treated and followed for 5 years.

Q: In which cases would you consider using DCBs to treat de novo coronary artery lesions?

A: To be honest, given the drawbacks of stents in the small vessel disease and complex lesion settings, here a DCB would be our first choice due to the inherent safety of this technology. For example, in a heavily calcified coronary lesion, despite proper lesion preparation, we often prefer using a DCB when we are not totally sure...
that the stent will accommodate perfectly with an adequate expansion and apposition. The takeaway here is that DCBs can also lead to restenosis. However, they are safe and do not lead to thrombosis or acute vessel occlusion. Only in case of flow-limiting dissections or acute recoil, a bailout stent should be used after a DCB. Also, we should always remember that a stent-like result after DCB angioplasty should not be expected or is not needed either.

Q.: What is the predilatation protocol, cross-over criteria, and specific DCB treatment technique in this setting?

A.: This is a long topic of discussion, and dedicated courses should be followed to 'have a good eye' on DCB angioplasty. Our initial suggestion is to adopt a stepwise approach when performing a DCB angioplasty, which means that the main goal is to achieve good results after proper predilatation with whichever tools are available at the cath lab. We can still cross over to a stent angioplasty at any time before drug delivery so make the final choice between DCB and DES after lesion preparation only. Proper predilatation means final stenosis < 30% and no major or flow-limiting dissections. After this goal is achieved, the DCB can be used to cover the entire segment treated while keeping inflation for, at least, 30 seconds (possibly 60). In our routine clinical practice we use semi-compliant balloons, and quite often scoring balloons, but other centers use non-compliant balloons as the first choice. The balloon-vessel ratio should often be 1:1, but exceptions exist depending on the target lesion. In the end, type A or B dissections should be sought, and not feared (figure 1). Our group has previously demonstrated how these dissections are safe and not associated with acute vessel occlusions. Recently, investigators from Japan have shown how dissections are associated with improved penetration and increased lumen gain at 6 months after paclitaxel-based DCB angioplasty. To be considered 'expert' DCB users, stenting rate after DCB should be < 10%.

**CONFLICTS OF INTEREST**

None reported.

**REFERENCES**

Use of new technologies in the transfer of patients with STEMI. Results from the pilot test ODISEA APP

Aplicación de las nuevas tecnologías en los traslados de pacientes con IAMCEST. Resultados de la prueba piloto ODISEA APP

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c Laboratori de Gràfics i Imatge, Institut d’Informàtica i Aplicacions, Universitat de Girona, Girona, Spain
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To the Editor,

The use of new technologies applied to cardiology has proven effective for the patients’ clinical improvement,1 especially in certain situations like arrhythmias, heart failure or secondary prevention.2,3

In particular, the use of smartphones applied to the healthcare networks of patients with ST-segment elevation acute myocardial infarction (STEMI) is effective to share electrocardiographic tracing and improve the coordination of the different healthcare workers involved in the management of the patients. The result is shorter primary angioplasty times.4,5

This scientific letter discusses the results of a pilot test on the working of an application for both tablets and smartphones (ODISEA APP [Myocardial Infarction Safety Transfer]) built to improve the healthcare networks of patients with STEMI (figure 1).

The primary goal of this app is to improve the coordination of the healthcare personnel involved in the management of patients with STEMI who require transfer to a PCI-capable center. This improvement should shorten primary angioplasty times and avoid unnecessary transfers. Other goals are to increase patient safety (by registering the medication administered, giving recommendations to the primary care physician, discussing doubts, etc...), improve coordination at the cath lab with elective cases, prepare, in advance, the material needed, and improve the patient’s location after the primary angioplasty.

This is how the app works: when a patient with STEMI is first helped by a primary care physician, a non-PCI-capable emergency doctor or the doctor from the emergency medical team (EMT) in the house or on the street, the app is opened with a smartphone/table using the healthcare worker’s identification and working station. Afterwards, a short questionnaire is rapidly filled out with data from the patient and the infarction. The electrocardiogram tracing is added using the camera on the smartphone or the table.

The app sends a warning message with this information to the devices the EMT physicians carry, both to coordination and to the mobile units close to the patient and the PCI-capable reference hospital cardiology personnel (interventional cardiologist, cardiologist on call, interventional cardiology nurse, and nursing team at the cardiac surgery intensive care unit).

Based on the data entered the app:

- Creates an estimate time of diagnostic electrocardiogram-guidewire passage.6
- Makes suggestions on the most adequate medical management and treatment for the patient [antiplatelet, anticoagulation therapy].
- Opens a chat so the primary care physician can clear up doubts and agree on the best possible treatment with EMT physicians, the cardiologist on call, and the interventional cardiologists involved. All of them have access, in real time, to the information registered: data on the patient and the infarction sustained, electrocardiogram records, treatment administered, serious complications, etc.

If transfer for primary angioplasty is activated, the geolocation of the patient is started on the device of the EMT physician doing the transfer. From that moment onwards, the entire healthcare personnel involved can follow, in real time, the transfer of the patient to the PCI-capable hospital. The interventional cardiology unit can coordinate more precisely the elective activity of each cath lab available with up-to-the-minute information on the patient’s exact location. Also, by activating a warning message on the estimated time of arrival.

The medication administered, and serious complications reported moments before the patient gets to the cath lab are recorded.

The patient gets to the reference hospital cath lab on a treatment agreed by the entire healthcare personnel after solving all possible

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Table 1. Comparative summary of patients from the ODISEA APP pilot test

<table>
<thead>
<tr>
<th></th>
<th>ODISEA (98 patients)</th>
<th>NON ODISEA (129 patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>61 (13.9)</td>
<td>63 (13.1)</td>
<td>.1</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>21 (21.4%)</td>
<td>32 (24.8%)</td>
<td>.5</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>44 (44.9%)</td>
<td>50 (38.8%)</td>
<td>.3</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>48 (49%)</td>
<td>59 (45.7%)</td>
<td>.6</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>34 (34.7%)</td>
<td>54 (41.9%)</td>
<td>.2</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>18 (18.4%)</td>
<td>31 (24%)</td>
<td>.3</td>
</tr>
<tr>
<td>Previous AMI, n (%)</td>
<td>16 (16.3%)</td>
<td>16 (12.4%)</td>
<td>.4</td>
</tr>
<tr>
<td>Previous heart surgery, n (%)</td>
<td>3 (2.1%)</td>
<td>2 (1.6%)</td>
<td>.4</td>
</tr>
<tr>
<td>Anterior location, n (%)</td>
<td>39 (39.8%)</td>
<td>43 (33.3%)</td>
<td>.3</td>
</tr>
<tr>
<td>Killip grade &gt; 2, n (%)</td>
<td>5 (5.1%)</td>
<td>8 (6.2%)</td>
<td>.7</td>
</tr>
<tr>
<td>Location of the first medical contact</td>
<td></td>
<td></td>
<td>.5</td>
</tr>
<tr>
<td>EMT, n (%)</td>
<td>35 (35.7%)</td>
<td>39 (30.2%)</td>
<td></td>
</tr>
<tr>
<td>Outpatient, n (%)</td>
<td>38 (28.6%)</td>
<td>36 (27.9%)</td>
<td></td>
</tr>
<tr>
<td>Non-PCI-capable hospital, n (%)</td>
<td>35 (35.7%)</td>
<td>54 (41.9%)</td>
<td></td>
</tr>
<tr>
<td>Distance in km, mean (SD)</td>
<td>42 (19.3)</td>
<td>36 (21.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Sudden death, n (%)</td>
<td>1 (1%)</td>
<td>1 (0.8%)</td>
<td>.8</td>
</tr>
<tr>
<td>Diagnostic ECG-guidewire passage time in min, mean (SD)</td>
<td>112 (28)</td>
<td>122 (24)</td>
<td>.3</td>
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<tr>
<td>Patients with diagnostic ECG-guidewire passage time &gt; 120 min, %</td>
<td>26.2%</td>
<td>35.7%</td>
<td>.1</td>
</tr>
<tr>
<td>Diagnostic ECG-start of transfer time in min, mean (SD)</td>
<td>32 (8)</td>
<td>36 (10)</td>
<td>.5</td>
</tr>
<tr>
<td>Transfer time until arrival at the cath lab in min, mean (SD)</td>
<td>67 (21)</td>
<td>70 (19)</td>
<td>.6</td>
</tr>
<tr>
<td>Cath lab-guidewire passage time in min, mean (SD)</td>
<td>17 (7)</td>
<td>19 (6)</td>
<td>.5</td>
</tr>
<tr>
<td>AMI CODE not properly indicated, n (%)</td>
<td>7 (7.1%)</td>
<td>17 (13.2%)</td>
<td>.1</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; ECG, electrocardiogram; EMT, emergency medical team; SD, standard deviation.
doubts, with all the relevant information previously known, and in perfect coordination with the entire team.

Finally, the interventional cardiologist performing the primary angioplasty adds information confirming, or not, the «Infarction Code», the angiographic result, the patient’s clinical status, the primary angioplasty times, the complications reported during the procedure, and information on the unit the patient is being transferred to. Afterwards, the case is eventually closed.

A final report is then, created with a summary including all the data entered throughout the process that is sent to all the healthcare workers involved (primary care physician, EMT, cardiologist on call, and interventional cardiologist), which improves positive feedback.

This app has been designed in observance of all data confidentiality rules and regulations, with an obligation to authenticate, and with safe servers for data collection in full compliance with the General Data Protection Regulation (GDPR).

A pilot test was run with this app between September 2021 and January 2022. A total of 227 STEMIs transferred for primary angioplasty were included (in 98 cases the ODISEA APP was used as opposed to 129 where it wasn’t). A summary of results is shown on table 1. No significant differences were reported between both groups regarding the patient’s past medical history, the infarction location, the Killip grade or the place where the first medical contact occurred. Statistically speaking, patients treated with the ODISEA APP were further away from the PCI-capable center. A non-significant tendency was seen towards shorter primary angioplasty times (diagnostic electrocardiogram-guidewire passage) in the ODISEA compared to the NON ODISEA group (112 min vs 122 min; P = .3), a non-significant reduction of cases with times > 120 min (26.2% vs 35.7%, respectively; P = .1), and a tendency towards fewer cases eventually diagnosed as non-acute coronary syndrome (7.1% vs 13.2%; P = .1).

Finally, we should mention that this app has been created by a working group including EMT physicians, primary care practitioners, doctors from non-PCI-capable hospitals, interventional cardiologists, and cardiologists from cardiac surgery intensive care units.

FUNDING

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AUTHORS’ CONTRIBUTIONS

All the authors contributed to the development of this application and drafted the manuscript.

CONFLICTS OF INTEREST

None whatsoever.

REFERENCES

Emergency transcatheter aortic valve implantation in cardiogenic shock: a case report

Implante percutáneo de válvula aórtica emergente en shock cardiogénico: a propósito de un caso

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Runner-up case presented at the Madrid ACCIS 2022 Meeting

To the Editor,

Transcatheter aortic valve implantation (TAVI) is a therapeutic alternative that has proven safe and effective across different clinical settings. Over the last few years, more and more cases of «emergency TAVI» have been reported. Currently, this term is often used for those implantation procedures performed during admission due to decompensated heart failure although this concept includes very different situations. The therapeutic option to treat cardiogenic shock should be «emergency TAVI», that is, implantation performed within the first 72 hours after admission. This is the case of a patient with severe aortic stenosis who was transferred to our center with signs of cardiogenic shock.

This is the case of a 67-year-old man. The patient was a former smoker and a regular drinker. Initially, he had been admitted to a different center with early signs of heart failure. Arterial pressure at admission was 120/90 mmHg with global congestion and need for low-flow oxygen therapy. Diuretic treatment was started, and the echocardiogram revealed the presence of severe aortic stenosis with left systolic dysfunction. The patient had signs of liver (alanine aminotransferase, aspartate aminotransferase, and bilirubin levels of 1244 u/L, 1808 u/L, and 2 mg/dL, respectively, and normalized international ratio of 2), and renal failure (creatinine levels of 2.01 mg/dL), and arterial lactate levels of 2.8 mmol/L. Cardiac markers were high (N-terminal B-type natriuretic propeptide, and high-sensitivity troponin I levels of 6753 pg/mL, and 468-450 ng/mL, respectively). Given the progressive worsening of the patient, transfer to our center cardiac surgery intensive care unit was decided. After the patient’s arrival, cardiac catheterization was performed with a Swan-Ganz catheter. It revealed:

- Pulmonary artery and aortic saturation of 56% and 98%, respectively (nasal cannula at 2L).
- Pressure: right atrium, 16 mmHg; pulmonary artery, 55/35/42 mmHg; pulmonary capillary wedge pressure, 32 mmHg; aorta, 110/80/90 mmHg.
- Cardiac output (thermodilution): 2.8 L/min.

The echocardiogram confirmed the presence of a left ventricular ejection fraction of 10% with moderate mitral regurgitation [video 1 of the supplementary data] and severe aortic stenosis [figure 1A]. The levels of arterial lactate upon the patient’s arrival were 3.6 mmol/L. Given the situation of normotensive cardiogenic shock, inotropic treatment with dobutamine [up to 12 mcg/kg/min] was initiated. It improved cardiac index up to 2.2 L/min/m² and brought lactate levels back to normal within the first 8 hours after admission. A computed axial tomography (that same afternoon) and coronary angiography (the next morning, figure 1B) were performed. The screening results obtained were favorable for transcatheter aortic valve implantation:

- Tricuspid aortic valve. Coronary artery calcium score, 2100.
- Aortic annulus: perimeter, 88 mm; area, 556 mm².
- Sinus segment: 35 mm x 33 mm x 33 mm.
- Distance between annulus and left main coronary artery: 11 mm; to right coronary artery, 17 mm.
- Significant lesion to the ostial left anterior descending coronary artery with distal TIMI-grade 3 flow (Thrombolysis in Myocardial Infarction) and no data suggestive of complications. Chronic total coronary occlusion of right coronary artery.
- Calcified femoral accesses without significant lesions and proper caliber.

When multi-organ failure recovered, and hemodynamic data collected with the Swan-Ganz catheter came back to normal, the heart team recommended «emergency TAVI» given the situation of cardiogenic shock, and management of coronary artery disease was deferred and treated in a second surgical act.

The patient was intubated before the procedure. After predilatation with a 25 mm balloon, a 34 mm Evolut PRO valve [Medtronic, United States] was implanted via left femoral artery in the
Cusp-overlap view to optimize commissural alignment and minimize damage to the conduction system. Final outcomes were excellent without gradient or residual aortic regurgitation. The patient showed transient left bundle branch block, which is why atrial pacing stress echocardiography was conducted that did not reach the Wenckebach point at 130 beats per minute, which is why the electrocatheter was eventually removed. Left femoral artery was closed with 2 Perclose Proglide sutures as the good results seen on the angiography confirmed (video 2 of the supplementary data). Hemodynamic improvement was immediate. The patient was progressively weaned off dobutamine and extubated early. Prognostic benefit treatment was optimized, and the cardiac magnetic resonance imaging showed a left ventricular ejection fraction of 28% with viability in the entire myocardium. The patient was discharged 2 weeks after admission for close follow-up, and to plan outpatient coronary revascularization.

This case exemplifies the delicate balance between the time when the cause for the shock was corrected and the hemodynamic stabilization and optimization of organ perfusion was achieved. A recent review and meta-analysis found no differences whatsoever between emergency and elective implantation. However, the rate of acute kidney injury was higher; due to the severity of these patients, the 1-month mortality rate after emergency implantation is twice as high compared to elective implantation [8.8% vs 4.4%]. If only patients with cardiogenic shock are considered, the 1-month mortality rate is higher [11.8% up to 33.3%]. In conclusion, we believe that «emergency TAVIs» is a therapeutic alternative associated with good clinical outcomes.

**FUNDING**

None whatsoever.

**AUTHORS’ CONTRIBUTIONS**


**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.M22000336.

**REFERENCES**

Postmyocardial infarction ventricular septal defect: too many doubts still to solve

Comunicación interventricular posinfarto: muchas dudas por resolver

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Runner-up case presented at the Madrid ACCIS 2022 Meeting

To the Editor,

This is the case of a young man with a postmyocardial infarction large ventricular septal defect (VSD) surgically repaired 10 days after venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy. The patient still had a large residual VSD that triggered a situation of refractory congestion due to pulmonary hyperflow that was successfully treated with percutaneous closure. The patient gave his informed consent so this case could be published anonymously.

This is the case of a 46-year-old man without a past medical history and inferior wall myocardial infarction and Killip class I. Cardiac catheterization confirmed the presence of multivessel disease. The culprit lesion found at the proximal right coronary artery [Thrombolysis in Myocardial Infarction (TIMI) grade-0 flow] was revascularized with a drug-eluting stent. The patient was admitted to the coronary care unit, and progressed into cardiogenic shock. Several transthoracic and transesophageal echocardiographic studies revealed the presence of severe biventricular dysfunction and a large, basal inferoseptal VSD [50 mm] of anfractuous non-restrictive trajectory (Qp/Qs ratio of 3) [figure 1].

Figure 1. Large inferoseptal ventricular septal defect up to the apical segments as seen on the transthoracic echocardiography (A) with a 50 mm maximum diameter as seen on the transesophageal echocardiography. (B) The long (C) and short (D) axes seen on the transesophageal echocardiography reveal the presence of a non-restrictive left-to-right shunt.

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The patient was intubated, treated with VA-ECMO and with an intra-aortic balloon pump. He required amines with fast stabilization. Direct heart transplantation was suggested due to the high surgical risk involved, but eventually delayed surgical repair was used.

The patient remained stable and without heart failure. After 9 days, he showed signs of hemolysis due to thrombosis of the ECMO filter with acute kidney injury and pulmonary edema that required continuous venovenous hemodiafiltration. Emergency surgery was decided with double coronary artery bypass graft and VSD closure with a pericardial surgical patch. The patient entered a state of deep shock due to severe ventricular dysfunction (left ventricular ejection fraction < 10%) during postoperative period. Afterwards, the patient improved gradually with decannulation and extubation 5 and 7 days, respectively after the procedure.

The patient showed pulmonary congestion and required venovenous hemodiafiltration followed by IV diuretics. The transthoracic and transesophageal echocardiographic follow-up studies confirmed the presence of a novel non-restrictive residual VSD. After a negative fluid balance, cardiac catheterization revealed these values: aortic pressure, 90/60 mmHg; pulmonary arterial pressure, 26/16/8 mmHg; pulmonary capillary wedge pressure; 7 mmHg, right atrial pressure, 4 mmHg, and a Qp/Qs ratio of 1.7.

Given the presence of residual VSD with congestion due to hyperflow, closure was indicated. Due to the high surgical risk involved (myopathy, renal failure, ventricular dysfunction), the percutaneous approach was used. VSD was closed via femoral vein using a 12 mm Amplatzer AVPII device (Abbott, United States) that resulted in the overt reduction of the angiographic shunt with a restrictive intra-device residual shunt (figure 2).

Venovenous hemodiafiltration and diuretics were removed after closure. Neurohormonal blockade was initiated, and the patient was discharged from the hospital after achieving euvoletic state with good functional class.

Postmyocardial infarction VSD is a rare mechanical complication. Its incidence rate has dropped (1%-3% down to 0.1%-0.3%) in the era of percutaneous revascularization. It often appears 3 to 5 days after infarction although it can occur within the first 24 hours or later. In the anterior acute myocardial infarction setting, VSD is often apical and has a simple trajectory. In the inferior wall acute myocardial infarction setting, however, VSD is often basal, large, and has an anfractuous and non-restrictive trajectory with worse prognosis due to the presence of a larger shunt and right ventricular damage. Definitive treatment is surgical repair, but it has a high mortality rate (up to 40%). The best time to perform surgery is still controversial: clinical practice guidelines recommend emergency surgery. However, experienced centers prefer delayed surgeries when the appearance of scar tissue allows proper suture.1 In the series published, the mortality rate associated with early surgeries is higher compared to delayed surgeries beyond the first week. However, selection bias can occur since the most severe patients are operated on early. While waiting, the use of mechanical support devices can prevent hemodynamic deterioration.2 However, the risk of complications associated with treatment is higher with longer waiting times. Regarding the device that should be selected, evidence here is based on small observational studies. Intra-aortic balloon pump can be an option, but it is insufficient in the presence of established shock; the Impella device (Abiomed, United States) allows proper left ventricular discharge. Setback here is the possibility of reversing the shunt causing arterial desaturation. VA-ECMO has been successfully used and reverses the situation of shock as a bridging therapy to surgery or, in cases of very large VSD, as a bridging therapy to heart transplantation.3 Total artificial heart has also been used in this setting yet experience is limited on this regard. In experimental models no device has been able to normalize the hemodynamic situation or balance the Qp/Qs ratio. However,
it seems that the combination of VA-ECMO plus Impella/intra-aortic balloon pump is the most favorable option.\(^a\) A special situation is the presence of pulmonary edema due to pulmonary hyperflow following left-to-right shunt. It looks like optimizing the left ventricular discharge could improve this situation by reducing the Qp/Qs ratio. However, management is still controversial. We have been gaining experience with percutaneous closure and it has been used as the definitive treatment in the management of small VSDs, and as a bridging therapy to surgery with larger VSDs although with risk of failure and embolization involved. Its use has also been reported in residual VSDs after cardiac surgery.\(^a\)

In conclusion, the management of postmyocardial infarction VSD is controversial. Surgery is the treatment of choice, and it seems like delaying surgery increases the chances of success. However, the optimal waiting time is still unknown. The use of mechanical support can prevent hemodynamic deterioration being VA-ECMO an attractive therapeutic option. Percutaneous closure can be an alternative in certain settings. Finally, evidence on this regard is scarce and based on observational studies only and questions still abound.

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AUTHORS’ CONTRIBUTIONS
All the authors made their contributions during the patient’s entire healthcare process while drafting and reviewing the case.

CONFLICTS OF INTEREST
None reported.

REFERENCES

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Retrograde closure of perimembranous ventricular septal defects. A paradigm shift

Cierre percutáneo de comunicaciones interventriculares perimembranosas por vía retrógrada. Cambio de paradigma

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To the Editor,
The percutaneous closure of ventricular septal defect (VSD) is still not widely used today due to its potential complications (atrioventricular block, valvular heart disease, hemolysis), and technical limitations, particularly, in low-weight patients.\(^1\)

Devices specifically designed for the closure of perimembranous VSD (pmVSD) have an asymmetric design that conditions implantation via antegrade venous access. Therefore, the standard procedure requires creating an arteriovenous loop across the defect to advance the device until its sequential release from the aorta or the left ventricle. An example of this is the Nit-Occlud Lé VSD-Coil device (PFM Medical, Germany) that has a good safety and efficacy profile.\(^2\) However, the creation of the loop can be the cause for transient atrioventricular blocks and hemodynamic instability especially in low-weight patients.\(^3\)

Also, the use of different unspecific occluders—with good clinical outcomes—for this indication has been described, especially if the defect comes with aneurysmal tissue.\(^4\) Thanks to their symmetric design and low profile, some devices can be released from the arterial side (retrograde), thus avoiding the creation of the loop. This simplifies the technique, shortens procedural time, and minimizes the dose radiation received by the patient. Such approach has already been described with good clinical outcomes with a specific design for the closure of the VSD, the Konar-MF (Lifetech, China).\(^5\) Given these potential benefits, we decided to start using this technique back in September 2019.

Ever since, transarterial retrograde access has been used in 12 out of every 20 patients treated with the percutaneous or postoperative closure of VSD. This approach became consolidated during the learning curve and ended up being the approach of choice when
dealing with favorable anatomies: non-supracristal perimembranous single defects without coronary leaflet prolapse, at least, 3 mm away from the aortic annular plane of < 6 mm in the right entrance and preferably with aneurysmal tissue. Different occluders with symmetric design were used like the ADO II (patient #4; videos 1 and 2 of the supplementary data), the Piccolo (patient #5; videos 3 and 4 of the supplementary data), the ASO (Abbott) or the Konar-MF (patient #10; videos 5 and 6 of the supplementary data).

We included the retrograde use of the ADO device (Abbott) in a patient with postoperative residual VSD without aortic edge with good clinical outcomes.

Procedure was scheduled in all the patients and performed under general anesthesia and with mechanical ventilation. Catheterization

Table 1. Patients treated with percutaneous closure of perimembranous ventricular septal defect via retrograde access

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Underlying heart disease</th>
<th>Indication for closure</th>
<th>Diameter of VSD in the LV Echo (mm)</th>
<th>Qp/Qs ratio</th>
<th>X-ray image time (min)</th>
<th>Success</th>
<th>Immediate complications</th>
<th>Fr</th>
<th>Device</th>
<th>Device waist (m)</th>
<th>Follow-up (m)</th>
<th>Complications at follow-up</th>
<th>Cause of death</th>
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<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>48</td>
<td>pmVSD</td>
<td>Postop</td>
<td>8.4</td>
<td>1.4</td>
<td>12.5</td>
<td>Partial</td>
<td>No</td>
<td>8</td>
<td>ADO</td>
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<td>98</td>
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<td>2</td>
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<td>1.4</td>
<td>11.6</td>
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<td>No</td>
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<td>ADO II</td>
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<td>59</td>
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<tr>
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<td>Refractory pulmonary hypertension in complex heart disease (Shone complex)</td>
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<tr>
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<td>17.8</td>
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<td>No</td>
<td>5.5</td>
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<td>Death</td>
<td>Refractory pulmonary hypertension in complex heart disease (Shone complex)</td>
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DCRV, double-chambered right ventricle; Echo, repercussion on echocardiography; Fr, French; kg, kilogram; LTE, limitation of therapeutic effort; LV, left ventricle; m, months; min, minutes; mm, millimeters; pmVSD, perimembranous ventricular septal defect; Postop, postoperative; Qp/Qs ratio, pulmonary flow/systemic flow; TOF, tetralogy of Fallot; VSD, ventricular septal defect; y, years.

Figure 1. Patient #10. A: Angiography and graphic representation of the Konar-MF device. B: Konar-MF final implantation position.
of the VSD and the right ventricle was performed with a right coronary artery curve catheter and a 0.035 in hydrophilic guide-wire. A Teflon-coated exchange guidewire was placed in the right ventricular apex, 1 catheter carrying the device was mounted on it and moved forward. Sequential release started from the right ventricular apex until contacting the defect. Afterwards, the retention body and disc were released while protected by the catheter across the aortic valvular plane. Monitorization during the procedure was performed under echocardiography (transthoracic if < 10 kg, transesophageal in the remaining cases) and angiography guidance through the carrier catheter. Final hemostasis occurred through manual compression.

The patients' median age and weight were 4 years (2 months to 38 years) and 22.2 kg (2.7-100), respectively. The largest diameter of the defect estimated through transesophageal or transthoracic echocardiography was 4.5 mm (3 mm to 8.4 mm) while the device waist diameter was 5.5 mm (4 mm to 12 mm). The variety of the devices implanted shows the progression of the technology available during the time of the series, and the lack of devices approved for retrograde use until the arrival of the Konar-MF device.

Procedure was successful in all the patients, and immediate total occlusion was achieved in 10 patients. No acute atrioventricular block events were reported. One embolization of the ADO II device to the pulmonary artery was described in the lowest-weight patient because the defect had been initially underestimated; the defect was recaptured and closed with a larger device. Grade II tricuspid valvular disease was described in the same patient immediately after implantation.

The median x-ray image time was 15.3 min [range, 7-32]. No complications associated with arterial access were reported.

The median of follow-up after the procedure was 20 months (2-67). During this time, 3 deaths that were not associated with the procedure whatsoever (table 1). The remaining patients are still being followed without presence of atrioventricular blocks or valvular heart disease. They all keep the full closure of the defect to this date.

This is the first case series ever conducted in Spain of closure of pmVSD via retrograde arterial access with a high rate of success and a low rate of complications.

Different unspecific devices for the closure of pmVSD with symmetric design (ADO II or Piccolo) or else the new Konar-MF device [figure 1]—specifically approved for this procedure—can be implanted via retrograde arterial access, which simplifies the routine closure technique making it feasible for low-weight children in whom the creation of an arteriovenous loops is associated with a higher risk of hemodynamic instability or transient atrioventricular block. Also, the low profile of the device does not increase the risk of damage to the femoral arterial access compared to the traditional technique. Therefore, we propose this therapeutic alternative in selected patients.

FUNDING
None whatsoever.

AUTHORS’ CONTRIBUTIONS
A. Rasines Rodríguez, and M. M. Aristoy Zabaleta: data curation, analysis, bibliographic search, and drafting of the manuscript. C. Abelleira Pardeiro: original idea, involved with the patient healthcare process, work supervision, data curation, analysis, and drafting of the manuscript. E. J. Balbacid Domingo: work creation and supervision, and directly involved with the patient’s healthcare process. S. Jiménez Valero, and F. Gutiérrez-Larraya Aguado: patient care, and critical review of the manuscript. All the authors reviewed and approved the manuscript final version.

CONFLICTS OF INTEREST
None reported.

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Percutaneous treatment of partial anomalous pulmonary venous connection with dual drainage

Tratamiento percutáneo de un drenaje venoso pulmonar anómalo parcial con drenaje dual

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CASE PRESENTATION

Anomalous pulmonary venous connection is a rare condition that occurs when 1 or more pulmonary veins abnormally return to the right atrium or systemic venous circulation. The most common type in adults is drainage of the left upper pulmonary vein (LUPV) into the left innominate vein. Anecdotally, an anomalous LUPV may have dual drainage into the left innominate vein and the left atrium (LA). In the absence of other congenital heart defects, partial anomalous pulmonary venous connection is often an incidental finding and individuals are usually asymptomatic.

In this article, we’ll be reporting on a case of dual drainage partial anomalous pulmonary venous connection where the LUPV is both connected to the left innominate vein and the LA in a patient with coronary heart disease and left ventricular systolic dysfunction.

This is the case of 56 year-old man with a past medical history of diabetes and dyslipidemia referred to the cardiac center due to an incidental finding on a thoracic computed tomography scan requested by the pulmonologist as part of a dyspnea diagnostic work-up. At the visit the patient presented with exertional dyspnea with NYHA functional class III and complained of angina on moderate exertion. The physical examination revealed normal auscultation and peripheral edema. The mentioned thoracic computed tomography scan revealed the presence of a LUPV connected to the LA and the left innominate vein trough a vertical vein (VV), as well as pulmonary artery dilation, cardiomegaly, and right pleural effusion [figure 1]. Transthoracic echocardiography showed a moderate left ventricular dysfunction [ejection fraction, 35%] with global hypokinesis, LA and right atrium enlargement, right ventricular dilation and dysfunction [a 14 cm tricuspid annular plane systolic excursion] and elevated pulmonary artery systolic pressure (63 mmHg) [video 1 of the supplementary data]. Right heart catheterization confirmed the presence of pulmonary hypertension [figure 2]. Coronary angiography revealed severe and diffuse 3-vessel coronary artery disease.

FUNDING
None whatsoever.

AUTHORS’ CONTRIBUTIONS
R. González-Manzanares, and G. Flores-Vergara drafted the manuscript, and completed the critical reviews. S. Ojeda, J. Suárez de Lezo, S. Espejo, 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.

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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. The remaining authors declared no conflicts of interest relevant to the content of this article.

SUPPLEMENTARY DATA

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Percutaneous treatment of partial anomalous pulmonary venous connection with dual drainage. How would I approach it?

Tratamiento percutáneo de un drenaje venoso pulmonar anómalo parcial con drenaje dual. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

Authors present here an incidental finding of an unusual yet interesting case of a partial anomalous pulmonary venous connection (PAPVC) in a 56-year-old man after a study of moderate exertional dyspnea and angina.

PAPVC is a congenital malformation that can be associated with interatrial septum defects [it has been reported in 10% to 15% of the cases] or happen in isolation. It can be unilateral or bilateral. If found on the right side, the PAPVC often drains into the superior vena cava (sometimes directly into the right atrium or the inferior vena cava), and its association with sinus venosus interatrial communication is a common finding. If on the left side, the left upper pulmonary vein (LUPV) often drains directly into the left innominate vein through an anomalous vertical vein (VV). The presence of 1 bilateral PAPVC is a rarer finding.

In many patients the diagnosis of this entity is merely incidental since patients are often asymptomatic especially for the lack of other congenital cardiac defects. Based on the degree of left-right shunt, the right cavities can be dilated and even in some cases, pulmonary hypertension due to vascular pulmonary vascular bed remodeling can occur. Traditionally, the management of this entity requires surgery to redirect pulmonary flow towards the left cavities through the creation of an intracardiac baffle or the reimplantation of pulmonary vein into the left atrium. Results are favorable in experienced centers since many of these procedures are performed during childhood.1

In this case, there is an anatomical particularity conditioning the therapeutic approach: the PAPVC of the LUPV is dual. What this means is that, on the one hand it drains correctly into the left atrium while on the other hand it communicates with the left innominate vein through the VV as confirmed on the images and reconstructions obtained from the multislice computed tomography (CT). In addition to these anatomical findings, we have the information obtained on the echocardiogram showing right cavity dilatation, additional biventricular dysfunction, and traces of severe pulmonary hypertension.

In this context it is advised to perform complete cardiac catheterization to complete the study and assess pulmonary pressures and resistances to discard the presence of significant coronary artery disease in this individual patient.

In patients with an indication for surgical repair due to PAPVC, the European Society of Cardiology clinical practice guidelines of 2020 recommend estimating pulmonary vascular resistances.2 If under 5 Wood units, the procedure is safe and improves functional class while lowering pulmonary pressures. The criterion of pulmonary systolic pressures < 50% of systemic pressure can also be used, as long as pulmonary resistances are less than one third compared to systemic resistances.

PAPVC with dual LUPV drainage is unusual. Its peculiarity is that it allows us to perform a percutaneous procedure to redirect the flow of the LUPV towards the left atrium by occluding the conduit that communicates with systemic venous circulation (usually the VV).3 This allows us to eliminate the left-right shunt and normalize the LUPV return flow thus preventing the setbacks and potential complications associated with heart surgery. In the case presented here, surgical risk is extremely high due to biventricular dysfunction, the presence of severe pulmonary hypertension, and severe 3-vessel coronary artery disease, which could be revascularized in a second surgical act. Therefore, the percutaneous option seems highly attractive.

From a technical point of view, venous access is needed to reach the left innominate vein and access the inside of left atrium through the VV and the LUPV. A femoral vein or left internal jugular vein can be used. Access through the VV can be performed using a long 260 cm
0.035 in hydrophilic guidewire while mounted on a Judkins right or mammary artery specific curve coronary catheter. Once the catheter has been advanced through the left atrium, the hydrophilic guidewire is exchanged for a high-support 260 cm 0.035 in guidewire on which a release system of a proper caliber with respect to the device selected is advanced.

The procedure can be performed without general anesthesia and with sedation only since transesophageal ultrasound is not required. However, it is important to have a good previous radiographic study where the CCTA plays an important role.

Selective angiographies of the VV even with the possibility of temporarily occluding the LUPV with an Amplatzer type of balloon to prevent rapid contrast washout allow us to choose the right device for proper anchoring purposes [with certain compression] avoiding embolization. For its special design and multiple sizes available the Amplatzer Vascular Plug-II device [Abbott, United States] would be my first option. An alternative to it would be the Amplatzer Duct Occluder (ADO)-I device whose design also makes it suitable for different anatomies.

Follow-up after the procedure should include an echocardiogram at 3-6 months to assess the reverse remodeling of right cavities and pulmonary systolic pressure. Performing a thoracic CCTA at 6 months is advised to confirm the complete occlusion of the shunt, and the correct position of the device into the VV.

FUNDING
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CONFLICTS OF INTEREST
None reported.

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Percutaneous treatment of partial anomalous pulmonary venous connection with dual drainage. Case resolution

*Tratamiento percutáneo de un drenaje venoso pulmonar anómalo parcial con drenaje dual. Resolución*

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CASE RESOLUTION

The heart team decision was to percutaneously treat both the coronary artery disease and the partial anomalous pulmonary venous connection (PAPVC). Percutaneous coronary intervention was successfully performed in the first place. Treatment of the PAPVC was performed 3 months later. Since it is recommended that the diameter of the device should be 30% to 50% larger than the vessel diameter, a 22 mm Amplatzer Vascular Plug II device (AVP-II) [Abbott, United States] was selected based on the VV computed tomography measurements.

The procedure was performed under local anesthesia and with fluoroscopic control. A 7-Fr introducer sheath was inserted into the right femoral vein. A 6-Fr multipurpose diagnostic catheter was advanced using a 0.035 in exchange guidewire to reach the VV through the left innominate vein (figure 1A). Angiography confirmed the presence of a left upper pulmonary vein (LUPV) with dual drainage and significant contrast flow from the LUPV to the innominate vein that filled the right chambers (left-to-right shunt) (figure 1, video 1 of the supplementary data). Using a femoral 7-Fr 90 cm Destination Guiding Sheath (Terumo, United States) the AVP-II device was placed and delivered into the VV (figure 2A, video 2 of the supplementary data). The correct position, absence of residual shunt, patency of innominate vein, and LUPV flow were confirmed by angiography in both the innominate vein (figure 2B,C) and pulmonary artery (figure 2D).

Two days later a control computed tomography (figure 3) and a transthoracic echocardiography with microbubble contrast agent were performed. They confirmed the correct position of the AVP-II device, and the lack of pulmonary infarction. At 7-month follow-up the patient remained asymptomatic and cardiac catheterization showed similar successful fluoroscopic findings (videos 3 and 4 of the supplementary data), and significantly improved pulmonary pressures (figure 4).

The differential diagnosis of a LUPV with dual drainage should include other left-side vascular structures such as persistent left superior vena cava, which is the most common thoracic venous anomaly and, in most cases, drains into the right atrium. However, it may be connected to the left atrium (LA) through a pulmonary vein. In this scenario the expected direction of blood flow is craniocaudal.1

The treatment of PAPVC is indicated with symptoms attributed to significant left-to-right shunt. Shunting is mainly determined by the number and size of anomalous pulmonary veins. In our case, we hypothesize that the dual LUPV connection and the coexistence of an increased LA pressure due to left ventricular dysfunction contributed to a disproportionate shunt for a single anomalous pulmonary vein. This eventually led to right chambers dilatation and symptomatic combined post- and pre-capillary pulmonary hypertension.

Although surgery is the treatment of choice, percutaneous treatment may be a feasible alternative in patients with a pulmonary vein dually draining into a left innominate vein and the LA2 since the sealing of the VV with a vascular device redirects all pulmonary vein blood flow into the LA. Before sealing, transient balloon occlusion should be considered to assess LA and pulmonary pressure changes. If pressure increases, sealing should be reconsidered and if performed, LA decompression with an atrial flow regulator should follow.3

FUNDING

None whatsoever.
Figure 2. Fluoroscopic image showing the Amplatzer Vascular Plug II device (AVP II) delivery using the Guiding Sheath (A). The angiograms reveal the correct position of the AVP II device, and the patency of the left innominate vein (LIV) flow: posterior-anterior (B) and left anterior oblique (C) views. Contrast injection into the pulmonary artery using a pigtail catheter with left atrium (LA) filling revealing the proper inferior position of the AVP II device, proper flow through the left upper pulmonary vein (LUPV), and lack of caudocranial flow through the occluded vertical vein (D). PA, pulmonary artery, RSVC, right superior vena cava.

Figure 3. Postoperative thoracic computed tomography. Multiplanar reformatted (A,C), and 3D reconstructed (B) images show the proper position of the Amplatzer Vascular Plug II device (AVP II) occluding the vertical vein that previously connected the left innominate vein (LIV) and the left upper pulmonary vein (LUPV). LA, left atrium; RA, right atrium; RSVC, right superior vena cava.

AUTHORS’ CONTRIBUTIONS
R. González-Manzanares and G. Flores-Vergara drafted the manuscript and completed its critical revisions. S. Ojeda, J. Suárez de Lezo, S. Espejo, 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
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SUPPLEMENTARY DATA
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**Figure 4.** Follow-up hemodynamic measurements showing decreased pulmonary artery pressure (PAP) (**A**) and left atrial (LA) pressure (**C**). Central venous pressure (CVP) is similar to the baseline procedure (**B**). Ao, aorta.

**REFERENCES**

Management of iatrogenic coronary artery fistula

Tratamiento de fístula arterial coronaria iatrogénica

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Figure 1.

Figure 2.

The authors describe the case of a 67-year-old woman who presented initially with an anterior ST-segment elevation myocardial infarction. Emergency coronary angiography revealed the presence of 95% stenosis in the middle segment of the left anterior descending coronary artery (LAD), and 90% stenosis in the middle segment of the right coronary artery (RCA). Primary percutaneous coronary intervention (PCI) of the mid LAD was performed. Two weeks later, elective PCI of the mid RCA was performed: we advanced a hydrophilic guidewire towards the distal RCA, predilated the lesion with a 2.25 mm × 15 mm balloon, implanted a 3.0 mm × 38 mm zotarolimus-eluting stent, and postdilated with 2.75 mm × 12 mm and 2.5 mm × 8.0 mm balloons. Although the angioplasty was successful, we observed contained contrast extravasation in a posterolateral artery branch [figure 1A,B; video 1 of the supplementary data]. Echocardiography revealed no significant pericardial effusion. Coronary angiography reassessment performed 3 days later documented an Ellis type 3 coronary perforation with an evident fistulous tract to the venous system [figure 2; video 2 of the supplementary data]. We advanced an Excelsior SL-10
microcatheter (Stryker, United States) towards the proximal end of the fistula (figure 3A) and delivered a 2 mm × 4 cm coil, which successfully occluded the vessel (figure 3B). There were no complications during hospitalization or at the follow-up.

Coronary artery perforation is a rare complication of PCI. Incidence rate is between 0.1% and 3.0%. Coronary perforations potentially result in severe complications like cardiac tamponade or arteriovenous fistula formation. Iatrogenic fistulae have a variable clinical course depending on the size and degree of left-to-right shunt. Treatment guidelines are not well established, and options reported include conservative, percutaneous or surgical management. Informed consent and authorization to publish these figures and videos were obtained from the patient.

**FUNDING**

None whatsoever.

**AUTHORS’ CONTRIBUTIONS**

P.D.A. Leite Medeiros was responsible for analyzing the case report and drafting the manuscript. J. Costa, and C. Galvão Braga performed the coronary intervention and reviewed both the manuscript and its figures. All authors approved the final version of the manuscript.

**CONFLICTS OF INTEREST**

The authors do not have any conflicts of interest.

**SUPPLEMENTARY DATA**

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Bail-out double-layer CP stent implantation due to severe endoprosthesis kinking

Rescate de torsión de endoprótesis mediante doble capa de CP stent

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This is the case of a 53-year-old man with aortic stenosis, ascending aortic aneurysm, and type B aortic dissection treated with Bentall procedure where a 40 mm uncovered self-expanding stent-graft (AMDS, JOTEC GmbH, Germany) was anastomosed to the aortic graft distal border with the intent to collapse the entry [figure 1A]. The patient’s written informed consent was obtained to run the tests and publish the case.

The follow-up radiographic monitoring revealed significant stent-graft kinking while the dissection entry remained opened [figure 1B,F].

Given the high risk involved in the reintervention, endovascular treatment was decided. Under intravascular echocardiography guidance a hydrophilic guidewire was used to cross the stent-graft lumen. Afterwards, the guidewire was exchanged for a different one with stronger support to proceed with dilatations using semi-compliant balloons with significant recoil being reported after balloon deflation [figure 2A,C].

To achieve greater radial strength, we decided to implant a double-layer stent. An uncovered stent to expand the stent-graft was implanted followed by 1 covered expandable polytetrafluoroethylene (e-PTFE) stent to seal the dissection entry. An 18 Fr DrySeal sheath (Gore Inc, Image in cardiology

Figure 1.

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Figure 1.
United States) was used to implant 2 60 mm 10-zig CP stents (NuMED Inc, United States), 1 covered and the other one not. Both stents were mounted on a 26 mm × 50 mm BIB balloon (NuMED Inc., United States). A 30 mm × 60 mm Crystal balloon (BALT, Germany) was used for postdilatation (figure 2D,E). The control computed tomography scan confirmed the dissection entry complete seal with persistent distal false lumen (figure 3A,D).

**FUNDING**

None whatsoever.

**AUTHORS’ CONTRIBUTIONS**

All authors contributed equally to this work.

**CONFLICTS OF INTEREST**

None reported.
This is the case of a 13-year-old teenage girl diagnosed with pulmonary atresia with intact ventricular septum treated in the neonatal period with valvulotomy with radiofrequency and percutaneous pulmonary valvuloplasty. Since then, the patient has developed severe pulmonary regurgitation and moderate tricuspid regurgitation. Valve implantation into the right ventricular outflow tract (RVOT) is decided due to worsening functional class with restrictive behavior of the right ventricle (without anticipated dilatation), and hepatic congestion. Cardiac catheterization reveals the presence of a dilated and pulsatile (pulmonary annulus: 29 mm) RVOT with supravalvular stenosis (minimum diameter: 21 mm), and a 34 mm post-stenotic dilatation (figure 1). A second-staged stent is implanted for percutaneous valve implantation. Given the absence of specific material for RVOTs so dilated, a 30 mm x 40 mm self-expandable Sinus-XL stent (Optimed, Germany) (off-label) is selected for being long enough, easy to implant, having enough navigability for the patient’s age (10-Fr sheath), and requiring less radial strength (favorable for dilated RVOTs).

A 14-Fr sheath was used to perform position angiographies (figure 1). A few hours later, the patient showed hemodynamic instability with transthoracic echocardiography findings compatible with cardiac tamponade. An emergency computed tomography scan (figure 2) confirmed the perforation of the pulmonary trunk at the operating room (figure 3; RA, right atrium; PA, pulmonary artery; RV, right ventricle). The stent was removed, and a pulmonary valve was implanted with favorable progression.
The design of the stent is similar to that used during hybrid procedures in certain neonatal heart diseases, which means that similar complications can be expected.

The patient’s parents’ informed consent was obtained to be able to publish her case.

**FUNDING**

None whatsoever.

**AUTHORS’ CONTRIBUTIONS**

A. Rasines Rodríguez: drafted the case. C. Abelleira Pardeiro: critical review and image selection. Direct patient care. E.J. Balbacid Domingo: critical review and image selection. Direct patient care. All authors: contributed to the study idea and design, data curation or its analysis and interpretation and final approval of the version that would eventually be published.

**CONFLICTS OF INTEREST**

None reported.