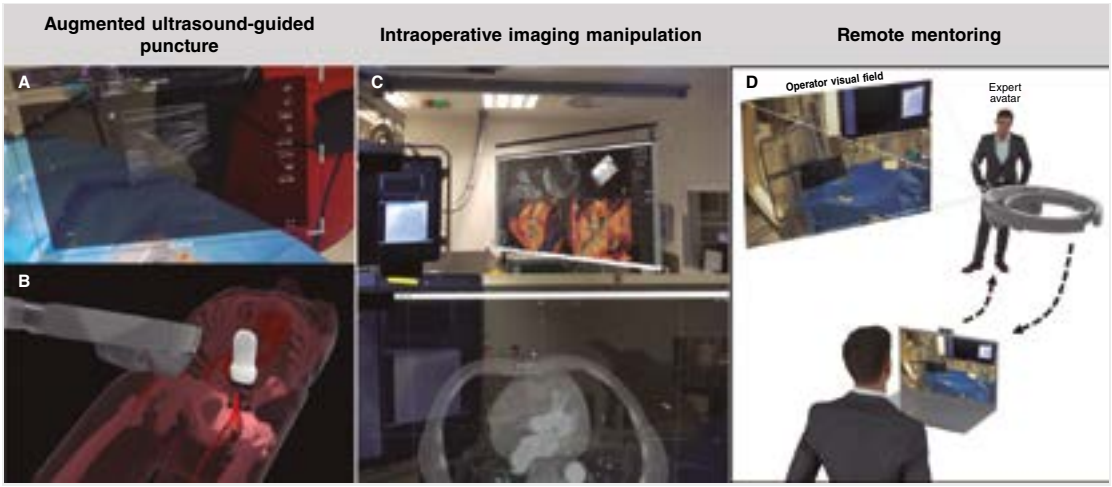
REC: INTERVENTIONAL CARDIOLOGY
REVISTA ESPAÑOLA DE CARDIOLOGÍA

Included in: Scopus, Latindex, DOAJ, and Dialnet

Volume 4, Issue 4 | October-December 2022

ISSN: 2604-7314; e-ISSN:2604-7322



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REC: INTERVENTIONAL CARDIOLOGY

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REC Interv Cardiol. 2022;4(4):261-266
https://doi.org/10.24875/RECICE.M22000335

REC: Interventional Cardiology: on the right track

REC: Interventional Cardiology: en el buen camino

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[b] *Associate Editor, REC: Interventional Cardiology*

At the time of writing, 4 years have gone by since *REC: Interventional Cardiology* made its publishing appearance for the first time. Overall, these have been very intense years due to the COVID-19 pandemic. In particular due to the uncertainty surrounding the birth of a new medical journal in today's competitive setting.

Still, we strongly believe that these 4 years have been more profitable for our young journal than we could have ever anticipated. Although we still are in the process of being included in certain citation indices, which will give us the impact metrics so attractive to authors, our journal has become established and publishes quality content on a regular basis. In this sense, and as we will be seeing next, *REC: Interventional Cardiology* has already been included in some citation indices and we are very close to being accepted in the most relevant ones.

REC: Interventional Cardiology is the official journal of the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) and stands tall as its official true means of expression. We can see that the decision to publish several consensus documents was correct as the thousands of visits received demonstrate.[1,2] A couple more documents are in the pipeline and many more will follow in the future.

Our editorials have been signed by top national and international authors, our review articles are recognized for their quality and rigor, and debates show in a clear concise way the opinions of subject matter experts on hot topics.

Original articles, scientific letters, clinical cases, and images fill up the pages of our journal with interesting content. These manuscripts are meticulously reviewed and have an attractive presentation. Finally, news pieces on innovation have introduced to us the latest technical breakthroughs in the field of interventional cardiology.[3]

But none of this would be possible without our reviewers. As we have already done in the past, we wish to thank them for the invaluable, unselfish, and quality work they do. Thank you all for your cooperation. We are aware of the obligations you all have, and that is why we value your contribution to our journal so much.

EDITORIAL ACTIVITY

The first aspect we wish to discuss is very well illustrated on figure 1, that is, the increasingly growing number of contents

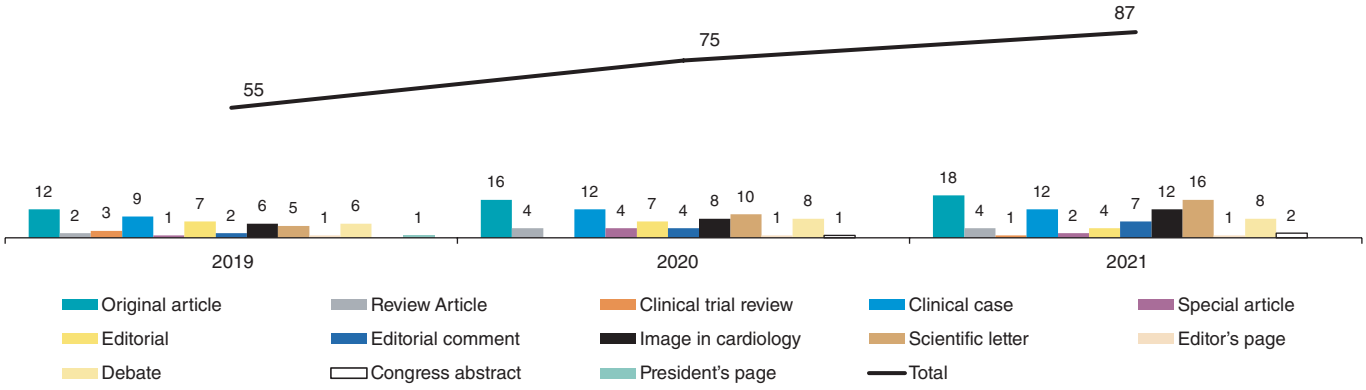

Figure 1. Total content published in 2019, 2020, and 2021. Congress abstracts are counted as a single unit. Each clinical case is counted as 3 units as it is organized into 3 independent articles: Case, How would I approach it?, and Resolution.

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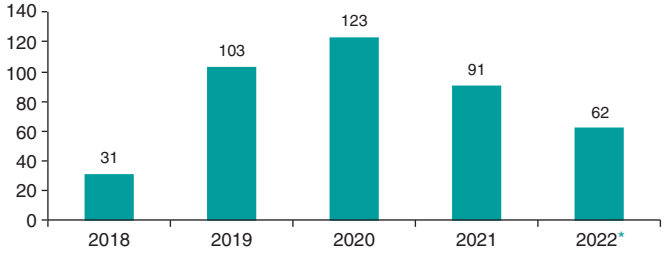

Figure 2. Overall number of manuscripts received per year. *Data until June 30, 2022.

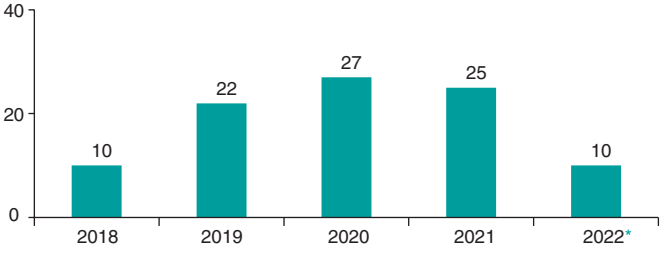

Figure 3. Number of original articles received per year. *Data until June 30, 2022.

published over the first few years of activity in both number and variety. In this sense, it has been very satisfactory to include abstracts on communications presented at ACI-SEC congresses.[5]

Over the last few years of activity, we have seen a peak in the volume of manuscripts submitted in 2020 (figure 2). This phenomenon has been seen in all medical journals. There are two reasons for this. One is that cardiologists had more spare time to write during lockdown, the other one is the proliferation of manuscripts on COVID-19.

Although all the manuscripts submitted had a variable degree of interest, our journal is no different to other medical journals and the limited space for publication makes us select those considered more valuable and relevant. Nonetheless, the gradual increase of space for original papers, scientific letters, and images in each issue has opened the door to many of these contents.

Of all the manuscripts received in 2021 and within the first semester of 2022 from countries other than ours, we should mention those submitted from Latin America and Europe.

Original articles

After the peak of papers received back in 2020, there has been a certain drop in the demand for publication in all sorts of articles (figure 2). In the case of original articles, in 2021 the number of manuscripts submitted slightly dropped (figure 3) though numbers were higher compared to 2019. We believe 2022 is going to end with a similar volume of original articles submitted compared to the previous year. The rate of acceptance of this type of papers in 2021 and within the first semester of 2022 is well above 80% (figure 4).

At this point, our main goal is to increase the number of original articles, which is why we want to ask the interventional cardiologist community to submit research papers. To guarantee that future issues are fully covered it is essential to have enough high-quality originals.

REC: Interventional Cardiology offers a fast, quality review process, and provides top coverage and circulation of the studies being published.

Scientific letters

Regarding scientific letters, the already discussed phenomenon of a peak in 2020 was much more pronounced compared to original articles (figure 5). The scientific letters rate of acceptance during 2021 and the first semester of 2022 was also high due to the high interest aroused (figure 6).

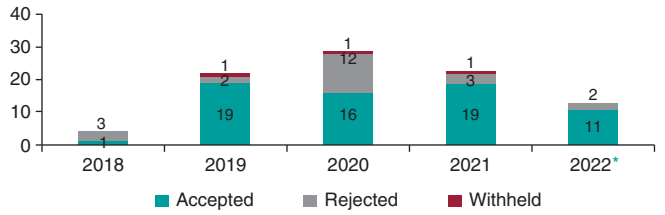

Figure 4. Editorial decisions made on original articles. *Decisions made until June 30, 2022.

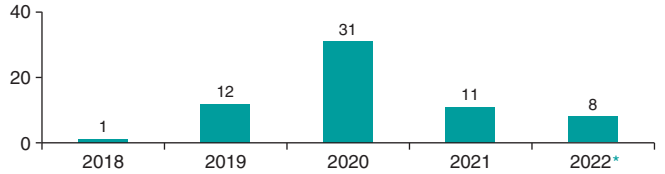

Figure 5. Number of scientific letters received per year. *Data until June 30, 2022.

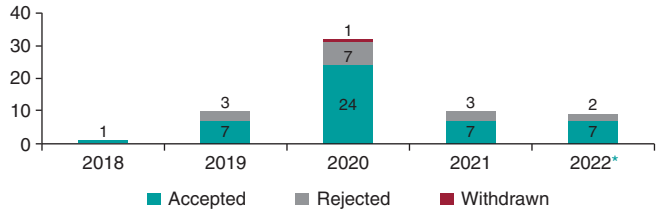

Figure 6. Editorial decisions made on scientific letters. *Decisions made until June 30, 2022.

Due to the volume of letters received since the publication of the last issue in 2020 the space available for this type of manuscripts grew to a maximum of 4 per issue. It is important to find balance and guarantee a constant demand for publication without generating a stock that can be too large.

Clinical cases

Something similar has happened with clinical cases and scientific letters. The higher number of articles submitted under this format during 2020 was followed by a slight decrease in 2021 (figure 7). The lower rate of acceptance from 2021 is striking (figure 8). The reason for this higher rate of rejection is the inbalance between the number of cases received (as this is a very popular format

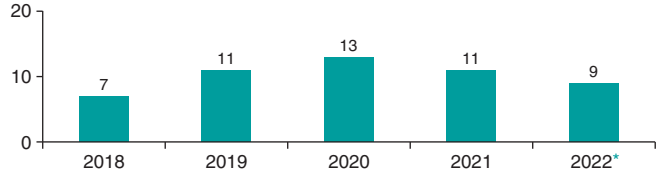

Figure 7. Number of clinical cases received per year. *Data until June 30, 2022.

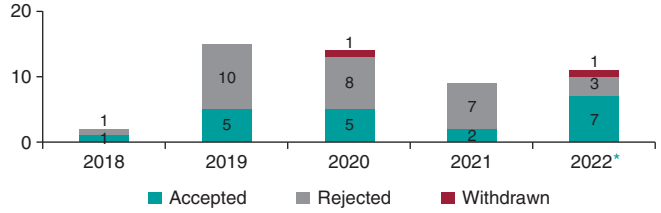

Figure 8. Editorial decisions on clinical cases. *Decisions made until June 30, 2022.

among interventional cardiologists) and the number of cases for publication (4 throughout the year). The accumulation of cases in the publication roster makes us be highly restrictive. However, within the first semester of 2022 the rate acceptance started to go up (figure 8).

Images in cardiology

Regarding the images, as with the rest of contents, we see a peak in 2020, and in 2021 a drop to numbers from 2019. However, the tendency within the first semester of 2022 is to exceed by far the images in cardiology submitted as compared to previous years (figure 9). The rate of acceptance in 2021 was somehow higher compared to clinical cases since, despite being a very popular typology too, up to 3 images per issue are being published (figure 10).

As with clinical cases, the accumulation of images pending publication, limits the possibility of acceptance.

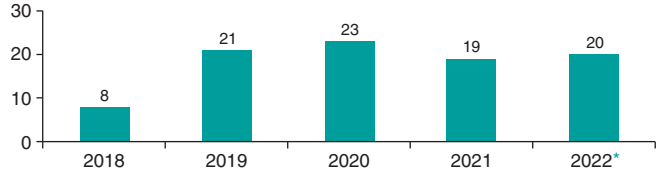

Figure 9. Number of images in cardiology received per year. *Data until June 30, 2022.

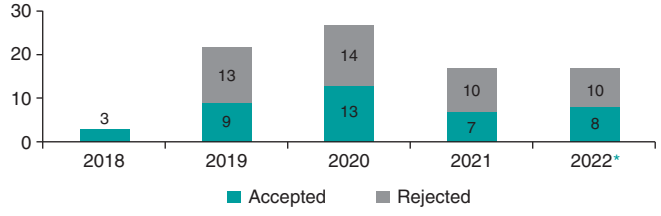

Figure 10. Editorial decisions on images in cardiology. *Decisions made until June 30, 2022.

Contents transferred from *Revista Española de Cardiología*

With its high impact factor, *Revista Española de Cardiología* draws a large number of manuscripts, much more than can be accepted, which leads to a high rate of article rejection despite their undoubted interest. *Revista Española de Cardiología's* editorial team gives us the possibility to review rejected manuscripts and offer authors the possibility to transfer their submissions to our journal.

Although the number of transferred manuscripts is still limited, we have the conviction that, little by little, this alternative will become more attractive and accepted as our journal keeps gaining traction in the most relevant citation indices.

LATEST EDITORIAL CHANGES IMPLEMENTED

As our journal continues to grow, we have been trying to include new improvements and functionalities we believe are useful to both authors and readers. Next, some of the improvements we implemented last year:

- Including the authors' Twitter profiles to help article dissemination in social media.
- Optional graphical abstract (central illustration) in original and special articles.
- All authors meeting the International Committee of Medical Journal Editors' authorship criteria can be included in the authorship byline.
- At the submission stage, authors must identify the specific part of the article stating that appropriate consents and ethical committee approval were obtained.

REVIEWERS

Table 1 shows the list of reviewers who have actively reviewed manuscripts for *REC: Interventional Cardiology* from July 1, 2021 through June 30, 2022. Table 2 lists 2021 elite reviewers.

We can never thank enough for your agile, rigurous, and unselfish work. Reviewers are essential in the process of selecting the journal contents and safeguarding the scientific quality of our manuscripts.

Figure 11 shows the very satisfactory mean editorial times, closely related to the excellent job done by reviewers.

INDEXATION

To the indexation of *REC: Interventional Cardiology* in the Directory of Open Access Journals (DOAJ), Latindex and Dialnet, we must add Scopus, in whose search engine appears since December 2021. In the same month, the journal was accepted for inclusion in the Committee on Publication Ethics (COPE) (figure 12).

Currently, *REC: Interventional Cardiology* is under evaluation in SciELO, Embase, MEDES, and Clarivate. The applications to Medline and PubMed Central will follow soon.

DISSEMINATION

The year 2021 marked the comeback of on-site meetings and the 32nd ACI-SEC Congress was held in Malaga, Spain from September

Table 1. *REC: Interventional Cardiology* reviewers who conducted their reviews from July 1, 2021 through June 30, 2022

César Abelleira	Antonio E. Gómez-Menchero
Juan H. Alonso-Briales	Nieves Gonzalo
Ignacio Amat	Enrique Gutiérrez-Ibañes
Eduardo Arroyo	Federico Gutiérrez-Larraya
Dabit Arzamendi	Felipe Hernández
Pablo Avanzas	Santiago Jiménez-Valero
Fernando Ballesteros	Alfonso Jurado
José A. Barrabés	María López-Benito
Teresa Bastante	José R. López-Mínguez
Salvatore Brugaletta	Diego López-Otero
Ramón Calviño	Ramón López-Palop
Xavier Carrillo	Íñigo Lozano
Mario Castaño	Gerard Martí
Alberto Cecconi	Javier Martín-Moreiras
Ángel Cequier	Luis Nombela
Belén Cid	Soledad Ojeda
Juan G. Córdoba	José M. Oliver†
Bernardo Cortese	Imanol Otaegui
Félix Coserría	Manuel Pan
José F. Díaz	Isaac Pascual
Alejandro Diego-Nieto	Armando Pérez de Prado
Jaime Elízaga	Eduardo Pinar
Rodrigo Estévez-Loureiro	Fernando Rivero
José A. Fernández-Díaz	Oriol Rodríguez
Cristina Fernández-Pérez	Gerard Roura
Ignacio Ferreira	Juan M. Ruiz-Nodar
José L. Ferreiro	José R. Rumoroso
Xavier Freixa	Pablo Salinas
Guillermo Galeote	Marcelo San Martín
Sergio García-Blas	Ángel Sánchez-Recalde
Tamara García-Camarero	Ana Serrador
Bruno García del Blanco	Javier Suárez de Lezo
Marcos García-Guimaraes	Ramiro Trillo
Arturo García-Touchard	Leire Unzué
Joan A. Gómez-Hospital	Beatriz Vaquerizo
Josep Gómez-Lara	José L. Zunzunegui

22 to September 24. As it has been the case since the beginning, the abstracts from the congress were published in *REC: Interventional Cardiology*,[4] and a huge effort was made so everything was readily available before the congress. In 2022 we have set ourselves

Table 2. Elite reviewers 2021*

Salvatore Brugaletta
Santiago Jiménez Valero
Alfonso Jurado-Román
Ángel Sánchez-Recalde

* Reviews conducted from September 1, 2020 through August 31, 2021.

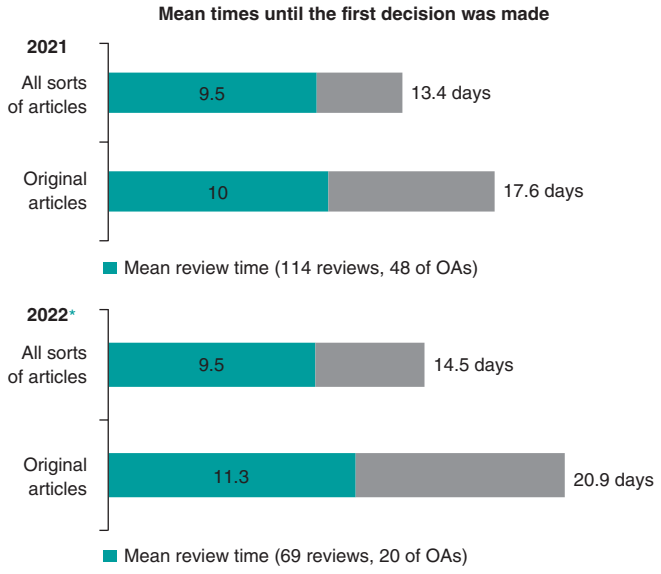

Figure 11. Mean editorial times from reception until the first editorial decision was made. OA, original articles. *Data until June 30, 2022.

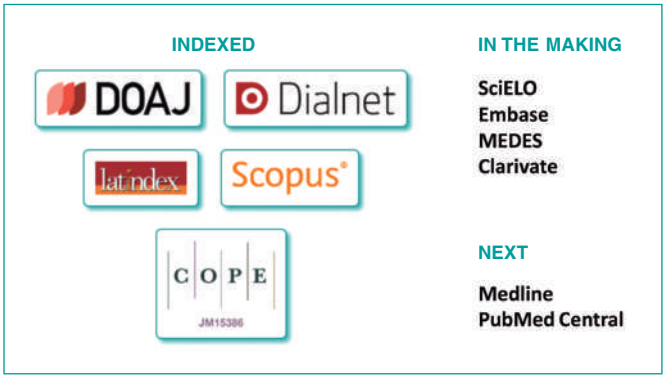

Figure 12. State of *REC: Interventional Cardiology* in citation indices.

the same goal, and the abstracts presented at the 33rd Interventional Cardiology Association of the Spanish Society of Cardiology Congress held in June in Alicante, Spain had already been published on our website by the end of May.[5]

Regarding the most widely read articles, some special papers gained great visibility. This was the case of the ACI-SEC technical document on the assessment of the endothelial function and spasm provocation test performed by intracoronary infusion of acetylcholine[1], with nearly 6000 visits. The position statement between the Spanish Society of Hypertension-Spanish League Against Arterial Hypertension (SEH-LELHA) and the ACI-SEC on

renal denervation to treat arterial hypertension[2] also generated over 3000 visits. Both articles were commented with their authors in our Editor's pick videos[6], embedded in the articles.

The section «Debate» in our website has been redesigned to offer a more attractive and intuitive picture for the readers.[7]

The different sources of traffic towards the website[8] maintain the same tendency: the main one being organic traffic (searches for keywords in browsers) followed by direct traffic and hyperlinks from different websites. In this sense, the official sites of the SEC[9] and the ACI-SEC[10] keep drawing the highest number of readers. We should mention the growing number of visits coming from repositories where the journal is indexed like DOAJ,[11] and Dialnet.[12]

Also, the active involvement from interventional cardiologists on Twitter makes this social network our main source of visits (74.41%), followed by Facebook (18.28%), and LinkedIn (3.66%).

Our subscribers receive a newsletter with the table of contents for each issue, and all the articles published in *REC: Interventional Cardiology* can be accessed from the spaces designed for such purpose in *Revista Española de Cardiología's* and the SEC's websites. Our contents are also spread through SEC Sunday newsletters and SEC News.

At the same time, we keep promoting *REC: Interventional Cardiology* in international congresses—some held in Latin America—and scientific meetings. In our country, the journal was present at the 10th course on prevention and treatment of complications in percutaneous interventional cardiology organized by Hospital de Bellvitge, Catalonia, Spain and the Online course on complications in hemodynamics organized by the Spanish Society of Pediatric Cardiology and Congenital Heart Disease.

AWARDS

At *REC: Interventional Cardiology* we gratefully recognise all the contributions made by the authors. Proof of this is the number of prizes awarded to the best original articles every year at the ACI-SEC congress.[13] Prize was €2500 total (€1500 for 1st prize, and €1000 for 2nd prize). Rules and regulations of these awards can be consulted on the journal website.[14] In the 32nd ACI-SEC Congress held in September 2021, the 1st prize was awared to the manuscript entitled «Impact of the COVID-19 pandemic on interventional cardiology activity in Spain».[15] This paper had wide impact, with more than 300 citations, many of them in the most prestigious cardiology medical journals. The 2nd prize was given to «Time trend in transcatheter aortic valve implantation: an analysis of the Spanish TAVI registry»[16] with a notable citation rate.

At the 33rd ACI-SEC Congress held in June 2022, the 1st prize was awarded to an article entitled «Predictors of postprocedural fractional flow reserve: insights from the FFR-SEARCH study»[17] from the renown Erasmus Medical Center, Rotterdam, The Netherlands. The 2nd prize was awarded to «Outcomes of nonagenarians after transcatheter aortic valve implantation»[18] (a substudy of the Spanish TAVI registry).

ACKNOWLEDGMENTS

As the editor-in-chief I wish to thank my associate editors Fernando Alfonso, Raúl Moreno, and the latest to join, Soledad Ojeda, Armando Pérez de Prado, and Rafael Romaguera. All of them make up the team I have the privilege to work with (figure 13).

We are fully aware that the ACI-SEC carries the journal financial burden and makes it feasible. Regarding funding, it is truly nice to see the support from all the companies in the interventional cardiology field that make our journal possible thanks to their contribution.

Also, I wish to thank the excellent job and effort put into every detail by the REC Publications editorial office staff: Iria del Río, Eva M. Cardenal, Belén Juan, María González Nogal, and Helena Gómez Lobo, our former TIC consultant Pablo Avanzas, the current TIC consultant Juan Quiles, the SEC's IT department, and the entire team at Permanyer Publications.

"When spider webs unite, they can tie up a lion"
Ethiopian proverb.

Figure 13. *REC: Interventional Cardiology* editorial team.

FUNDING

None reported.

CONFLICTS OF INTEREST

None whatsoever.

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REC Interv Cardiol. 2022;4(4):267-268
https://doi.org/10.24875/RECICE.M22000327

Editorial

Complete revascularization and diabetes in the real world: observational data as a necessary addition to clinical trials

Revascularización completa y diabetes en el mundo real: datos observacionales como complemento necesario de los ensayos clínicos

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https://doi.org/10.24875/RECICE.M22000308

Diabetes mellitus is a comorbidity that is present in 20% to 30% of the patients with coronary artery disease and an indication for revascularization. Also, it poses a scenario of greater complexity for several reasons. The presence of diabetes is associated with more extensive, diffuse, calcified coronary artery disease, and graft and stent failure. All of it is associated with a higher risk of repeat revascularizations and worse prognosis for the patients, which is why diabetes is a differential element here since it establishes the revascularization method in patients with multivessel disease based on the clinical practice guidelines.[1] Currently, the recommendation of coronary artery bypass graft (CABG) is superior to percutaneous coronary intervention (PCI) in diabetic patients. This indication comes from numerous studies being the FREEDOM trial[2] one of the most important of all. However, are patients from the routine clinical practice or real-world patients similar to those included in these clinical trials?

In this sense, the study conducted by Puyol-Ruiz et al.[3] recently published in *REC: Interventional Cardiology* provides valuable observational information on the results of coronary revascularization in diabetic patients in the routine clinical practice. This study shows the results from a historical cohort (2012-2014) of 733 patients with diabetes and multivessel coronary artery disease with a clinical indication for coronary angiography. Authors divide the study population based on the degree of revascularization (complete or incomplete) and the clinical profile consistent, or not, with the inclusion criteria of the FREEDOM clinical trial.[2] In this cohort, 80.8% and 14.5% of the patients were revascularized percutaneously and surgically, respectively compared to 4.8% who received medical therapy only. Authors found a tendency towards a lower rate of clinical events at 35-month follow-up in patients with complete revascularization. Also, both the risk profile and the rate of events of the FREEDOM study population (41%) was significantly lower compared to the non-FREEDOM study population (59%): lower rate of death (5.5% vs 38.4%; $P = .006$), cardiac death (3.2% vs 31.2%; $P = .002$), and major adverse cardiovascular events (6.5% vs 40.0%; $P = .012$). Therefore, we can deduce that patients from the FREEDOM trial are a selected subpopulation of lower risk representative of less than half of the real-world patients with diabetes and multivessel disease. Other studies that have tried to identify, in a population from the real-world clinical practice, the group of patients potentially eligible for clinical trial show similar prevalences (around 50%) of selection criteria for clinical trials on coronary revascularization, a population that also shows a significantly lower rate of cardiovascular adverse events.[4]

On the other hand, regarding the interpretation of these data, we should remember that over 10 years have passed since the FREEDOM trial, and the recruitment phase into the cohort of the study conducted by Puyol-Ruiz et al.[3]. Let's see what elements have changed in the revascularization of diabetic patients through all this time.

Modern PCI is not similar to the one described in the FREEDOM trial that used first-generation drug-eluting stents (sirolimus in 51%, and paclitaxel in 43%). Current platforms have exceeded paclitaxel-eluting stents in multiple clinical settings including diabetic patients.[5] Sirolimus-eluting stents had higher rates of thrombosis and stent failure compared to current stents in relation to the mechanisms of hypersensitivity to polymer.[6] Also, ultrathin strut drug-eluting stents have proven to be associated with a lower rate of adverse events compared to first-generation stents (> 120 µm).[7] As a matter of fact, more recent studies with all-comers design have demonstrated that state-of-the-art stents like the polymer-free amphilimus-eluting stent improves results even more (target lesion failure) compared to second-generation reference stents.[8] This huge improvement in stent technology seen over the last few years, the calcified plaque modification techniques used, and the intracoronary imaging modality-guided PCI performed or with pressure guidewires lead us to think that the current PCI results improve significantly those reported both in the FREEDOM trial and in this cohort of patients. Such statement can be confirmed in the comparison between the SYNTAX II cohort and the SYNTAX PCI group that used paclitaxel-eluting stents.[9,10]

However, CABG results have also improved, at least, in the clinical trials. For example, the 1-year rate of adverse events (death, myocardial infarction, stroke or repeat revascularization) has dropped from 12.4% in the CABG group of the SYNTAX trial[10] down to 6.9% in the CABG group of the FAME 3 trial.[11] This reduction is probably

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Online: 02-09-2022.

due to better perioperative care and the optimal medical therapy since no major changes in the surgical technique have been reported.

Regarding the impact diabetes has on the results of complete revascularization, the results from the study conducted by Puyol-Ruiz et al.[3] are consistent with a meta-analysis of 28 studies and 83 695 patients published by Zimarino et al. This analysis revealed that complete revascularization produced similar benefits in diabetic and non-diabetic patients in terms of mortality and adverse events reporting, in the former, significantly lower rates of new myocardial infarctions.[12] Despite this benefit, the numbers of residual coronary artery disease are still high both in the present study (CABG 49/106 [46.2%], PCI 396/592 [66.9%]), and in other PCI cohort studies (28.6%)[13] or CABG (33.1% with residual SYNTAX score > 18.5[14]). Therefore, there is this doubt on whether incomplete revascularization is just a technical problem or else a risk marker associated with a more advanced stage of the disease.

In conclusion, the therapeutic management of multivessel coronary artery disease in diabetic patients is still challenging for cardiology today. While clinical trials keep being conducted in selected low-risk populations it'll be of paramount importance to complement them with information from the results of the actual clinical practice as this article did. In future studies we should make all the necessary efforts to use pragmatic designs where exclusion criteria are minimized to encourage their immediate applicability to the routine clinical practice.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

P. Salinas designed, supervised, reviewed, and drafted the manuscript. A. Travieso drafted and reviewed the original manuscript version.

CONFLICTS OF INTEREST

None reported.

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REC Interv Cardiol. 2022;4(4):269-270
https://doi.org/10.24875/RECICE.M22000315

Editorial

Management of coronary artery perforations during chronic total coronary occlusion percutaneous coronary intervention

Tratamiento de las perforaciones coronarias durante la intervención percutánea de oclusiones totales crónicas

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Coronary artery perforation is one of the most feared complications of chronic total occlusion (CTO) percutaneous coronary intervention (PCI), as it can lead to pericardial effusion, tamponade, hemodynamic deterioration, need for emergency pericardiocentesis or surgery, or death.[1] The incidence of perforation is higher in CTO PCI compared with non-CTO PCI, likely due to higher anatomic complexity of CTOs and the use of advanced wiring techniques, such as antegrade dissection and re-entry and retrograde crossing.[2]

Coronary perforations have traditionally been classified according to severity using the Ellis classification.[3] Because perforation location has important implications for management, another key classification of coronary perforations is according to location, as follows: *a)* large vessel perforation; *b)* distal vessel perforation; and *c)* collateral vessel perforation, in either a septal or an epicardial collateral.[4]

The first step in perforation management is immediate balloon inflation proximal to or at the site of perforation to prevent accumulation of blood in the pericardial space and tamponade. The balloon should be the same size as the perforated vessel and the inflation often last for several minutes unless the patient develops severe ischemic symptoms.[5]

Large vessel perforations are usually treated with covered stents, such as the PK Papyrus (Biotronik, United States), and the Graftmaster Rx (Abbott Vascular, United States).[6] Delivery of the covered stent can be achieved using either a single guide catheter ("block and deliver" technique)[7] or 2 guide catheters ("ping pong", also called "dueling guide catheter" technique)[8]. Both techniques are used to minimize bleeding into the pericardium while preparing for delivery and deployment of the covered stent. Covered stents require excellent guide catheter support for delivery and should be post-dilated aggressively after deployment to achieve good expansion. Large vessel perforations of CTO vessels can be sealed by coil deployment proximal to the perforation. Another option for treating large vessel perforations is through extraplaque crossing of the CTO segment (either antegrade or retrograde) followed by stenting: the tissue flap created can successfully seal the perforation.[9,10]

The most widely used treatment for distal vessel perforations is coil[11] and autologous fat embolization[12]. Sometimes both fat and coil embolization are needed.[12] Thrombin injection[13] and embolization of microparticles, or other materials, such as gelfoam[14] are also sometimes used.

In most cases embolization can be achieved through a single guide catheter using the "block and deliver" technique.[7] The starting point for fat or coil delivery is advancing a microcatheter just proximal to the perforation site. Fat can be delivered through any microcatheter, but many coils are not compatible with the microcatheters typically used for PCI, such as the Corsair, Corsair XS, Caravel (Asahi Intecc, Japan), Turnpike, Turnpike LP, Mamba (Boston Scientific, United States) and Teleport (OrbusNeich, China) and instead require larger 0.035 inch lumen microcatheters (such as the Progreat, Terumo, Japan). Use of 0.014 inch coils (typically used for neurovascular applications, such as the Axium coils [Medtronic, United States) are compatible with all coronary microcatheters, facilitating use in the cardiac catheterization laboratory. Based on the coil mechanism of release, coils are classified as pushable and detachable. Pushable coils are inserted into the microcatheter and pushed with a coil pusher until they exit the microcatheter. Pushable coil delivery is unpredictable and irreversible. In contrast, detachable coils can be delivered to the desired location and then retracted and repositioned until optimal positioning is achieved, followed by release using a dedicated release device that connects with the back end of the coil.

Septal collateral perforations are unlikely to have adverse consequences and usually no specific treatment is required. In contrast, perforation of epicardial collaterals branch can rapidly lead to tamponade and may be difficult to control. Embolization of epicardial perforations may need to be performed from both sides of the perforation.[15]

In cases of pericardial effusion and tamponade, emergency pericardiocentesis should be promptly performed.[5] Although hemodynamic instability requires immediate pericardiocentesis, smaller size pericardial infusions can often be managed conservatively, as the accumulated blood increases the pressure in the pericardial space potentially preventing further bleeding.

Prevention is critical to decrease the incidence of perforation during CTO PCI. Key preventive strategies include: *a)* confirmation of guidewire position within the vessel architecture in multiple angiographic projections before balloon dilation and/or microcatheter

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Online: 05-07-2022.

advancement, usually through injection of the donor vessel to opacity the distal portion of the CTO vessel; *b)* use of intravascular imaging to determine the need for lesion preparation, and to guide balloon and stent size; *c)* outlining the anatomy of the collateral channels before and during crossing.[5]

Meticulous CTO PCI technique, continuous surveillance of the patient and availability and knowledge of how to treat coronary perforations can reduce the morbidity and mortality associated with this complication during CTO PCI.

FUNDING

No funding.

CONFLICTS OF INTEREST

S. Kostantinis has no conflicts of interest to disclose. E.S. Brilakis declares consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor of Circulation), Amgen, Asahi Intecc, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, CSI, Elsevier, GE Healthcare, IMDS, InfraRedx, Medicure, Medtronic, Opsens, Siemens, and Teleflex; research support from Boston Scientific, GE Healthcare; owner, Hippocrates LLC; shareholder of MHI Ventures, Cleerly Health, Stallion Medical.

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REC Interv Cardiol. 2022;4(4):271-278
https://doi.org/10.24875/RECICE.M22000308

Original article

Clinical impact of complete revascularization on real-life diabetic patients

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VÉASE CONTENIDO RELACIONADO:
https://doi.org/10.2487510.24875/RECICE.M22000327

ABSTRACT

Introduction and objectives: The need for complete coronary artery revascularization after acute coronary syndrome in diabetic patients with multivessel coronary artery disease was discussed, even more so if they reflect the routine clinical practice ("real world"). Therefore, the objective of this study is to analyze cardiovascular complications in diabetics with and without complete revascularization included in clinical trials and in the routine clinical practice.
Methods: This was a single-center retrospective study of diabetic patients with multivessel coronary artery disease. We analyzed 733 diabetic patients: 299 (40.8%) with compatible criteria to be included in clinical trials, and 434 real-world patients (59.2%).
Results: Real-world patients make up 59.2% of the sample. They are characterized by a higher percentage of risk factors, older mean age, and more comorbidities. Diabetics with multivessel coronary artery disease included in the trials have a lower risk of overall mortality (HR, 0.30; 95%CI, 0.16-0.57; $P < .001$), cardiac death (HR, 0.33; 95%CI, 0.15-0.71; $P = .03$), and major adverse cardiovascular events (HR, 0.58; 95%CI, 0.38-0.86; $P = .008$). On the other hand, receiving complete revascularization reduces the risk of cardiac death (HR, 0.32; 95%CI, 0.13-0.83; $P = .019$), and major adverse cardiovascular events (HR, 0.50; 95%CI, 0.29-0.89; $P = .017$) in real-world diabetic patients.
Conclusions: It is suggested that fully revascularizing real-world patients would improve survival prognosis. In addition, diabetics included in clinical trials present fewer complications compared to those not included.

Keywords: Diabetes. Revascularization. Real world. Multivessel coronary artery disease.

Impacto clínico de la revascularización completa en pacientes diabéticos de la vida real

RESUMEN

Introducción y objetivos: Se debate la necesidad de realizar revascularización coronaria completa tras un síndrome coronario agudo en pacientes diabéticos con enfermedad coronaria multivaso, y más aún si estos son reflejo de los pacientes de la práctica clínica habitual (mundo real). Por ello, el objetivo de este trabajo es analizar las complicaciones cardiovasculares en pacientes diabéticos con y sin revascularización completa incluibles en ensayos clínicos como de la práctica clínica habitual.
Métodos: Estudio unicéntrico retrospectivo de pacientes diabéticos con enfermedad coronaria multivaso. Se analizaron 733 pacientes diabéticos: 299 (40,8%) con criterios compatibles de inclusión de ensayos clínicos y 434 (59,2%) del mundo real.
Resultados: Los pacientes del mundo real constituyen el 59,2% de la muestra. Se caracterizan por presentar mayor porcentaje de factores de riesgo, mayor edad media y comorbilidad. Los diabéticos con enfermedad coronaria multivaso incluibles en ensayos tienen menor riesgo de mortalidad total (HR = 0,30; IC95%, 0,16-0,57; p < 0,001), de mortalidad de causa cardiaca (HR = 0,33; IC95%, 0,15-0,71; p = 0,03) y de sufrir eventos cardiovasculares adversos mayores (HR = 0,58; IC95%, 0,38-0,86; p = 0,008). Por otro lado, recibir revascularización completa desciende el riesgo de mortalidad de causa cardiaca (HR = 0,32; IC95%, 0,13-0,83; p = 0,019) y de eventos cardiacos adversos mayores (HR = 0,50; IC95%, 0,29-0,89; p = 0,017) en los pacientes diabéticos del mundo real.

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Received 8 February 2022. Accepted 11 May 2022. Online: 13-06-2022.

Conclusiones: Se sugiere que revascularizar completamente a los pacientes del mundo real mejoraría el pronóstico en cuanto a supervivencia. Asimismo, los diabéticos incluibles en ensayos clínicos presentan menos complicaciones que los diabéticos no incluibles.

Palabras clave: Diabetes. Revascularización. Mundo real. Enfermedad coronaria multivaso.

Abbreviations

CR: complete revascularization. **IR:** incomplete revascularization. **MACCE:** major adverse cardiovascular and cerebrovascular events. **MACE:** major adverse cardiovascular events. **MCAD:** multivessel coronary artery disease.

INTRODUCTION

Cardiovascular diseases—the most prominent of which is ischemic heart disease (IHD)—are a problem of global health and responsible for 1 out of every 3 premature deaths worldwide.[1] In Spain, IHD is thought to increase health spending and morbidity due to the ageing of the population, and the greater number of survivors.[2]

Diabetes mellitus is closely associated with ischemic heart disease. It makes patients—most of them elderly patients—have a very high cardiovascular risk.[3] Hypoglycemia and hyperinsulinemia are both associated with a higher risk of developing multivessel coronary artery disease (MCAD).[4] In the long-term, this leads to a grim prognosis and more cardiovascular death in these diabetic patients.[5]

Due to the high incidence rate of MCAD, several studies have been conducted to see what type of revascularization is the most suitable one for the profile of these patients. It has been suggested that anatomic complete revascularization (CR) is associated with a lower rate of major adverse cardiovascular events (MACE)—a composite endpoint of death, non-fatal myocardial infarction, and need for new revascularization—compared to anatomic incomplete revascularization (IR).[6] As a matter of fact, it has been reported that the risk of MACE increases significantly when performing IR with minimal residual disease in coronary vessels.[7] Therefore, the treatment recommended is to perform anatomic CR. When this is not feasible, functional CR—currently widely used—is advised.

On the one hand, in patients with stable angina refractory to conservative treatment or non-ST-segment elevation acute coronary syndrome (NSTEACS), single-stage CR is advised through surgical coronary revascularization or percutaneous coronary intervention.[8] On the other hand, in patients with ST-segment elevation acute coronary syndrome (STEACS) staged CR has been suggested by treating, first of all, the culprit coronary artery causing the clinical signs, and then the remaining stenotic arteries.[9] However, in the routine clinical practice, it has been observed that patients with greater comorbidities and worse prognosis are often treated with IR, which worsens even more their clinical evolution since the survival associated with cardiac death, and MACE is lower.[10]

However, one of the main problems we face is passing scientific knowledge from clinical trials on to the routine clinical practice. It has been reported that most of the patients from cardiology units meet some of the exclusion criteria posed by these clinical trials. Such patients are highly heterogeneous, older, and have several cardiovascular risk factors and concomitant diseases, which worsens their prognosis. Therefore, the findings from clinical trials should be used with caution in the overall population.[11,12]

Thus, the objective of this study was to analyze whether there are significant differences regarding mortality and cardiovascular events between patients treated with CR or IR, which is why patients with clinical trial inclusion criteria and patients with characteristics from the routine clinical practice (real world) were included.

METHODS

This was a retrospective, single-center study that used data anonymization and included 733 diabetic patients with MCAD treated with coronary angiography from January 1, 2012 through December 31, 2014. Participants were divided into 2 groups based on whether or not they met the FREEDOM clinical trial inclusion criteria.[13] In this study, those who met these criteria were considered participants eligible for clinical trials while the rest (the non-eligible ones) were categorized as patients from the routine clinical practice or real-world patients.

Due to data anonymization, it was not necessary to request any approval from the ethics committee since it had already been obtained by Chueca González et al.[10] who used the same patient selection. The different informed consents authorize us to treat data to conduct this study.

Study population

Patients over 18 years old with an indication for revascularization—both percutaneous coronary intervention and surgery—due to acute coronary syndromes (STEACS, NSTEACS or unstable angina), refractory stable angina, refractory heart failure, valvular heart disease, cardiac arrest, new revascularization or cardiogenic shock were included in the study Patients with previous cardiac surgeries due to coronary artery disease and valvular heart disease, as well as patients with valvular heart diseases plus a surgical indication were excluded from the study.

The following were categorized as real-world patients (non-FREEDOM): those with STEACS within the 72 previous hours, those with a past medical history of percutaneous transluminal angioplasty, stroke or major bleeding within the previous 6 months, those with functional class III or IV according to the New York Heart Association, in-stent restenosis, known dementia or dependency, at least moderate, according to the Barthel index, and finally those with an extracardiac disease (chronic obstructive pulmonary disease, hepatopathies, chronic kidney disease) bringing survival under 5 years. All the criteria developed have been described previously.[10]

Definitions

When coronary angiography was performed, patients were considered diabetic if they had already been diagnosed as such in their health record or if they were on hypoglycemic treatments like diet, oral antidiabetic drugs or insulin.

MCAD consists of the existence of ≥ 70% luminal stenosis in 2 or more epicardial vessels covering, at least, 2 or more different coronary artery territories. Also, such lesions are prone to revascularization via angioplasty and surgery according to the clinical practice guidelines and the criterion of interventional cardiologists and cardiac surgeons.

Coronary lesions were treated with anatomic CR. Epicardial vessels > 2 mm in caliber with > 70% stenosis were treated regardless of whether the areas compromised were viable or necrotic.

The indication to perform the coronary angiography was given based on the patient's clinical course that led to his admission. Acute coronary syndromes with and without ST-segment elevation according to the third universal definition of infarction were included.[14] Also, this test was performed on other diseases like unstable angina, refractory stable angina to medical treatment, and other (decompensated heart failure, cardiogenic shock, cardiac arrest, ventricular arrhythmias).

Left ventricular ejection fraction was categorized as dichotomic with values ≥ 40% or < 40%.

To assess the stage of kidney failure the glomerular filtration rate was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. It was defined as reduced with glomerular filtration rates < 45 mL/min/1.73 m^3, which is consistent with stage 3B chronic kidney disease.

Regarding the variables that should be measure at the follow-up, events such as death, non-fatal myocardial infarction, and new revascularization were categorized as MACE. On the other hand, major adverse cardiovascular and cerebrovascular events (MACCE) were considered a composite endpoint of death, non-fatal myocardial infarction, new revascularization, and stroke.

Statistical analysis

All statistical analyses were conducted using the statistical software package SPSS version 21.0 for Windows. Quantitative variables were studied using the Student *t* test for independent samples, and expressed as mean ± standard deviation. Cualitative variables were compared using the chi-square test and expressed as percentages and absolute numbers. Also, the odds ratios (OR) were obtained too. Multivariate analysis was conducted through survival analysis using Cox regression method. Also, survival charts and hazard ratios (HR) with their corresponding 95% confidence intervals were obtained for the significant covariables of the univariate analysis. *P* values ≤ .05 were considered statistically significant.

RESULTS

A total of 733 diabetic patients met the inclusion criteria to participate in the study. A total of 299 of these patients (40.8%) had criteria that were compatible with the clinical trials, and 434 (59.2%) with the real world. The presence of CR was less common in both groups compared to participants treated with IR. Among the patients in whom CR was achieved, this type of revascularization turned out to be more common in those with criteria from the FREEDOM trial (43.5%).

Patients' baseline characteristics

Multiple parameters collected at admission were analyzed to perform coronary angiography (table 1).

Differences were found when patients were compared based on their clinical characteristics (patients from clinical trials and from the real world) and type of revascularization received. The most significant differences were found in real-world patients. On the one hand, mean age (69.8 years) was older with more patients > 80 years compared to the group with clinical trial criteria (mean, 66.2 years). On the other hand, in this group there was a higher incidence rate of coronary artery disease with damage to 3 vessels (54.6%) compared to patients from clinical trials (44.8%). Regarding the indication of coronary angiography, a higher rate of acute coronary syndromes—both STEACS and NSTEACS—in such subgroup was reported. They were eventually treated with IR (61% and 80.6%; *P* < .001) more often. However, patients with characteristics from clinical trials had NSTEACS, and unstable and stable angina as the main indications for coronary angiography. In these patients, CR was achieved more often compared to real-world diabetics.

Major events at 30-day and 35-month follow-up

When it comes to patients with clinical trial inclusion criteria, achieving CR suggested the occurrence of fewer major events—both overall mortality and cardiovascular system-related mortality—especially at 35-month follow-up without any significant differences being reported (table 2).

The same tendency was seen in real-world patients. Therefore, CR reduced the risk of overall mortality (OR, 0.84; 95%CI, 0.74-0.95; *P* = .006), cardiac death (OR, 0.81; 95%CI, 0.73-0.91; *P* = .002), and MACE (OR, 0.84; 95%CI, 0.74-0.96; *P* = .012) at 35-month follow-up (table 3). In the survival analysis, the same tendency was found in the said subgroup of participants at 35-month follow-up. CR reduced the risk of cardiac death (HR, 0.35; 95%CI, 0.13-0.90; *P* = .029), and MACE (HR, 0.5; 95%CI, 0.28-0.89; *P* = .019). Similarly, EuroSCORE-II > 5 increased the risk of cardiac death (HR, 2.74; 95%CI, 1.11-6.75; *P* = .028). Finally, a higher risk of MACE (HR, 2.08; 95%CI, 1.03-4.23; *P* = .042), and MACCE (HR, 2.36; 95%CI, 1.13-4.95; *P* = .023) was reported (figure 1).

When survival was analyzed in the 4 groups of patients (figure 2), those with FREEDOM clinical trial inclusion criteria had a lower risk of overall mortality (HR, 0.30; 95%CI, 0.16-0.57; *P* < .001), cardiac death (HR, 0.33; 95%CI, 0.15-0.71; *P* = .03), MACE (HR, 0.58; 95%CI, 0.38-0.86; *P* = .008), and MACCE (HR, 0.59; 95%CI, 0.40-0.89; *P* = .01). On the one hand, achieving CR lowered the risk of cardiac death (HR, 0.32; 95%CI, 0.13-0.83; *P* = .019), and MACE (HR, 0.50; 95%CI, 0.29-0.89; *P* = .017). On the other hand, EuroSCORE > 5 when coronary angiography was performed was associated with higher rates of overall mortality (HR, 2.16; 95%CI, 1.06-4.41; *P* = .034), cardiac death (HR, 3.48; 95%CI, 1.49-8.16; *P* = .004), MACE (HR, 2.18; 95%CI, 1.26-3.78; *P* = .005), and MACCE (HR, 2; 95%CI, 1.18-3.40; *P* = .011). It was reported that if the patient had heart failure, this increased the risk of MACE (HR, 2.44; 95%CI, 1.25-4.74; *P* = .009), and MACCE (HR, 2.77; 95%CI, 1.39-5.53; *P* = .004). On the remaining variables, a lower overall mortality rate was confirmed if the patient was a non-smoker (HR, 0.46; 95%CI, 0.24-0.89; *P* = .02), and a higher risk of MACCE was reported if he had hypertension (HR, 1.50; 95%CI, 1.01-2.24; *P* = .049) or 3-vessel disease (HR, 1.44; 95%CI, 1.06-1.97; *P* = .022).

Table 1. Patients' baseline characteristics based on compliance of the FREEDOM criteria

	Total	CR in patients from CT	IR in patients from CT	*P*	Total	CR in patients from the RCP	IR in patients from the RCP	*P*
N	40.8 (299)	43.5% (130)	56.5% (169)	< .001	59.2% (434)	28.3% (123)	71.7% (311)	< .001
Age	66.2 ± 9	64.1 ± 9.1	68 ± 8.4	< .001	69.8 ± 9.6	67.5 ± 9.9	70.7 ± 9.3	.002
+ 80 years	6 (18)	16.7 (3)	83.3 (15)	.10	15.4 (67)	17.9 (12)	82.1 (55)	.364
Woman	30.1 (90)	40 (36)	60 (54)	.45	31.1 (135)	28.1 (38)	71.9 (97)	.95
3 vessels	44.8 (134)	30.6 (41)	69.4 (93)	< .001	54.6 (171)	35.3 (30)	61.8 (141)	< .001
Indication				.42				.01
STEACS	2(6)	16.7 (1)	83.3 (5)		32.5 (141)	39 (55)	61 (86)	
NSTEACS	35.5 (106)	40.6 (43)	59.4 (63)		32 (139)	19.4 (27)	80.6 (112)	
Unstable angina	28.4 (85)	47.1 (40)	52.9 (45)		15.7 (57)	27.9 (19)	72.1 (49)	
Stable angina	28.1 (84)	47.6 (40)	52.4 (44)		13.1 (57)	29.8 (17)	70.2 (40)	
LVEF < 40%	14.4 (43)	32.6 (14)	67.4 (29)	.14	29.8 (129)	21. (28)	78.3 (101)	.048
Hypertension	84.3 (252)	42.9 (108)	57.1 (144)	.63	84.1 (365)	26 (95)	74 (270)	.046
Dyslipidemia	66.9 (200)	45 (90)	55 (110)	.46	61.1 (265)	25.7 (68)	74.3 (197)	.127
Obesity	28.1 (84)	52.4 (44)	47.6 (40)	.07	27.9 (121)	27.3 (33)	72.7 (88)	.813
Tobacco use history	46.5 (139)	51.1 (71)	48.9 (68)	.019	43.5 (189)	29.1 (55)	70.9 (134)	.078
Treatment of DM		43.5 (130)	56.5 (169)	.67		28.3 (123)	71.7 (311)	.83
Diet	7.7 (23)	52.2 (12)	47.8 (11)			31.8 (7)	68.2 (15)	
Oral antidiabetic drugs	65.9 (197)	43.1 (85)	56.9 (112)			27.3 (73)	72.7 (194)	
Insulin	26.4 (79)	41.8 (33)	58.2 (46)			29.7 (43)	70.3 (102)	
Previous infarction	12.7 (38)	28.9 (11)	71.1 (27)	.053	17.3 (75)	32 (24)	68 (51)	.439
Heart failure	4.3 (13)	23.1 (3)	76.9 (10)	.129	9.2 (40)	7.5 (3)	92.5 (37)	.002
Peripheral arterial disease	8.4 (25)	32 (8)	68 (17)	.227	13.8 (60)	15 (9)	85 (51)	.014
Stroke	6.4 (19)	31.6 (6)	68.4 (13)	.28	9.4 (41)	22 (9)	78 (32)	.34
COPD	13.7 (41)	46.3 (19)	53.7 (22)	.691	18.7 (81)	21 (17)	79 (64)	.103
GFR < 45	7.4 (22)	18.2 (4)	81.8 (18)	.013	13.8 (60)	16.7 (10)	83.3 (50)	.031
Previous PCI	17.1 (51)	35.3 (18)	64.7 (33)	.195	22.1 (96)	25 (24)	75 (72)	.41
EuroSCORE II	2.27±2.27	1.84 ± 1.62	2.59 ± 2.63	.004	7.57 ± 11.2	5.71 ± 7.98	8.39 ± 12.24	.025

COPD, chronic obstructive pulmonary disease; CR, complete revascularization; CT, clinical trials; DM, diabetes mellitus; GFR, glomerular filtration rate; IR, incomplete revascularization; LVEF, left ventricular ejection fraction; NSTEACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RCP, routine clinical practice; STEACS, ST-segment elevation acute coronary syndrome.
Data are expressed as no. (%).

Type of procedure received

Regarding the therapies received, we found a higher rate of percutaneous coronary interventions (80.8%) performed in all the study subgroups. Real-world patients were treated with coronary artery bypass graft more often compared to patients from clinical trials. Finally, conservative treatment was more common (9%) in real-world patients with IR (table 4).

DISCUSSION

The main conclusions of this study are: *a)* although patients potentially eligible for clinical trials receive CR more often no significant differences have been found regarding survival or adverse cardiovascular events; *b)* real-world patients are treated with IR more often. In these patients, less mortality has been suggested, both overall and cardiac, as well as fewer MACE at 35-month follow-up have been reported if CR is achieved; *c)* patients with FREEDOM clinical trial criteria have higher survival rates compared to real-world diabetics; *d)* most patients are treated with percutaneous coronary intervention.

One of the main problems when analyzing the repercussions of CR is the lack of clinical trials with patients similar to those found in the routine clinical practice or the real word. This complicates the extrapolation of results to the overall population since, in most

Table 2. Major events at 30-day and 35-month follow-up in patients with criteria from the FREEDOM clinical trial

Event	30 days		*P*	35 months		*P*
	CR	IR		CR	IR	
Mortality	0.4 (1)	0.4 (1)	.863	2.8 (5)	6.7 (12)	.285
Cardiac death	0	0.4 (1)	.375	1.1 (2)	4.5 (8)	.154
Acute myocardial infarction	0.4 (1)	0.7 (2)	.715	2.4 (4)	5.4 (9)	.359
Stroke	0	0.7 (2)	.209	1.2 (2)	1.9 (3)	.883
MACE	0.7 (2)	1.5 (4)	.601	9.7 (19)	17.9 (35)	.348
MACCE	0.7 (2)	2.2 (6)	.277	11.2 (22)	18.9 (37)	.451

CR, complete revascularization; IR, incomplete revascularization; MACE, major adverse cardiovascular events (death, non-fatal myocardial infarction, and need for new revascularization); MACCE, major adverse cardiovascular and cerebrovascular events (death, non-fatal myocardial infarction, need for new revascularization and stroke).
Data are expressed as no. (%).

Table 3. Major events at 30-day and 35-month follow-up in patients from the routine clinical practice

Event	30 days		*P*	35 months		*P*
	CR	IR		CR	IR	
Mortality	1.8 (6)	8.5 (29)	.257	5.5 (14)	38.4 (98)	.006
Cardiac death	1.5 (5)	8.1 (27)	.195	3.2 (8)	31.2 (78)	.002
Acute myocardial infarction	0.7 (3)	1.7 (7)	.911	7.7 (21)	17.2 (47)	.626
Stroke	0	0.3 (1)	.522	1.5 (3)	4.9 (10)	.650
MACE	1.7 (5)	7.9 (24)	.225	6.5 (15)	40 (92)	.012
MACCE	1.7 (5)	7.9 (24)	.225	8.3% (19)	41.3 (95)	.089

CR, complete revascularization; IR, incomplete revascularization; MACE, major adverse cardiovascular events (death, non-fatal myocardial infarction, and need for new revascularization); MACCE, major adverse cardiovascular and cerebrovascular events (death, non-fatal myocardial infarction, need for new revascularization and stroke).
Data are expressed as no. (%).

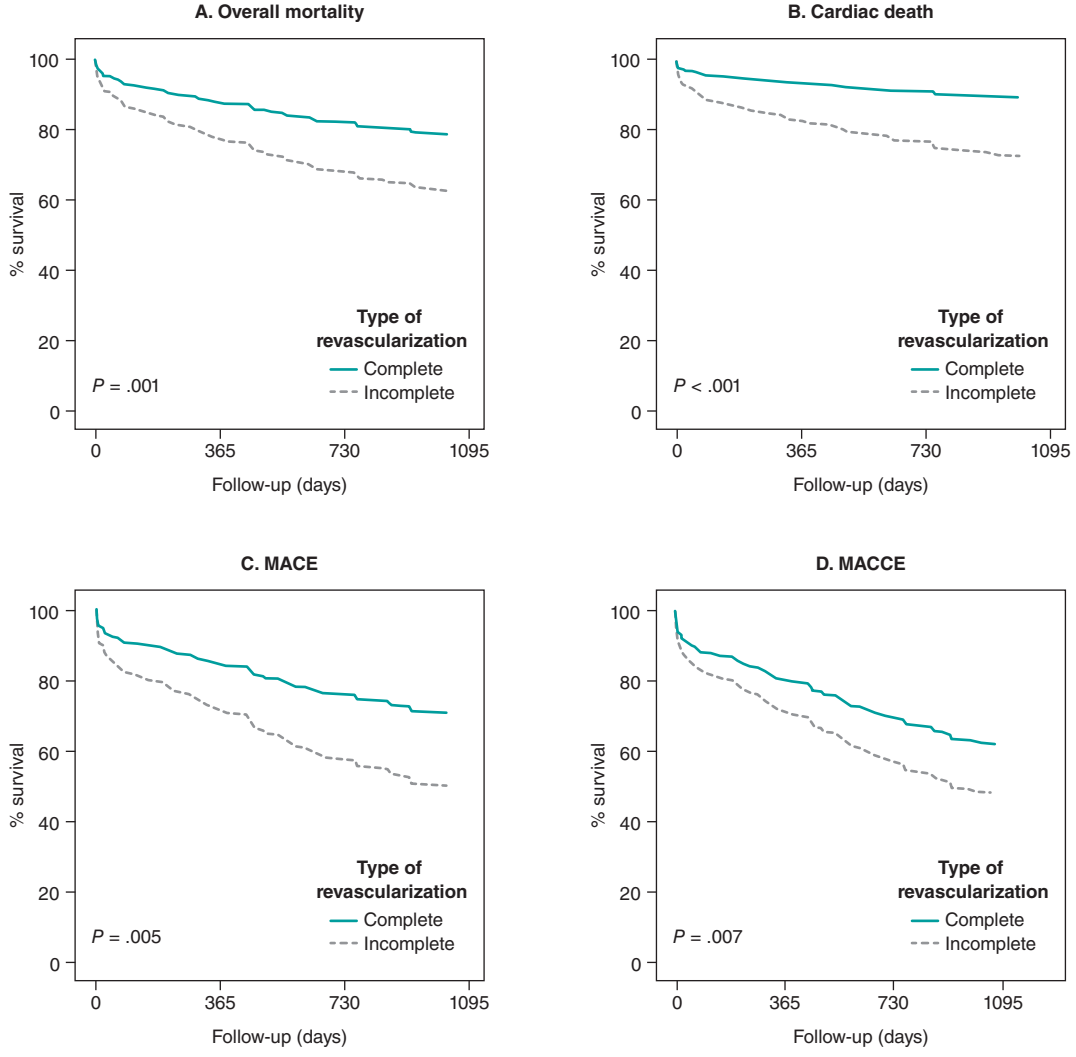

Figure 1. Evolution of survival in diabetic patients from the routine clinical practice with multivessel coronary artery disease. MACE, major adverse cardiovascular events (death, non-fatal myocardial infarction, and need for new revascularization); MACCE, major adverse cardiovascular and cerebrovascular events (death, non-fatal myocardial infarction, need for new revascularization and stroke).

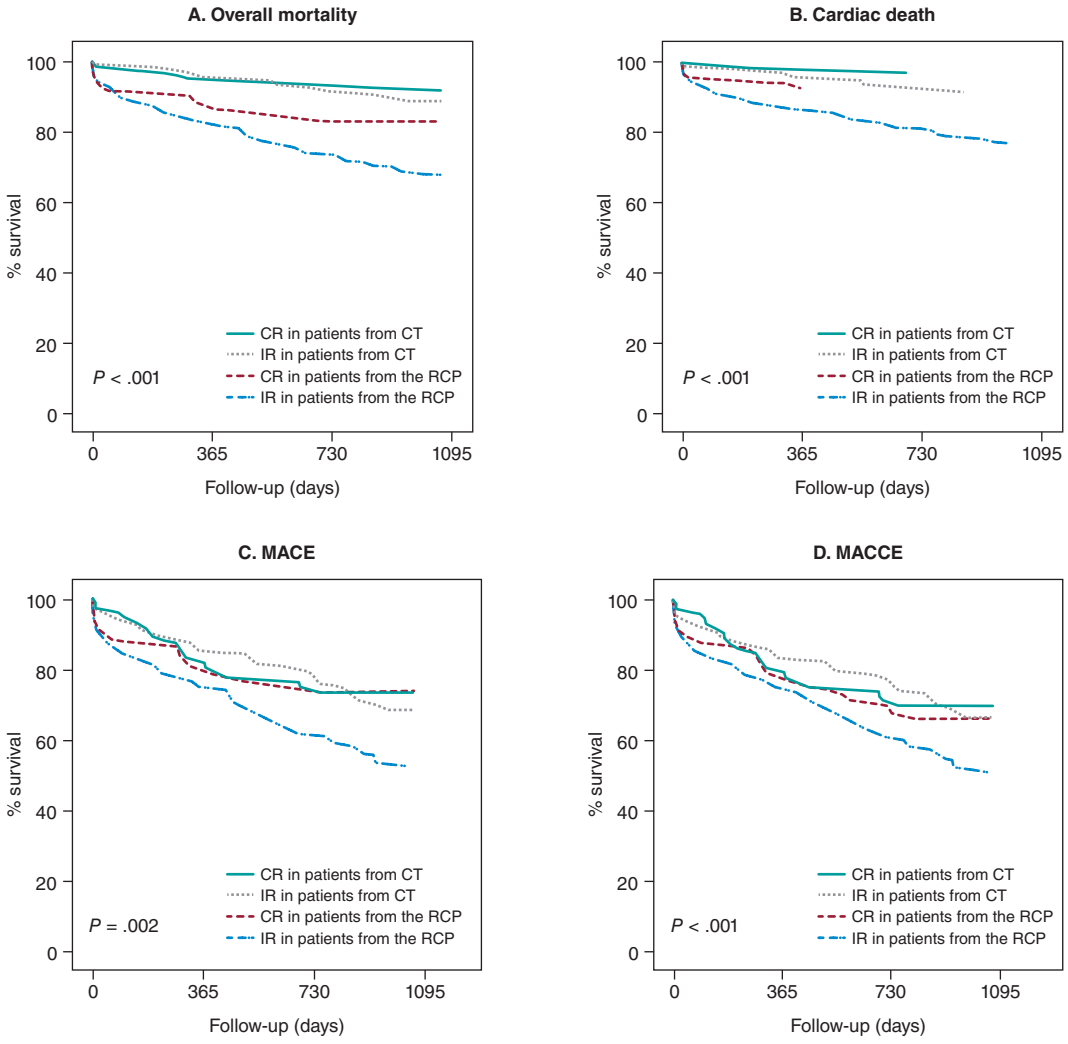

Figure 2. Evolution of survival in diabetic patients con multivessel coronary artery disease. CT, clinical trials; CR, complete revascularization; IR, incomplete revascularization; MACCE, major adverse cardiovascular and cerebrovascular events (death, non-fatal myocardial infarction, need for new revascularization and stroke); MACE, major adverse cardiovascular events (death, non-fatal myocardial infarction, and need for new revascularization); RCP, routine clinical practice.

Tabla 4. Type of procedures performed per group of patients

Treatment	CR in patients from CT	IR in patients from CT	CR in patients from the RCP	IR in patients from the RCP	Total
Conservative	0	4.1 (7)	0	9 (28)	4.8 (35)
PCI	78.5 (102)	87 (147)	76.4 (94)	80.1 (249)	80.8 (592)
CABG	21.5 (28)	8.9 (15)	23.6 (29)	10.9 (34)	14.5 (106)

CABG, coronary artery bypass graft; CR, complete revascularization; CT, clinical trials; IR, incomplete revascularization; PCI, percutaneous coronary intervention; RCP, routine clinical practice.
Data are expressed as no. (%).

studies, homogeneous participants can be found often with a better clinical profile.[11,12] This reality would explain why CR does not improve the survival rate of such patients who are younger and have fewer comorbidities and cardiovascular risk factors, while in diabetics from the routine clinical practice CR does provide improvements because these are older patients with more MCAD and comorbidities (reduced ejection fraction, arterial hypertension, heart failure, peripheral arterial disease, and chronic kidney disease with, at least, a 3B stage). However, the current scientific evidence available recommends performing a therapeutic effort to achieve CR. It has been suggested that it improves survival in both overall mortality and cardiac death in real-world patients, and avoids IR that is an independent predictor of mortality (HR, 2.46; 95%CI, 1.46-4.13; P = .001).[10] On the other hand, The Complete Trial[9] confirmed less cardiac death and fewer new reinfarctions (HR, 0.74; 95%CI, 0.60-0.91; P = .004) when CR was performed in patients with STEACS compared to patients in whom only the culprit vessel was treated. Finally, a recent metanalysis confirmed that CR also reduces the overall mortality rate (RR, 0.73; 95%CI, 0.66-0.81), the need for new revascularizations (RR, 0.77; 95%CI, 0.66-0.88), and

the occurrence of new myocardial infarctions (RR, 0.74; 95%CI, 0.64-0.85).[15]

In the first place, this study included diabetic patients who would not be eligible for clinical trials because they are a too heterogeneous population whose characteristics and comorbidities resemble those of real-world patients too much. Secondly, the study deals with a discussed topic these days because cardiovascular diseases, ischemic heart disease among them, are the leading cause of death in developed countries. Diabetes is especially associated with it most often leading to MCAD. Therefore, it is necessary to assess whether CR provides benefits regarding survival always focusing on the patient and his clinical-functional status because, at times, there is controversy on whether to treat all lesions or only the culprit lesions causing the problem.

Finally, if CR provides the benefits suggested in this and other studies, it could improve the survival of diabetic patients and their quality of life and that of their relatives. Also, it would reduce the health spending and the years of life lost or the disability-adjusted years of life by reducing mortality, the need for reinterventions to treat new infarctions and strokes, as well as the need for new revascularizations.

Limitations

This study was conducted from a statistical analysis of a database already used by Chueca González et al.[10]. It was a retrospective, single-center registry, which limits the possibilities of establishing causality and extrapolating the results to the overall population. Similarly, since the population was designed for a different study, statistical power was probably lost since the size of the sample and the characteristics of the participants included are different from the ones a study like the present one would require.

Another aspect we should mention is the technology of the stents currently used compared to those used during this study recruitment process. Since they appeared, different types and generations of stents associated with different antiproliferative drugs have been manufactured. This has improved secondary survival and minimized the occurrence of in-stent stenosis. Therefore, the study results could be different compared to those obtained today.

Finally, the definitions of CR vary based on the study. Some recommend it in the presence of > 50% occlusions of luminal diameter. Others with occlusions > 70%. In some cases, only coronary vessels with minimum diameters of 2 mm are considered. In other cases, these diameters need to be 1.5 mm. Specifically, this study only considered vessels with stenosis > 70% with minimum calibers of 2 mm.

CONCLUSIONS

This study suggests that diabetics eligible for clinical trials have fewer complications compared to non-eligible diabetic patients. Also, this suggests that real-world diabetics have worse prognosis in case of MCAD. Under this circumstance, it is suggested that achieving CR would improve their long-term survival.

In conclusion, further studies, and clinical trials including real-world patients are advised. Also, they would need to include updated diagnostic criteria and new therapeutic techniques—both pharmacological and interventional—to obtain new evidence to guide us on the therapeutic effort needed to treat patients who require coronary artery revascularization whether through angioplasty or surgery.

FUNDING

This study was funded by the Cardiovascular Biomedical Research Center Network (CB16/11/00360), Instituto de Salud Carlos III. Also, it has been co-funded by the European Regional Development Fund.

The statistical analysis of this manuscript was funded by the Chair of Advanced Therapies in Cardiovascular Diseases at Universidad de Málaga, Spain (CIF Q-2918001-E).

AUTHORS' CONTRIBUTIONS

F. Puyol-Ruiz: study design, data curation, and drafting of the manuscript. M. Jiménez-Navarro: study design, data curation, and critical review of the manuscript. EM. Chueca-González, F. Carrasco-Chinchilla, J. L. López-Benítez, J. H. Alonso-Briales, J. M. Melero- Tejedor, and J. M. Hernández-García: data curation.

CONFLICTS OF INTEREST

None reported.

ACKNOWLEDGEMENTS

We wish to thank María Jiménez Salva for her constant support and collaboration while drafting this manuscript.

WHAT IS KNOWN ABOUT THE TOPIC?

- Due to the ageing of the population, health spending and morbidity due to ischemic heart disease and diabetes are expected to grow.
- Diabetes increases the number of cases of MCAD, which is associated with a worse prognosis.
- Results from clinical trials should be applied to real-world patients with caution.

WHAT DOES THIS STUDY ADD?

- More than half of diabetic patients with MCAD had exclusion criteria to participate in the FREEDOM clinical trial
- Real-world diabetics have a worse prognosis against MCAD.
- Anatomic CR reduces the risk of cardiac death and MACE at 35-month follow-up.
- More studies and clinical trials are needed with real-world patients.

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REC Interv Cardiol. 2022;4(4):279-286
https://doi.org/10.24875/RECICE.M22000289

Original article

Effectiveness of spherical tip noncompliant balloon for stent postdilatation: the REPIC02-RECONQUISTHA study

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ABSTRACT

Introduction and objectives: Noncompliant balloon postdilatation of coronary stents improves clinical results. Regular noncompliant balloons (RegNC) have less crossability and a tapered-tip that can complicate successful stent postdilatation. The mechanical conditions of a new spherical tip non-compliant balloon (SphNC) could facilitate stent postdilatation. We tried to evaluate the effectiveness of a new SphNC in the routine percutaneous coronary intervention (PCI) practice.

Methods: Prospective multicenter technical registry to assess the effectiveness of a new SphNC for stent postdilatation with 2 study arms: use of SphNC as the first choice or as the secondary choice after RegNC failure. The primary endpoint was technical success defined as advancing the SphNC across the stent segment. Secondary endpoints were angiographic success defined as technical success and residual stenosis < 30% with final TIMI grade-3 flow, and procedural success defined as angiographic success without mechanical stent complications or any perioperative major adverse cardiovascular events.

Results: The SphNC was used in 263 lesions (177 lesions as first choice, and 86 after RegNC failure) in 250 procedures. The use of the complex technique to advance the SphNC was low (9.9%). Technical, angiographic, and procedural success rates were 98.9%, 98.3%, and 98.3%, respectively, as the first choice, and 98.8%, 97.7%, and 96.5%, respectively, after RegNC failure. SphNC had similar size (3.39 mm ± 0.6 mm vs 3.34 mm ± 0.6 mm; *P* = nonsignificant), and shorter lengths (11 mm ± 2 mm vs 12 mm ± 3 mm; *P* = .005) compared to RegNC. No stent-related mechanical complications were reported.

Conclusions: SphNC for coronary stent postdilatation in the routine PCI clinical practice has a very high technical success rate as the first choice (98.9%), as well as in cases of RegNC failure (98.8% with low complex technique requirements, and a safe profile).

Keywords: Complex PCI. Stent postdilatation. Tapered-tip balloon. Spherical tip balloon.

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Received 14 January 2022. Accepted 8 March 2022. Online: 22-04-2022.

Efectividad del balón no distensible con punta esférica en posdilatación coronaria: estudio REPIC02-RECONQUISTHA

RESUMEN

Introducción y objetivos: La posdilatación de *stents* coronarios con balones no distensibles mejora los resultados clínicos. Los balones no distensibles normales (RegNC) presentan peor navegabilidad y tienen una punta cónica que puede dificultar la posdilatación exitosa. Las condiciones mecánicas de un nuevo balón no distensible con punta esférica (EsfNC) podrían facilitar la posdilatación del *stent*. Evaluamos la efectividad del EsfNC en la posdilatación coronaria para la intervención coronaria percutánea en la práctica clínica habitual.

Métodos: Registro técnico prospectivo y multicéntrico para evaluar la efectividad de un nuevo EsfNC en posdilatación coronaria, con 2 grupos de estudio: uso de EsfNC como primera opción o uso de EsfNC ante el fracaso de RegNC. El evento primario fue el éxito técnico, definido como conseguir avanzar el EsfNC hasta el segmento que posdilatar dentro del *stent*. Los eventos secundarios fueron el éxito angiográfico, definido como éxito técnico junto con estenosis residual < 30% con flujo final TIMI 3, y el éxito del procedimiento, definido como éxito angiográfico sin complicación mecánica del *stent* ni eventos cardiovasculares mayores periprocedimiento.

Resultados: Se usó EsfNC en 263 lesiones (en 177 como primera opción y en 86 tras el fracaso de RegNC), en 250 procedimientos. Se usaron técnicas complejas para avanzar el EsfNC en el 9,9% de los procedimientos. Los porcentajes de éxito técnico, angiográfico y de procedimiento fueron del 98,9%, el 98,3% y el 98,3% como primera opción, y del 98,8%, el 97,7% y el 96,5% tras fracaso de RegNC, respectivamente. Los EsfNC tuvieron similar calibre (3,39 ± 0,6 frente a 3,34 ± 0,6 mm; p = no significativo) y longitud más corta (11 ± 2 frente a 12 ± 3 mm; p = 0,005) que los RegNC. No se comunicaron complicaciones mecánicas del *stent*.

Conclusiones: La posdilatación coronaria con EsfNC para la intervención coronaria percutánea en la práctica clínica habitual muestra un porcentaje muy alto de éxito técnico, tanto en primera opción (98,9%) como en casos de fracaso de RegNC (98,8%), con baja necesidad de técnicas complejas y buen perfil de seguridad.

Palabras clave: Intervención coronaria percutánea compleja. Posdilatación coronaria. Balón no distensible. Balón no distensible punta esférica.

Abbreviations

NC: noncompliant balloon. **PCI:** percutaneous coronary intervention. **RegNC:** regular noncompliant balloon. **SphNC:** spherical tip noncompliant balloon.

INTRODUCTION

Optimal stenting is crucial in the long-term clinical outcomes while proper stent expansion and apposition reduce the risk of thrombosis and restenosis.[1] Coronary stent postdilatation increases luminal area while reducing stent strut malapposition.[2,3]

Unlike semicompliant balloons, noncompliant (NC) balloon postdilatation allows uniform dilatation at higher pressures, which reduces the risk of damage to the vessel wall (edge dissection or coronary perforation),[4] and is associated with greater stent expansion and a lower rate of target lesion revascularization.[5] Therefore, postdilatation using NC balloons is a common strategy to increase the luminal area of underexpanded stents or increase the stent proximal caliber in long lesions or in bifurcation techniques like the proximal optimization technique (POT) or the conventional kissing-balloon technique in a safe and predictable way.[6,7]

The navigability of NC balloons is more limited, a significant setback in cases of coronary tortuosity, calcified lesions or proximal stent edge malapposition. Regular noncompliant balloons (RegNC) include a cone-shaped tip that can collide with the struts or with the proximal stent edge, thus conditioning a force vector opposed to the push force that can potentially interfere with its advancement (figure 1A), and eventually lead to mechanical stent failure in cases of inadequate coaxiality. In these cases, the use of complex techniques (buddy-wire, buddy-balloon, anchoring...) or specific devices (guide catheter extension systems) are often needed to advance the balloon, which increases the cost of the procedure.

The cone-shaped tip has been replaced by a spherical tip in a new NC balloon (NC Conqueror Spherical tip, APT Medical, China) (SphNC). Despite its greater crossing profile (0.039 in), the spherical tip contributes to decomposing and reducing the resistance force vector opposed to the push vector (figure 1B), facilitating the advancement of the balloon until reaching the inside of the stent and the post-dilatable segment.

Our objective is to assess the effectiveness of this new SphNC in coronary postdilatation during percutaneous coronary intervention (PCI) in the routine clinical practice.

METHODS

The RECONQUISTHA trial is a prospective and multicenter technical registry conducted in 16 high volume PCI-capable centers (> 500 PCIs/year)[8] designed to assess the effectiveness of SphNC in coronary postdilatation during PCI in the routine clinical practice. Since it is a technical registry that used no personal or clinical data on a device approved with CE marking no ethics committee approval or informed consent forms were required.

Inclusion and exclusion criteria

The only inclusion criterion was the indication for coronary postdilatation with the SphNC according to the operator (long, calcified, ostial lesion, bifurcation and angiographic or stent balloon

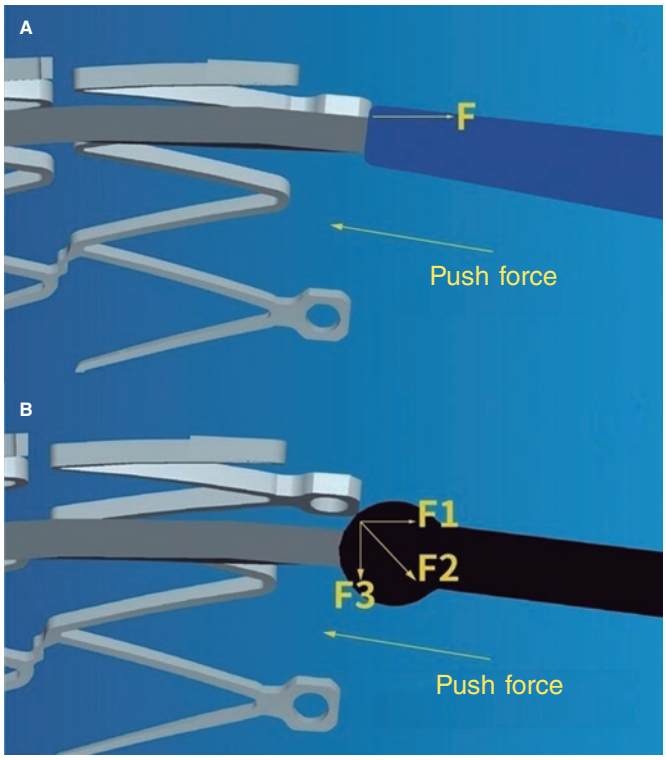

Figure 1. **A:** the cone-shaped tip of a regular noncompliant balloon can collide with the stent struts thus conditioning a force (F) vector opposed to the push force that can potentially interfere with its advancement. **B:** the spherical tip contributes to decomposing and reducing the resistance force vector opposed to the push vector, thus facilitating the balloon advancement towards the inside of the stent. Courtesy of APT Medical, China.

underexpansion). The exclusion criteria were the use of a ≤ 5-Fr guide catheter, vessel size < 2mm or > 5mm, jailed branch post-dilatation without previous opening of the stent struts of the main vessel towards such branch or finding 1 of the following scenarios before postdilatation: mechanical stent failure, stent edge dissection ≥ C, coronary perforation or TIMI grade ≤ 2 flow in the main vessel or lateral branch.

Procedure

All lesions were treated with stenting according to the operator's criterion and according to the routine clinical practice (arterial access, guide catheter caliber, predilatation or plaque modification, and intracoronary imaging). Also, they should be treated with standard antithrombotic treatment (dual antiplatelet therapy with acetylsalicylic acid, and $P2Y_{12}$ receptor inhibitors prior to the PCI plus weight-adjusted unfractionated heparin at doses of 100 IU/kg with further boluses to achieve activated coagulation times between 250 s and 300 s).

The use of the SphNC was considered in 2 different clinical settings that categorized the lesions into 2 study groups: use of SphNC as first-line treatment, and use of SphNC as a second choice after failed RegNC advancement. Complex techniques like the buddy-wire, buddy-balloon, anchoring or guide catheter extension system were allowed to advance both the RegNC and the SphNC. In cases where the second choice after failed RegNCn advancement was used despite the use of a complex technique, the same complex technique with the SphNC was advised too.

Figure 2. Actual appearance of the spherical tip noncompliant balloon used in the study. Courtesy of APT Medical, China.

The spherical tip noncompliant balloon

The NC Conqueror Spherical tip balloon (APT Medical, China) is a rapid exchange balloon catheter for percutaneous coronary interventions that is compatible with a 0.014 in intracoronary guidewire. This device has a distinctive tungsten radiopaque spherical tip (0.039 in crossing profile) designed to minimize resistance while advancing the balloon towards the inside of the stent (figure 2). It is available in calibers ranging from 2 mm to 5 mm in intervals of 0.25 mm to 0.5 mm, and lengths of 6 mm, 8 mm, 12 mm, 15 mm, 20 mm, and 30 mm. Nominal pressure stands at 12 atm, and rated pressure burst at around 20 atm (18 atm in 4.5 mm to 5 mm calibers). The device has the CE marking.

Definition of endpoints

The study primary endpoint was technical success defined as the successful advancement of the SphNC until reaching the stent post-dilatable segment. Secondary endpoints were angiographic success—defined as technical success with residual stenosis < 30% with final TIMI grade-3 flow—and procedural success defined as angiographic success without mechanical stent failure or perioperative major adverse cardiovascular events like myocardial infarction—based on the criteria established by the Academic Research Consortium [ARC]-2[9]—stroke, coronary perforation, need for emergency heart surgery or death.

The hypothesis was to consider the study positive if technical success was achieved in > 80% of the lesions regarding the use of the SphNC as the go-to option (according to data published on technical success rates with postdilatation balloons[10]), and in > 30% regarding the use of the SphNC after failed RegNC advancement (random criterion based on the success of the new balloon in 1 out of 3 cases of failed RegNC advancement).

Data curation

The characteristics of the lesion and the PCI, the indication for postdilatation, any information on the devices used, and quantitative and procedural angiographic results were collected prospectively. Data was introduced in an anonymized electronic database specifically designed for the purpose of the study. Lesions were categorized based on the classification established by the American College of Cardiology and the American Heart Association (ACC/AHA).[11] Coronary calcification was defined as moderate whenever

Table 1. Characteristics of the lesions

	Total (N = 263)	SphNC as the go-to option (N = 177)	SphNC after failed RegNC (N = 86)	P*		Total (N = 263)	SphNC as the go-to option (N = 177)	SphNC after failed RegNC (N = 86)	P*
Target vessel				.27	*AHA classification*				.1
LAD	40.7% (107)	41.8% (74)	38.4% (33)		A	2.7% (7)	4% (7)	0% (0)	
LCx	20.5% (54)	17.5% (31)	26.7% (23)		B1	23.6% (62)	26% (46)	18.6% (16)	
RCA	30% (79)	31.1% (55)	27.9% (24)		B2	45.2% (119)	44.1% (78)	47.7% (41)	
LMCA	7.6% (20)	8.5% (15)	5.8% (5)		C	26.4% (57)	26% (46)	33.7% (29)	
CABG	1.2% (3)	1.1% (2)	1.2% (1)		*Baseline TIMI flow*				.65
Location				.98	0	21.7% (57)	20.9% (37)	23.3% (20)	
Proximal	42.6% (112)	42.9% (76)	41.9% (36)		1	1.1% (3)	1.7% (3)	0% (0)	
Medial	43.3% (114)	42.9% (76)	44.2% (38)		2	8.4% (22)	8.5% (15)	8.1% (7)	
Distal	14.1% (37)	14.1% (25)	12% (12)		3	68.8% (181)	68.9% (122)	68.6% (59)	
Calcification				.54	*Bifurcation*	29.7% (78)	27.7% (49)	33.7% (29)	.31
Moderate	39.5% (104)	41.2% (73)	36% (31)		2 stents	7.6% (20)	5.6% (10)	11.6% (10)	.16
Severe	18.6% (49)	16.9% (30)	22.1% (19)		*Ostial*	11.1% (24)	13% (23)	8.1% (7)	.24
Tortuosity				< .001	*CTO*	5.7% (15)	7.9% (14)	1.2% (1)	.03
Moderate	35.7% (94)	35% (62)	37.2% (32)		*STEMI*	16.3% (43)	13.6% (24)	22.1% (19)	.08
Severe	6.1% (16)	1.7% (3)	15.1% (13)		*Lesion on the QCA*				
Lesion angulation				< .001	MLD (mm)	1.01 ± 1.04	1.05 ± 1.06	0.9 ± 1	.27
< 30 °	62.4% (164)	70.1% (124)	46.5% (40)		VRD (mm)	3.34 ± 0.62	3.3 ± 0.59	3.44 ± 0.65	.09
30°-70 °	30.8% (81)	26% (46)	40.7% (35)		Percent diameter stenosis (%)	83 ± 17	82 ± 17	84 ± 16	.48
> 70 °	6.8% (18)	4% (7)	12.8% (11)		Stenotic area (%)	88 ± 13	87 ± 14	89 ± 12	.13

AHA, American Heart Association; CABG, coronary artery bypass graft; CTO, chronic total coronary occlusion; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery; MLD, minimal lumen diameter; QCA, quantitative coronary angiography; RCA, right coronary artery; RegNC, cone-shaped tip regular noncompliant balloon; SphNC, spherical tip noncompliant balloon; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; VRD, vessel reference diameter.

* *P* between SphNC groups as the go-to option, and SphNC after failed RegNC.

coronary radiopacities would be found prior to the injection of contrast or severe whenever these radiopacities would damage both sides of the arterial lumen.[12] Coronary tortuosity was defined as moderate if ≥ 3 consecutive curvatures between 45° and 90° were found during diastole or severe if any previous curvatures between 90° and 180° would be found or that encompassed the lesion.[13] Angulation inside the lesion was measured as the angle between the start and the end of stenosis. The presence of ostial stenosis > 50% in the branch lateral to the lesion or the need to place the protection guidewire in the lateral branch was considered bifurcation. The stent suboptimal expansion was defined as residual stenosis ≥ 10% on the coronary quantitative angiography after the PCI. Residual stenosis ≥ 30% was considered stent underexpansion (the use of intracoronary imaging was not mandatory). Mechanical stent failure was defined as longitudinal stent deformation or fracture. The patients' personal or clinical data were not collected.

Statistical analysis

In each of the study groups the overall and individual data were analyzed (SphNC as the go-to option, and as the second choice after failed RegNC advancement). Data was expressed as percentages regarding the categorical variables or as mean and standard deviation regarding the continuous ones. Categorical variables were compared using the chi-square test (or Fisher's exact test when appropriate). Continuous variables were compared using the Student *t* test. *P* values < .05 were considered statistically significant.

RESULTS

From February through June 2021, the SphNC was used in 263 lesions (in 177 lesions as the go-to option, and in 86 lesions after failed RegNC advancement) in a total of 250 procedures. All the lesions were treated with state-of-the-art drug-eluting stents. The characteristics of the lesions and the PCIs, and the immediate angiographic results—both overall and with the use of the SphNC as the first choice or after failed RegNC advancement—are shown on table 1 and table 2. A total of 9.9% of the lesions required complex techniques to move the SphNC forward. Lesions in the failed RegNC group were more unfavorable with a lower rate of direct stenting, greater tortuosity and angulation inside the lesion, more need for cutting balloon during predilatation, shorter SphNC

Table 2. Characteristics of percutaneous coronary intervention and angiographic outcomes

	Total (N = 263)	SphNC as the go-to option (N = 177)	SphNC after failed RegNC (N = 86)	P*
Plaque modification				
Noncompliant balloon	44.9% (118)	47.5% (84)	39.5% (34)	.45
Scoring balloon	12.5% (33)	9% (16)	19.8% (17)	.14
Cutting balloon	4.9% (13)	2.3% (4)	10.5% (9)	.01
Lithotripsy balloon	1.9% (5)	1.7% (3)	2.3% (2)	.66
Rotational atherectomy	1.9% (5)	1.1% (2)	3.5% (3)	.33
Direct stenting	14.1% (37)	16.9% (30)	8.1% (7)	.05
Stent				
Caliber (mm)	3.07 ± 0.52	3.04 ± 0.49	3.12 ± 0.57	.3
Length (mm)	27 ± 11	27 ± 10	27 ± 11	.95
Atm	14 ± 2	15 ± 2	14 ± 2	.02
Number of stents in the lesion				.47
1	81.4% (214)	81.4% (144)	81.4% (70)	
2	13.7% (36)	12.4% (22)	16.3% (14)	
3	5% (13)	6.2% (11)	2.3% (2)	
Overall stent length (mm)	32 ± 18	32 ± 18	32 ± 16	.96
Postdilatation indication				.29
Long lesion	39.9% (105)	44.6% (79)	30.2% (26)	
Suboptimal expansion	30.8% (81)	28.2% (50)	36% (31)	
POT	16% (42)	13% (23)	22.1% (19)	
Calcified lesion	6.8% (18)	7.3% (13)	5.8% (5)	
Aorto-ostial lesion	3% (8)	3.4% (6)	2.3% (2)	
Kissing balloon	1.9% (5)	2.3% (4)	1.2% (1)	
Other	1.5% (4)	1.1% (2)	2.3% (2)	
SphNC				
Caliber (mm)	3.36 ± 0.55	3.34 ± 0.53	3.39 ± 0.6	.5
Length (mm)	12 ± 3	13 ± 2	11 ± 2	< .001
Atm	18 ± 3	18 ± 2	18 ± 3	.09
Complex technique				.52
Guide catheter extension system	7.6% (20)	7.9% (14)	7% (6)	
Buddy-wire	1.9% (5)	1.1% (2)	3.5% (3)	
Anchoring	0.4% (1)	0.6% (1)	0% (0)	
Intracoronary imaging	9.5% (27)	9.1% (16)	10.4% (9)	.51
QCA after PCI				
MLD (mm)	3.23 ± 0.58	3.19 ± 0.56	3.29 ± 0.61	.21
Percent diameter stenosis (%)	4 ± 5	3 ± 5	4 ± 5	.18
Stenotic area (%)	6 ± 8	5 ± 8	7 ± 8	.05
Stent expansion				.03
Optimal	97.7% (257)	99.4% (176)	94.2% (81)	
Suboptimal	1.9% (5)	0.6% (1)	4.7% (4)	
Underexpansion	0.4% (1)	0% (0)	1.2% (1)	
Final TIMI grade-3 flow	99.6% (262)	99.4% (176)	100% (86)	1

Atm, balloon inflation atmospheres; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; POT, proximal optimization technique in bifurcation; QCA, quantitative coronary angiography; RegNC, cone-shaped tip regular noncompliant balloon; SphNC, spherical tip noncompliant balloon; TIMI, Thrombolysis in Myocardial Infarction.
* *P* between SphNC groups as the go-to option, and SphNC after failed RegNC.

length, and a higher rate of angiographic data of suboptimal stent expansion.

The overall rates of technical, angiographic, and procedural success were very high and similar between both groups (table 3).

The rate of technical success in the same lesion where the RegNC had failed was very high (98.8%): only 1 SphNC failed too (figure 3). The SphNC and the RegNC had a similar mean caliber (3.39 ± 0.6 mm vs 3.34 ± 0.6 mm; *P* = .06) while the SphNC had a shorter mean length (11 ± 2 mm vs 12 ± 3 mm; *P* = .005). The length of the SphNC was shorter, similar or longer in 36%, 46.5%, and 17.5% of the lesions, respectively. The same complex techniques were used to advance the RegNC and the SphNC in 7 lesions (the guide catheter extension system and the buddy-wire technique were used in 6 and 1 cases, respectively). The buddy-wire technique was used in 2 lesions to advance the SphNC, but not previously with the RegNC. In 1 lesion where the RegNC could not be advanced despite anchoring, the SphNC was moved forward without the need for a complex technique. Both the RegNC and the SphNC had been previously used on 3 and 9 occasions, respectively for predilatation purposes.

Table 3. Rates of primary and secondary endpoints

	Total (N = 63)	SphNC as the go-top option (N = 177)	SphNC after failed RegNC (N = 86)	P*
Primary endpoint				
Technical success	98.9% (260)	98.9% (175)	98.8% (85)	1
Secondary endpoint				
Angiographic success	98.1% (258)	98.3% (174)	97.7% (84)	.66
Procedural success	97.7% (257)	98.3% (174)	96.5% (83)	.33
Mechanical stent failure	0% (0)	0% (0)	0% (0)	N/A
Perioperative complications	0.4% (1)	0% (0)	1.2% (1)	.32

N/A, non-applicable; RegNC: cone-shaped tip regular noncompliant balloon; SphNC, spherical tip noncompliant balloon.
* *P* between SphNC groups as the go-to option, and SphNC after failed RegNC.

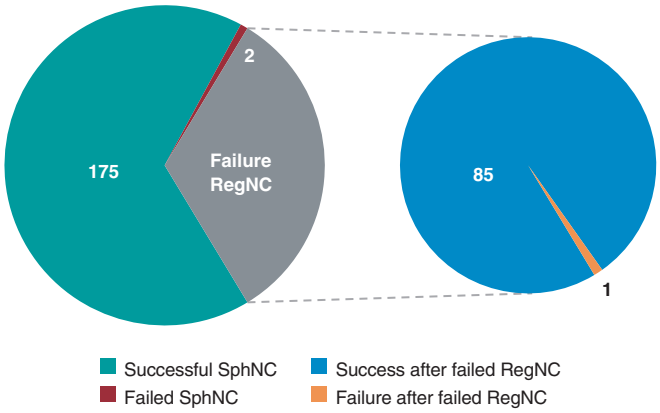

Figure 3. Overall technical success and failure of the spherical tip noncompliant balloon (SphNC), as well as in cases of failed regular noncompliant balloon (RegNC); section chart on the right.

The description of failed primary and secondary endpoints with the SphNC is shown on table 4. In 2 of the 3 cases without technical success regarding the SphNC, a shorter RegNC was eventually advanced. No instances of mechanical stent failure were reported. One proximal fracture of the catheter hypotube was reported due to excessive resistance during push in 1 SphNC. Nonetheless, the device could be retrieved uneventfully. Only 1 major adverse cardiovascular event was reported: 1 distal branch perforation due to an angioplasty guidewire unrelated with the use of the SphNC that occurred while unsuccessfully trying to advance the RegNC. However, according to the definitions of the study protocol, it was adjudicated as lack of procedural success.

DISCUSSION

As far as we know, it is the first time that a clinical trial—the REPIC02-RECONQUISTHA—reports on the most extensive experience using SphNC for coronary stent postdilatation. The registry included 16 high volume PCI-capable centers and collected data from 263 lesions where SphNCs were used at the operator's discretion both as the go-to and second choice after failed RegNC advancement in the same lesion. Based on the initial hypothesis, the study can be considered positive; findings can be summarized as follows: *a)* very high rates of technical, angiographic and procedural success defined, respectively, as the capacity to move forward towards the inside of the stent and reach an adequate expansion without mechanical stent failure or periprocedural complications; *b)* very high rates of technical, angiographic and procedural success in the same lesions where the RegNC failed; and *c)* lower need for complex techniques to achieve technical success.

Over the last few years, the arrival of new techniques and modern devices has facilitated the performance of successful PCIs on more complex lesions in the routine clinical practice. Although the operators were not specifically encouraged to include complex lesions in the study, our data show this reality where over 70% of the lesions were type B2/C, and nearly 50% showed significant calcification, tortuosity or angulation inside the lesion. These characteristics reduce the success of the PCI[14,15] and can eventually lead to stent malapposition[16] and underexpansion[17] or difficulties advancing the devices until reaching such stents, which means that the availability of effective and safe postdilatation balloons is essential to perform successful PCIs.

There is no data in the medical literature to compare or discuss our findings. Our study can be considered positive as it exceeded 80% of the success anticipated in the initial hypothesis. Despite the complexity of the lesions reported, the overall and subgroup outcomes of use of the SphNCs as the go-to option are nothing new since they can be expected in the assessment of any NC balloons (rate of success and proper stent expansion > 90%)[10] since it is rare to find difficulties or impossibilities if complex techniques are used to advance these devices. However, these maneuvers can lead to severe complications like mechanical stent deformation.[18,19] The lack of mechanical stent failure in our series places the SphNC as an effective and safe device for coronary postdilatation.

After the first 200 procedures, the percentage of cases where the SphNC was used in lesions where the RegNC would have failed was low. Since focus was on assessing the SphNC performance in this context, only inclusions in this subgroup were allowed later on. As already mentioned, the rate of RegNC failure is rare, and the rhythm of inclusion of the next 50 procedures was a slower. We designed this study group considering that the sequential use of a SphNC in the same lesion where a RegNC had failed would show the potential benefit of this new device. The SphNC achieved technical success in 98.8% of the lesions in this subgroup and validated its superiority in the exact same lesions where the RegNC had failed, which can be considered the most valuable piece of information from our study. The mean SphNC length was shorter compared to the RegNC (a 1 mm difference, which is statistically significant due to similar and narrow standard deviations, yet of uncertain practical significance). However, the operators used SphNCs and RegNCs of similar length in most of the lesions. In this study subgroup, lesions were more unfavorable, which may explain the rate of failure with RegNCs, the discretely low rate of angiographic and procedural success reported, and the presence of the complications described (fracture of the SphNC hypotube or coronary perforation).

It has been reported that the tortuosity and angulation seen until the lesion are predictors of failed PCI or perioperative complications.[14,15,20] In our series, their prevalence was high—around 40%—and up to 50% in lesions where the RegNC failed. Several complex techniques for the management of these anatomies have been described,[21] but they increase procedural time and cost. Eddin et al.[22] determined that tortuosity and angulation were the main predictors for the use of a guide catheter extension system. Also, angulations > 45° proximal to the lesion predict its use with a 73% sensitivity and a 74% specificity. In different series, tortuosity and angulation justify the use of a guide catheter extension system in 22% to 43% of the cases.[18] Despite the significant tortuosity and angulation of our series, the need for a guide catheter extension system or any other kind of complex technique to advance the SphNC was low (< 8% and 10% respectively), which is why this device emerges as a useful tool in the coronary tortuosity setting with potential to reduce procedural costs.

The study design was moderately ambitious since we hypothesized that if the SphNC were successful in 1 out of 3 lesions where the RegNC had failed this outcome would have been good enough for the new device. The fact that it exceeded the success rate of 30% proposed in the hypothesis makes us think of the results as positive. To better understand these outcomes, 5 videos have been provided as supplementary data including examples of failed RegNCs and succesful SphNCs in the same lesion.

Limitations

Despite its prospective design, the study has several limitations. The indication of postdilatation with SphNC based only on the operator's criterion may have conditioned selection biases, thus preventing the inclusion of very unfavorable lesions. The study

Table 4. Description of cases of failed spherical tip noncompliant balloon

Case of failed SphNC	Failed event	Use of SphNC	Postdilatation indication	Success of other NC balloons	Complex technique	Complication
Lesion #46	Technical success	Go-to option	Suboptimal expansion	Yes	No	No
Lesion #71	Technical success	Go-to option	Long lesion	No	No	No
Lesion #83	Technical success	Failed RegNC	POT	Yes	No	Hypotube rupture
Lesion #84	Angiographic success (QCA)	Failed RegNC	Suboptimal expansion	N/A	Guide catheter extension system	No
Lesion #224	Angiographic success (TIMI flow)	Go-to option	Suboptimal expansion	N/A	No	No
Lesion #258	Procedural success	Failed RegNC	POT	N/A	No	Coronary perforation

NA, non-applicable; POT, proximal optimization technique in bifurcation; QCA, quantitative coronary angiography; RegNC, cone-shaped tip regular noncompliant balloon; SphNC, spherical tip noncompliant balloon; TIMI, Thrombolysis in Myocardial Infarction.

design does not allow us to assess the superiority of the SphNC over the RegNC regarding the lower need for complex techniques, mechanical stent failure or better angiographic and procedural outcomes. The use of intracoronary imaging was low, and a more comprehensive assessment of stent expansion with imaging techniques could have changed the data of the PCI final outcomes and, consequently, the secondary endpoints. The SphNC recrossing after first inflation was anecdotal and is, therefore, ill-advised. We should mention that our results cannot be extrapolated to coronary predilatation because the device has not been tested prior to stenting. Finally, the lack of follow-up to monitor the patients' clinical course does not allow us to assess the clinical impact derived from the use of SphNC.

CONCLUSIONS

Coronary postdilatation with the SphNC during PCI in the routine clinical practice has a very high rate of technical success both as first choice (98.9%), and in cases of failed RegNC advancement (98.8%) with a lower need for complex techniques, and a good safety profile.

FUNDING

RECONQUISTHA is an investigator-initiated trial promoted and developed by Fundación EPIC, Spain as the clinical research organization sponsored by IZASA Medical, Spain. All the authors received research grants for their participation in the study.

AUTHORS' CONTRIBUTIONS

J. A. Linares Vicente: design, data curation, analysis, and interpretation, and manuscript drafting. A. Pérez de Prado, and J. R. Rumoroso Cuevas: design, data curation, manuscript drafting, and critical review of its content. K. García San Román, F. Lozano Ruiz-Póveda, G. Veiga Fernández, A. Gómez Menchero, G. Moreno Terribas, G. Miñana Escrivà, J. Sánchez Gila, C. Arellano Serrano, G. Martín Cáceres, P. Bazal Chacón, P. Martín Lorenzo, F. Rebollal Leal, and J. Moreu Burgos: data curation, critical review of the content of the manuscript, and final approval.

CONFLICTS OF INTEREST

A. Pérez de Prado is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. J. A. Linares has received lecture fees from IZASA Medical, Spain.

WHAT IS KNOWN ABOUT THE TOPIC?

– Coronary stent postdilatation with NC balloons is associated with better clinical outcomes. The complexity of PCIs in the routine clinical practice is on the rise. The navigability of RegNCs is limited, and their cone-shaped tip can complicate moving forward inside of the stent. Therefore, success could be limited in in complex lesions.

WHAT DOES THIS STUDY ADD?

– In the routine clinical practice, coronary postdilatation using SphNC while performing a PCI has a very high rate of technical success even in complex clinical settings where the RegNC has failed (especially in coronary tortuosity), a lower need for complex techniques, and a good safety profile. Therefore, it could be considered as the go-to option for coronary postdilatation when performing complex PCIs.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000289.

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REC Interv Cardiol. 2022;4(4):287-293
https://doi.org/10.24875/RECICE.M22000290

Original article

Clinical predictors and angiographic features of acute myocardial infarction due to systemic embolism

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ABSTRACT

Introduction and objectives: Systemic coronary artery embolism is one of the mechanisms of acute myocardial infarction of nonatherosclerotic origin. However, the epidemiological, clinical, and angiographic profile of this entity has not been properly established yet. Our objective was to describe the clinical characteristics, angiographic features, and prognosis of acute coronary syndromes (ACS) due to systemic embolism (ACS-E), compare them to those due to coronary atherosclerosis (ACS-A), and identify predictive clinical factors of ACS-E.
Methods: All consecutive patients with ACS—admitted to a tertiary hospital from 2003 through 2018—were classified as ACS-E (n = 40) or ACS-A (n = 4989), and prospectively recruited on a multipurpose database.
Results: Patients with ACS-E were younger (27.5% vs 9.6% were < 45 years old, $P < .001$), more often women (42.5% vs 22.5%, $P = .003$), and had higher rates of atrial fibrillation (AF) (40.0% vs 5.3%, $P < .001$), previous stroke (15.0% vs 3.6%, $P < .001$), active neoplasms (17.5% vs 6.9%, $P = .009$), and previous valvular surgery (12.5% vs 0.5%, $P < .001$). Also, a higher proportion of them were on warfarin (27.5% vs 2.9%, $P < .001$). The most frequent culprit vessel was the left anterior descending coronary artery in both groups. A percutaneous coronary intervention was attempted in all patients with ACS-A, and in 75.0% of those with ACS-E ($P < .001$) being successful in 99.1% and 80.0%, respectively. The in-hospital all-cause mortality rate was 15.0% regarding ACS-E, and 4.0% in the control group ($P < .001$). A multivariate analysis was performed to study the independent predictors of ACS-E, identify AF, previous valvular surgery, and active neoplasms, younger age, and female sex.
Conclusions: ACS-E and ACS-A have different clinical and angiographic characteristics. Atrial fibrillation, previous valvular surgery, active neoplasms, younger age, and female sex were all independent predictors of ACS-E.

Keywords: Coronary artery embolism. Atrial fibrillation. Acute coronary syndrome. Myocardial infarction.

Predictores clínicos y características angiográficas del infarto agudo de miocardio por embolia sistémica

RESUMEN

Introducción y objetivos: La embolia coronaria de origen sistémico representa uno de los mecanismos de infarto agudo de miocardio de causa no aterosclerótica. Sin embargo, el perfil epidemiológico, clínico y angiográfico de esta entidad no ha sido aún bien definido. Nuestro objetivo fue describir las características clínicas y angiográficas y el pronóstico de los síndromes coronarios agudos (SCA) de origen embólico (SCA-E), compararlos con aquellos debidos a aterosclerosis (SCA-A) e identificar predictores clínicos de SCA-E.
Métodos: Todos los pacientes con SCA atendidos en un hospital terciario entre 2003 y 2018 se clasificaron en SCA-E (n = 40) o SCA-A (n = 4.989) e incluidos de forma prospectiva en un registro multipropósito.
Resultados: Entre los pacientes con SCA-E existía mayor proporción de jóvenes (27,5 frente a 9,6% tenían menos de 45 años, p < 0,001), mujeres (42,5 frente a 22,5%, p = 0,003), fibrilación auricular (FA) (40,0 frente a 5,3%, p < 0,001), neoplasias activas (17,5 frente a 6,9%, p = 0,009), cirugía valvular previa (12,5 frente a 0,5%, p < 0,001) y una mayor proporción de los mismos se encontraba en tratamiento con warfarina (27,5 frente a 2,9%, p < 0,001). El vaso responsable con mayor frecuencia fue la descendente anterior en ambos grupos. En todos los pacientes con SCA-A se llevó a cabo una intervención coronaria percutánea, frente al 75,0% de los pacientes con SCA-E (p < 0,001), la cual se completó con éxito en el 99,1% y el 80,0% de los casos,

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Received 25 January 2022. Accepted 15 March 2022. Online: 07-04-2022.

respectivamente. La mortalidad por todas las causas en el grupo de SCA-E fue del 15,0% frente al 4,0% en el grupo control (p < 0,001). Se llevó a cabo un análisis multivariante para estudiar predictores independientes de SCA-E, identificando la FA, la cirugía valvular previa, la presencia de una neoplasia activa, una menor edad y el sexo femenino.
Conclusiones: Los SCA-E y los SCA-A presentan características clínicas y angiográficas diferentes. La FA, la cirugía valvular previa, la presencia de una neoplasia activa, ser más joven y el sexo femenino son predictores independientes de SCA-E.

Palabras clave: Embolia coronaria. Fibrilación auricular. Síndrome coronario agudo. Infarto de miocardio.

Abbreviations

ACS: acute coronary syndrome. **ACS-A:** acute coronary syndrome due to atherosclerosis. **ACS-E:** acute coronary syndrome due to systemic embolism. **AF:** atrial fibrillation. **AMI:** acute myocardial infarction. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Systemic coronary artery embolism is one of the mechanisms of acute myocardial infarction (AMI) of non-atherosclerotic origin and represents 3% to 14% of all acute coronary syndromes (ACS) reported, according to angiographic and autopsy studies. However, the real prevalence of this entity remains unknown due to the uncertainty of its diagnosis in the acute setting.[1,2]

Atrial fibrillation (AF), cardiomyopathies, valvular heart disease, malignancies, and infective endocarditis have previously been associated with ACS due to systemic embolism (ACS-E).[1,3] Nevertheless, the epidemiological, clinical, and angiographic profile of this entity has not been properly established yet.

Our objective was to describe the clinical characteristics, angiographic features, therapeutic management, and prognosis of ACS-E, compare it to ACS due to coronary atherosclerosis (ACS-A), and identify predictive clinical factors of ACS-E.

METHODS

Study population

All consecutive patients with ACS—admitted to a tertiary hospital from January 2003 through December 2018—were evaluated, classified as ACS-E or ACS-A, and prospectively recruited on a multipurpose database. The protocol was approved by the local ethics committee (internal code 22/137-E), and patients' informed consent was waived because it involved only the analysis of data obtained during standard clinical practice.

AMI was defined as elevated cardiac troponin levels (myocardial injury) with clinical evidence of acute myocardial ischemia including symptoms, new ischemic electrocardiographic changes, development of pathological Q waves on the electrocardiogram, new regional wall motion abnormalities in a pattern consistent with ischemic aetiology, and/or angiographic identification of a coronary thrombus.[4] All patients underwent a thorough diagnostic work-up including detailed clinical histories and physical examinations, serial electrocardiograms, blood tests, transthoracic echocardiographies, and invasive coronary angiographies. Intracoronary imaging techniques like optical coherence tomography or intravascular ultrasound were left to the operator's discretion.

Diagnosis of ACS-E was achieved according to the angiographic evidence of coronary artery thrombosis without atherosclerotic components, concomitant multi-site coronary artery embolism or concomitant systemic embolization excluding left ventricular thrombus due to AMI.[1] Only emboli of principal coronary arteries were considered. Patients with the following angiographic findings were systematically excluded: *a)* presence of atherosclerosis at culprit lesion level, *b)* evidence of > 25% coronary artery stenosis outside the culprit lesion, *c)* plaque rupture or coronary erosion at culprit lesion level found on the intravascular imaging, *d)* coronary artery ectasia, and e) other causes of non-atherosclerotic AMI (vasospasm, spontaneous coronary artery dissection).

Angiographic evaluation of the culprit site was performed by 2 expert operators with an intention to rule out *a)* the presence of thrombus (defined as noncalcified filling defect outlined by contrast media), *b)* presence of angiographic stenosis, and c) signs of atherosclerosis (eg, vessel wall calcification). The rest of the angiogram was assessed looking for angiographic stenosis or atherosclerosis.

Clinical events

Epidemiological data, clinical features, angiographic characteristics, management, and outcomes were prospectively collected as patients were recruited and retrospectively analysed. The long-term follow-up of ACS-E was performed by monitoring any recurrences of systemic emboli (including cardiogenic stroke), and the occurrence of major adverse cardiovascular and cerebrovascular events including cardiac death, myocardial infarction, new percutaneous coronary intervention (PCI), hospitalization due to heart failure or stroke more than 30 days after admission due to ACS-E.

In the present study, we first performed a detailed description of the episodes of ACS-E followed by a comparison to ACS-A to identify clinical peculiarities, and predictors.

Statistical analysis

Quantitative variables were expressed as median and interquartile range [IQR] or mean and standard deviation. The assessment of normality and equality of variances for continuous data was performed using the Shapiro-Wilk test and the Levene test, respectively. Thereafter, continuous variables were compared using the Student *t* test, the Fisher-Pittman permutation test or the median test when appropriate. Categorical variables were expressed as frequencies and percentages.

Variables in which statistically significant differences were seen in the univariate model and those clinically relevant were introduced

in a multivariate analysis using stepwise logistic regression to identify clinical predictors of ACS-E.

All tests were 2-sided, and differences were considered statistically significant with *P* values < .05. Statistical analyses were performed using Stata/IC12.1 statistical software package (StataCorp, College Station, Texas, United States).

RESULTS

During the study period, a total of 5029 patients with ACS were included. After applying the previously described diagnostic criteria, 40 patients (0.8%) were classified as ACS-E and 4989 (99.2%) as ACS-A.

Acute coronary syndrome due to systemic embolism population

Regarding patients with ACS-E, 17 were women (42.5%), and the population's mean age was 60.3 years old. A total of 2 patients (5.0%) had a past medical history of exertional angina, 4 (10.0%) carried a prosthetic valve, and 2 (5.0%) and 1 (2.5%) had non-corrected severe mitral regurgitation, and severe aortic stenosis, respectively. The mean left ventricular ejection fraction was 55.0% ± 12.3%, and 16 patients (40.0%) had any form of AF. Also, 1 patient (2.5%) was diagnosed with infective endocarditis in the aortic valve right after being admitted due to ACS. Regarding other medical conditions, 7 patients (17.5%) had active neoplasms, and 3 (7.5%) chronic kidney disease. Information associated with other baseline characteristics is shown on table 1 of the supplementary data.

A total of 32 patients (80.0%) had ST-segment elevation myocardial infarction (STEMI) 3 of whom received fibrinolytic therapy, undergoing bailout PCI in 2 of the cases. A total of 28 patients (70.0%) underwent a primary PCI and the remaining 12 (30.0%) were catheterized in another scenario. The most frequent culprit vessel was the left anterior descending coronary artery (LAD) that accounted for 13 (32.5%) of the cases followed by the right coronary artery (n = 10; 25.0%), and the left circumflex artery (n = 9; 22.5%). Besides, the proximal (n = 12; 30.0%) and medium (n = 12; 30.0%) segments of the vessels were the ones most often compromised (table 2 of the supplementary data).

On the coronary angiography, 25 patients (62.5%) showed TIMI grade-0 flow (Thrombolysis in Myocardial Infarction) before crossing the wire. Twenty-nine cases (72.5%) received thrombus aspiration therapy and 7 underwent balloon angioplasty. None of the patients were treated with stenting, but TIMI grade-3 flow was observed in 32 cases (77.5%) after the PCI (table 3 of the supplementary data). Regarding intracoronary imaging during the PCI, pre- and postoperative optical coherence tomography and intravascular ultrasound were performed in 3 (7.5%) and 1 (2.5%) patients, respectively. Antithrombotic treatment at presentation and after PCI is shown on table 4 of the supplementary data.

Comparison between acute coronary syndrome due to systemic embolism and acute coronary syndrome due to atherosclerosis

Baseline characteristics

Compared to ACS-A, there was a significantly higher proportion of patients under 45 and over 80 years old in the ACS-E group. Besides, a higher proportion of women was observed (42.5% vs 22.5%; *P* = .003). Among these patients, cardiovascular risk factors were less prevalent compared to those with ACS-A, although statistically significant differences were only seen regarding dyslipidemia. A significantly higher proportion of patients with ACS-E had active neoplasms, AF, previous strokes, and had undergone heart valve surgery. Also, 27.5% of the patients from the ACS-E group were on warfarin (*P* < .001) at presentation whereas the patients with ACS-A often had a past medical history of angina (34.0% vs 5.0%; *P* < .001). The inter-group differences regarding other medical conditions are also shown on table 1.

Table 1. Baseline epidemiological and clinical characteristics

	ACS-A N = 4989	ACS-E N = 40	*P*
Age (years)	63.0 ± 13.4	60.3 ± 18.7	.129
Age < 45 years	480 (9.6)	11 (27.5)	< .001
Age > 80 years	559 (11.2)	9 (22.5)	.025
Female sex	1120 (22.5)	17 (42.5)	.003
Diabetes	1087 (21.8)	4 (10.0)	.070
Hypertension	2632 (52.8)	16 (40.0)	.108
Dyslipidemia	2192 (43.9)	11 (27.5)	.037
Smoking	3101 (62.2)	22 (55.0)	.353
BMI	27.6 ± 4.1	27.1 ± 4.2	.424
Chronic kidney failure	239 (4.8)	3 (7.5)	.425
Peripheral vascular disease	241 (4.8)	1 (2.5)	.493
Stroke	181 (3.6)	6 (15.0)	< .001
Active neoplasm	343 (6.9)	7 (17.5)	.009
AF	262 (5.3)	16 (40.0)	< .001
Treatment with warfarin	143 (2.9)	11 (27.5)	< .001
Previous valvular surgery	25 (0.5)	5 (12.5)	< .001
Past medical history of angina	1698 (34.0)	2 (5.0)	< .001

ACS-A, acute coronary syndrome due to atherosclerosis; ACS-E, acute coronary syndrome due to systemic embolism; AF, atrial fibrillation; BMI, body mass index; NSTEMI, non-ST-elevation acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Clinical and angiographic characteristics and outcomes

Regarding the episode of ACS, no differences were seen regarding the presentation as STEMI between both groups (ACS-E, 80.0% vs ACS-A, 67.0%; *P* = .082). However, patients with ACS-A showed significantly longer times between the diagnosis of ACS and the performance of a coronary angiography (1.16 ± 0.8 hours vs 0.81 ± 0.5 hours; *P* = .003). No differences were seen regarding the rate of cardiogenic shock.

The presence of other moderate or severe stenoses, apart from the culprit one, was significantly more frequent among patients with ACS-A (table 2). PCI was attempted in all the patients with ACS-A and in 75.0% of those with ACS-E (*P* < .001) being successful in 99.1% and 80.0%, respectively. Conversely, adjuvant treatment with GP IIb/IIIa inhibitors was used in 55.0% of the patients with ACS-E and 36.0% of the patients from the ACS-A group (*P* = .020).

Table 2. Lesions distribution

	ACS-A N = 4989	ACS-E N = 40	*P*
Culprit lesions			
LMCA	113 (2.3%)	1 (2.5%)	.921
LAD	2274 (45.6%)	15 (37.5%)	.108
Cx	1064 (21.3%)	11 (27.5%)	.344
RCA	1902 (38.1%)	10 (25.0%)	.125
Number of vessels with moderate lesions (> 50%)	1.6 ± 0.0	0.8 ± 0.1	< .001
Number of vessels with severe lesions (> 70%)	1.3 ± 0.0	0.8 ± 0.1	< .001

ACS-A, acute coronary syndrome due to atherosclerosis; ACS-E, acute coronary syndrome due to systemic embolism; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Complications during PCI and hospitalization in the ACS-E group are shown on table 3 including death that occurred in 5 patients (12.5%) due to heart failure/cardiogenic shock and anoxic encephalopathy after cardiac arrest in another case. A control coronary angiography was performed in 14 cases (40.0%) with persistence of culprit vessel compromise in 2 (14.3%). The median follow-up after the episode was 5.8 ± 4.8 years. Three days after emergency thrombus aspiration due to acute LAD occlusion, a 51-year-old woman with acute myeloid leukemia presented a recurrent ACS-E with new compromise of both the LAD and a marginal branch. No recurrent emboli in other systemic territories were identified in any of the cases. However, major adverse cardiovascular and cerebrovascular events at the follow-up occurred in 13 patients with ACS-E (38.2%) while death occurred in 12 patients (35.3%) being attributed to cardiac causes in 6 cases (50.0%) (table 3). The overall major adverse cardiovascular and cerebrovascular events-free survival during hospitalization and at the follow-up was estimated using Kaplan-Meier curves (figure 1).

The in-hospital all-cause mortality rate was 15.0% in the ACS-E group and 4.0% in the control group ($P < .001$).

Predictors of acute coronary syndrome due to systemic embolism

To determine the clinical predictors of ACS-E, a multivariate analysis was performed including those variables with statistically significant differences in the univariate model and those considered clinically relevant. Therefore, younger age, female sex, an active neoplasm, previous heart valve surgery, and a past medical history of AF were identified as independent predictive factors for ACS-E (table 4, figure 2).

DISCUSSION

The main findings of our study include *a)* the prevalence of ACS-E in patients admitted due to AMI was low (0.8%); *b)* the in-hospital mortality rate was higher among patients with ACS-E as compared to ACS of atherosclerotic origin; and *c)* being younger, female sex, an active neoplasm, previous heart valve surgery, and AF were identified as ACS-E predictors.

Systemic coronary artery embolism is one of the underlying mechanisms of AMI of non-atherosclerotic cause.[4] First autopsy studies reported a prevalence of coronary emboli in patients with AMI of 13%[5] although subsequent studies conducted at the clinical setting described a frequency of around 3%.[1] The low prevalence seen in our series (0.8%) may be associated with strict diagnostic criteria

Table 3. Complications during PCI, hospitalization, and follow-up in patients with ACS-E

During PCI	
Cardiac arrest	3 (7.5)
Slow flow/no reflow	8 (20.0)
Perforation	1 (2.5)
Embolization[a]	15 (37.5)
Coronary dissection	0 (0)
Coronary perforation	1 (2.5)
Cardiac tamponade	0 (0)
During admission	
Vascular complications[b]	2 (5.0)
Heart failure	12 (30.0)
Arrhythmic complications[c]	7 (17.5)
Extracardiac complications[d]	9 (22.5)
Death	6 (15.0)
At the follow-up	
MACCE	13 (38.2)
AMI	4 (11.8)
New PCI	2 (5.9)
Stroke	2 (5.9)
Hospitalization	11 (32.4)
Heart failure	11 (32.4)
NYHA	
I	24 (70.6)
II	6 (17.6)
III	1 (2.9)
IV	4 (11.8)
Systemic embolism	0 (0)
Pulmonary embolism	1 (2.9)
Death[e]	12 (35.3)

AMI, acute myocardial infarction; PCI, Percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events; NYHA, New York Heart Association Functional Classification.
[a] In 2 cases, embolization of thrombotic material reached a different vessel from the culprit one.
[b] 1 case of femoral pseudoaneurysm and radial pseudoaneurysm, respectively were treated with conservative measures.
[c] 4 cases of bradyarrhythmia and 3 cases of tachyarrhythmia.
[d] 8 cases of infection and 1 case of stroke coexisting with subarachnoid haemorrhage.
[e] Due to heart failure in 5 cases, ventricular arrythmia in the AMI setting in 1 case and multiorgan failure due to advanced pulmonary neoplasm in a different case. In the remaining the patients, the cause of death could not be identified.

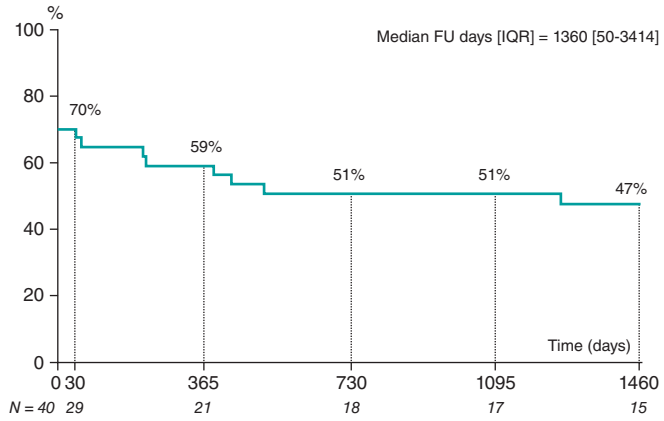

Figure 1. MACCE-free survival during admission and at the 4-year follow-up in patients with ACS-E. ACS-E, acute coronary syndrome due to systemic embolism, FU, follow-up; IQR, interquartile range; MACCE, major adverse cardiovascular and cerebrovascular events.

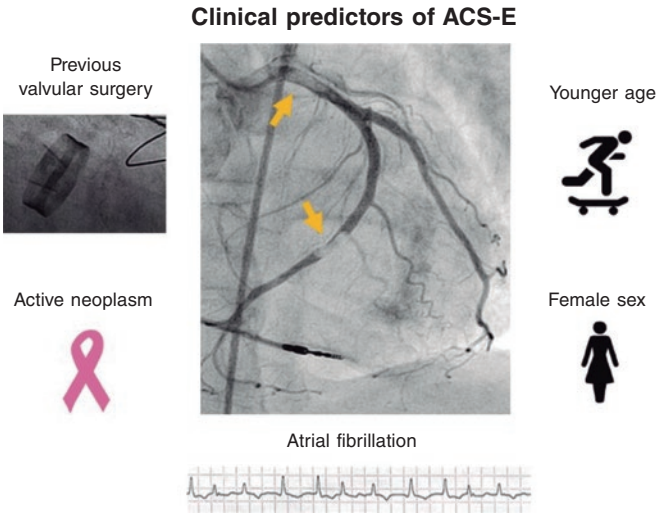

Figure 2. Independent clinical predictors of ACS-E. ACS-E, acute coronary syndrome due to systemic embolism.

Table 4. Multivariate analysis to identify clinical predictors of acute coronary syndrome due to systemic embolism

Variables*	Adjusted OR (95%CI)	*P*
Age (years)	0.95 (0.92-0.97)	< .001
Female sex	2.80 (1.37-5.65)	.007
Dyslipidemia	0.45 (0.22-0.93)	.024
Active neoplasm	3.37 (1.33-8.54)	.019
Previous valvular surgery	4.28 (1.19-15.5)	.038
Past medical history of angina	0.17 (0.05-0.55)	< .001
AF	16.10 (7.23-35.9)	< .001

95%CI, 95% confidence interval; AF, atrial fibrillation; OR, odds ratio.
* Variables from the univariate model introduced in the analysis included: age, female sex, diabetes, dyslipidemia, stroke, active neoplasm, previous valvular surgery, past medical history of angina, AF, and chronic treatment with oral anticoagulants.

excluding patients with coronary artery stenosis > 25% outside the culprit lesion, and emboli due to secondary coronary arteries. However, the real occurrence of ACS-E remains unknown since the early presentation can be indistinguishable from an ACS-A.[6]

Also, the limited rate of coronary artery emboli reported compared to other vascular territories may also be associated with intrinsic anatomical and physiological characteristics like aortic caliber differences, the acute angle at which the coronary arteries originate at the sinus of Valsalva,[7] and the position of the coronary ostia behind the valve cusps during systole.[3,8]

Although some series comparing ACS-A and ACS-E have not described gender differences when focusing on STEMI,[2] in our study, the proportion of women was significantly higher among ACS-E (43% vs 22%; *P* = .003). Similarly, Shibata et al. reported rates of 40% vs 29% (*P* = .087).[1] Besides, according to the aforementioned authors, a lower prevalence of traditional cardiovascular risk factors was seen within the embolic group of our cohort, although statistically significant differences were only noticed regarding dyslipidemia (27.5% vs 43.9%; *P* = .037).

Regarding the compromise of coronary arteries, the LAD was the most commonly affected vessel in both the ACS-E and the ACS-A (table 3). Similarly, a previous autopsy study had shown that coronary emboli are up to 4 times more common in the LAD compared to the right coronary artery, and in the LAD compared to the the left circumflex artery.[5] Also, in a recent systematic review including 129 case reports and case series of coronary emboli, Lacey et al. described that the LAD was the most frequently affected vessel (45.3%).[6] However, such differences in the distribution of culprit coronary vessels may be explained by bias associated with the fact that arteries with larger territories are more likely to be involved in autopsies[1] and case reports.

On the interventional treatment used, in our study, 30 patients (75.0%) from the ACS-E group underwent thrombus aspiration followed by balloon angioplasty in 8 cases. None of the patients from this group were treated with stenting. Similarly, Shibata et al. performed initial thrombus aspiration in 96.6% of embolic patients undergoing PCI followed by balloon angioplasty in 14.3% of the cases and stenting in 17.9%.[1] Thrombus aspiration has proven to be a feasible option to treat AMI with angiographic evidence of thrombus including cases associated with coronary emboli.[9] However, these devices may be less useful to aspirate large thrombi due to the smaller diameter of the lumen of the inner catheter.[10] Besides, in specific situations like small arteries or distal coronary occlusions, simple wire manipulation added to antithrombotic drugs (including glycoprotein IIb/IIIa inhibitors, which were more frequently used in the ACS-E group) may be the preferred option to achieve reperfusion.[2]

At the follow-up after an episode of ACS-E (5.8 ± 4.8 years) in our series, the major adverse cardiovascular and cerebrovascular events occurred in 37.1% of the patients. However, no recurrences of systemic emboli were documented in accordance with other previous series.[2] The in-hospital all-cause mortality rate was significantly higher among patients with ACS-E (15% vs 4%; *P* < .001) mainly due to cardiovascular causes. Shibata et al. reported no differences in the 30-day mortality rate, but significantly higher cardiovascular and all-cause mortality rates in ACS-E compared to ACS-A.[1] Similarly, Popovic et al. observed that 64% of all deaths reported at the follow-up after an episode of STEMI due to coronary embolism were due to cardiac causes.[2]

Finally, after multivariate analysis, AF, previous heart valve surgery, active neoplasm, female sex, and younger age were identified as clinical predictors of ACS-E. AF has been described as the most frequent condition predisposing to coronary artery

embolism being present in 40.0% of ACS-E in our study and in up to 73% in other current series.[1,3] However, early studies reported that valvular heart disease, especially rheumatic, and infective endocarditis represented the most common causes of coronary artery embolism.[5,11] This disparity may be associated with the advances made in antibiotic therapy implementation over the last few decades, and the remarkable increase of AF prevalence parallel to the gradual aging of the population.[1,2,12,13] Furthermore, it has been reported that the risk of AMI associated with AF is significantly higher in women[14,15] and patients without coronary artery disease.[15-18]

On the other hand, it is fully recognized that patients with active neoplasms are at a significantly higher risk of developing thrombotic events, both venous and arterial.[19] The pathogenesis of cancer-associated coagulopathy is complex including a multifactorial interaction among the patient's comorbidities, the specific malignancy, and treatment with several chemotherapeutic agents or immunomodulatory drugs that often lead to hypercoagulability, platelet activation, and endothelial injury.[20] Besides, it has also been described that malignancy is associated with a higher risk of developing AF following interactions at the pathophysiological level.[21,22] In our series, 17.5% of the patients presented active neoplasms in accordance with Popovic et al.[2] who reported a prevalence of 15.1% notably higher than the one reported by Shibata et al.[1] and Lacey et al.[6] of 10% and 1.4%, respectively.

Limitations

The present study presents several limitations. First, being a retrospective study may have resulted in a certain degree of bias. Secondly, applying strict diagnostic criteria which excluded patients with ≥ 25% coronary artery stenosis outside the culprit lesion may have omitted cases of ACS-E in patients with concomitant coronary artery disease. Thirdly, in contrast with all previous reports on this matter, only emboli of major coronary arteries were considered, which possibly resulted in a lower number of ACS-E being diagnosed. Finally, including patients over a long period of time may explain some differences in treatment modalities, and the low use of intracoronary imaging seen in our series.

CONCLUSIONS

ACS-E and ACS-A have different clinical and angiographic characteristics. Female sex, younger age, past medical history of active neoplasms, previous valvular surgery, and AF were all independent predictors of ACS-E. Patients with ACS-E had a higher in-hospital mortality rate mainly due to cardiovascular causes.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were prepared by A. Jerónimo, A. Travieso, A. McInerney, B. Hennessey, and L. Marroquín. Statistical analysis was conducted by A. Jerónimo, M.J. Pérez-Vyzcaino, and N. Gonzalo. The manuscript first draft was written by A. Jerónimo, and N. Gonzalo, and all authors commented on previous versions of the manuscript. All authors read and approved the manuscript final version.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

– According to angiographic studies and autopsies, systemic coronary artery embolism is representative of 3% to 14% of all ACSs. However, the real prevalence of this entity remains unknown due to uncertainty of its diagnosis in the acute setting. AF, infective endocarditis, valvular heart disease, and malignancies have been associated with ACS-E, but the clinical and angiographic profile of this entity has not been properly established to this date.

WHAT DOES THIS STUDY ADD?

– Our study describes the epidemiological, clinical, and angiographic characteristics of patients with ACS-E comparing them to ACS-A and admitted to a single centre during the same period of time. On this regard, patients with ACS-E were younger compared to those with ACS-A, female in a higher proportion, and more often had AF, previous stroke, previous valvular surgery, and active neoplasms. The left anterior descending coronary artery was the most common culprit vessel in both groups, but patients with ACS-A presented with a significantly higher proportion of other significant stenoses. On the therapeutic approach regarding the PCI, thrombus aspiration was the most frequent strategy in ACS-E without stenting in any of the cases. Besides, the in-hospital all-cause mortality rate was significantly higher among patients with ACS-E mainly due to cardiovascular causes. A younger age, female sex, active neoplasms, previous valvular surgery, and a past medical history of AF were identified as independent clinical predictors of ACS-E.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000290.

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REC Interv Cardiol. 2022;4(4):294-303
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Original article

EPIC03-BIOSS observational prospective study. Performance analysis of the BIOSS LIM C dedicated stent in coronary bifurcation lesion angioplasty

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ABSTRACT

Introduction and objectives: To describe the efficacy of the BIOSS LIM C dedicated sirolimus-eluting stent to treat coronary bifurcation lesions, and impact on the bifurcation angle and carina through quantitative coronary angiography.
Methods: Observational prospective study including 124 patients with bifurcation lesions treated with a BIOSS LIM C dedicated sirolimus-eluting stent excluding restenotic lesions and those without main vessel involvement.
Results: The stent was successfully deployed in 121 patients (97.6%) while in 18 (14.5%) double stenting was used. The quantitative coronary analysis has shown proper stent expansion with a mean residual stenosis of 18% in the proximal segment, nearly 0% in the distal segment, and 21% in the side branch. The angiographic results of double stenting showed higher mean diameters (2.12 ± 0.30 vs 1.60 ± 0.42; $P < .001$), and lower residual stenosis (18.36 ± 9.94 vs 28.49 ± 14.19%, $P < .01$). Distortion imposed on the bifurcation angulation was minimal with an absolute reduction of 5 degrees (52.8 ± 18.4 vs 47.5 ± 17.2; $P = .001$).
Conclusions: The dedicated BIOSS LIM C stent has had a very high success rate to treat coronary bifurcation lesions. Angiographic results are good with a remarkably low impact on the native bifurcation angulation, and excellent results from double stenting. We think this can be a very useful device to treat coronary bifurcation lesions with the advantage of easing out the bailout deployment of a second stent into the side branch.

Keywords: Dedicated stent. Bifurcation lesion. BIOSS LIM C sirolimus-eluting stent.

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Received 8 December 2021. Accepted 2 June 2022. Online: 02-09-2022.

Estudio observacional prospectivo EPIC03-BIOSS. Análisis del *stent* dedicado BIOSS LIM C en angioplastias en bifurcación

RESUMEN

Introducción y objetivos: El estudio EPIC03-BIOSS se llevó a cabo para describir la eficacia del *stent* farmacoactivo dedicado BIOSS LIM C en el tratamiento de las lesiones en bifurcación, así como la modificación inducida sobre la lesión en bifurcación por angiografía cuantitativa automatizada.
Métodos: Estudio observacional prospectivo en el que se incluyeron 124 pacientes con lesión en bifurcación tratados con *stent* farmacoactivo BIOSS LIM C, excluidas las lesiones por reestenosis y aquellas en las que no había afección del vaso principal.
Resultados: El *stent* se implantó con éxito en 121 pacientes (97,6%); en 18 (14,5%) se utilizó una técnica de 2 *stents*. El análisis por angiografía cuantitativa automatizada mostró una estenosis residual media del 18% en el segmento proximal, de prácticamente el 0% en el segmento distal y del 21% en la rama lateral. Los resultados angiográficos para la técnica de doble *stent* muestran unos diámetros (2,12 ± 0,30 frente a 1,60 ± 0,42 mm; p < 0,001) y estenosis residuales (18,36 ± 9,94 frente a 28,49 ± 14,19%; p < 0,01) significativamente mejores. La distorsión sobre la angulación nativa del vaso resultó mínima, con una reducción absoluta de unos 5° (52,8 ± 18,4 frente a 47,5 ± 17,2°; p = 0,001).
Conclusiones: El *stent* BIOSS LIM C consigue una elevada tasa de éxito para el tratamiento de las lesiones en bifurcación. Los resultados angiográficos son buenos, destacando la escasa distorsión sobre la angulación nativa del vaso y los excelentes resultados. Consideramos que puede ser un buen dispositivo para el tratamiento de las bifurcaciones, la ventaja de poder facilitar la implantación no prevista de un segundo *stent*.

Palabras clave: *Stent* dedicado. Lesión en bifurcación. *Stent* liberador de sirolimus BIOSS LIM C.

Abbreviations

MB: main branch; **OCT:** optical coherence tomography; **POT:** proximal optimization technique; **QCA:** quantitative coronary angiography: **SB:** side branch.

INTRODUCTION

Percutaneous treatment of coronary bifurcation lesions can represent up to 20% of all coronary lesions treated.[1] The definition of bifurcation lesion given by the European Bifurcation Club[2] includes those that effect a relevant side branch (SB) whether by its angiographic diameter or the myocardium at risk associated with such SB.

The pseudo-fractal anatomy of coronary bifurcation lesions[3] involves a significant caliber difference between proximal and distal segments. The study of the structural limits of tubular stents has favored the development of treatment techniques[4,5] designed to optimize implantation in an anatomy that is not completely cylindrical with good angiographic and clinical results.[6-10] Also, a progressive escalated strategy has been agreed based on parameters of damage to the SB from the provisional stenting technique to the complex double stenting one.

Although specific platforms have been designed to treat coronary bifurcation lesions, these have been limited for expert operator use only. On the one hand, dedicated stents can be categorized into stents designed to treat the main vessel by securing proper access to the SB, (Nile Croco & Pax, Minvasys, France, the Multi-Link Frontier, Abbott Vascular Devices, United States or the TAXUS Petal, Boston Scientific, United States). On the other hand, stents designed to treat the SB first to later complete the main branch (MB) with a tubular stent (Tryton Side Branch stent, Tryton Medical, United States; Sideguard, Cappella Inc, United States). However, because of the discrete results reported or their complexity, they have not become entirely popular.

The BIOSS LIM C stent[11] (Balton, Poland) is a 70 µm ultra-thin-strut chrome-cobalt platform with a sirolimus-eluting biodegradable polymer of polylactic acid. It is a dedicated stent for bifurcations

Figure 1. Image of the BIOSS stent design. Note the structure in 2 bodies with central space for the side branch.

that consists of 2 segments of different size linked by 2 long connective struts (figure 1). Goal is to keep the pseudo-fractal correlation between the proximal and distal portions of the SB and facilitate the technique to access the SB or the provisional stenting technique. Former studies have given good results with successful implantation rates of 100%, and target lesion revascularization rates from 6.8% to 9.8%.[12-14]

The objective of this study is to describe immediate angiographic results assessed through quantitative coronary angiography (QCA) in terms of deformation of the lesion native angulation and expansion, especially at the level of the polygon of confluence and at the origin of the side branch.

METHODS

Patients

This is a prospective, multicenter registry started by independent investigators that included patients with ischemic heart disease

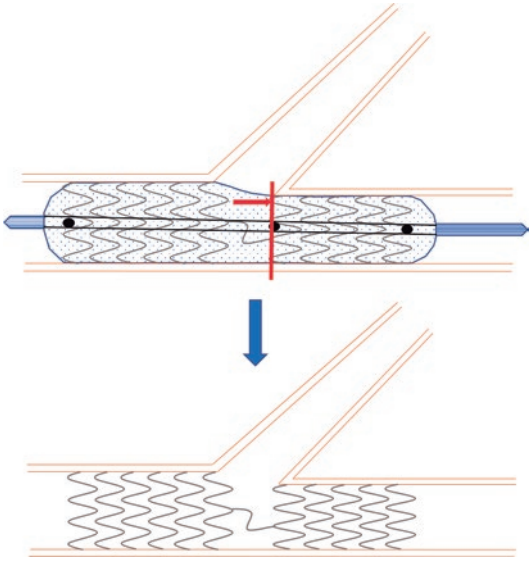

Figure 2. Scheme of the positioning of the BIOSS stent for correct implantation. Central marker needs to be adjusted to the carina of bifurcation, and the ostium of the distal main branch.

referred for percutaneous coronary revascularization of a bifurcated lesion considered as a lesion with distal branches with a minimum diameter of 2 mm.

Patients with lesions damaging the bifurcation on the SB only were excluded. Also, patients with restenosis, complete total coronary occlusions, a contraindication for dual antiplatelet therapy, cardiogenic shock, minors or patients who gave their express rejection to be included.

Study was conducted according to the Declaration of Helsinki and the study protocol was approved by the different ethics committees of participant centers. The specific written informed consent was obtained from all the patients included in the study.

Procedure

Stenting was performed following the implantation recommendations of every device (figure 2) by implanting and performing the final control in the angiographic view with better deployment of bifurcation. Anticoagulation with sodium heparin or low-molecular weight heparin was administered according to the usual standards of every cath lab. Specific treatment of each coronary bifurcation lesion was left to the operator's criterion. Predilatation of both branches, the provisional stenting technique or the early double stenting technique were allowed whenever, at least, 1 dedicated stent from the study was used.

Procedural success was defined as the implantation of a BIOSS LIM C stent into the bifurcation lesion with residual stenosis on visual estimate < 30% in the MB and 50% in the SB.

Clinical follow-up

Telephone or on-site follow-up was conducted at 30 days and 12 months. Patients were surveyed on adverse cardiovascular events of death, myocardial infarction, stroke, stent thrombosis, need for new revascularization or bleeding.

Angiographic analysis

Angiographic analysis was conducted independently by an imaging lab (BARCICORE-Lab, Spain) using a specific dedicated software for bifurcations (QAngio XA 7.3, The Netherlands) with which all angiographic measurements were acquired including the measurements of bifurcation angulation. Two analysts selected the images before and after implantation without the intracoronary guidewire and in the same view (< 10º of difference). Angiographic analysis was conducted in end-diastole following the lab internal protocols.

Software used allows us to measure the 3 segments of a bifurcation simultaneously (proximal MB, distal MB, and SB) and obtain individual results from all the segments including the polygon of confluence of bifurcation. All analyses were conducted taking the proximal and distal borders of the stent deployed as the reference framework. When the double stenting technique was used, the distal border of the stent implanted into the SB was used as the analysis distal limit. In case of single-stent implantation, only the proximal 5 mm of the SB were used. Figure 3 shows an example of angiographic analysis.

Statistical analysis

All quantitative data are expressed as mean ± standard deviation (SD) while qualitative data are expressed as number (percentage). For the quantitative angiographic analysis (QCA) between angiographic values before and after implantation, Student *t* test was used for paired data (quantitative data) while the McNemar test (qualitative data) was used when appropriate. For comparison purposes between the cohorts treated with provisional stenting and double stenting, Student *t* test or the Mann-Whitney *U* test (quantitative data) were used. Also, the chi-square test or Fisher's exact test (qualitative data) were used, when appropriate. *P* values ≤ .05 were considered statistically significant. Statistical analyses were conducted using the statistical software package SPSS version 20.

RESULTS

Baseline clinical data

From August 2018 through February 2021 a total of 124 patients were included in the study (figure 4). The demographic data of patients are shown on table 1. We should mention the rates of patients with diabetes [26.9% (32/124)], and acute coronary syndrome [52,8% (66/124)], 12,8% (16/124) of whom had ongoing ST-segment elevation. No significant differences were reported in the baseline clinical characteristics between the single-stent and the double stenting cohorts.

Angiographic and procedural data

Angiographic and procedural data are shown on table 2 and table 3. Most procedures were performed via radial access (120, 96.8%) and the angiography revealed the presence of 3-vessel coronary artery disease in 19 patients (15.3%). In 10 cases (8%) the target lesion was found in the left main coronary artery. Regarding complexity, in 55 cases (44.3%) the lesions treated fell into the B2/C categories of the American Heart Association/American College of Cardiology while 32 lesions (25.8%) were categorized as moderate or severe.

When we analyzed the differences between the cohorts treated with the provisional stenting technique and the double stenting one (table 2 and table 3) we saw that in the latter the rate of true

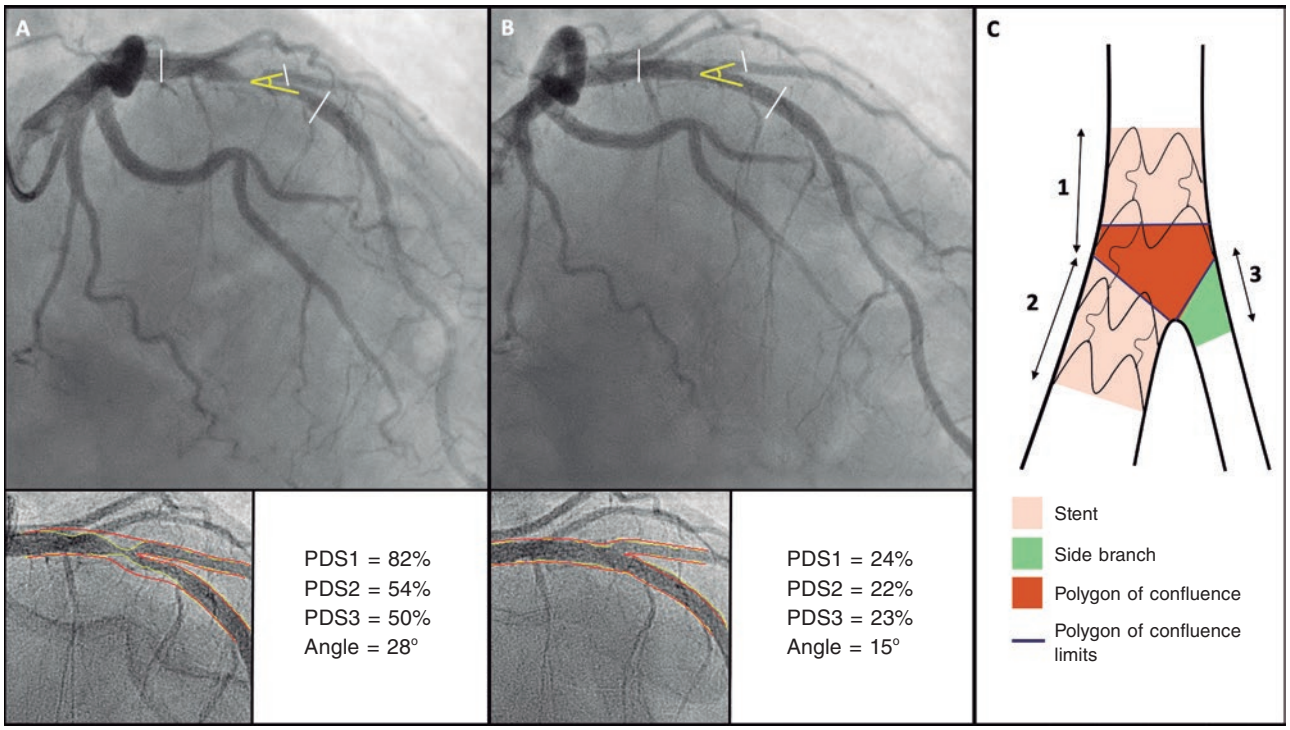

Figure 3. Quantitative coronary angiography showing the percentage diameter stenosis (PDS) at the proximal main vessel (1), distal main vessel (2), and 5 mm proximal to the side branch (3) before (**A**) and after the procedure (**B**). Also, it measures changes to the bifurcation angle between the distal branches. Image **C** shows the limits of each segment (1, 2, and 3), and the borders of the polygon of confluence.

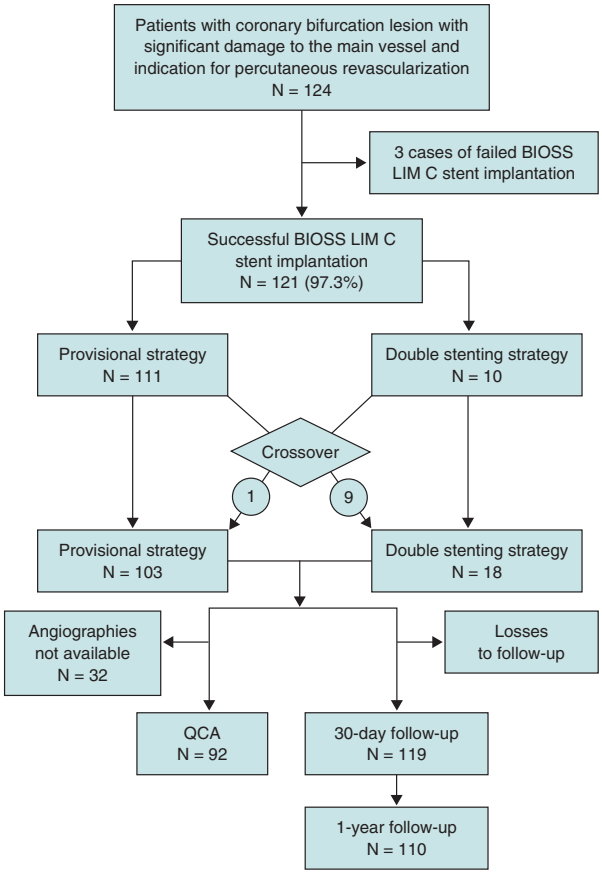

Figure 4. Flowchart of the EPIC03-BIOSS study. QCA, quantitative coronary angiography.

bifurcations, proximal tortuosity, and use of imaging modalities was significantly higher.

During the procedure (table 3) the BIOSS LIM C stent was successfully implanted in 121 patients (97.6%). In the 3 cases when the stent was not implanted, the lesions showed moderate or severe calcification and proximal tortuosity. One case out of the 121 treated with stenting became complicated with SB occlusion following a dissection that could not be revascularized. In 30 (26.5%) out of the 113 cases (90.4%) where the early provisional stenting strategy was used, the POT (proximal optimization technique) was used. In 43 (38.1%) it was necessary to dilate the SB through kissing-balloon or simple dilatation (table 3). Finally, in 9 cases (7.2%) initially treated with the single-stent strategy, a second stent was needed in the SB. The double stenting strategy was initially adopted in 11 patients (9.6%). However, after SB dilatation and stent implantation into the MB the implantation of a second stent was deemed as unnecessary in 2 of them (18.2%). Therefore, 18 patients (14.5%) were eventually treated with the double stenting technique. The rates of predilatation, rotational atherectomy, use of POT, and successful implantation were similar in both cohorts.

Quantitative angiography of bifurcation

The angiographic images of 92 patients were available (table 4). Mean residual stenosis of 18% was seen in the proximal segment and nearly 0% in the MB distal segment. In the SB, the postoperative mean residual stenosis was 21% with significant residual stenosis in 5% of all patients treated with the provisional stenting technique.

Comparing patients treated with the single-stent technique or the double stenting technique (table 4) revealed that, at proximal

Table 1. Description of population

	Total
Baseline demographics	124
Feminine sex	23 (18.47%)
Age	65.48 (11.09)
Arterial hypertension	79 (63.2%)
Dyslipidemia	72 (57.6%)
Diabetes Mellitus	32 (25.6%)
On insulin	8 (6.4%)
Current smoker	39 (31.2%)
Chronic kidney disease	10 (8%)
Peripheral vasculopathy	8 (6.4%)
Baseline treatment	
Acetylsalicylic acid	81 (64.8%)
Clopidogrel	34 (27.2%)
Ticagrelor	18 (14.4%)
Prasugrel	2 (0.6%)
Oral anticoagulant drugs	9 (7.2%)
Vitamin K inhibitor	1 (0.8%)
Direct-acting oral anticoagulants	8 (6.4%)
Indication	
Stable angina	37 (29.6%)
Silent ischemia	12 (9.6%)
Ventricular dysfunction	3 (2.4%)
STEACS	6 (4.8%)
NSTEACS/unstable angina	16 (12.8%)
NSTEACS/myocardial infarction	34 (27.2%)
STEACS	16 (12.8%)
AMI	25 (20%)
Previous CABG	4 (3.2%)
Previous PCI	29 (23.2%)
Ejection fraction (%)	54.31 (12.29)
Atrial fibrillation	9 (7.2%)
Heart failure	16 (12.8%)

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; NSTEACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEACS, ST-segment elevation acute coronary syndrome.

Table 2. Angiographic data on visual estimate

	Total	Provisional	Complex	*P*
Radial access	120 (96%)	110 (97.3%)	10 (90.9%)	.314
LMCA lesion	11 (8.8%)	10 (8.8%)	1 (9.1%)	.830
Proximal LAD	77 (61.6%)	71 (62.8%)	6 (54.5%)	.746
Coronary artery disease				.524
1 vessel	55 (44%)	51 (46.4%)	4 (36.4%)	
2 vessels	47 (37.6%)	43 (39.1%)	4 (36.4%)	
3 vessels	19 (15.2%)	16 (14.5%)	3 (27.3%)	
Right dominance	109 (87.2%)	99 (87.6%)	10 (90.9%)	.773
Damaged bifurcation				.693
LMCA-LAD/LCX	10 (8%)	8 (7.3%)	2 (18.2%)	
LAD/Diagonal	71 (56.8%)	53 (57.5%)	4 (54.6%)	
LCX/OMA	28 (22.4%)	25 (22.2%)	3 (27.3%)	
RCA/PL	15 (12.0%)	15 (13.2%)	0 (0%)	
Medina classification				.001
100	8 (6.4%)	8 (7.3%)	0 (0%)	
010	18 (14.4%)	18 (15.9%)	0 (0%)	
001	0 (0%)	0 (0%)	0 (0%)	
110	38 (30.4%)	38 (33.6%)	0 (0%)	
101	5 (4%)	5 (4.4%)	0 (0%)	
011	10 (8%)	6 (5.3%)	4 (36.4%)	
111	44 (35.2%)	38 (33.6%)	6 (54.5%)	
True	59 (47.2%)	49 (43.3%)	10 (100%)	
Calcification (moderate or severe)	32 (25.6%)	28 (24.8%)	4 (36.4%)	.542
Proximal tortuosity	25 (20%)	20 (17.7%)	5 (45.5%)	.04
Thrombus	15 (20%)	14 (12.4%)	1 (0.9%)	1.000
Type of lesion				.362
A	3 (2.4%)	3 (2.7%)	0 (0%)	
B1	37 (29.6%)	31 (27.4%)	6 (54.5%)	
B2	45 (36%)	43 (38.1%)	2 (18.2%)	
C	10 (8%)	10 (8.8%)	0 (0.0%)	

LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMCA, left main coronary artery; OMA, obtuse marginal artery; PL, posterolateral; RCA, right coronary artery.

segment level, expansion results are better with the double stenting technique with residual stenosis of 11% (vs 19% with the single-stent) although starting from greater baseline reference diameters (3.65 ± 0.98 vs 4.75 ± 1.42). The double stenting technique showed excellent results on the SB with a significantly greater minimum lumen diameter (2.31 ± 0.50 vs 1.62 ± 0.43, $P = .01$), and minimum residual stenosis of 5.9% (vs 24.3% with the provisional stenting technique) with special attention to the lack of stenosis > 50%. Results were similar in the distal segment.

Quantitative angiography of the polygon of confluence

At the polygon of confluence (table 5) results show residual stenoses of 17.15% ± 10.96% at the polygon core, and 19.21% ± 20.56% for the ostium of the SB. When the provisional stenting and double

Table 3. Procedural description and follow-up

	Total	Provisional	Complex	*P*
Procedure	124	106 (85.5%)	18 (14.5%)	
Early strategy	124	113 (90.4%)	11 (9.6%)	
Guide catheter				.289
6-Fr	113 (90.4%)	104 (92%)	9 (81.8%)	
7-Fr	10 (8%)	8 (7.1%)	2 (18.2%)	
8-Fr	1 (0.8%)	1 (0.9%)	0 (0%)	
SB predilatation	100 (80%)	90 (79.6%)	10 (90.9%)	.690
Rotational atherectomy	0 (0%)	0 (0%)	0	1.000
Stenting	121 (97.6%)	111 (98.2%)	10 (90.9%)	.314
Length of stent	19.73 (3.23)	19.57 (3.21)	21.45 (3.04)	.064
POT	33 (26.6%)	30 (26.5%)	3 (27.3%)	.800
SB dilatation	47 (37.9%)	43 (38.1%)	4 (36.4%)	.449
Kissing after stenting the MB	21 (44.7%)	21 (48.8%)	0 (0%)	
SB dilatation only	26 (55.3%)	22 (51.2%)	4 (100%)	
Additional stenting	17 (13.7%)	16 (14.2%)	1 (9.1%)	
Stent into the SB	18 (14.5%)	9 (8%)	9 (81.8%)	.000
Kissing after stenting the SB	16 (88.9%)	7 (77.8%)	9 (100%)	
Imaging modalities	11 (8.9%)	8 (7.1%)	3 (27.3%)	.023
IVUS	9 (7.3%)	7 (6.2%)	2 (18.2%)	
OCT	2 (1.6%)	1 (0.9%)	1 (9.1%)	
Complications	1 (0.8%)	1 (0.9%)	0	
Occlusion of the SB	1 (0.8%)	1 (0.9%)	0 (0%)	
Success (lack of stenosis ≥ 50%)	114 (91.2%)	104 (92%)	10 (90.9%)	.338
TIMI-flow grade at MB				.638
3	114 (91.9%)	103 (91.2%)	11 (100%)	
2	0 (0%)	0 (0%)	0 (0%)	
1	3 (2.4%)	3 (2.7%)	0 (0%)	
TIMI-flow grade at SB				.638
3	114 (91.9%)	103 (91.2%)	11 (100%)	
2	0 (0%)	0 (0%)	0 (0%)	
1	3 (2.4%)	3 (2.7%)	0 (0%)	
MB stenosis	3.27% (6.14)	3.24% (6.25)	3.57% (4.76)	.892
SB stenosis	14.74% (19.94)	15.55% (20.45)	4.29% (4.5)	.211
≥ 50% stenosis of MB	0 (0%)	0 (0%)	0 (0%)	1.000
≥ 50% stenosis of SB	7 (7.1%)	7 (7.7%)	0 (0%)	.585
≥ 30% stenosis of SB	22 (22.4%)	22 (24.2%)	0 (0%)	.158
12-month follow-up	110 (88.7%)	92 (86.8%)	18 (100%)	
Death	0 (0%)	0 (0%)	0 (0%)	
Stent related AMI	2 (1.8%)	1 (1.1%)	1 (5.5%)	.223
Re-PCI	6 (5.4%)	5 (5.4%)	1 (5.5%)	.555
Thrombosis	1 (0.9%)	0 (0%)	1 (5.5%)	.115

AMI, acute myocardial infarction; IVUS, intravascular ultrasound; OCT optical coherence tomography; POT, proximal optimization therapy; Re-PCI, re-percutaneous coronary intervention; SB, side branch; MB, main branch; TIMI, Thrombolysis in Myocardial Infarction.

stenting techniques were compared (table 5), data from the QCA show better minimum lumen diameters for the double stenting technique in the bifurcation core and the ostium of the SB, and almost identical for the ostium of the distal segment.

Bifurcation angle (table 4) showed a slight change after stenting with a statistically significant reduction from 52.8 ± 18.4 º down to 47.5 ± 17.2º ($P = .001$). In the double stenting cohort, angulation modification was similar—in absolute terms—with a reduction of some 4º. However, this difference was not statistically significant (table 4). No significant correlation between the degree of angulation modification and the SB residual stenosis was reported ($P = .86$).

Clinical outcomes

Only 1 procedural complication was reported consisting of the occlusion of the SB in a patient treated with the provisional stenting technique that could not be solved. No major clinical events, cases of stent thrombosis or target lesion revascularization were reported at 30 days.

One year after implantation, 110 patients (88.7%) were contacted. A case of definitive device thrombosis (0.91%) was reported at 1-year follow-up especially in a case of double stenting treated with primary angioplasty. This case added to other 5 cases of new target lesion revascularization due to restenosis (4.54%) reveal a 12-month rate of target lesion failure of 5.45%. Two of these restenoses were found in the ostium of the SB and the remaining 3 were in the main vessel. No deaths and 3 infarctions (2.72%) were reported all of them associated with the device in relation to stent thrombosis and, in the other 2 cases, due to restenosis with minimum mobilization of troponin.

DISCUSSION

The study main findings are: *a)* the BIOSS LIM C dedicated stent has a high rate of success at 30 days in patients with complex coronary bifurcation lesions; *b)* such device is basically used with the provisional stenting strategy and is associated with a very reduced need for stenting in the SB; *c)* immediate angiographic outcomes show the proper behavior from the stent in the 3 bifurcation segments, as well as in the polygon of confluence where the contact surface between the stent and the artery is minimum.

Table 4. Quantitative coronary angiography of bifurcation in the entire cohort. Comparison between simple and double stent

N = 92 lesions	Entire population (N = 92)			1-stent technique (N = 75)			2-stent technique (N = 17)		
Total	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***
Minimum lumen diameter, mm	0.97 ± 0.48	1.70 ± 0.44	< .001	0.99 ± 0.48	1.60 ± 0.42	< .001	0.85 ± 0.47	2.12 ± 0.30	< .001
Maximum percentage diameter stenosis, %	62.78 ± 17.70	26.62 ± 14.03	< .001	61.63 ± 17.92	28.49 ± 14.19	< .001	67.86 ± 16.25	18.36 ± 9.94	< .001
Carinal angle, degrees (º)	52.8 ± 18.4	47.5 ± 17.2	.001	52.3 ± 13.4	46.4 ± 18.1	.002	55.3 ± 13.3	51.9 ± 12.5	.161
Proximal main branch									
Length, mm	11.15 ± 5.28	10.86 ± 5.22	.154	11.56 ± 5.59	11.21 ± 5.53	.155	9.06 ± 2.50	8.97 ± 2.69	.776
Reference lumen diameter, mm	3.83 ± 1.13	3.88 ± 0.80	.674	3.65 ± 0.98	3.84 ± 0.71	.089	4.75 ± 1.42	4.10 ± 1.12	.066
Minimum lumen diameter, mm	1.63 ± 0.85	2.96 ± 0.62	< .001	1.60 ± 0.77	2.85 ± 0.46	< .001	1.78 ± 1.15	3.50 ± 0.93	< .001
Percentage diameter stenosis, %	55.36 ± 20.81	18.09 ± 10.34	< .001	54.12 ± 20.78	19.44 ± 10.01	< .001	61.16 ± 20.58	11.77 ± 9.78	< .001
Binary stenosis (SD ≥ 50%), N (%)	58 (63.0)	0	< .001	45 (60.0)	0	< .001	13 (76.5)	0	< .001
Distal main branch (BIOSS)									
Length, mm	10.35 ± 5.36	9.96 ± 5.46	.190	10.61 ± 5.69	10.28 ± 5.76	.105	9.13 ± 3.24	8.66 ± 3.43	.082
Reference lumen diameter, mm	2.33 ± 0.45	2.34 ± 0.42	.797	2.29 ± 0.45	2.32 ± 0.42	.547	2.49 ± 0.39	2.42 ± 0.40	.409
Minimum lumen diameter, mm	1.19 ± 0.56	2.28 ± 0.36	< .001	1.24 ± 0.56	2.27 ± 0.37	< .001	0.99 ± 0.53	2.34 ± 0.30	< .001
Percentage diameter stenosis, %	48.43 ± 23.07	0.12 ± 15.00	< .001	46.67 ± 22.98	-0.62 ± 15.06	< .001	60.61 ± 19.77	3.40 ± 14.74	< .001
Binary stenosis (SD ≥ 50%), N (%)	43 (46.7)	0	< .001	31 (41.3)	0	< .001	12 (70.6)	0	< .001
Side branch									
Length, mm	6.32 ± 3.81	6.27 ± 3.47	.689	5.20 ± 0.99	5.21 ± 0.89	.905	11.58 ± 6.88	11.25 ± 6.08	.549
Reference lumen diameter, mm	2.18 ± 0.48	2.22 ± 0.49	.199	2.12 ± 0.46	2.16 ± 0.42	.268	2.42 ± 0.51	2.49 ± 0.71	.536
Minimum lumen diameter, mm	1.41 ± 0.64	1.75 ± 0.52	< .001	1.46 ± 0.57	1.62 ± 0.43	.022	1.19 ± 0.88	2.31 ± 0.50	< .001
Percentage diameter stenosis, %	34.16 ± 27.52	20.94 ± 19.14	< .001	30.06 ± 25.34	24.35 ± 17.13	.070	52.24 ± 30.19	5.88 ± 20.77	< .001
Binary stenosis (SD ≥ 50%), N (%)	22 (23.9)	5 (5.4)	< .001	13 (17.3)	5 (6.6)	.044	9 (52.9)	0	< .001

PDS, percentage diameter stenosis.

Demographic data confirm that this is a non-selected population with a prevalence of risk factors, comorbidities, heart disease, and anatomical characteristics of the lesions we see in the routine clinical practice of any cath lab these days.

The device had a high rate of implantation success that was consistent with the easiness of its design being successfully implanted in > 97% of the cases. Success rate is similar to that reported in most studies with tubular stents used in bifurcations, something unreported in previous series of dedicated stents (Axxess, Frontier, and Nile studies). For example, the Frontier stent[15] had a rate of restenosis of nearly 29.9%. The Nile stent[16,17] was successfully used in tortuous arteries and distal segments with acceptable results with a rate of target lesion revascularization of 8.4%. However, it required distribution of angiographic stenosis focused on the carina. The self-expandable Axxess stent[18] showed favorable results with a 1-year rare of cardiovascular events and restenosis of 7.7% and 6.4%, respectively. Nonetheless, it only treated the polygon of confluence and the segment immediately proximal to the ostia of the branches. Also, it was limited to certain angles and lengths needing, on many occasions, the use of additional stents.

In 14.5% of the cases, the double stenting technique was used. This is a dedicated stent in such a way that, when crossing the SB, the lack of struts in the polygon of confluence facilitates its advance without requiring previous opening. Results from the study support just how easy it is to use it with the double stenting technique. In all the cases where it was used, a second stent was successfully implanted into the SB. In 6 (66%) out of the 9 cases where the double stenting strategy was planned, the SB stent was directly implanted without dilatation. This data, though very limited, could signal a possible advantage of the BIOSS LIM C dedicated stent to facilitate access of a second stent to the SB when necessary. On the other hand, angiographic results after implantation are particularly remarkable for the double stenting technique: both the minimum lumen diameters and the residual stenosis of the proximal segments and the SB are better compared to those seen in the cohort where the provisional stenting technique was used.

Table 5. Quantitative coronary angiography. Polygon of confluence. Comparative between simple and double stent

	N = 92 lesions			Provisional technique (N = 75)			Double stenting technique (N = 17)		
	Pre	Post	*P*	Pre	Post	*P*	Pre	Post	*P*
Bifurcation core									
Reference lumen diameter, mm	4.04 ± 1.13	3.97 ± 0.80	.531	3.83 ± 0.97	3.88 ± 0.69	.618	4.82 ± 1.34	4.35 ± 1.10	.095
Minimum lumen diameter, mm	2.09 ± 0.94	3.28 ± 0.78	< .001	1.87 ± 0.72	2.93 ± 0.49	< .001	2.25 ± 0.98	3.63 ± 0.90	< .001
Percentage diameter stenosis, %	48.49 ± 17.94	17.15 ± 10.96	< .001	47.57 ± 18.23	18.76 ± 10.68	< .001	52.39 ± 15.70	10.31 ± 9.63	< .001
Binary stenosis (SD ≥ 50%), N (%)	46 (50.0)	0	< .001	35 (46.7)	0	< .001	11 (64.7)	0	.001
Distal main branch ostium (BIOSS)									
Reference lumen diameter, mm	2.34 ± 0.45	2.35 ± 0.43	.842	2.29 ± 0.45	2.32 ± 0.42	.544	2.55 ± 0.40	2.48 ± 0.43	.406
Minimum lumen diameter, mm	1.38 ± 0.53	2.40 ± 0.37	< .001	1.40 ± 0.50	2.39 ± 0.36	< .001	1.32 ± 0.67	2.45 ± 0.41	< .001
Percentage diameter stenosis, %	40.59 ± 21.36	-3.67 ± 15.54	< .001	38.61 ± 20.61	-4.57 ± 15.76	< .001	48.95 ± 23.07	0.13 ± 14.37	< .001
Binary stenosis (SD ≥ 50%), N (%)	34 (37.0)	0	< .001	23 (30.7)	0	< .001	11 (64.7)	0	.001
Side branch ostium									
Reference lumen diameter, mm	2.21 ± 0.50	2.24 ± 0.51	.280	2.14 ± 0.46	2.17 ± 0.41	.375	2.51 ± 0.56	2.57 ± 0.72	.553
Minimum lumen diameter, mm	1.56 ± 0.52	1.80 ± 0.55	< .001	1.58 ± 0.47	1.65 ± 0.45	.219	1.47 ± 0.71	2.40 ± 0.52	< .001
Percentage diameter stenosis, %	28.21 ± 21.77	19.21 ± 20.56	.004	24.91 ± 20.30	23.13 ± 17.97	.501	42.19 ± 22.82	2.58 ± 22.99	< .001
Binary stenosis (SD ≥ 50%), N (%)	16 (17.4)	5 (5.4)	.012	9 (12.0)	5 (6.7)	.267	7 (41.2)	0	.016

PDS, percentage diameter stenosis.

If procedural data are analyzed, something that calls our attention is the SB predilatation in 47 cases where the SB was not damaged significantly. The protocol did not define the obligation to predilate the SB. According to the investigator's criterion in each case, the observation of a lesion that did not reach a 50% stenosis was still considered to pose risk of carina displacement.

Another aspect we should mention is the strikingly low use of the POT reported in 33 cases (26%), and similarly in both cohorts. On this regard, we should mention that the device is designed with a proximal segment of a greater caliber in such a way that with simple inflation this proximal postdilatation is already incorporated. The POLBOS I[19] and II[14] clinical trials showed that the use of POT improved the rate of target lesion revascularization. Also, a tendency towards less late lumen loss was reported. However, POT was used at a rate of 37%, which is similar to that of our cohort.

One of the main study endpoints was to assess the potential disadvantage of design in 2 stent segments. This design provides a space for the polygon of confluence—of 0.9 mm to 1.5 mm—between both segments linked by 2 connectors. In this space, the metal-to-artery ratio is significantly lower, which may contribute to a relatively systematic underexpansion.

Results of the provisional cohort on the polygon of confluence show that mean residual stenosis is 19% at the core of the polygon and 23% in the ostium of the SB. These data suggest a certain impact in the angiographic results of this relative lack of scaffold between both segments that we believe could be the cause for a certain degree of underexpansion at the polygon of confluence.

Another study primary endpoint was to see the degree of damage in the bifurcation native angulation. Godino et al.[20] analyzed changes to the bifurcation angle after angioplasty using the 1 or 2-stent technique in a cohort of 215 patients. They described a mean reduction of around 10º of the angle in the left main coronary artery, and 7º in the remaining bifurcations with the double stenting technique. However, with the provisional stenting technique no significant differences were reported. In our study, the results seen in the overall population show a statistically significant change—although not very relevant numerically—of the bifurcation angle that went from 53º to 47º. Contrary to what was reported by Godino et al.[20], in our study, in the 2-stent cohort, changes to the bifurcation angle were not significant with mean reductions of 3º. However, in the provisional stenting cohort, a significant reduction of the angle was seen of 6º. In any case, we consider that this just has simple statistical significance; it seems very unlikely that a 5º variation of the bifurcation angle can be seen through visual estimate, and much less that any clinical disadvantages can occur.

Overall, the follow-up results were good and consistent with what was described in former studies.[14,19] There was a significant loss of cases for the QCA since 92 cases were available only. Another study limitation is that regarding the analysis of the double stenting technique. Although the QCA data suggest good results for the double stenting technique, the study was not designed to draw comparisons between the provisional and the double stenting techniques. Also, the information collected is limited, and the number of patients treated with the double stenting technique is not enough to reach any conclusions.

An additional limitation we would like to mention is the low use of imaging modalities. Probably in coronary bifurcation lesions its systematic use can be beneficial.

In conclusion, we believe that this study conducted at several centers with different operators reveals how relatively easy it is to use the BIOSS LIM C stent to treat coronary bifurcation lesions. We're pretty sure this is significant enough to simplify the double stenting approach where the scarce distortion overlapping the

bifurcation native angulation called our attention. On the other hand, the weak spot would be the feeble metal scaffold that remains in the polygon of confluence probably due to a certain degree of underexpansion. However, the good clinical outcomes reported at 1-year follow-up are indicative that such design is not really a problem.

Limitations

This was a prospective observational study, which means that any comparisons among the routine techniques used to treat coronary bifurcation lesions can be limited. The informed consent from all the patients was not obtained. Although information from 88% of the cohort was obtained, losses to follow-up were slightly higher than they should have been.

CONCLUSIONS

The BIOSS LIM C dedicated stent works well to treat coronary bifurcation lesions. Angiographically, the stent has a space at the polygon of confluence to facilitate access to the SB. This is associated with a lower metal-to-artery ratio conditioning residual stenosis of around 20%. However, such residual stenosis does not necessarily trigger more events at 1 year and, at the end, this carinal design allows easy access to the SB in case a second stent would be needed and with excellent results. Finally, the stent-induced distortion on the angle of the carina is limited, around 5º.

FUNDING

The study was funded with a graft from Fundación EPIC, which was unconditionally funded by the LOGSA group.

AUTHORS' CONTRIBUTIONS

As the study lead co-investigators, B. García del Blanco, and A. Pérez de Prado drafted the protocol, managed funds, directed the project, recruited the patients, wrote part of the article, and made their contributions to the overall drafting of the article. J. Gómez-Lara conducted the angiographic analysis at the core lab, the statistical analysis, drafted part of the article, and made his contributions to the article overall draft. I. In his capacity of sub-investigator, Otaegui Irurueta recruited patients by performing procedures and protocol follow-ups, entered the data required in the data curation notebook, depurated and finalized the data entered in the database, was involved in statistical analysis, drafted part of the article, participated in the article overall draft by compiling all the sections drafted from the remaining authors, and responded to the corrections requested by reviewers. M.A. Carmona Ramírez dealt with all regulatory actions needed to start the study and include the different participant centers both with the Spanish Agency of Medicines and Medical Devices and the different centers and ethics committees. As study sub-investigators, the remaining authors recruited patients, performed the procedures and follow-ups according to protocol, filled out the data curation notebook, and responded to all the questions asked.

CONFLICTS OF INTEREST

A. Pérez de Prado 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 research grants from the following research sponsors (Fundación EPIC): Abbott, Biosensors, Biotronik, Bristol-Myers-Squibb, Boston Scientific, Cardiva, iVascular, Shockwave Ltd, Terumo, Volcano Philips; also, fees for his theoretical or practical proctoring for Braun, Boston Scientific, and Terumo. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Dedicated stents facilitate better adaptation to fractal anatomy of coronary bifurcation lesions with less bifurcation angle distortion and access to the side branch. The BIOSS LIM C stent has shown favorable results in randomized clinical trials compared to second-generation tubular stents.

WHAT DOES THIS STUDY ADD?

- In this study, the angiographic pattern of coronary bifurcation lesions with the implantation of BIOSS LIM C dedicated stent is shown. Also, it shows the feasibility of its systematic use—with a high rate of success and scarce damage to bifurcation angulation—can have. Residual underexpansion at the polygon of confluence is acceptable for the provisional stenting technique despite a reduced metal-to-artery ratio, and excellent for the double stenting technique.

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REC Interv Cardiol. 2022;4(4):304-310
https://doi.org/10.24875/RECICE.M22000320

Original article

Left atrial appendage closure versus DOAC in elderly patients: a propensity score matching study

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ABSTRACT

Introduction and objectives: Information comparing left atrial appendage closure (LAAC) to direct oral anticoagulation (DOAC) therapy is scarce. Our aim is to compare the clinical outcomes between LAAC and DOACs on an elderly population (> 80 years of age).
Methods: We retrospectively collected 1144 octogenarian patients with atrial fibrillation from 3 different tertiary hospitals. A total of 970 patients received DOACs and 174 patients were treated with LAAC. At baseline, both groups had similar cardiovascular risk factors. The LAAC group had more history of bleeding, anemia or previous cancer. We conducted a propensity score matching study and obtained 2 different paired groups of 58 patients with similar baseline risk factors, comorbidities, and risk scores who received DOACs or were treated with LAAC. The outcomes of the therapeutic strategy used (DOACs or LAAC) were assessed using the Cox regression analysis.
Results: During a median follow-up of 2.0 years [range 0.9-3.5] no differences regarding the primary endpoint (a composite of death, major bleeding, and stroke) were found (HR, 1.05; 95%CI, 0.15-7.51). Bleeding events were similar in both groups with no statistically significant differences being reported (HR, 1.79; 95%CI, 0.73-4.41). Mortality rate was numerically higher in patients on DOACs (31.8%) vs LAAC (26.4%). However, this finding did not reach statistical significance (HR, 0.70; 95%CI, 0.33-1.47; $P = .343$).
Conclusions: Compared to DOACs, LAAC has not shown any differences regarding embolic events, bleeding, and mortality in a population of elderly patients > 80 years of age. In our population, LAAC is a strategy as safe and effective as DOACs, and is an alternative to be taken into consideration in real-world patients > 80 years.

Keywords: Atrial fibrillation. Left atrial appendage closure. Direct oral anticoagulants. Embolic risk. Bleeding risk.

Cierre de orejuela izquierda frente a ACOD en pacientes mayores: análisis con emparejamiento por puntuación de propensión

RESUMEN

Introducción y objetivos: Existe poca información comparativa entre el cierre de la orejuela izquierda (COI) y los anticoagulantes orales de acción directa (ACOD). Nuestro objetivo fue comparar los resultados clínicos entre el COI y los ACOD en una población de pacientes mayores de 80 años.
Métodos: Se analizaron 1.144 pacientes octogenarios con fibrilación auricular provenientes de 3 hospitales terciarios. De ellos, 970 recibían ACOD y 174 fueron sometidos a COI. Ambos grupos presentaban similares factores de riesgo cardiovascular. El grupo de COI tenía mayor porcentaje de antecedentes de hemorragia, anemia y cáncer previo. Se llevó a cabo un análisis emparejado y se obtuvieron 2 grupos de 58 pacientes con similares factores de riesgo, comorbilidad y escalas de riesgo que fueron sometidos a COI o recibían tratamiento con ACOD. Los resultados de acuerdo con la estrategia terapéutica se obtuvieron mediante regresión de Cox.

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Received 20 February 2022. Accepted 15 June 2022. Online: 26-08-2022.

Resultados: Durante una mediana de seguimiento de 2 años [rango: 0,9-3,5] no hubo diferencias en cuanto al evento combinado primario de muerte, hemorragia mayor o ictus (HR = 1,05; IC95%, 0,15-7,51). Las hemorragias fueron similares en ambos grupos, sin diferencias estadísticamente significativas (HR = 1,79; IC95%, 0,73-4,41). La mortalidad fue mayor en los pacientes con ACOD (31,8%) frente a aquellos con COI (26,4%), sin diferencias significativas (HR = 0,70; IC95%, 0,33-1,47).
Conclusiones: En comparación con los ACOD, el COI no ha mostrado diferencias en cuanto a eventos embólicos, hemorragias y mortalidad en una población de pacientes de edad avanzada. En nuestra cohorte, el COI es una alternativa que puede considerarse para los pacientes mayores de 80 años.

Palabras clave: Fibrilación auricular. Cierre de orejuela izquierda. Anticoagulantes orales directos. Riesgo embólico. Riesgo hemorrágico.

Abbreviations

AF: atrial fibrillation. **DOACs:** direct oral anticoagulants. **LAAC:** left atrial appendage closure.

INTRODUCTION

Atrial fibrillation (AF) has emerged as a clinically relevant issue of public health since it is associated with significant mortality and morbidity rates.[1] AF is known to be a powerful risk factor for stroke independently increasing up to 5-fold across all ages. A total of 23.5% of all strokes occurred at 80-89 years of age are due to AF.[2] The prevalence of AF is predicted to rise within the next few decades because of the growing population of elderly patients. Unfortunately, these patients are not often given oral anticoagulants. Only 35% of the patients aged ≥ 85 years without any clear contraindications for anticoagulation therapy receive the prescription.[3] The reasons could be the increased risk of bleedings, especially intracranial and fatal bleedings,[4] and also the frailty status of these patients. Since 2011, direct oral anticoagulants (DOACs) have shown a better risk-benefit ratio in patients with AF confirmed by a lower rate of stroke, intracranial hemorrhage, and mortality compared to warfarin.[5] Still, with an improved safety and efficacy profile DOACs still present several shortcomings. The rate of discontinuation, the persistent risk of bleeding in high-risk populations or the risk of stroke when prescribed at a lower than recommended dosage are a matter of concern.[6]

Left atrial appendage closure (LAAC) was developed as an alternative to warfarin therapy in patients with AF. Several randomized controlled trials and few large registries have addressed the safety and efficacy profile of this technique.[7,8] Recently, the evidence provided by long-term follow-up registries confirm that efficacy has similar endpoint rates compared to randomized controlled trials, and lower rates of stroke compared to the rates expected in untreated patients of similar risk.[9]

However, to this date, information comparing LAAC to DOACs therapy is scarce,[10] and no comparison between both alternatives has been conducted in the elderly population. The aim of our study was to compare the clinical outcomes between LAAC and DOACs of an elderly population (> 80 years of age) using a propensity score matching study.

METHODS

Study population

This retrospective multicenter study included a cohort of 1144 consecutive octogenarian patients with non-valvular AF treated with DOACs (N = 970) or LAAC (N = 174) from January 2014 through December 2018 at 3 Spanish and Canadian hospitals (Hospital Álvaro Cunqueiro, Vigo, Spain, Hospital Universitario, Salamanca, Spain, and Institut Universitaire de Cardiologie et Pneumologie de Quebec, Canada).

Authors defined non-valvular AF as AF unrelated to rheumatic mitral stenosis or prosthetic mechanical heart valves.[11] Because the goal of the trial was to evaluate LAAC compared to DOACs in patients with non-valvular AF, patients treated with LAAC who received postoperative oral anticoagulation were not included in the study.

All the patients treated with LAAC were discussed and approved for LAAC by a multidisciplinary team. Regarding anticoagulated patients, the optimal dose of DOACs was based on the European recommendations.[12] Electronic medical records were reviewed in all the patients to collect data regarding the baseline clinical variables, the therapeutic strategy, and the events occurred at the follow-up. The CHA_2DS_2-VASc and HAS-BLED scores were estimated for each patient.

The study was conducted in full compliance with the principles established in the Declaration of Helsinki and approved by the local ethics committee. Due to the retrospective nature of the study and its general interest, it was approved by each center local ethics committee without the need for informed consent.

Follow-up and outcomes

Primary endpoint was a composite of death, major bleeding, and stroke. Primary efficacy endpoints were all-cause mortality, and embolic events. Primary safety endpoint was the risk of major bleeding. Outcomes were censored at the last medical contact site in primary or secondary care, which was censored in November 2019 or until the end of anticoagulant therapy in the case of the DOAC group or the beginning of such therapy in the case of the LAAC group.

Embolic events were defined as a composite of any ischemic stroke, pulmonary embolism or peripheral embolism. Ischemic stroke was confirmed through concomitant imaging studies of the brain including computed tomography scan or magnetic resonance imaging. Major bleeding (MB) was defined using the definition established by the International Society on Thrombosis and Hemostasis.[13] Bleeding was divided into intracranial hemorrhage (ICH) and non-ICH.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 25.0 and Stata 15.1 statistical software packages. Continuous variables were expressed as mean ± standard deviation and compared using the chi-square test. Categorical variables were expressed as percentages and compared using the Student *t* test.

A Cox analysis was performed to evaluate the unadjusted impact of LAAC vs DOAC on mortality, embolic and bleeding events. Due to the important differences reported in the baseline characteristics of patients treated with LAAC compared to those treated with DOACs we complemented our analysis with a propensity score matching (PSM) study. Patients were matched on a 1:1 ratio based on their nutritional status and on the propensity score using a < 0.2 caliper. Propensity score was estimated through logistic regression with the therapeutic group (LAAC or DOAC) as the dependent outcome with 21 baseline characteristics (table 1) as the independent variables. After PSM, we identified 58 patient-pairs with balanced baseline characteristics and no significant differences (table 2). Estimates were reported as hazard ratios (HR) with their 95% confidence intervals (95%CI). *P* values < .05 were considered statistically significant. Kaplan-Meier estimates were used to graphically evaluate the rate and timing of the events according to the therapeutic group (LAAC vs DOAC).

RESULTS

Baseline characteristics

Out of a total cohort of 1144 patients with AF, 970 patients were treated with DOACs while 174 underwent successful LAAC. The baseline clinical characteristics of the 2 groups (unmatched population) are shown on table 1. Patients from the DOACs group were slightly older being women more predominant. Previous history of bleeding was more common in patients treated with LAAC and the same thing happened with anemia, previous cancer, and dementia. Both groups had similar cardiovascular risk factors. Among the patients from the LAAC group less than 30% received dual antiplatelet therapy (27.6%), and 75.9% single antiplatelet therapy.

Regarding thrombotic and bleeding risk, the CHA_2DS_2-VASc and the HAS-BLED scores were significantly higher in the LAAC group (5.2 ± 1.3 vs 4.3 ± 1.3 for CHA_2DS_2VASc, and 3.5 ± 0.8 vs 2.5 ± 0.9 for HAS-BLED).

Table 1. Comparison of baseline characteristics between patients treated with DOACs or LAAC

Variables	DOACs (N = 970)	LAAC (N = 174)	*P*
Age (years)	87.6 ± 3.6	83.6 ± 2.7	< .001
Female sex (%)	67.3	41.4	< .001
Body mass index (kg/m²)	29.1 ± 4.7	26.9 ± 3.7	< .001
Cardiovascular risk factors			
Hypertension (%)	70.3	90.2	< .001
Diabetes (%)	20.3	37.4	< .001
Cardiovascular history			
Peripheral arterial disease (%)	12.2	29.9	< .001
Ischemic heart disease (%)	14.4	35.1	< .001
Previous heart failure (%)	25.8	42.0	< .001
Previous embolic events (%)	26.4	17.5	.006
Comorbidities			
Previous bleeding (%)	10.1	57.5	< .001
Anemia (%)	27.2	69.5	< .001
COPD (%)	8.7	20.1	< .001
Dementia (%)	5.1	7.5	< .001
Previous cancer (%)	8.7	22.4	< .001
Laboratory data			
Creatinine (mg/dL)	1.0 ± 0.3	1.4 ± 0.9	< .001
Echocardiographic data			
LVEF < 40% (%)	5.3	9.2	.042
Severe aortic stenosis (%)	3.8	6.3	.129
Concomitant therapy			
Chronic use of NSAIDs (%)	4.6	14.9	< .001
PPI (%)	50.3	86.2	< .001
Risk scores			
CHA_2DS_2-VASc (points)	4.3 ± 1.3	5.2 ± 1.3	< .001
HAS-BLED (points)	2.5 ± 0.9	3.5 ± 0.8	< .001

COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Clinical outcomes

Entire population

The median follow-up was 2.0 years [range 0.9-3.5]. The events shown on table 3 section "before PSM" we collected and analyzed at the follow-up. Embolic events tend to be more frequent among patients on DOACs without statistical significance. Major bleeding events were statistically significant in patients treate with LAAC compared to DOAC (*P* < .001).

Based on the univariate analysis, LAAC was associated with a higher rate of death, major bleeding, and stroke compared to DOACs (HR, 1.54; 95%CI, 1.06-2.24; *P* = .024). Regarding the efficacy endpoint of all-cause mortality and embolic events no significant differences were observed between both groups (HR, 0.87; 95%CI, 0.53-1.44). The same thing happened with embolic events and stroke (HR, 0.59; 95%CI, 0.26-1.36, and HR, 0.82; 95%CI, 0.33-2.08, respectively). Major bleeding was significantly higher in the LAAC group (HR, 3.43; 95%CI, 2.05-5.76) based on the univariate analysis. ICH did not differ between LAAC and DOACs (HR, 1.49; 95%CI, 0.43-5.19). Based on the univariate analysis, the all-cause mortality rate was not statistically significance (HR, 1.09; 95%CI, 0.80-1.50).

Propensity score matching study

After PSM a total of 58 patients were obtained in each group. The 2 groups were uniform regarding age (85.8 ± 3.7 vs 85.6 ± 2.5 years,

Table 2. Comparison of baseline characteristics after propensity score matching between patients treated with DOACs or LAAC

Variables	DOACs (N = 58)	LAAC (N = 58)	*P*	SMD
Age (years)	85.8 ± 3.7	85.6 ± 2.5	.758	-0.068
Female sex (%)	46.6	44.8	.852	0.035
Body mass index (kg/m²)	27.4 ± 4.2	27.8 ± 4.4	.667	0.092
Cardiovascular risk factors				
Hypertension (%)	81.0	87.9	.305	0.232
Diabetes (%)	32.8	29.3	.688	-0.071
Cardiovascular history				
Peripheral arterial disease (%)	13.8	13.8	1.000	0.000
Ischemic heart disease (%)	24.1	13.8	.155	-0.216
Previous heart failure (%)	37.9	34.5	.699	-0.070
Previous embolic events (%)	27.6	24.1	.672	-0.078
Comorbidities				
Previous bleeding (%)	37.9	43.1	.570	0.104
Anemia (%)	70.7	62.1	.326	-0.187
COPD (%)	12.1	17.2	.431	0.129
Dementia (%)	3.4	8.6	.242	0.288
Previous cancer (%)	13.8	10.3	.569	-0.082
Laboratory data				
Creatinine (mg/dL)	1.2 ±0.5	1.2 ± 0.6	.809	-0.028
Echocardiographic data				
LVEF < 40% (%)	6.9	8.6	.729	0.059
Severe aortic stenosis (%)	5.2	5.2	1.000	0.000
Concomitant therapy				
Chronic use of NSAIDs (%)	10.3	5.2	.298	-0.246
PPI (%)	79.3	77.6	.821	-0.050
Risk scores				
CHA_2DS_2-VASc (points)	4.7 ± 1.5	4.7 ± 1.1	.834	-0.040
HAS-BLED (points)	3.2 ± 1.0	3.2 ± 0.7	.826	-0.043

COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SMD, standardized mean difference.

P = .758), cardiovascular risk factors (32.8% vs 29.3% diabetes, *P* = .688; 81.0% vs 87.9% hypertension, *P* = .305), previous heart failure (37.9% vs 43.1% *P* = .570), creatinine levels (1.2 ± 0.5 mg/dL vs 1.2 ± 0.6mg/dL *P* = .809), and ischemic and bleeding risk (CHA_2DS_2-VASc, 4.7 ± 1.5 vs 4.7 ± 1.1; *P* = .834, and HAS-BLED, 3.2 ± 1.0 vs 3.2 ± 0.7 *P* = .834) as shown on table 2.

At the follow-up, events were collected for both groups (see table 3 section "after PSM"). Patients on DOACs had more cardiovascular mortality compared to patients treated with LAAC (*P* = .555). Major bleeding was higher in patients treated with LAAC without statistical significance (*P* = .056).

Regarding to primary endpoint (death, major bleeding, and stroke) after PSM, LAAC had a higher risk rate (HR, 1.62; 95%CI, 0.62-3.65) compared with DOACs. The primary efficacy endpoint (all-cause mortality, and embolic events) did not differ between both groups (HR, 0.83; 95%CI, 0.29-2.35).

No differences regarding embolic events were apparent between the 2 matched groups (HR, 1.05; 95%CI, 0.15-7.51) (figure 1). No statistically significant differences were found regarding the ischemic stroke (HR, 2.12; 95%CI, 0.19-23.39).

Safety endpoint (major bleeding) did not differ in either group (HR, 1.79; 95%CI, 0.73-4.41) (figure 2) after PSM.Also, ICH did not differ in either one of the 2 categories (HR, 0.61; 95%CI, 0.05-6.78).

Mortality rate was numerically higher in patients on DOACs. After the PSM study, this finding did not reach statistical significance (HR, 0.70; 95%CI, 0.33-1.47) (figure 3).

DISCUSSION

This study has been designed with the intent to compare LAAC to DOACs in an elderly population (> 80 years old). The main finding of our study is that after PSM both DOACs and LAAC groups proved to have similar outcomes regarding the efficacy and safety profile.

As far as we are concerned this is the first study to compare both strategies in this population. We selected the cut-off value of 80 years not only because age is a known risk factor for stroke,[2] but also because age is associated with bleeding events and fewer prescriptions of anticoagulants.[14]

Many studies have evaluated clinical outcomes with different antithrombotic strategies in elderly patients with AF. Two studies[15,16] compared warfarin with aspirin supporting the use of anticoagulation in elderly and very elderly patients. Nonetheless, therapy with vitamin K antagonists is under-implemented in this population mostly due to the risk of falling (26.7%), poor prognosis (19.3%), bleeding history (17.1%), participant or family refusal (14.9%), older age (11.0%), and dementia (9.4%).[17]

As it has been discussed, DOACs provided an alternative to vitamin K antagonists. Dabigatran in both doses compared with warfarin—in patients aged ≥ 75 years—was associated with a similar or higher risk of major non-intracranial bleeding.[18] Similarly, rivaroxaban described higher major gastrointestinal bleeding rates among the elderly population with no significant interaction between age and treatment efficacy.[19] Apixaban proved beneficial compared to warfarin reducing the rates of stroke and major bleeding in our target population.[20] Finally, edoxaban also proved beneficial in very elderly patients regarding major bleeding.[21]

Clinical trials[21-24] comparing DOACs to warfarin led to the current guideline recommendation of DOACs as first-line therapy even in the elderly population.[11,25] However, DOACs may present several limitations in this type of patients. We know from clinical registries that approximately 1 in 7 patients with AF receive reduced doses of DOACs even though they never met the criteria for reduced doses.[26] Interestingly, this finding is more common among the elderly population. The rates of adverse events were higher in off-label dosed patients (HR for all-cause mortality, 2.18 [1.57-3.02]; HR for stroke, 1.50 [0.77-2.94]).[27] In this sense, we did not evaluate the dose of DOACs in our patients, but it is known from previous registries that almost one third of the patients received inappropriate doses.[28] Another important issue with DOACs is compliance. Recent data from studies conducted in the UK revealed poorer compliance with DOACs due to the lack of routine monitoring and,

Table 3. Clinical events in patients treated with DOAC and LAAC before and after propensity score matching between groups

Before PSM					
Event	**DOAC (N = 970)**		**LAAC (N = 174)**		***P***
	No.	Incidence rate (per 100 person/years)	No.	Incidence rate (per 100 person/years)	
Mortality	308	13.5 (12.1-15.1)	46	14.7 (11.0-19.7)	.543
CV mortality	96	4.2 (3.5-5.2)	9	2.9 (1.5-5.5)	.617
Ischemic stroke	47	2.1 (1.6-2.8)	5	1.6 (0.7-3.9)	.248
TIA	26	1.2 (0.8-1.7)	1	0.6 (0.1-4.3)	.460
Peripheral embolism	2	0.1 (0.0-0.3)	0	-	-
ICH	14	0.6 (0.4-1.0)	3	0.9 (0.3-2.9)	.905
Major bleeding	48	2.1 (1.6-2.8)	21	7.5 (4.9-11.4)	< .001
Minor bleeding	54	2.5 (1.9-3.2)	12	4.0 (2.3-7.0)	.318
After PSM					
Event	**DOAC (N = 58)**		**LAAC (N = 58)**		***P***
	No.	Incidence rate (per 100 person/years)	No.	Incidence rate (per 100 person/years)	
Mortality	20	15.2 (9.8-23.5)	12	11.2 (6.4-19.7)	.343
CV mortality	6	4.5 (2.0-10.1)	3	2.8 (0.9-8.7)	.555
Ischemic stroke	1	0.8 (0.1-5.5)	2	1.9 (0.5-7.7)	.547
TIA	1	0.8 (0.1-5.5)	0	-	-
Peripheral embolism	0	-	0	-	-
ICH	2	1.6 (0.4-6.2)	1	0.9 (0.1-6.6)	-
Major bleeding	4	3.0 (1.1-8.1)	9	9.2 (4.8-17.7)	.056
Minor bleeding	6	4.6 (2.1-10.3)	2	1.9 (0.5-7.5)	.292

CV, cardiovascular; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; LAAC, left atrial appendage closure; PSM, propensity score matching; TIA, transient ischemic attack.

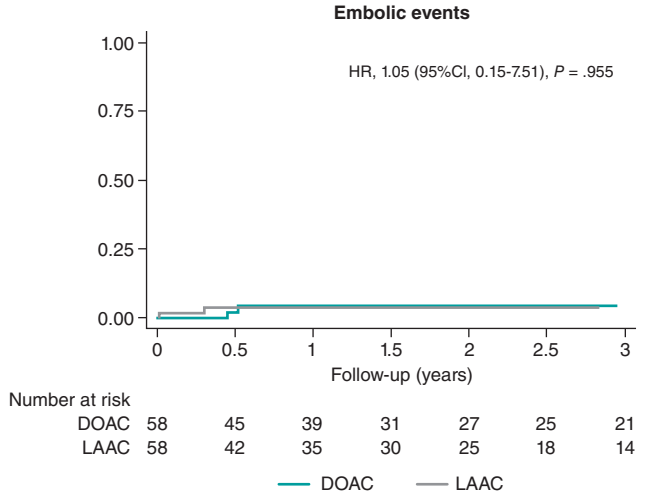

Figure 1. Analysis of embolic events at the follow-up between matched groups. 95%CI, 95% confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; LAAC, left atrial appendage closure.

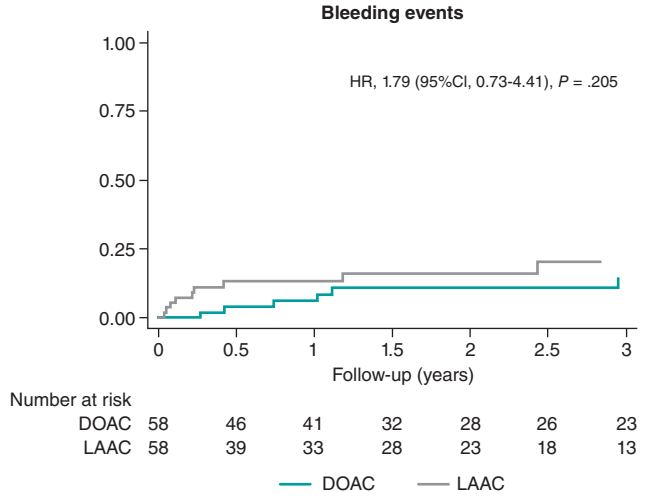

Figure 2. Analysis of major bleeding events at the follow-up between matched groups. 95%CI, 95% confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; LAAC, left atrial appendage closure.

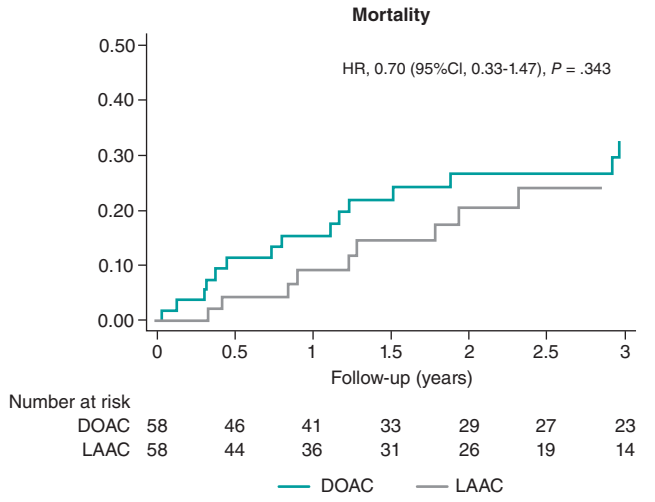

Figure 3. Analysis of mortality at the follow-up between matched groups. 95%CI, 95% confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; LAAC, left atrial appendage closure.

in some cases, the twice-daily dosing regime.[29] Non-compliance in this group revealed adverse outcomes including mortality and stroke.[30] Third, frailty is of major concern among the elderly population receiving anticoagulant drugs. A prospective study in hospitalized elderly patients showed that frailty is associated with a higher mortality rate at admission and a 2-fold increased risk of death at 1 year, particularly in anticoagulated patients.[31] The risk of falling is an important parameter of frailty. In a recent study of older adults with a history of falls and AF, the risk of ICH at the follow-up was 1.9 times higher.[32]

LAAC may be a recommended therapeutic alternative in patients with AF ineligible for long-term oral anticoagulation who need stroke and embolism prevention according to the last EHRA/EACPI consensus statement.[33] The PROTECT AF and PREVAIL 5-year outcome data were combined in a meta-analysis,[34] and proved that LAAC with the Watchman device is equivalent to warfarin in stroke prevention and requires additional decreases of major bleeding and mortality. The safety and efficacy profile of the Amplatzer Cardiac Plug was examined in a multicenter study[8] showing high procedural success rates and favorable outcomes preventing AF related thromboembolism.

A subanalysis of the EWOLUTION registry including patients aged ≥ 85 years showed that LAAC is a safe and effective procedure in these patients without any differences compared to younger patients regarding the annual stroke rates (2.0 vs 2.5 in ≥ 85 and < 85, respectively).[35]

Notwithstanding the above, the information available on this strategy compared to DOACs is scarce. To this date, only 2 studies have addressed this issue. The PRAGUE-17 was a prospective, multicenter, randomized non-inferiority trial conducted by Osmancik et al. that tried to compare LAAC with DOACs in high risk patients with AF (CHA_2DS_2-VASc ≥ 3, and HAS-BLED ≥ 2).[36] Patients were younger compared to our cohort, mean age was 73.4 ± 6.7 in the LAAC group and 73.2 ± 7.2 in the DOACs group. They had similar CHA_2DS_2VASC scores (4.7 ± 1.5) in both groups, also similar to our cohort of patients. LAAC was non-inferior to DOAC therapy regarding the composite clinical and bleeding events through a median follow-up of 20.8 months. The rates of stroke and transient ischemic attack, cardiac death, clinically significant bleeding, and nonprocedural clinically significant bleeding did not differ between the study arms. These findings are consistent with the results obtained by Godino et al.[10] Compared to our data, they selected a younger population (mean age 74.2 ± 7.7 in the LAAC group compared to 77.7 ± 6.9 in the DOACs group) with similar CHA_2DS_2VASc scores (4.3 ± 1.5 and 4.8 ± 1.5 in the LAAC and DOACs groups, respectively). They found similar outcomes between the 2 groups after PSM regarding thromboembolic events, ischemic stroke, transients ischemic attack, systemic embolism, and acute myocardial infarction, which is consistent with our own conclusions. Looking at the bleeding events, DOACs did not show an increased risk of major bleeding. In our population, results are consistent with previous findings even though we were dealing with older patients. Despite not being anticoagulated patients, the LAAC group did not have fewer bleeding events. Our hypothesis is that maybe many of them were treated with antiplatelet therapy.

Our observations are consistent with the previous studies mentioned, which supports the use of LAAC as an alternative to DOACs among elderly patients.

Study limitations

Our study has several limitations. First, its observational retrospective nature. Second, although rigorous matching was performed with 21 variables to neutralize the different clinical profile of patients, we cannot exclude the influence of other uncollected variables. Third, after PSM we achieved 2 well-balanced groups—though with a small sample size—that could lead to the underestimation of events at the follow-up. Also, we only selected patients with successful LAAC.

Despite all these limitations, we presented interesting data based on a multicenter study of consecutive octogenarian patients with non-valvular AF treated with DOAC vs LAAC.

CONCLUSIONS

This multicenter observational study proves the safety and efficacy profile after LAAC, with no differences regarding embolic and bleeding events, and mortality compared to DOACs in a propensity-matched population of real-world elderly patients > 80 years successful treated with LAAC without complications.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All authors contributed to patient recruitment, data curation, and process of manuscript review. J. Rodés-Cabau, A. Íñiguez-Romo, S. Raposeiras-Roubín, and R. Estévez-Loureiro were responsible for the study design. S. Raposeiras-Roubín, and B. Caneiro-Queija conducted the statistical analysis. B. Caneiro-Queija, S. Raposeiras-Roubín, and R. Estévez-Loureiro were responsible for preparing the manuscript.

CONFLICTS OF INTEREST

R. Estévez-Loureiro is proctor for Watchman and has received honoraria from Boston Scientific. I. Cruz-González is proctor for Watchman and LifeTech and has received honoraria from Boston Scientific and Abbott Vascular. Rodés-Cabau has received a research grant from Boston Scientific. The remaining authors declared no other conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Patients who are often treated with LAAC tend to be poor candidates for anticoagulation. As a matter of fact, older patients are excluded from randomized clinical trials and are more prone to receive reduced doses of DOACs. We know from previous trials about the noninferiority of LAAC compared to DOACs.

WHAT DOES THIS STUDY ADD?

- There was no current information on real-world older populations receiving DOACs compared to LAAC.
- Although our data come from a registry they reflect our routine clinical practice; in a comparable profile population of older patients, LAAC might be as safe and effective as DOACs.

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REC Interv Cardiol. 2022;4(4):311-318
https://doi.org/10.24875/RECICE.M22000331

Review article

Vascular access approach for structural heart procedures

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ABSTRACT

Vascular access is an essential part of all interventional procedures whether coronary or structural. Over the last 15 to 20 years, in coronary interventions, traditional femoral access has been mostly replaced by the radial approach. Nonetheless, the femoral approach through both artery and vein is still the main approach for structural heart procedures. Over the last few years, femoral access has evolved from a puncture guided by anatomical references to more accurate ultrasound-guided approaches. The relatively recent introduction of interventions such as transcatheter aortic valve replacement has conditioned the use of large introducers and ultimately the need for specific hemostatic systems, above all, percutaneous closure devices. This manuscript reviews different anatomical concepts, puncture techniques, diagnostic assessments, and closure strategies of the main arterial and venous approaches for the diagnosis and treatment of different structural heart procedures.

Keywords: TAVI. Vascular. Accesses. Structural.

Abordaje de los accesos vasculares en intervencionismo en cardiopatía estructural

RESUMEN

El acceso vascular es una parte esencial de cualquier procedimiento intervencionista coronario o estructural. En procedimientos coronarios, el acceso femoral tradicional prácticamente ha sido sustituido por el radial desde hace 15-20 años. No obstante, el acceso femoral, tanto arterial como venoso, sigue siendo la principal vía de abordaje para el intervencionismo estructural. El acceso femoral ha ido evolucionando con el paso del tiempo de una punción mediante referencias anatómicas a una punción mucho más precisa guiada por ecografía. La llegada de técnicas como el recambio valvular aórtico percutáneo ha condicionado el uso de introductores arteriales de gran tamaño y, por tanto, la necesidad de sistemas de control de la hemostasia, principalmente los sistemas percutáneos de cierre vascular. Este artículo revisa diversos conceptos anatómicos, técnicas de punción, evaluación diagnóstica y estrategias de cierre de las principales vías de acceso arterial y venoso utilizadas en el diagnóstico y el tratamiento de diferentes patologías estructurales.

Palabras clave: TAVI. Vascular. Accesos. Estructural.

Abbreviations

CFA: common femoral artery. **PDA:** patent ductus arteriosus. **TAVI:** transcatheter aortic valve implantation.

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Received 22 April 2022. Accepted 5 July 2022. Online: 23-09-2022.

ARTERIAL ACCESSES

Arterial puncture technique

Vascular access is an essential part of all interventional procedures whether coronary or structural. Over the last 15 to 20 years, traditional femoral access has been replaced by the radial approach in coronary interventions. However, the femoral approach is still the most widely used regarding structural hear procedures. Brachial, cubital, axillary or carotid accesses are also used, but to a lesser extent. Knowledge of anatomy and the puncture technique is essential. This is particularly relevant in accesses different from the radial/cubital one where the rate of complications is higher especially if large catheters and devices are used.

Femoral artery access

Common femoral artery (CFA) is the best puncture site because of its larger size and location on the femoral head favoring its palpation and compression view. The CFA is in the lateral femoral sheath, the common femoral vein is in the medial sheath while the femoral nerve rests outside the sheath, lateral to the artery. Distally, it can be divided into superficial and deep femoral arteries. High punctures above the inguinal ligament complicate arterial compression and trigger possible retroperitoneal bleeding. Low punctures in the superficial or deep femoral artery, however, increase the chances of pseudoaneurysm, hematoma or ischemia and arteriovenous fistula because, at that level, the vein and the artery often overlap, and can be crossed inadvertently.

There are 3 basic ways to catheterize the CFA:

1) Skin-based punctures

The most widely used in the past. Typically, here we'd be palpating the arterial beat 2-to-3 cm underneath the inguinal skin fold. Local anesthesia is administered followed by a needle using the modified Seldinger technique. Then, the anterior wall is punctured to prevent bleeding into the artery posterior region. Once pulsatile flow is obtained, the guidewire is inserted towards the abdominal aorta under fluoroscopy guidance. Alternatively, a micropuncture system can be used to open a smaller orifice (almost 60% smaller) with the potential to minimize complications. Afterwards, a 0.018 in guidewire is used followed by a 4-Fr introducer sheath through which a 0.035 in guidewire can be inserted. Skin-based punctures are not optimal if accuracy is what we're after.

2) Based on radiographic references

The femoral head is seen on the fluoroscopy and a radiopaque marker is placed in its inferior border as a height reference. If punctured with an inclined needle between 30º to 45°, this becomes be the perfect spot to insert the needle and try to pinch the artery halfway through the femoral head (figure 1). If punctured a little more vertically, the skin should be accessed a little more cranially. Inguinal ligament is often found 15 mm above the medial femoral head. In most patients, femoral artery bifurcations can often be found distal to the femoral head inferior side. That's why the medial femoral head is the target here. If large caliber introducer sheaths should be needed like for transcatheter aortic valve implantation (TAVI), a variation of this technique should be used and contrast injected through an advanced catheter via a different arterial access towards the CFA to spot it correctly.

3) Ultrasound-guided

Most interventional cardiologists trained over the last 15 years have limited experience with the femoral approach following the popularity gained by the radial access. Therefore, it seems logical somehow to think that femoral access training should be based on ultrasound guidance. An 8-to-12 MHz vascular linear probe is introduced into a sterile bag. 2D echo shows the CFA directly, its bifurcation, and the femoral head. The CFA should be assessed in the long axis from its bifurcation until it later enters the pelvis by measuring its caliber and assessing the presence of atheromatous plaques. The artery should be assessed in its short or cross-sectional axis that shows the typical «Mickey mouse head» look in the arterial bifurcation with the medial vein and the superficial femoral artery on the deep femoral artery, and the entire CFA cut section to assess which section is healthier by moving the transducer cranially (video 1 of the supplementary data). The vein looks different from the artery because it is much more compressible and for the direction and velocity of flow on the color Doppler echocardiography. Ultrasound-guided assessment allows us to select the arterial region with less calcium in the anterior wall. Infiltration with a local anesthetic at this spot and ultrasound-guided puncture—that reveals the entry of the needle in the center of the artery—facilitate the proper functioning of the closure systems. After introducing the 0.035 in guidewire, the ultrasound shows that the puncture site is the proper one since the guidewire is particularly echogenic and easily visible. This approach does not require the use of contrast or x-rays during puncture. In the FAUST trial[1]—a prospective multicenter trial that randomized 1004 patients to fluoroscopy or ultrasound-guided femoral access for TAVI—ultrasound-guided puncture was associated with a higher rate of success in the first attempt (83% vs 46%; $P < .01$), fewer attempts (1.3 vs 3.0; $P < .01$), less risk of venous puncture (2.4 vs 15.8; $P < .01$), shorter mean access times (136 vs 148 seconds; $P < .01$), and fewer access site related complications (1.4% vs 3.6%; $P = .04$).

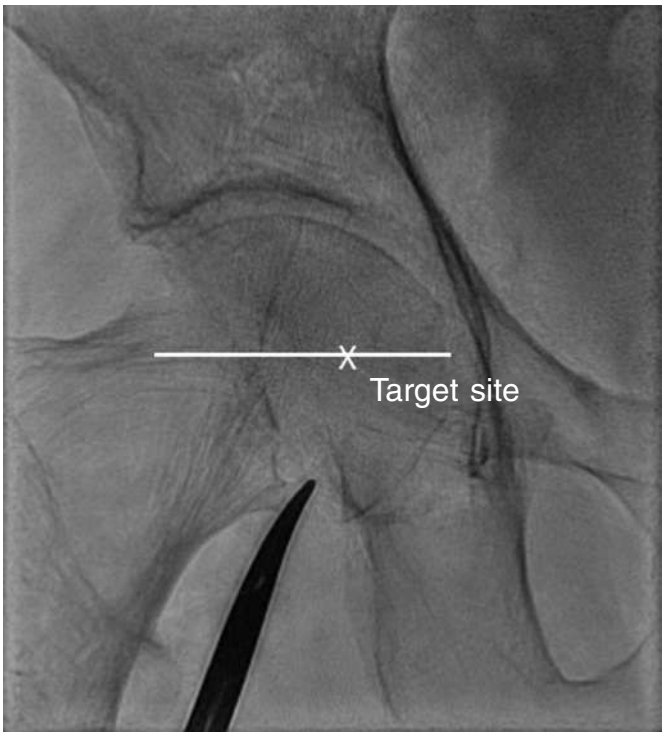

Figure 1. Radiographic references of punctures on the femoral artery.

The basic complications of arterial puncture in structural heart procedures (TAVI) are shown on table 1. Old age, feminine sex, low weight or obesity, peripheral vascular disease, kidney disease, hemorrhagic diathesis, baseline anticoagulation, and introducer sheaths of a larger size are associated with more complications.[2]

Table 1. Main complications of femoral artery access

	Incidence rate %
Hematoma	2.2-12.5
Retroperitoneal hemorrhage	1-2.2
Iliofemoral rupture	0.7-7.1
Pseudoaneurysm	2-6
Arterial dissection	2-7.4
Local infection	1.6-6.3

Although the rates of vascular complications were high in the past, they have dropped significantly over the last few years.[2]

ARTERIAL CLOSURE DEVICES

Arterial closure devices were introduced for the first time at the beginning of the 1990s. For arterial accesses with > 8-Fr introducer sheaths the closure devices available are suture-mediated or bioresorbable implantation-based. Table 2 describes the 3 large caliber vascular closure devices most widely used to this date.

Proglide

The Perclose/Proglide (Abbott Vascular, United States) is the most widely used suture-mediated device today as it is easier to use compared to the Prostar XL. It is inserted into the artery through a 0.035 in guidewire until pulsatile blood flow is seen through the lateral port. A lever releases feet inside the lumen that are pulling the artery anterior wall while releasing needles and creating a knot. The closure of the artery ties the knot. Introducer sheaths > 8-Fr require preclosure before inserting the introducer sheath following the steps already mentioned but sparing the knot tying, a maneuver that is performed at the end of the procedure. Regarding the suture-mediated device proper tunneling of subcutaneous cellular tissue is performed to make sure that the suture knot comes down. Overall, regarding TAVI procedures, preclosure is often performed using 2 devices that are released in different orientations (usually perpendicular) that are tied when the device is eventually removed resulting in an X-shape suture on the arterial surface.

Manta

The Manta device (Teleflex, United States) is available in 2 different sizes (14-Fr and 18-Fr) for arteriotomies of 10-Fr-to-14-Fr, and 15-Fr-to-20-Fr, respectively. After pinching the artery, its depth should be measured using a specific sheath. Although its performance is better in non-calcified arteries, some operators rather use it in calcified arteries because that's where suture-mediated closure systems work worse. Closure device is mounted on a specific introducer sheath until a click sound is heard. Afterwards, the whole kit is removed until the previously measured depth and the intraarterial anchor is released using a lever. Device is pulled until a green-yellowish color can be seen in a tension indicator and, while keeping the tension, a blue cylinder is advanced that lowers a radiopaque closure and fixes the collagen material over the arterial surface. After checking hemostasis, the guidewire is removed (usually a 0.035 in high-support guidewire) and suture is cut. The anchor is then resorbed, and metal closure is useful to pinch > 2.5 cm above or below if re-accessing the artery is required.

PARTICULARITIES OF ARTERIAL ACCESS IN TAVI

TAVI has revolutionized the management of severe aortic stenosis turning into the treatment of choice for a great deal of patients. In TAVI selecting this or that access route conditions the results, which is why proper planning and selection is of paramount importance.

Results from the different studies published have proven unfavorable for transthoracic compared to transfemoral accesses, which is why the latter should always be prioritized.[3] Also, the ongoing technological advances made, and the operators' increased experience have reduced the rate of major vascular complications from > 10% in the early series down to < 3% over the last few years.[4]

Transfemoral access

Planning

In most cases, transfemoral access can be performed completely percutaneously under superficial sedation. To guarantee success, meticulous planning through coronary computed tomography angiography (CCTA) is essential and, ideally, volumetric reconstruction and analysis using specific software. Such analysis should assess, above all, the vessel minimum diameter from femoral bifurcation until the origin of the common iliac artery. A minimum of 5.5 mm for 14-Fr devices and 6 mm to 6.5 mm for the 18-Fr ones are required. However, expert operators can use accesses of smaller diameters for the lack of calcification in the 360° of the arterial wall. Tortuosities, the presence of calcified plaques, and the quality of distal beds should also be assessed. Similarly, the entire descending aorta should be studied considering transfemoral access as an entire entity from the femoral artery until the aortic annulus. When in doubt on the actual puncture site, performing an in-situ ultrasound often helps since the size of the vessel and quality of the arterial wall can be assessed very precisely. Therefore, we can have a severely diseased vessel where the ultrasound shows the presence of an area spared for puncture and posterior percutaneous closure.

Technical aspects

The puncture site extends 1 cm above the femoral bifurcation until the origin of the epigastric artery. Distally, the ideal thing to do is to get away from the bifurcation to prevent damaging the ostium of the deep femoral artery during puncture or closure. Also, to have enough space if a bailout covered stent should eventually be implanted. Proximally, puncture limit is set by the epigastric artery that—on its way down towards the anterior rectum muscle—marks the outside of the abdomen.

Ultrasound-guided puncture reduces the number of complicatios.[1] The common femoral artery should be screened to select the segment with the lowest degree of calcification and smallest plaque especially in the anterior wall. The presence of anterior extensive calcification and eccentric plaques immediately proximal to the puncture site can be significant limitations to suture-mediated closure devices; in these cases, surgical approach can be considered (figure 2). Other alternatives like micropuncture or placing a pigtail catheter at the puncture site via contralateral femoral access are less common. Some centers place a safety guidewire anterogradely from the radial artery or via contralateral femoral access to perform an emergency occlusion with a balloon or implant a covered stent if closure fails; in these cases, balance between the potential benefit of the safety guidewire and the risk of vascular complications associated with a secondary femoral access should be observed.

If femoral access is achieved successfully, but there is stenosis at a more proximal level (external or common iliac artery) successive

Table 2. Main devices for percutaneous vascular closure

Company	Name	Type	FDA indication	Characteristics
Abbot	Perclose Proglide	Suture-based	CFA accesses (5-Fr-to-21-Fr), vein (5-Fr-to-24-Fr)	Monofilament polypropylene suture with premounted knot Minimum residual intravascular material Keeps access guidewire No re-access restrictions Preclosure with 2 devices if > 8-Fr
Abbot	Prostar XL	Suture-based	CFA accesses (8.5-Fr-to-24-Fr)	2 braided polyester sutures 4 nitinol needles Minimum residual intravascular material Keeps access guidewire Preclosure if > 10-Fr
Teleflex	Manta	Bioresorbable implantation	CFA accesses 10-Fr to-20-Fr devices	No need for preclosure Residual intravascular anchor

CFA, common femoral artery; FDA, Food and Drug Administration.

dilatations using sheaths of growing sizes or balloon dilatations can be considered. In some cases, intravascular lithotripsy can be useful. In the presence of severe tortuosities, a very high-support guidewire can be used (Lunderquist, Cook Medical, United States).

The 3 most common closure modalities are *a)* 2 suture-based closure devices (Proglide) in a twirl motion (one at the 11 o'clock position and the other one at the 1 o'clock position); *b)* 1 suture-mediate device and 1 collagen device (AngioSeal, Terumo, Japan); and *c)* 1 collagen closure device (Manta). The use of suture-mediated closure devices has a greater learning curve. However, it is associated with fewer serious complications or open bailout surgeries. Occasionally, more than 2 devices for complete closure are required.[5] If closure system fails—with suture—keeping the guidewire inside the artery facilitates placing new devices (1 or several Proglide devices with different rotation or a new collagen-based device). If the early failing device is a collagen-based device and a bailout parallel guidewire hasn't been left in place we won't have a guidewire meaning that the fastest solutions available will be stent-graft implantation (stent covered with a membrane to prevent bleeding) or a call to the surgery unit for bailout surgical closure. Otherwise, in case of unfailed closure with residual bleeding, half the dose of protamine can be added followed by prolonged compression. Also, it is very effective to pull down small Teflon pledgets through the Proglide suture (figure 2). Protamine at full doses can trigger the thrombosis of the arterial system, which is why half the dose of sodium heparin administered is advised. At the end of the procedure, some operators perform control CCTAs via secondary arterial access. However, for the lack of external bleeding, the lack of complications and presence of distal flow can be confirmed on an ultrasound. Regarding secondary access for angiographies while the valve is being placed, some centers select the contralateral femoral access. However, if possible, radial access should always be prioritized since it is associated with a lower risk of bleeding and vascular complications.[6]

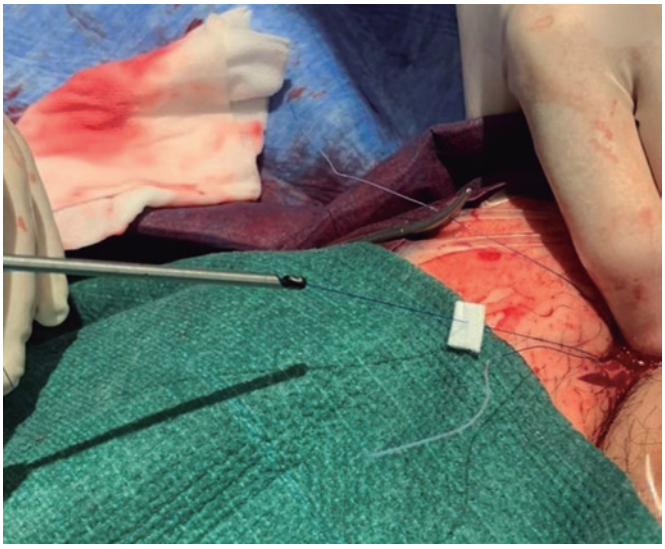

Figure 2. Pull down of Teflon pledgets through a suture of the Proglide device.

Transaxillary access

Axillary/subclavian access should not be used as the priority access in patients with good transfemoral access. Although some studies have shown good results, the Spanish registry showed a higher rate of complications compared to transfemoral access.[7] Therefore, it is considered as the alternative access of choice when the transfemoral one is not good enough.

Overall, left access is the preferred one because it does not share a common origin with the carotid artery, and access looks more like the femoral one because of the greater curvature of the aorta and perpendicularity to the annular view. However, right access is barely used as it's spared for patients with patent left internal mammary artery graft or severe stenosis of the left subclavian artery. Horizontalization of the annular view is ill-advised (> 30° to 45°) since access often occurs through the aorta lesser curvature side and is misaligned with the valve plane.

Same as it happens with transfemoral access planning using CCTA is essential to assess the presence of calcifications, stenosis, and minimum caliber, especially at the origin of the subclavian artery for being the region more prone to atherosclerosis. We should also mention the subclavian artery different histological make-up including a tunica media with more elastic fibers and a thinner adventitia layer compared to the femoral one that includes a tunica media with smooth muscle cells and a thicker and more fibrous adventitia layer.[8] These characteristics turn the subclavian into a fragile artery that is more prone to ruptures or dissections. Access is often attempted using surgical techniques although percutaneous access has been reported in different series.[9] The introducer sheath should not be advanced too much leaving, at least, 5 cm until the valve plane for the correct deployment of the prosthesis. In some cases, a Dacron tube graft can be sutured proximally to the artery and distally to the introducer sheath. Using the percutaneous technique, a radial-femoral loop

should be created before accessing to place an occlusion balloon in case of bleeding or during the device exchange.

Transcarotid access

It's considered as an alternative access of choice in patients without suitable transfemoral accesses in some experienced centers. Although the risk of stroke is similar to that of transfemoral approach, the main risk here is damage to peripheral nerves like the facial or recurrent laryngeal nerves—branch of the vagus nerve—complications reported in up to 2.2% of the cases.[10,11]

Technique that should be used here is basically surgery, and the right side is often used by performing a small 5 cm incision along the anterior border of the sternocleidomastoid muscle. Afterwards, the muscle needs to be retracted for direct exposure and puncture of the artery. Proximal clamp can be used to confirm the presence of collateral circulation and there is often continuous cerebral monitorization during the procedure. Same as it happens with subclavian access, the introducer sheath should not be advanced too much leaving enough space for the correct deployment of the valve.

Transcaval access

Transcaval access has been recently developed for alternative vascular access in percutaneous coronary interventions. Goal here is to prevent the morbidity associated with transthoracic access and add the advantages associated with venous transfemoral access (almost no complications at femoral level and the possibility of conscious sedation). However, this access requires the capacity to perform punctures from the vena cava towards the abdominal aorta through the retroperitoneum and then advance the introducer sheath and the TAVI release system. This step requires meticulous preoperative planning with CCTA. Transcaval access is feasible because the interstitial hydrostatic pressure of retroperitoneal space exceeds venous pressure, which is why the blood that comes out of the abdominal aorta during the procedure returns to venous circulation without accumulating in the retroperitoneum. On the other hand, the abdominal aorta entry zone should not have calcifications to advance the material properly and effectively close this cavoaortic shunt at the end of the procedure using an Amplatzer occluder device (often a VSD Occluder, Abbott Vascular).

The main data on transcaval access come from a multicenter, prospective registry of 100 patients.[12] This registry confirmed a rate of procedural success of 99%, yet rates of potentially fatal hemorrhages and vascular complications of 7% and 13%, respectively. Therefore, to this date, its use is basically marginal.

Direct aortic surgical access

Direct aortic surgical access requires general anesthesia and was developed as an alternative to transapical access to overcome the complications and myocardial damage associated with apical access. It requires partial upper sternotomy towards the second or third right intercostal space. It is barely used today.

Particularities of arterial access in other structural heart procedures

Paravalvular leaks

Paravalvular leak closure is probably one of the most complex techniques out there and with greater heterogenicity among operators. Paravalvular leaks can be divided into aortic and mitral.

Aortic paravalvular leaks

Access is basically retrograde (aorta-ventricle). Therefore, arterial puncture is essential. In most cases, an Amplatzer Vascular Plug 3 device (AVP3) (Abbott Vascular) is implanted. These devices require introducer sheaths between 6-Fr and 7-Fr. The Amplatzer Vascular Plug 4 device is suitable for smaller leaks because it can be advanced through a 4-Fr diagnostic catheter. These procedures can be performed via radial access[13] although most operators rather use the femoral artery to prevent the risk of spasm in cases where significant catheter manipulation is required. Overall, the use of a high-support guidewire in the left ventricle is enough to provide support to advance the delivery catheters. In this sense, high-support guidewires like the ones used in TAVI procedures are advised to prevent left ventricular perforations. Otherwise, the creation of an arteriovenous loop may be required and even an arterioarterial prosthetic loop (especially useful in leaks over self-expanding TAVIs).[14] In both cases, additional specific venous or arterial accesses will be needed. Finally, we should mention that despite the limited size of introducer sheaths, the use of vascular closure systems is advised since we're mostly dealing with patients with mechanical valves who, therefore, need to restart anticoagulation early.

Mitral paravalvular leaks

Most operators use antegrade access (left atrium-ventricle) through a femoral vein and via transseptal access. To perform this technique, it is essential to use good 3D transesophageal echocardiography imaging support plus a catheter with flexion capabilities to guide the latter over the origin of the leak. In most cases, placing a high-support guidewire inside the left ventricle makes the creation of an arteriovenous loop unnecessary (that would require arterial access). Therefore, in most cases, 1 single venous access is often enough. The devices used are often the same ones used in aortic leaks and the necessary catheters have the same size. We should mention that occasionaly mitral leaks require multiple device implantation. If simultaneous implantation of 2 or more devices is required, it may be necessary to perform as many venous accesses as devices will be eventually implanted. Alternatively, mitral paravalvular leaks can be crossed retrogradely (ventricle-left atrium). This technique requires manipulating catheters inside the left ventricle with the corresponding high risk of arrhythmia. It can be an alternative when antegrade crossing becomes complicated, and is easier in posterior compared to anterior leaks (since the guidewire always moves through the aorta). Obviously, this technique arterial puncture and the creation of an arteriovenous loop at left atrium level.

Coarctation of aorta

The percutaneous treatment of choice of coarctation of aorta is stenting. Therefore, large size arterial access is required (10-Fr-to-14-Fr) often via femoral access. The caliber of the femoral introducer sheath depends on the selection of balloons and stents that will eventually be used. Stents can be covered or not. Covered stents are often used for complex coarctations like those with complete obstructions or critical stenoses with risk of rupture, those associated with aneurysms, pseudoaneurysms, ductus arteriosus or diseased wall (bicuspid Valve, Turner). In elderly patients the use of covered stents can cover dissections or ruptures. Apart from the risk of proximal branch occlusion, the setback of using covered stents is that these need sheaths that should be > 3-Fr compared than the ones needed for the balloon. Overall, the sheaths should be 2-Fr-to-3-Fr larger than the minimum size required by the balloon to give the stent enough space to move freely inside.

Regarding femoral arterial access, we should not forget that the arterial vasculature of patients with coarctation of aorta has a smaller than normal diameter in the lower limbs. Also, an additional radial arterial access can be useful for visualization purposes, as well as the angiography during the procedure. Also, to cross critical coarctations or complete occlusions. In rare cases, carotid access can be necessary to reach the descending aorta (neonates, critical stenoses).[15]

Regarding closure, since the sheath is often 12-Fr-to-14Fr, vascular closure with the aforementioned specific devices or else delayed manual compression after heparinization has been reversed is often advised.[16]

Closure of the ductus arteriosus

To perform the closure of ductus arteriosus, the femoral vein and artery are often catheterized. Left and right heart catheterization is advised to register pulmonary and systemic pressures, which is why it is reasonable to use venous access using a 7-Fr introducer sheath. Large sized occlusion devices for ductus arteriosus are also compatible with 7-Fr and often implanted through the venous side, which is why an early 5-Fr arterial access can be planned—often via femoral access—thus, the need for an arteriovenous loop can be anticipated. However, it can also be performed via radial access with a potential reduction of vascular complications. When femoral venous access is not possible (femoral bilateral occlusion or the inferior vena cava) and access underneath the right atrium is preferred (as in the case of the percutaneous closure of ductus arteriosus or interatrial septum defects), the use of other access routes like the transhepatic one have been described.[17]

Regarding the caliber of vascular accesses, we should take into consideration both the technique selected and the type and size of device used. There are 2 different percutaneous treatment options available regarding persistent ductus arteriosus: coils or occlusion devices. If we're dealing with a small ductus (< 4 mm) 1 or several controlled-release coils compatible with small sized catheters (4-Fr) and even microcatheters can be used. For larger ductus, occlusion devices are preferred. They are all self-expandable nitinol coils compatible with 5-Fr-to-7-Fr introducer sheaths depending on their size.

Catheterization of ductus arteriosus is performed via antegrade access (from the pulmonary artery) or retrogradely (from the aorta). If so, an arteriovenous loop is required. In both cases, the device introducer sheath is inserted through the antegrade venous side from where it is implanted. Regarding closure, since these are not large caliber accesses—the largest one being via venous access—manual compression is often performed.

VENOUS ACCESS

Ultrasound-guided venous puncture technique

Transfemoral venous access is the most widely used to perform non-TAVI percutaneous structural heart procedures. Right heart chambers can be accessed via femoral vein. Left heart chambers, however, are accessed through transseptal punctures.

Traditionally, venous puncture has been performed using anatomy-guided references. Experienced operators achieve reasonable rates of success through this method. However, there is a non-negligible chance of complications like inadvertent arterial puncture, venoarterial fistula, pneumothorax (in the internal jugular venous access), nervous lesion or multiple failed catheterization attempts. The risk and the consequences of these complications depend on the type of patients treated. Risk factors like obesity, cachexia, previous radiotherapy or previous surgical scars, among others, can impact the success of catheterization and the appearance of complications.[18]

The safest technique for venous catheterization is ultrasound guided. To identify the vein that should be punctured and establish its association with the accompanying artery pressure with the ultrasound probe should be exerted in such a way that the vein—not the artery—will often collapse (see sections above).

There are 2 techniques available to perform ultrasound-guided venous punctures: the cross-sectional approach (out-of-plane) and the longitudinal one (in-plane).[19] Both have advantages and disadvantages. The former allows us to see, in the same view, the adjacent structures we should avoid during puncture. However, with this approach it is more difficult to see the tip of the puncture needle. Therefore, the angle of the probe should be adjusted to make the views of needle and probe meet. The latter allows us to follow the trajectory of the needle since it first enters the skin until it contacts the target vein. However, the adjacent structures—above all the accompanying artery—cannot be seen in the same view. The target vein can be better seen using the Valsalva maneuver.

Percutaneous closure devices via venous access

Traditionally, venous puncture wound hemostasis has been performed through prolonged manual compression followed by the application of compressive bandage. With the use of larger introducer sheaths to perform structural heart procedures—above all in femoral venous access—safer and more effective methods to achieve hemostasis are under way.

Figure-of-eight subcutaneous suture technique

This technique consists of passing a subcutaneous suture proximally and cross-sectionally to the entry of the venous introducer sheath. Afterwards, the opposite side is crossed, and a subcutaneous suture is performed distally to the sheath entry. Suturing creates a skin and subcutaneous cellular tissue-cinching effect by exerting pressure on the femoral vein. This technique is complemented with mild compressive bandage. A modified technique has been described by performing the subcutaneous suture longitudinally—not cross-sectionally—to the trajectory of the vein looking to minimize the possibility of inadvertent puncture of the vein.[20]

Vascular closure devices

Angioseal has been used via femoral venous access with up to 8-Fr sheaths with good results.[21] The use of percutaneous suture devices like the Proglide has proven safe and effective in the femoral venous access with sheaths of up to 24-Fr.[22] Implantation technique is the same as the one used in the artery (see sections above). Depending on the result of the closure, it can be combined with the subcutaneous «figure-of-eight» suture in cases when early hemostasis is not complete. It is often completed with mild compressive bandage.

Particularities of percutaneous mitral valve repair

The most widely used percutaneous coronary intervention on the mitral valve is the so-called «edge-to-edge» repair using the MitraClip (Abbott Vascular, United States) or Pascal devices (Edwards

Lifesciences; United States). However, there are direct annuloplasty devices available that replicate a similar repair compared to the surgical one. Also, other transcatheter mitral valve repair options are being developed—some of them completely percutaneous—with good results.

The most widely used vascular access regarding percutaneous coronary interventions on the mitral valve is the femoral vein given its caliber, accessibility, and how easy it is to close after the procedure has been completed. Selecting the left or the right femoral vein depends on the patient's clinical circumstances (having 2 accesses available, previously operated vascular disease in either one of the 2 accesses, etc.), and the operator's preference regarding implantation. Therefore, the most widely used access is the right femoral vein that is more comfortable for the operator and uses less radiation.

The possibility of performing implantation via right jugular access has been reported. However, only anecdotal cases have been published due to the difficulties associated with femoral access like the presence of an occluded filter in the inferior vena cava or very sharp angulations of venous iliofemoral axis.[23] Technically, implantation is more difficult and has multiple considerations although puncture is basically the same as the routine one.

Ultrasound-guided venous puncture limits its possible complications and should be generalized. In most cases, preclosure devices are implanted before starting the procedure. After inserting a high-support guidewire until the superior vena cava (or inferior if access is jugular) access dissection with forceps is attempted followed by access predilatations with different caliber dilators. Then, the guide catheter is advanced until it reaches the right atrium. Its advance is less complicated compared to the arterial access and with less resistance too. The caliber of the MitraClip guide catheter can be up to 24-Fr—22-Fr with the Pascal device for valve implantation (mitral or aortic in the mitral position)—varies depending on the type of device that should be implanted.

Particularities of tricuspid valve interventional procedures

Percutaneous coronary interventions of the tricuspid valve have evolved over the last decade acting efficiently on leaflet coaptation with suture or ring annuloplasties and eventually with orthotopic or heterotopic percutaneous valve repair.[24]

The access most widely used is venous access via femoral or jugular vein or both. Depending on the type of procedure used, an additional venous or arterial access or should be attempted—preferably radial—given its lower rate of vascular complications.

Currently, the most widely used device to treat tricuspid regurgitation is the TriClip device (Abbott Vascular) since it was awarded the CE marking back in 2020. With the development of the specific TriClip device—that has a specific wheel to distance itself from the interatrial septum—the right or left venous access does not affect implantation. Therefore, most operators use the right femoral vein as the access route.[25]

Regarding the implantation of orthotopic or heterotopic valves, access of choice is right femoral access with different calibers depending on the device that should be used (between 14-Fr and 30-Fr).

Particularities of interventional pulmonology procedures

Percutaneous coronary interventions on the pulmonary valve or artery always require a highly variable venous access in its diameter depending on the technique that should be used. Access via femoral vein is the most common one. Therefore, increasing the size of introducer sheaths is not such a big deal as it is the case with arterial accesses.

Percutaneous pulmonary valve implantation requires the use of 16-Fr-to-22-Fr introducer sheaths depending on the model. In many cases, high-support guidewires are required to rectify curvatures in the trajectory of right heart chambers.

Acute treatment of pulmonary thromboembolic disease requires the use of thrombus extraction systems. Since the main determinant of the system that should be used is the size of target thrombus and since the pulmonary artery can accommodate large thrombi, some systems required large caliber accesses. For example, the Penumbra system (Penumbra Inc, United States) can navigate through 8-Fr, Nautilus system (iVascular, Spain) through 10-Fr, and the Flowtriever system (Inari Medical Inc, United States) through 16-Fr-to-24 Fr.

In other cases of more distal thrombectomy or pulmonary angioplasty in chronic thromboembolic disease much smaller introducer sheaths are required (6-Fr-to-7-Fr). Guide catheter extension systems (catheters inside catheters) can be very useful in some cases of difficult access and may require larger introducers sheaths.

Particularities of the left atrial appendage closure

Percutaneous closure of left atrial appendage is often performed via femoral venous access. Some operators perform an additional arterial access to monitor arterial pressure invasively. This arterial access should be performed via radial access to reduce hemorrhagic complications. In some cases, the guidewire is performed with intracardiac ultrasound guidance. In this case, an additional venous femoral access is required.

A key aspect to select the caliber of the venous introducer sheath through which the device should be implanted is the type and size of the introducer sheath. The most widely used devices in our setting are the Amplatzer/Amulet (Abbott Vascular), the Watchman (Boston Scientific, United States), and the Lambre (Lifetech, China).[26] Size of introducer sheaths goes from 8-Fr-to-10-Fr (with Lambre) up to 12-Fr-to-14-Fr (with Amulet and Watchman Flx).

Regarding vascular closure, most operators still use manual compression or «figure-of-eight» suture for venous access. However, the aforementioned vascular closure devices can also be used.

Particularities of venous access in other structural heart procedures

There are other structural heart procedures that require venous access, mainly via femoral vein. Some of the most prevalent ones are the closure of patent foramen ovale and interatrial communications. In some cases, these are intracardiac ultrasound-guided procedures, meaning that they require an additional venous femoral access. There are several devices manufactured by different companies to close these entities. However, the most common ones are the Amplatzer PFO occluder, the Amplatzer ASD occluder, and Gore devices, above all, the Gore Cardioform device (WL Gore & Associates, United States). In case of the Amplatzer devices, 8-Fr-to-12-Fr introducer sheaths are required. The Gore system requires short 11-Fr introducer sheaths that are already pre-mounted on a delivery sheath. Overall, the rate of vascular complications is low since these are often young patients who require 1 single femoral venous access only. In case of inferior vena cava occlusion, jugular vein implantation has been reported.[27]

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All the authors contributed to the manuscript draft and critical review.

CONFLICTS OF INTEREST

X. Freixa is a proctor for Abbott Medical. R. Romaguera is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. Also, he is a proctor for Boston Scientific and has received conference fees from Medtronic. R. Trillo is a proctor for Medtronic and Boston Scientific. A. Jurado-Román has received conference fees from Boston Scientific.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000331.

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REC Interv Cardiol. 2022;4(4):319-328
https://doi.org/10.24875/RECICE.M22000328

Review article

Coronary physiology at the cath lab◊

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RESUMEN

El estudio de la fisiología coronaria ha pasado de ser una técnica de investigación hace algunos años a convertirse en una herramienta necesaria para el abordaje óptimo de los pacientes con enfermedad coronaria epicárdica y para evaluar la microcirculación. La realización de estas técnicas requiere el uso de una guía de presión para la que hacen falta medios técnicos, tiempo y práctica en su ejecución, y es en parte por ello que su utilización es baja. Existe la necesidad de conocer la evidencia actualizada, las técnicas disponibles y la forma idónea de aplicarlas para ofrecer el mayor beneficio a los pacientes. Esta revisión ofrece un resumen práctico sobre el estado actual de los estudios de fisiología coronaria, con el fin de facilitar el mejor uso posible de esta herramienta diagnóstica esencial.

Palabras clave: Enfermedad coronaria. Fisiología coronaria. Angina microvascular.

Fisiología coronaria en el laboratorio de hemodinámica

ABSTRACT

The study of coronary physiology has evolved from a research topic to a necessary component for the optimal management of patients with coronary artery disease when assessing both epicardial and microvascular coronary segments. The performance of these techniques requires the use of pressure wires with additional supporting systems, time, and practice, which explains the overall low rate of usage. It is essential to know the updated evidence, the techniques available, and how to perform them properly to offer the greatest possible benefit to our patients. This review provides a practical overview on coronary physiology, and it is ultimately aimed at improving the quality of care.

Keywords: Coronary artery disease. Coronary physiology. Microvascular angina.

Abbreviations

FFR: fractional flow reserve. **iFR:** instantaneous wave-free ratio. **IMR:** index of microcirculatory resistance. **Pd/Pa:** distal to aortic coronary pressure. **QFR:** quantitative flow ratio.

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◊ Part of the content of this article has been previously published on the official website of the Latin American Society of Interventional Cardiology (SOLACI): https://proeducar.solaci.org/es/blog/post/fisiologia-coronaria.

Received 25 April 2022. Accepted 1 July 2022. Online: 02-09-2022.

INTRODUCTION

For decades angiography has been used as the reference procedure to diagnose coronary artery disease. However, this technique spares the physiological repercussion of epicardial coronary stenoses. Thus, by the end of the 20th century the functional characterization of coronary circulation thanks to the development of various tools both invasive (specific intracoronary guidewires) and non-invasive (angiography-derived indices) started gaining interest. The result was a change of paradigm in the diagnosis and management of coronary artery disease from an angiography to an ischemia-based strategy.[1] This has become possible thanks to the abundant scientific evidence available supporting the use of physiological indices leading the ischemia-based strategy to the highest level of recommendation in the latest European guidelines on the management of myocardial revascularization.[2] However, the recent publication of some clinical trials has put into question the impact of coronary physiology in certain clinical settings like multivessel disease and ST-segment elevation acute coronary syndrome (STEACS).[3,4] On the other hand, these techniques take time, the use of coronary invasive instruments and, at times, the administration of vasodilators that are not always well tolerated by the patients. Also, a certain clinical experience is required. For all this, the adoption of physiology techniques to guide revascularization is still far from overall implantation.[5]

Over the following paragraphs we'll be taking a practical approach on the physiological assessment of coronary stenosis and microcirculation using invasive and angiography-derived indices. Details of the physiological concepts behind every index will be left out or specific texts will be pointed out for that matter.

Physiological assessment of coronary stenoses

Invasive indices

Coronary fractional flow reserve (FFR) index is the ratio of maximum myocardial blood flow in the presence of a single stenosis with respect to the anticipated normal flow for the lack of stenosis; it is expressed as a fraction of its normal anticipated value. It is obtained by measuring intracoronary pressure with guidewires specifically designed for that matter. Determining FFR requires the vasodilation of microcirculation by using drugs, adenosine mainly—IV regadenoson and intracoronary nitroprusside have been used with similar results.[6] Also, the measurement of minimal distal to aortic coronary pressure ratio (Pd/Pa) after the injection of intracoronary contrast (cFFR).[7] Therefore, it is a hyperemic coronary physiological index. It is based on the fact that, in a situation of maximum hyperemia, a linear correlation between relative flow and relative intracoronary pressure is achieved since coronary resistance is both stable and minimum.[8] Its result is independent of microcirculation, heart rate, arterial blood pressure, and other hemodynamic variables. The European guidelines on the management of chronic coronary syndrome give FFR an indication I, Level of Evidence A, for risk stratification in symptomatic patients who are unresponsive to medical therapy and asymptomatic patients in whom non-invasive tests show a high risk of events, and an indication type IIa when the results of non-invasive tests are inconclusive.[1]

A summary of the FAME trials (Fractional flow reserve vs angiography for multivessel evaluation) is shown on table 1.[4,9-11] These results reinforce the need for studying the physiology field and individualizing the management of our patients inside the heart team.

Hyperemia, especially the one obtained with IV adenosine—needed to obtain FFR—takes time, is expensive, changes systemic hemodynamics, and can cause unpleasant side effects (conduction disorders, chest pain, nausea, dyspnea, dizziness, flashing, and headache). Therefore, after its arrival, resting indices—that do not require hyperemic drugs—soon gained popularity. Overall, these indices are phasic—unlike FFR that is rather based on mean pressures—and are measured in the middle or late portion of the diastolic period when there is a greater transstenotic flow naturally.[6] Although the first description of a resting index was given by Grüntzig in his early publication of coronary angioplasty,[12] its clinical use did not become popular until the appearance of the instantaneous wave-free ratio (iFR, Philips, The Netherlands). Several studies were conducted to compare the diagnostic concordance of iFR and FFR, as well as iFR, FFR, and other reference parameters of ischemia.[13,14] Two multicenter randomized clinical trials—the DEFINE-FLAIR (Functional lesion assessment of intermediate stenosis to guide revascularization) and the iFR-SWEDEHEART (Evaluation of iFR vs FFR in stable angina or acute coronary syndrome)—randomized 4529 patients to receive FFR or iFR-guided percutaneous revascularization in both patients with ACS and chronic coronary syndrome.[15,16] Both studies demonstrated the non-inferiority of the iFR compared to the FFR with low rates of events defined as all-cause mortality, acute myocardial infarction or unplanned revascularization at 1 year: iFR, 4.12% vs FFR, 4.05%; hazard ratio (HR), 1.13; 95% confidence interval (95%CI), 0.72-1.79; $P = .60$). Also, in the iFR groups, the number of functionally significant stenoses and rates of revascularization were lower, procedural time was shorter, and there were fewer patients with adverse symptoms associated with the administration of adenosine.[15,16] Over the last few years, several resting indices have been developed based on the concept previously described: DFR (diastolic hyperemia-free ratio, Boston Scientific, United States),[17] and the resting diastolic pressure ratio (dPR) (ACIST, United States).[18,19] Except for the resting full-cycle ratio (RFR) (Abbott, United States),[18] that is a non-hyperemic index to assess pressure along the entire cardiac cycle (table 2), all resting indices are highly reproducible, and identical to iFR both numerically and in their concordance with FFR.[19] The prognostic capability of the Pd/Pa ratio is less robust compared to the FFR[21] since its correlation with FFR in non-culprit lesions of patients who had an ACS is 80%;[22] after the arrival of non-hyperemic indices, its clinical significance is scarce.

Supplementary data provides a detailed description on the practical management of invasive physiological indices.

Procedure

Figure 1 shows the steps needed to measure resting indices and FFR. Supplementary data gives a step-by-step detailed description. Figure 2 shows the utility of pressure guidewires for the diagnosis and location of significant stenoses.

Problems, causes, solutions, and specific settings

Table 3 shows some of the main problems that can be found when performing pressure guidewire studies, their causes, and possible solutions. Supplementary data provides a detailed description on how to deal with these problems, and a description on the use of pressure guidewire in different clinical settings (diffuse coronary artery disease, ostial lesions, aortic stenosis, ACS, post-angioplasty assessments).

Angiography-derived indices

The physiological study of epicardial stenoses is limited in the routine clinical practice due to the need for pressure guidewires

Table 1. Summary of results from the FAME trial

Study	Year	N	Population	Comparison	Follow-up	Primary endpoint	Death	Myocardial infarction	New revascularization	Other results
FAME[9]	2009	CCS: 677 UA: 328	Stenosis ≥ 50% in 2 or more vessels, eligible for PCI	PCI with angiography-guided vs FFR-guided DES (≤ 0.80)	1 year	Death, AMI, new revascularization: 13.2% vs 18.3%; HR, 0.72; 95%CI, 0.54-0.96	1.8% vs 3.0%; HR, 0.58; 95%CI, 0.26-1.32	5.7% vs 8.7%; HR, 0.66; 95%CI, 0.42-1.04	6.5% vs 9.5%; HR, 0.68; 95%CI, 0.45-1.05	No differences in the events reported separately No differences in the rate of angina reported Less use of resources with FFR
FAME 2[10]	2012	CCS: 888	≥ 1 stenosis in 1 epicardial coronary artery with FFR ≤ 0.80	PCI with second-generation stents and OMT vs OMT	7 months (mean)	Death, AMI, emergency revascularization: 4.3% vs 12.7%; HR, 0.32; 95%CI, 0.19-0.53	0.2% vs 0.7%; HR, 0.33; 95%CI, 0.03-3.17	3.4% vs 3.2%; HR, 1.05; 95%CI, 0.51-2.19	Emergency: 1.6% vs 11.1%; HR, 0.13; 95%CI, 0.06-0.30 Non-emergency: 1.6% vs 8.6%; HR, 0.17; 95%CI, 0.08-0.39	No significant differences in the composite of death and AMI or cardiac death
FAME 2 – 5 years[11]	2018	CCS: 888	≥ 1 stenosis in 1 epicardial coronary artery with FFR ≤0.80	PCI with second-generation stents and OMT vs OMT	5 years	Death, AMI, emergency revascularization: 13.9% vs 27.0%; HR, 0.46; 95%CI, 0.34-0.63	5.1% vs 5.2%; HR, 0.98; 95%CI, 0.55-1.75	8.1% vs 12.0%; HR, 0.66; 95%CI, 0.43-1.00	Emergency: 6.3% vs 21.1%; HR, 0.25; 95%CI, 0.18-0.41 Non-emergency: 7.6% vs 35.1%; HR, 0.18; 95%CI, 0.12-0.26	No significant differences regarding death and AMI The percentage of patients with angina is lower within the first 3 years being this difference non-significant at 5 years
FAME 3[4]	2022	CCS: 1500	3-vessel disease	Non-inferiority design: FFR-guided PCI (≤ 0.80) vs coronary revascularization surgery	1 year	Death, AMI, stroke. new revascularization: 10.6% vs 6.9%; HR, 1.5; 95%CI, 1.1-2.2; *P* = .35 for non-inferiority	1.6% vs 0.9%; HR, 1.7; 95%CI 0.7-4.3	5.2% vs 3.5%; HR, 1.5; 95%CI, 0.9-2.5	5.9% vs 3.9%; HR, 1.5; 95%CI, 0.9-2.3	No significant differences in the composite endpoint of death, infarction, stroke Less major bleeding, kidney damage, AF, and rehospitalization at 30 days with PCI

95%CI, 95% confidence interval; AF, atrial fibrillation; AMI, acute myocardial infarction; CCS, chronic coronary syndrome; DES, drug-eluting stent; FAME, fractional flow reserve vs angiography for multivessel evaluation; FFR, fractional flow reserve; HR, hazard ratio; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; UA, unstable angina.

Table 2. Indices used to study epicardial coronary stenoses

	Vasodilation	Period of cycle	Cut-off value	Scientific evidence
FFR	Hyperemic	–	≤ 0.80	RCTs: FAME, FAMEII, FAME III, DEFER, DANAMI-3-PRIMULTI, COMPARE ACUTE, FLOWER-MI, FUTURE
iFR	Non-hyperemic	Diastolic	≤ 0.89	RCTs: DEFINE-FLAIR, iFR-SWEDEHEART Observational: SYNTAX II
DFR	Non-hyperemic	Diastolic	≤ 0.89	Observational: Johnson et al.[14]
dPR	Non-hyperemic	Diastolic	≤ 0.89	Observational: Lee et al.,[15] Van't Veer et al.[16]
RFR	Non-hyperemic	The full cycle	≤ 0.89	Observational: Lee et al.[15]
Pd/Pa	Non-hyperemic	The full cycle	0.91-0.93	Observational: Kobayashi et al.,[20] Lee et al.[15]

DFR, diastolic hyperemia-free ratio; dPR, resting diastolic pressure ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; Pd/Pa, distal to aortic coronary pressure ratio; RCT, randomized clinical trials; RFR, resting full-cycle ratio.

and, in some cases, hyperemic agents that take up higher costs and possible side effects.[23] Therefore, new angiography-derived indices like QFR, angio-FFR, CAAS-vFFR, and vFFR have been produced. These are based on 3D reconstructions of coronary tree through the angiography and then computational flow dynamics software or mathematical simplifications of it as a surrogate of coronary flow.

QFR (quantitative flow ratio; Qangio XA 3D, Medis Medical Imaging Systems, The Netherlands) uses a 3D reconstruction of the angiography. Afterwards, assuming a constant pressure and velocity of flow along a normal epicardial vessel, a proxy of the FFR value is estimated using different models: the fixed model (fQFR) uses information from a database from which FFR values and flow velocities have been previously obtained; the contrast-QFR

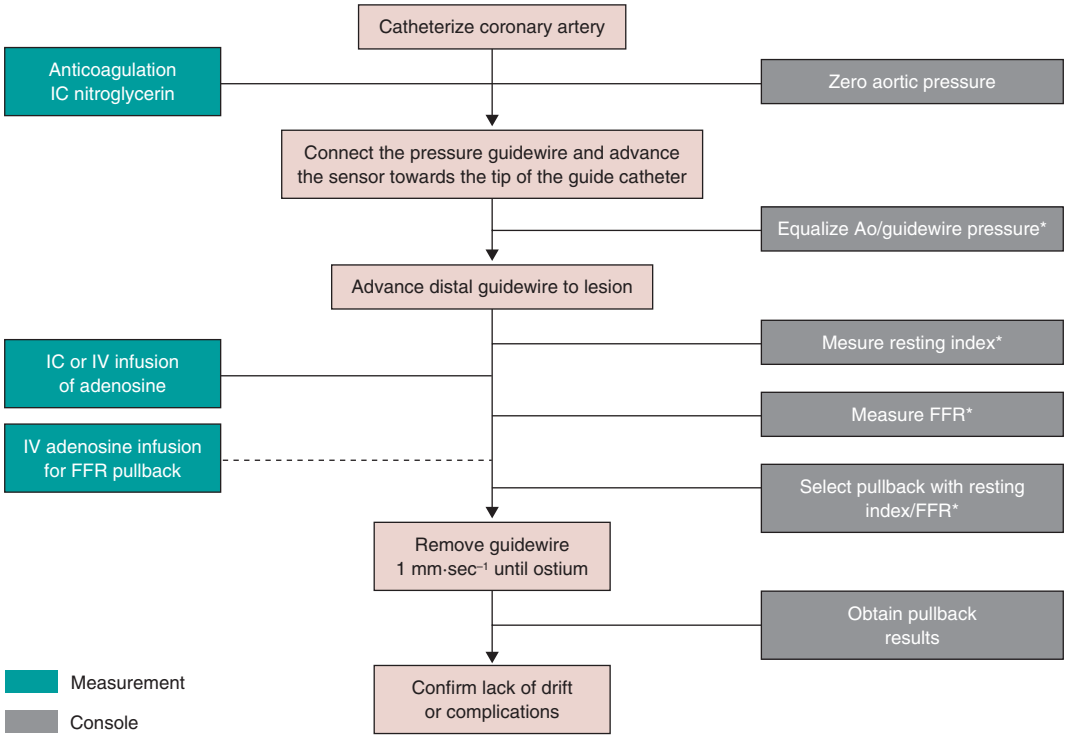

Figure 1. Steps to use intracoronary pressure guidewire to measure resting indices and fractional flow reserve. Ao, aorta, FFR, fractional flow reserve; IC, intracoronary; IV, intravenous. * Catheter purged with saline solution and no guidewire introducer sheath.

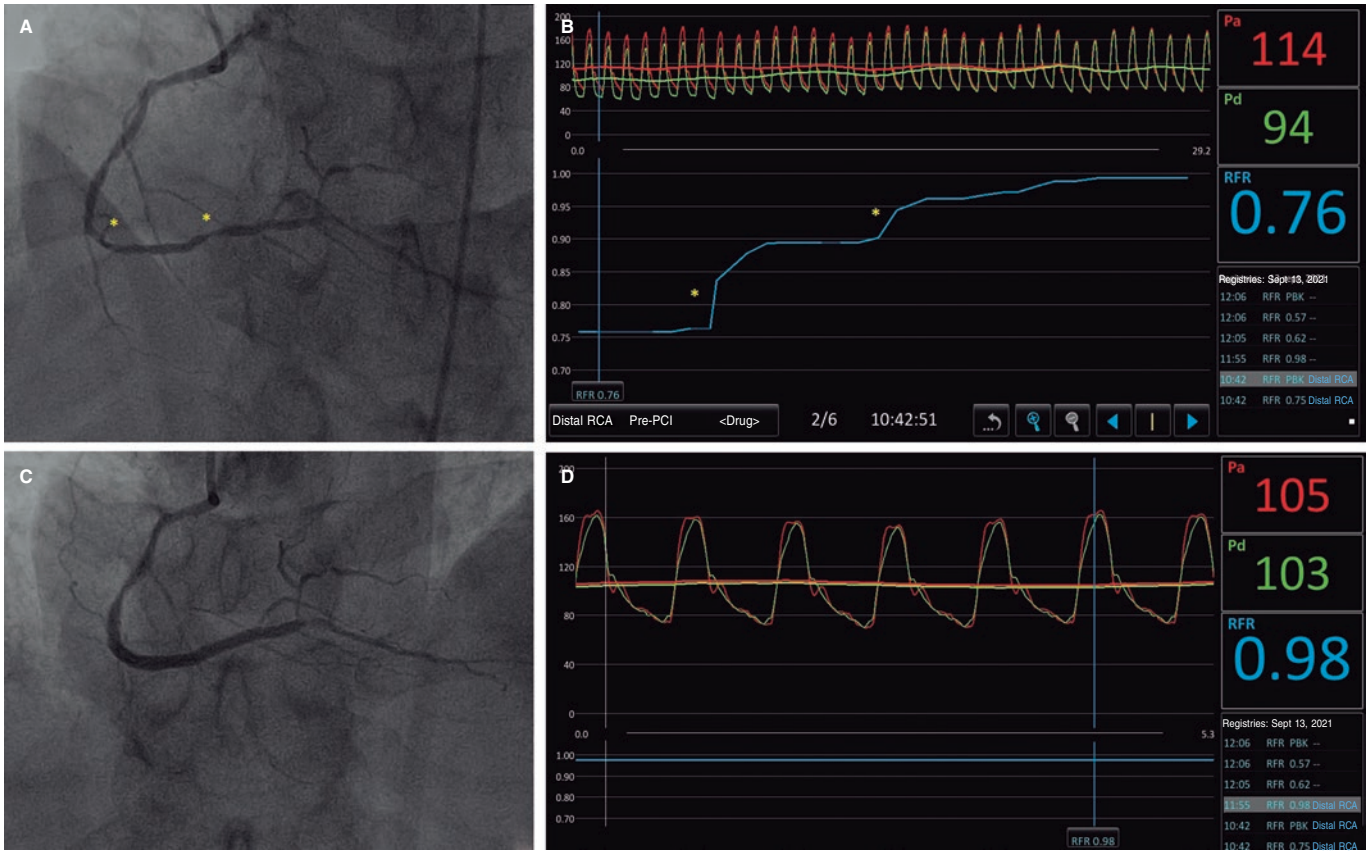

Figure 2. **A:** angiography of right coronary artery showing diffuse damage with more severe lesions at distal level (asterisks). **B:** pullback resting full-cycle ratio (RFR) measurement showing 2 focal jumps corresponding to the asterisks shown on **A. C:** final angiographic outcomes after implantation of 2 drug-eluting stents. **D:** final RFR with optimal result of 0.98.

Table 3. Pressure guidewire: main problems, causes, and possible solutions

Problem	Cause	Recommendations
Aortic pressure damping	Catheter/vessel mismatch Ostial lesion	Use a guide catheter of a smaller diameter Disengage the ostium to take better measurements
Falsely reduced aortic pressure	Loose connections of the guide catheter Avoid removing the guidewire introducer sheath Presence of contrast in the catheter	Double check all connections before taking any measurements Always remove the guidewire introducer sheath Purge the guide catheter with a saline solution
Loss of drift	Need for multiple connections/disconnections Prolonged procedure	Repeat equalization and measurement Equalizing should precede any measurements after the PCI Use fiber optic guidewires if prolonged procedure is anticipated
Spasm, pseudostenosis	Presence and manipulation of intracoronary guidewire Excessive tortuosity	Always administer IC nitrates before the procedure Additional dose of IC nitrates if suspected pseudostenosis Consider alternative methods in case of excessive tortuosity
Scarce response to adenosine	Use of caffeine, theobromine (chocolate), theophylline Inappropriate intracoronary administration	Talk to the patients and tell them that the use of coffee/chocolate/theophylline is ill-advised 24 hours before the procedure IC administration or IV perfusion of adenosine at 210 µg/kg/min Guarantee proper catheterization for the administration of IC adenosine Neve use IC adenosine with a catheter with lateral holes
Excessive measurement variability	Patient moving Arrythmias (AF)	Make sure that the patient is comfortable Repeat measurement in the presence of cough or sudden moves Select measurement sites manually on the console

AF, atrial fibrillation; IC, intracoronary; IV, intravenous; PCI, percutaneous coronary intervention.

model (cQFR) takes into account the flow velocity of the contrast injected into the epicardial artery by counting frames; and the QFR-adenosine model (aQFR) that studies it after inducing hyperemia through the administration of adenosine. The 3 models were tested against FFR, and the best diagnostic accuracy was obtained with the QFR-adenosine (87%) and cQFR (86%) models.[24] Several studies conducted later have demonstrated the utility and high accuracy of this model for the functional diagnosis of epicardial stenosis,[25,26] and how safe the revascularization decision is based on such model.[27,28] The FAVOR III China trial of 3825 patients confirmed fewer major adverse events (HR, 0.65; 95%CI, 0.51-0.83; $P = .0004$) in patients with delayed revascularization based on QFRs ≤ 0.80 triggered by fewer myocardial infarctions and ischemia-guided revascularizations compared to angiography-guided revascularizations.[28]

Another index is the CAAS-VFFR (Cardiovascular angiographic analysis system for vessel FFR, CAAS-vFFR, Pie Medical, The Netherlands). It is based on a 3D reconstruction of the angiography acquired followed by an estimate of the pressure gradient through a lesion. Its validation study included patients with stable disease and non-ST-segment elevation acute coronary syndrome and showed a 93% accuracy for the diagnosis of lesions with FFR ≤ 0,80, and a 95% inter-observer correlation.[29]

Angio-FFR index (Cathworks, Israel) is also widely used. Unlike the former indices presented above, it uses, at least, 3 different angiographic views to sketch a 3D functional angiography mapping. Fearon et al.[30] studied it in a large population and confirmed sensitivity, specificity, and diagnostic accuracy values of 94%, 91%, and 92%, respectively for FFR ≤ 0.80 with 96% high inter-observer consistency.

Other indices like the vFFR (virtual fractional flow reserve, VirtuHeart Medical Physics Group, United Kingdom) demonstrated, in its validation study, high diagnostic accuracy, sensitivity, and specificity of 97%, 86%, and 100%, respectively.[31] This index, however, is still in the pipeline.

Recently, a meta-analysis conducted by Collet et al.[32] demonstrated that angiography-based FFR measurements have an overall sensitivity and specificity of 89% and 90% compared to invasive FFR. However, there can be a relatively large gray area (0.75-0.86) where the invasive determination of FFR could be indicated.[33] Assuming this gray area, the diagnostic accuracy of these methods could be > 95% like the FAVOR II China trial proved,[25] preventing the need for an invasive study in 64% of the lesions.[34]

Despite the promising results obtained, these analyses have certain limitations. One of the main ones is to obtain proper angiographies for analysis without structure panning or overlapping.[35] Another one is anatomy since the contouring of ostial or bifurcation lesion borders is more difficult to achieve meaning that its study may be biased. In a recent analysis on the population of the SYNTAX II trial, QFR assessment vs hybrid iFR/FFR assessment demonstrated a diagnostic accuracy of QFR close to 74% with a 8.3% rate of false positives and a 17.9% rate of false negatives being the main reasons for this mismatch the lesions found in marginal branches, small vessels or bifurcation regions.[35] Also, the state of microcirculation is especially interesting since these techniques assume maximum vasodilation to estimate pressure from the flow obtained. However, the degree of response to hyperemia—whether due to contrast or pharmacological agents—is variable based on each patient's state of microcirculation and, therefore, subject to error. Mejía-Rentería et al.[36] reported on how the state of microcirculation impacts this type of non-invasive assessments of coronary flow reserve (CFR), and saw that the greatest source of mismatch came from an impaired microvascular function measured as an impaired value of the index of microcirculatory resistance (IMR) or situation of acute myocardial infarction. One could think that image processing time and its analysis can be longer compared to the physiological study using pressure guidewires. However, if trained, it has been confirmed that the study can be conducted faster compared to the traditional determination of FFR.[37,38] Finally, a pending limitation that needs solving is observer-dependent variability (0.01 ± 0.08 match for repeat measurements), the quality of angiography, and the degree of FFR-based stenosis.[39]

Supplementary data provides a detailed description on the practical management of QFR, angio-FFR, and vFFR.

Physiological assessment of coronary microcirculation

Invasive indices

Although coronary artery disease is often associated with damage to epicardial arteries, up to 25% of the patients with typical angina do not show significant epicardial stenoses.[1] Microvascular dysfunction is a contributing factor of angina and individualized treatment has proven to improve the patients' quality of life,[40] which is why a proper intracoronary diagnosis of microvascular disease in symptomatic patients without stenosis or with moderate coronary stenoses has a recommendation IIa in the European guidelines on the management of chronic coronary syndrome.[1]

Arterioles, the main component of coronary vascular resistance, plays a very dynamic role in coronary blood flow and are regulated by multiple metabolic, myogenic, endothelial, neural, and hormonal mechanisms.[41,42] Impaired microcirculation can occur through any of these pathways and bring about unfavorable prognosis similar to that of obstructive epicardial disease.[43] The size of these vessels complicates their angiographic assessment, and the use of other methods is essential. CFR measures the ratio of coronary flow in hyperemia compared to resting flow with normal values between 3 and 4 indicative that coronary flow increases by a factor of 3 or 4 with maximum hyperemia. CFR results represent the capacity to increase flow both of epicardial arteries and microvasculature. Reduced CFR is associated with a significant increase of mortality (HR, 3.78; 95%CI, 2.39-5.97), and major adverse cardiovascular events (HR, 3.42; 95%CI, 2.92-3.99) in multiple diseases including patients with ACS, microvascular dysfunction, heart transplant, and diabetes mellitus.[44]

Microcirculatory resistance can be measured through thermodilution or intravascular Doppler ultrasound in baseline conditions or in hyperemia.[45] The IMR—reference index to study microcirculation—is based on measuring distal pressure and coronary flow through thermodilution as assessed by the inverse of the arrival (transit) time of a room temperature saline solution bolus to the artery distal segment during maximum hyperemia. High IMR > 25 is associated with poor cardiovascular prognosis; the combination of low CRF and high IMR is associated with worse prognosis.[46,47] Recently, a new method based on thermodilution and a continuous flow of saline solution (RayFlow catheter, Hexacath, France) to estimate absolute coronary flow in hyperemic conditions and absolute microvascular resistance[48,49] has been described. Its advantage is that it does not depend on baseline values, which lowers the significance of hemodynamic changes. It does not depend on the operator either. Its clinical utility still needs to be proven given the limitation interpreting absolute values.

The Doppler guidewire estimates the CRF by dividing flow velocity in hyperemia by the baseline flow velocity. Cut-off values of ≤ 2.5 are consistent with a diagnosis of microvascular dysfunction in healthy epicardial arteries.[50] The prognostic value of CRF measured invasively through Doppler in patients with angina is independent from the findings of non-invasive modalities with a 5-year HR of 2.97 (95%CI, 1.39-6.34) for major adverse cardiovascular events.[51] Hyperemic microvascular resistance (HMR) can also be estimated by dividing intracoronary pressure by hyperemic flow velocity considering that HMR > 1.9 $mmHg \cdot cm^{-1} \cdot s^{-1}$ is diagnostic of microcirculatory dysfunction.[50] However, it has been reported that HMR ≥ 2.5 $mmHg \cdot cm^{-1} \cdot s^{-1}$ has better sensitivity and specificity for the diagnosis of microvascular dysfunction.[52]

Practical approach

Thermodilution

Supplementary data provides a detailed description on the practical management of thermodilution both through boluses (figure 3) and continuous perfusion (figure 4), as well as physiological study using Doppler guidewires (figure 5).

Angiography-derived indices

Although assessing the state of microcirculation using the IMR has largely proven its clinical benefit,[50,53] its study in the routine clinical practice is limited since pressure guidewires and hyperemic agents are needed. Therefore, recently, different alternatives have been developed to estimate the angiography-derived index of microvascular resistance (IMRangio) using computational fluid dynamics. Several formulae can be used.

The first description was given by De Maria et al.,[54] who saw the good diagnostic capabilities (92.4%) of IMRangio vs invasive IMR using a different QFR-adenosine formula in patients with myocardial infarction, and a high correlation between a high value on the IMRangio and the presence of microvascular obstruction as seen on the magnetic resonance imaging.

IMRangio has been studied in both stable patients and patients with ACS[55] obtaining a good correlation between IMR and IMRangio and a high diagnostic accuracy of the latter when used with adenosine in patients with ACS and stable patients. However, it was seen that the correlation between IMR and cQFR-derived IMRAngio (NH-IMRangio) did not hold up in non-culprit arteries of the acute event or in cases of greater clinical stability only showing a good correlation in the infarction culprit arteries. Authors think that a possible explanation to this phenomenon would be the greatly impaired vasodilator capability of patients with ST-segment elevation acute myocardial infarction. Therefore, they proposed a hybrid algorithm by means of which it would only be necessary to use adenosine in cases with NH-IMRangio levels > 30 U and < 90 U, which would stop the use of adenosine in 38% of the cases. Also, in cases of ST-segment elevation acute myocardial infarction—where maybe the use of hyperemia may be more limited due to the clinical situation—this group showed that NH-IMRangio levels > 43 could detect IMR values > 40 very precisely and be predictor of long-term events[56] without having to use adenosine.

Tebaldi et al.[57] use a formula based on the cQFR value (NH-IMR-angio) to assess the state of microcirculation in patients with stable angina finding a high correlation between IMRangio > 44.2 and invasive IMR > 25.

Parallel to this, another group used a different formula including the cQFR value[58] to assess microvascular function in patients with chronic and acute coronary syndrome that confirmed a good overall diagnostic accuracy. Also, this group proved it could have an added value to reduce the rate of false positives of QFR since an impaired microvascular function can affect the accuracy of the QFR study.[36] Recently, a meta-analysis of aggregate data demonstrated the good diagnostic performance of IMRangio compared to invasive IMR, with sensitivity, specificity, accuracy, positive predictive, and negative predictive values of 82%, 83%, 83%, 76%, and 85%.[59]

FlashAngio (Rainmed, China) is yet another software to determine non-invasive IMR,[60,61] with similar diagnostic results. Added to its diagnostic value, Choi et al.[61] proved the prognostic value of such index, since high IMRangio levels (< 40 U) were associated with cardiac death and rehospitalization due to long-term cardiovascular problems.

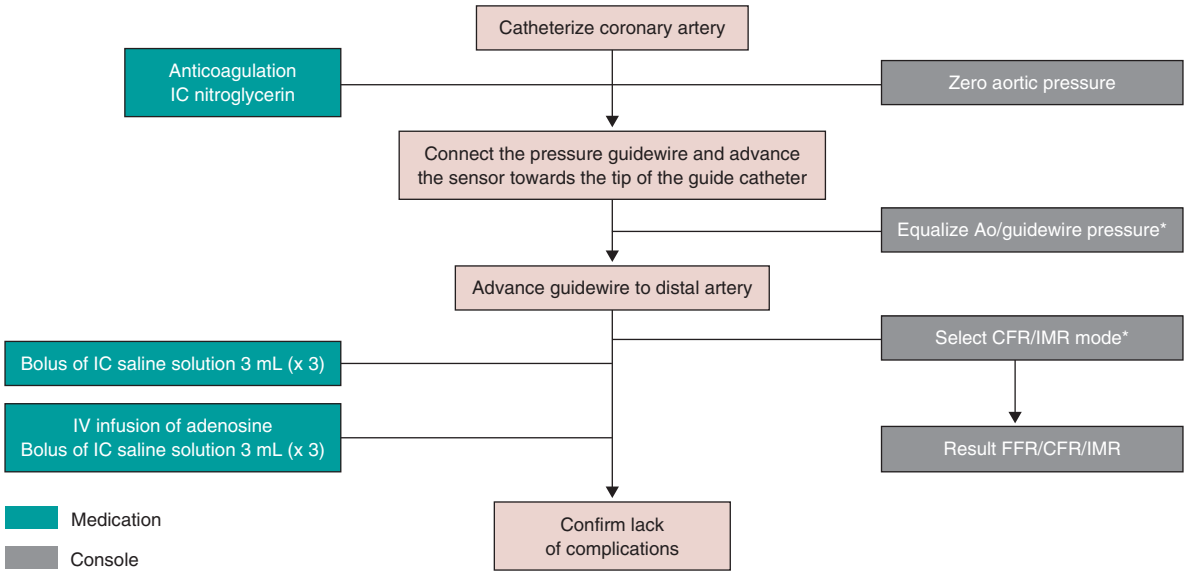

Figure 3. Steps for the study of microcirculation with bolus thermodilution. Ao, aorta; CFR, coronary flow reserve; FFR, fractional flow reserve; IC, intracoronary; IMR, index of microcirculatory resistance; IV, intravenous. * Catheter purged with saline solution and no guidewire introducer sheath.

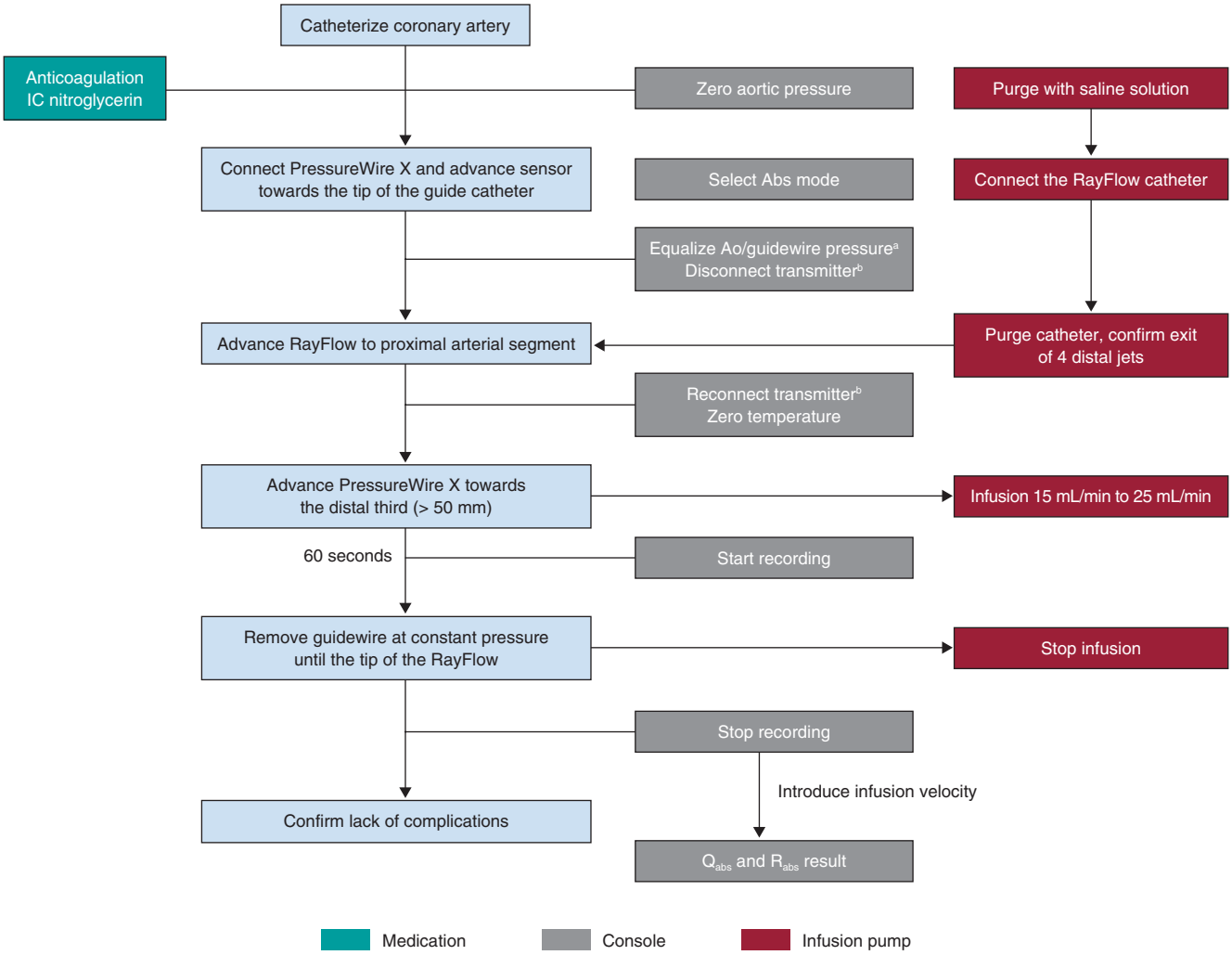

Figure 4. Steps for the study of microcirculation with continuous thermodilution. Ao, aorta, IC, intracoronary; IV, intravenous. [a] Catheter purged with saline solution and no guidewire introducer sheath. [b] Do not switch the transmitter of during the entire procedure.

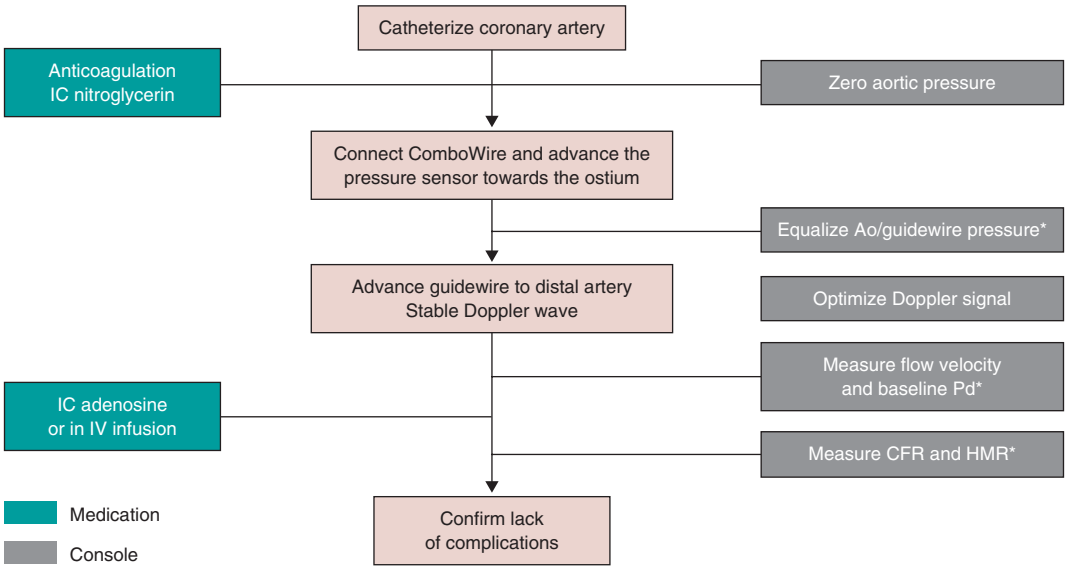

Figure 5. Steps for the study of microcirculation with intracoronary Doppler guidewire. Ao, aorta; CFR, coronary flow reserve; HMR, hyperemic microvascular resistance; IC, intracoronary; IV, intravenous; Pd, distal coronary pressure. * Catheter purged with saline solution and no guidewire introducer sheath.

Supplementary data provides a detailed description on the practical management of IMRangio.

CONCLUSIONS

The study of coronary physiology is a tremendous breakthrough for the management of patients with coronary artery disease. Being able to fine tune the functional severity of epicardial lesions and how microcirculation impacts the symptomatology of patients allows us to personalize treatment to reduce symptoms and, in many cases, improve prognosis. Great advances have been made in this field achieving further physiological knowledge and greater diagnostic accuracy both with invasive and non-invasive tests. Although extensive, knowledge in this field still shows gaps that will still be solved with new studies. All this development requires specific and updated training so we can take advantage of knowledge and technology for the benefit of our patients.

FUNDING

None reported.

AUTHORS' CONTRIBUTION

J.P. Vilchez-Tschischke, J. Sanz Sánchez, and E. Fernández Peregrina contributed to the design, drafting, and review process of the article, J.L. Díez Gil, M. Echevarría Pinto, and H.M. Garcia-Garcia contributed to both the drafting of the manuscript and the critical review of its intellectual content.

CONFLICTS OF INTEREST

J. Sanz Sánchez received conference fees from Cordis, and Terumo. H.M. Garcia-Garcia received conference fees from Biotronik, Abbot, Boston Scientific, Neovasc, Medtronic, Shockwave, Philips, and Corflow. The remaining authors declared no conflicts of interest whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000328.

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REC Interv Cardiol. 2022;4(4):329-330
https://doi.org/10.24875/RECICE.M22000323

Debate: Percutaneous revascularization strategies for distal left main coronary artery disease. The EBC MAIN approach

A debate: Estrategias de revascularización percutánea para la enfermedad del tronco común distal. Abordaje según el EBC MAIN

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Question: What aspects do you think might explain the significant differences reported between the results from the EBC MAIN (European bifurcation club left main coronary stent study),[1] and the DKCRUSH-V (Double kissing crush vs provisional stenting for left main distal bifurcation lesions) clinical trials?[2]

Answer: Both studies differ in several aspects we could categorized into 4: those that are operator-related; study design-related; patient and lesion-related, and those associated with the results from the provisional stenting technique.

The double kissing (DK) is a complex technique where most of the evidence available in the medical literature (including the DKCRUSH-V[2]) comes from the same group of expert operators who have been using such technique for years now.[3,4] However, the operators from the EBC MAIN[1] belong to the European Bifurcation Club that has spent years promoting and refining the provisional stenting technique.

Regarding the study design, the group of patients randomized to 2 different stents is also different from one trial to the other: in the DKCRUSH-V only patients treated with the DK crush technique were while in the EBC MAIN most patients were treated with the culotte technique or the T stenting technique. Another different aspect between both trials is the use of systematic angiographic assessments at 1-year in the DKCRUSH-V trial (66% of the patients). It is precisely at this point when event curves separate, and significant differences arise. This strategy can introduce a bias in the study in favor of the double stenting technique that has better angiographic appearance.

The type of patients included is also different and can condition the results. The SYNTAX score was different between both studies being more complex the lesions of the of all DKCRUSH-V trial (31% vs 23%). Also, the length of the lesion in the collateral branch (usually the left circumflex artery) turned out to be longer in the DKCRUSH-V trial: 16 mm vs 7 mm. Therefore, these bifurcations with very long lesions in the side branch penalize the provisional stenting group.

Another aspect that calls our attention in the group of patients randomized to the provisional stenting technique in the DKCRUSH-V trial are the poor results obtained in this group. These results compare to the experience of many other groups and the results obtained on the EBC MAIN trial. Therefore, the rate of stent thrombosis (acute/subacute) in this group is high (2.5%) compared to the 0.8% reported from the EBC MAIN provisional stenting technique group. Also, the crossover rate to 2 stents is the highest of all in the provisional stenting group of the DKCRUSH-V trial compared to the EBC MAIN (47% vs 22%). These differences could be associated with the type of complexity of bifurcation (more complex in the DKCRUSH-V study).

Q.: In the light of the evidence available and based on your own experience, when do you recommend provisional stenting and when an early double stenting technique to treat distal left main coronary artery stenoses?

A.: According to the DKCRUSH-V trial[2] and a meta-analysis recently published,[3,4] if the provisional stenting technique does not give good results in complex bifurcation the recommendation of using «complex techniques (2 elective stents) for complex bifurcations» can be accepted. The problem consists of identifying this type of unfavorable bifurcations for a simple strategy. The DEFINITION trial (Definitions and impact of complex bifurcation lesions on clinical outcomes after percutaneous coronary intervention using drug-eluting stents)[5,6] proposes a score based on 2 major criteria and 6 minor ones to distinguish simple from complex bifurcations. On the contrary, such meta-analysis[3] identifies patients eligible who would benefit from the DK-Crush technique much easier: patients with long lesions > 10 mm in the collateral branch.

I'm more inclined towards easy rules and I'd make a slight modification of the Medina classification[7] by adding, at the end, a letter based on the length of the collateral branch: S (short) < 10 mm, and L (long) > 10 mm. Therefore, we'd be recommending the provisional stenting strategy in the presence of these bifurcations:

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- 1, 1, 1, S
- 1, 0, 1, S
- 0, 1, 1, S
- 1, 1, 0
- 0, 1, 0
- 1, 0, 0

However, in the following types of bifurcation we'd rather use the double stenting technique:

- 1, 1, 1, L
- 1, 0, 1, L
- 0, 1, 1, L

Special situations like bifurcations with wiring of the collateral branch are difficult or restenosis of a simple technique can also be considered indications for the use of the elective double stenting technique in the bifurcation.

Q.: In how many angioplasties performed on the distal left main coronary artery is the double stenting technique often used?

A.: As a matter of fact, I think that we'd be under the numbers reported in the EBC MAIN trial (around 10%). For example, in our participation in the OPTIMAL trial of 21 patients included to this date with left main coronary artery disease, none of them was treated with the double stenting technique.

Q.: What is your favorite double stenting technique in the distal left main coronary artery and why?

A.: According to the data published in the medical literature available, I'd have to say the DK crush technique since it's the most favored of all in the comparative studies conducted.[3] However, such studies have the limitations already mentioned here.[4] In its latest consensus document, the European Bifurcation Club[8] recommends the provisional stenting technique when planning to use 1 single stent. Also, when the use of 2 stents can be anticipated before the procedure. In my opinion, the T stenting technique is the best one when the left main coronary artery/left circumflex artery has a configuration of 90º more or less. In such a way that the implantation of the second stent can be performed precisely into the ostium of the collateral branch by covering it completely without causing significant invasion of the carina. In case of a narrower angle, the DK-culotte technique would be the preferred one since it is impossible to make a perfect adjustment of the second stent without invading the main vessel or leaving a space without «stenting» the collateral branch. This technique can be used starting with the main vessel (provisional stenting philosophy) or the collateral branch (inverted culotte). The most practical thing to do would be to start with the diseased branch and then move on with a combo of POT (proximal optimization technique) plus double kissing balloon. This technique has been described recently,[9] and we don't have comparative studies against the DK crush technique. However, when refined[8] it achieves an excellent stent expansion and apposition across all the bifurcation segments, which should lead to clinical outcomes.

Q: In your opinion, do you think that the use of intravascular imaging modalities to guide these procedures on the left main coronary artery is important?

A.: The use of intravascular imaging—mainly the intravascular ultrasound (IVUS)—in the percutaneous treatment of left main coronary artery has been a constant recommendation over the last few years.[10,11] However, this recommendation is only based on the opinion of experts and observational studies. Therefore, in the latest European guidelines[12] the recommendation of using IVUS in the percutaneous management of the left main coronary artery is weak (only IIa B). To achieve recommendation I, a randomized clinical trial would be needed to confirm that there are fewer clinical events. That is the objective of the OPTIMAL trial we are involved with right now. Although a study of this magnitude could change the clinical guidelines, the recruitment of patients is sometimes difficult to see because of our conviction that IVUS is necessary to perform stenting properly, and operators don't want to leave randomized patients away from the benefits the technique has to offer. By describing this problem we face on a daily basis at the cath lab I think I have already answered to this question.

FUNDING

None whatsoever.

CONFLICTS OF INTEREST

Conference or workshop minor fees from Abbott, Boston, Phillips, and Worldmedica have been declared.

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REC Interv Cardiol. 2022;4(4):331-332
https://doi.org/10.24875/RECICE.M22000332

Debate: Percutaneous revascularization strategies for distal left main coronary artery disease. Approach from the DKCRUSH-V trial

A debate: Estrategias de revascularización percutánea para la enfermedad del tronco común distal. Abordaje desde la perspectiva del DKCRUSH-V

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Question: What aspects do you think might explain the significant differences reported between the results from the EBC MAIN (European bifurcation club left main coronary stent study),[1] and the DKCRUSH-V (Double kissing crush vs provisional stenting for left main distal bifurcation lesions) clinical trials?[2]

Answer: The EBC MAIN trial has proven the non-inferiority of the step-by-step provisional stenting technique approach compared to the early double stenting strategy in 467 patients with distal left main coronary artery bifurcation disease (Medina 1,1,1 or 0,1,1). No significant differences were reported regarding the overall rate of major adverse cardiovascular events, target lesion failure, acute myocardial infarction, and stent thrombosis.[1]

On the other hand, the DKCRUSH V trial randomized 482 patients with distal left main coronary artery bifurcation disease (Medina 1,1,1 or 0,1,1) to receive treatment with the provisional technique vs the DK-crush technique. The latter had a lower rate of major adverse cardiovascular events with statistically significant differences regarding target lesion failure (10.7% vs 5%) (hazard ratio, 0.42; 95% confidence interval, 0.21-0.85; $P = .02$), acute myocardial infarction (2.9% vs 0.4%; $P = .03$), and stent thrombosis (3.3% vs 0.4%; $P = .02$) at 1-year follow-up.[2] Results were better in the most complex coronary bifurcation lesions defined, above all, as those with greater side branch damage (> 70% of stenosis and > 10 mm of lesion length), severe calcification or well-defined angles (> 70 or < 45°).

Some have tried to compare data from the EBC MAIN to data from the DKCRUSH-V. However, there are aspects that just don't make them comparable trials for study design reasons or for the overall results of the DK-crush technique: the complexity of bifurcation and the degree of damage to the side branch was lower in the EBC MAIN compared to the DKCRUSH-V defined by severity of stenosis > 70% and length > 10 mm. As a matter of fact, the mean side branch lesion length was 7 mm in the EBC MAIN vs 16 mm in the DKCRUSH-V, which can be seen in the rate of double stenting of the provisional group (22% in the EBC-MAIN vs 47% in the DKCRUSH-V). Similarly, the low rate of double stenting of the provisional group was left to the operator's criterion allowing residual lesion in the ostial left circumflex artery of 90% vs 75% in the DKCRUSH-V. In my opinion, another factor penalizing the double stenting group is that only 5% of the patients were treated with the DK-crush technique since the most widely used ones were the culotte (53%), and the T or TAP (T and protrusion) techniques (33%). Also, 6% of the patients from the double stenting group could not receive the second stent unlike the DKCRUSH-V trial where the procedural success of the DK-crush group was 100%. The use of imaging modalities in both studies was similar in around 40% of the cases.[3]

Q.: In the light of the evidence available and based on your own experience, when do you recommend provisional stenting and when an early double stenting technique to treat distal left main coronary artery stenoses?

A.: Obviously, the only lesions eligible for 2-stent implantation into the distal left main coronary artery are those found in bifurcations we call complex or true bifurcations, that is, when both left main coronary artery branches are damaged (Medina 1,1,1 or 0,1,1). However, among these lesions, the complexity of left main coronary artery bifurcation lesions depends on many different factors, among them, the DEFINITION II trial criteria are the most widely used of all. As far as I know, they're the most important ones of all regarding the selection of the bifurcation technique that will eventually be used: simple or complex (left main coronary artery bifurcation with side branch stenosis > 70% and lengths > 10 mm, moderate-to-severe calcifications, bifurcation angles < 45° or > 70°, multiple lesions, main vessel reference diameters > 2.5 mm, main vessel lesion lengths > 25 mm or presence of thrombus in the lesion).[4]

This trial proved that complex bifurcations, under these criteria, are associated with fewer events if treated with the complex double stenting technique compared to the provisional stenting technique. In my opinion, the most valuable criteria that should be used when having to decide between provisional or complex stenting techniques—rather than the severity of stenosis in the side branch—are

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side branch lesion lengths > 10 mm, moderate-to-severe calcifications, and bifurcation angles < 45º. Angles > 70º can be solved much easier using the provisional 1-stent technique with minimal protrusion in bailout T or TAP.

Q.: In how many angioplasties performed on the distal left main coronary artery is the double stenting technique often used?

A.: Provisional stenting technique used systematically is valid to treat most distal left main coronary artery disease including true bifurcations with side branch damage, assuming that 20% to 40% of the patients will end up with a second stent in the side branch. At our center, however, there are patients we directly treat with 2 stents for being high-complexity patients. The rate of left main coronary artery true bifurcations is somewhere between 25% and 30%.

Q.: What is your favorite double stenting technique in the distal left main coronary artery and why?

A.: I'd say scientific evidence is rather clear on what the double stenting technique of choice should be to treat complex distal left main coronary arteries. In addition to the aforementioned results from the DKCRUSH-V and the DEFINITION II trials where 77.8% of the patients treated with 2 stents received the DK-crush technique,[1,4] 2 meta-analyses recently published have confirmed the superiority of the DK-crush technique vs other bifurcation techniques. In the one conducted by Di Gioia et al.[5] of a total of 5711 patients, 5 different bifurcation techniques used in the studies were compared (provisional stenting, T-stent, TAP, crush, culotte, and DK-crush). It was found that patients treated with the DK-crush technique had lower rates of major adverse cardiovascular events, significant differences regarding the need for new target lesion revascularization (odds ratio, 0.36; 95% confidence interval, 0.22-0.57), and no differences regarding cardiac death, myocardial infarction or stent thrombosis. The biggest clinical benefits from using the DK-crush technique were reported in lesions with side branch disease > 10 mm in length, that is, the most complex bifurcations of all. The second meta-analysis conducted this year by Park et al.[6] after the publication of the EBC MAIN results—with a total of 8318 patients—reached the same conclusions. In the conventional meta-analysis, the DK-crush technique proves non-superior to the provisional stenting technique except for cases with side branch disease and lengths > 10 mm where there is a lower rate of cardiac death, and target vessel revascularization. However, when a multiple comparison analysis was conducted, the DK-crush technique had a lower rate of major adverse cardiovascular events regarding cardiac death, acute myocardial infarction, target vessel revascularization, and stent thrombosis compared to the provisional stenting technique and any other double stenting technique including T-stent, TAP, dedicated bifurcation stents, crush, and cullote.[6]

Among the complex double stenting techniques, the culotte one is a very flexible technique we can use to choose the branch we want to treat first, the main vessel or the side branch. Recently, changes have been made that improve its result by minimizing stent overlap in the main vessel and adding a first kissing balloon (KB) after the first stent implantation (DK-mini-culotte) thus improving stent comformability at bifurcation level and improving the success rate of the final KB.[7] However, we still don't have any evidence on the results of the DK-crush technique.

Despite the results published with the DK-crush technique, it has not become the technique of choice in most centers because it is technically very challenging since 8 very well-defined steps are involved that can't be omitted since the technique needs to be refined in every step of the way. However, the main setback of this technique is that it is very much time-consuming. Also, the material needed is often unusual and without proper optimization, which means that it can jeopardize results in the real-world. Early POT (proximal optimization technique) is very important here, also KB with non-compliant high-pressure balloons, and final POT. Similarly, the technique needs to be refined based on the recommendations established in the EBC MAIN trial regarding POT, and the KB.

Finally, since this is a time-consuming and challenging technique that takes up a lot of resources, changes to this technique to optimize results and improve procedural times are almost non-stop. One of them is high-pressure stent postdilatation of the side branch at ostial level (proximal SB optimization) that improves stent comformability at carina level and facilitates later recrossing.[8] The other one is the DR-crush (double rewire crush) technique that facilitates sequential dilatation of the side and main branches thus avoiding early KB, which simplifies the entire procedure with very good results at 2 years.[9]

Q: In your opinion, do you think that the use of intravascular imaging modalities to guide these procedures on the left main coronary artery is important?

A: I believe we all agree that the use of imaging modalities to treat these bifurcation lesions at the left main coronary artery is mandatory to both plan the strategy that should be followed and assess the final outcomes. It is the only way to offer the best possible results in a lesion of such prognostic impact. Regarding the most appropriate technique, I think it should be the one the operator is more familiar with. Although it is true that intravascular ultrasound has gained traction to treat the left main coronary artery, since distal segment is involved and as long as we're not dealing with short left main coronary arteries or excessively large calibers preventing good contrast, the optical coherence tomography would also be useful thanks to its high spatial resolution.

FUNDING

None reported.

CONFLICTS OF INTEREST

None whatsoever.

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REC Interv Cardiol. 2022;4(4):333-342
https://doi.org/10.24875/RECICE.M22000293

Percutaneous valvuloplasty in neonates with severe and critical aortic stenosis: evolution and poor prognosis prediction

Valvuloplastia percutánea en estenosis aórtica grave y crítica en neonatos: evolución y predictores de mal pronóstico

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To the Editor,

Critical, severe, and congenital aortic stenosis (AS) is challenging regarding the decision-making process, and has high mortality and morbidity rates,[1] being percutaneous treatment the one more commonly used in most centers. The objective of this study was to assess the clinical and echocardiographic progression of congenital ASs treated with percutaneous valvuloplasty (PV), and the predictive factors of worse disease progression.[2,3]

RSevere (peak velocity > 4 m/s or mean gradient > 40 mmHg), and critical ASs (ductus-dependent systemic flow) were included retrospectively based on the first postnatal echocardiography diagnosed during the fetal stage and until the first month of life and then treated with PV in a tertiary center from 2009 through 2019. The criteria established by the Declaration of Helsinki were followed, and the patients' informed consent was waived.

Left ventricular ejection fraction (LVEF), endomyocardial fibroelastosis, flows in ductus, foramen ovale, ascending aorta, aortic arch, mitral regurgitation, and hydrops were all analyzed. The size and shape of the aortic valve, the size, function, and ventricular fibroelastosis at birth, the immediate control after PV and at the follow-up, the hemodynamic gradients of PV, and complications were collected. PV was considered effective with peak residual hemodynamic gradients ≤ 35 mmHg or 50% decrease with normal LVEF. The need for Ross surgery, heart transplant, and death were regarded as unfavorable disease progression. Qualitative variables were expressed as percentages, and the quantitative ones as median and interquartile range [IQR]. The contrast of univariate hypothesis was conducted using the Mann-Whitney *U* test, and Fisher's exact test. Confounding variables distinction was conducted through multivariate analysis using the linear regression inverse verisimilitude method. The significance level of the alpha risk was .05%.

A total of 23 patients were obtained, 6 of whom (26.09%) were women. Overall, 7 patients (30.44%) were associated with aortic coarctation, and 2 (11.39%) with moderate-to-severe mitral stenosis. A total of 6 critical ASs (26.09%) were found, 2 of which (11.39%) were unicuspid, 8 (34.78%) pure bicuspid, and 12 (52.17%) tricuspid; a total of 8 raphes were reported between the non-coronary and right coronary leaflets, and 2 between the right and left coronary leaflets.

Regarding the moment of diagnois, 6 ASs (26.09%) were diagnosed during the prenatal stage and 17 (73.91%) during the neonatal period. A total of 3 ASs (13.05) from the prenatal group had severe dysfunction with grade 4 friboelastosis and flow reversal in the ascending and transverse aortic arch. One of them had hydrops and the other one was treated with an elective fetal valvuloplasty that was performed on week 26.

A total of 6 patients (26.09%) presented with cardiogenic shock at birth. Only in critical ASs systo-diastolic dysfunction was reported with median LVEF of 42.50% [IQR, 40.00-57.25], which was lower compared to the severe ones (P = .011). A total of 10 patients (47.83%) had mitral regurgitation, 2 of them (8.70%) severe.

The PV was performed after a median 42 days of life [IQR, 12.25-56], 7 of which (30.43%) wre performed within the first week of life. The balloon used was the TYSHAK mini or II (NuMED Inc., United States). The balloon/valvular diameter ratio was 1.00 [IQR, 0.91-1.03], which was significantly higher in the unicuspid valve group. The vascular access was the femoral artery. The overall effectiveness rate was 78.26%, 83.33% (n = 5/6) in critical ASs, and 76.5% (n = 13/17) in the severe ones.

After a median follow-up of 4 years [IQR, 3,5-6,25] the survival rate was 92.31%. A total of 15 patients (65.22%) remained reintervention-free. Reinterventions (figure 1) occurred within the first year of life: 4 patients needed a new PV, 3 patients required Ross surgery, and 2 surgical valvulotomy (1 died due to postoperative cardiogenic shock), and 1 heart transplant due to heart failure and pulmonary hypertension (the patients died due to rejection, and pulmonary hypertension).

During the patient's disease progression, a 69.57% rate of aortic regurgitation was reported, 33% moderate and 8% severe (figure 2). No statistically significant differences were seen regarding disease progression into moderate-to-severe aortic regurgitation based on the balloon-to-annulus ratio (P = .435) or on the rate of procedural success (P = .446).

Statistically significant differences were reported in the univariate contrast for the risk factors of unfavorable progression in critical ASs (P = .021), greater systolic transvalvular gradient at birth (P = .027),

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Online: 23-05-2022.

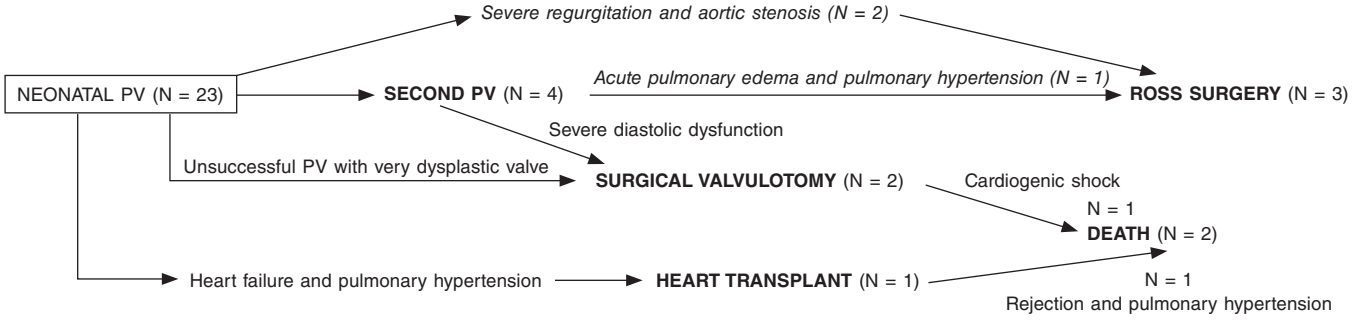

Figure 1. Need for new procedures in individuals after percutaneous valvuloplasty (PV).

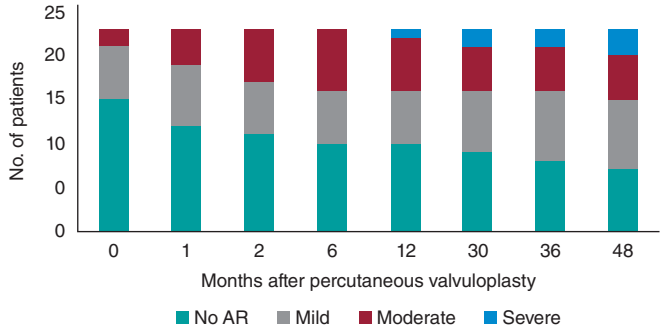

Figure 2. Evolution of aortic regurgitation (AR).

shorter diameter of aortic annulus (P = .017), ductus-dependent systemic flow (P = .003), mechanical ventilation (P = .009), lower weight at birth (P = .001), younger age during the first PV (P = .013), lower LVEF (P = .021), and smaller diameter of the aortic annulus after PV (P = .009). No differences were seen based on valvular morphology (P = 1).

In the multivariate analysis (table 1) of previously significant and clinically relevant variables statistical significance was obtained for a smaller diameter of the aortic annulus (hazard ratio, 2.82; P = .016).

This study—that shows the complexity and heterogeneity of AS—found that after a neonatal aortic PV has occurred some type of

Table 1. Predictors of unfavorable disease progression

	Fisher's exact test or Mann Whitney *U* test	Multivariate test: inverse verisimilitude method of a bivariate analysis			Fisher's exact test or Mann Whitney *U* test	Multivariate test: inverse verisimilitude method of a bivariate analysis	
Variables	***P***	**HR (95% confidence interval)**	***P***	**Variables**	***P***	**HR (95% confidence interval)**	***P***
Critical AS	.021*			Mitral stenosis at birth	.481		
Prenatal diagnosis	.275			Mitral regurgitation at birth	.069		
Unicuspid valve	.462			Z-score of mitral valve annulus at birth	.268		
Affected by aortic coarctation	.369			Z-score of aortic valve annulus at birth	.017*	1.234 (0.436-3.4494)	.692
Affected by Shone syndrome	.146			Z-score of LV end-diastolic diameter	1.000		
LVEF at birth	.101			LV end-diastolic gradient before the PV	.841		
LV S-wave at birth	.222			Inotropic score at birth	.500		
Diastolic dysfunction at birth	.131			Infusion of prostaglandins	.003*		
Mean gradient of AS at birth	.143			Mechanical ventilation	.009*		
Systolic gradient of AS at birth	.027*	0.983 (0.906-1.066)	.676	Lower weight at birth	.001*		
Aortic regurgitation at birth	.481			Age at cardiac catheterization	.013*	0.896 (0.569-1.344)	.596
Aortic annulus diameter at birth	.039*			Aortic systolic hemodynamic pressure before the PV	.687		

(Continues)

Table 1. Predictors of unfavorable disease progression *(continued)*

	Fisher's exact test or Mann Whitney *U* test	Multivariate test: inverse verisimilitude method of a bivariate analysis			Fisher's exact test or Mann Whitney *U* test	Multivariate test: inverse verisimilitude method of a bivariate analysis	
Variables	***P***	**HR (95% confidence interval)**	***P***	**Variables**	***P***	**HR (95% confidence interval)**	***P***
Mean aortic hemodynamic pressure before the PV	.622			LV S-wave on echocardiography after the PV	.106		
Aortic diastolic hemodynamic pressure before the PV	.107			Echocardiographic aortic regurgitation after the PV	.609		
Mean LV hemodynamic pressure before the PV	.154			Z-score of the aortic annulus on the echocardiography after the PV	.009*	0.355 (0.153-0.826)	.016*
LV systolic hemodynamic pressure before the PV	.424			Monitorization of mitral regurgitation after the PV	.635		
Aortic systolic hemodynamic pressure after the PV	.398			Monitorization of mitral stenosis after the PV	.100		
LVEF after the PV	.021*	1.007 (0.896-1.131)	.910				

95%CI, 95% confidence interval; AS, aortic stenosis; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; PV, percutaneous aortic valvuloplasty:
* Statistically significant variables.

new intervention was required in a third of the patients with similar results to those reported by other series.[4] Due to the complex decision-making process it is important to know which characteristics are associated with grimmer prognosis.[5,6] It has been reported that worse prognosis is associated with lower weight, ductus-dependent systemic flow, and mechanical ventilation, critical AS, and a greater systolic aortic transvalvular gradient at birth, smaller annular sizes, and worse LVEF after the PV. Also, when the latter is performed earlier. These factors are often concomitant. However, only the diameter of the annulus has statistical significance in a multivariate analysis. A larger sample would have probably resulted in more significant variables. Even so, it seems obvious that the group of patients with poor clinical progression often share the same characteristics, indicative that they make up a totally different spectrum of the disease with different therapeutic needs while requiring multidisciplinary and individualized assessments.

FUNDING

The authors declare that no funding whatsoever was received to conduct this study.

AUTHORS' CONTRIBUTIONS

Freixa-Benavente had the study idea, curated data, analyzed, drafted, and submitted the manuscript. P. Betrián-Blasco supervised the study, recruited patients and data, and analyzed them; also, he reviewed the manuscript final version and gave his approval. F. Rosés-Noguer, and G. Giralt-García reviewed the manuscript, and made significant remarks. Q. Ferrer-Menduiña supervised the study, recruited the patients, data, and drafted the manuscript; also, she reviewed the manuscript final version and gave her approval.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

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https://doi.org/10.24875/RECICE.M22000296

Minimally invasive hybrid technique for left ventricular aneurysm repair surgery due to ischemic cardiomyopathy

Técnica híbrida mínimamente invasiva para reconstrucción de aneurisma ventricular izquierdo por miocardiopatía isquémica

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To the Editor,

Chronic heart failure (CHF) is the third leading cause of cardiovascular death in developed countries, and is mostly of ischemic etiology.[1]

Despite the optimal medical therapy based on the clinical practice guidelines, many patients remain symptomatic for whom different procedures have become available over the last few years to stop pathological ventricular remodeling.

The Revivent system (BioVentrix Inc., United States) is a hybrid ventricular reconstruction procedure that works by implanting micro-anchors via endovascular access and left mini thoracotomy to create a longitudinal plication of scar tissue without the need for mid sternotomy or extracorporeal circulation. Basically it is indicated in patients with ischemic heart disease and anterolateral or apical aneurysmal regions with transmural scar in both the left ventricle (LV) and right septum (RS)—according to the magnetic resonance imaging—to prevent muscle tears, and who still have persistent advanced CHF and NYHA functional class (FC) > III despite the optimal medical therapy.[2] Biffi et al. confirmed an in-hospital mortality rate of 1.4%, and a 1-year survival rate of 90% in 203 patients.[3] The STICH[4] and RESTORE[5] clinical trials revealed in-hospital mortality rates of 6% and 5.1%, respectively, and 18-month survival rates of 85% and 88%, respectively, after surgical therapy in patients with a similar profile.

The objective of this letter is to report on the clinical characteristics of the procedure and the 90-day results of the first 2 patients treated at our center. Both gave their informed consent prior to publishing their cases.

Patient no. 1 is a 67-year-old man without cardiovascular risk factors admitted with signs of anterolateral infarction with ST-segment elevation due to thrombotic occlusion in the left anterior descending coronary artery. Plain old balloon angioplasty was performed followed by dual drug-eluting stent implantation on a second stage. The patient was classified as NYHA FC II, and was on daily furosemide 180 mg, and eplerenone 50 mg. The echocardiogram revealed the presence of a dilated LV, a left ventricular ejection fraction (FEVI) of 12%, a large apical aneurysm, and severe pulmonary hypertension. The 60-day magnetic resonance imaging revealed the presence of akinesis in the anteroseptal, anterolateral, and apical segments without viability data (figure 1A). The pre-transplantation study performed anticipated unfavorable prognostic outcomes, which is why the Revivent therapy was proposed 6 months after the infarction.

The procedure was transesophageal echocardiography (TEE) and fluoroscopy guided. The LV apex and anterolateral side were accessed via left mini thoracotomy. A 14-Fr introducer sheath was implanted via right jugular vein to advance a Swan-Ganz catheter. Afterwards, the EnSnare device with 3 interlaced loops (EnSnare Merit Medical Systems Inc., United States) was inserted until the RV. A transseptal guidewire was inserted from the LV through fluoroscopy and TEE guidance that was captured using the snare in the RV and then removed via jugular vein. This circuit is used to implant the first endocavitary anchor that, once cinched, allows the partial obliteration of the aneurysm. Ventricular reduction was completed by implanting 4 pairs of additional extracardiac anchors. The proper reduction and plication was confirmed via fluoroscopy and TEE (figure 1B,F).

After an immediate postoperative without complications the patient was discharged from the hospital on day 13 after the procedure and classified as NYHA FC I-II. After 3 months he was classified as NYHA FC I, which reduced the need for furosemide down to 20 mg/day. The control computed tomography (CT) scan is shown on figure 1G.

Patient no. 2 is a 50-year-old man with a past medical history of peripheral arterial vasculopathy and dilated cardiomyopathy of ischemic origin. He presented with residual LVEF after the infarction of 15% with a LV anterolateral aneurysm. The patient was classified as NYHA FC III and was on daily furosemide 180 mg, eplerenone 50 mg, and chlorthalidone 25 mg.

The procedure was performed in a similar way compared to the former case. No significant complications were reported, and the patient was discharged on day 20 of the postoperative period and classified as NYHA FC II that improved at 3 months (I-II), which

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Online: 13-06-2022.

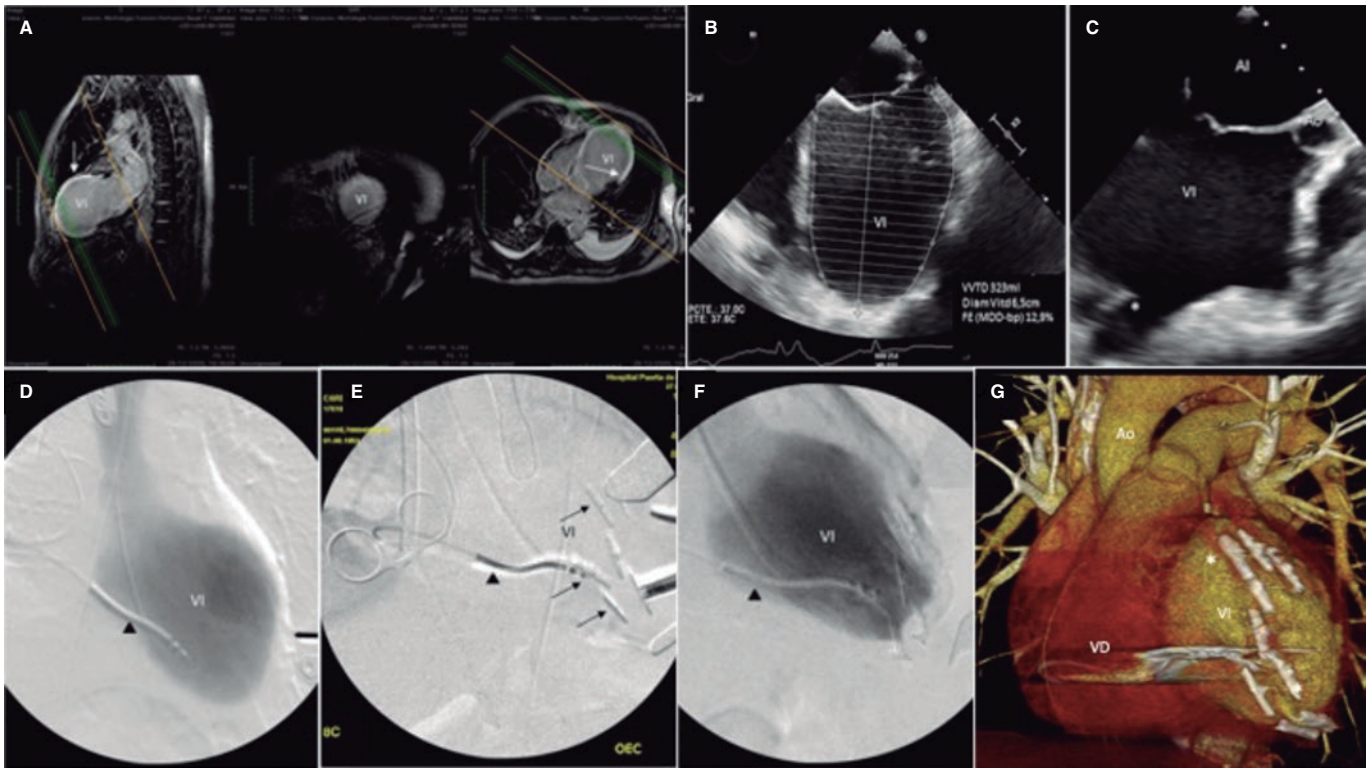

Figure 1. **A:** preoperative magnetic resonance imaging. Two-chamber long axis view, and 3-chamber long axis view, ischemic scar (arrows). **B:** preoperative transesophageal echocardiography (TEE), 4-chamber view, LV end-diastolic volume. **C:** intraoperative TEE, 3-chamber view, remodeled LV chamber, first anchor. **D:** intraoperative fluoroscopy, ventriculography, implantable cardioverter-defibrillator leads (arrowhead). **E:** reconstruction anchors (arrows). **F:** ventriculography final outcomes. 3D CT scan reconstruction. **G:** Final outcomes (asterisks). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Table 1. Volumes, ventricular diameters, and left ventricular ejection fraction before and after implantation

	Patient no. 1			Patient no. 2		
	Before implantation	After implantation	Third month	Before implantation	After implantation	Third month
LVEDV (mL)	285	224	200	178	131	73
LVESV (mL)	227	161	139	150	108	54
LVEDD (mm)	70	63	65	68	53	50
LVEF (%)	12	28	28	15	20	26

LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

is why the dose of furosemide was reduced to 120 mg/day. In both cases ventricular parameters improved (table 1).

These 2 patients are the first cases ever reported in the medical literature treated with the Revivent system in Spain. Cardiac surgeons and interventional cardiologists alike participated in the procedure. Although an initial learning curve is required, no complications were reported, and both the functional class, and the volumes improved. The 2 patients had long hospital stays, which were attributed to the management of hydroelectrolytic balance in patients with severe CHF. Since control echocardiograms were performed 3 months after surgery, it is anticipated that left ventricular end-diastolic volume (LVEDV) will be reduced even further.[6]

Randomized clinical trials are needed with a large number of patients to determine whether the Revivent system is an effective, safe, and long-lasting therapeutic option in patients with post-ischemic severe ventricular dilatation and dysfunction.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

J. E. De Villarreal: drafted the manuscript, processed, and edited the images, 1st, 2nd, and 3rd reviews; M. del Trigo: edited the manuscript 2nd review; C. Esteban Martín: edited the manuscript 1st review; J. Goicolea Ruigómez: edited the manuscript 2nd review; S. Mingo: collaborated to acquire the images and the

echocardiography volumes; A. Forteza Gil: edited the manuscript 1st and 3rd reviews.

CONFLICTS OF INTEREST

None reported.

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https://doi.org/10.24875/RECICE.M22000303

Micra leadless pacemaker and transcatheter aortic valve implantation at the same procedure

Implante de marcapasos sin cables Micra y prótesis aórtica transcatéter en un mismo procedimiento

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To the Editor,

Transcatheter aortic valve implantation (TAVI) is a common therapeutic option in patients with degenerative severe aortic stenosis. In our setting, the need for definitive pacemaker implantation after TAVI is around 14%,[1] which is an additional cause for morbidity and longer length of stay. In elderly patients both aspects can be especially relevant. Micra leadless pacemaker (Medtronic, United States) is a recent alternative to traditional endocavitary pacemakers. The lack of electrodes or need for subcutaneous bag to carry the generator added to femoral venous access implantation reduce some of the complications associated with conventional pacemakers (especially pneumothorax, hematoma, bag and electrode-related infections). Although initially available for VVI pacing mode only, the new Micra AV (Medtronic, United States) has appeared recently. It maintains atrioventricular synchrony in patients in sinus rhythm by detecting atrial mechanical contraction and the corresponding ventricular pacing.

After over 120 Micra implantations including an early favorable experience after TAVI,[2] and widening the indication to patients in sinus rhythm too, we thought of the possibility of implanting both devices at the same procedure. In this work we present the very first series of patients who, after TAVI, were implanted with the Micra leadless pacemaker as permanent pacing therapy at the same procedure. Patients gave their informed consent to analyze and publish the results.

A total of 3 patients treated with TAVI due to symptomatic severe aortic stenosis developed an advanced atrioventricular conduction disorder during the procedure. Table 1 shows the characteristics of patients and procedures. Once the hemostasis of the femoral arterial access used for valve implantation was achieved, the Micra leadless pacemaker via femoral venous access was implanted (figure 1). The procedure went on for an average 28 minutes (19 to 36 min interval), and it was completed successfully in all 3 patients.

Although limited to very short series, the experience with leadless pacemakers in patients treated with TAVI is satisfactory.[2-4] Retrospectively, shorter length of stay, less tricuspid regurgitation, and lack of complications like pneumothorax, bleeding or bag-related infections have been reported compared to conventional pacemaker implantation.[3,4]

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Online: 13-06-2022.

Table 1. Characteristics of patients and procedures.

	Patient #1	Patient #2	Patient #3
Sex	Woman	Man	Man
Age	85	82	89
Baseline rhythm	Paroxysmal AF	Sinus rhythm	Sinus rhythm
Baseline AV conduction	normal	First-degree AV block	First-degree AV block
Baseline QRS (ms)	168	149	133
Conduction disorder	RBBB	RBBB	RBBB
Permanent anticoagulation	Apixaban	no	no
LVEF (%)	60	60	60
TAVI arterial access site	Right femoral	Right femoral	Right femoral
TAVI	26 mm Corevalve	29 mm Corevalve	34 mm Corevalve
AV conduction after implantation	Complete AV block	Complete AV block	Complete AV block
Type of pacemaker	VVI Micra pacing	AV Micra pacing	AV Micra pacing
Micra venous access	Right femoral	Right femoral	Right femoral
R-wave (mV)	Non-measurable	14	14
Impedance (Ohm)	1.023	950	710
Threshold (V x 0.24 ms)	1	0.25	0.38
Overall cath lab time (min)	152	189	164
Micra implantation time, cath lab (min)	19	31	36
Length of stay (days)	6	5	3
Pacing at follow-up (%)	72	96	20

AV, atrioventricular; RBBB, right bundle branch block; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

There are certain risks involved in conventional pacemaker implantation within the same procedure after TAVI: *a)* anticoagulation needed to perform the valvular procedure increases the risk of bleeding in the vascular access site (subclavian/cephalic). Therefore, the site becomes less controllable and compressible than the femoral access site needed for Micra implantation, and *b*) pneumothorax, especially serious in elderly patients who, at times, are on mechanical ventilation. In contrast, Micra implantation requires sedoanalgesia to advance the introducer sheath (23-Fr) through the inferior vena cava, Therefore, implantation after TAVI requires extending sedoanalgesia only. In addition to the potential benefits of performing both techniques simultaneously, it is not required to leave temporary ventricular electrodes until definitive pacemaker implantation. The risk of displacement (with loss of ventricular capture), the need for relocation, ventricular perforation, and endovascular infection can also be prevented with the strategy presented here.

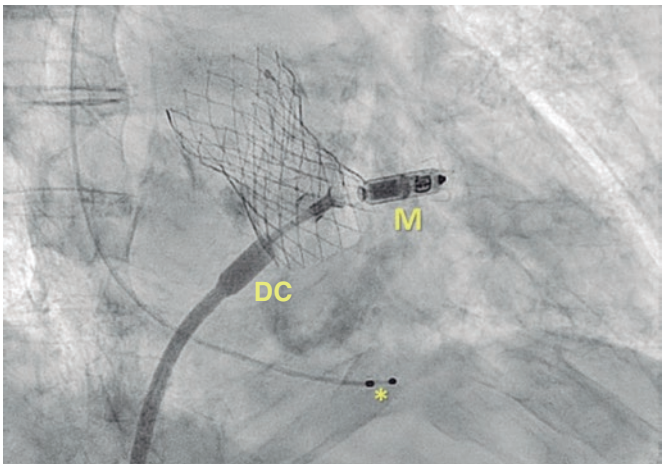

Figure 1. Transcatheter aortic valve already implanted plus Micra (M) device at the moment of delivery. * Indicative of temporary ventricular electrodes. DC, delivery catheter.

The limitations of Micra pacemaker implantation include costs—higher compared to conventional pacemakers (compensated by a shorter length of stay)—and longer cath lab time (though not as long as the time it takes to start a new procedure, transfer the patient, administer new sedation, etc.). The durability of the device also could be considered a limitation (around 10 years). Therefore, in the post-TAVI setting, the Micra device is spared for patients ≥ 80 years. Because of the preliminary nature of our work further studies will be necessary to confirm the benefits of this new therapeutic strategy.

In conclusion, this was the very first series of patients treated with TAVI and Micra at the same procedure. Results are favorable and confirm not only that post-TAVI Micra implantation is an appealing strategy to reduce the complications associated with conventional pacemakers, but also that it is feasible at the same procedure. It reduces substantially the length of stay and the risks associated with temporary ventricular electrodes. The current possibility of implanting the Micra device while keeping atrioventricular synchrony widens the indications for patients in sinus rhythm.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

T. Bastante: drafted the manuscript; F. Alfonso: critical review. All the authors: they contributed substantially to the study design, data curation, analysis and interpretation, and final approval of the version that would be published.

CONFLICTS OF INTEREST

F. Alfonso is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. The authors declared no conflicts of interest whatsoever.

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https://doi.org/10.24875/RECICE.M22000322

Use of extended realities in interventional cardiology: mixed reality for TAVI procedure

Aplicaciones de las realidades extendidas en cardiología intervencionista: la realidad mixta aplicada al procedimiento TAVI

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To the Editor,

A novel aspect of medical imaging visualization are the so-called extended realities, a term that includes a plethora of very different technologies such as virtual, augmented, and mixed reality. The latter being the most recent one of all. The ultimate feature of mixed reality headsets is their capacity to perceive the real world while mixing virtual models to complement the sources of information traditionally available. In principle, there are multiple possible applications to the medical field being particularly interesting their integration into surgical and interventional procedures. Currently, the main limitation preventing their clinical applicability is that no commercial applications remain available in the market for users. Also that, for every specific new case, specific solutions need to be developed.

In the context of the «3D Augmented Reality Cath Lab» research project (the HAMMOND project) only 1 preliminary clinical experience integrating the mixed reality HoloLens 2 headset (Microsoft, United States) has taken place (figure 1) in the percutaneous coronary intervention setting. Prior to the research ethics committee approval (CASVE-PI-GR-20-2001) a mixed reality application was developed for cardiac catheterization care that was tried in 9 patients treated with transcatheter aortic valve implantation (TAVI).

Figure 1. HoloLens extended mixed reality headset 2.

The descriptive results of this early experience with mixed reality in the different stages of TAVI procedures—shown on figure 1 and video 1 of the supplementary data—follow next:

- Vascular puncture guidance support: holograms with echocardiogram imaging were generated in real time (figure 2A). Therefore, through the creation of large virtual «screens» with better ergonomics the operator can visualize both his hands and the imaging support simultaneously. The fine resolution and little latency of the system used allowed us to gain ultrasound-guided arterial access as seen on the HoloLens 2 headset

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Online: 29-08-2022.

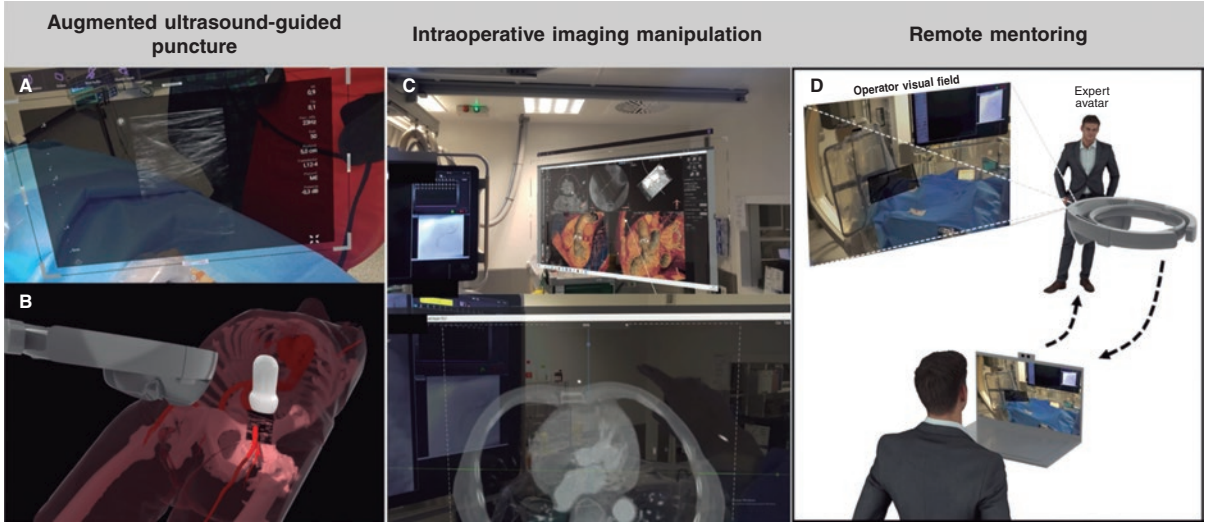

Figure 2. A: vascular ultrasound integration during puncture. **B:** schematic representation of simultaneous integration in vascular puncture.[1] **C:** image from the software analysis of the manageable computed tomography scan in conditions of asepsis; **D:** remote mentoring simulation.

in 5 consecutive cases. Room for improvement has been identified and is in the pipeline right now: the integration of the ultrasound image acquired with the ultrasound probe in such a way that the holograms would be visualized in the «real» position towards the inside of the patient (figure 2B). Currently, several early experiences have been reported with this type of integration[1] like hologram-guided punctures mixed with computed tomography (CT) images. The use of holograms from CT generated organs overlapping the patient's real anatomy has been reported allowing us to simplify complex vascular procedures.[2]

- Interaction with CT generated images in conditions of asepsis: the capacity of augmented reality headsets to be used via voice commands or the user's own hands (as seen on video 1 of the supplementary data) allows the operator to check different sources of information without losing sterility or interfering with the procedure. Figure 2C and video 1 of the supplementary data exemplify this application with the intraoperative examination of the patient's CT scan of using the 3mensio Structural Heart software (Pie medical imaging, The Netherlands).

- Remote procedural supervision: remote mentoring has proven an extremely useful imaging modality during the COVID-19 pandemic.[3,4] In our own single experience with 9 cases including 4 transcatheter aortic valve implantation procedures, 3 bicaval valve implantation procedures for tricuspid regurgitation, and 2 chronic total coronary occlusions, the images and the sound captured by the HoloLens 2 headset can be remotely transmitted to the expert in real time. Therefore, he can not only see the x-ray and the ultrasound images as it is the case with conventional remote mentoring (teleconference), but also the operator's point of view. Also, the mentor can control the information available through the virtual windows that the operator can see life, for instance, the CT working station. Alternatively, different solutions of telepresence and remote communication have become available like the Mesh software (Microsoft, United States) that allow the operator to visualize the mentor as a real-time hologram (figure 2D).

Mixed reality-based technology is giving its first early steps regarding surgical and interventional procedures. Our early experience shows—using scientific methodology—the current actual clinical experience applied to TAVI procedures beyond the future potential benefits of this technology.

The limitations identified when implementing this technology in the interventional cardiology field are basically the complexity associated with the process of integrating hologram-like real-time ultrasound images into the patient's anatomical structures. Improving this aspect requires better software (by developing applications specifically designed for the use this technology in the interventional cardiology field) and hardware (to facilitate the spatial location of both holograms and patients).

In conclusion, mixed reality can improve the integration of different imaging modalities while performing cardiovascular procedures on our patients. Also, it allows the operator to focus on a single working site, which has the potential of improving the patient's safety parameters. Thanks to these advantages and the fact that technology has finally reached its maturity at an affordable cost, the continuity of this line of work could be crucial to push interventional cardiology into the future.

FUNDING

The HAMMOND project received a grant from Castille and León Regional Health Authority (GRS 2275/A/2020), and Instituto de Salud Carlos III (DTS21/00158).

AUTHORS' CONTRIBUTIONS

A. Redondo, and I.J. Amat-Santos contributed substantially to the study design, data curation, analysis or interpretation. C. Baldrón, and J.M. Aguiar contributed to the study design, data curation and interpretation. J.R. González Juanatey, and A. San Román gave their final approval. All the authors performed a critical review of the manuscript intellectual content, and take full responsibility for the accuracy and truthfulness of the study.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000322.

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REC Interv Cardiol. 2022;4(4):343-348
https://doi.org/10.24875/RECICE.M22000300

Clinical case

Percutaneous closure of fistula between pulmonary trunk and Fontan circulation

Cierre de fístula entre tronco pulmonar y circuito de Fontan de forma percutánea

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https://doi.org/10.24875/RECICE.M22000302

CASE PRESENTATION

Fontan procedure is a complex surgery with more risks compared to other cardiac surgeries. Also, complications have been associated with it because of its physiology being the most common of all elevated blood pressure in the cavopulmonary connection, low cardiac output syndrome, hypoxemia, and arrhythmias; others like plastic bronchitis, protein-losing enteropathy, ascites, pleural effusion, portal hypertension, and hepatic fibrosis can also occur. Similarly, connections between the pulmonary and the systemic circuits can be established triggering higher pressures of Fontan circulation.

This is the case of a 17-year-old male patient diagnosed at birth with tricuspid atresia with restrictive interventricular communication (IVC), large vessel malapposition, and severe mixed pulmonary stenosis (PS). The patient's corresponding informed consents—that remain on file—were obtained to conduct this study.

At the age of 7 the patient was treated with a single-stage fenestrated Fontan procedure with independent anastomoses of the superior vena cava and, on the other hand, right atrial roof with right pulmonary branch, ventricular septal defect enlargement, and pulmonary artery trunk ligation (video 1 of the supplementary data). Lesion was solved with continuous suture during surgery in the left circumflex coronary artery. Disease progression was good, and the patient remained asymptomatic for the next 7 years with excellent functional capacity and 95% oxygen saturation. At the follow-ups, the echocardiographic presence of severe subvalvular pulmonary stenosis was confirmed with pulmonary artery trunk dilatation and turbulent flow inside. No other findings were reported.

In the clinical examination performed at 14 years, the transthoracic echocardiography revealed the presence of severe subvalvular pulmonary stenosis (figure 1) with a gradient of 90 mmHg through it plus suspected fistulization between the pulmonary artery trunk and Fontan circulation (figure 2) with a pulsatile flow with a maximum systolic gradient of 73 mmHg. Diastolic flow was maintained from the pulmonary artery trunk towards the right atrium while connected to the pulmonary branches. Cardiac catheterization was performed. It revealed a mean Fontan pressure of 16 mmHg and oximeter jump between the pulmonary artery compared to the rest of circulation (91% vs 78%) discarding aortopulmonary collaterality. Ventriculography revealed the presence of severe subvalvular pulmonary stenosis with aneurysmal dilatation of pulmonary artery trunk and presence of a fistula between the trunk and the right pulmonary artery (figure 3 and video 2 of the supplementary data). Also, the presence of a pseudoaneurysm of posterior location and left to the aorta (30 mm x 38 mm) with a wide entry (figure 4 and video 3 of the supplementary data), and calcification in pairs with mobility basically of the posterior wall associated with the coronary event of the surgical procedure.

After the diagnosis of fistula between the pulmonary artery trunk and Fontan circulation plus the left ventricular pseudoaneurysm, a medical-surgical session was presented where the fistula was percutaneously closed and subvalvular pulmonary stenosis was solved. Regarding the pseudoaneurysm, due to the size of the entry orifice, the percutaneous procedure was ill-advised. This, added to serial radiographic stability, suggested the use of conservative approach.

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Online: 05-07-2022.

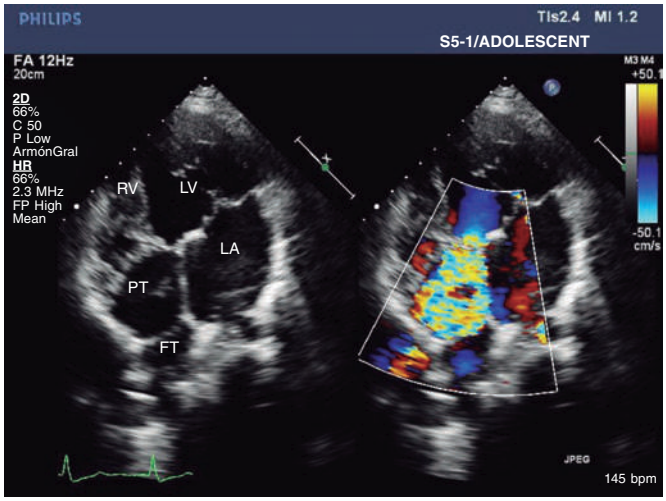

Figure 1. Echocardiographic apical four-chamber view showing the origin of turbulent flow in the subpulmonary region until the roof of pulmonary trunk. FT, Fontan tube; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle.

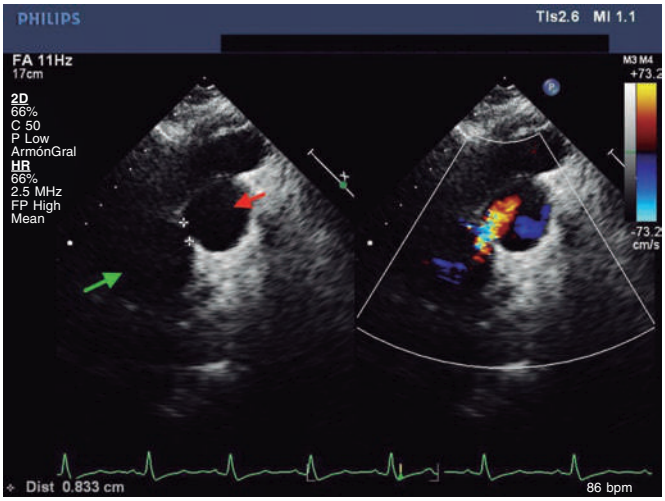

Figure 2. Echocardiographic right parasternal view showing the connection between the pulmonary trunk and pulmonary circulation with passage of flow. Green arrow: pulmonary trunk. Red arrow: right pulmonary branch.

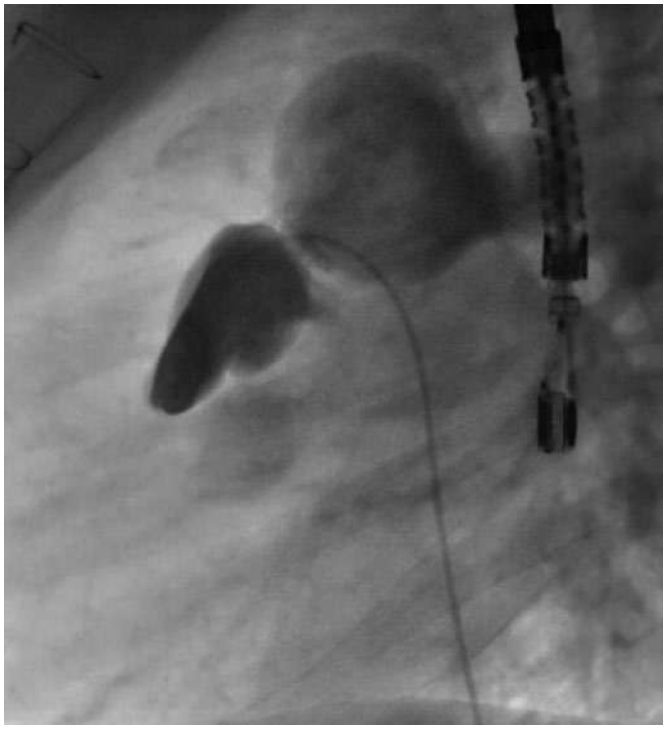

Figure 3. Lateral angiography in the pulmonary trunk showing the fistula towards the right branch.

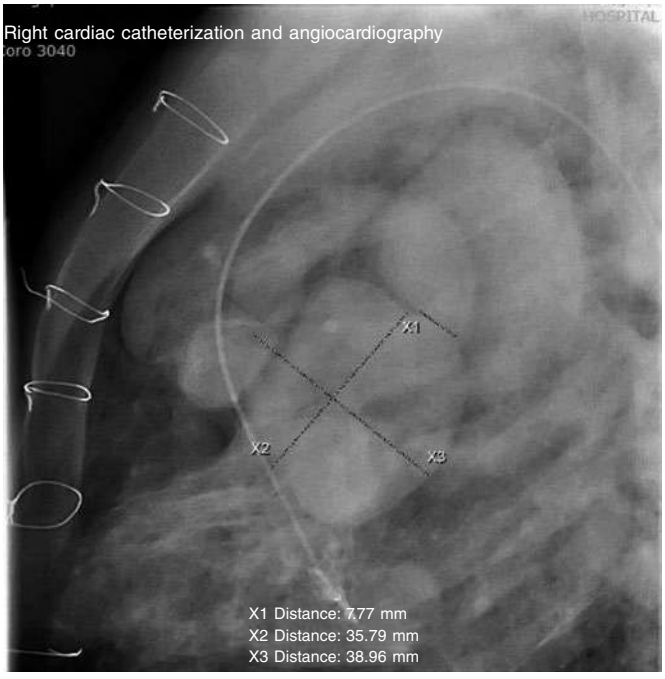

Figure 4. Ventriculography showing pseudoaneurysm, pulmonary trunk, and anterior aorta in vessel malapposition with passage of contrast from the pulmonary trunk towards Fontan circulation. X1: fistula between the pulmonary trunk and the right branch. X2 and X3: dimensions of pulmonary trunk.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

J.M. Blanco Borreguero drafted and reviewed the manuscript. I. Guillén Rodríguez assisted the patient and supervised the manuscript. L. Marcos Fuentes assisted the patient and provided the images. A. Capilla Miranda drafted and reviewed the manuscript. J.F. Coserria Sánchez supervised the manuscript, assisted the patient, and provided the images.

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.M22000300.

https://doi.org/10.24875/RECICE.M22000301

Percutaneous closure of fistula between pulmonary trunk and Fontan circulation. How would I approach it?

Cierre de fístula entre tronco pulmonar y circuito de Fontan de forma percutánea. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

There is no doubt that, procedurally, the case of fistulization reported between the pulmonary artery trunk and the right pulmonary branch is an interesting case similar to common situations reported in the routine clinical practice where pulmonary trunk surgical ligation is not complete thus leaving residual passage between the heart and Fontan circulation. This is unsought because it sends already oxygenated blood back to the lung, which overloads a circulation so sensitive as the Fontan one that lacks heart pump and works through venous pressure gradient.

In this type of procedures, closing the junction between the branch and the pulmonary trunk is often enough. Different strategies exist for this purpose. First, we need to think about the approach that should be used to close the defect. In this case, although the existence of fenestration (communication between Fontan circulation and the systemic atrial region) facilitates occlusion using the antegrade (through the ventricle) and retrograde (coming from the pulmonary artery) approaches, the latter is often easier and faster to use. Procedure can be performed via femoral access. The bigger the patient the easier the procedure. However, in very small patients, it is often easier to perform via jugular access that allows direct and straight access to the pulmonary branch in Fontan circulation. Also, it provides great support to perform the procedure.

While closing the defect, if there is a stenosis in that region, a polytetrafluoroethylene (PTFE) covered stent can be implanted to both treat the stenosis and close the antegrade passage. In the absence of stenosis, we can proceed by closing the defect directly. Since it is a region previously ligated through surgery, it is often too rigid and gives devices enough support, which means that significant device oversizing or large retention discs to achieve stability are not usually needed. If there are doubts on the consistency of the defect, a compliant balloon can be used for assessment purposes.

We often use the Amplatzer Vascular Plug II occluder device (Abbot Cardiovascular, United States) that, in this particular case, could be 12 mm or 14 mm in size—meaning having to use 5-Fr or 6-Fr sheaths capable of navigating with standard Teflon coated or a little more rigid guidewires like the ones used to implant IAC devices. Coming from the pulmonary branch, implantation is based on leaving the distal disc and the body of the device inside the aneurysm, retrieving device and sheath en bloc until the device reaches the end, and

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eventually releasing the proximal disc that will stay inside the right branch. Type II Amplatzer occluder devices—that have a better profile—can be used in defects ≤ 5 mm leaving in this case the body in the defect and a large retention disc in each side. If compliance of the defect and stability worry us due to its specific characteristics, interatrial communication occluder devices can be used. For the diameters needed in these cases, IAC devices have very large discs compared to the body of the device and defect that should be occluded. Depending on the diameter selected—7-Fr or 9-Fr sheaths—are needed, and probably more rigid guidewires, especially from femoral access.

In most cases, the exclusive closure of the connection with the branch is performed by preserving Fontan circulation, and opening a way for a seesaw high-pressure passage in the trunk. This type of flow barely generates any complications. In this case, and given the aneurysmal dilation of the trunk, and to prevent its progression, its closure at valvular and subavalvular stenosis level seems reasonable prior to the closure of the connection between trunk and branch (in procedures performed from the pulmonary artery). Such closure could be performed with an AVP-II device, and probably with a 6-Fr sheath and a standard or a little more rigid guidewire. We could even think of using an Amplatzer VSD occluder device. Its advantages are that it is more rigid and contains polyester fabric in the nitinol mesh thus promoting an earlier closure of flow through it compared to devices that don't have it except for a mesh like the AVP II. The use of an Amplatzer VSD occluder device would require 7-Fr or 8-Fr sheaths, and a more rigid guidewire.

In conclusion, very many different approaches can be used: antegrade (by fenestration), retrograde, femoral or jugular being the process of selection in elderly patients with non-complex anatomies less important. However, it is more relevant in younger patients or with complex anatomies in whom retrograde and jugular accesses often guarantee immediate support, which facilitates the procedure significantly.

FUNDING

None whatsoever.

CONFLICTS OF INTEREST

None.

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https://doi.org/10.24875/RECICE.M22000302

Percutaneous closure of fistula between pulmonary trunk and Fontan circulation. Case resolution

Cierre de fístula entre tronco pulmonar y circuito de Fontan de forma percutánea. Resolución

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https://doi.org/10.24875/RECICE.M22000301

CASE RESOLUTION

Traditionally, the percutaneous closure of this type of defects has been performed using coil embolization procedures and ductus arteriosus closure devices. However, since the appearance of the Amplatzer Vascular Plug (Abbott, United States) its effectiveness in the embolization of certain types of collaterals and fistulae in congenital heart diseases has been recognized.[1] Amplatzer Septal Occluders devices (Abbott, United States)—designed for septal defect closure—can be used in certain situations to close non-septal defects, among them, pulmonary systemic fistulae[2] and, in general, communications between systemic and pulmonary circulation.

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Online: 05-07-2022.

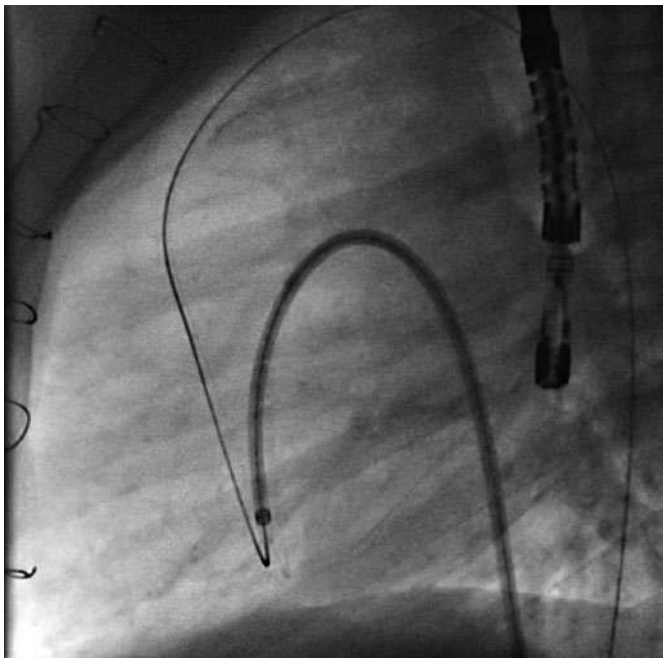

Figure 1. Ascent of the 180º 6-Fr Amplatzer TorqVue sheath towards the left ventricle.

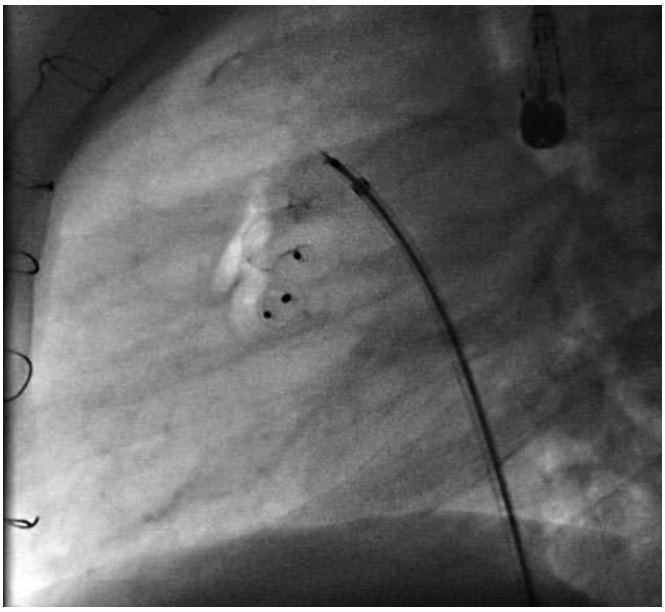

Figure 2. Muscular Amplatzer VSD occluder device implanted at subvalvular pulmonary stenosis level, and Amplatzer Septal Occluder implanted in the communication between the pulmonary trunk and the pulmonary branch.

Once the fistula between the pulmonary artery trunk and Fontan circulation was diagnosed, the procedure was performed under general anesthesia, and fluoroscopy and transesophageal echocardiography guidance. Cardiac catheterization was performed via right femoral vein (6-Fr) and right femoral artery (5-Fr).

The retrograde ascending aortic route was used. The left ventricle was accessed and a 0.014 in moderate support guidewire (PT2) (Boston, United States) was used to pass antegradely the subpulmonary stenosis, and the pulmonary trunk until the superior vena cava passing through the fistula. After capturing the border of the guidewire using a 20 mm Gooseneck snare (EV3), an arteriovenous loop was created to facilitate the placement of an 0.035 in Emerald guidewire (CORDIS, United States) and the ascent of a 180º 6-Fr Amplatzer TorqVue sheath (Abbott, United States) via venous access (figure 1).When the border of the sheath was placed inside the left ventricle, a 10 mm muscular Amplatzer VSD occluder device (Abbott, United States) was implanted at subvalvular pulmonary stenosis level followed by a 10 mm Amplatzer Septal Occluder that was successful and uneventfully implanted in the communication between the pulmonary trunk and the pulmonary branch (figure 2) reducing Fontan pressures down to 14 mmHg without flow obstructions towards the branches (videos 1-3 of the supplementary data). The muscular Amplatzer VSD occluder device implanted at subvalvular pulmonary stenosis level was selected for its greater consistency to withstand the hemodynamic stress at that area. The Amplatzer Septal Occluder implanted between the pulmonary trunk and the pulmonary branch was selected for its proper size and morphology regarding the defect. Both devices were implanted so that the jet of pulmonary stenosis would not dilate the pulmonary trunk or triggered the formation of thrombi.

Finally, left ventriculography revealed the absence of contrast passage towards the pulmonary trunk and Fontan circulation, and the presence of a pseudoaneurysm already present in a former study (figure 3) with a 24 mm × 26 mm orifice opening and a 32 mm × 36 mm saccular formation with calcification in its anterior side. The patient remained on the same treatment prior to the procedure (acetylsalicylic acid, and enalapril), and antiplatelet therapy was reinitiated 24 hours later. The imaging modalities performed at the follow-up confirmed the absence of pseudoaneurysm development, which is why a conservative approach has been adopted ever since.

The patient's corresponding informed consents—that remain on file—were obtained to conduct this study.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

J.M. Blanco Borreguero drafted and reviewed the manuscript. I. Guillén Rodríguez assisted the patient and supervised the manuscript. L. Marcos Fuentes assisted the patient and provided the images. A. Capilla Miranda drafted and reviewed the manuscript. J.F. Coserria Sánchez supervised the manuscript, assisted the patient, and provided the images.

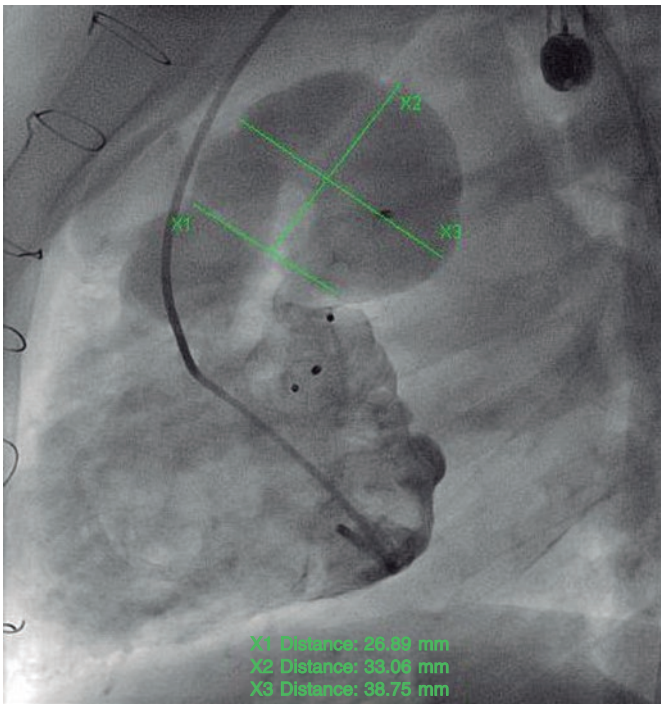

Figure 3. Ventriculography after device implantation showing the aneurysm of pulmonary trunk with visualization of the pseudoaneurysm.

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.M22000302.

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REC Interv Cardiol. 2022;4(4):349-350
https://doi.org/10.24875/RECICE.M22000275

Double pre-stenting for percutaneous pulmonary valve implantation

Doble stent *previo al implante de válvula pulmonar*

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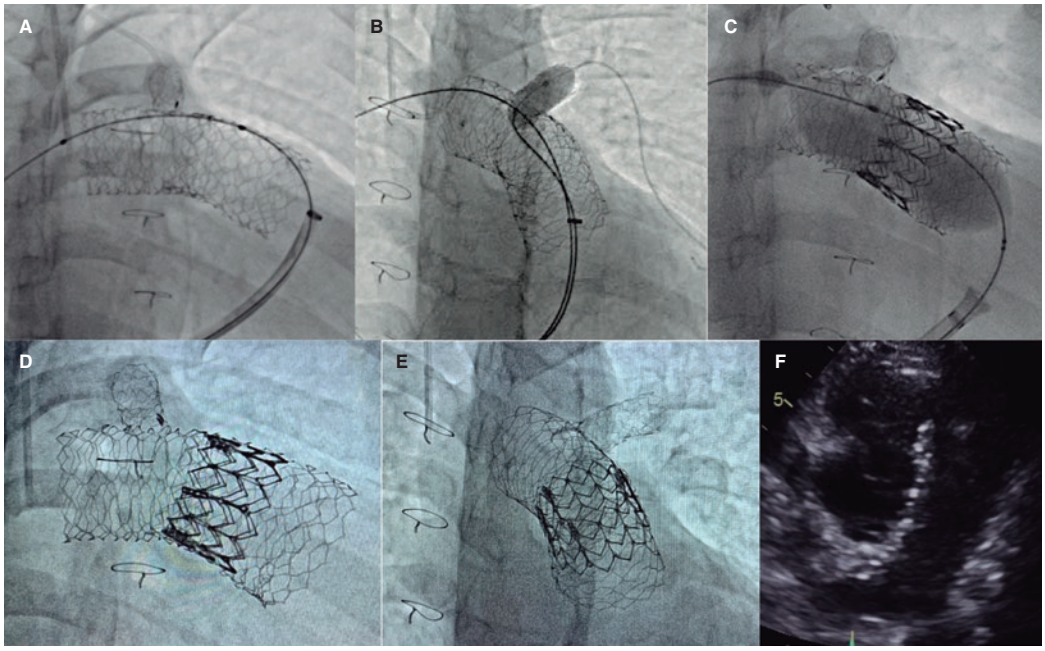

Figure 1.

Pre-stenting of the right ventricular outflow tract (RVOT) is often performed before percutaneous pulmonary valve implantation to guarantee a stable landing zone. One common off-label indication is the presence of a large native RVOT, which requires the anchoring of an extra-large stent.

This is the case of a 17-year-old woman with a repaired Fallot´s tetralogy admitted for the assessment of severe pulmonary regurgitation with RV dilatation (video 1 of the supplementary data). The patient was ranked as NYHA functional class III. The cardiac magnetic resonance imaging revealed the presence of a large RVOT with diameters of 27 mm x 26 mm (video 2 of the supplementary data).

For SAPIEN XT valve implantation (Edwards Lifesciences, United States) and to prevent stent migration, the "double-stent" technique was used. A 57 mm AndraStent XXL stent (Andramed, Germany) was pre-mounted on a 26 mm balloon followed by distal-to-proximal implantation from right pulmonary artery to pulmonary trunk. Afterwards, a second 48 mm AndraStent XXL stent was pre-mounted on a 30 mm balloon and partially implanted overlapping the former stent (figure 1A). A stent that remained in the left pulmonary branch that was implanted at a younger age was dilated with a 10 mm balloon through the new stents (figure 1B). Then, a 29 mm SAPIEN XT valve with 2 extra mL for balloon inflation was advanced and implanted successfully (figure 1C,F). No residual gradient or significant regurgitation were reported. The patient was discharged 2 days later and remains in NYHA class I after 8 months. The father's patient has given his verbal consent for the publication of this case report.

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Received 10 December 2021. Accepted 7 February 2022. Online: 16-03-2022.

Double overlapping pre-stenting with the AndraStent XXL stent provides valid anchoring support for percutaneous pulmonary valve implantation in large native RVOTs.

FUNDING

None reported.

AUTHORS' CONTRIBUTIONS

All the authors drafted this manuscript, read and approved its final version.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000275.

REC Interv Cardiol. 2022;4(4):351-352
https://doi.org/10.24875/RECICE.M22000294

Left main coronary artery embolization after transcatheter paravalvular leak closure

Embolización en el tronco coronario tras el cierre percutáneo de fuga paravalvular

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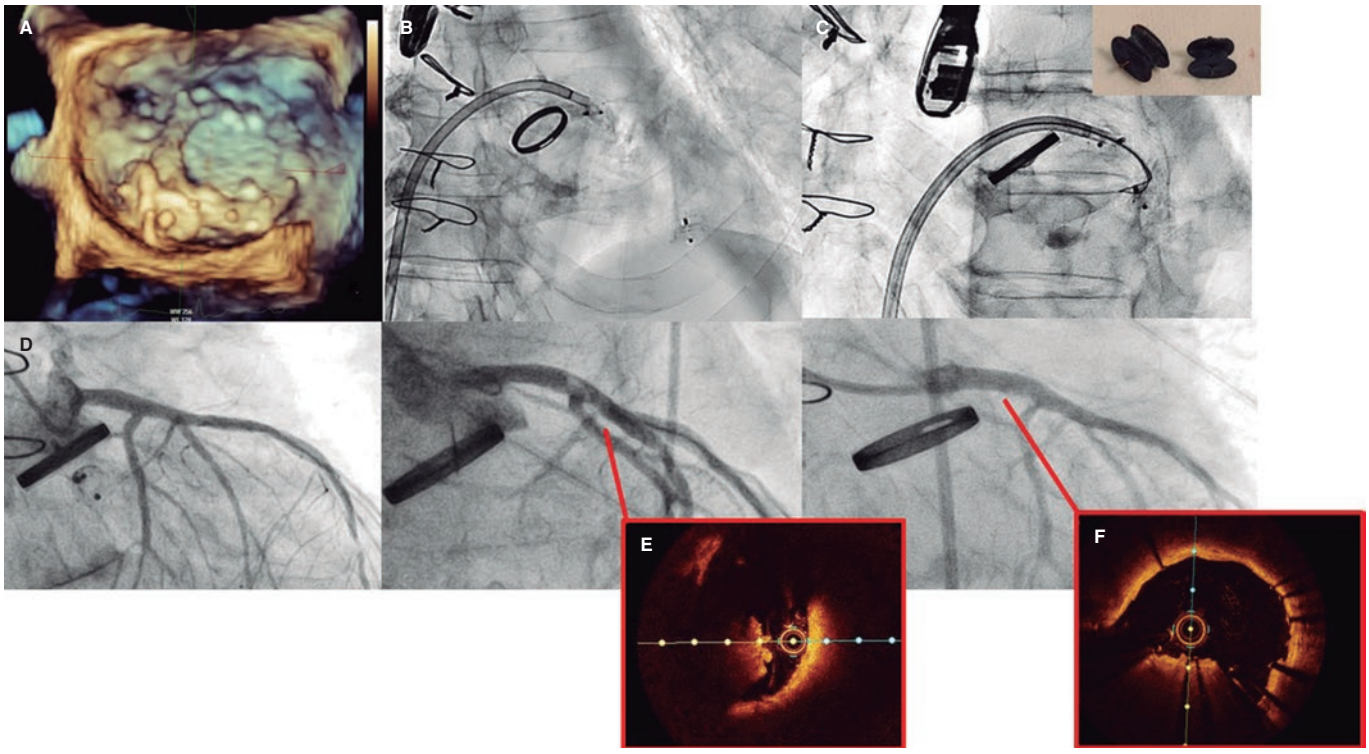

Figure 1.

This is the case of a 72-year-old man with mitral and aortic mechanical prosthetic valves, chronic kidney disease, and severe pulmonary hypertension. In 2019, a mitral anterolateral paravalvular leak (PVL) was percutaneously closed with implantation of 2 devices (the AVP III 10 mm x 5 mm, and the AVP III 8 mm x 4 mm, St Jude Medical, United States) due to heart failure. The patient's clinical progression was favorable with moderate mitral regurgitation. One year later, the patient's symptoms worsened, and the transesophageal echocardiogram performed revealed severe mitral regurgitation due to recurrent PVL around the devices (figure 1A). A second percutaneous closure attempt was scheduled to close the PVL. The initial procedure was to implant another device next to the other devices, but they embolized into the left ventricle when the deflectable catheter touched them (figure 1B). They were captured using a gooseneck loop snare through the PVL and then retrieved using 2 sheaths in the left atrium (figure 1C). Two hours later, the patient developed hemodynamic instability, and ST-segment elevation. An emergency coronary angiogram revealed the presence of severe stenosis in the left main coronary artery (LMCA) that was not present in the previous angiogram (figure 1D). The optical coherence tomography demonstrated calcium embolization (figure 1E) that was treated with stenting (figure 1F). Eventually, the patient underwent the surgical repair of the PVL. As far as we know,

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Received 24 Juanuary 2022. Accepted 25 march 2022. Online: 27-04-2022.

this is the first time that coronary artery embolization of calcified tissue in the LMCA is ever reported during maneuvers to retrieve embolized devices in the left ventricle. The non-occlusive nature of the LMCA embolus may have led to a better prognosis. The patient accepted the publication of the case and have his informed written and signed consent.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

A. Pardo Sanz gathered all the information, prepared, and drafted the case report. L. Salido Tahoces was one of the interventional cardiologists involved. J.L. Mestre Barcelo, and M. Abellás Sequeiros helped prepare the case. J.L. Zamorano Gómez is the head of the cardiology unit and collaborated during the manuscript review process. Á. Sánchez-Recalde is the head of the interventional cardiology unit, and one of the operators of the case.

CONFLICTS OF INTEREST

None reported.

REC Interv Cardiol. 2022;4(4):353-354
https://doi.org/10.24875/RECICE.M22000307

Giant mitral paravalvular leak closure using double transapical access

Cierre de fuga paravalvular mitral gigante con doble acceso transapical

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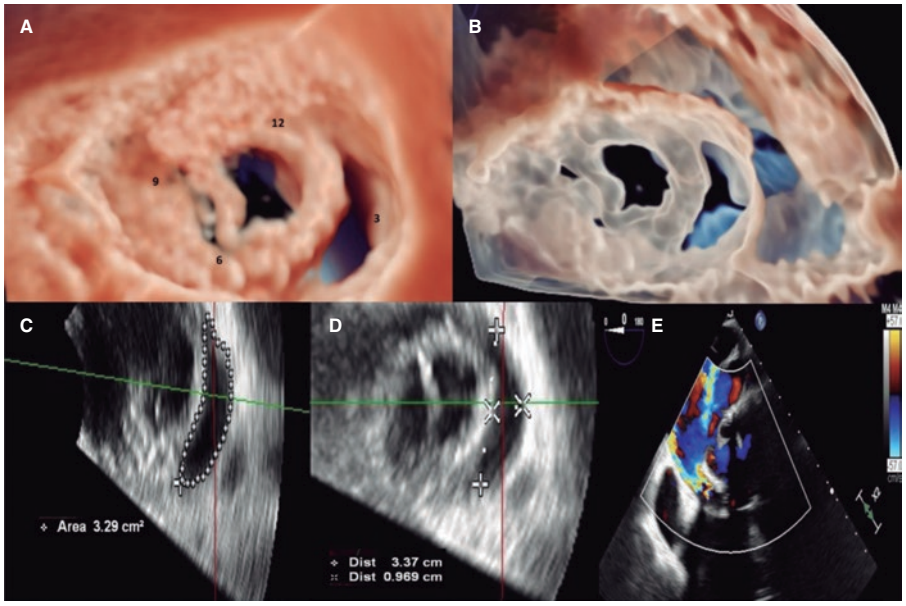

Figure 1.

This is the case of a 75-year-old man with heart failure (HF) due to severe aortic regurgitation caused by infective endocarditis treated with aortic and mitral bioprosthetic valve replacement. At 6 months, HF relapsed due to severe mitral paravalvular leak (PVL) regurgitation caused by a giant 33 mm x 9 mm crescent-shaped leak of medial-posterior location (2 to 5 o'clock position), with an area of 3.29 cm^2 (figure 1A-E, video 1 of the supplementary data). The patient was deemed at prohibitive surgical risk, and gave his informed consent to undergo catheter based PVL closure. The procedure was performed in a hybrid operating room under general anesthesia, continuous real-time 2D/3D transesophageal echocardiography (TEE) color Doppler imaging and fluoroscopic guidance. An open surgical retrograde double transapical access (hybrid technique) was preferred due to the considerably huge size of the leak and the possible need for multiple simultaneous large devices. Through the 2 short sheaths placed at the left ventricle apex we easily passed the leak in sequence with 2 0.035-in hydrophilic guidewires that were later exchanged for 2 extra-stiff guidewires placed in the pulmonary veins (figure 2A-B). Afterwards, we implanted a 18 mm x 10 mm rectangular waist (RW) paravalvular leak device (PLD, Occlutech, Sweden) followed by a 14 mm x 6 mm RW PLD, simultaneously (figure 2C-F, video 2 of the supplementary data). The final 2D/3D TEE confirmed the effective closure of this gigantic mitral PVL (figure 3A-D). The postoperative course was uneventful, and the patient was discharged with an improved clinical condition. At 2-month follow-up, 2D/3D TEE color Doppler imaging confirmed the stable position of the device with trivial residual leak. In the case of this giant mitral PVL, the choice of specifically designed device technology and the double transapical access were the key to success.

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Received 11 March 2022. Accepted 11 May 2022. Online: 26-05-2022.

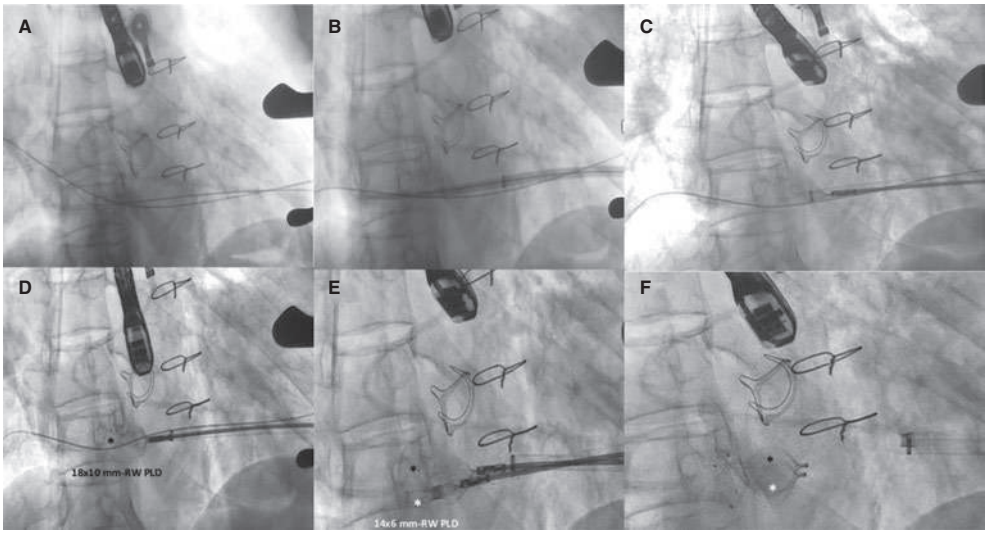

Figure 2.

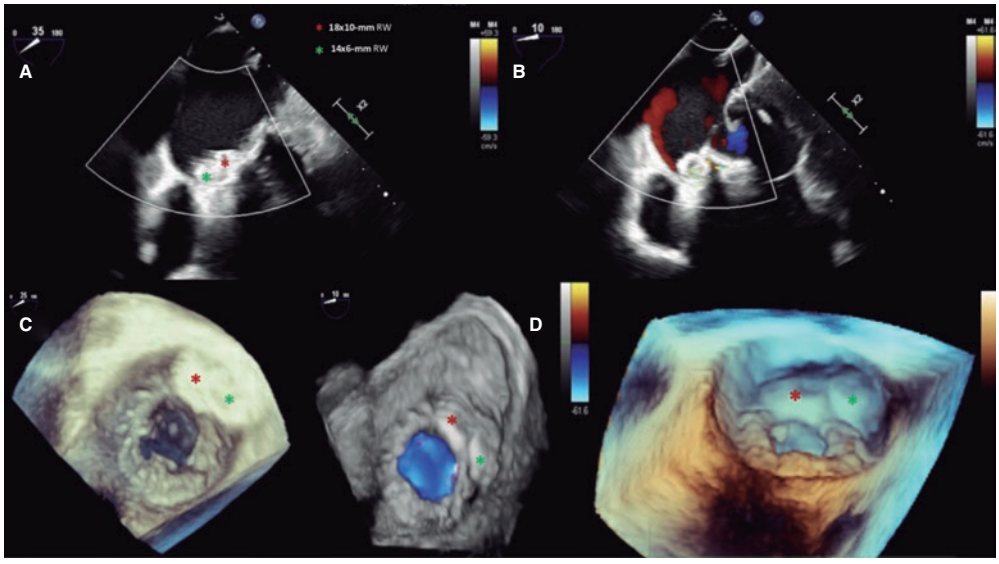

Figure 3.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

E.M. Onorato drafted the initial manuscript. All authors critically reviewed the manuscript and approved its final version.

CONFLICTS OF INTEREST

E.M. Onorato is a consultant for Occlutech. The remaining authors declared no conflicts of interest whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000307.