REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

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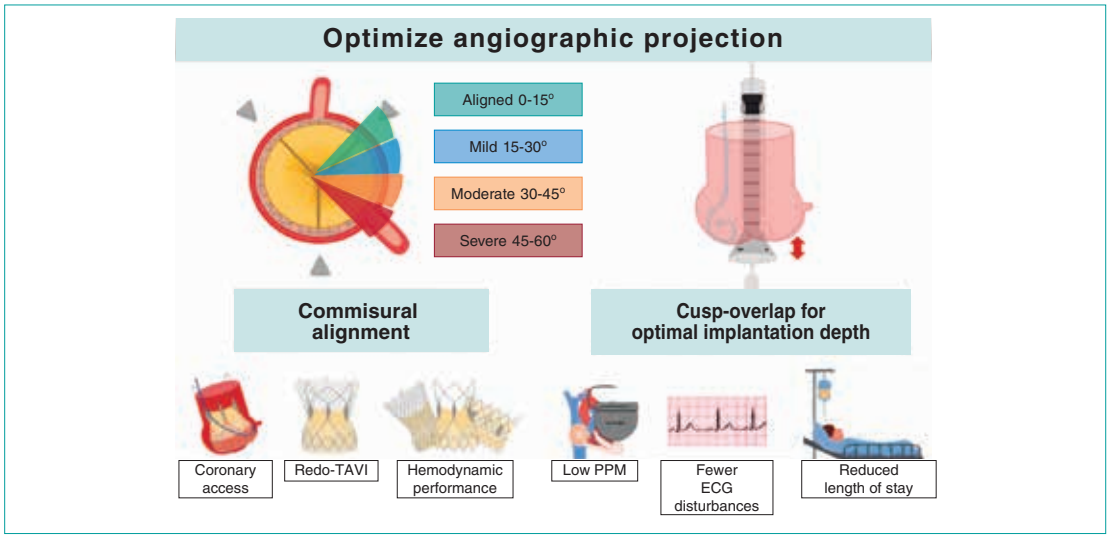

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA | Asociación de Cardiología Intervencionista

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REC publications

REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

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REC: Interventional Cardiology goes from strength to strength

REC: Interventional Cardiology consolida su impacto y gana reconocimiento

José M. de la Torre-Hernández,[a,*] Fernando Alfonso,[b] Raúl Moreno,[b] Soledad Ojeda,[b] Armando Pérez de Prado,[b] and Rafael Romaguera[b]

[a] *Editor-in-chief, REC: Interventional Cardiology*
[b] *Associate editor, REC: Interventional Cardiology*

In June 2023, the first impact factor for *REC: Interventional Cardiology* was announced. We all factor level while received the news with great excitement, those of us who work directly on the journal as well as our authors, reviewers, and readers. The figure added to the numerous indexations already achieved by our journal. Although this was undoubtedly a great accomplishment after years of hard work and dedication, it also marked the beginning of an annual continuous review process, with a load of commitment and expectations. Once a scientific publication enters this dynamic—as it happens with annual distinctions awarded in other professional fields—the expectations on its progress introduce a certain level of anxiety concerning the annual reviews.

The interim edition of Journal Citation Reports (JCR)[1] was released just a few weeks prior to the drafting this "Editor's page". In this report, *REC: Interventional Cardiology* maintains its impact factor (figure 1). This is, obviously, excellent news.

The new impact factor (1.2)—which is slightly lower than the year before (1.4)—suggests stability, as it is the result of a more balanced distribution of citations, with several articles generating 1 to 3 citations compared with the large volume of citations generated by a single article[2] the previous year. Additionally, there is a slight increase in citable articles (54 vs 52)—a sign of growth—which is why we believe that this new impact factor is more realistic and solid.

More and more of our readers and authors are quoting the journal papers in their publications, which undoubtedly increases its visibility and impact.

While bibliometric impact is very important for a scientific journal, we cannot overlook the utility of our journal in teaching and clinical practice, where the real value of our journal lies.

As we have always pointed out, and will continue to do so, these achievements can be attributed to the entire interventional cardiology community, the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) governing boards that have served throughout the years, authors, reviewers, and all team members from the editorial office.

MOST SIGNIFICANT CHANGES

As a result of the continuous process of improvement undergone by our journal, a series of changes have been made. The first one aimed at ensuring not only a deeper scientific review of the manuscripts but also that, regardless of their limitations, their methodology is detailed in a way that facilitates the reproducibility of the studies. To this end, a checklist has been implemented for authors and editors alike so they can review all methodological aspects involved.

Another key aspect has been the rigorous review of the English version of our articles. As part of our commitment to the quality of our publication, additional controls have been implemented to make sure that the quality of the English version of our journal is consistent with the standard set by *Revista Española de Cardiología*.

Finally, at the end of 2023, the "Case report" section of our journal was discontinued. Although we had a hard time making this decision given the success of this section, it was mainly triggered by the inherent difficulty of these papers in presenting the proper editorial quality. In fact, this type of articles is absent in higher-tier publications. Moreover, since only one case was being published per issue, the rejection rate was very high, causing frustration among many authors who were submitting genuinely interesting cases. Nonetheless, isolated cases can still be submitted as "Images in cardiology", and case series (at least 3) as "Scientific letters".

We hope that all these improvements will be positively considered by the indexing agencies.

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@RevEspCardiol #recintervcardiol

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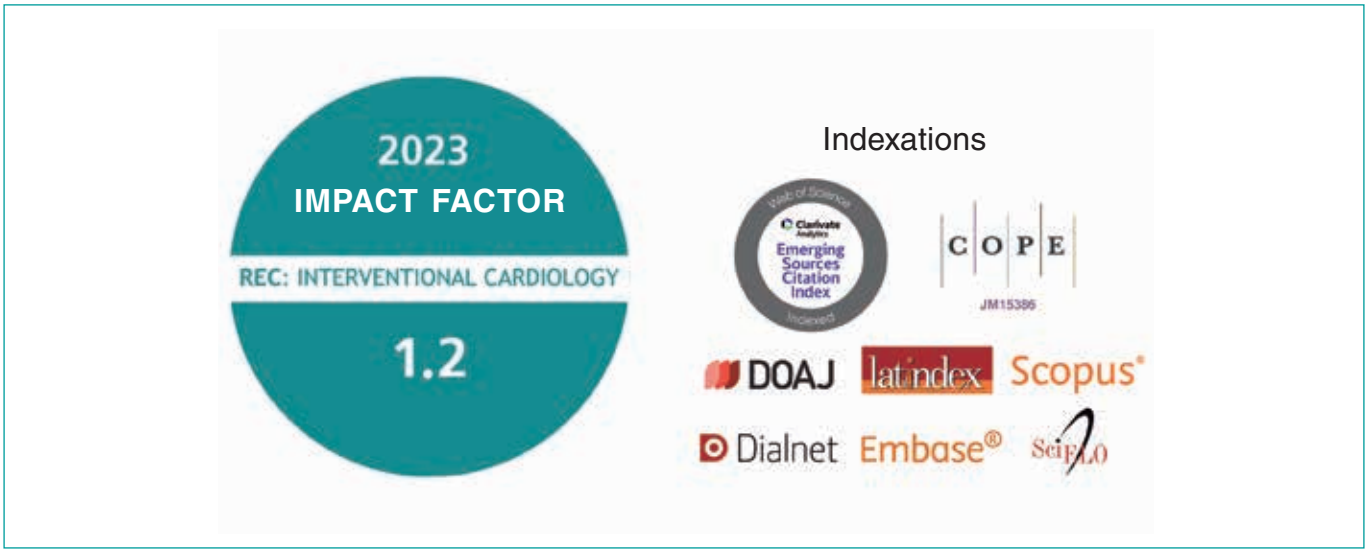

Figure 1. Impact factor and quartile of the interim edition of the Journal Citation Reports, and current indexing of *REC: Interventional Cardiology*.

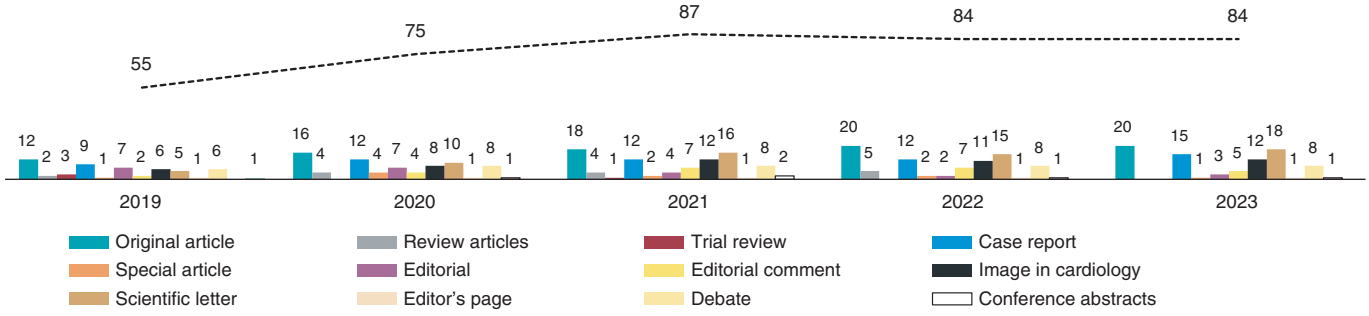

Figure 2. All sections published from 2019 through 2023. Conference abstracts are counted as 1 unit. Each case report is counted as 3 units, as it includes 3 independent articles: Presentation, How would I approach it?, and Resolution.

EDITORIAL ACTIVITY

Since the inception of our journal, all quarterly issues have included original articles (OA), review articles, scientific letters, cases, images, debates, and editorials on topics of special interest. Moreover, ACI-SEC-sponsored consensus documents appear periodically, as well as the compilation of the abstracts presented in its annual congress.

The overall number of published sections illustrated by figure 2 shows how, after the growth experienced throughout the early years, it has remained stable in recent years.

Our journal is bilingual, and research can be submitted in both Spanish and English. In recent years, there has been an increased number of manuscripts received in English (figure 3).

Before discussing content by type, we would like to mention that the journal is joining a paperless trend inspired by immediacy and accessibility, environmental commitment, and cost optimization. Therefore, as of 2024, our journal no longer has a print version, only a digital one.

Below, we present statistical data on the different types of articles. Of note that data for 2024 correspond only to the first half of the year.

Original articles

OAs are the most valuable content of a scientific journal. Attracting high-quality OAs is the top priority for a journal. Receiving enough OAs is the only way to guarantee that the highest-quality ones will be selected for publication. In 2023 we experienced a notable increase in the number of OAs received as shown in figure 4. The current year trend is similar in the number of OAs being published.

As we mentioned before, more OAs are now being received in English, which, to some extent, is indicative of a greater international interest in our journal (figure 5). In fact, a significant proportion of the manuscripts received come from different countries—36 overall—with notable representations from Portugal, Mexico, Italy, Argentina, and the United States.

An unquestionable indicator of the quality of a scientific journal—also easily noticeable by the authors—is the speed at which editorial decisions are made. In this regard, we can be very satisfied with our turnaround time (figure 6), which remains very reasonable compared with those of other prestigious journals.

If we want *REC: Interventional Cardiology* to establish itself as a highly recognized publication in our field, it is essential that we

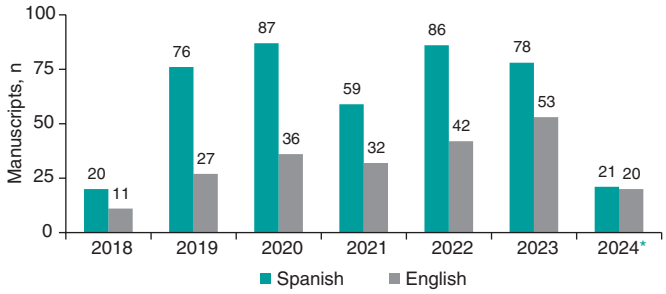

Figure 3. Original language of the manuscripts received.
* Data up to June 30th, 2024.

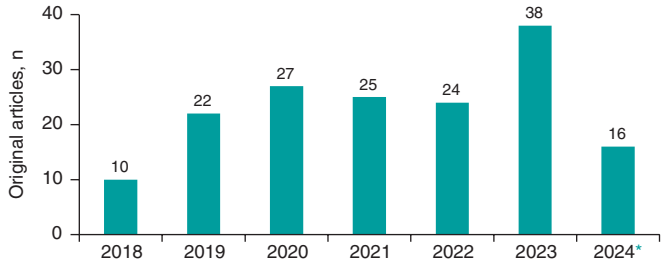

Figure 4. Submission of original articles.
* Data up to June 30th, 2024.

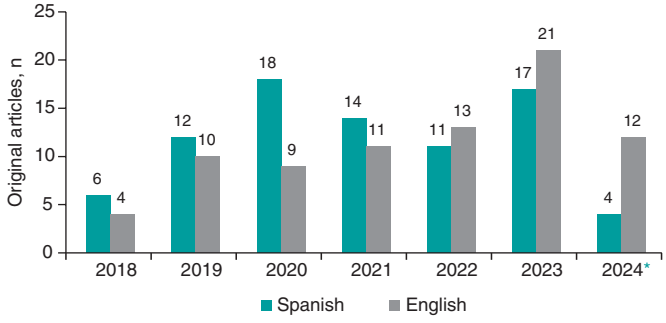

Figure 5. Submission of original articles by language.
* Data up to June 30th, 2024.

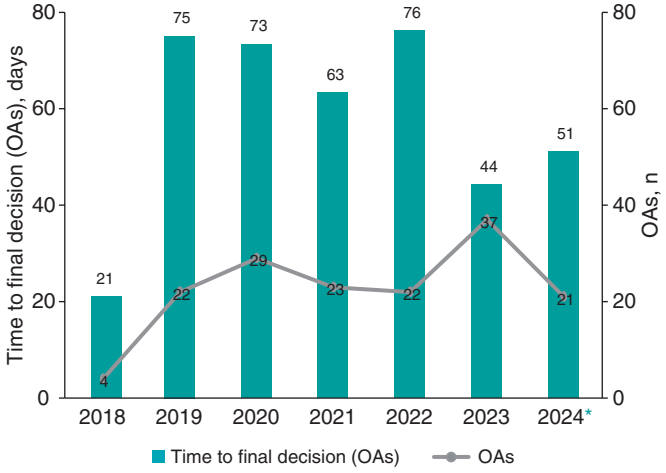

Figure 6. Mean number of days to make a final decision on original articles (OAs). Bars show the mean time it takes to make a decision. Gray line shows the volume of articles on which a decision was made each year.
* Data up to June 30th, 2024.

receive more OAs, which is why we invite the interventional cardiology community to keep on submitting their research articles.

Scientific letters

Scientific letters can be described as brief OAs, sometimes descriptive of small case series. Figure 7 shows the significant peak reached in submissions during the first phase of the COVID-19 pandemic. Although 2023 was again a very fruitful year, figures for the first half of 2024 indicate a clear decline. The decision to reject isolated cases for review in this format might explain the lower submission rate. However, in some cases, authors have accepted our suggestion to turn initially submitted OAs into scientific letters. We believe that, under proper circumstances, this can be an interesting alternative.

Images in cardiology

This section is very popular, which is not surprising since the interventional cardiology field generates an excellent and increasingly varied iconography. But, although images have become an endless source of manuscript production—all of them quite interesting by the way—only a fraction can be published due to editorial space constraints. The excessive stock of images awaiting publication led us to withhold the receipt of new images for a few months last year. In June 2024, however, this section was reinstated (figure 8).

Content transferred from *Revista Española de Cardiología*

One of the advantages of being part of the same editorial family is the ability to offer the transfer of manuscripts from the lead journal to its sister publications. *Revista Española de Cardiología* is a well-established international journal with a very high impact factor that draws multiple manuscripts. But, although the rate of rejection is high, many of the articles being rejected are of undeniable interest. However, this offer to go from a higher to a lower-impact journal always runs the risk of being rejected.

As shown in figure 9, 2023 saw an increase in the offer of transfers for OAs. As we predicted last year, authors have been responding more and more positively to this possibility. We are confident that the consolidation of the impact factor will make this option even more appealing to the authors.

Special contents

As it happens every year, each issue has featured editorials, reviews, consensus articles from ACI-SEC or in collaboration with other SEC associations or scientific societies, and other types of special documents (figure 10).[3-6]

In issue #3 of our journal, as usual, we published the abstracts presented at the ACI-SEC congress held in Las Palmas de Gran Canaria, Spain from June 12th through 14th, 2024.[7] These abstracts became available ahead of print since June 3rd. From this "Editor's page", we encourage their authors to complete the scientific process and submit the OAs of their research to our journal.

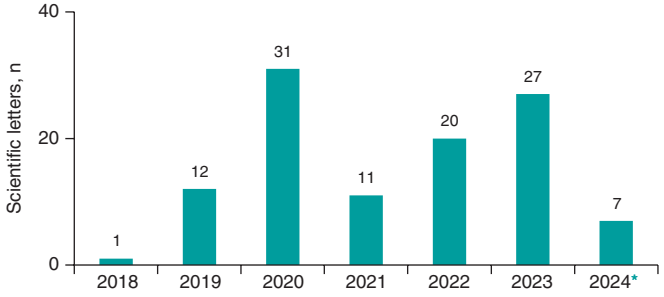

Figure 7. Submission of scientific letters.
* Data up to June 30th, 2024.

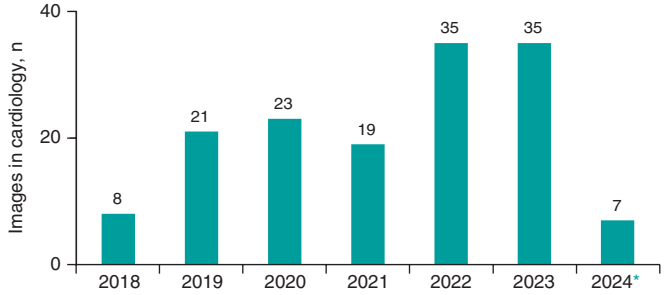

Figure 8. Submission of images in cardiology.
* Data up to June 30th, 2024.

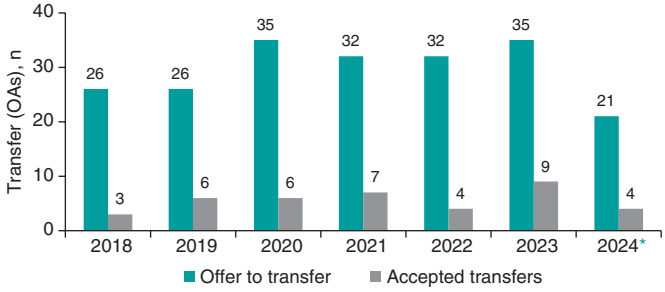

Figure 9. Offers to transfer original articles from *Revista Española de Cardiología* and number offers accepted within the same period.
* Data up to June 30th, 2024.

In May 2024, a tribute was held for Carlos Macaya on the 30th anniversary of the Benestent trial,[8] and our journal participated with a printed reprint on the history of the stent (figure 11).[9]

This year also saw the unexpected passing of the great master and pioneer of TAVI, Dr. Alain Cribier. Our journal joined the many tributes paid to him by commissioning an editorial to Eulogio García et al.[10] (figure 12).

REVIEWERS

Reviewers deserve special recognition in the editorial process of a scientific journal. Without their contribution, it would be nearly impossible to ensure the publication of high-quality, properly reviewed content. They perform this work anonymously, selflessly, and altruistically, dedicating part of their valuable time to reviewing and improving the quality of the manuscripts assigned to them. Thanks to their competence and efficiency, we have been

https://doi.org/10.24875/RECICE.M23000420
Diagnosis and treatment of patients with ANOCA. Consensus document of the SEC-Clinical Cardiology Association/ SEC-Interventional Cardiology Association/ SEC-Ischemic Heart Disease and Acute Cardiac Care Association/SEC-Cardiovascular Imaging Association
Carlos Escobar, Josep Gómez Lara, Javier Escaned, Antoni Carol Ruiz, Enrique Gutiérrez Ibañes, Leticia Fernández Friera, Sergio Raposeiras-Roubín, Joaquín Alonso Martín, Jaume Agüero, Jose María Gámez, Pablo Jorge-Pérez, Román Freixa-Pamias, Vivencio Barrios, Ignacio Cruz González, Amparo Martínez Monzonís, Ana Viana Tejedor

https://doi.org/10.24875/RECICE.M24000464
Edge-to-edge therapy in acute mitral regurgitation. Proposal for a management protocol of the Ischemic Heart Disease and Acute Cardiac Care, Interventional Cardiology, and Cardiovascular Imaging Associations of the Spanish Society of Cardiology
Ana Viana-Tejedor, Carlos Ferrera, Rodrigo Estévez-Loureiro, Manuel Barreiro-Pérez, Pilar Jiménez Quevedo, Luis Nombela-Franco, Pablo Jorge-Pérez, Isaac Pascual, Amparo Martínez Monzonís, Ana Belén Cid Álvarez

https://doi.org/10.24875/RECICE.M24000443
Use of cardiovascular registries in regulatory pathways: perspectives from the EU-MDR Cardiovascular Collaboratory
Ernest Spitzer, José M. de la Torre Hernández, Ingibjörg Jóna Guðmundsdóttir, Eugene McFadden, Claes Held, Claude Hanet, Eric Boersma, Claire B. Ren, Victoria Delgado, David Erlinge, Armando Pérez de Prado, Jeroen J. Bax, Jan G.P. Tijssen

https://doi.org/10.24875/RECICE.M24000456
Spanish cardiac catheterization in congenital heart diseases registry. Third official report from the ACI-SEC and the GTH-SECPCC (2022)
Fernando Ballesteros Tejerizo, Félix Coserría Sánchez, Alfonso Jurado-Román, Ignacio Cruz-González, María Álvarez-Fuente, Ignacio J. Amat-Santos, Pedro Betrián Blasco, Roberto Blanco Mata, José Ignacio Carrasco, Juan Manuel Carretero Bellón, Marta Flores Fernández, Alfredo Gómez-Jaume, Alejandro Gutiérrez-Barrios, Beatriz Insa Albert, Lorenzo Jiménez Montañés, Federico Gutiérrez-Larraya Aguado, Luis Andrés Lalaguna, Raúl Millán Segovia, Miguel José Navalón Pérez, Soledad Ojeda Pineda, Fernando Rueda Núñez, Joaquín Sánchez Gila, Ricardo Sanz-Ruiz, María Eugenia Vázquez-Álvarez, Juan Ignacio Zabala Argüelles

Figure 10. Sample of some special content published over the past year.[3-6]

https://doi.org/10.24875/RECICE.M24000463
Inception of the coronary stent: a story of successful collaboration between innovative scientists and the biotechnology industry
Fernando Macaya-Ten, Nieves Gonzalo, Javier Escaned, Carlos Macaya

Figure 11. Review article by Macaya-Ten et al.[9] presented as part of the tribute paid to Carlos Macaya on May 22nd, 2024.

Table 1. Reviewers of *REC: Interventional Cardiology* who conducted reviews from July 1st, 2023 through June 30th, 2024

César Abelleira	Enrique Gutiérrez-Ibañes
Juan H. Alonso-Briales	Felipe Hernández
María Álvarez-Fuente	Rosa A. Hernández-Antolín
Ignacio Amat	Pilar Jiménez-Quevedo
Eduardo Arroyo	Santiago Jiménez-Valero
Dabit Arzamendi	Alfonso Jurado
Lluís Asmarats	Chi-Hion Li
Pablo Avanzas	José A. Linares
Enrique Balbacid	Ramón López-Palop
Fernando Ballesteros	Íñigo Lozano
Manuel Barreiro	Gerard Martí
Teresa Bastante	Dolores Mesa
José A. Baz	Xavier Millán
Tomás Benito	Guillem Muntané
Sara Blasco	Manuel Pan
Salvatore Brugaletta	Eduardo Pinar
Ramón Calviño	Ander Regueiro
Pilar Carrillo	Fernando Rivero
Xavier Carrillo	Oriol Rodríguez
Belén Cid	Sandra Rosillo
Juan G. Córdoba	Fernando Rueda
Ignacio Cruz	Juan M. Ruiz-Nodar
Héctor Cubero	Valeriano Ruiz-Quevedo
Javier Cuesta	José Rumoroso
José A. de Agustín	Manel Sabaté
María Del Trigo	Pablo Salinas
José F. Díaz	Neus Salvatella
Alejandro Diego-Nieto	Ángel Sánchez-Recalde
Felipe Díez-Delhoyo	Juan Sanchis
Pablo Díez-Villanueva	Marcelo Sanmartín
Jaime Elízaga	Jorge Sanz-Sánchez
Ignacio Ferreira	Fernando Sarnago
Xavier Freixa	Javier Suárez de Lezo
Tamara García-Camarero	Luis Teruel
Bruno García del Blanco	María Thiscal López-Lluva
Marcos García-Guimaraes	Helena Tizón
Carmen Garrote	Francisco Torres
Javier Goicolea	Ramiro Trillo
Joan A. Gómez-Hospital	Leire Unzue
Josep Gómez-Lara	Beatriz Vaquerizo
Antonio E. Gómez-Menchero	Maite Velázquez
David González-Calle	José L. Zunzunegui
Nieves Gonzalo	

https://doi.org/10.24875/RECICE.M24000457

The challenging pathway to TAVI: in memory of Alain Cribier

Eulogio García, Leire Unzué, Rodrigo Teijeiro

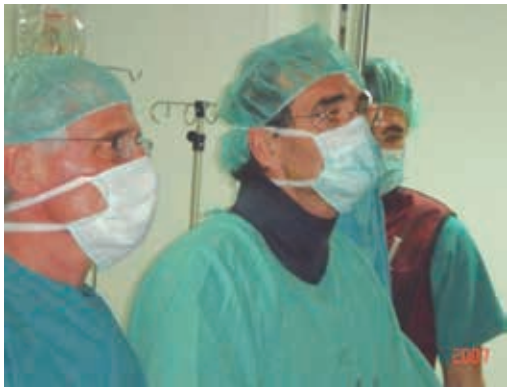

Figure 12. Commemorative editorial article by Eulogio García et al.[10] about Alain Cribier.

Table 2. Elite reviewers in 2023

Bruno García del Blanco
Josep Gómez-Lara
Pablo Salinas
Ángel Sánchez-Recalde
Ricardo Sanz-Ruiz

able to maintain excellent review deadlines in our journal, which have remained optimal throughout the years. There has been a slight increase this past year though (figure 13). This spike may be related to a certain overload effect. The number of medical reports in our specialty, as well as their frequency, has increased, and we have probably been over-relying on the same group of reviewers—those who most frequently accept to review and do so most effectively. We believe it is crucial to start adding new reviewers, combining different profiles for the same manuscript, thus giving the more experienced ones a break while bringing in younger reviewers.

Table 1 lists all reviewers who worked on manuscripts for *REC: Interventional Cardiology* from July 1st, 2023 through June 30th, 2024. Table 2 shows those who, in 2023, were named elite reviewers based on the number, speed, and quality of their reviews.

DISSEMINATION

At the recent ACI-SEC congress, awards were given to the best articles published in *REC: Interventional Cardiology* for an overall prize of €2500 (€1500 for 1st prize and €1000 for 2nd)[11,12] (figure 14).

OAs, review and special articles are the most visited sections on our website. In this regard, and as I am writing these lines, the OAs that have gained the most interest among those published throughout last year are *"Angina or ischemia with no obstructed coronary arteries: a specific diagnostic and therapeutic protocol"*, by Rinaldi et al.,[13] and *"Initial experience with the new percutaneous pulmonary self-expandable Venus P-valve"*, by Álvarez-Fuente et al.[14]

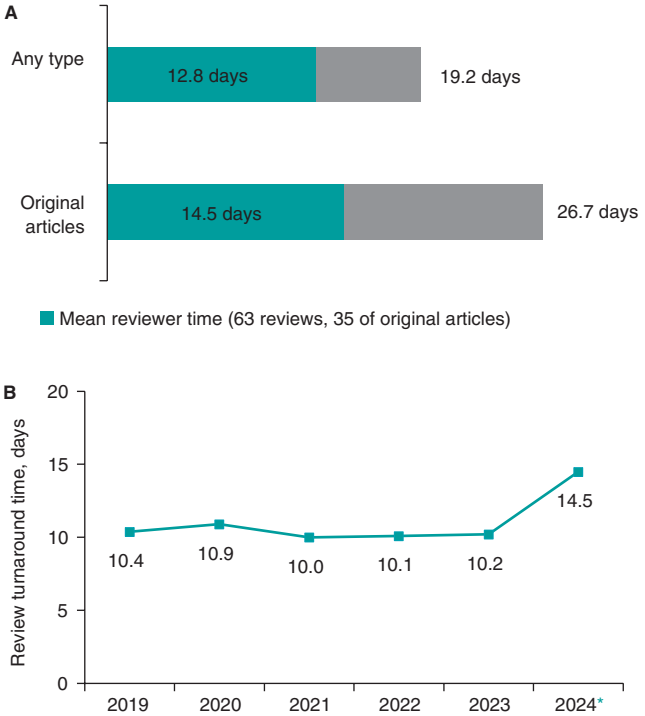

Figure 13. A: mean review time within the first half of 2024 (general and for original articles). **B:** Mean review time from submission to first decision for original articles. * Data for 2024 up to June 30th.

The consensus article on the diagnosis and treatment of patients with ANOCA by Escobar et al.[3]—a product of the collaboration among 4 SEC scientific associations—has been the most consulted special content of all.

Spain is the country where our journal is read the most, followed by Mexico, the United States, Argentina, and Colombia. Most visitors arrive at our website through keyword searches on search engines (57 378 sessions in the past 12 months), direct publication searches (11 711), and the social media (3000), especially X,[15] where we have more than 22 000 followers.

In issue #1 of 2024 we published our last "Editor's video".[16] Although this format where the author of a highlighted article from each issue briefly explained the most interesting aspects of their research was very well-received, it has been discontinued across all *REC Publications* so our budgetary efforts can go to other publication areas.

ACKNOWLEDGMENTS

As Editor-in-chief, I would like to once again express my deepest gratitude to the entire team of associate editors: Fernando Alfonso, Raúl Moreno, Soledad Ojeda, Armando Pérez de Prado, and Rafael Romaguera (figure 15). They truly are a winning team.

Being the official journal of ACI-SEC is one of the most notable virtues of *REC: Interventional Cardiology*. Perhaps the most significant and one which would explain its exemplary trajectory since its inception. Most journals are not backed by a professional association of this caliber, which is a truly remarkable asset. The former original board of directors of ACI-SEC and the most recently elected one have unconditionally supported this great project since day one.

In line with the financial sustainability of the journal, it is worth noting that the SEC has decided to contribute by covering 50% of the costs required to fund the editorial office.

However, this project came to fruition, continues to grow, and will continue to do so due to the invaluable and generous financial support from companies from the interventional cardiology sector. We are truly grateful to all of them.

Figure 14. Original articles from *REC: Interventional Cardiology* awarded at the Interventional Cardiology Association of the Spanish Society of Cardiology annual congress[11,12] held in June 2024.

Figure 15. *REC: Interventional Cardiology* editorial team. From right to left: José M. de la Torre-Hernández, Fernando Alfonso, Armando Pérez de Prado, Soledad Ojeda, Raúl Moreno, and Rafael Romaguera.

As always, we would like to especially highlight the excellent work and dedication of the staff involved with the editorial office of *REC Publications* (Iria del Río, Eva M. Cardenal, Belén Juan, María González Nogal, Helena Gómez Lobo, and Javier Esquinas), our IT consultant (Juan Quiles), the departments at Casa del Corazón, and the entire team at Publicidad Permanyer S.L.

"It's not so much how you start, but how you grow and remain on top."

Julio de la Torre

FUNDING

None declared.

CONFLICTS OF INTEREST

None declared.

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Editorial

Drug-coated balloons on the "big stage": is this technology ready for an all-comer population with *de novo* lesions?

El balón liberador de fármaco en la palestra, ¿está la tecnología preparada para la población general con lesiones de novo*?*

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Percutaneous coronary interventions with drug-eluting stent (DES) implantation have become a well-established treatment for obstructive coronary artery disease, improving long-term outcomes.[1] However, despite recent improvements including thinner strut platforms and more biocompatible polymers, the Achilles' heel of DES strategy remains the risk of DES-related adverse events such as in-stent restenosis or stent thrombosis in the short term,[2] along with an increase in hard clinical events at a rate of 2.0 to 3.5% yearly after the first year.[3,4]

Drug-coated balloons (DCB) have been developed as an alternative to percutaneous coronary intervention with DES implantation in selected populations for the treatment of coronary artery disease. The main advantage of this technology is its ability to deliver an antiproliferative drug to the treated lesion without leaving any layer of metal, which might cause late adverse events. Another advantage is the potential reduction in the duration or discontinuation of dual antiplatelet therapy, especially in patients at high risk of bleeding.

Several studies have investigated the role of DCB in real-world patients, who are those mainly affected by in-stent restenosis or de novo small vessel disease.[5-9] The only randomized study of DCB in de novo small vessels with a clinical primary endpoint was BASKET-SMALL-2. This study demonstrated the noninferiority of DCB vs DES (vessel size 2-3 mm), which was maintained up to 3 years follow-up in terms of all clinical endpoints.[5]

The initial fear of leaving behind a residual coronary dissection, especially in *de novo* lesions, could limit the widespread use of DCB. However, it has been shown that a nonflow-limiting dissection after DCB treatment tends to heal during the first few months, with both the paclitaxel and sirolimus technologies, without leading to acute or subacute vessel closure.[10,11]

The main message regarding DCB is that they should be used as the final step of percutaneous coronary intervention and only when a proper lesion preparation has been performed with a fully expanded balloon of the correct size for the vessel, with accurate management of calcifications and no residual stenosis greater than 30% that could impair drug delivery to the vessel and limit the potential of this technology.

Recently, a new generation of DCB eluting sirolimus (SCB, Magic Touch, Concept Medical, United States) has been introduced that uses nanoparticles composed of a dual layer of phospholipids encapsulating the antiproliferative agent. Histopathologic studies have demonstrated therapeutic concentrations of the drug within the vessel wall for up to 60 days after percutaneous coronary intervention.[12]

Notably, the angiographic performance of this class of drug seems to be inferior to that provided by paclitaxel. The recently published TRANSFORM I trial showed that SeQuent Please DCB (B. Braun, Germany) outperformed SCB in terms of angiographic parameters at 6 months of follow-up, but without showing any difference in clinical endpoints. This lower performance of SCB seems to occur particularly in cases of complex lesions, emphasizing the importance of adequate lesion preparation, especially with the less lipophilic drug sirolimus (figure 1).[13] Somewhat reassuringly, the performance of SCB in terms of clinical endpoints has been demonstrated in all-comer populations, especially in the prospective EASTBOURNE study, which showed a good safety and efficacy profile up to 2 years of follow-up in 2123 patients/2440 lesions.[14]

The next step to ensure wider use of this new generation DCB will be direct comparison with DES, as in the TRANSFORM II (NCT04893291) trial. This is an international, multicenter, prospective, investigator-driven, open-label, randomized (1:1) clinical trial designed to test the efficacy of SCB vs DES in native coronary artery vessels with diameters between 2.0 and 3.5 mm. Inclusion and randomization are being performed after adequate lesion preparation in the absence of flow-limiting dissection and acute vessel recoil. The study population has been calculated expecting the noninferiority of SCB in terms of target lesion failure at 12 months, and its sequential superiority in terms of net-adverse clinical events, including BARC 3-5 bleeding events. Interestingly, patients will be followed up clinically for 5 years to observe the potential superiority of DCB in the long-term. This trial, which includes 7 Spanish centers, is including patients at 40 centers allocated in 11 countries in Europe, Asia, and South America.[15] By November 20th, 2023, 600 patients out of the planned 1820 had been enrolled.

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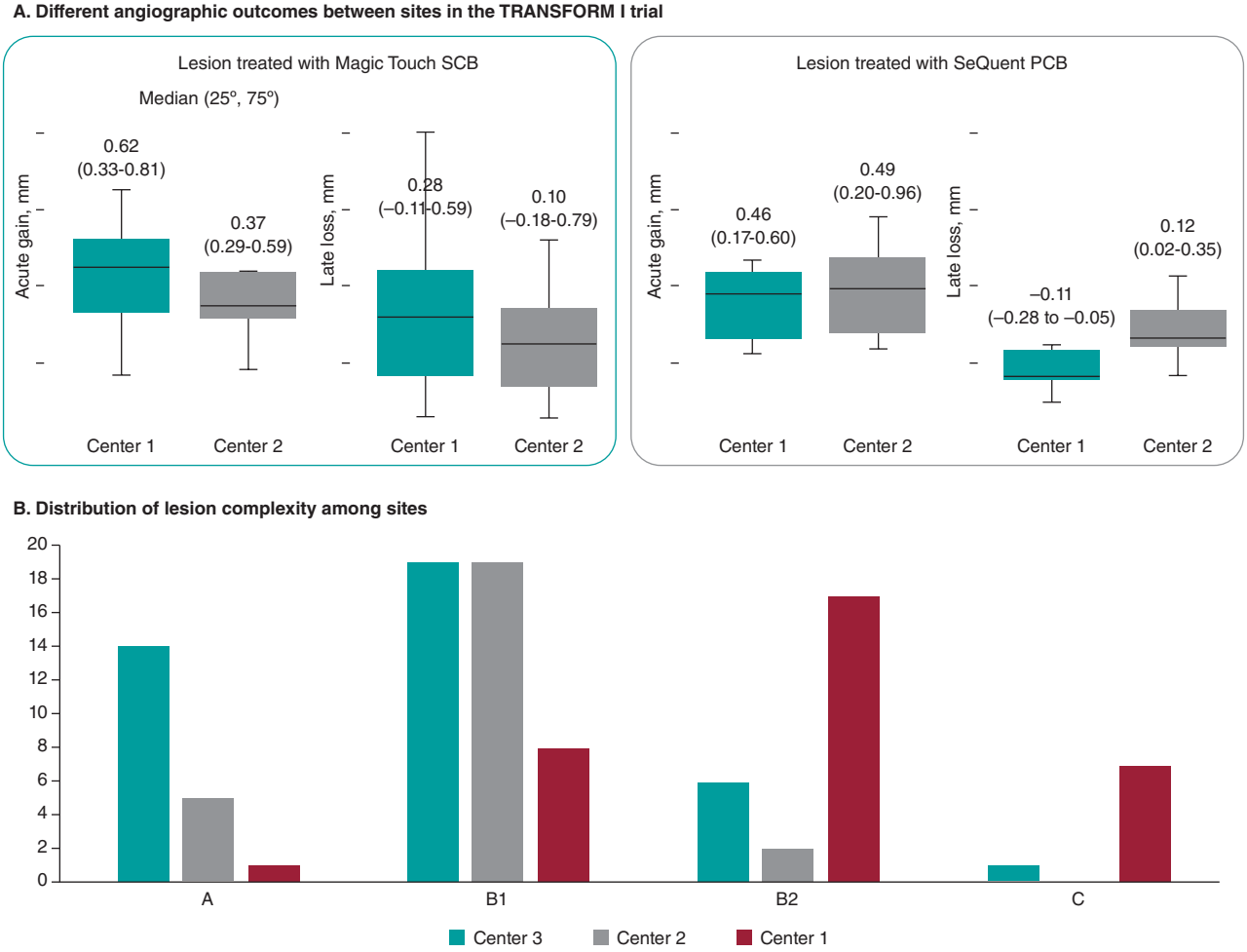

Figure 1. Differences in terms of types of lesion and outcomes among 2 top enroller centers for the TRANSFORM II trial. PCB, paclitaxel-coated balloon; SCB, sirolimus-coated balloon.

The TRANSFORM II trial will be an essential test of the maturity of DCB in such an established, prognostically significant arena, challenging DES as the gold standard for the treatment of patients with native coronary artery disease.

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CONFLICTS OF INTEREST

B. Cortese serves on the advisory board or as a consultant for several companies producing or marketing DCB: Cordis, Medalliance, BBraun, Concept Medical, Medtronic, Innova HTS, and ANT.

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Editorial

Clinical evaluation requirements under the new European Union medical device regulation

La evaluación clínica de los productos sanitarios en el foco del nuevo reglamento europeo de productos sanitarios

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Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 was published to regulate medical devices with the aim of bolstering the safety, quality, and efficacy of medical products in Europe.[1]

The regulation covers medical products intended for the diagnosis and treatment of numerous cardiovascular conditions, including high-risk devices such as pacemakers, defibrillators, artificial hearts, stents, cardiovascular sutures, heart valves, catheters, cardiovascular wires, and cardiac ablation instruments. According to the classification rules outlined in the regulation, all these high-risk medical products are classified as Class III.

The process for obtaining the CE mark for a medical device requires the manufacturer to demonstrate that the product meets the established safety and performance requirements and to conduct a clinical evaluation to validate the intended indication and purpose of use. For Class III product certification, a notified body designated by a member state authority must verify that the manufacturer has the objective technical and clinical documentation required to demonstrate that the product meets all the claims made by the manufacturer on the product. The authorized body issues a "CE Declaration of Conformity" including the manufacturer's information, the product's unique identifier, class, intended purpose, test reports and documentation, date and issue of validity, and details of the notified body involved in the process of granting the CE mark. The manufacturer's company must also implement a quality management system to ensure that the manufactured products meet specified standards. After auditing the manufacturer's facilities, the body issues an "EU quality management system certificate" detailing the scope of the quality system and type of manufactured products.

In other words, for the marketing of Class III medical products, the manufacturer must hold 2 different EU certificates issued by a notified body: one for the product and one for the quality management system.

Health care workers or users of a medical product can easily identify which notified body participated in its assessment by checking the product label, which is identified by a 4-digit number appearing alongside the CE mark. The name of the organization behind that number can be found on the European Commission's website.[2] For example, if the digits 0318 appear next to the CE mark on the label or the instructions for use of a medical product, it indicates that the evaluation was conducted by the National Certification Center for Medical Product, the sole notified body designated by the Ministry of Health.

The main change introduced in the regulation on product requirements involves the clinical evaluation. The assessment is especially strict for Class III products, which, as previously mentioned, are high risk. The first requirement is that the clinical evaluation validating the indication for use must be based on clinical data obtained from clinical investigations conducted with the product itself or a product that is technically, biologically, and clinically equivalent. The second requirement is that manufacturers must have access to the primary clinical data supporting the clinical evaluation of the medical product in question, either because they own them, or because the data have been published, or because they have a contractual agreement with the owner allowing permanent access and availability.

Although it may seem trivial, since the publication of the regulation, the availability of a compliant clinical evaluation has been the Achilles' heel for manufacturers of medical products intending to market their products in Europe in the coming years.

During the 3 decades since the implementation of the directives, special emphasis has been placed on ensuring the safety and quality of medical products, while the available objective evidence supporting their clinical benefit has been relegated to a secondary role. Consequently, manufacturers of medical products that have been on the market for years have had to make considerable efforts and investments to obtain sufficient clinical data with the necessary level of evidence to support the clinical risk-benefit ratio established by the new legislation. Many have had to devise new clinical evaluation plans or review existing ones, including conducting specific postmarket clinical follow-up studies to provide clinical data with an adequate level of evidence. Therefore, we could say that a culture of the need for clinical research and publication of the obtained data is emerging in the medical products sector.

On the other hand, to minimize potential discrepancies between notified bodies in the assessment of the clinical evaluation of Class III implantable medical products (such as pacemakers), the

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regulation has established a centralized supervision procedure by a panel of experts in medical products from the European Medicines Agency (EMA). The role of this panel is to review and confirm the adequacy of both the clinical evaluation conducted by the manufacturer and the assessment made by the notified body, and provide any recommendations deemed appropriate regarding the decision on certifying the medical product. These recommendations may include proposing to certify or not certify the product, or to limit or restrict indications, among others.

An interesting point is that 18 out of the 43 applications received by the panel so far correspond to medical products within the "circulatory system" clinical area. In particular, the clinical evaluations of some stents, implantable defibrillators, and various types of heart valves have already undergone this procedure, and the resulting public opinions can be consulted in a list within the framework of the European Commission's clinical evaluation consultation procedure.[3]

In addition, manufacturers of these types of products can seek guidance from the panel of experts before starting clinical development to confirm that the strategy designed for clinical development is appropriate and ensure that the resulting clinical evaluation will fully comply with the current legislation. If manufacturers decide to submit this voluntary query, the response issued by the panel will be binding. In other words, manufacturers will not be able to implement a different clinical evaluation plan from that recommended by the panel if they want to obtain the CE mark for the product.

The cornerstone of the CE certification model described is the competence of the personnel conducting the evaluation tasks. The personnel involved in the process of conducting or assessing the clinical evaluation of a medical product must have adequate knowledge. At the forefront of this chain are the manufacturers because they have had to review the competence of their staff to ensure that clinical evaluations are conducted by personnel experienced in clinical evaluation, competent in bibliographic searches, and with sufficient clinical knowledge and use of the products. Next are the notified bodies, which have to ensure that they have sufficient personnel with relevant clinical knowledge to issue a clinical judgment on the product's risk-benefit ratio after analyzing and scientifically testing the clinical data collected in the clinical evaluation provided by the manufacturers. Furthermore, clinicians internal to the notified bodies must verify that the personnel conducting the clinical evaluations provided by the manufacturers are qualified to perform the task. Further along the review chain, notified bodies are audited by European teams of qualified professionals, who, in turn, must verify that the competencies of the personnel conducting the assessments of the clinical evaluations in the notified bodies meet the criteria of experience and training established in the regulation.

This regulation also encourages the manufacturers of medical products to hire health care workers with clinical experience, who have their own opinions on the products they use in their routine clinical practice. These professionals can participate in the early stages of product design, engage in usability testing, and, naturally, as occurs with drugs, promote clinical research both before and after product marketing. This helps to confirm the clinical benefit of medical products throughout their life cycle.

Health care workers must be aware of the value of their experience and clinical knowledge in ensuring that the medical products entering the market are truly innovative and meet the needs of patients.

The responsible and committed contribution made by each of the parties involved in conducting and reviewing the clinical evaluation of medical products will, on the one hand, provide greater assurance of the rigor, robustness, and sufficiency of the clinical data supporting a product's indication. On the other hand, it will serve to standardize the criteria applied in the evaluation and ensure that the level of evidence required for all medical products bearing the CE mark under the new regulation is the same. These measures will restore confidence in the legislative model of medical products, ensuring that all manufacturers marketing their medical products in the European common market play by the same rules. Therefore, that the CE certification under which products are marketed will provide identical safeguards to patients, regardless of the country of origin, manufacturer, or issuing body.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used in the preparation of this article.

CONFLICTS OF INTEREST

None declared.

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Original article

Prognosis of patients with supranormal ejection fraction undergoing percutaneous aortic valve replacement

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ABSTRACT

Introduction and objectives: Several studies have shown that reduced (< 50%) left ventricular ejection fraction (LVEF) is an independent risk factor for cardiovascular events and mortality in patients with severe aortic stenosis (AS) undergoing valve replacement. Although patients with preserved LVEF (> 50%) have a better prognosis, there is a group with supranormal LVEF (≥ 70%) whose prognosis seems to differ due to their characteristics. The aim of this study was to evaluate outcomes after transcatheter aortic valve implantation (TAVI) in patients with severe AS and supranormal LVEF.
Methods: We performed a retrospective cohort study that included 1160 patients undergoing TAVI between 2007 and 2021 at *Hospital Clínico San Carlos* (Madrid, Spain). The patients were classified according to preoperative LVEF into reduced (< 50%), normal (50% to 69%), and supranormal (≥ 70%). Clinical, echocardiographic variables, and the following outcomes were compared: death from any cause at 30 days and at 1 year, death from cardiovascular causes at 1 year, and rehospitalization due to cardiovascular causes at 1 year.
Results: Of the 1160 patients with severe AS who underwent TAVI during the study period, 276 (23.8%) had reduced LVEF, 702 (60.5%) had normal LVEF, and 182 (15.7%) had supranormal LVEF. Patients with supranormal LVEF were predominantly men (82.9 ± 5.3 years) and had lower ventricular volumes, higher relative wall thickness, and concentric geometry. There were no differences in 30-day or 1-year mortality. However, rehospitalization for cardiovascular causes at 1 year was significantly higher in the supranormal LVEF group (LVEF < 50%: 29.2%; LVEF 50% to 69%: 27.4%; LVEF ≥ 70%: 34.4%; $P < .043$).
Conclusions: Patients with severe AS and supranormal preprocedural LVEF (≥ 70%) who underwent TAVI had a higher rate of cardiovascular rehospitalization at 1 year, with no differences in mortality.

Keywords: Supranormal ejection fraction. Severe aortic stenosis. TAVI. Rehospitalization.

Pronóstico de los pacientes con fracción de eyección supranormal tratados con recambio valvular aórtico percutáneo

RESUMEN

Introducción y objetivos: Se ha evidenciado en diversos estudios que la fracción de eyección del ventrículo izquierdo (FEVI) reducida (< 50%) es un factor de riesgo independiente de eventos y mortalidad en pacientes con estenosis aórtica (EA) grave tratados con recambio valvular. A pesar de que aquellos con FEVI conservada (> 50%) muestran mejor pronóstico, existe un grupo con FEVI supranormal (≥ 70%) que parece tener un pronóstico diferente por sus características particulares. El objetivo de este estudio fue evaluar los resultados del implante percutáneo de válvula aórtica (TAVI) en pacientes con EA grave y FEVI supranormal.

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Métodos: Estudio de cohorte retrospectiva que incluyó 1.160 pacientes tratados con TAVI en 2007-2021 en el Hospital Clínico San Carlos (Madrid, España). Se clasificaron según su FEVI preoperatoria en reducida (< 50%), normal (50-69%) y supranormal (≥ 70%). Se compararon variables clínicas y ecocardiográficas, y los siguientes desenlaces: mortalidad por cualquier causa a los 30 días y al año, muerte por causa cardiovascular al año y rehospitalización por causa cardiovascular al año.
Resultados: De los 1.160 pacientes con EA grave que recibieron un TAVI durante el periodo del estudio, 276 (23,8%) se registraron con FEVI reducida, 702 (60,5%) con FEVI normal y 182 (15,7%) con FEVI supranormal. Los pacientes con FEVI supranormal eran predominantemente varones (82,9 ± 5,3 años), tenían menores volúmenes ventriculares, mayor grosor parietal relativo y geometría concéntrica. No hubo diferencias en la mortalidad a 30 días ni al año; sin embargo, la rehospitalización por causa cardiovascular al año fue significativamente superior en el grupo de FEVI supranormal (FEVI < 50%, 9,2%; FEVI 50-69%, 27,4%; FEVI ≥ 70%, 34,4%; p < 0,043).
Conclusiones: Los pacientes con EA grave tratados con TAVI que presentaban FEVI supranormal (≥ 70%) preprocedimiento tuvieron una mayor tasa de rehospitalización por causa cardiovascular al año, sin diferencias en la mortalidad.

Palabras clave: Fracción de eyección supranormal. Estenosis aórtica grave. TAVI. Rehospitalización.

Abbreviations

AS: aortic stenosis. **LVEF:** left ventricular ejection fraction. **LVOT:** left ventricular outflow tract. **RPT:** relative parietal thickness. **TAVI:** transcatheter aortic valve implantation. **VTI:** velocity time integral.

INTRODUCTION

Aortic stenosis (AS) is the second most common valvular heart disease, affecting 12% of people older than 75 years.[1,2] Without treatment, the survival rate for symptomatic severe AS is less than 3 years.[3] Transcatheter aortic valve implantation (TAVI) is recommended for symptomatic patients and for asymptomatic patients with a reduced left ventricular ejection fraction (LVEF) of less than 50%.[4]

Reduced LVEF is recognized as an independent risk factor for events and mortality in patients with severe AS.[5] However, the prognosis of severe AS in patients with preserved LVEF (> 50%) remains uncertain, especially in the presence of markers of subclinical myocardial injury, such as hypertrophy and fibrosis.[6] Among these patients, those with a supranormal LVEF (≥ 70%) may have a worse prognosis after TAVI due to specific ventricular geometry and functional characteristics.[7]

The aim of this study was to evaluate the prognosis of patients with supranormal LVEF (≥ 70%) undergoing TAVI and study their echocardiographic and clinical characteristics.

METHODS

We conducted a retrospective cohort study of patients with severe AS who underwent TAVI at *Hospital Clínico San Carlos* in Madrid, Spain, between June 2007 and December 2021. Severe AS was defined according to current guideline criteria: mean gradient > 40 mmHg, peak velocity > 4 m/s, aortic valve area < 1 cm², or indexed aortic valve area < 0.6 cm²/m². The decision to perform TAVI was made by a multidisciplinary medical-surgical team. Patients were categorized into 3 groups based on their preprocedural LVEF, as assessed by echocardiography: reduced (< 50%), normal (50%-69%), and supranormal (≥ 70%). Clinical data were collected from medical records. Patients were excluded if they did not survive the procedure, had previous cardiac valve surgery, had cardiomyopathy unrelated to valvular disease, had a life expectancy of less than 1 year, or had missing data in their preprocedural echocardiographic study or clinical follow-up.

The clinical endpoints used to evaluate the prognosis of patients with supranormal LVEF (≥ 70%) undergoing TAVI were all-cause mortality at 30 days and 1 year, cardiovascular mortality at 1 year, and cardiovascular-related rehospitalization at 1 year. We also assessed their correlation with echocardiographic and clinical characteristics.

The study was conducted in accordance with the principles of the Declaration of Helsinki by the World Medical Association and received approval from the ethics committee of *Hospital Clínico San Carlos* in Madrid, Spain. Since the study was retrospective and posed no risk to patients, informed consent was not required. All data were handled with the utmost confidentiality by the researchers.

Echocardiography

Two-dimensional Doppler echocardiography was performed using the available equipment and following clinical practice guidelines.[8] Measurements included septal thickness, posterior wall thickness, end-diastolic diameter, and left ventricular outflow tract (LVOT) diameter in the parasternal long-axis view. Peak and mean valvular gradients were assessed using continuous Doppler in multiple windows to obtain the highest velocity. The velocity-time integral (VTI) was measured with pulsed Doppler by placing the sample volume just before the aortic valve annulus. The aortic valve area was then calculated using the continuity equation:

$$\frac{\text{LVOT area} \times \text{LVOT VT}}{\text{AV VTI}}$$

Ventricular volumes and LVEF were calculated using the biplane Simpson method. The left ventricular (LV) mass was calculated using the Devereux formula and indexed to body surface area. Relative parietal thickness (RPT) was calculated using the following formula:

$$\frac{\text{Septal wall} + \text{posterior wall}}{\text{LV end-diastolic diameter}}$$

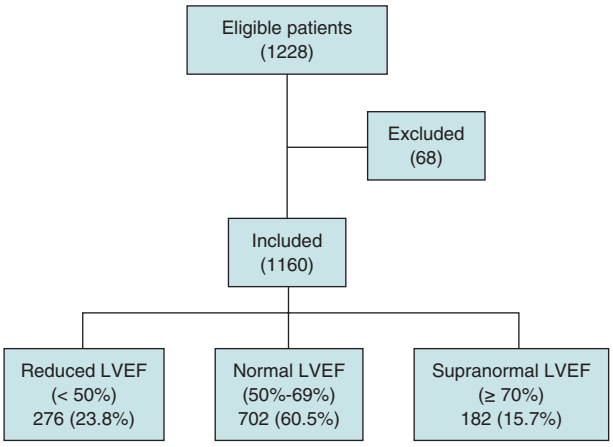

Figure 1. Flow chart illustrating the patients included and excluded from the study, the final sample analyzed, and its distribution among the 3 study groups. LVEF, left ventricular ejection fraction.

The indexed stroke volume was obtained using the following formula:

$$\frac{\text{LVOT area} \times \text{LVOT VTI}}{\text{CS}}$$

Statistical analysis

The statistical analysis was conducted using available commercial software (IBM SPSS 28.0). Normally distributed continuous variables are expressed as the mean and standard deviation, with a 95% confidence interval (95%CI). Categorical variables are expressed as absolute numbers and percentages. The Student t-test was used to compare variables with a normal distribution. Analysis of variance and the Tukey post hoc test were used to compare means, while the chi-square test was used to compare prevalences among the 3 groups. A univariable logistic regression analysis was applied to evaluate predictors of hospitalization and mortality. *P* values < .05 were considered statistically significant.

RESULTS

Of the 1228 patients who underwent TAVI during the study period, 1160 were included in the analysis. Among these, 276 patients (23.7%) had a reduced LVEF (< 50%), 702 patients (60.5%) had a normal LVEF (50%-69%), and 182 patients (15.6%) had a supranormal LVEF (≥ 70%). Sixty-eight patients were excluded based on the following criteria: 23 due to death during the procedure, 15 with previous cardiac valve surgery, 6 with cardiomyopathy unrelated to valvular disease, 18 with a life expectancy of less than 1 year, and 6 with missing data in the preprocedural echocardiographic study or clinical follow-up (figure 1).

The baseline characteristics of the study population are shown in table 1. The mean age was 82.2 ± 5.8 years and was slightly lower in the reduced LVEF group than in the other 2 groups. Male sex was more common in the group with LVEF ≥ 70% (*P* < .005). Patients with LVEF < 50% had a higher prevalence of prior myocardial infarction, coronary artery disease, and revascularization, along with a higher EUROSCORE II (22.5 [14.7-32.0]; *P* < .001). This group also more frequently required the intervention as an emergency procedure (*P* < .001).

Echocardiographic data

Patients with LVEF ≥ 70% had smaller LV end-diastolic and end-systolic volumes, and greater septal wall thickness and RPT than the other 2 groups. In this group, left ventricular mass index (LVMI) was 126.3 ± 32.8 g/m², reflecting a predominant phenotype of concentric hypertrophy and remodelling. A similar pattern was observed in patients with normal LVEF (50%-69%), although this group had a larger end-diastolic LV volume (table 2). In contrast, patients with LVEF < 50% had a greater LV mass, with an LVMI of 147.6 ± 40.2 g/m² (*P* < .001), a low RWT (< 0.42), and an elevated end-diastolic volume, indicating a predominant phenotype of eccentric hypertrophy. In addition, this group had a lower indexed stroke volume (32.5 ± 11.8; *P* < .001).

Perioperative clinical endpoints

There were no significant differences among the 3 groups regarding intra- and postoperative mortality.

Clinical endpoints at follow-up

During the 1-year follow-up, 164 patients (14.13%) died, with no significant differences among the 3 groups (LVEF < 50%, 14.6%; LVEF 50%-69%, 12.6%; LVEF ≥ 70%, 12.7%; *P* < .736). However, significant differences were found in the rate of cardiovascular rehospitalization at 1 year, with higher rates in the supranormal LVEF group (LVEF ≥ 70%, 34.4%; LVEF < 50%, 29.2%; LVEF 50%-69%, 27.4%; *P* < .043). Clinical endpoints are shown in table 3.

Univariable regression analysis

In patients with supranormal LVEF, coronary artery disease and increased interventricular septal thickness were predictors of cardiovascular hospitalization at 1 year (table 4). In this group, indexed LV end-diastolic volume and a history of coronary artery disease were predictors of all-cause mortality at 1 year (table 5). In the general population, no predictors of 1 year mortality were identified, except for age (table 6).

DISCUSSION

This study demonstrates that LVEF is an important prognostic factor in patients with severe AS treated with TAVI. While no differences in mortality were observed at 1 month or 1 year, patients with supranormal LVEF (≥ 70%) had a higher rate of rehospitalization at 1 year than those with reduced (< 50%) or normal (50%-69%) LVEF.

LVEF has been widely recognized in the literature as a prognostic factor in various clinical contexts. A study by Wehner et al.[9] reported that an LVEF of 60% to 65% is associated with the best prognosis, while patients with LVEF ≥ 70% have a 5-year mortality rate similar to those with reduced LVEF. A study by Gu et al.,[10] found higher mortality and hospitalization rates at 5 years in patients hospitalized for heart failure with LVEF > 65% than in those with normal LVEF.

In patients with AS undergoing TAVI, the OCEAN-TAVI registry found that LVEF > 65% was an independent predictor of death and rehospitalization at the 3-year follow-up (hazard ratio [HR], 1.16; 95%CI, 1.02-1.31; *P* = .023).[11] There were no significant differences in mortality among the study groups, except for the rehospitalization rate. It remains to be elucidated whether longer-term follow-up could also detect differences in mortality.

Table 1. Patients' baseline characteristics

Characteristics	LVEF < 50% (n = 276)	LVEF 50%-69% (n = 702)	LVEF ≥ 70% (n = 182)	*P* value
Age (years)	81.6 ± 6.3	82.2 ± 5.9	82.9 ± 5.3	< .050
Male sex	38.1%	58.2%	68.3%	< .001
Hypertension	80.7%	82.9%	86.0%	.363
Diabetes mellitus	41.7%	35.6%	33.9%	.182
Body mass index	27.1 ± 4.4	28.4 ± 5.2	27.7 ± 5.1	< .002
Hyperlipidemia	56.9%	59.8%	56.0%	.254
Previous PTA	30.6%	19.4%	16.8%	< .001
Previous CABG	9.6%	4.5%	3.3%	< .002
Previous infarction	20.6%	9.1%	7.6%	< .001
Coronary artery disease	45.6%	32.7%	34.7%	< .002
Left main coronary artery disease	5.6%	3.4%	1.8%	.222
Incomplete revascularization	20.7%	30.4%	35.3%	.174
COPD	16.7%	15.1%	14.5%	.714
Smoking	37.2%	41.7%	14.4%	.034
Atrial fibrillation	38.6%	37.8%	42.1%	.570
Glomerular filtration	61.2 (46.0-77.9)	63.1 (46.8-79.4)	60.9 (45.5-75.2)	.311
Cancer	16.0%	15.5%	18.7%	.725
EuroSCORE II	22.5 (14.7-32.0)	14.3 (7.4-18.0)	11.8 (8.9-18.9)	< .001
Dyspnea	87.5%	87.5%	91.7%	.289
Emergency procedure	33.9%	17.5%	14.1%	< .001
Valve-in-valve	3.6%	3.3%	2.7%	.881
Post-TAVI outcome				
Peak gradient (mmHg)	18.3 ± 7.3	19.3 ± 8.9	19.4 ± 8.7	.223
Mean gradient (mmHg)	9.3 ± 3.8	9.9 ± 4.8	10.0 ± 5.7	.229

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; PTA, percutaneous transluminal angioplasty; TAVI, transcatheter aortic valve implantation.

Table 2. Patients' baseline characteristics

Characteristics	LVEF < 50%	LVEF 50%-69%	LVEF ≥ 70%	*P* value
RPT	0.48 (0.41-0.58)	0.57 (0.50-0.65)	0.60 (0.52-0.69)	< .001
Indexed LVESV (mL/m²)	31 (25-39)	38 (31-45)	39 (31-49)	< .001
Indexed LVEDV (mL/m²)	63 (48-80)	48 (38-59)	45 (35-56)	< .001
LVMI (g/m²)	147.6 ± 40.2	128.8 ± 34.2	126.3 ± 32.8	< .001
IVS (mm)	12.1 ± 2.6	13.6 ± 2.4	14.1 ± 2.7	< .001
Indexed stroke volume (mL/m²)	32.5 ± 11.8	38 ± 11.5	40 ± 11.6	< .001

IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; RPT, relative parietal thickness.

In patients with AS undergoing surgical interventions, LVEF is a recognized prognostic marker. In a study by Dahl et al.,[12] reduced LVEF (< 50%) was a clear predictor of 5-year risk. The study revealed that patients with supranormal LVEF experienced longer hospital stays, increased need for mechanical ventilation, a higher incidence of hemodialysis, and a greater rate of rehospitalization. This latter finding is consistent with the findings of the present study. There is no clear explanation for these results, but they may

Table 3. Clinical endpoints

Variables	LVEF < 50% (n = 276)	LVEF 50%-69% (n = 702)	LVEF ≥ 70% (n = 182)	*P* value
Perioperative				
Intraoperative mortality	0.4%	1.4%	0.6%	.345
Postoperative mortality	2.8%	3.7%	4.3%	.676
Follow-up				
All-cause mortality at 30 days	2.4%	3.9%	5.0%	.359
Cardiovascular mortality at 1 year	12.8%	9.6%	15.2%	.370
All-cause mortality at 1 year	14.6%	12.6%	12.7%	.736
Cardiovascular rehospitalization at 1 year	29.2%	27.4%	34.4%	< .043

LVEF, left ventricular ejection fraction.

Table 4. Supranormal left ventricular ejection fraction and predictors of cardiovascular hospitalization at 1 year

Characteristics	HR	95%CI	*P* value	HR
Age	1.077	0.991-1.169	.080	
Hypertension	1.687	0.546-5.213	.364	
Diabetes mellitus	1.846	0.767-4.440	.171	
Body mass index	1.012	0.933-1.099	.770	
Coronary artery disease	0.327	0.137-0.780	.012	
Smoking	1.796	0.650-4.965	.259	
EuroSCORE II	1.046	0.998-1.096	.060	
RPT	1.004	0.041-24.392	.998	
Indexed LVEDV	0.979	0.949-1.010	.188	
IVS	0.965	0.933-0.998	.036	
				1.0

95%CI, 95% confidence interval; HR, hazard ratio; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; RPT, relative parietal thickness.

Table 5. Supranormal left ventricular ejection fraction and predictors of 1-year mortality

Characteristics	HR	95%CI	*P* value	HR
Age	1.180	0.976-1.426	.087	
Hypertension	2.181	0.167-28.575	.552	
Diabetes mellitus	0.875	0.154-4.968	.154	
Body mass index	1.004	0.796-1.265	.976	
Coronary artery disease	3.372	0.612-18.575	.012	
Smoking	7.453	0.691-61.024	.259	
EuroSCORE II	0.921	0.831-1.022	.120	
RPT	0.011	0.000-154.979	.998	
Indexed LVEDV	1.094	1.018-1.177	.015	
IVS	1.004	0.943-1.068	.912	
				1.0

95%CI, 95% confidence interval; HR, hazard ratio; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; RPT, relative parietal thickness.

Table 6. Predictors of 1-year mortality in the general population

Characteristics	HR	95%CI	*P* value	HR
Age	1.070	1.002-1.143	.043	
Hypertension	1.268	0.545-2.947	.582	
Diabetes mellitus	1.458	0.764-2.784	.253	
Body mass index	0.949	0.882-1.020	.152	
Coronary artery disease	1.593	0.867-2.929	.134	
Smoking	1.794	0.899-3.581	.097	
EuroSCORE II	1.046	0.973-1.033	.868	
RPT	0.252	0.022-2.836	.264	
Indexed LVEDV	0.986	0.967-1.006	.188	
IVS	1.000	0.974-1.027	.036	
				1.0

95%CI, 95% confidence interval; HR, hazard ratio; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; RPT, relative parietal thickness.

be related to the persistence of myocardial hypertrophy or diastolic dysfunction following the intervention.[13]

According to previous studies, increased (> 80 mL/m²) and reduced (< 55 mL/m²) ventricular volumes are risk factors to consider in patients with severe AS.[14,15] In this analysis, in the subgroup of patients with supranormal LVEF, indexed LV end-diastolic volume was a predictor of 1-year mortality (HR, 1.094; 95%CI, 1.018-1.177; $P < .015$). A low indexed stroke volume has also been associated with worse prognosis in patients with AS, both with reduced and preserved LVEF.[16] Patients with preserved LVEF may have a low stroke volume when the ventricular cavity is small and they have restrictive physiology that limits the stroke volume, even with a supranormal ejection fraction.[17] In most studies, these patients have a worse prognosis, with a higher mortality risk and less event-free time.[18,19]

Supranormal LVEF represents a new phenotype in patients with preserved LVEF (> 50%), with distinctive clinical and hemodynamic characteristics. There is no universal agreement on the exact LVEF value to define supranormal. According to the American College of Cardiology, a LVEF ≥ 70% is considered supranormal,[20] while other groups set this threshold at ≥ 65%. For this study, LVEF ≥ 70% was used as the reference to better highlight clinical and echocardiographic differences among the study groups, which likely influenced the prevalence observed in the population.

In a study by Wehner et al.,[9] which reviewed 403 977 echocardiograms from 203 135 patients without prespecified diagnoses, an LVEF ≥ 70% was found in 3% (13 553) of participants. In the present study of patients with severe AS, 15% had LVEFs ≥ 70%. Other studies, such as the OCEAN-TAVI registry,[11] reported a higher percentage of patients with supranormal LVEF and AS (47%), likely because they used a lower cutoff for supranormal LVEF (≥ 65%). These findings suggest that severe AS is associated with a higher-than-normal LVEF, likely due to left ventricular (LV) remodelling and concentric hypertrophy resulting from elevated afterload.[21-24] In our study, the LVMI was elevated in most patients, regardless of LVEF. Patients with normal and supranormal LVEF predominantly exhibited concentric geometry, characterized by a reduced LV cavity and increased septal thickness. In contrast, patients with reduced LVEF showed predominantly eccentric geometry with a dilated LV.

Finally, our results suggest that while widely used risk scales like EuroSCORE II remain valid, echocardiographic factors should also be considered when determining the timing and type of intervention.[25]

Limitations

This retrospective, observational study was conducted at a single center. All patients underwent TAVI, and there was no comparison with those treated with surgical valve replacement. The medical and pharmacological treatment were not specified, which is an important omission given recent advancements in heart failure management. In addition, a 1-year follow-up may be too short to detect differences in mortality between the groups and a longer-term follow-up might reveal differences.

CONCLUSIONS

LVEF remains an important prognostic factor in decision-making for patients with severe AS. In this study, patients with reduced (< 50%), normal (50%-69%), or supranormal (≥ 70%) preprocedural LVEF who underwent TAVI showed no differences in 1-year mortality. However, those with supranormal LVEF (≥ 70%) had a higher rate of cardiovascular-related rehospitalization at 1 year, suggesting that this subgroup may have unfavorable factors, such as significant diastolic dysfunction. Further research is needed to investigate and confirm these findings.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This study adhered to the Declaration of Helsinki and received approval from the ethics committee of Hospital Clínico San Carlos in Madrid, Spain. As the study was retrospective and posed no risk to patients, informed consent was not required. All information was handled with strict confidentiality by the researchers. Consecutive patients were recruited during the study period without sampling or randomization, so sex or gender biases were not considered in the analysis

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used during the performance of the study.

AUTHORS' CONTRIBUTIONS

E. Martínez Gómez, X. Solar, D. Faria, L. Nombela Franco, and J.A. de Agustín contributed to the conception and design, data acquisition, analysis, and interpretation of the study. E. Martínez Gómez, X. Solar, D. Faria, L. Nombela Franco, P. Jiménez Quevedo, G. Tirado, E. Pozo Osinalde, C. Olmos Blanco, P. Mahía Casado, P. Marcos Alberca, M. Luaces, J.J. Gómez de Diego, L. Collado Yurrita, A. Fernández-Ortiz, J. Pérez-Villacastín, and J.A. de Agustín contributed to the drafting of the article or its critical revision. All authors approved the final version of the article.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- LVEF is a highly significant prognostic marker in cardiology. Paradoxically, studies have shown that patients with a supranormal LVEF have a worse prognosis in some scenarios, such as AS.

WHAT DOES THIS STUDY ADD?

- This study shows that patients undergoing TAVI with supranormal LVEF (≥ 70%) have higher rehospitalization rates at 1 year than those with reduced (< 50%) or normal (50%-69%) LVEF.

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Original article

Treatment of functionally nonsignificant vulnerable plaques in multivessel STEMI: design of the VULNERABLE trial

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ABSTRACT

Introduction and objectives: The optimal treatment of nonculprit angiographic intermediate lesions (diameter stenosis 40%-69%) in patients with ST-segment elevation myocardial infarction (STEMI) is still unknown. Lesions with fractional flow reserve (FFR) ≤ 0.80 are indicative of ischemia and benefit from revascularization. However, lesions with FFR > 0.80 and optical coherence tomography (OCT) findings of vulnerability have been hypothesized to cause adverse events during follow-up. The study aims to compare the efficacy of a preventive treatment with stent implantation plus optimal medical therapy vs optimal medical therapy alone for nonculprit intermediate lesions with FFR > 0.80 and OCT findings of plaque vulnerability in STEMI patients at 4 years of follow-up.
Methods: This parallel-group, multicenter, controlled, single-blind, and 1:1 randomized trial will enroll a total of 600 STEMI patients with ≥ 1 intermediate nonculprit lesions with FFR > 0.80 and OCT findings of plaque vulnerability. The primary endpoint is target vessel failure, defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization. The study will include a parallel registry of patients with FFR > 0.80 but without OCT findings of vulnerability. Vulnerable plaques are defined as lipid-rich fibroathermas with plaque burden ≥ 70% and a thin fibrous cap (≤ 80 µm).
Results: The VULNERABLE trial will reveal the role of preventive treatment with stent implantation for nonculprit and functionally nonsignificant vulnerable plaques in STEMI patients.
Conclusions: This is the first randomized trial of OCT-guided treatment of vulnerables plaques.
Registered at ClinicalTrials.gov (NCT05599061).

Keywords: Fractional flow reserve. Optical coherence tomography. ST-segment elevation myocardial infarction. Vulnerable plaque.

Tratamiento de placas vulnerables funcionalmente no significativas en el IAMCEST multivaso: diseño del estudio VULNERABLE

RESUMEN

Introducción y objetivos: El tratamiento óptimo de las lesiones angiográficas intermedias (diámetro de estenosis 40-69%) no culpables en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST) está por determinar. La reserva fraccional de flujo (RFF) permite diagnosticar lesiones causantes de isquemia (RFF ≤ 0,80) que se benefician de una revascularización. No obstante, las lesiones con RFF > 0,80 y criterios de vulnerabilidad por tomografía de coherencia óptica (OCT) también se ha hipotetizado que pueden causar eventos adversos en el seguimiento. El objetivo es comparar la eficacia del tratamiento preventivo con implantación de *stent* más tratamiento médico óptimo de lesiones intermedias no culpables con RFF > 0,80 y características de placa vulnerable frente a solo tratamiento médico óptimo en pacientes con IAMCEST a 4 años de seguimiento.
Métodos: Estudio de grupos paralelos, multicéntrico, controlado, aleatorizado 1:1 y simple ciego. Se incluirán 600 pacientes con IAMCEST y al menos una lesión intermedia no culpable que presenten RFF > 0,80 y características de placa vulnerable por OCT. El objetivo primario se define como fallo del vaso diana, compuesto de muerte cardiaca, infarto del vaso diana y necesidad de revascularización del vaso diana. El estudio incluye un registro paralelo para pacientes con RFF > 0,80 sin características de placa vulnerable. Se define placa vulnerable como fibroateromas lipídicos con carga de placa ≥ 70% y capa fibrosa fina (≤ 80 µm).
Resultados: El estudio VULNERABLE permitirá conocer el papel del tratamiento preventivo con *stent* de placas vulnerables no culpables funcionalmente no significativas en pacientes con IAMCEST.
Conclusiones: Se trata del primer estudio aleatorizado para el tratamiento de placas vulnerables guiado por OCT.
Registrado en ClinicalTrials.gov (NCT05599061).

Palabras clave: Reserva fraccional de flujo. Tomografía de coherencia óptica. Infarto agudo de miocardio con elevación del segmento ST. Placa vulnerable.

Abbreviations

FFR: fractional flow reserve. **MLA:** minimum lumen area. **OCT:** optical coherence tomography. **OMT:** optimal medical therapy. **PDE:** percent diameter stenosis. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

The presence of multivessel disease, defined as angiographic lesions with a percent diameter stenosis (PDS) ≥ 50% by visual estimation in patients with ST-segment elevation myocardial infarction (STEMI), is estimated to be approximately 50%.[1] The COMPLETE trial compared angiography-guided preventive revascularization with stent implantation added to optimal medical therapy (OMT) for nonculprit lesions with a PDS ≥ 70% vs OMT alone.[2] The trial found that angiography-guided preventive revascularization significantly reduced adverse cardiovascular events at 3 years of follow-up.[2] Although the COMPLETE trial required physiological assessment using fractional flow reserve (FFR) for lesions with a PDS between 50% and 69% to guide the decision on revascularization, in practice, it was performed in only a very small percentage of patients.

The FLOWER-MI and FRAME-AMI trials[3,4] investigated preventive stenting of FFR-guided nonculprit lesions—obtained through intracoronary pressure wire—compared with angiography-guided

complete revascularization (visual estimation). Both trials mainly included intermediate lesions and demonstrated that pressure wire-guided preventive revascularization significantly reduces the need for revascularization, with similar or superior efficacy to angiography-guided complete revascularization.[3,4] Despite these findings, clinical practice guidelines based on the COMPLETE trial recommend preventive stenting of nonculprit lesions guided by angiography alone.[5,6]

It is important to note that FFR is considered the gold standard for detecting myocardial ischemia (FFR ≤ 0.80). However, deferring treatment of nonculprit lesions that do not cause ischemia (FFR > 0.80) through OMT raises concerns in selected cases in which the anatomical features of the lesion suggest signs of vulnerability. In the FLOWER-MI trial, the group of patients randomized to undergo pressure-wire-guided revascularization with an FFR > 0.80 (referred for OMT) had more adverse events than those in the same group with FFR values ≤ 0.80 (referred for percutaneous revascularization).[7] Several studies using intravascular imaging modalities have also demonstrated an association between the presence of fibrolipid plaques with high lipid content and thin fibrous caps—known as vulnerable plaques—and the development of future adverse events due to plaque rupture.[8,11]

The VULNERABLE trial aims to evaluate the efficacy of a combined strategy using intracoronary physiological techniques and intravascular imaging to guide the treatment of intermediate nonculprit lesions in STEMI patients. The study hypothesis is that preventive stenting—in addition to OMT—in intermediate nonculprit lesions with FFR values > 0.80 and characteristics of vulnerable plaque will be superior to OMT alone. The present article includes the rationale and design of the study.

METHODS

Design

The VULNERABLE trial (NCT05599061) includes 3 groups based on the results obtained during the combined functional and anatomical assessment using pressure wires and optical coherence tomography (OCT). Figure 1 shows the study flowchart, which illustrates the 3 groups: patients with FFR ≤ 0.80 treated with stent (search failures), patients with FFR > 0.80 without vulnerable plaque characteristics (included in the registry group), and patients with FFR > 0.80 and vulnerable plaque characteristics (included in the randomized clinical trial).

This is a multicenter, controlled, prospective, randomized, parallel-group, single-blind study with patients included in the clinical trial group. The study will be conducted in accordance with the recommendations outlined in the Declaration of Helsinki on clinical research and has been approved by the lead ethics committee (*Hospital Universitari de Bellvitge*) and endorsed by the remaining ethics committees of participating centers. The participating centers and principal investigators are shown in table 1 of the supplementary data.

The study has been entirely designed and initiated by researchers and is sponsored by the Spanish Society of Cardiology Working Group on Intracoronary Diagnostic Techniques, which includes a steering committee, a data and safety monitoring board, and an independent event adjudication committee. The members of these committees are listed in table 2 of the supplementary data. The steering committee and all study investigators are committed to accurate data collection and adherence to the study protocol. The funding entity (Abbott Vascular, United States) plays no role in the

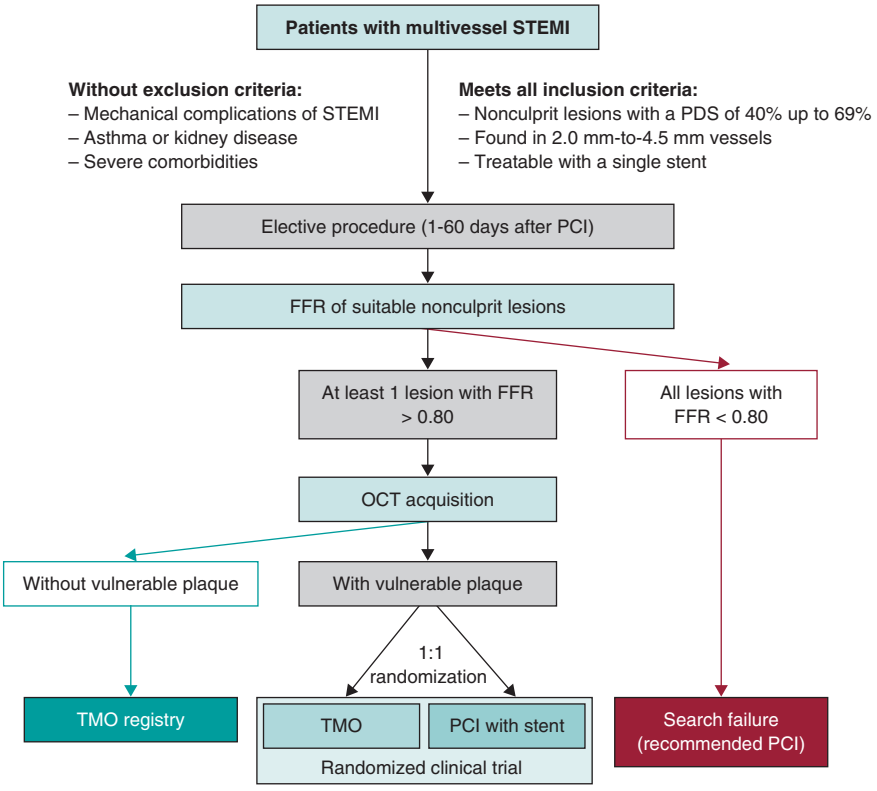

Figure 1. Study diagram. FFR, fractional flow reserve; OCT, optical coherence tomography; OMT, optimal medical treatment; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 1. Objectives of the VULNERABLE trial

Primary endpoint
Compare the percentage of TVF between the 2 groups of patients assigned to the randomized clinical trial (FFR > 0.80 with characteristics of vulnerable plaque by OCT): preventive revascularization with stent + OMT vs OMT alone
Key secondary endpoints
Compare the percentage of TVF between patients allocated to the registry group (FFR > 0.80 without characteristics of vulnerable plaque by OCT and treated with the OMT) and patients allocated to the randomized OMT group (FFR > 0.80 with characteristics of vulnerable plaque)
Other secondary endpoints
Compare the rate of all-cause mortality reported between the 2 subgroups of randomized patients
Compare the percentage of cardiac deaths reported between the 2 subgroups of randomized patients
Compare the percentage of all myocardial infarctions reported between the 2 subgroups of randomized patients
Compare the percentage of target vessel myocardial infarctions reported between the 2 subgroups of randomized patients
Compare the percentage of target vessel revascularization needs between the 2 subgroups of randomized patients
Evaluate the percentage of restenosis and stent thrombosis in the preventive revascularization group with stent + OMT of the randomized clinical trial
* Although all objectives are marked with a complete 4-year follow-up, an interim study will be conducted at 2 years. ** All objectives will be calculated on an intention-to-treat basis according to the statistical plan. An exploratory per-protocol analysis will also be conducted based on the assessment by the study's core imaging laboratory.

FFR: fractional flow reserve; OCT: optical coherence tomograph; OMT: optimal medical treatment; TVF: target vessel failure.

Table 2. Inclusion and exclusion criteria of the VULNERABLE trial

Inclusion criteria
Patients older than 18 years
With STEMI (ST-segment elevation > 1 mm in, at least, 2 contiguous leads or true posterior ST-segment elevation with > 2 mm depression in anterior leads or new onset left bundle branch block) treated with successful revascularization of the culprit lesion within 72 hours from symptom onset
Presenting with multivessel disease with, at least, 1 angiographically intermediate lesion (PDS of 40% up to 69% by visual estimation) in a native vessel different from the culprit vessel
Planned FFR-guided percutaneous revascularization with a single 2.0 mm-to-4.5 mm stent
Between 1 and 60 days after the index procedure (revascularization of the STEMI culprit vessel)
Exclusion criteria
Life expectancy < 4 years
Women of childbearing age who wish to become pregnant
Known intolerance to acetylsalicylic acid, heparin, everolimus, or iodinated contrast
Unresolved mechanical complications or infarct-related cardiogenic shock
Lesions suitable for the study located in the left main coronary artery, vessels with previous revascularization, in coronary bifurcations with > 2.5 mm side branches, severe angulations, or segments with severe calcification
History of severe asthma
Chronic kidney disease with glomerular filtration rate < 45 mL/min

FFR: fractional flow reserve; PDS: percent diameter stenosis; STEMI: ST-segment elevation myocardial infarction.

study design, data collection, analysis, or the writing of the study results. The study sponsor (Foundation for Education in Interventional Cardiology Procedures [EPIC]), along with the principal investigators, is responsible for data management and confidentiality.

Endpoints

The primary objective of the VULNERABLE study (NCT05599061) is to compare the efficacy of preventive stenting combined with OMT vs OMT alone for intermediate lesions in noninfarct-related arteries with an FFR > 0.80 and vulnerable plaque characteristics as identified by OCT over a 4-year follow-up period. The primary endpoint of the study is the rate of target vessel failure (TVF), which is defined as a composite of cardiac death, target vessel myocardial infarction, or the need for target vessel revascularization.

The study also aims to evaluate several secondary endpoints, which are summarized in table 1. Among these secondary objectives, a key focus is the comparison of the TVF rate (the primary endpoint) between the registry group (patients with FFR > 0.80 without vulnerable plaque characteristics treated with OMT) and the randomized OMT arm of the clinical trial (patients with FFR > 0.80 and vulnerable plaque characteristics). The study endpoints are defined in table 3 of the supplementary data.[12,13]

Patient inclusion and exclusion criteria

The inclusion and exclusion criteria for the study are detailed in table 2. In brief, all patients with STEMI who have undergone successful revascularization of the culprit lesion and have at least 1 intermediate lesion (visually defined as having a DS of 40%-69%) in a noninfarct-related artery will be eligible for the study if percutaneous revascularization with a single stent guided by FFR is being considered. The study procedure must be conducted between 1 and 60 days after the revascularization of the culprit lesion. Patients must provide informed consent prior to the elective procedure for evaluating the nonculprit lesion.

Study protocol for nonculprit lesions and randomization

Eligible lesions will first be assessed with a pressure wire following the standard procedures in each center. Lesions with an FFR ≤ 0.80 will be considered search failures, and revascularization will be recommended based on clinical indications.[5,6]

Lesions with an FFR > 0.80 will be further evaluated with OCT according to the standard acquisition methods to detect vulnerable plaques in each center. The decision on whether a lesion meets the criteria for vulnerable plaque will be made by an accredited local investigator during the study procedure.

Patients with at least 1 lesion with an FFR > 0.80 without vulnerable plaque characteristics on OCT will be included in the registry

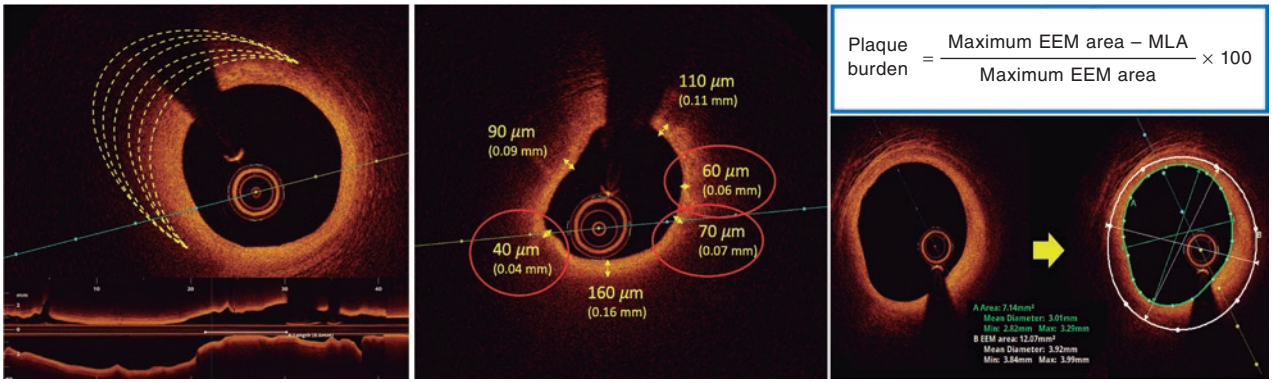

Figure 2. Vulnerable plaque criteria by optical coherence tomography. EEM, external elastic membrane; minimal lumen area.

group of the study. The protocol recommends OMT for all lesions with an FFR > 0.80 without vulnerable plaque characteristics. These patients will receive the same clinical follow-up as those in the randomized clinical trial group.

Patients with at least 1 lesion with an FFR > 0.80 that meets the criteria for a vulnerable plaque on OCT will be included in the clinical trial group. These patients will be randomized 1:1 to either preventive stenting combined with OMT or OMT alone (figure 1). Randomization will be conducted without stratification by center or clinical condition, using telematic algorithms. This process will be carried out online via the data collection platform provided by pInvestiga (Pontevedra, Spain).

The supplementary data provide additional details on the FFR assessment method, including special situations where the lesion under study could not be fully evaluated, instances of unstable nonculprit plaques, complications related to diagnostic techniques, or patients with more than 1 nonculprit lesion.

Study device and implantation procedure

Patients with an FFR > 0.80 and vulnerable plaque characteristics identified by OCT assigned to the percutaneous coronary intervention group will be treated with an everolimus-eluting stent (Xience, Abbott, United States). According to the protocol, stent implantation must be guided by OCT. The criteria for OCT-guided stent implantation are detailed in table 4 of the supplementary data.

Optimal medical therapy

All patients included in both the randomized clinical trial and the registry must receive treatment in accordance with the European Society of Cardiology guidelines for managing acute coronary syndromes.[5] The study protocol emphasizes managing modifiable risk factors—such as diet, smoking, obesity, exercise, and psychological status—as well as nonmodifiable risk factors, with set targets for blood pressure (systolic < 130 mmHg and diastolic < 80 mmHg), low-density lipoprotein cholesterol (< 55 mg/dL), and glycated hemoglobin A1c (< 7%). Pharmacological therapy should include beta-blockers and renin-angiotensin system inhibitors. Dual antiplatelet therapy is also recommended, but only during the first year after the index procedure, at the discretion of each center. As per the protocol, patient treatment details will be reported annually, and 2 lipid profile tests will be conducted throughout the study.

Vulnerable plaque criteria on optical coherence tomography and investigator training

Based on histopathological data, a plaque is defined as vulnerable when it is caused by a fibroatheroma with a large necrotic core composed of cellular debris and a high number of inflammatory cells, covered by a thin fibrous cap (≤ 65 µm).[14] The criteria for identifying a vulnerable plaque in the study are adapted from the classic histopathological definition but modified for OCT assessment. These criteria are shown in figure 2.

According to the protocol, 3 simultaneous criteria are required to define a vulnerable plaque by OCT:

The presence of a fibro-lipid plaque with a necrotic core covering more than 90° of the perimeter of the vessel over a length of more than 5 mm. A necrotic core is defined as a hypointense image with poorly defined borders that attenuates the OCT light beam, preventing visualization of the artery behind the core.

The presence of a thin fibrous cap, defined as ≤ 80 µm (65 + 15 µm axial resolution) in ≥ 3 consecutive images. The fibrous cap is defined as the tissue separating the necrotic core from the vessel lumen. Investigators will be trained to differentiate other findings that could be mistaken for a thin cap on OCT. Figure 3 shows examples of analogous OCT images that may mimic a thin fibrous cap but do not correspond to vulnerable plaques.

Investigators will be required to measure a plaque burden of ≥ 70% in the cross-sectional area corresponding to the minimal luminal area (MLA) within the lesion. To perform this assessment, it is necessary to measure the vessel perimeter by delineating the external elastic membrane (EEM). Due to the difficulty of assessing the vessel perimeter in fibro-lipid plaques, especially at the MLA site, investigators will be trained to choose a section as close as possible to the MLA, where at least 60% of the vessel perimeter

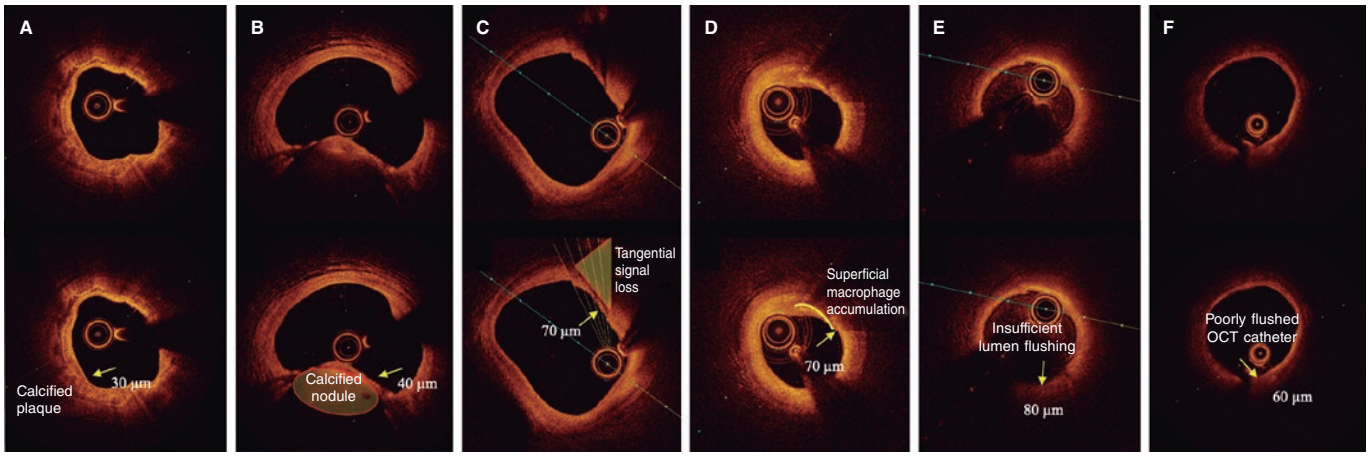

Figure 3. Distinction between vulnerable plaques and other findings by optical coherence tomography (OCT). **A:** plaque with superficial calcium (hypointense core with well-defined margins that do not attenuate the passage of light; arrow) and a thin fibrous cap. **B:** calcified nodule (arrow) protruding into the lumen and attenuating the signal, despite being composed of calcium. **C:** tangential signal loss (arrow) due to insufficient light beams caused by the peripheral, noncentral position of the OCT probe. **D:** superficial accumulation of macrophages (arrow) with a hyperintense appearance relative to the adjacent intima, with signal attenuation behind. **E:** presence of blood in the lumen due to inadequate flushing (arrow) during image acquisition, which distorts the arterial wall image, creating the appearance of hypointense regions. **F:** presence of blood between the probe and the OCT catheter (arrow) due to inadequate flushing, which distorts the arterial wall image and mimics hypointense regions.

can be visualized if it is not possible at the same point. This allows for calculation using the following formula (figure 4):

$$\frac{\text{Maximum EEM area} - \text{MLA}}{\text{Maximum EEM area}} \times 100$$

As per protocol, at least 1 local investigator from each participating center must have completed an online training course for the detection and assessment of vulnerable plaques using OCT, following the study criteria. Upon completing this course and passing a specific questionnaire, the investigator will be certified and approved to participate in the study.

Angiographic and optimal coherence tomography quantification analyses

The study includes an independent imaging laboratory for angiographic quantification and OCT analysis (Barcelona Cardiac Imaging Core Laboratory [BARCICORE-Lab]) to monitor adherence to the study criteria for diagnosing vulnerable plaques. A blinded analysis of the study results will be conducted, and patients will be assigned according to the protocol for exploratory analysis. A detailed explanation of the angiographic and OCT analysis conducted by the study laboratory is shown in the supplementary data.

Clinical follow-up and blinding

Patients in both the registry group and the randomized clinical trial group will undergo clinical follow-up for 4 years. Follow-up will include telephone consultations at 1 and 3 years, and in-person visits at 2 and 4 years. Each follow-up will involve an electrocardiogram and blood tests with cholesterol determination.

Patients in the randomized clinical trial group will be blinded to their assigned treatment group (single-blind). The details of blinding and monitoring are specified in the supplementary data.

Sample size calculation

The sample size has been calculated for the randomized clinical trial group. The number of patients included in the registry and search failures will depend on the total number needed to achieve the estimated sample size for the randomized trial.

According to previous studies on patients with acute coronary syndrome, theTVF rate for nonculprit lesions meeting vulnerable plaque criteria treated with OMT is estimated to be around 8% to 10% at 4 years. In similar lesions treated with stenting, the rate is approximately 4%.[2,7,9] The studies used for the sample size calculation are summarized in table 5 of the supplementary data. Based on the study hypothesis, preventive stenting in nonculprit lesions with an FFR > 0.80 and vulnerable plaque characteristics is expected to reduce the primary endpoint by 60%. The estimated rate of TVF in the OMT group at 4 years is 10%. Assuming an annual loss to follow-up rate of 1.5% (total 6%), randomizing 600 participants 1:1 to preventive stenting plus OMT vs OMT alone will provide 80% power to demonstrate the superiority of preventive stenting with a 2-sided alpha error of .05.

Statistical analysis plan

The primary and secondary endpoints will be analyzed using the intention-to-treat principle at the 4-year follow-up. Comparisons will estimate event proportions between groups using logistic regression and will be reported as odds ratios with 95% confidence intervals. Only 1 event per patient will be counted for the primary endpoint. *P* values < .05 will be considered statistically significant for the primary endpoint. Kaplan-Meier curves will be used to visualize the time to the first event between groups.

For primary endpoint composites with missing data, a specific monitoring plan will determine if the missing data are random. In cases where data are adjudicated as missing at random, imputation methods will be used. For nonrandom missing data, sensitivity analyses using worst-case and last observation carried forward methods will be conducted.

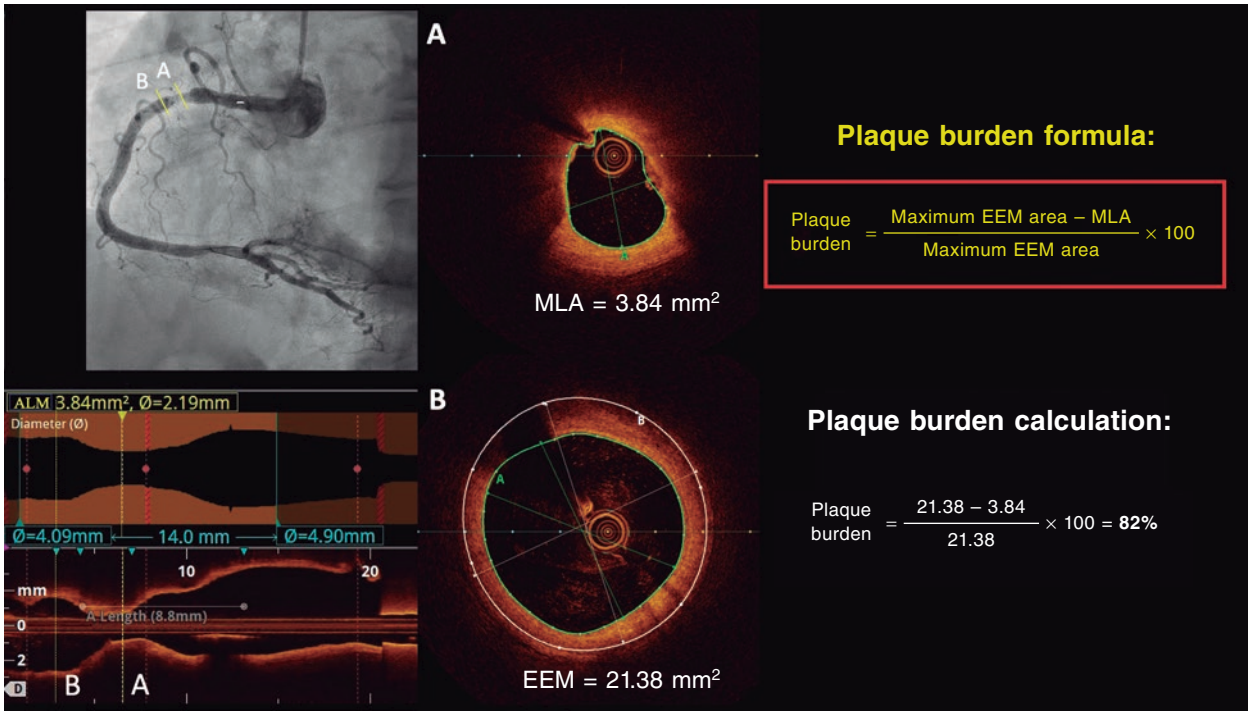

Figure 4. Plaque burden assessment by optical coherence tomography. **A:** cross-section of the minimal lumen area. **B:** cross-section where the external elastic membrane (EEM) was measured. Since the EEM cannot usually be assessed in the cross-section corresponding to the MLA, an approximate estimation is made by measuring the EEM within 10 mm proximal or distal to the MLA (preferably distal) in the absence of side branches. The EEM will be assessed in the first cross-section where 60% of the EEM perimeter can be evaluated.

Subgroup analyses will be performed for the primary and secondary endpoints, which involves comparing TVF rates between registry patients and those randomized to OMT in the clinical trial. Prespecified subgroups include: age > 75 years, sex, diabetes mellitus, left ventricular ejection fraction ≤ 35% at the time of the procedure, lesions in the proximal or mid-left anterior descending artery, and lesions in vessels with a reference diameter ≤ 2.75 mm.

Additionally, a hypothesis-generating parallel analysis will be conducted according to the study protocol. Patients will be included in the analysis only if the imaging laboratory confirms that their assigned treatment group, as determined by the local investigator, is consistent with the presence of vulnerable plaque identified by OCT. Patients will be excluded if there is a discrepancy between the investigator's assignment and the imaging laboratory's findings.

Interim analysis

After 2 years of follow-up, an interim analysis of the data is planned to monitor the primary endpoint in the randomized clinical trial group. Clinical follow-up will be extended if the events observed in the OMT arm of the randomized clinical trial are less than 4%.

DISCUSSION

The VULNERABLE trial aims to investigate the combined use of intracoronary physiology and images to guide the treatment of intermediate nonculprit lesions in STEMI patients.

Several lipid-lowering and anti-inflammatory drugs have been shown to reduce thrombotic events in patients with STEMI, likely by stabilizing functionally nonsignificant vulnerable plaques.[15,17] In the PACMAN-AMI trial, treatment with alirocumab in addition to statins significantly reduced atheroma, decreased lipid content, and led to thickening of the fibrous cap compared with placebo in coronary regions with angiographically nonobstructive atherosclerosis (DS, 20%-50%).[18] However, it is noteworthy that only 31% of patients in that study exhibited all 3 markers of reduced atherosclerosis, and data on more significant plaques (eg, 40%-69% stenosis with vulnerability criteria) were not specified.[19]

The use of stents in patients with vulnerable plaques is intended to enhance neointimal healing of the struts, which thickens the fibrous cap and stabilizes the plaque. The randomized PREVENT trial assessed the effectiveness of preventive stenting for functionally nonsignificant vulnerable lesions in patients with chronic coronary syndrome compared with OMT. Vulnerable plaques were identified using various intravascular imaging techniques, with most being guided solely by intravascular ultrasound. The study found that preventive stenting resulted in a statistically significant reduction in the rate of TVF at 2 years of follow-up (0.4% vs 3.4%; $P = .0003$).[11]

Finally, several observational trials have demonstrated that OCT is an effective method for detecting vulnerable plaques and monitoring the response to intensive treatments aimed at stabilizing these plaques through fibrous cap thickening.[18,20] The PECTUS-obs trial included 438 acute coronary syndrome patients with nonculprit lesions with FFR > 0.80 treated with the OMT alone.[10] All lesions were examined using OCT, with criteria similar to those used in the VULNERABLE trial to define vulnerable plaques. In that study, 34% of patients had at least 1 vulnerable lesion, which was associated with a higher risk of adverse events (15.4% vs 8.2% for the composite endpoint of death, myocardial infarction, or revascularization in the groups with and without vulnerable

plaques, respectively). The VULNERABLE trial is the first to use OCT to guide the treatment of vulnerable plaques in functionally nonsignificant lesions.

CONCLUSIONS

The VULNERABLE trial aims to evaluate the effectiveness of preventive stenting plus OMT vs OMT alone for vulnerable plaques, as defined by OCT, in functionally nonsignificant intermediate lesions in nonculprit vessels of patients with STEMI. In addition, the study will provide information on the clinical relevance of the presence of vulnerable plaques in nonculprit lesions.

FUNDING

This study has been funded by Abbott Vascular.

ETHICAL CONSIDERATIONS

The study is being conducted following the recommendations outlined in the Declaration of Helsinki on clinical research, has been approved by *Hospital Universitari de Bellvitge* research ethics committee, and endorsed by the remaining ethics committees of participating centers. Informed consent acceptance and signature are required prior to performing any elective procedures to study the nonculprit lesion. Potential sex and gender biases are considered.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the drafting of this manuscript.

AUTHORS' CONTRIBUTIONS

J. Gómez-Lara and E. Gutiérrez-Ibañes drafted this document. The remaining signatories reviewed the document, made changes at their discretion, and approved the final text.

CONFLICTS OF INTEREST

J. Gómez-Lara and E. Gutiérrez-Ibañes received a grant from Abbott Vascular for this study. A. Jurado-Román has received fees from Abbott, Boston, and Shockwave. E. Fernández received fees from Abbott and Hexacath. C. Cortés received a Río Hortega Contract from Instituto de Salud Carlos III. S. Brugaletta received fees from Abbott, Microport, and General Electric. T. García-Camarero received fees from Medtronic and Boston. J.A. Linares Vicente received fees from Abbott Vascular, Braun, AstraZeneca, Bayer, and IZASA. O. Rodríguez-Leor received fees from Shockwave, WorlsMedica, and Medtronic. S. Ojeda received fees from Abbott, Boston, WorldMedica, and Biosensors. A. Pérez de Prado received grants and fees from Abbot, Boston, iVascular, and Terumo. H.M. García-García received fees from ACIST, Boston Scientific, Medis, Biotronik, InfraRedx/Nipro, Chiesi, and Cordis. S. Ojeda and A. Pérez de Prado are associate editors of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial processing of the manuscript has been followed. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Thin-cap fibroatheromas, also known as vulnerable plaques, are responsible for most acute coronary syndromes. Approximately 50% of patients with STEMI have additional angiographic lesions beyond the culprit lesion, which are associated with a significant number of adverse ischemic events. Preventive stenting for severe nonculprit lesions (DS ≥ 70%) has been shown to reduce the number of adverse events. However, the effectiveness of preventive stenting for angiographically intermediate nonculprit lesions (SD, 40%-69%) that have characteristics of vulnerable plaques remains to be determined.

WHAT DOES THIS STUDY ADD?

- VULNERABLE is the first randomized trial to evaluate the preventive treatment of angiographically intermediate, nonculprit lesions that exhibit features of vulnerability identified by OCT in patients with STEMI.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000468.

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Original article

Distal radial access for coronary procedures in an all-comer population: the first 1000 patients in a prospective cohort

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ABSTRACT

Introduction and objectives: Distal radial access (DRA) for coronary procedures is currently recognized as an alternative to conventional transradial access, with documented advantages primarily related to access-related complications. However, widespread adoption of DRA as the default approach remains limited. Therefore, this prospective cohort study aimed to present our initial experience with DRA for coronary procedures in any clinical settings.
Methods: From August 2020 to November 2023, we included 1000 DRA procedures (943 patients) conducted at a single center. The study enrolled a diverse patient population. We recommended pre- and postprocedural ultrasound evaluations of the radial artery course, with ultrasound-guided DRA puncture. The primary endpoint was DRA success, while secondary endpoints included coronary procedure success, DRA performance metrics, and the incidence of access-related complications.
Results: The DRA success rate was 97.4% (n = 974), with coronary procedure success at 96.9% (n = 969). The median DRA time was 40 [interquartile range, 30-60] seconds. Diagnostic procedures accounted for 64% (n = 644) of cases, while 36% (n = 356) involved percutaneous coronary intervention (PCI), including primary PCI in 13% (n = 128). Pre-procedure ultrasound evaluation and ultrasound-guided DRA were performed in 83% (n = 830) and 85% (n = 848) of cases, respectively. Access-related complications occurred in 2.9% (n = 29).
Conclusions: This study shows the safety and feasibility of DRA for coronary procedures, particularly when performed under ultrasound guidance in a diverse patient population. High rates of successful access and coronary procedure outcomes were observed, together with a low incidence of access-related complications. The study was registered on ClinicalTrials.gov (NTC06165406).

Keywords: Vascular access. Distal radial artery. Coronary angiography. Percutaneous transluminal coronary angioplasty. Doppler ultrasound. Access-related complications.

Acceso radial distal para procedimientos coronarios en cualquier escenario clínico: experiencia de los primeros 1.000 pacientes de una cohorte prospectiva

RESUMEN

Introducción y objetivos: Actualmente, el acceso radial distal (ARD) para procedimientos coronarios es una alternativa al acceso radial convencional, con algunas ventajas descritas principalmente en términos de complicaciones relacionadas con el acceso. A pesar de la evidencia, pocos centros han establecido el ARD como acceso sistemático para procedimientos coronarios. El objetivo de esta cohorte prospectiva es presentar la experiencia inicial en nuestro centro con el ARD en pacientes con indicación de procedimientos coronarios en cualquier escenario clínico.

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Métodos: Se incluyeron 1.000 procedimientos de ARD (943 pacientes) realizados en un único centro de agosto de 2020 a noviembre de 2023. El estudio fue realizado con pacientes en cualquier escenario clínico. Se recomendó la valoración por ultrasonido del trayecto de la arteria radial antes y después del procedimiento, así como la punción ecoguiada. El objetivo principal fue el éxito del ARD. Como objetivos secundarios se consideraron el éxito del procedimiento coronario, el desempeño del ARD y las complicaciones relacionadas con el acceso.
Resultados: El éxito del ARD fue del 97,4% (n = 974) y el éxito del procedimiento coronario fue del 96,9% (n = 969). El tiempo de acceso del ARD fue de 40 segundos [rango intercuartílico, 30-60]. Se realizaron procedimientos diagnósticos en el 64% (n = 644) e intervencionismo coronario percutáneo (ICP) en el 36% (n = 356), incluyendo ICP primario en el 13% (n = 128) de los pacientes. La valoración por ultrasonido antes del procedimiento se llevó a cabo en el 83% (n = 830) y la punción ecoguiada en el 85% (n = 848). La incidencia de complicaciones relacionadas con el acceso fue del 2,9% (n = 29).
Conclusiones: Este estudio muestra la viabilidad y la seguridad del ARD principalmente guiado por ultrasonido para los procedimientos coronarios en cualquier escenario clínico, con un alto porcentaje de éxito del acceso y de éxito del procedimiento, además de una baja incidencia de complicaciones relacionadas con el acceso. El estudio fue registrado en ClinicalTrials.gov (NTC06165406).

Palabras clave: Acceso vascular. Arteria radial distal. Coronariografía. Angioplastia coronaria transluminal percutánea. Ultrasonido Doppler. Complicaciones relacionadas con el acceso.

Abbreviations

CAG: coronary angiography. **DRA:** distal radial access. **DRart:** distal radial artery. **PRart:** proximal radial artery. **TRA:** transradial access.

INTRODUCTION

Currently, distal radial access (DRA) in the anatomical snuffbox for both noncoronary and coronary procedures is gaining popularity. Since its introduction by Babunashvili et al.,[1] in 2011, several observational studies have validated the feasibility and safety of DRA,[2-4] comparing it with conventional transradial access (TRA). DRA has shown advantages such as a lower incidence of radial artery occlusion (RAO) and shorter hemostasis time, with minimal access-related complications.[5,6] The usefulness of ultrasound to guide DRA and evaluate access-related complications has also been described.[7,8] Recent randomized trials comparing DRA with TRA have reported conflicting results regarding RAO incidence, crossover rates, and access times.[9-11] Nevertheless, meta-analyses consistently support the benefits of DRA, albeit with a higher crossover rate.[12-13] One of the limitations of most studies on DRA is the restricted inclusion of patients in emergent situations or complex percutaneous coronary interventions (PCI), such as ST-segment elevation myocardial infarction (STEMI); therefore, the feasibility of the approach in this context is somewhat scarce.[2,9-11,14] Despite current evidence, the use of DRA as the default access for coronary procedures is still not widely implemented in most centers. Hence, this prospective single-center cohort aimed to present the experience of our first 1000 DRA in patients undergoing coronary procedures in any clinical settings.

METHODS

Population and study design

The Distal Radial Access for Diagnostic and Interventional Coronary Procedures in an all-comer population (DISTAL) registry is a prospective observational investigation aiming to assess the performance of DRA and compare clinical and procedural characteristics in a diverse population undergoing coronary procedures. This interim analysis presents our initial experience with DRA conducted at a single center. All DRA procedures performed by 4 experienced operators, previously proficient in TRA, were included in the study from August 2020 to November 2023.

This study was approved by the Ethics Committee of our institution (CEIC-2804) and was conducted following the principles of the Declaration of Helsinki. All patients gave their informed written consent before the procedure.

Inclusion and exclusion criteria

The study included patients aged 18 years and older undergoing diagnostic or therapeutic coronary procedures using DRA in any clinical setting. Patients with an unsuitable distal radial artery (DRart) assessed by ultrasound (non-permeable or diameter <1 .8 mm) were excluded, as were patients with no palpable pulse of DRart with such unsuitability characteristics. Additional exclusion criteria encompassed participation in other clinical trials, known allergy to iodinated contrast, inability to provide informed consent, and women of childbearing age without a negative pregnancy test. While the Barbeau test was recommended, it was not mandatory for inclusion.[15]

Endpoints

The primary endpoint was the success of DRA and the main secondary endpoint was the success of the coronary procedure. Other secondary endpoints included DRA procedure time, total procedure duration, the incidence of radial artery spasm, exposure to ionizing radiation, patient comfort levels, hemostasis time, access-related complications, and the impact of ultrasound guidance on DRA performance. Detailed definitions of these endpoints are provided in the supplementary data.

Distal radial access technique

The DRA technique has been previously described,[2,4,16-18] and is explained in detail in the supplementary data. Key aspects of interest included patient selection, the decision to use ultrasound-guided puncture[19] (figure 1) vs blind with palpation puncture at the discretion of the operator, patient positioning for right (r) or left (l) DRA, the puncture technique itself, and the hemostasis procedure (figure 2).

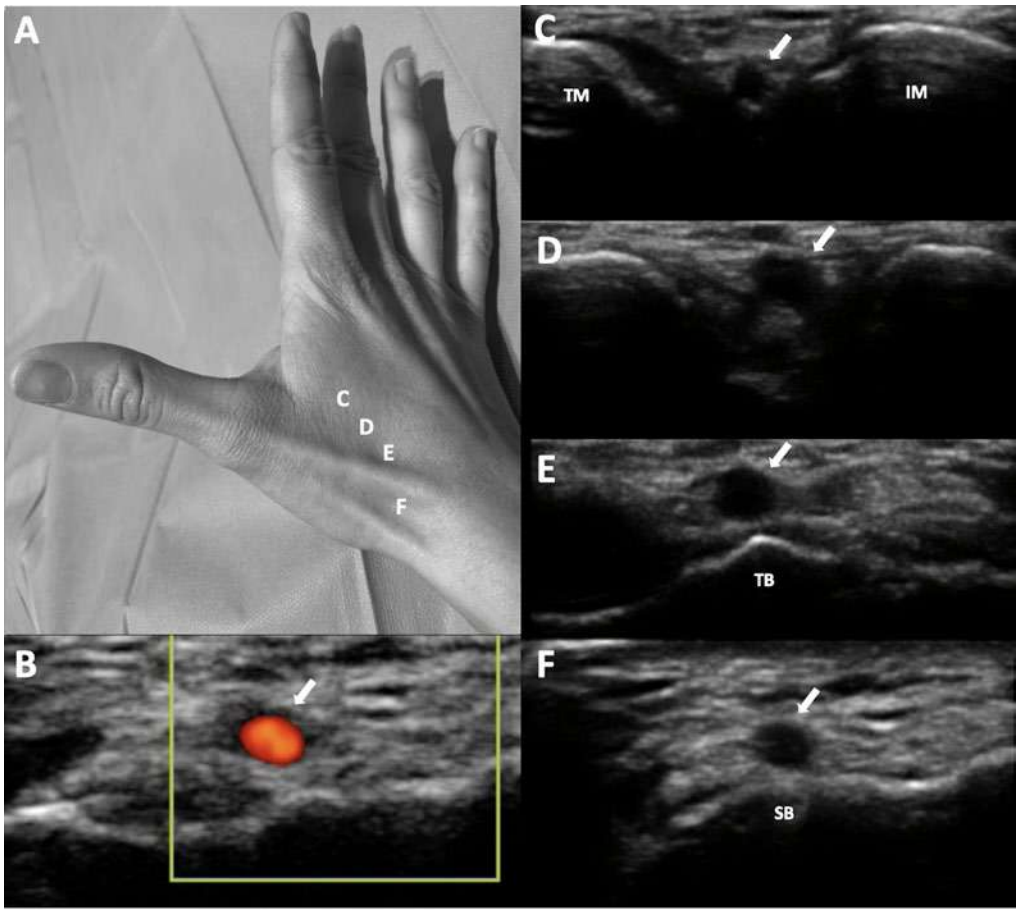

Figure 1. **A:** markers for ultrasound positioning in the anatomical snuffbox. **B:** patency of the distal radial artery (DRart) confirmed by color Doppler ultrasound. **C-D:** course of DRart between the metacarpal bones. **E-F:** recommended puncture sites of the DRart on a surface bone.
IM, index metacarpal; SB, scaphoid bone; TB, trapezium bone; TM, thumb metacarpal.

Statistical analysis

Sample size and statistical power calculations were performed using the GRANMO calculator.[20] A sample size of 1000 procedures was determined to provide a statistical power greater than 99% to detect a difference of 3% or more in the proportion of DRA success (primary endpoint) at our center, assuming an alpha risk of 1%. This calculation was based on a reference proportion from previous medical literature estimated around 95%.[11,18,21]

Categorical variables are presented as counts (percentages), while continuous variables were assessed for normal distribution using the Kolmogorov-Smirnov test. Normally distributed variables are expressed as mean (standard deviation), and nonnormally distributed variables as median [interquartile range].

To evaluate the impact of the learning curve, comparisons were made among quartiles of the study period for variables including access failure, DRA time, total procedure time, and access-related complications. Analysis of variance or the Kruskal-Wallis test was used depending on the normality of the variable. Logistic regression analysis (logit command) was used with the first quartile as the reference to compare percentages among quartiles.

Statistical analyses were conducted using SPSS Statistics 20.0 software (IBM, United States) and STATA 12 (StataCorp, College Station, United States). A p-value < 0.05 was considered statistically significant for all tests.

RESULTS

From August 2020 to November 2023, a total of 1000 DRA procedures (943 patients) were performed. Table 1 shows the patients' baseline clinical characteristics. The mean age was 68 years, and 29% of the patients were women. A total of 47% of the procedures were performed on an outpatient basis. In 35% of cases, the indication was acute coronary syndrome (13% STEMI).

Table 2 presents the characteristics of the radial artery and the DRA procedure. High rates of preprocedure ultrasound evaluation and ultrasound-guided technique for DRA were noted (83% and 85%, respectively). Notably, the percentage of coronary procedures showing insufficient catheter length due to DRA was low (3.7%).

Table 3 summarizes the characteristics of coronary procedures, including the extent of coronary artery disease, types of procedures, and features of patients who underwent PCI. In general, 64% of the procedures were only diagnostic, while 36% included PCI.

Table 4 depicts the clinical endpoints. The DRA success rate was 97.4% and the coronary procedure success rate was 96.9%. The median access time was 40 (interquartile range [IQR], 30-60) seconds, and 4% of patients experienced radial artery spasm. The overall rate of access-related complications was low (2.9%).

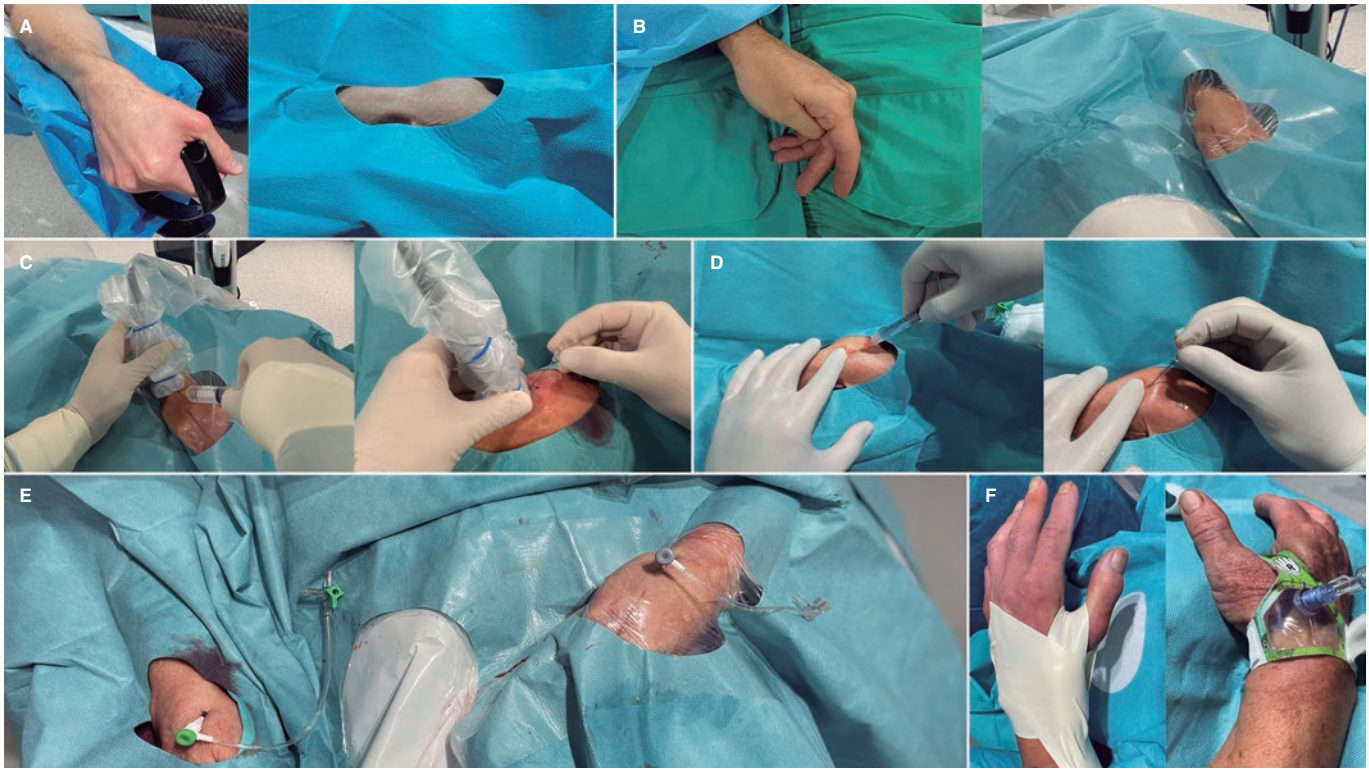

Figure 2. Distal radial access (DRA) technique. Position of the hand for **A)** right DRA and **B)** left DRA. **C:** ultrasound-guided DRA technique. **D:** blind with palpation DRA puncture. **E:** final position of the introducer sheaths on the right and left DRA. **F:** hemostasis devices in DRA.

Combined preprocedure ultrasound evaluation and ultrasound-guided puncture were performed in 82.8% of cases, with successful DRA achieved in 97.7% compared with 95.9% in those who did not undergo ultrasound guidance ($P = .183$). Based on the strength of the arterial pulse—absent, weak, normal, and strong—ultrasound-guided puncture was performed in 100%, 91%, 89.7%, and 45.5% of cases, respectively. Access time was longer with ultrasound-guided puncture than with nonultrasound-guided puncture (40 s [30-70] vs 35 s [30-45]; P < .001). The success of DRA in relation to the use of ultrasound-guided technique among all strengths of arterial pulse is detailed in table 1 of the supplementary data.

Arterial patency after removal of the hemostatic device was assessed in 907 patients (90.7%), revealing RAO in only 1% (n = 10).

In the quartile analysis, a shift in the selection of DRA side was observed, with lDRA initially more commonly used, shifting to rDRA as the preferred access in later quartiles (figure 3A). DRA failure rates were low in all quartiles but decreased significantly from the third quartile onwards (figure 3B). Access time decreased significantly from the second quartile onwards and remained stable thereafter (figure 3C). However, no significant differences were found in total procedure duration between quartiles (figure 3D).

DISCUSSION

Using data from a large prospective registry of patients who underwent DRA for coronary procedures, with high use of ultrasound-guided techniques, our study showed that DRA achieves high rates of access and procedural success, coupled with a low incidence of access-related complications in an all-comer population.

The usefulness of ultrasound in the distal radial access technique

Understanding the anatomy of the anatomical snuffbox is crucial for successful DRA, and ultrasound serves as a valuable tool in achieving this, offering demonstrated advantages.[5,16,17,22] In our study, preprocedure ultrasound evaluation and ultrasound-guided DRA techniques were used in most patients. In addition to assessing arterial diameters and evaluating calcification and tortuosity, ultrasound enabled us to exclude patients with unsuitable distal radial arteries. Overall, we found no significant differences between ultrasound-guided and nonultrasound-guided DRA, although the former was associated with longer access times. However, the role of ultrasound is particularly noteworthy in cases of weak or absent arterial pulses, which are often underrepresented in prior studies. The presence of a suboptimal arterial pulse can stem from various factors, including small DRart, hypotension, collateral blood supply, or depth of DRart.[11] In our study, most patients with weak pulses underwent ultrasound-guided puncture, with a favorable trend toward successful access in those who did. However, in patients with normal to strong pulses, no differences in DRA success were found, and even prolongation of access time was observed with its use. Therefore, in this type of pulse, an ultrasound-guided puncture is probably not necessary.

Feasibility, safety, and technical issues in distal radial access

This study corroborates the previously reported advantages of DRA,[3,9,10,12,13,18] such as a low rate of RAO, acceptable access time, short hemostasis time, and adequate patient comfort.

Furthermore, the absence of an increased risk of hand dysfunction after DRA has been demonstrated,[23] even compared with TRA at 12 months

Table 1. Baseline clinical characteristics

Clinical characteristics	n = 1000
Age, (years), mean (SD)	68.1 (11.7)
Female, n (%)	289 (28.9)
Weight, (kg), mean (SD)	78.0 (14.8)
Height, (cm), mean (SD)	167.9 (8.1)
Body mass index, (kg/m^2), mean (SD)	28.0 (4.5)
Hypertension, n (%)	735 (73.5)
Dyslipidemia, n (%)	578 (57.8)
Diabetes mellitus, n (%)	353 (35.3)
Current smoker, n (%)	246 (24.6)
Family history of premature coronary heart disease, n (%)	54 (5.4)
Previous peripheral artery disease, n (%)	50 (0.5)
Previous stroke, n (%)	41 (4.1)
Previous heart failure, n (%)	252 (25.2)
GFR (mL/minute/1.73m^2), mean (SD)	72.4 (20.0)
Dialysis, n (%)	27 (2.7)
Left ventricular ejection fraction, mean (SD)	52.6 (16.2)
Atrial fibrillation, n (%)	170 (17.0)
OAC	
Acenocoumarin, n (%)	170 (17.0)
Direct OAC, n (%)	81 (8.1)
Previous CAG, n (%)	251 (25.1)
Previous CABG, n (%)	43 (4.3)
Previous PCI, n (%)	218 (21.8)
Previous ischemic heart disease	
Previous STEMI, n (%)	133 (13.3)
Previous NSTEMI, n (%)	69 (6.9)
Previous CCS, n (%)	53 (5.3)
CAG indication	
Chronic coronary syndrome, n (%)	207 (20.7)
STEMI, n (%)	128 (12.8)
NSTEMI, n (%)	224 (22.4)
Staged PCI, n (%)	60 (6.0)
Diagnostic, n (%)	381 (38.1)
Preoperative CAG in patients with VHD, *n (%)*	183 (18.3)
Dilated cardiomyopathy, *n (%)*	158 (15.8)
Ventricular tachycardia, *n (%)*	24 (2.4)
Others, *n (%)*	16 (1.6)
Outpatient coronary arteriography, *n (%)*	470 (47)

CABG, coronary artery bypass grafting; CAG, coronary angiography; CCS, chronic coronary syndrome; GFR, glomerular filtration rate; NSTEMI, non–ST-segment elevation myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; VHD, valvular heart disease.
Data are expressed as No. (%) or mean ± standard deviation.

Table 2. Characteristics of the DRA procedure

Procedure characteristics	n = 1000
Preprocedure characteristics	
Arterial pulse strength scale	
Absent, n (%)	12 (1.2)
Weak, n (%)	167 (16.7)
Normal, n (%)	652 (65.2)
Strong, n (%)	169 (16.9)
Radial artery preprocedure ultrasound evaluation, n (%)	830 (83.0)
Arterial tortuosity	
Radial, n (%)	23 (2.3)
Subclavian, n (%)	62 (6.2)
Calcified radial artery, n (%)	26 (2.6)
Distal radial artery size, mm (SD)	2.3 (0.3)
Proximal radial artery size, mm (SD)	2.5 (0.4)
Depth of the distal radial artery, mm (SD)	3.8 (1.0)
DRA technique	
CAG by the same DRA, n (%)	57 (5.7)
Ultrasound-guided access, n (%)	848 (84.8)
DRA side	
Right DRA, n (%)	627 (62.7)
Left DRA, n (%)	373 (37.3)
Introducer size	
5 French, n (%)	256 (25.6)
6 French, n (%)	744 (74.4)
Introducer sheath type	
Prelude Ideal (Merit Medical) Introducer Kit, n (%)	950 (95.0)
Radifocus Introducer II Kit A (Terumo Corporation), n (%)	50 (5.0)
Short length of the radial catheter	37 (3.7)
Postprocedure arterial patency evaluation, n (%)	907 (90.7)
Postprocedure puncture site bleeding, n (%)	55 (5.5)

CAG, coronary angiography; DRA, distal radial access.
Data are expressed as No. (%) or mean ± standard deviation.

of follow-up, documented by Al-Azizi et al.[24] Here, we focus on controversial issues that may have hampered wider adoption of this technique, and our results may provide additional support for DRA.

High success rates of DRA in coronary procedures have been reported in numerous studies.[2-4,17,18,25] In addition, recent clinical trials and meta-analyzes describe a higher crossover rate compared with TRA.[9-13]

Table 3. Characteristics of the coronary procedure

Procedure characteristics	n = 1000
Coronary disease extent	
One vessel, *n (%)*	285 (28.5)
Two vessels, *n (%)*	174 (17.4)
Three vessels, *n (%)*	176 (17.6)
LMCAD, *n (%)*	55 (5.5)
Coronary bypass graft, *n (%)*	27 (2.7)
Characteristics of the coronary procedure	
Type of coronary procedures	
Diagnostic, n (%)	644 (64.4)
PCI, n (%)	356 (35.6)
Ambulatory PCI, n (%)	90 (9.0)
PCI culprit lesion	
LMCAD, *n (%)*	9 (0.9)
Left anterior descending artery, *n (%)*	164 (16.4)
Circumflex coronary artery, *n (%)*	95 (9.5)
Right coronary artery, *n (%)*	100 (10.0)
Coronary bypass graft	2 (0.2)
Specific techniques	
Wire-based intracoronary physiological assessment, *n (%)*	57 (5.7)
Optical coherence tomography, *n (%)*	21 (2.1)
Intravascular ultrasound, *n (%)*	30 (3.0)
Guide catheter extension system, *n (%)*	15 (1.5)
Rotational atherectomy, *n (%)*	16 (1.6)
Cutting balloon, *n (%)*	34 (3.4)
Intracoronary lithotripsy, *n (%)*	8 (8.0)
Thrombus aspiration, *n (%)*	81 (8.1)
Intracoronary perfusion catheter, *n (%)*	7 (0.7)
Special PCI procedures	
Complex bifurcation, *n (%)*	60 (6.0)
Chronic total occlusion, *n (%)*	16 (1.6)
Volume of contrast, (mL), mean (SD)	85.0 (53.1)
Heparin dose, (IU), median [IQR]	5000 (3000-8500)

LMCAD, left main coronary artery disease; PCI, percutaneous coronary intervention.

Table 4. Clinical endpoints

Clinical endpoints	n = 1000
Primary endpoint	
DRA success, n (%)	974 (97.4)
Coronary procedure success by DRA, n (%)	969 (96.9)
Secondary endpoints	
Access time, (sec), median [IQR]	40 (30-60)
Procedure time, (min), median [IQR]	29.0 [17.3-45.0]
Radial artery spasm, n (%)	44 (4.4)
DAP, (Gy.m^2), median [IQR]	32.7 [19.2-63.0]
Fluoroscopy time (min), median [IQR]	4.6 [2.5-10.0]
VAS patient comfort for access, mean (SD)	2.2 (0.6)
VAS patient comfort for hemostasis, mean (SD)	2.1 (0.4)
Hemostasis time, (hour), mean, (SD)	2.9 (1.1)
Access-related complications (all), n (%)	29 (2.9)
Radial artery occlusion, *n (%)*	10 (1.0)
Hematoma, *n (%)*	
Type I-a, n (%)	11 (1.1)
Type I-b, n (%)	1 (0.1)
Type II, n (%)	1 (0.1)
Type III, n (%)	1 (0.1)
Type IV, n (%)	0 (0)
Radial pseudoaneurysm, *n (%)*	0 (0)
Radial dissection, *n (%)*	5 (0.5)
Arteriovenous fistula, *n (%)*	0 (0)

DAP, dose-area product; DRA, distal radial access; VAS, visual analog scale.
Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

In contrast to our results, trials comparing DRA with TRA have reported lower access success and longer puncture times.[9-11] Conversely, our study demonstrates remarkably high success rates for DRA and coronary procedures, as well as shorter access time, consistent with registries in which DRA is the default approach among experienced operators, as shown by the largest registries published to date, the DISTRACTION and KODRA studies.[2-4,18,21]

The KODRA trial included 4977 DRA procedures from a Korean registry.[21] The authors reported a DRA success rate of 94.4%, with a crossover rate of 6.7%. In contrast to our work, the use of ultrasound-guided puncture in KODRA was low (6.4%). Additionally, the authors found predictors of DRA failure, such as the presence of a weak pulse and limited operator experience (less than 100 cases).

The equivalence of rDRA and lDRA has previously been demonstrated, and contemporary studies use mainly rDRA.[9-11,17] As in the first registries, which suggested a potential advantage of lDRA, we started our experience with lDRA but, based on operator comfort and preference, the use of the rDRA increased over time.

Although the feasibility and benefits of DRA over TRA in STEMI have been observed, the literature on the topic remains scarce.[2,9-11] In our registry, all attempted DRA procedures in patients with STEMI were successful. However, the first DRA in STEMI was performed after the operators had surpassed the learning curve for the technique (up to case 320). Similarly, the use of DRA for complex PCI has been previously described.[22,26,27] In our cohort, all complex PCI procedures were performed without crossover.

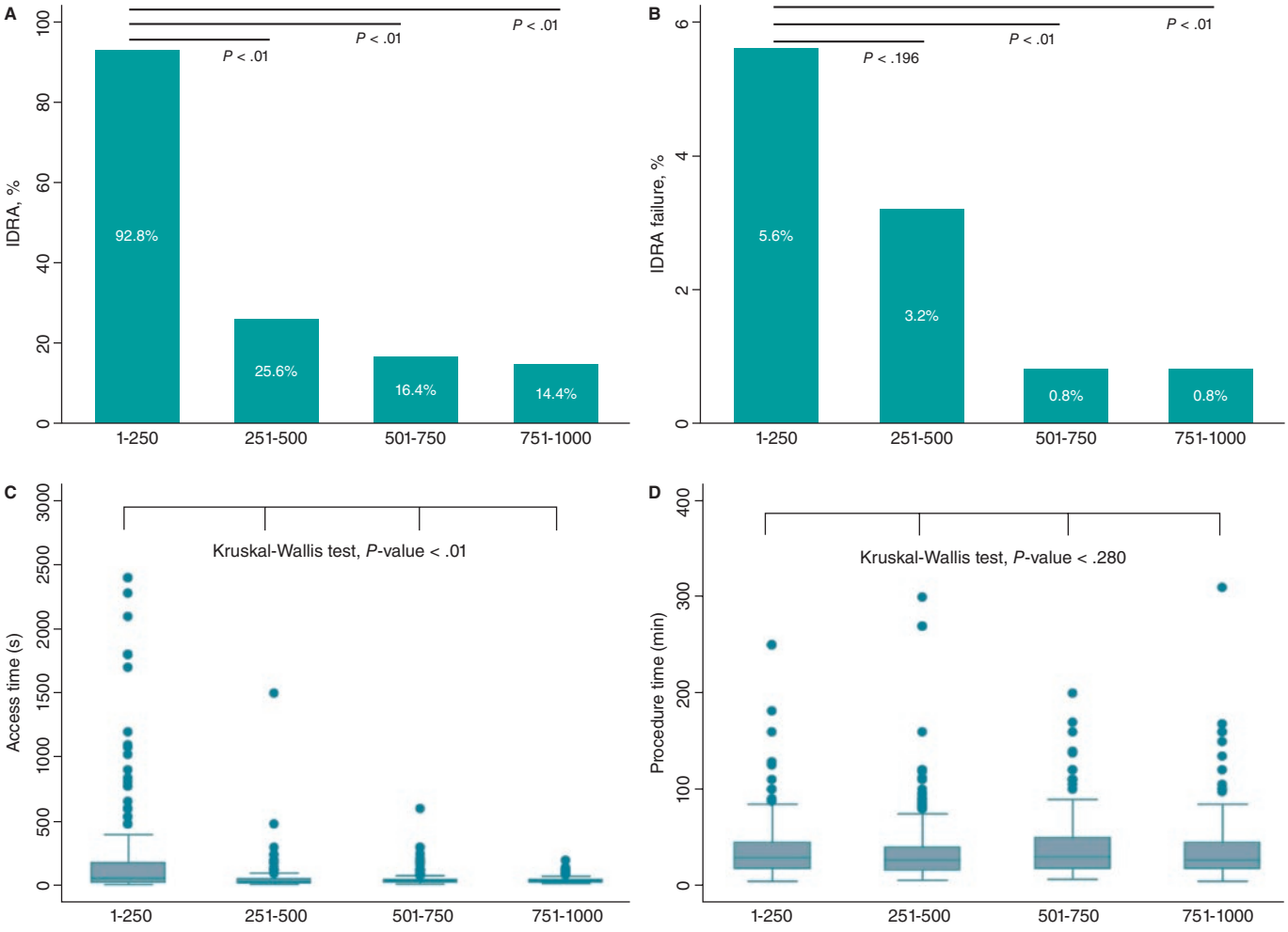

Figure 3. Stratified analysis by quartiles of patients over the study period. **A:** use of left vs right distal radial access (DRA). **B:** DRA access failure rate by quartile. **C:** DRA access time in seconds. **D**: total procedural time in minutes.

The puncture site in DRA, situated 5 cm distal to TRA, may lead to an inadequate catheter length in specific contexts (such as tall patients, dilated aorta, subclavian artery tortuosity, and the need for retrograde access to PCI for chronic total occlusions).[28] We found a low incidence of short catheter length during DRA procedures, with only 1 crossover due to severe tortuosity of the subclavian artery.

DRA-related complications have been consistently reported to be low.[2,9-11,18] Similarly, we found a very low rate of complications, the most common being type I-a hematoma. In our study, the incidence of in-hospital RAO was 1%.

The number of DRA procedures to overcome the learning curve and maintain a success rate above 94% is around 150 to 200.[2,8] However, in our early experience, we achieved this percentage after the first 20 cases per operator.[17] In this study, operators navigated the learning curve in the first quartile; however, success significantly improved to more than 99% in the last 2 quartiles, probably because DRA became the default access for coronary procedures among operators.

Limitations

First, this study was an interim analysis of the leading participating site and coordinator of the DISTAL registry (NTC06165406), conducted because substantial enrollment from other sites was lacking. Although the data cannot be fully extrapolated to other centers, recalculation of the sample size was considered sufficient to evaluate the results.

Second, patient enrollment was not consecutive because the decision to use DRA was at the operators' discretion. Only one-third of coronary procedures during the study period used this approach. However, we included all patients in whom operators intended to use DRA in any clinical setting were included, with only 21 patients excluded due to DRart ≤1.8mm. Third, this was a descriptive cohort of DRA, without a comparison control group. Fourth, the scale used to assess the arterial pulse is subjective. However, this scale is widely used in routine clinical practice and has been used in multiple DRA studies. Finally, radial artery patency was not evaluated in 9.7% of the patients before discharge, and no evaluation was conducted at 1 month; therefore, the in-hospital rate of radial artery occlusion may be underestimated and no mid-term data are available on the patency of the DRart.

CONCLUSIONS

This study shows the safety and feasibility of DRA primarily guided by ultrasound for coronary procedures in an all-comer population, with high rates of both access and procedural success, in addition to a very low rate of access-related complications.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of our institution (CEIC-2804) and was conducted following the principles of the Declaration of Helsinki. All patients gave their informed written consent before the procedure.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Not used.

AUTHORS' CONTRIBUTIONS

K. Rivera and D. Fernández-Rodríguez conceived and designed the study. K. Rivera, D. Fernández-Rodríguez, M. García-Guimarães, J. Casanova-Sandoval, and J. L. Ferreiro analyzed data, and drafted the manuscript. All authors contributed to the treatment of patients, data acquisition and mining, and review and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

J. L. Ferreiro reports *a)* honoraria for lectures from Eli Lilly Co, Daiichi Sankyio, Inc, AstraZeneca, Pfizer, Abbott, Boehringer Ingelheim, Bistol-Myers Squibb, Rovi, Terumo and Ferrer; *b)* consulting fees from AstraZeneca, Eli Lilly Co, Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Inc, Bristol-Myers Squibb and Biotronik; c) research grants from AstraZeneca. The remaining authors have no conflicts of interest to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

- Previous studies have demonstrated the safety and feasibility and safety DRA. Compared with TRA, DRA has several advantages, despite the high prevalence of crossover and controversial incidence of radial artery occlusion.

WHAT DOES THIS STUDY ADD?

- The results of this cohort show the safety and feasibility of DRA in an all-comer population throughout the spectrum of DRart pulses. Our study demonstrates that preprocedure ultrasound evaluation and the ultrasound-guided DRA technique help to achieve a low crossover rate, which is especially useful in patients with an unfavorable arterial pulse. According to our observations, DRA in urgent/emergent procedures and complex PCI is feasible and safe once the learning curve has been overcome and the operator is familiar with the technique.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000470.

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Original article

Management of collaterals after Glenn procedure and its impact on patients with a single ventricle: a single-center study

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ABSTRACT

Introduction and objectives: The bidirectional Glenn shunt (BDG) is an essential step in the repair of a physiologically single-ventricle heart. BDG increases pulmonary blood flow, allows growth of the pulmonary arteries, and improves SaO_2. The procedure also allows unloading of ventricular volume, thereby improving survival. Our aim was to register all patients who developed collaterals following BDG, document the management methods used, and assess their impact.
Methods: We included 56 patients who underwent BDG procedures at a median age of 2.08 (1-3) years. After BDG, peripheral pulmonary stenting was used in 2 patients. Symptomatic hyperviscosity was present in 10 patients (17.86%), who underwent venesection. BDG was unsuccessful in 2 patients. Venovenous collaterals were observed in 41 patients (73.2%), and aortopulmonary collaterals in 37 (66.1%).
Results: Hematocrit levels were significantly higher in patients with venovenous collaterals (50.00 ± 8.76) than in those without ($P = .031$). Mean pulmonary artery pressure was also significantly higher in patients with venovenous collaterals (15 [12-18] mmHg; $P = .025$). One patient had undergone successful closure of venovenous collaterals to epicardial veins and abdominal veins 3 years previously. Seven patients underwent transcatheter closure (TCC) of collaterals. Of these, 4 patients underwent TCC of venovenous collaterals to left and right pulmonary veins; 1 patient underwent closure of an aortopulmonary collateral; 1 patient underwent a failed attempt at venovenous collateral closure that was complicated by an ischemic stroke; and 1 patient had localized extravasation upon separation of the cable. A highly statistically significant increase in SaO_2 was observed after TCC of venovenous collaterals (69.83 ± 10.91 vs 82.83 ± 9.87; $P = .008$).
Conclusions: TCC of collaterals is a technically demanding but effective management strategy following BDG to improve patients' SaO_2 and quality of life. Awareness of possible complications and their effective management is crucial.

Keywords: Venovenous. Aortopulmonary collaterals. Pulmonary vein. Coil embolization. Device embolization. Transcatheter closure.

Tratamiento de colaterales tras cirugía de Glenn y su impacto en pacientes con ventrículo único: un estudio unicéntrico

RESUMEN

Introducción y objetivos: La derivación bidireccional de Glenn (DBG) es un paso esencial en la reparación cardiaca fisiológica del ventrículo único. La DBG aumenta el flujo sanguíneo pulmonar, permite el crecimiento de las arterias pulmonares y mejora la saturación arterial de oxígeno. También permite la descarga del volumen ventricular, mejorando así la supervivencia. El objetivo del estudio fue registrar a todos los pacientes tras DBG que desarrollaron canales colaterales, los métodos de abordaje y su impacto.
Métodos: Se incluyeron 56 pacientes que habían sido tratados con DBG, con una mediana de edad de 2,08 (1-3) años. Se colocó un *stent* pulmonar periférico tras la DBG a 2 pacientes. De todos ellos, 10 (17,86%) presentaban hiperviscosidad sintomática y se les realizó una flebotomía. La DBG falló en 2 pacientes. Cuarenta y un pacientes (73,2%) tenían colaterales venovenosas y 37 (66,1%) colaterales aortopulmonares.
Resultados: Los pacientes con colaterales venovenosas presentaban valores de hematocrito significativamente mayores (50,00 ± 8,76), desde el punto de vista estadístico, en comparación con los pacientes sin colaterales venosas (p = 0,031). Los pacientes con colaterales venovenosas presentaban una presión arterial pulmonar media significativamente mayor (15 [12-18] mmHg), desde el punto de vista estadístico (p = 0,025). Se llevó a cabo el cierre percutáneo (CP) de las colaterales en 7 pacientes. Uno de ellos tuvo un cierre satisfactorio de las colaterales venovenosas a las venas epicárdicas y abdominales 3 años antes. Cuatro pacientes se sometieron a CP de colaterales venovenosas a venas pulmonares izquierdas y derechas. Se realizó un cierre de una colateral

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aortopulmonar a 1 paciente. En 1 paciente se falló en un intento de cierre de colaterales venosas que se complicó con un accidente vascular cerebral. Un paciente presentó extravasación localizada al separar el cable. Se produjo un aumento estadísticamente muy significativo de la saturación de oxígeno tras el CP de las colaterales venovenosas (69,83 ± 10,91 frente a 82,83 ± 9,87; p = 0,008). ***Conclusiones:*** El CP de las colaterales es técnicamente exigente, pero es un tratamiento eficaz tras la DBG para mejorar la saturación y la calidad de vida del paciente. Es crucial conocer las posibles complicaciones y su tratamiento eficaz.

Palabras clave: Venovenoso. Colaterales aortopulmonares. Vena pulmonar. Embolización con *coils*. Embolización del dispositivo. Cierre percutáneo.

Abbreviations

APC: aortopulmonary collateral. **BDG:** bidirectional Glenn shunt. **MBT:** modified Blalock-Taussig. **TCC:** transcatheter closure.

INTRODUCTION

The occurrence of congenital heart disease is between 6 and 13 per 1000 live births.[1] In developed countries, prenatal diagnosis is currently used to detect congenital heart disease (CHD) before birth. In developing countries, only a minority of children with CHD are detected and few benefit from surgical treatment, causing a pattern of late presentation accompanied by a high complication rate.[2]

The term *single ventricle* is generally used to describe any CHD with 1 functioning ventricle, including double inlet left ventricle, single ventricle, common ventricle, and univentricular atrioventricular (AV) connection. Other lesions, such as hypoplastic left heart syndrome (HLHS), tricuspid atresia, unbalanced AV septal defect, mitral atresia with normal aortic root, and heterotaxy syndromes with 1 functioning ventricle, can also be added to this group.[3]

The bidirectional Glenn shunt (BDG) and hemi-Fontan are surgical techniques used to create a superior cavopulmonary anastomosis (CPA) in patients with an anatomic or functional single ventricle. Whether it is right or left, the single ventricle must provide blood supply to the higher resistance systemic circulation and the lower resistance pulmonary circulation until surgical correction is undertaken. The BDG procedure or hemi-Fontan helps to eliminate the volume load on the single ventricle and facilitate subsequent Fontan surgery.[4]

Systemic venous collateral channels in patients with univentricular hearts after CPA or Fontan operations may cause significant systemic desaturation. After CPA, the pressure difference between the superior vena cava (SVC) and inferior vena cava leads to the development of venous connections between the 2 systems to decompress elevated pressure in the SVC system. Venovenous collaterals can emerge at any time following the CPA.[5]

Evaluation for venous collaterals should be performed routinely in all patients undergoing pre-Glenn and pre-Fontan catheterization. Venovenous collaterals draining below the heart will be separated from the systemic circulation after Fontan completion. These collaterals need not be embolized unless the patient has an interrupted inferior vena cava with the exclusion of the hepatic veins from the Fontan circulation, as in the Kawashima operation. In contrast, venovenous collaterals that drain into pulmonary veins or the atrium will continue to cause cyanosis due to right-to-left shunts and should be embolized.[6]

Spicer et al.[7] reported an 84% incidence of aortopulmonary collaterals (APC) in children undergoing pre-Fontan cardiac catheterizations. APCs developed in the univentricular heart often have extensive communication and commonly involve networks of smaller lacy vessels between larger collaterals. Total closure of the APCs is not feasible in such situations. In addition, extensive embolization of all APCs adds to the total catheterization procedure time and potential complications without further clinical benefit. Bradley et al.[8] recommend selective embolization of moderate to large APCs in patients undergoing univentricular heart repair. Furthermore, the pulmonary blood flow supplied by the APCs may be important in cyanotic patients. Closure of APCs in such patients may decrease the systemic saturation to dangerously low levels.

We aimed to register all patients referred to our hospital following BDG from March 2022 to February 2023. We conducted a full assessment of their hemodynamics and collateral channels, including venovenous collaterals to systemic veins or pulmonary veins and APCs. We also explored different management methods and evaluated the impact of this management on patients with single-ventricle physiology.

METHODS

The study included 56 patients who underwent BDG. We excluded critically ill patients. All patients underwent a comprehensive medical history, which included demographic data (current age, sex, weight, height, body surface area), perinatal history, developmental history, history of venesection, history of hospitalization, and surgical data. The surgical data included age at the time of the intervention, date of intervention, and any other surgical procedures performed prior to BDG, such as previous pulmonary artery banding or a modified Blalock-Taussig (MBT) shunt. The history also included information on previous invasive hemodynamic studies, previous transcatheter interventions (such as pulmonary artery stenting or closure of venovenous collaterals), and current medical treatment. The clinical examination consisted of assessing arterial blood pressure, pulse, respiratory rate, and baseline SaO_2. We also conducted a local cardiac examination, observation of subcutaneous superficial collaterals on the chest, and examination of thoracic scars. Heart sounds and murmurs, as well as both lungs, were auscultated. Twelve-lead surface electrocardiography was performed to assess heart rate and rhythm, axis, the presence of any conduction disturbances, and arrhythmias. A chest X-ray was performed to assess the cardiac shadow, pulmonary vasculature, and the presence of previous stents, embolization devices, and sutures from previous sternotomy.

A full transthoracic echocardiographic examination was performed to determine cardiac and visceral situs, the location of the cardiac

apex, AV and ventriculoarterial connections, the relationship and abnormalities of the great vessels, description of the AV connection as being double inlet, atresia of 1 of the inlets, or a common AV valve, description of the ventriculoarterial connection, and determination of the morphology and systolic function of the dominant ventricle (right, left, or indeterminate).

Available multislice computed tomography data were included to confirm the anatomy, determine systemic and pulmonary venous drainage, evaluate the peripheral pulmonary tree, assess the BDG size and patency, and determine the presence of venovenous collaterals and APC. Routine laboratory investigations were conducted before catheterization, including a complete blood count, international normalized ratio, kidney function tests, and virology.

Invasive cardiac catheterization involved a complete hemodynamic study of patients before Fontan completion and desaturated patients. The procedure was performed under 100% oxygen supplementation. The usual access points were the right femoral artery and right or left subclavian veins. Injection of the BDG was carried out in the posteroanterior (PA) view to assess BDG patency and the size of the pulmonary tree. Innominate vein injection in the PA view was used to assess the presence of venovenous collaterals. Descending aorta injection in the PA view was conducted to determine the presence of APC. Pressures and saturations were recorded from various cardiac chambers.

Percutaneous interventions were performed when indicated, including peripheral pulmonary stenting or closure of venovenous collaterals or APC. Venovenous collaterals were only closed in desaturated patients who were not candidates for Fontan completion (due to impaired ventricular function, severe AV valve regurgitation, or mean pulmonary artery pressure [PAP] > 14 mmHg), after excluding patients with pulmonary hypertension or SVC syndrome. Major APCs were closed in patients with evidence of ventricular volume overload (eg, elevated ventricular end-diastolic pressure), causing back pressure on pulmonary veins and arteries.

Statistical analysis

Qualitative data are expressed as frequencies and percentages and quantitative data as mean ± standard deviation. A standard t-test, 1-way analysis of variance, and independent samples t-test were used. Linear regression and Pearson correlation analysis were used to determine the correlation of variables of interest. The data were analyzed using commercially available software (SPSS version 19.0), and $P < .05$ was considered statistically significant. All data and materials from the study are available upon request.

RESULTS

Our registry included 56 patients who underwent BDG and were referred to our hospital between March 2022 and February 2023. The median age of the patients was 9.67 (7.42-12.17) years (min-max, 2.25-34.67 years), with 31 male patients (55.4%) and 25 female patients (44.6%).

Thirty patients (53.6%) had only BDG, while 26 patients (46.4%) had undergone other procedures before BDG: pulmonary artery banding in 15 patients (26.8%), MBT shunt in 10 patients (17.9%), and both in 1 patient (1.7%). Of the 10 patients who had MBT shunt operations, 7 (70%) had a right MBT shunt, and 3 (30%) had a left MBT shunt. Three patients (5.4%) underwent surgical septectomy with BDG. One patient (1.8%) underwent permanent pacemaker insertion via redo sternotomy.

Table 1. Basic anatomy by transthoracic echocardiography

Basic anatomy	N	Percentage
D-TGA	10	17.9
DORV	16	28.6
Tricuspid atresia	9	16.1
Tetralogy of Fallot	4	7.1
Unbalanced CAVC	3	5.4
Pulmonary and tricuspid atresia	3	5.4
DILV	6	9.8
Anatomical single ventricle	1	1.8
DIRV, DORV, DOLV, D-malposed great vessels	2	3.6
CAVC balanced type (Rastelli type A)	1	1.8

CAVC, common atrioventricular canal; DILV, double inlet left ventricle; DIRV, double inlet right ventricle; D-malposed, double-malposed; DOLV, double outlet left ventricle; DORV, double outlet right ventricle; D-TGA, dextro-transposition of the great arteries.

Five patients (8.9%) underwent percutaneous interventions: Rashkind balloon atrial septostomy after birth and before in 2 patients (3.6%); peripheral pulmonary stenting after BDG in 2 patients (3.6%), and venovenous collateral closure in 1 patient (1.8%).

The median age at BDG was 2.08 (1-3) years (min-max, 0.42-17 years). A total of 47 patients (83.9%) had a right-sided BDG, 8 patients (14.3%) had bilateral BDG, and only 1 patient (1.8%) had a left-sided BDG.

All patients had intact peripheral pulsations, and 54 patients (96.4%) had clubbing. Only 1 patient (1.8%) had SVC syndrome (figure 1 of the supplementary data), and another patient (1.8%) exhibited surface venous collaterals on the chest and abdomen associated with deep cyanosis shortly after BDG (figure 2 of the supplementary data). Both patients underwent surgical intervention to reverse the BDG procedure. Mean baseline SaO_2 was 78.27 ± 8.47%, ranging from 55% to 99%. The hemoglobin indices of the studied patients are presented in table 1 of the supplementary data.

Two of the patients (3.6%) were anemic with hemoglobin levels below the normal range for age and sex (1 girl aged 2 years and 3 months with a hemoglobin level of 8 g/dL, and a 13-year-old boy with a hemoglobin level of 11.8 g/dL). Thirty-eight patients (67.9%) had polycythemia with hemoglobin levels ranging from 14.5 to 21.1 g/dL and a mean of 16.92 ± 1.75 g/dL. Additionally, 31 patients (55.4%) had elevated hemoglobin values ranging from 44.8 to 71, with a mean of 54.37 ± 6.43. Ten patients (17.9%) required venesection before cardiac catheterization. Among them, 4 (7.14%) had venesection for the first time, while the other 6 patients (10.7%) had multiple previous venesections due to symptoms of hyperviscosity (eg, fatigue, headache, dyspnea, and visual disturbances). Echocardiographic data are included in table 1 and table 2.

A total of 30 patients underwent multislice computed tomography. Of these patients, 2 (6.7%) were found to have aneurysmally dilated BDG (figure 3 of the supplementary data).

Three patients experienced significant left pulmonary artery stenosis, which was later successfully treated with transcatheter stenting.

All patients underwent cardiac catheterization, which included invasive assessment of pressures and SaO_2 from various cardiac

Table 2. Echocardiographic data

Variables	N
Morphology of dominant ventricle	
Left ventricle	26 (46.4%)
Right ventricle	27 (48.2%)
Undetermined single ventricle	1 (1.8%)
Ventricular systolic function	
Preserved	48 (85.7%)
Impaired	8 (14.3%)
Glenn location	
Right	48 (85.7%)
Left	1 (1.8%)
Bilateral	7 (12.5%)

chambers. The results of this assessment can be found in table 2 of the supplementary data. Venovenous collaterals and APC were comprehensively assessed, and all the data collected are presented in table 3.

Among the 56 patients who underwent catheterization, 52 (92.9%) had collaterals, including venovenous and/or APC. Only 4 patients (7.1%) had no collaterals. Of the total, 19 patients (36.5%) were managed with medical treatment and regular follow-up. Another 20 patients (38.5%) were referred for surgical assessment for Fontan completion. Seven patients (13.5%) underwent TCC of collaterals (table 4 and figure 1, figure 2 and figure 3). Two patients (3.8%) were scheduled for TCC of collaterals in a subsequent session due to financial obstacles. Additionally, 2 patients underwent unsuccessful attempts to close venovenous collaterals (3.8%), 2 patients (3.8%) were referred for revision of the Glenn shunt due to a failed procedure, and 2 patients (3.8%) were referred for revision of the Glenn shunt and biventricular repair.

Three patients developed complications during TCC of collaterals. The first patient experienced complications due to coil embolization in the innominate vein during the attempt to close venovenous collaterals; however, the coil was successfully snared.

The second patient was an 18-year-old woman who underwent elective TCC of a venovenous collateral using an Amplatzer Duct Occluder II (Abbott, United States). After the device was delivered to the collateral, occluding its proximal portion, difficulties arose in separating the device cable. However, after some manipulations and selective injection at the origin of the collateral, localized extravasation was observed at the proximal site. The catheter was retracted to the innominate vein and reinjected after several minutes, revealing decreased extravasation and successful sealing of the perforation. A follow-up chest X-ray showed no further complications (figure 4).

The third patient was a 13-year-old boy who underwent injection of the azygos vein, revealing 2 large right and left venovenous collaterals to the pulmonary veins. Closure of these collaterals was attempted but was unsuccessful. Due to the prolonged procedure, the patient experienced acute left-sided weakness after catheterization. Cerebral magnetic resonance imaging and angiography showed an acute hemorrhagic infarction in the right basal ganglionic and periventricular areas, along with occlusion of the right middle

Table 3. Angiographic assessment of collaterals

Catheterization	N = 56
Aortopulmonary collaterals	
Presence	
Yes	37 (66.1%)
Number	
One	9 (24.3%)
Multiple	28 (75.7 %)
Size	
Small	28 (75.7%)
Moderate/large	69 (24.3%)
Origin	
Descending aorta	23 (62.2%)
Aorta	11 (29.7%)
Left subclavian artery	0 (0.0%)
RIMA and aortic arch	1 (2.7%)
LIMA	1 (2.7%)
Aorta and left subclavian artery	1 (2.7%)
Drainage	
Left	19 (51.4%)
Right	7 (18.9%)
Both	11 (29.7%)
Venovenous collaterals	
Presence	
Yes	41 (73.2%)
Number	
One	7 (18.4%)
Multiple	31 (81.6%)
Size	10 (25.0%)
Small	
Moderate/large	30 (75.0%)
Origin	
Left innominate vein	35 (89.7%)
Right innominate vein	1 (2.6%)
Subclavian vein	1 (2.6%)
Azygos and hemi-azygos	1 (2.6%)
SVC	1 (2.6%)
Drainage	
Pericardium	3 (7.7%)
Epicardial	14 (35.9%)
IVC	9 (23.1%)
Coronary sinus	7 (17.9%)
Abdominal vain	2 (5.1%)
Azygous	3 (7.7%)
Left pulmonary	5 (12.8%)

IVC, inferior vena cava; LIMA, left internal mammary artery; RIMA, right internal mammary artery; SVC, superior vena cava.

Table 4. Details of transcatheter closure of collaterals in 6 patients

Type of collaterals	Collateral course	Coil/device	Access and course	Complications	Effect on SO_2
VV collateral	Medium-sized (4 mm) from innominate vein to one of the left pulmonary veins	AGA ADO II 4x6 device	Right subclavian vein- innominate vein- VV collaterals	Localized extravasation	SaO_2 increased from 55% before the procedure to 75% after
VV collaterals	Two large collaterals arising from the innominate vein to the left upper pulmonary vein	2 AGA ADO I devices (8/6 and 6/4)	Left internal jugular vein- innominate vein- VV collaterals Right subclavian vein- innominate vein- VV collaterals	First attempt failed due to high tortuosity Second attempt was successful	SaO_2 increased from 83% before the procedure to 93% after
VV collaterals	Large tortuous collaterals from innominate vein to left upper pulmonary vein	Two Cook detachable coils (5/3 and 5/5)	Right subclavian vein- innominate vein- VV collaterals Left internal jugular vein- innominate vein- VV collaterals	No complications	SaO_2 increased from 80% before the procedure to 92% after
MAPCAs collaterals	Two MAPCAs one from the RIMA and a large one from the posterior part of aortic arch filling both pulmonary arteries	Three Cook detachable coils (6.5/5; 5/5, and 5/3)	Right femoral artery - aorta- APC	No complications	SaO_2 increased from 83% before the procedure to 80% after
VV collaterals	From left innominate vein to right upper pulmonary vein	Cook detachable coil (6.5/5)	Right subclavian vein- innominate vein -venovenous collaterals Left internal jugular vein- innominate vein- venovenous collaterals to left and right upper pulmonary veins	No complications	SaO_2 increased from 69% before the procedure to 90% after
VV collaterals	Large VV collateral from innominate vein to paravertebral systemic veins	Cook detachable Coil (5x5)	Right subclavian vein- Innominate vein VV collaterals Left internal jugular vein- innominate vein VV collaterals	No complications	SaO_2 increased from 60% before the procedure to 76% after

ADO, Amplatzer Duct Occlude; APC, aortopulmonary collateral; MAPCAS, major aortopulmonary collaterals; RIMA, right internal mammary artery; SaO_2, oxygen saturation; VV, venovenous.

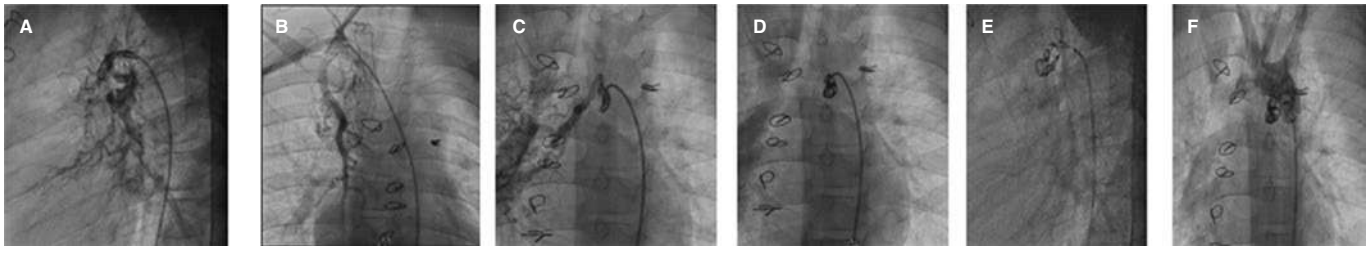

Figure 1. Aortography in lateral and right anterior oblique cranial views showing 2 major aortopulmonary collateral arteries, one from the right internal mammary artery and the other from the posterior part of aortic arch filling both pulmonary arteries. **A, B,** successful transcatheter closure of aortopulmonary collaterals. **C, D, E,** closure of aortopulmonary collaterals by 3 coils. **F,** final injection after aortopulmonary collateral coil closure.

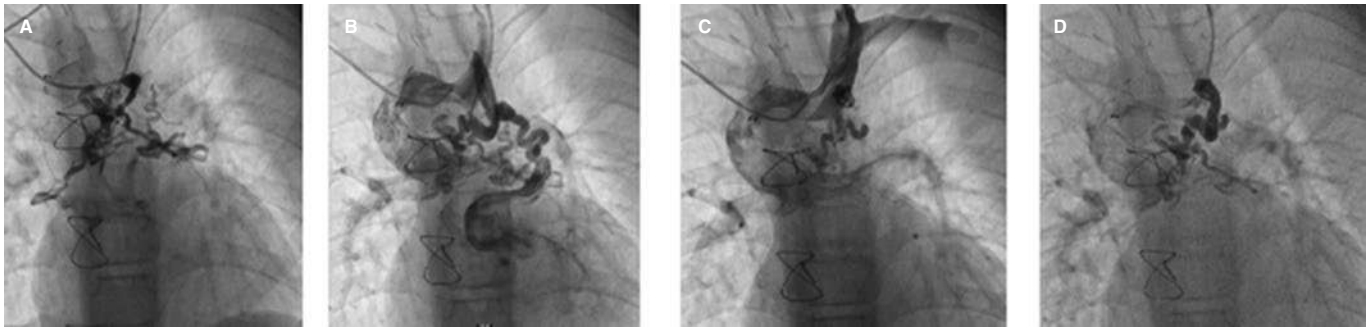

Figure 2. Successful transcatheter closure of venovenous collaterals. **A,** venovenous collaterals draining into right and left upper pulmonary veins. **B,** coil closure of the proximal part of the collaterals. **C, D,** result after transcatheter closure of venovenous collateral by the coil shows residual sluggish flow to collaterals.

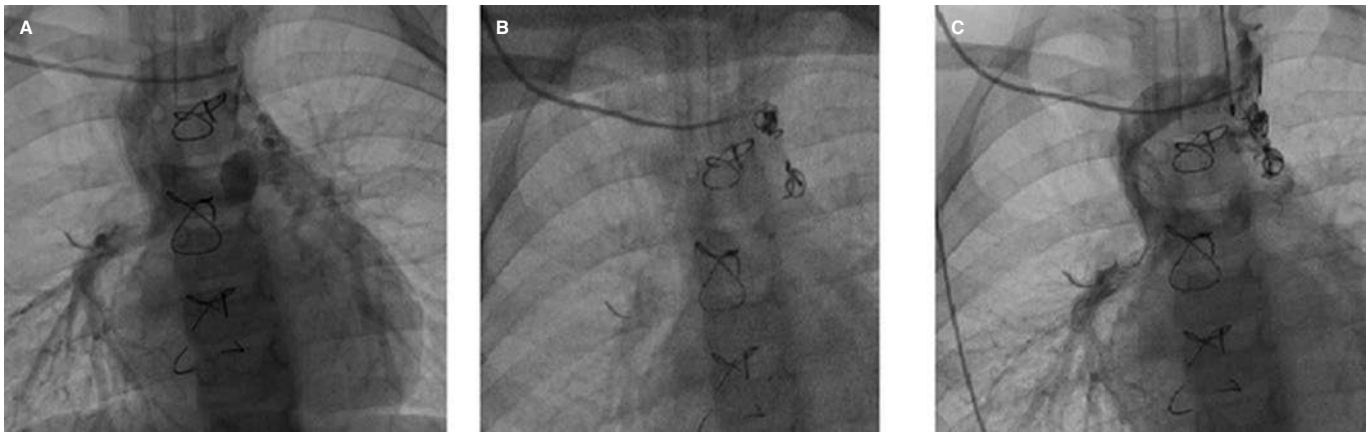

Figure 3. Successful transcatheter closure of a venovenous collateral. **A,** Glenn shunt and venovenous collateral to the left upper pulmonary vein. **B,** transcatheter closure of the venovenous collateral by 2 coils. **C,** final injection after closure of the venovenous collateral with significantly diminished flow to the left upper pulmonary vein.

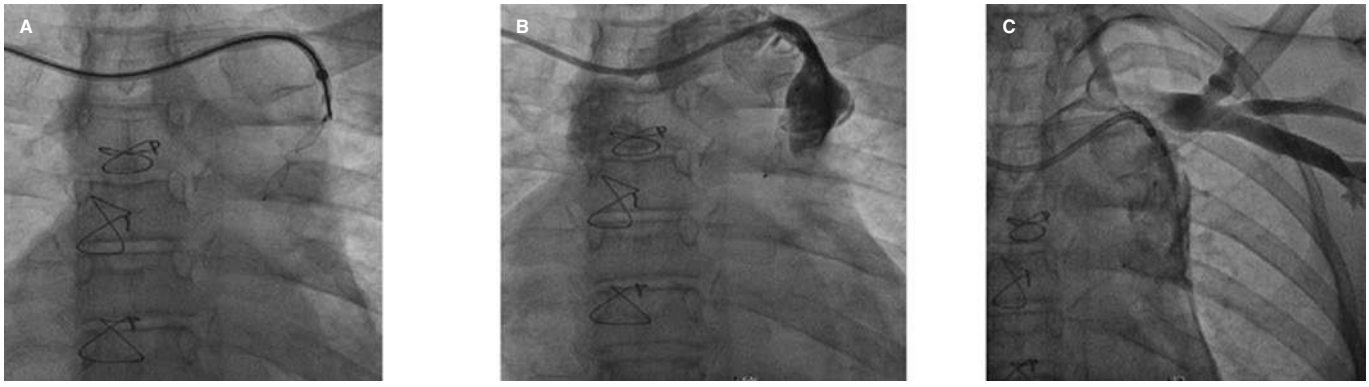

Figure 4. Venovenous collateral angiography in posteroanterior view. **A,** well-seated Amplatzer Duct Occluder II in venovenous collateral. **B,** extravasation at the proximal origin of collateral after cable separation. **C,** injection after several minutes showing sealing of extravasation.

Table 5. Comparison between SaO_2 at baseline and after management among patients who underwent transcatheter closure of venovenous collaterals

SaO_2 (%)	Baseline	After management	Difference	Test value	*P*	Sig
			Mean ± SD			
Mean ± SD	69.83 ± 10.91	82.83 ± 9.87	13.00 ± 3.09	4.210*	.008	HS
Range	55-83	71-93				

SD, standard deviation; SaO_2, oxygen saturation.
P value > .05: nonsignificant; *P* value < .05: significant; *P* value < .01: highly significant.
* Paired *t*-test.

cerebral artery starting from the distal M1 segment, consistent with an embolic event. The patient subsequently underwent mechanical thrombectomy and experienced minimal residual weakness on the left side and dysarthria.

SaO_2 significantly increased after TCC of venovenous collaterals (69.83 ± 10.91 vs 82.83 ± 9.87), with a *P* value of .008 (table 5).

Basal SO_2 was lower in patients with venovenous collaterals, although this difference was not statistically significant. Hematocrit levels and mean PAP were significantly higher in patients with venovenous collaterals than in those without venovenous collaterals (*P* = .031 and *P* = .025, respectively; table 3 of the supplementary data).

End-diastolic pressure (EDP) was positively correlated with mean PAP with a *P* value of .001 (figure 4 of the supplementary data).

Age at BDG procedure was positively correlated with aemoglobin (HCT) and aemoglobin levels (*P* = .001 and *P* = .002, respectively), with patients who underwent BDG at older ages showing higher hemoglobin and HCT levels.

Length of time since the BDG procedure was negatively correlated with baseline SO_2 (*P* = .023), with the longer the time since Glenn shunting, the lower the patient's baseline SO_2. In addition, there was a highly significant positive correlation between the length of time since the Glenn procedure and HCT level (*P* = .002), indicating

that the longer the time since Glenn shunting, the higher the patient's HCT level.

DISCUSSION

Our patients underwent BDG surgery at a median age of 2.08 [IQR, 1-3] years. We found 3 other recent registries conducted in developing countries similar to ours: Azhar et al.[9] in Saudi Arabia, Meyer et al.[10] in South Africa, and Tariq et al.[11] in Pakistan. The median ages of patients in these registries were 10 months, 2.5 years, and 1.9 years, respectively. In older registries, such as those reported by Talwar et al.[12] in India, Al-Dairy et al.[13] in Iran, and Sen et al.[14] in India, the median ages of patients were 3 years, 5 years, and 7.5 years, respectively, indicating a younger age at BDG in recent registries.[9-14] In contrast to registries in developing countries, the Western literature reports a median age at BDG of less than 1 year, as reported by Kogon et al.[15] in Atlanta (United States), LaPar et al.[16] in Virginia (United States), Reddy et al.[17] in California (United States), and Shuler et al.[18] in Cincinnati (United States).

Ideally, children should undergo BDG between the ages of 6 and 12 months followed by Fontan completion 1 year later.[19] The relatively older age of children undergoing the BDG in developing countries may be due to late presentation, delayed diagnosis, lack of primary health care facilities—especially in rural areas—, lack of timely referral, and families' reluctance to allow their children to undergo the staged surgical correction for financial reasons.[20]

Regarding post-BDG interventions, 2 patients (3.6%) underwent peripheral pulmonary artery stenting before presenting to our hospital, and we performed left pulmonary artery stenting in 3 patients (5.4%). In contrast to our study, only 1 patient in the study by Yamada et al. [21] underwent right pulmonary artery stenting. The discrepancy in intervention rates between the 2 studies can be explained by the older age of our patients and efforts to reduce their comorbidities to enhance functional capacity and improve their quality of life, especially since most were not suitable for Fontan completion.

The most common basic anatomy included transposition of the great arteries, double outlet right ventricle, and tricuspid atresia. This finding is consistent with those of Naik et al.[22] and Sen et al.[1] In contrast, Atz et al.[23] studied 382 patients in the United States and found that the most common basic anatomy was HLHS (25.6%), followed by tricuspid atresia (18%) and double inlet left ventricle (13%). The absence of HLHS in registries conducted in developing countries may be attributed to its poor prognosis and low survival rate. Among the 56 patients in our study, 41 (73.2%) had venovenous collaterals. McElhinney et al.[24] studied 54 patients, with only 18 (33.3%) having venovenous collaterals. The higher percentage in our study may be due to the longer interval from surgery to catheterization, as the median interval from surgery to catheterization was 1.3 years in McElhinney et al.[24] and 7.5 years in our study.

In our study, 37 patients (66.1%) had APC. This percentage is similar to that reported by Triedman et al.,[25] who diagnosed APC in 65% of patients.

In our study, 6 patients underwent TCC of venovenous collaterals: 5 patients during this registry and 1 patient in 2019. There was a statistically significant increase in SaO_2 (%) after the procedure (69.83 ± 10.91 vs 82.83 ± 9.87; P = .008). McElhinney et al.[24] also reported successful coil embolization of 10 collateral channels in 6 patients, resulting in an increase in SaO_2 of between 9% and 20% (median increase in SaO2 of 16%).

Lu et al.[26] reported a cohort study of 9 patients aged 5 to 15 years (median 9 years) with progressive cyanosis after BDG. Successful TCC of the azygos/hemiazygos veins was achieved using coils in 4 patients, patent ductus arteriosus occluders in 3 patients, atrial septal defect occluders in 2 patients, and a patent ductus arteriosus occluder together with coils in 1 patient. Femoral artery SaO_2 increased from 81% to 88%.

In our registry, out of the 6 patients who underwent TCC of venovenous collaterals, only 2 had venovenous collaterals to systemic veins (1 had collaterals to epicardial and abdominal veins, and the other to paravertebral veins), whereas the other 4 patients had venovenous collaterals to pulmonary veins.

We also found that 7 out of 8 patients with a pre-existing bilateral SVC connection developed venovenous collaterals. Additionally, 10 out of 11 patients with inadequate PA distribution/PA distortion and 6 out of 8 patients with impaired ventricular systolic function developed venovenous collaterals. However, these findings were not statistically significant. According to Magee et al.,[27] venovenous collateral development was associated with an abnormal superior vena cava connection, pulmonary artery distortion, increased mean SVC pressure, increased mean PA pressure, lower right atrium mean pressure, and an increased mean gradient between the SVC and right atrium. Only the last factor was independently associated with collateral development.

McElhinney et al.[24] reported that, in patients who developed venous collateral channels, the mean transpulmonary pressure gradient was higher early the BDG procedure (P = .005). This correlation was no longer significant at follow-up, mostly due to decompression of the SVC system through the venous collateral channels. In our patients, no correlation between transpulmonary pressure gradient (SVC-left atrium) and the presence of venovenous collaterals at follow-up.

In our center, we avoid closure of venovenous collaterals in patients with marked elevation in PAP (pulmonary hypertension) as it is a contraindication; venovenous collaterals decompress the congested venous system. However, in patients with normal PAP, or mean PAP ranging from 14 to 20 mmHg (no pulmonary hypertension, who are nevertheless not good candidates for Fontan completion) plus desaturation, we proceed with venovenous collateral closure.

In the present study, 37 of the 56 patients (66.1%) were found to have APCs. One patient underwent successful TCC of aortopulmonary collaterals. Patients with these collaterals were younger at the time of the Glenn procedure and time since the operation was longer. This finding is consistent with that of Grosse-Wortmann et al.,[28] who measured APC blood flow noninvasively in BDG and Fontan patients using MRI. These authors found that a higher Qp/Qs ratio was associated with younger age at the time of CPA and concluded that patients who proceeded to CPA at a younger age were more likely to develop APCs.

We found a highly significant positive correlation between EDP and mean PAP (P value of .001). Consistent with our findings, Schwartz et al.[29] reported that, at pre-Fontan catheterization, high mean PAP was associated with high single-ventricle EDP. These authors suggested that this association underscores the significance of EDP in individuals with single-ventricle heart disease. They also noted that EDP plays a major role in determining pulmonary artery and central venous pressures, elevations of which are linked to increased morbidity.

CONCLUSIONS

TCC of collaterals is a technically demanding but effective post-BDG management strategy to improve SaO_2 and quality of life.

Awareness of potential complications and their effective management is essential.

FUNDING

None.

ETHICAL CONSIDERATIONS

This study was approved by the research ethics committee of the faculty of medicine of Ain Shams University (FMASU MS 507/2022). Verbal and written informed consent was obtained from participants aged 18 years and older or from the participant's guardian in patients aged less than 18 years after the aim of the study was explained to them. Our research was carried out in accordance with internationally accepted recommendations for clinical investigation (Declaration of Helsinki of the World Medical Association). Possible sex/gender biases have been considered in the preparation of this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

Y.A. Ali collected data, revised the statistical analysis, and drafted the manuscript. N. El-Sayed Nour El Deen collected data and performed the statistical analysis. G.S. Elshahed supervised data collection, revised the results, and edited the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

WHAT IS KNOWN ABOUT THE TOPIC?

- Closure of venous collaterals to pulmonary veins improves SaO_2.

WHAT DOES THIS STUDY ADD?

- TCC of collaterals post-BDG is technically demanding.
- Awareness of possible complications and their effective management is essential.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000472.

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Original article

Cost-effectiveness analysis of radiofrequency renal denervation for uncontrolled hypertension in Spain

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ABSTRACT

Introduction and objectives: Radiofrequency (RF) renal denervation (RDN) has been shown to be a safe and effective treatment option for patients with uncontrolled hypertension. This analysis sought to explore the cost-effectiveness of this therapy in Spain.
Methods: A decision-analytic Markov model projected clinical events, quality-adjusted life years (QALY) and costs over the patients' lifetime. Treatment effectiveness in the base case analysis was informed by the change in office systolic blood pressure observed in the full cohort of the SPYRAL HTN-ON MED trial (–4.9 mmHg vs sham control). Alternate scenarios were calculated for effect sizes reported in the HTN-ON MED subcohort of patients on 3 antihypertensive medications treated outside the United States, the HTN-OFF MED trial, and the Global SYMPLICITY Registry high-risk and very high-risk cohorts. The analysis was conducted from the Spanish National Health System perspective and a willingness-to-pay a threshold of €25 000 per QALY gained was considered.
Results: RF RDN therapy resulted in clinical event reductions (10-year relative risk 0.80 for stroke, 0.88 for myocardial infarction, and 0.72 for heart failure) and a lifetime gain of 0.35 (13.99 vs 13.63) QALYs. Incremental lifetime costs were €5335 (€26 381 vs €21 045), resulting in an incremental cost-effectiveness ratio of €15 057 per QALY gained. Cost-effectiveness was further improved among all the other clinical evidence scenarios.
Conclusions: The results of this study suggest that RF RDN can provide a cost-effective alternative in the treatment of uncontrolled hypertension in Spain.

Keywords: Denervation. Hypertension. Cost-effectiveness analysis. Spain.

Análisis de coste-efectividad de la denervación renal por radiofrecuencia para la hipertensión no controlada en España

RESUMEN

Introducción y objetivos: La denervación renal (DNR) por radiofrecuencia (RF) es una alternativa terapéutica eficaz y segura en pacientes con hipertensión no controlada. Este estudio evalúa el coste-efectividad de esta terapia en España.
Métodos: Se empleó un modelo de Markov para estimar los eventos clínicos, los años de vida ajustados por calidad (AVAC) y los costes durante toda la vida de los pacientes. La eficacia del tratamiento en el caso base se obtuvo del cambio en la presión arterial sistólica en consulta observado en la cohorte completa del estudio SPYRAL HTN-ON MED (–4,9 mmHg frente a control simulado). Se exploraron escenarios alternativos empleando el tamaño del efecto observado en el subgrupo de pacientes del estudio HTN-ON MED en 3 fármacos antihipertensivos tratados fuera de Estados Unidos, el estudio HTN-OFF MED, y las cohortes de alto y muy alto riesgo del registro Global SYMPLICITY. Se consideró la perspectiva del Sistema Nacional de Salud y con un umbral de disposición a pagar de 25.000 €/AVAC.

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***Resultados*:** La DNR por RF se asoció a una reducción de los eventos clínicos (riesgo relativo a 10 años de 0,80 en ictus, 0,88 en infarto de miocardio y 0,72 en insuficiencia cardiaca). Durante un horizonte temporal de toda la vida se observaron una ganancia de 0,35 AVAC (13,99 vs 13,63) y un coste incremental de 5.335 € (26.381 frente a 21.045 €), obteniendo una ratio coste-efectividad incremental de 15.057 €/AVAC. En los demás escenarios analizados se obtuvieron mejores resultados.
Conclusiones: Los resultados de este estudio sugieren que la DNR por RF puede representar una alternativa coste-efectiva en el tratamiento de la hipertensión no controlada en España.

Palabras clave: Denervación. Hipertensión. Análisis coste-efectividad. España.

Abbreviations

HT: hypertension. **ICER:** incremental cost-effectiveness ratio. **SBP:** systolic blood pressure. **RDN:** renal denervation. **R-HT:** resistant hypertension. **QALY:** quality-adjusted life year.

INTRODUCTION

Uncontrolled hypertension (HT) poses a significant global clinical and economic burden. The prevalence of uncontrolled HT varies greatly, based on the population evaluated and the definition adopted.[1] In Spain it is estimated that 32.9% of the adult population aged 30 to 79 have HT, with 57.1% of those treated achieving well-controlled levels.[2] Uncontrolled HT is most common among aging, obese, or chronic kidney disease patient populations, although various risk factors and secondary causes (including poor medication adherence) can also contribute to its development.[1] As is well established, patients with uncontrolled HT have an increased risk of cardiovascular events, including stroke, myocardial infarction (MI), and heart failure (HF), as well as their sequelae.[1,3]

Radiofrequency (RF) renal denervation (RDN) is a device-based interventional treatment option intended to permanently disrupt sympathetic nervous signaling to the kidneys, achieving lasting reductions in blood pressure.[4]

Over more than a decade, a large body of trials and real-world evidence has supported the viability, safety, and effectiveness of RF RDN, with the most recent SPYRAL HTN-ON MED[5] and HTN-OFF MED trials[6] contributing data from second-generation RF RDN devices. The SPYRAL HTN-ON MED[5] and HTN-OFF MED trials[6] were sham-controlled studies that evaluated the therapy in the presence and absence of antihypertensive medications, respectively. Other trial data and findings from the international, multicenter open-label Global SYMPLICITY Registry (GSR),[7] which has enrolled more than 3000 participants to date, provide evidence on the safety, effectiveness, and longer-term outcomes of RF RDN treatment.[7]

Most recently, the latest guidelines from the European Society of Hypertension, and the joint expert statement from the Spanish Society of Hypertension-Spanish League for the Fight Against Hypertension and the Interventional Cardiology Association of the Spanish Society of Cardiology, recommend RDN as an adjunctive treatment option for uncontrolled HT, including resistant hypertension (R-HT).[8,9] This consensus statement specifically recognizes the value of RDN for patients at high cardiovascular risk with hypertension-mediated organ damage or cardiovascular disease. Furthermore, RF RDN has recently received approval from the United States Food and Drug Administration as an adjunct therapy in hypertensive patients without adequate blood pressure control.[10]

While its clinical viability is widely established, less is currently known about the potential cost-effectiveness of RF RDN based on the latest clinical evidence. The present study aimed to address this gap by assessing the cost-effectiveness of RF RDN treatment within the Spanish health system.

METHODS

A decision-analytic, state-transition Markov model was used to project outcomes, including costs and health benefits associated with RF RDN, over a lifetime. This analysis model, adopting the perspective of the Spanish National Health System, was built on the foundation of an earlier model.[11] Key parameter inputs can be found in table 1.

Model structure

The Markov model consisted of 7 primary health states: HT alone, stroke, MI, other symptomatic coronary heart disease (CHD) or angina pectoris (AP), HF, end-stage renal disease (ESRD), and death (figure 1 and supplementary material in Sharp et al.[11]). Transitions could occur monthly, and half-cycle correction was implemented. The model was encoded in Microsoft Excel (Microsoft, United States), with supporting statistical analyses conducted in JMP Pro 16 (SAS Institute, United States).

Transition probabilities and relative risk reductions

Transition probabilities to subsequent health states were informed by multivariate risk equations derived from large cohort studies.[31-34] Baseline risks for the control cohort were calculated by applying cohort characteristics and office systolic blood pressure (SBP) level to these equations. Corresponding transition probabilities for the RF RDN arm were determined by multiplying these baseline risks by office SBP reduction-specific relative risks (RR), derived from a meta-regression of 47 randomized controlled trials (RCT) of intentional HT treatment.[35] Mortality rates were informed by Spanish general population lifetable data and postevent survival data specific to Spain where available (table 1 of the supplementary data, and Sharp et al.[11]).

Clinical data

Cohort characteristics and treatment efficacy for the base case analysis were obtained from the SPYRAL HTN-ON MED full cohort

Table 1. Model inputs

Parameter	Value	Distribution	SE	Source
Age, y	55.0	Normal	0.53	Kandzari et al.[5]
Gender (% female)	19.9%	Beta	0.02	Kandzari et al.[5]
Baseline systolic BP	163 mmHg	Normal	0.40	Kandzari et al.[5]
Treatment effect	4.9 mmHg	Normal	0.54	Kandzari et al.[5]
Discount rate (costs)	3.00% p.a.	-	-	López-Bastida et al.[12]
Discount rate (health outcomes)	3.00% p.a.	-	-	López-Bastida et al.[12]
Costs				
HT (year 1+)	€251	Gamma	€25	Soto et al.[13]
Stroke (acute)	€4787[a]	Gamma	€479	Ribera et al.[14]; Navarrete-Navarro et al.[15]
Stroke (remainder of year 1)	€6647[a]	Gamma	€665	
Stroke (year 2+)	€4135[a]	Gamma	€414	
MI (acute)	€7674	Gamma	€96	Darbà et al.[16]
MI (year 1+)	€950	Gamma	€135	Escobar et al.[17]
Stable AP (year 1+)	€615	Gamma	€74	Schwander et al.[18]
Unstable AP (acute)	€2910	Gamma	€51	Schwander et al.[18]
Unstable AP (year 1+)	€615	Gamma	€74	Schwander et al.[18]
HF (year 1+)	€5808	Gamma	€300	Delgado et al.[19]
ESRD (year 1+)	€25 574[b]	Gamma	€2557	Villa et al.[20]
RF RDN therapy	€7484	Gamma	€748	Estimated by Medtronic
Utilities				
HT	0.96	Beta	0.10	Sullivan et al.[21]
Stroke	0.63	Beta	0.03	Grosso et al.[22]; Darlington et al[23]
MI (months 1-6)	0.76	Beta	0.09	Aasa et al.[24]; Glasziou et al.[25]
MI (months 6+)	0.88	Beta	0.02	Grosso et al.[22]; Pignone et al.[26]
Stable AP	0.84	Beta	0.02	Sullivan et al.[21]
Unstable AP	0.74	Beta	0.02	Glasziou et al.[25]
HF	0.71	Beta	0.07	Chen et al.[27]; Fryback et al.[28]
ESRD	0.63	Beta	0.06	Lee et al.[29]

AP, angina pectoris; BP, blood pressure; ESRD, end-stage renal disease; HF, heart failure; HT, hypertension; MI, myocardial infarction; p.a., per annum; RF RDN, radiofrequency renal denervation; SE, standard error.
[a] Stroke costs were determined assuming 85% ischemic stroke costs from Ribera A et al.[14] and 15% hemorrhagic stroke costs from Navarrete-Navarro et al.[15]
[b] ESRD costs were determined based on epidemiological data and the cost associated with the different treatment modalities.[20,30]

trial.[5] Study participants were, on average, aged 55 years, with a baseline office SBP of 163 mmHg, and were prescribed 1 to 3 medications (mean, 1.9).[5] The RF RDN arm received denervation treatment with the Symplicity Spyral multielectrode renal denervation system (Medtronic, United States) plus maintained antihypertensive medications, while the sham control group received antihypertensive therapy only. The trial-reported office SBP reduction observed at 6 months for the RF RDN arm was −9.9 mmHg vs −5.0 mmHg for the sham arm, resulting in an effect size of −4.9 mmHg.[5] Additional scenario analyses were conducted using evidence from several other subcohorts and studies. These included the SPYRAL HTN-ON MED subcohort of patients on 3 medications treated outside the United States[36] to represent an R-HT cohort more comparable to the European setting (office SBP effect size vs sham −6.9 mmHg), the SPYRAL HTN-OFF MED trial[6] in which patients received the therapy in the absence of antihypertensives (effect size −6.6 mmHg), the high-risk and very high-risk cohorts of the GSR[37] (effect sizes −21.5 mmHg and −31.6 mmHg vs baseline, respectively, calculated as the average of the reductions reported at 6, 12, 24, and 36 months), and, for completeness, a scenario with the SPYRAL HTN-ON MED[5] effect size of −4.9 mmHg calculated based on reported cohort characteristics for a Spanish R-HT sample[38]. Scenarios based on SPYRAL HTN-OFF MED[6] and GSR[7] were calculated using the cohort characteristics of these respective study cohorts and sub-cohorts where applicable.

Table 2. Base case results: clinical events over 10 years and a lifetime, and cost-effectiveness result over a lifetime

	10-year time horizon				Lifetime horizon			
Base case	**SoC**	**RF RDN**	**Diff**	**RR**	**SoC**	**RF RDN**	**Diff**	**RR**
Stroke	9.0%	7.2%	1.8%	0.80	34.4%	28.8%	5.6%	0.84
MI	7.5%	6.6%	0.9%	0.88	35.4%	34.7%	0.7%	0.98
AP/other CHD	14.5%	13.0%	1.6%	0.89	28.2%	26.4%	1.9%	0.93
HF	5.0%	3.6%	1.4%	0.72	19.5%	15.2%	4.2%	0.78
ESRD	0.40%	0.40%	0.0%	0.96	1.04%	1.08%	0.04%	1.04
CVD	5.3%	4.5%	0.8%	0.85				
ACD	11.2%	10.5%	0.7%	0.94				
Costs					€21 045	€26 381	€5335	
LYs					15.8	16.08	0.28	
QALYs					13.63	13.99	0.35	
ICER					**€15 057 per QALY**			

ACD, all-cause death; AP, angina pectoris; CHD, coronary heart disease; CVD, cardiovascular death; Diff., difference; ESRD, end-stage renal disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life years (discounted); MI, myocardial infarction; QALYs, quality-adjusted life years (discounted); RF RDN, radiofrequency renal denervation; RR, relative risk; SoC, standard of care.

Costs and health-related quality of life

Clinical event costs were sourced from published literature.[13-20] Given the perspective of the analysis; only direct medical costs were considered. All costs were expressed in 2022 euros, with relevant consumer price index data used to adjust historical costs, where necessary.[39] The cost of RF RDN therapy was assessed using a micro-costing approach that considered preprocedure and procedure costs including personnel, device and catheterization laboratory overhead costs, as well as postoperative hospitalization. Health-state specific utilities, expressed as a numerical value ranging from 0 (death) to 1 (perfect health), were derived from published literature and were age-adjusted in the analysis.[21-29] In conjunction with life years (LY) gained, these values inform the resulting quality-adjusted life years (QALY), a measure of the quantity and quality of life, in the model. Where multiple Spanish publications could be sourced, we prioritized contemporary publications with a greater sample size, after consideration by the clinical authors. Where Spanish publications could not be sourced, we reverted to non-Spanish values.

Model validations

Comprehensive model validations were conducted. The approach and validation results are shown in supplementary data and table 2, 3, 4, and 5 of the supplementary data.

Analysis outcomes and interpretation

The primary analysis outcome was the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs gained between the RF RDN cohort and the comparator by the incremental QALYs gained, and measured in euros per QALY observed. Additional and supporting outcomes included strategy-specific costs, LY, and QALY gain over a lifetime, and clinical events over 10 years and lifetime with associated risk reductions from RF RDN. Costs and QALYs were discounted at 3% per annum and cost-effectiveness was evaluated against a willingness-to-pay (WTP) threshold of €25 000 per QALY gained, which is commonly referenced for Spain.[12,40]

Sensitivity analysis

Comprehensive deterministic and probabilistic sensitivity analyses (DSA and PSA) were conducted to evaluate the robustness of results under varied assumptions, including differences in the cohort characteristics and effect sizes modeled, and higher or lower baseline event risks, achieved by applying adjustment factors of 2.0 and 0.5 to the underlying risk equations. The PSAs involved 10 000 repeated calculation runs each, with random sampling from the distribution of input parameters in each analysis cycle (table 6 of the supplementary data).

RESULTS

Base case analysis

Over 10 years, the base case results indicate that RF RDN treatment results in the following risk reductions vs sham control: RR, 0.80 for stroke; 0.88 for MI; 0.72 for HF; 0.89 for AP/other symptomatic CHD; 0.96 for ESRD; 0.85 for cardiovascular death, and 0.94 for all-cause death. Lifetime risk reductions were somewhat less pronounced. Over the lifetime, survival with RF RDN was improved by 0.57 years (23.21 vs 22.64 years). Lifetime costs were €26 381 for RF RDN vs €21 045 for standard of care (an increment of €5335) and total QALYs were 13.99 and 13.63 (an increment of 0.35 QALYs), resulting in a cost-effective lifetime ICER of €15 057 per QALY gained. Cost savings with RF RDN resulted primarily from acute and follow-on costs for stroke, followed by HF and AP (table 2 and figure 1 of the supplementary data).

Sensitivity and scenario analyses

RF RDN remained cost-effective among all conducted sensitivity and scenario analyses, which included a broad range of cohort characteristics, effect sizes, cost and utility assumptions, and general population mortality rates (table 3).

Table 3. Results of scenario analyses (different cohorts and effect sizes)

Base case	Costs (€)		QALYs		Δ Costs (€)	Δ QALYs	ICER (€ per QALY)
	RF RDN	SoC	RF RDN	SoC			
HTN-ON MED (office SBP effect size –4.9 mmHg vs sham)	26 381	21 045	13.99	13.63	5335	0.35	15 057
HTN-ON MED (office SBP effect size –9.9 mmHg vs BL)	25 418	21 045	14.13	13.63	4372	0.49	8884
HTN-ON MED subcohort on 3 AH medications treated OUS (office SBP effect size –6.9 mmHg vs sham)	25 989	21 045	14.04	13.63	4944	0.41	12 043
HTN-OFF MED (office SBP effect size –6.6 mmHg vs sham)	26 286	21 320	15.22	14.82	4967	0.39	12 701
GSR high-risk cohort (office SBP effect size –21.5 mmHg vs BL)	25 174	22 967	12.21	11.35	2207	0.86	2569
GSR very high-risk cohort (office SBP effect size –31.6 mmHg vs BL)	23 941	23 292	12.00	10.89	649	1.12	580
Spanish resistant hypertension cohort (office SBP effect size –4.9 mmHg vs sham)	21 277	15 437	9.58	9.31	5840	0.27	21 675
Risk function adjustment factor of 2.0 for MI/CHD/stroke (office SBP effect size –4.9 mmHg vs sham)	30 782	25 691	12.71	12.31	5091	0.41	12 555
Risk function adjustment factor of 0.5 for MI/CHD/stroke (office SBP effect size –4.9 mmHg vs sham)	23 191	17 558	14.91	14.63	5633	0.27	20 702

AH, antihypertensive; BL, baseline; CHD, coronary heart disease; GSR, Global SYMPLICITY Registry; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; SBP, systolic blood pressure; OUS, outside the United States; QALYs, quality-adjusted life years; RF RDN, radiofrequency renal denervation; SBP, systolic blood pressure; SoC, standard of care.

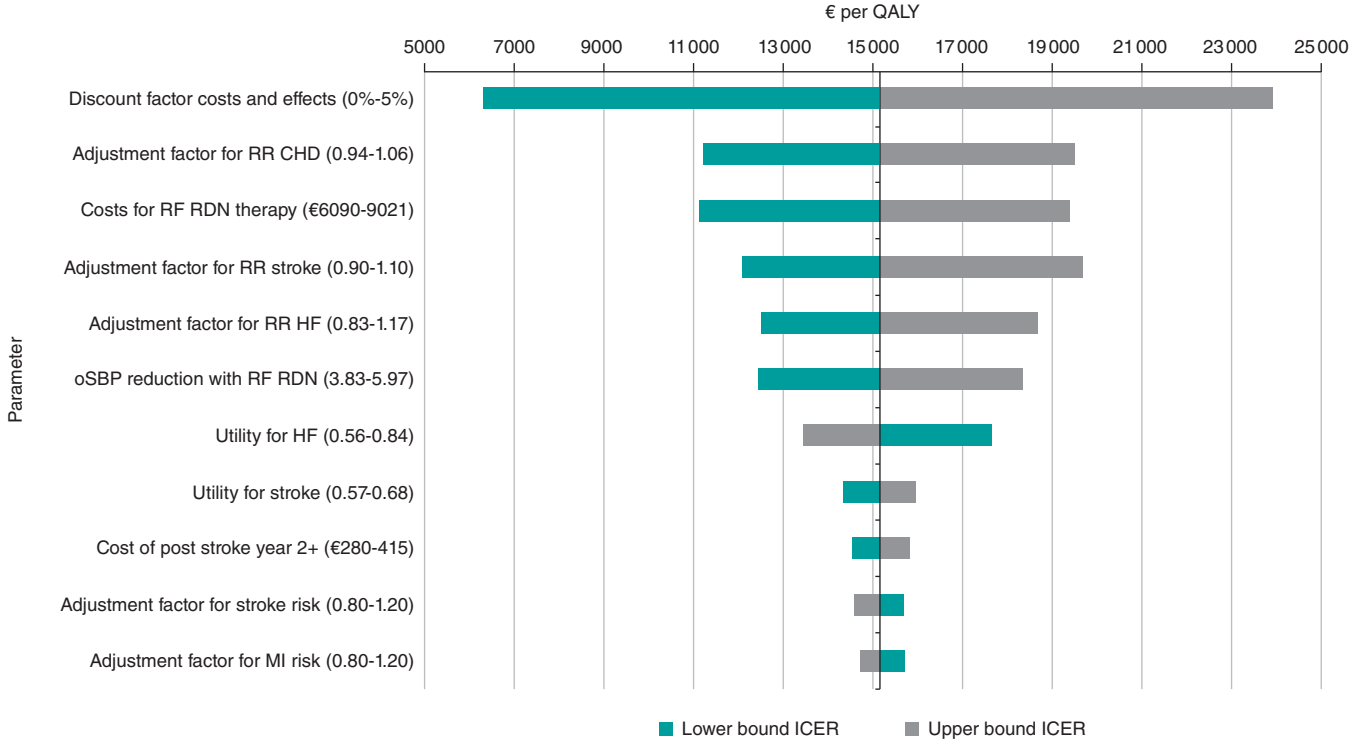

Figure 1. Tornado diagram illustrating the deterministic sensitivity analysis results. CHD, coronary heart disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; oSBP, office systolic blood pressure; RF RDN, radiofrequency renal denervation; RR, relative risk.

In the DSA, the most influential parameters were the discount rate applied to costs and effects, the adjustment factor for CHD risk, and the cost of RF RDN therapy, followed by variations in adjustment factors of the underlying risk functions and treatment effect size. For the tested ranges, the WTP of €25 000 per QALY was not exceeded (figure 1).

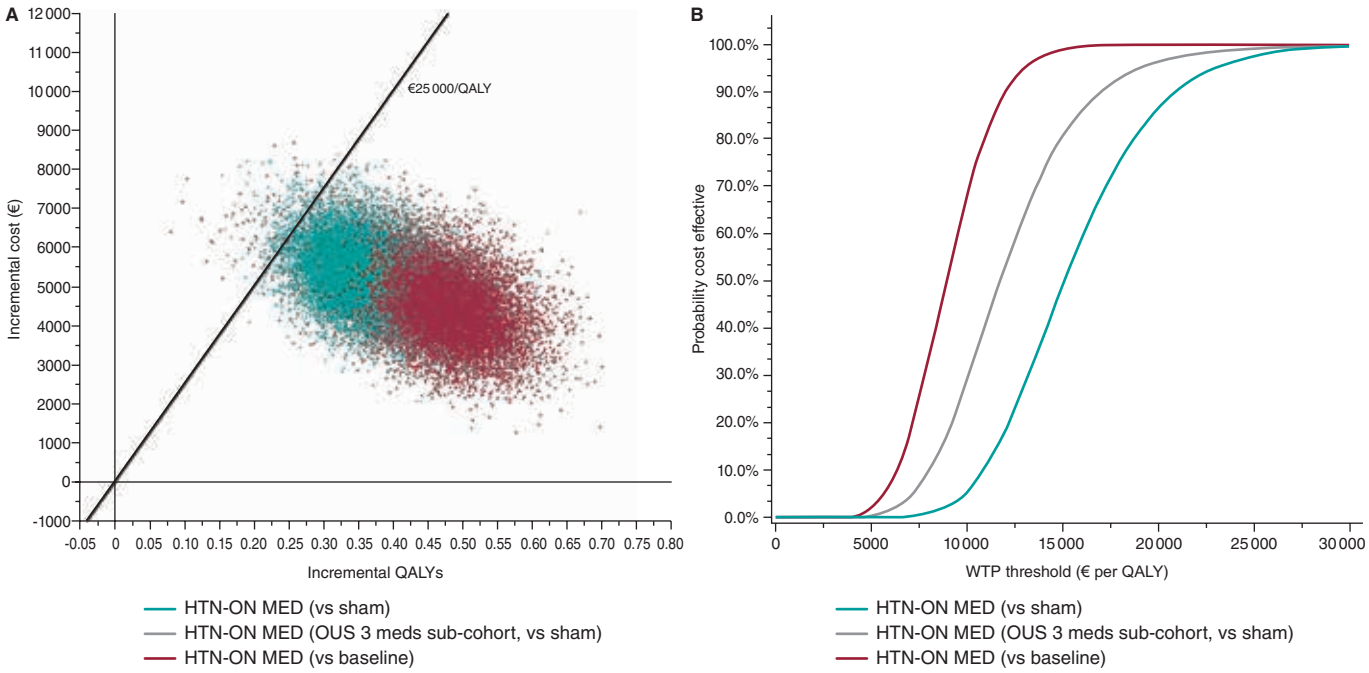

Figure 2. Central illustration. Probabilistic sensitivity analysis scatterplot (A) and cost-effectiveness acceptability curves (B) for the HTN-ON MED full cohort vs sham, and vs baseline, and for the HTN-ON MED subcohort of patients on 3 antihypertensives, treated outside the United States. The figure on the left shows the simulation results of probabilistic sensitivity analyses conducted for the HTN-ON MED base case (vs sham), for the subcohort on 3 medications treated outside the United States (vs sham), and for assumed effect size vs baseline blood pressure. The line in the graph represents the Spanish WTP threshold of €25 000 per QALY. Combinations of QALY gain and costs to the right of this line are considered cost-effective. The figure on the right provides the probability of the therapy being cost-effective at different WTP thresholds and demonstrates a high likelihood that RF RDN is a cost-effective intervention. OUS, outside the United States; QALY, quality-adjusted life year; WTP, willingness-to-pay.

In the PSA, the probability that simulations were below the cost-effectiveness threshold of €25 000 per QALY ranged from 97.4% to 100% (figure 2).

DISCUSSION

This study explored the health-economic value of RF RDN treatment within the Spanish National Health System, using contemporary clinical evidence and cost data. The results of the analysis suggest that RF RDN treatment is associated with clinically meaningful reductions in cardiovascular events, resulting in improved health outcomes and cost savings that partly, but not fully, amortize the upfront cost of RF RDN treatment. The results of the model demonstrate that, compared with current standard practice and with an ICER below Spain's WTP threshold, RF RDN is a cost-effective treatment option for patients with uncontrolled HT—including resistant HT—and hypertensive patients with high and very high cardiovascular risk. The results were found to be robust among a variety of tested cohort characteristics, effect sizes, and adjustments of the projected baseline event risks, and applied to patients not treated with antihypertensive medications, as demonstrated by the analysis using SPYRAL HTN-OFF MED[6] data.

These findings are in line with those recently published for the United Kingdom (UK) health system, where RF RDN resulted in comparable QALY gains and an ICER well below the UK NICE cost-effectiveness threshold, suggesting RF RDN is a cost-effective treatment option in that health care system.[11]

Among the strengths of the current analysis is its reliance on a granular modeling framework able to model cohort-specific baseline risks and effect size-specific risk reductions derived from a large-scale meta-regression of HT RCTs. At the same time, the analysis has several limitations. First, any model representation is only an approximation of clinical reality and may not reflect all possible disease progression pathways experienced by the analyzed cohort. Nevertheless, the clinical events modeled encompass the events and disease states most relevant to HT and its treatment and are in line with prior assessments of HT treatments.[41-43] Second, the analysis relies on the currently available 6-month data of the SPYRAL HTN-ON MED[5] trial and assumes this effect size is maintained over a lifetime. This assumption, however, seems well supported by the large body of RF RDN evidence available to date, which suggests that treatment effects are maintained, might even increase over time rather than decrease, and do not require retreatment to be maintained.[7,44-46] Third, the use of the SPYRAL HTN-ON MED[5] observed effect size of −4.9 mmHg change in office SBP vs sham control in the base case is among the lowest effects in the more recent body of RF RDN evidence. Nevertheless, the SPYRAL HTN-ON MED trial[5] is the largest sham-controlled RCT of latest-generation RF RDN devices. Finally, quality of life data for Spain are still limited. For this reason, international data were used to inform utility estimates.

CONCLUSIONS

The results of the present analysis, based on contemporary clinical evidence, suggest that RF RDN can be a cost-effective treatment option and might meaningfully reduce clinical events in patients with uncontrolled HT in Spain.

FUNDING

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ETHICAL CONSIDERATIONS

Ethics committee approval was not applicable to this work due to the nature of the study, which is an economic evaluation of a health technology. As this study does not involve the participation of individuals, informed consent was not required. Additionally, possible sex and gender biases have been considered and addressed in the preparation of this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

Methodology was developed by J.B. Pietzsch and K.N. Cao, and was reviewed by O. Rodríguez-Leor, F. Jaén-Águila, T. García-Camarero, and J.A. García-Donaire. Model inputs research was conducted by J.B. Pietzsch, K.N. Cao, A.M. Ryschon, C. Mansilla-Morales, M. Álvarez-Orozco and M. Kolovetsios. The analysis was carried out by K.N. Cao, A.M. Ryschon, and J.B Pietzsch. K.N. Cao, J.B. Pietzsch, and A.M. Ryschon prepared the original draft, while O. Rodríguez-Leor, F. Jaén-Águila, T. García-Camarero, J.A. García-Donaire, C. Mansilla-Morales, M. Álvarez-Orozco and M. Kolovetsios contributed to the review and editing process. Supervision was provided by J.B. Pietzsch, O. Rodríguez-Leor, and J.A. García-Donaire.

CONFLICTS OF INTEREST

O. Rodríguez-Leor, J.A. García-Donaire, F. Jaén-Águila, and T. García-Camarero acknowledge receiving grants from Medtronic to conduct this project. O. Rodríguez-Leor has received grants from Shockwave outside the submitted work. T. García-Camarero has received honoraria from Boston Scientific and Palex outside the submitted work. A.M. Ryschon, K.N. Cao, and J.B. Pietzsch are employed by Wing Tech Inc., a health-economic consulting firm providing consulting services to Medtronic, including for the development of the health-economic analysis framework underlying the current study, and to develop this work. C. Mansilla-Morales, M. Álvarez-Orozco, and M. Kolovetsios are employed full-time by Medtronic.

The authors hereby declare that this economic support has not interfered with the conduct of this project. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

WHAT IS KNOWN ABOUT THE TOPIC?

- It is well established that reductions of elevated blood pressure benefit patients by lowering their cardiovascular event risks.
- Such event reductions not only improve patient survival and quality of life, but concurrently also reduce health care utilization and costs.
- RF RDN is an adjunctive treatment option for patients with uncontrolled HT, including R-HT.

WHAT DOES THIS STUDY ADD?

- In the current analysis, blood pressure reductions observed in recent RF RDN studies were used to calculate the expected lifetime benefit and cost implications for the therapy in the Spanish health care system.
- The analysis found that RF RDN, based on an assumed long-term treatment effect, can contribute to a meaningful patient benefit at acceptable incremental costs to the Spanish health care system, rendering the therapy a cost-effective intervention relative to Spain's WTP threshold of €25 000 per QALY gained.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000475.

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Special article

Edge-to-edge therapy in acute mitral regurgitation. Proposal for a management protocol of the Ischemic Heart Disease and Acute Cardiac Care, Interventional Cardiology, and Cardiovascular Imaging Associations of the Spanish Society of Cardiology

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ABSTRACT

The approach to patients with acute mitral regurgitation poses a therapeutic challenge. These patients have a very high morbidity and mortality rate, thus requiring a multidisciplinary approach. This document presents the position of 3 associations involved in the management of these patients: the Ischemic Heart Disease and Acute Cardiovascular Care Association, the Interventional Cardiology Association, and the Cardiac Imaging Association. The document discusses aspects related to patient selection and care, technical features of the edge-to-edge procedure from both the interventional and imaging unit perspectives, and the outcomes of this process. The results of mitral repair and/or replacement surgery, which is the first-line treatment option to consider in these patients, have not been included as they exceed the scope of the aims of the document.

Keywords: Mitral regurgitation. Acute myocardial infarction. Left ventricular ejection fraction. Papillary muscle rupture. Transcatheter edge-to-edge mitral valve repair.

Tratamiento de borde a borde en la insuficiencia mitral aguda. Propuesta de protocolo asistencial de las Asociaciones de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares, de Cardiología Intervencionista y de Imagen Cardiaca de la Sociedad Española de Cardiología

RESUMEN

El tratamiento de los pacientes con insuficiencia mitral aguda supone un reto terapéutico. Estos pacientes tienen una morbimortalidad muy elevada, que requiere un abordaje multidisciplinario. El presente documento recoge el posicionamiento de tres asociaciones implicadas en el tratamiento de estos pacientes: la Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares, la Asociación de Cardiología Intervencionista y la Asociación de Imagen Cardiaca. Incluye aspectos relacionados con la selección y los cuidados del paciente, los aspectos técnicos del tratamiento de borde a borde desde el punto de vista intervencionista y de la imagen cardiaca, y los resultados de este proceso. No se han incluido los resultados de la cirugía de reparación o sustitución mitral, que es la primera opción terapéutica a considerar en estos pacientes, por exceder los objetivos del documento.

Palabras clave: Insuficiencia mitral. Infarto agudo de miocardio. Fracción de eyección del ventrículo izquierdo. Rotura del músculo papilar. Tratamiento de reparación percutánea de borde a borde.

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Abbreviations

LV: left ventricle. **MR:** mitral regurgitation. **PMR:** papillary muscle rupture. **TEER:** transcatheter edge-to-edge repair.

PATIENT SELECTION, OPTIMAL TIMING, AND MANAGEMENT IN THE CARDIAC INTENSIVE CARE UNIT

In severe acute mitral regurgitation (MR), the sharp increase in left ventricular (LV) end-diastolic volume leads to a rapid rise in LV and left atrial end-diastolic pressure. This ultimately results in marked pulmonary congestion and the development of acute pulmonary edema.[1] Concurrently, the large volume of regurgitation reduces forward flow and cardiac output. Patients with pre-existing MR and normal ventricles have better hemodynamic tolerance; conversely, those with with associated ischemia and ventricular dysfunction experience clinical worsening.[1,2]

The etiology of acute MR can be divided into 2 groups (table 1): ischemic and nonischemic. Ischemic causes include acute ischemia of the papillary muscle, its rupture in the context of acute myocardial infarction, ventricular remodeling, and increased leaflet traction and tethering. Nonischemic causes encompass chordal rupture in myxomatous valve disease and complications from interventional cardiology procedures. Other causes include endocarditis, trauma, and dynamic MR due to anterior systolic motion of the mitral valve in patients with hypertrophic or stress-induced cardiomyopathy.[2,3]

Patients with acute MR are usually symptomatic. The clinical presentation varies depending on the mechanism, speed of onset, presence of prior MR, and ventricular function. Flash pulmonary edema can occur in patients with dynamic MR and normal ventricular function, often due to increased afterload. In these patients, blood pressure may remain normal or be elevated.[1-4] The most severe form of severe acute MR is cardiogenic shock, which is. It commonly arises in patients with LV systolic dysfunction but can also develop in those with preserved ventricular function and sudden onset of MR due to papillary muscle rupture (PMR). In intermediate stages, patients may have acute pulmonary edema and maintained blood pressure without progressing to shock.[3,5]

The primary objective of treatment should be clinical and hemodynamic stabilization (figure 1). These patients should be promptly transferred to a tertiary referral center with specialized acute/intensive cardiac care units, cath labs, and cardiac surgery units. High-dose intravenous loop diuretics are the cornerstone of medical treatment, preferably administered in continuous infusion. Inotropic agents are recommended in patients with LV systolic dysfunction. In patients with normal or elevated blood pressure, intravenous vasodilators—mainly nitroprusside or nitroglycerin—are recommended because they reduce LV afterload and thereby mitigate MR severity.[6-8] The use of vasopressors is reserved to patients in cardiogenic shock with hypotension and persistent hypoperfusion despite inotropic therapy. Because these drugs increase afterload and may exacerbate MR, they should be administered at the lowest effective dose to maintain adequate tissue perfusion pressure.[1,7,8]

Noninvasive mechanical ventilation can be beneficial in patients experiencing flash pulmonary edema, commonly associated with hypertension. Positive pressure ventilation improves ventilation-perfusion matching, reduces alveolar edema, decreases dead space, and enhances pulmonary blood flow distribution. However, patients in cardiogenic shock due to severe acute MR require early orotracheal intubation and mechanical ventilation to achieve adequate stabilization, reduce adrenergic stimulation, and ensure effective oxygenation.[8]

Continuous and accurate monitoring of electrocardiographic, hemodynamic, and gasometric parameters is essential. This includes placing an arterial line for invasive arterial monitoring, establishing central venous access in patients with cardiogenic shock, measuring central venous pressure, continuously quantifying urine output, and performing gasometric checks at intervals tailored to the patient's clinical status. If there is inadequate response to diuretics, early initiation of continuous renal replacement therapy is recommended to promptly reduce pulmonary congestion.[9,10]

If initial pharmacological treatment fails and clinical and hemodynamic deterioration persists within the first 12 to 24 hours, consideration should be given to initiating mechanical circulatory support.[11] In such cases, consulting the center's shock team is recommended to collectively determine the most appropriate treatment sequence and select the device to be used. This decision should weigh 4 key factors: *a)* patient-related factors and comorbidities; *b)* the underlying cause and mechanism of MR, and ventricular function; *c)* the patient's hemodynamic status and severity of shock; and *d)* the center's experience. A detailed approach to circulatory support is beyond the scope of this document. Briefly, intra-aortic balloon pump may be useful in patients with myocardial infarction-induced MR in preshock conditions (stage B of the SCAI [Society for Cardiovascular Angiography and Interventions] classification, when the patient is hypotensive or tachycardic but maintains adequate tissue perfusion), or in early shock stages (stage C of the SCAI, when inotropes, vasopressors, or mechanical support are needed to maintain systemic perfusion).[12,13] In more advanced shock stages (stage D of the SCAI classification, when there is no response to measures established in the previous stage), and especially in the presence of PMR, the preferred device is peripheral venoarterial extracorporeal membrane oxygenation with or without LV unloading using an intra-aortic balloon pump or the Impella device (Abiomed, United States), with special caution required in cases involving PMR.[13,14] In patients with ischemic MR in the context of myocardial infarction due to papillary muscle ischemia or ischemic dilated cardiomyopathy, or LV dysfunction with preserved right ventricular function, Impella can be highly effective as it allows direct LV unloading, thus reducing LV end-diastolic pressures and MR while enhancing cardiac output[11] (figures 1 and 2 of the supplementary data). A key aspect to be considered is early initiation of mechanical circulatory support in patients with an indication to anticipate and prevent the onset of established multiple organ failure.

Coronary revascularization is strongly recommended when MR is associated with acute ischemia.[15] In the context of acute myocardial infarction and percutaneous revascularization, the severity of MR may vary from the acute phase near angioplasty to the most chronic stage. Nevertheless, the persistence of significant MR adversely affects patients' short- and mid-term prognosis.[16] Definitive treatment requires mitral valve replacement or repair.

Currently, the optimal timing for performing percutaneous coronary interventions in the mitral valve remains under debate. The

Table 1. Etiology, pathophysiology, and clinical presentation of acute mitral regurgitation

Etiology	Pathophysiology	Clinical presentation	Treatment
Papillary muscle ischemia	Increase in left ventricular end-diastolic pressure	Acute heart failure/acute pulmonary edema	Diuretics
Infarction-related papillary muscle rupture	Increase in left atrial pressure	Flash acute pulmonary edema	Inotropes (dobutamine, milrinone)
Ruptured chordae tendineae	Increase in pulmonary capillary wedge pressure	Cardiogenic shock	Vasodilators (nitroprusside) / vasopressors
Anterior systolic motion (obstructive hypertrophic cardiomyopathy, tako-tsubo syndrome)	Decreased output due to reduced antegrade flow		Revascularization
Dilated cardiomyopathy - secondary mitral regurgitation			Mechanical circulatory support (intra-aortic balloon pump, extracorporeal membrane oxygenator, Impella)
Endocarditis			Edge-to-edge repair
Trauma			Surgery
Perioperative complication			

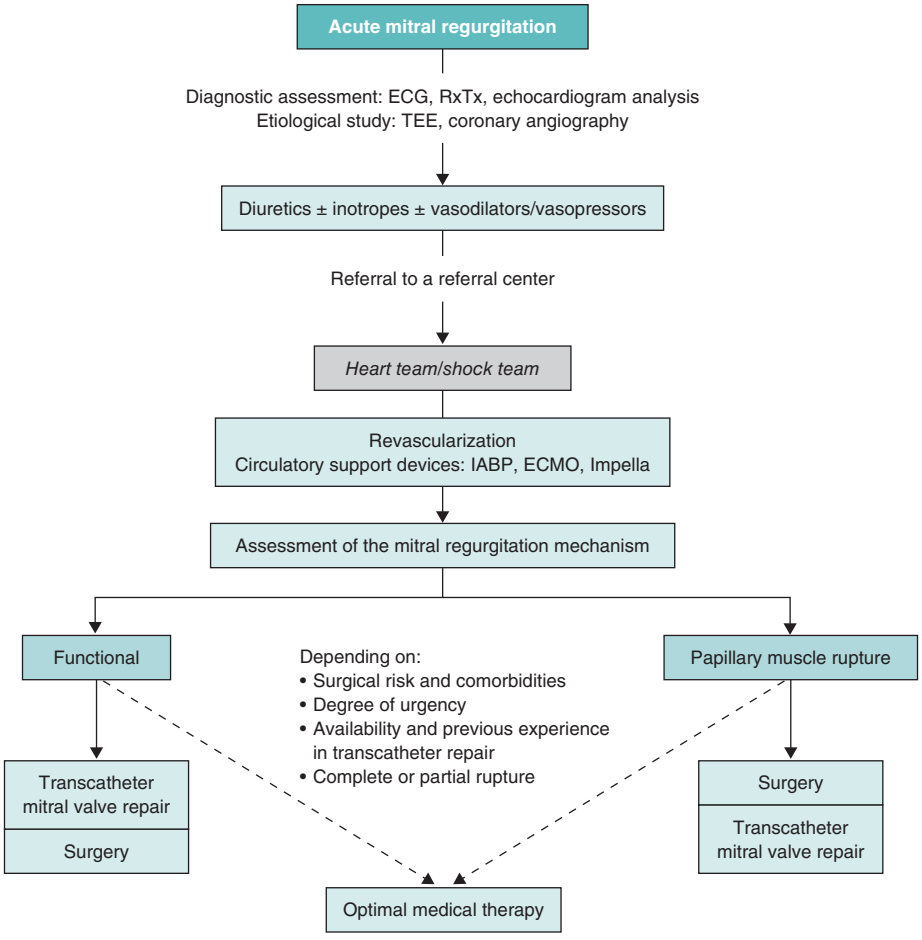
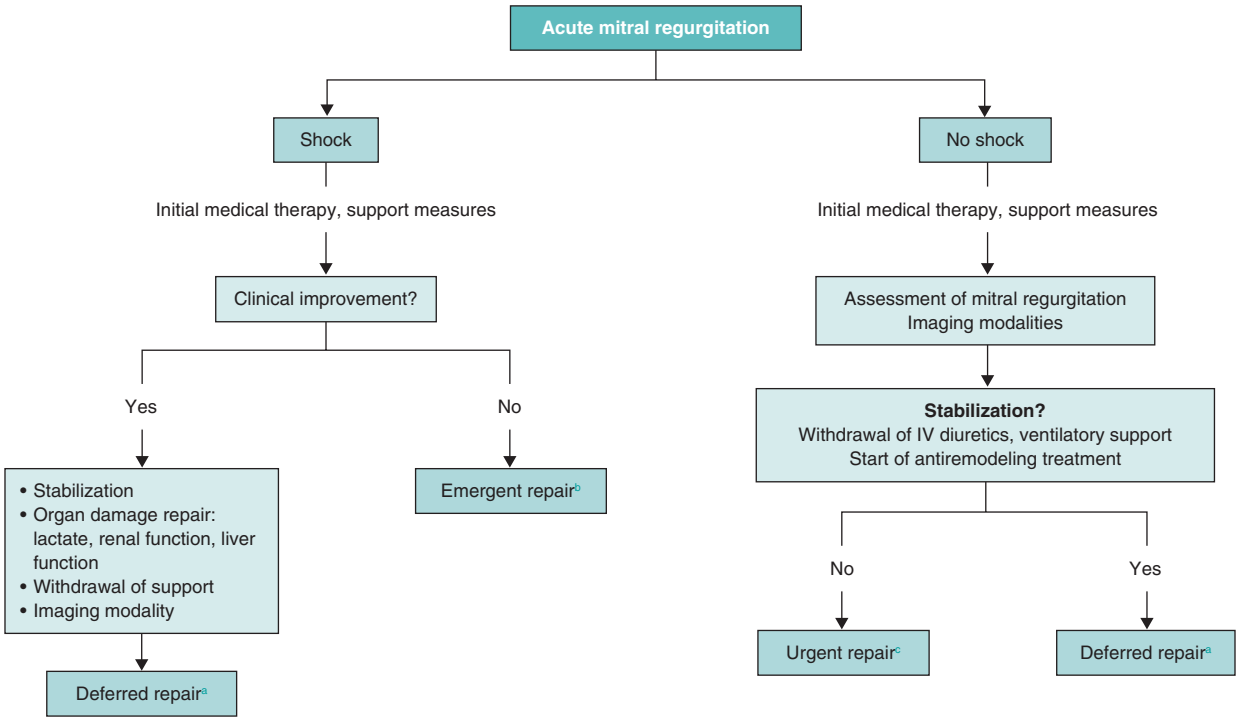


Figure 1. Treatment algorithm for acute mitral regurgitation. ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump; RxTx, chest X-ray; TEE, transesophageal echocardiography.

timing varies based on the underlying cause, ventricular function, and the patient's clinical status and any comorbidities. When the clinical and hemodynamic situation allows, a deferred implant is preferable. However, this is not always possible, and sometimes acute treatment of MR with edge-to-edge repair is necessary to stabilize the patient.



[a] Deferred repair: during hospitalization after adequate anatomical assessment of mitral regurgitation.
[b] Emergent repair: within the first 24 hours depending on the center logistics.
[c] Urgent repair: within the first 72 hours.

Figure 2. Optimal timing of mitral valve repair therapy.

Thus, in patients with flash pulmonary edema and normal LV function, in whom MR is usually associated with hypertension, and who respond well to medical treatment with oxygen therapy/noninvasive mechanical ventilation and diuretics, as well as in unstable patients with adequate treatment response, repair should be deferred. This deferred repair should occur after resolution of the acute heart failure, when the patient is in a state of euvolemia, and the diuretic dose has been adjusted.

In some patients with MR-related heart failure who cannot discontinue intravenous diuretic therapy, urgent repair within the first 72 hours should be considered. In the most severe cases—such as patients with MR in cardiogenic shock and inadequate response to treatment, and persistence of refractory shock—the feasibility of emergent mitral valve repair within the next 24 hours should be evaluated. Alternatives such as heart transplantation should also be considered (figure 2). In these more unstable patients, transcatheter repair can alter the severity spectrum, even with partial reductions in MR severity, facilitating the transition to a more stable condition that allows definitive treatment.[3]

ROLE OF IMAGING MODALITIES IN THE QUANTITATIVE ASSESSMENT OF ACUTE MITRAL REGURGITATION

A high level of suspicion is required to identify patients with significant acute-onset MR. Transthoracic echocardiography can be performed at the bedside, including in the emergency room, and should be the initial imaging method for evaluating acute dyspnea. Echocardiography is the preferred imaging modality to identify the underlying mechanism of MR and rule out other causes of a new systolic murmur in this clinical setting. Transesophageal echocardiography is often necessary to confirm the diagnosis, assess the severity of MR, and determine the treatment strategy, including identifying suitable candidates for edge-to-edge mitral valve repair (TEER) (figure 3).

Echocardiographic assessment should carefully evaluate the left ventricle (including ejection fraction, dimensions, and wall motion abnormalities), mitral valve anatomy (annulus, leaflets, chordae tendineae, and papillary muscles), and determine the etiology, mechanism, and severity of MR. Quantifying MR requires an integrated approach using qualitative, semiquantitative, and quantitative parameters as per current guidelines.[17,18] Color Doppler often shows markedly eccentric flow, which can underestimate MR severity. The vena contracta width and continuous-wave Doppler signal density are simple techniques to quickly assess significant MR. The velocity-time integral curve in continuous-wave Doppler typically has a triangular shape due to rapid late systolic deceleration, indicating an abrupt increase in left atrial pressure, known as a "v-wave". Ischemic MR is more pronounced in early and late systole due to opposing traction forces (systolic LV contraction). The severity of MR correlates with its holosystolic duration. However, some Doppler parameters may better evaluate chronic rather than acute MR. Hypotension and elevated left atrial pressure lead to a low transmitral gradient and reduced MR jet velocity on color Doppler, potentially underestimating or failing to detect MR. Anatomical features like flail leaflets, PMR, or a hyperdynamic left ventricle in pulmonary edema or cardiogenic shock should confirm the diagnosis, even when color Doppler does not show a large MR jet.

Echocardiography often reveals the underlying cause of acute MR. Among older patients, a frequent cause is chordal rupture associated with fibroelastic degeneration. Ischemic MR, resulting from leaflet tethering, is characterized by wall motion abnormalities in the region supplied by the culprit coronary artery, leading to leaflet tethering. This type of acute ischemic MR may occur during active or reversible myocardial ischemia and can resolve following

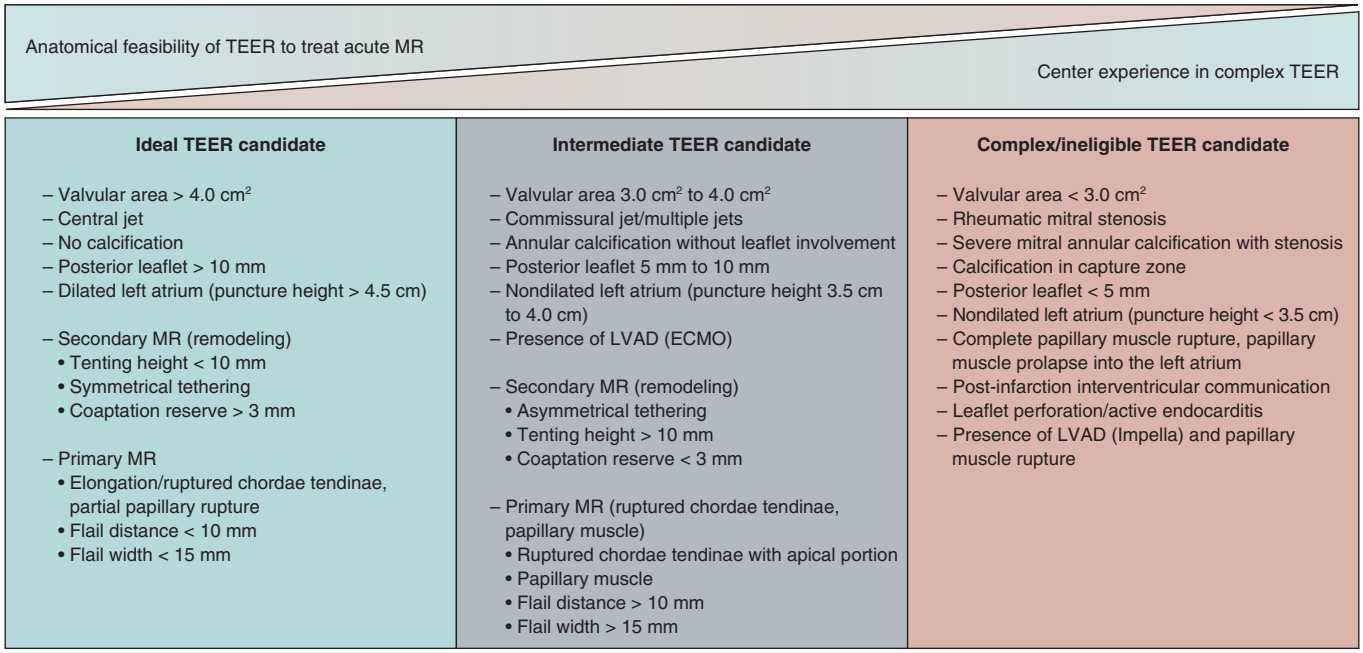


Figure 3. Eligibility assessment for transcatheter edge-to-edge mitral valve repair. ECMO, extracorporeal membrane oxygenator; LVAD, left ventricular assist device; MR, mitral regurgitation; TEER, transcatheter edge-to-edge repair.

ischemia treatment, highlighting the importance of reassessment postrevascularization.[19]

Acute MR due to LV remodeling occurs when the normal spatial relationship between the mitral valve apparatus and the left ventricle is distorted. Adverse remodeling of the left ventricle, characterized by dilation and shape change, causes one or both mitral leaflets to move apically and radially away from the ventricular center, driven outward by the displacement of papillary muscles secondary to remodeling. This pattern is most clearly observed in apical 3- and 4-chamber views.[20] The leaflets are typically normal in the acute phase, but a remodeling process with increased thickness has been described during follow-up.[21] The mitral annulus may also be dilated, a feature more commonly seen in nonacute MR cases. While both regional and global remodeling can lead to MR, the specific location of the remodeling is critical. Inferolateral myocardial infarctions are more likely to be associated with significant MR than anterior myocardial infarctions.[19] The differences between regional and global remodeling typically result in different tethering patterns. Patients with symmetrical tethering exhibit central jets, and those with asymmetrical tethering, eccentric jets.

The most severe form of acute MR is PMR. Common 2-dimensional echocardiographic features include a flail mitral leaflet with severed chordae or a papillary muscle head moving freely within the left heart. Due to differences in coronary vascular anatomy, posteromedial PMR is more common than anterolateral PMR. New-onset leaflet prolapse during the acute phase of myocardial infarction may indicate imminent PMR requiring careful attention. LV function often becomes hyperdynamic due to a sudden decrease in afterload, whereas regional wall motion abnormalities may be subtle or overlooked. Color Doppler assessment typically shows eccentric MR, which can lead to- underestimation of its severity.

TRANSCATHETER INTERVENTION IN ACUTE MITRAL REGURGITATION

To date, surgical treatment remains the primary approach for acute MR, despite the selective nature of patients in surgical studies and the limitations of observational evidence. In the SHOCK Trial Registry, only 38% of postmyocardial infarction acute MR patients complicated by cardiogenic shock underwent mitral valve surgery, with a mortality rate of 40% in these cases.[22] Similarly, a study examining evaluated the presence of PMR in a large cohort of patients with MR found that only 57.5% underwent surgical treatment,[23] a decision influenced by the patients' age, comorbidities, and clinical stability. This group of patients had a 36% mortality rate. Even among those who underwent surgery, outcomes were suboptimal due to early mortality, high transfusion rates, renal insufficiency, and prolonged mechanical ventilation.[24]

Therefore, developing less invasive approaches to address MR in this context, where patients often have a high surgical risk, is crucial to potentially expand the number of patients benefiting from MR correction.

Transcatheter techniques for treating MR have seen significant advancements in recent years. Among all available devices, transcatheter edge-to-edge repair (TEER) with the MitraClip system (Abbott Vascular, USA) is the most widely used and has accumulated extensive clinical experience. TEER with MitraClip has proven to be a safe and effective method for reducing MR in high-surgical-risk patients, and for improving symptoms, quality of life, and prognosis in those with functional and degenerative MR.[25-28] In the randomized CLASP IID trial,[29] the PASCAL Precision system (Edwards Lifesciences, United States) has also demonstrated safe and effective performance compared with MitraClip in patients with degenerative MR. Similarly, registry data have shown no significant differences with MitraClip in secondary MR.[30]

However, while most TEER procedures are performed in stable patients with advanced functional status and chronic MR, patients with acute MR are underrepresented in the literature. Acute MR represents a significant unmet need where the use of transcatheter interventions has grown significantly in recent years.

Increasing evidence supports the safety and efficacy profile of TEER in patients who develop severe symptomatic acute functional

MR. The EREMMI group (European registry of MitraClip in acute MR following an acute myocardial infarction) has published the largest series to date on this topic. The first article—published in 2020—revealed the European experience with MitraClip in this context.[31] The study included 44 patients with a mean age of 70 years and high surgical risk (median EuroSCORE II of 15.1%) from 2016 through 2018. Notably, the median time from acute myocardial infarction diagnosis to MitraClip intervention was 18 days, and from MR onset to treatment was 12.5 days, indicating insufficient stabilization with medical management alone. Patients were markedly symptomatic, with 63.6% classified as New York Heart Association (NYHA) class IV at the time of the procedure. In this series, technical success reached 86.6%. During follow-up, the 30-day mortality rate was 9.1%, a figure deemed acceptable considering that surgery for acute ischemic MR has the highest mortality rate among all surgical procedures performed for acute MR.[32] At 6 months, MR ≤ 2+ was reported in 72.5%, with 75.9% of surviving patients achieving NYHA functional class I-II.

Subsequently, the researchers examined the role of TEER in treating acute severe MR in a cohort of 93 patients with cardiogenic shock.[33] Technical success was high, and although 30-day mortality was higher among those in cardiogenic shock, the difference compared with nonshock patients was not statistically significant (10% vs 2.3%; $P = 0.212$). Conversely, mortality rates were markedly low in nonshock patients, even in a population at very high risk, highlighting the beneficial hemodynamic impact of percutaneous MR correction. Therefore, provided the TEER team has ample experience, cardiogenic shock should not preclude consideration of this therapeutic approach. These findings, together with recent insights into the efficacy of TEER in patients with shock,[34-36] should position this therapy as a viable strategy due to its safety and efficacy.

When comparing patients with a left ventricular ejection fraction above or below 35%, the study found no significant differences in either in-hospital mortality or at 1 year (11% vs 7%, $P = .51$, and 19% vs 12%, $P = .49$), nor in the 3-month rehospitalization rate. Therefore, the positive effect of transcatehter treatment is maintained in patients with lower ejection fractions.[37]

Finally, the most extensive analysis of the group compared 3 strategies for the management of MR early after infarction: conservative management, surgical intervention, and TEER.[38] The series included involved 471 patients, with 266 managed conservatively and 205 undergoing intervention (106 surgically and 99 with TEER). Consistent with prior research, medically managed patients experienced the highest mortality rates, twice that of the intervention groups. Notably, surgical correction resulted in poorer outcomes compared with MitraClip, with hospital mortality exceeding twice that at 1 year, largely driven by higher in-hospital mortality (16% vs 6%; $P = .03$). This trend was independent of the patients' surgical risk profiles.

In the context of PMR, the largest series treated with TEER has been reported.[39] The study included 23 patients, with a mean age of 68 years, and 56% were male. All were deemed ineligible for surgery due to high surgical risk. Nearly 90% were in cardiogenic shock, with 17 receiving mechanical circulatory support (11 with intra-aortic balloon pump, 2 with Impella, and 4 with venoarterial extracorporeal membrane oxygenation). Immediate success after the intervention was achieved in 87% of the patients, resulting in rapid hemodynamic improvement. Hospital mortality was 30%, which, while still high, was deemed acceptable given that these patients had no surgical options and faced poor prognoses with medical management alone. Importantly, 5 discharged patients underwent successful surgical mitral valve replacement during follow-up, highlighting the importance of stabilizing patients before considering deferred surgical interventions

In this scenario, guidelines and recommendations[40-42] advise transcatheter therapy only in selected high-risk patients who are unsuitable for surgery. However, due to the difficulty of decision-making, limitations in offering surgery more broadly, and the complexity of managing patients in cardiogenic shock, most patients should be evaluated by a shock team to consider various therapeutic options, including percutaneous interventions (figure 1).

There are several potential advantages to the trancatheter approach in the management of acute MR. These patients often show significant clinical deterioration, primarily due to the development of MR affecting a small and noncompliant left atrium. This leads to markedly elevated pulmonary pressures and a low effective ejection volume, which are the main physiological factors causing the disease. TEER induces almost immediate hemodynamic improvement by reducing MR. This decreases pressures in the left chambers and pulmonary artery, increases cardiac output, and facilitates faster recovery with minimal tissue damage.[43] Furthermore, TEER does not rule out scheduled cardiac surgery in the event of device failure or recurrent MR. Indeed, the role of TEER as a bridge to lower-risk surgery is appealing. In patients with poor progress, heart transplantation remains a viable option.

While outcomes with TEER in this condition are promising, evidence is currently limited to retrospective observational analyses of small patient populations. There may be selection bias among patients treated with TEER, as only those who responded well to medical therapy and cardiac support likely underwent the intervention. Long-term clinical and echocardiographic follow-up is also sparse. In additional, nearly all studies have included patients treated before 2020, before the introduction of newer generations of devices with independent capture capabilities or larger sizes, potentially limiting the effectiveness of TEER.

To provide more robust information on the appropriateness of this treatment for acute MR, ideally, prospective registries and a well-designed, executed randomized trial should be developed.

Currently, 2 very early-phase trials are underway that could shed light in this scenario. The international multicenter trial EMCAMI (Early Transcatheter Mitral Valve Repair After Myocardial Infarction; ClinicalTrials.gov: NCT06282042) was designed to prospectively evaluate the role of early treatment with MitraClip edge-to-edge repair vs conservative conventional treatment in acute MR occurring within 90 days of acute myocardial infarction, focusing on mortality and heart failure readmissions. The MINOS trial (Transcatheter Mitral Valve Repair for Inotrope Dependent Cardiogenic Shock; ClinicalTrials.gov: NCT05298124) will assess these treatment strategies in patients with cardiogenic shock and acute MR.

Technical and organizational considerations

The use of TEER in acute MR poses technical and organizational challenges, with several important considerations.

The left atrium is usually small and noncompliant. Therefore, transseptal puncture and positioning to achieve sufficient height above the valve can be complex and requires experience. Likewise, puncturing outside the fossa ovalis may be required. Systems allowing radiofrequency puncture for a precise entry point may be recommended for accurate placement.[44]

The complexity of valvular anatomy, especially in cases of primary MR in which large, wide gaps and commissural jets are common, suggests the use of the new features of the MitraClip G4 or PASCAL Ace devices,[45,46] which allow independent leaflet capture and optimization to improve outcomes. With these new generation devices, most cases are technically feasible. For primary MR due to posterior

medial prolapse, stabilizing the papillary muscle and controlling additional movement typically occurs after deploying multiple devices, preventing further tissue tears. Care must be taken to avoid device interference with the muscle and prevent additional damage or complete rupture in cases of partial tears.

Clinical deterioration can be rapid in some patients, raising the question of whether specialized mitral valve teams should be prepared to perform emergency treatment. If patients are too unstable for transfer, these teams may even need to travel to centers lacking such capabilities. In this context, teams should aim to initiate treatment within 24 hours of clinical deterioration for primary MR and patients in cardiogenic shock, and as promptly as feasible in other patients. These treatments should be considered within the framework of a "shock code", a concept still under development in many regions, and organized based on available resources.

CONCLUSIONS

Patients with acute MR require a multidisciplinary approach both for their diagnostic assessment and in decision-making about treatment strategy. TEER is an effective treatment option for acute MR, either as a definitive treatment or as a bridge to a more stable scenario for other treatments, with a high procedural success rate and improved patient prognosis in centers experienced with the technique. Proper patient selection, meticulous anatomical evaluation, and choosing the optimal timing for implantation are key to treatment success.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

All authors contributed to the writing of the text and its critical review, and approved the article final version.

CONFLICTS INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECIC.M24000464.

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Review article

Inception of the coronary stent: a story of successful collaboration between innovative scientists and the biotechnology industry

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ABSTRACT

All cardiologists should delve into history to understand the current state of the art of their specialty. In the last century, the coronary stent was a pivotal achievement of research and biotechnological engineering. Since then, technology has advanced, and substantial improvements have been incorporated into this device, which has become the gold standard for treating coronary artery disease. This article summarizes the history of the coronary stent from its inception to the present day. The document reviews key historical and scientific milestones that have contributed to making percutaneous angioplasty a safe and highly effective procedure due to coronary stents. The evolution of the stent has been closely linked to the growth and maturation of interventional cardiology to date.

Keywords: Stent. Drug-eluting stent. Percutaneous transluminal coronary angioplasty.

Origen del *stent* coronario: una historia de éxito entre científicos innovadores e industria biotecnológica

RESUMEN

Todo cardiólogo debe realizar un viaje atrás en la historia para entender el estado actual de su especialidad. El *stent* coronario es uno de los logros más importantes de la investigación y de la ingeniería biomédica del último siglo. Su tecnología ha ido evolucionando e incorporando mejoras sustanciales que hoy en día hacen de este dispositivo un estándar de gran calidad para el tratamiento de la enfermedad coronaria. En este artículo se resume la historia del *stent* coronario desde su génesis hasta el presente. Se repasan los hitos históricos y científicos más remarcables que contribuyeron a hacer de la angioplastia percutánea un procedimiento seguro y altamente efectivo gracias al *stent* coronario. La evolución del *stent* ha ido de la mano del crecimiento y la maduración de la cardiología intervencionista.

Palabras clave: *Stent*. *Stent* liberador de fármaco. Angioplastia coronaria transluminal percutánea.

BEGINNINGS AND DEVELOPMENT OF CORONARY ANGIOPLASTY (1970s AND 1980s)

Spectacular advances have been made in interventional cardiology over the past decades, hand in hand with biotechnological progress. The development of coronary stents has been pivotal by enabling the reliable establishment and expansion of percutaneous angioplasty. Stents were introduced to address the issues posed by plain old balloon angioplasty, which became evident in its early stages. Therefore, it is important to reflect on how it all started (table 1)[1].

In the early 1970s, the treatment of coronary artery disease was limited to the use of nitroglycerin and propranolol, with few diagnostic tests and very little scientific evidence. However, some important milestones had already been achieved, setting the stage for the significant advancement of percutaneous treatment.[1] Coronary angiography was rarely indicated, being restricted to patients with severe symptoms and in anticipation of possible treatment with coronary artery bypass graft surgery, which was the only revascularization modality available at the time. Andreas Roland Grüntzig, a German radiologist and cardiologist who worked in

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Table 1. Milestones in the development of interventional cardiology

Year	Milestone
1929	Werner Forssmann performs the first transluminal cardiac catheterization
1953	Sven Seldinger introduces percutaneous access
1958	Mason Sones performs the first coronary angiography (via surgical brachial access)
1963	Charles Dotter performs the first peripheral angioplasty
1968	Eberhard Zeitler expands peripheral angioplasty across Europe
1968	Melvin Judkins develops the percutaneous coronary angiography technique
1977	Andreas Grüntzig performs the first percutaneous coronary balloon angioplasty
1979	Geoffrey Hartzler performs the first coronary angioplasty in acute myocardial infarction
1986	Jacques Puel implants the first coronary stent (Wallstent)
1991	Cannon and Roubin report the first stent implantation in acute myocardial infarction
1994	Regulatory approval of the first scientifically evidence-based stent (Palmaz-Schatz)

Zurich, Switzerland and later in Atlanta, United States, was a figure of exceptional ability and perseverance who pioneered the balloon angioplasty technique, overcoming the prevailing scepticism and opposition in his field. Having inherited the legacy of peripheral angioplasty from Charles Dotter through Eberhard Zeitler, Grüntzig developed the angioplasty balloon. He initially applied the technique to peripheral artery disease in 1974 and then boldly expanded its use to treat the human coronary tree on September 16th, 1977.[2]

After the initial clinical success, the limitations of balloon angioplasty began to emerge, especially as it was applied in different clinical and anatomical scenarios. Concerns included acute occlusion due to elastic recoil, dissection, and thrombosis. These issues resulted in perioperative infarctions, the need for cardiac surgery, or repeat angioplasty during follow-up.[3] Restenosis was a delayed phenomenon but its high incidence (20%-40%) also posed challenges.[4] To prevent elastic recoil and occlusive dissections, the radial force exerted by the angioplasty balloon needed to be maintained with an intraluminal prosthesis.

CREATION AND APPROVAL OF CORONARY STENTS (1980-1994)

The origin of the term *stent* (recognized by the Royal Spanish Academy)[5] is unknown but is widely believed to be named after the British dentist Charles Thomas Stent (1807-1885). In 1856, Stent patented a thermoplastic material for making dental impressions, which he named "Stent's paste".[6] After the patented paste fell out of use, the term continued to be used for any prosthetic material that could replace biological tissue. Its use expanded to include tubular prostheses used in hepatobiliary and urology surgery.[6] Charles Dotter—also a pioneer in this field—reported his experience of inserting metal coils into dog arteries for the first time in 1969 to demonstrate the feasibility of implanting an intraluminal containment device.[7] However, it was not until the 1980s, after the limitations of balloon angioplasty became evident, that the term *stent* gained broader usage. During this time, significant emphasis was placed on developing the technology used today.

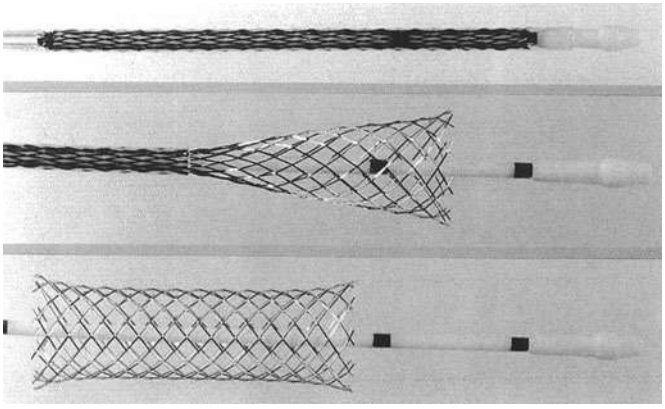

Figure 1. Self-expanding Wallstent. Stent deployment process demonstrating significant longitudinal shortening (shown from top to bottom).

In 1980, a meeting in Switzerland between 2 expatriate Swedes, Åke Senning, a cardiothoracic surgeon who had been a supporter of Andreas Grüntzig, and engineer Hans Wallsten, marked the beginning of a successful project. Along with French engineer Christian Imbert, they eventually developed the first stent for use in coronary arteries: the Wallstent. The term was not an eponym of the engineer but derived from implanting a prosthesis (stent) into the vessel wall.[1] The The Wallstent consisted of a self-expandable mesh of stainless steel wire released by a delivery system (figure 1). They founded the company MedInvent (later acquired by Schneider, Switzerland), sought researchers to test the device, and contacted Ulrich Sigwart (Lausanne) and Jacques Puel (Toulouse).[1]

The experimental protocol for the Wallstent initially involved use in animals, followed by application in human peripheral arteries, and finally in the coronary arteries of patients. The Toulouse center encountered fewer difficulties in initiating animal experimentation and reached human trials sooner. Thus, in December 1985, Hervé Rousseau and Francis Joffre, both radiologists from Jacques Puel's department in Toulouse, France, implanted the first peripheral stent-graft. In March 1986, Jacques Puel implanted the first coronary stent-graft in a patient who developed restenosis after balloon angioplasty in the left anterior descending coronary artery.[1] Meanwhile, in June 1986, Ulrich Sigwart implanted the first coronary stent-graft to treat an acute occlusive dissection in a proximal left anterior descending coronary artery following balloon angioplasty. This was the first time a patient avoided emergency surgery for this complication.[1,8]

Later, Sigwart became a spokesperson in the public arena and in publications, perhaps aided by his better command of the English language.[1] In March 1987, the first report of the joint experience was published in *The New England Journal of Medicine*.[9] The article reported the implantation of 24 coronary stents in 19 patients to treat restenosis (n = 17), acute occlusion following balloon angioplasty (n = 4), or deterioration of coronary artery bypass grafts (n = 3). Years later, Sigwart recounted that the journal requested he avoid the verb *stenting* and instead use the noun *stent* to refer to the new device.[10] The initial multicenter experiences with the Wallstent were led by centers in Toulouse, Lausanne, and Rotterdam. In 1991, Serruys et al.[11] described the follow-up of the first 105 treated patients: the mortality rate was 7.6%; the incidence of occlusion was 24% (mostly within the first 2 weeks), and the rate of restenosis was between 14% and 32% (depending on the definition).

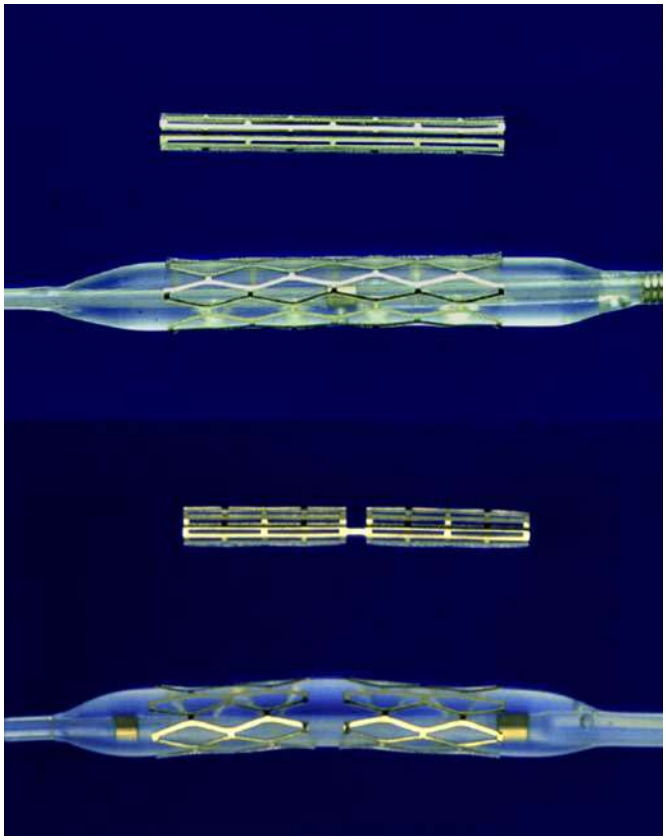

Figure 2. Balloon-expandable Palmaz-Schatz stent (top) and PS 153 series (bottom), consisting of 3 shorter stents connected by a bridge to enhance flexibility and navigation.

At the same time, across the ocean, Julio Palmaz, an Argentine interventional radiologist based in the United States, attended Grüntzig's live sessions in 1977. Witnessing the complications of angioplasty, he spotted the opportunity to develop a device for their prevention. He designed his first prototype in his kitchen using copper wire and a soldering iron. He later used stainless steel and invented the first balloon-expandable stent, which he implanted in dog aortas.[1,12] Palmaz subsequently relocated to San Antonio (Texas, United States), where he refined the device using cutting machines on steel tubes.[13] In the United States, he met Richard Schatz, a military cardiologist who assisted him in adapting the model for use in coronary arteries by connecting 2 small stents with a bridge, thereby enhancing the flexibility and navigability of the entire system (figure 2). After securing the necessary investment, they founded Expandable Grafts Partnership (later acquired by Johnson & Johnson, United States) to manufacture the prototypes and fund further research.[12]

Due to research restrictions in the United States, the first human trials were conducted abroad.[1,12] In October 1987, Julio Palmaz and Goetz Richter implanted the first Palmaz-Schatz stent in peripheral arteries in Freiburg, Germany. Later that year, Palmaz, Schatz, and. Eduardo Sousa implanted the first Palmaz-Schatz stent in coronary arteries in Sao Paulo, Brazil (21 months after the first coronary Wallstent). Unfortunately for Julio Palmaz, the milestone of the first balloon-expandable stent implantation had been achieved 3 months earlier by Gary Roubin and Spencer King III at Emory University, Atlanta, Georgia, United States. Their device was a metal wire structure coiled around a balloon (figure 3) invented by the Italian radiologist Cesare Gianturco, who had previously worked with Grüntzig.

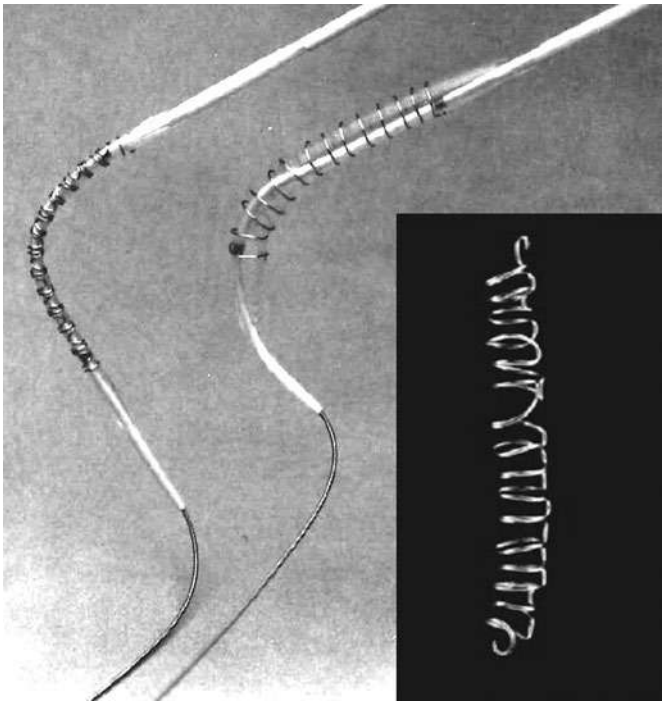

Figure 3. Balloon-expandable Gianturco-Roubin stent, featuring a helical coil formation.

The US Food and Drug Administration approved the Gianturco-Roubin stent (Cook Medical Inc., United States) in 1993, but not the Palmaz-Schatz, which required2 randomized clinical trials. These trials were completed and published in 1994, leading to Food and Drug Administration approval.[1,12,14,15] Here we review these 2 landmark trials that scientifically validated the use of the stent in cardiology.

The Belgian Netherlands Stent (BENESTENT) trial, presented by Serruys et al.[15] in 1994, randomized 520 patients with stable angina and single-vessel coronary artery disease to undergo balloon angioplasty or Palmaz-Schatz stent implantation. The trial included 28 centers, mostly in Europe. All patients received aspirin for 6 months, and those who underwent stent implantation also received warfarin for 3 months. At 7 months, stent treatment decreased the composite rate for adverse events by 32%, primarily due to a lower need for repeat revascularization. The rate of binary restenosis (≥ 50%) was 22% in the stent group vs 32% in the balloon group (figure 4). Stent thrombosis occurred in 3.5% of the patients. Stent-treated patients experienced more vascular and hemorrhagic complications and longer hospital stay. At 1-year follow-up, the relative reduction in combined events remained at 26% in favor of the stent, with an incidence of repeat angioplasty of 10% vs 21% in the balloon group[16].

The Stent Restensosis Study (STRESS), reported by Fischman et al.[14] the same year, randomized 410 patients from 20 centers, mostly in North America. The antithrombotic regimen included indefinite aspirin for all patients and a 1-month regimen of warfarin for those receiving the Palmaz-Schatz stent. At 6 months, the incidence of combined adverse events was similar (19.5% in the stent group vs 23.8% in the balloon group; $P = .16$), but there was a trend toward a lower need for repeat revascularization in the stent group (10.2% vs 15.4%; $P = .06$). The rate of binary restenosis was also lower in stent-treated patients (32% vs 42%; $P < .05$). Stent thrombosis occurred in 3.4% (7/205) of the patients treated per protocol and in 21.4% (3/14) of those who underwent stent implantation as

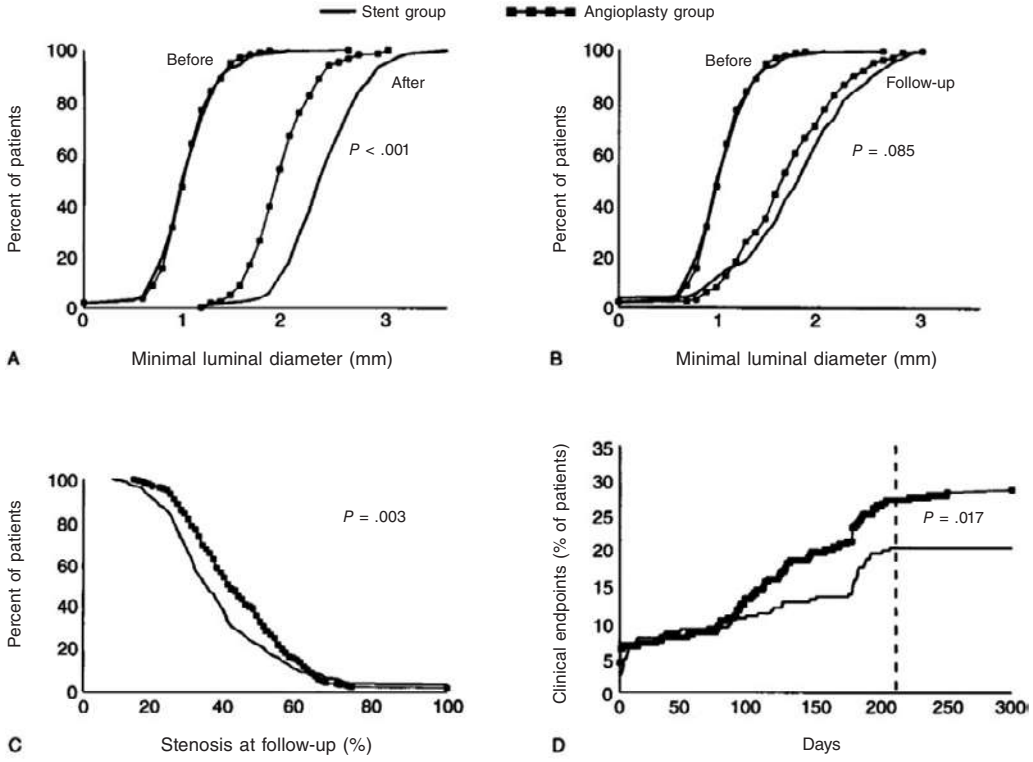

Figure 4. Graphs from the BENESTENT study illustrating acute luminal gain (**A**) and follow-up (**B**). Frequency distribution of restenosis (**C**) and cumulative clinical events (**D**). (Reproduced with permission from Serruys et al.[15]).

a bailout therapy for angioplasty (crossover). Again, vascular and hemorrhagic complications, and the length of stay were more significant in stent-treated patients. At nearly 1 year of follow-up, numerical differences favored the stent, although they were not statistically significant (unplanned revascularization: 12% vs 17%; $P = .09$).[17]

Finally, despite the obstacles and delays, the Palmaz-Schatz stent became the gold standard for a time due to the supporting evidence, its greater safety profile, and its ease of use. Other stents, despite their significant initial expansion, lacked study support and concerns remained about the incidence of thrombosis and restenosis. In terms of these complications, the Gianturco-Roubin stent proved inferior to the Palmaz-Schatz stent,[18] while the Wallstent showed issues of longitudinal shortening, implantation imprecision, and side branch compromise due to its small cell size. Because of these factors, these stents were gradually phased out and eventually disappeared from the market.

Starting in 1994, the use of stents expanded due to the BENESTENT and STRESS trials. However, doubts remained about whether the costs associated with this new intervention would translate into significant benefits. Several subsequent studies convinced the medical community of the superiority of stents over simple balloon angioplasty in various scenarios. Two landmark studies showed clear benefits in reducing restenosis rates: one in chronic occlusions (32% vs 74%; $P > .001$) in 1996[19] and another in isolated disease of the proximal left anterior descending coronary artery (19% vs 40% at 12 months; $P = .02$) in 1997.[20] In addition, the strategy of stent angioplasty vs balloon angioplasty with the possibility of bailout stenting favored the first-line use of stents for their clinical benefits and cost-effectiveness.[21] In acute myocardial infarction, the Stent-PAMI trial established the indication for the use of stents over balloon angioplasty.[22]

PROGRESS AND PLATFORM MODERNIZATION (1990S)

During the 1990s, several important advancements enhanced the safety and efficacy of stents (table 2).[1] These included the use of intravascular ultrasound to optimize implantation, advances in hemostasis, and the expansion of radial access. In addition, the shift from anticoagulation to dual antiplatelet therapy reduced the hemorrhagic complications observed in the BENESTENT and STRESS trials.[14,15] Last but not least, technological improvements in stent platforms were key to making this treatment more widespread.

The initial stents had clear technical shortcomings that needed to be addressed to expand their use to various anatomical scenarios, such as tortuosities, bifurcations, and calcified lesions. At the initiative of interventional cardiologists themselves, the possibility of cutting the Palmaz-Schatz stent at the articulated bridge was proposed to provide a short stent ("disarticulated Palmaz" or "hemi-Palmaz") for short lesions with more challenging anatomical access.[23] However, it was the incorporation of laser cutting technology that revolutionized stent design. Cordis, a Johnson & Johnson company based in the United States, improved the Palmaz-Schatz platform by introducing the Spiral and later the Crown[24] (figure 5). This evolution eventually led to the Bx Velocity, a laser-cut tubular stent with zigzag rings and wavy connectors that provided greater flexibility while maintaining the closed-cell design (connectors at all the bending angles of the rings), which limited its navigation in curves (figure 5). Building on the Bx Velocity platform, Cordis launched the first drug-eluting stent in history: the Cypher.[12]

In 1990, Medtronic Inc. (United States) introduced the Wiktor—a balloon-expandable helical coil stent similar to the Gianturco-Roubin stent but made of tantalum, which is more radiopaque (figure 6). However, due to its fragility and weak radial force, the Wiktor was surpassed by newer platforms and was eventually withdrawn from

Table 2. Advances in angioplasty in the 1990s

Years	Advances	Resultados
1989-1993	Radial access for coronary angiography and coronary angioplasty	Beginning of a new era in minimally invasive arterial access
1993-1994	Reduction in access gauge down to 6-Fr Femoral hemostatic closures	Fewer hospitalizations and hemorrhagic complications
1994	Publication of the BENESTENT[15] and STRESS[14] trials	The stent demonstrates its effectiveness in angioplasty
		The Palmaz-Schatz stent is established as the gold standard
	Use of intravascular ultrasound to optimize stent implantation	Adequate expansion due to high implant pressures led to minimal thrombosis and reduced restenosis
1995-1998	Studies on dual antiplatelet therapy	Minimization of thrombosis
		Discontinuation of oral anticoagulation
		Less bleeding
1994-2000	Enhancements to the Palmaz-Schatz (Cordis, United States) and emergence of new modern platforms: Micro Stent (Arterial Vascular Engineering, United States), Multi-Link (Advanced Cardiovascular Systems, United States), etc.	Expansion of the indication for stent angioplasty
		Tubular/modular stents outperform self-expanding and helical stents

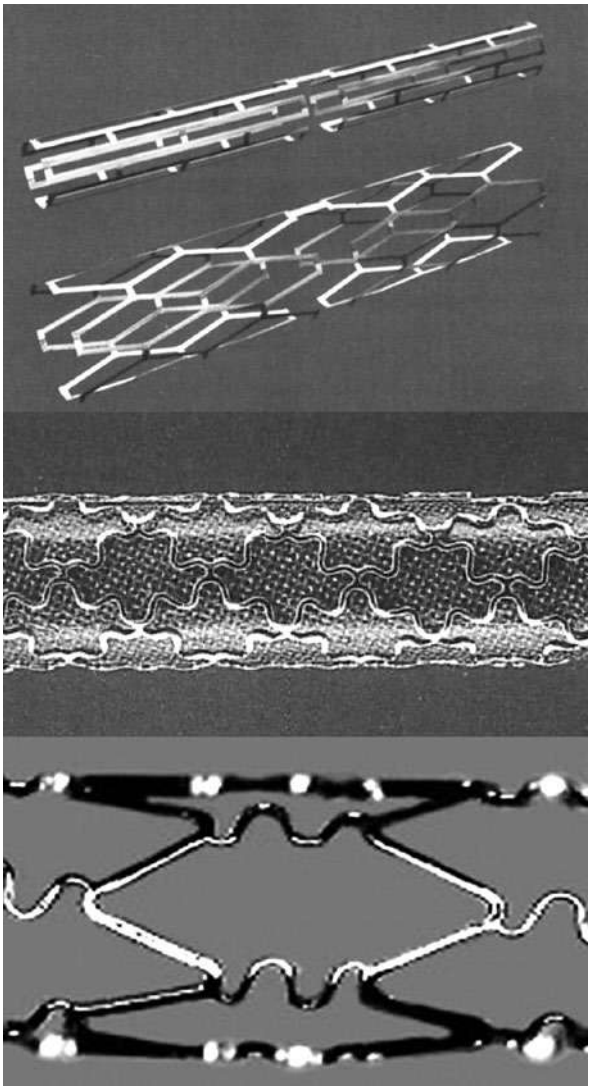

Figure 5. Cordis stents: evolution of the Palmaz-Schatz platform, from the articulated PS 153 series (top), through the Crown (center), to the Bx Velocity platform (bottom).

the market.[24] Around 1994, Arterial Vascular Engineering (AVE, United States) launched the Micro Stent, featuring a modular design: round cobalt alloy wire with smooth curved angles forming rings that were then joined with welds at alternate vertices, creating open cells. This design improved flexibility and navigation without losing radial strength.[24] AVE was acquired by Medtronic in 1998. In subsequent iterations of the Micro Stent (GFX, GFX2, S670, S7), the strut thickness (the wire that composes the stent mesh) was gradually reduced, and stainless steel was replaced by a cobalt-nickel alloy in the Driver stent in 2002 (figure 6). Well into the 21st century, Medtronic used the Driver platform to create the Endeavor drug-eluting stent. In 2010, the transition to the Integrity platform involved using a continuous sinusoidal-shaped wire, laser welded at multiple points to protect its integrity.

On the other hand, Advanced Cardiovascular Systems (United States), a company previously acquired by Eli Lilly's Medical Device and Diagnostics Division (United States) and later by Guidant, created the Multi-Link stent, which was approved for use in Europe in 1995 and in the United States in 1997. This tubular stainless steel stent had an open-cell design, with flat struts and rounded angles at the rings.[24] Its modern design made it highly competitive and it dominated the market alongside the AVE stent.[12] Guidant continued to enhance the Multi-Link platform by thinning the struts, incorporating curved connectors, and switching to a chromium-cobalt alloy in the Vision model (figure 7). The Multi-Link Rx (50-µm strut) demonstrated superiority over the Bx Velocity stent (140 µm strut) in terms of 12-month restenosis in the ISAR-STEREO-2 trial (18% vs 31%; $P < .001$),[25] which demonstrated the importance of strut thickness in reducing vessel wall damage and the occurrence of restenosis. The chromium-cobalt Multi-Link platform later served as the foundation for the drug-eluting stents Xience V (Abbott Vascular, United States) and Promus (Boston Scientific, United States).

The NIR stent by Medinol (Israel), distributed by Boston Scientific, was a closed-cell stainless steel stent designed for flexible navigation. Once expanded, its cell geometry provided substantial rigidity and, therefore, radial strength[24] (figure 8). This platform was used for the first paclitaxel drug-eluting stent, the Taxus, launched by Boston Scientific in 2003. In the late 1990s, Boston Scientific, which had distributed the Wallstent and the NIR, developed and marketed its own stents, the Express and Veriflex/Liberté, which would later serve as the basis for subsequent versions of the Taxus (figure 8).

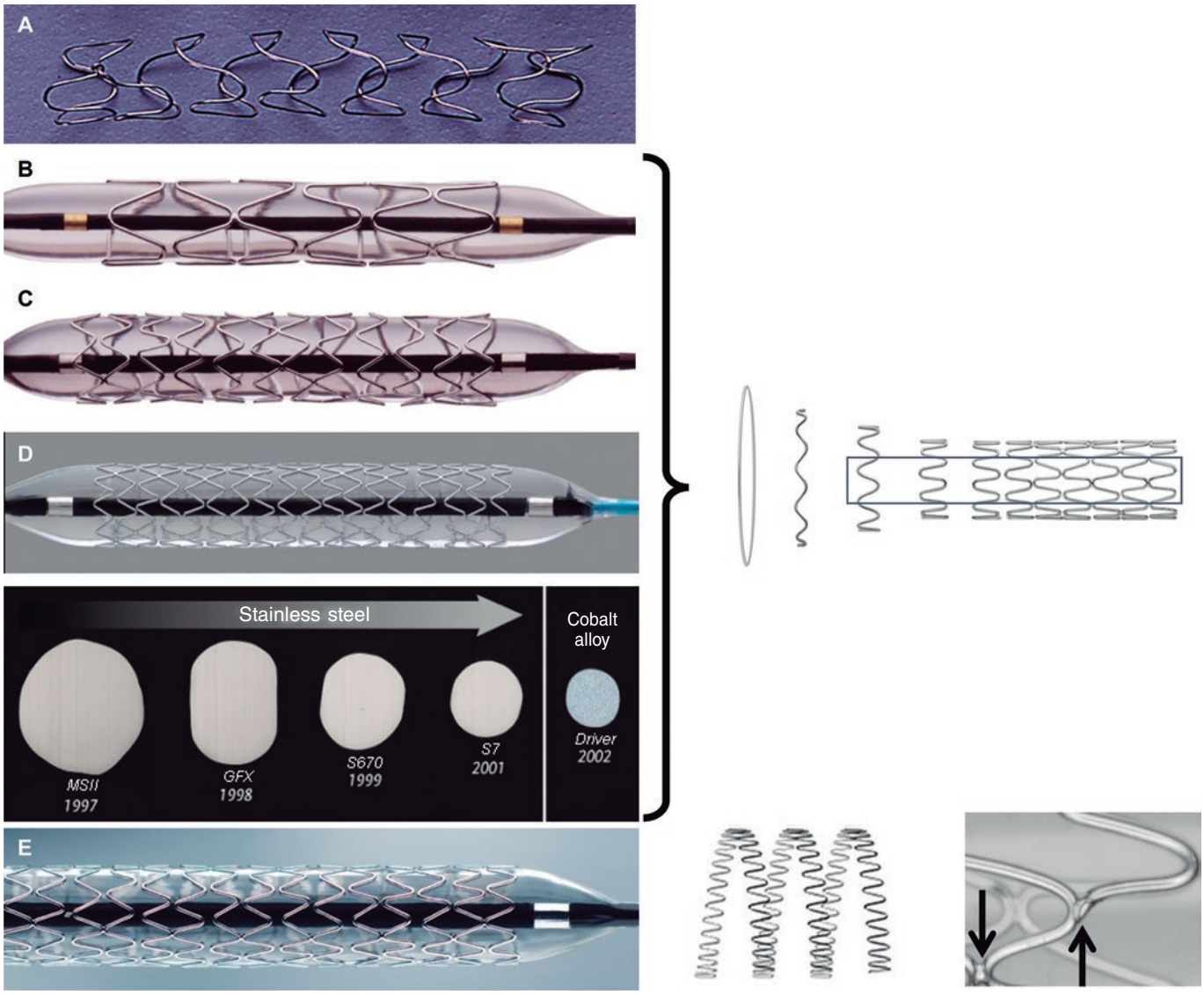

Figure 6. Medtronic and AVE stents: helical Wiktor stent (**A**) and modular AVE microstent (B), with their GFX2 (**C**) and Driver (**D**) iterations. Diagram showing strut developments throughout successive platforms. Image of the Integrity platform (**E**) with laser welded continuous wire technology.

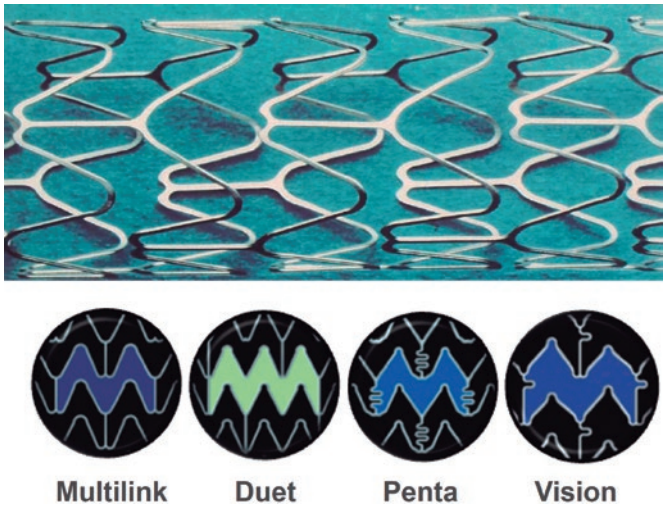

Figure 7. ACS-Guidant stents. Multi-link platform in its successive iterations with modifications in cell structure and connectors.

Many stents launched during the 1990s were compared based on their technical characteristics and direct comparison studies generally yielded equivalent data.[26] After this technological revolution at the end of the century, it became evident that balloon-expandable tubular stents (Palmaz-Schatz and Multi-Link) and modular design stents (Micro Stent) had outperformed self-expanding and helical stents. Advances in angioplasty during these years (table 2) firmly established stents as the standard for percutaneous treatment of coronary artery disease. However, restenosis remained a significant issue for both stents and angioplasty in general. The incidence of restenosis had decreased from 30% to 40% with balloon angioplasty to 20% to 30% in the early studies of the Palmaz-Schatz stent.[14,15] After successive improvements in stent platforms and implantation techniques, restenosis rates were reduced, but still hovered around 20% 1 year after implantation.[27] Furthermore, the expanded use of stents in more complex scenarios (saphenous vein grafts, small vessels, long lesions, etc.) suggested an even higher incidence of restenosis. Addressing this issue became a priority, leading to the next revolution in interventional cardiology as the 21st century began.

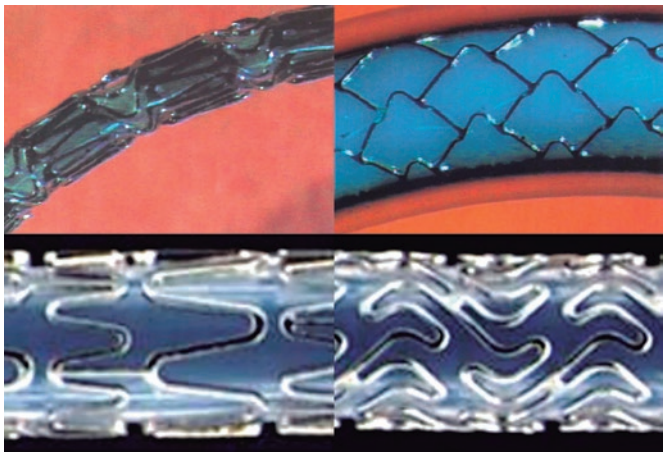

Figure 8. Platforms used by Boston to develop the Taxus. NIR stent from Medinol (top); Express platform (bottom left); Veriflex platform used for the Taxus Liberté (bottom right).

TACKLING RESTENOSIS IN THE 21ST CENTURY: THE ERA OF DRUG-ELUTING STENTS

Once the use of stents became widespread, restenosis and thrombosis emerged as complications that needed to be understood and addressed. Initially, heparin coatings were devised for stents to prevent these 2 processes. While they seemed to have a protective effect against thrombosis, their effect on restenosis was uncertain. Despite the clear advancement that coronary stents represented for angioplasty, they triggered a vascular response leading to sustained inflammatory processes, tissue growth, and late lumen loss.[28] It became evident that restenosis primarily resulted from the proliferative activity of vascular smooth muscle cells.[29] Consequently, efforts focused on halting this cellular response. Brachytherapy, involving the transcatheter delivery of ionizing radiation to the lesion, emerged as a method to mitigate this proliferative response. However, the difficulty of applying this therapy, coupled with the occurrence of very late thrombosis, likely related to inhibition of endothelialization and restenosis at the irradiated segment edges, limited its success.[30] Subsequently, attention shifted to the development of antiproliferative drugs.

Sirolimus (rapamycin) is an antifungal agent first isolated in 1965 from a bacterium found on Easter Island (Chile).[31] This agent is an inhibitor of the mTOR (mammalian target of rapamycin) protein with antiproliferative and immunosuppressive effects that had already been used in cancer treatment and as a therapy after organ transplantation. This molecule was selected by the research team at Cordis to create the first drug-eluting stent, the Cypher. Sirolimus was incorporated into a polymer carrier that coated the metal surface of the stent, allowing its controlled release to the endothelium. In contrast, paclitaxel (taxol) is an antimitotic agent extracted from the bark of the Pacific yew tree that was first isolated in 1967.[32] Paclitaxel exerts a cytotoxic effect by blocking microtubule disassembly, thereby disrupting the cell cycle and mitosis. Boston Scientific chose paclitaxel to develop the first generation of the Taxus stent, embedding the drug in a polymer carrier as well. Concurrently, paclitaxel was also being used in the development of drug-eluting balloons by Bruno Scheller and Ulrich Speck's team in Germany, aiming to address the issue of restenosis.[33]

The first implantation of a drug-eluting stent was a Cypher and took place in December 1999 in Sao Paulo, Brazil. The team included Eduardo Sousa and Patrick Serruys. The experience with the initial 30 patients and their 1-year follow-up without any cases of restenosis marked the beginning of a new era.[34] This was followed by the RAVEL clinical trial with 238 patients randomized to receive either a Bx Velocity or a Cypher. At 6 months, late lumen loss was 0.80 ± 0.53 mm with the Bx Velocity and −0.01 ± 0.33 mm with the Cypher ($P < .001$). Binary restenosis was 26.6% and 0%, respectively ($P < .001$).[35] In addition, the TAXUS II trial randomized 536 patients to receive either an NIR or a Taxus stent with 2 different forms of paclitaxel release (slow or moderate). At 6 months, late lumen loss on intravascular ultrasound was > 20% with NIR and < 8% with Taxus. The restenosis rate decreased from 19% to 2.3% with the slow-release Taxus stent and to 4.7% with the moderate-release stent ($P < .001$). After 1 year, events were halved, similar to the findings of the RAVEL trial.[36]

A few years after the widespread adoption of drug-eluting stents, certain data emerged that tempered the initial enthusiasm. Late thrombosis events (beyond the first month) began to be reported, raising concerns.[37] Antiproliferative drugs led to delayed endothelialization, and there were reports of local inflammatory reactions, presumably related to the polymer.[38] It was hypothesized that these reactions could explain the observed cases of late thrombosis. Subsequent pathology studies demonstrated more frequent and earlier development of neoatherosclerosis in drug-eluting stents compared with conventional stents.[39] Meta-analyses confirmed a very slight increase in the risk of thrombosis overall, with no differences in mortality, while also confirming the surprising effectiveness of the new stents.[40]

After the initial success of Cypher and Taxus, new and improved stents began emerging with advancements in drug formulation, polymer coatings, and metal platforms [41] (table 3). These innovations allowed the treatment of more complex lesions due to improved delivery systems. Stainless steel platforms gave way to chrome-cobalt and chrome-platinum alloys, enabling thinner struts that reduced vascular damage while maintaining radial strength. Open-cell designs with fewer connectors became standard among brands. Companies developed sirolimus analogs and used new, biocompatible polymers with thinner coatings on the strut surface.

Numerous head-to-head randomized clinical trials directly compared second-generation drug-eluting stents with first-generation and traditional bare-metal stents.[42] While the superiority of drug-eluting stents over bare-metal stents was generally accepted in most scenarios, demonstrating the advantages of the new generations was more challenging. From 2008 onward, several studies used optical coherence tomography to assess vascular responses to different stents. These findings were corroborated by pathological studies, which showed increased inflammatory responses and fibrin accumulation with first-generation stents[43] This generational shift led to the phased withdrawal of Cypher and Taxus, with Xience (Abbott Vascular, USA) emerging as the preferred stent due to its superior outcomes, establishing it as the best-in-class for subsequent comparisons.

LATEST ADVANCES AND BIORESORBABLE STENTS

Drug-eluting stents (1999) represented one of the major revolutions in interventional cardiology following angioplasty balloons (1977) and conventional stents (1986). Starting from the second generation, drug-eluting stents have become the gold standard due to their safety and effectiveness. Subsequent generations of stents have incorporated biodegradable polymers, eliminated polymers, or included special coatings to promote endothelialization and biocompatibility (table 4). Moreover, further advancements achieved even thinner struts. However, advances in stent coating types have not consistently demonstrated a benefit.[44] Nonetheless, some data suggest that the evolution toward ultra-thin struts may indeed offer

Table 3. First and second generation drug-eluting stents (polymer and thin struts)

Name	Company	Platform	Metal	Strut thickness	Drug	Polymer thickness
Cypher	Cordis (J&J)	Bx Velocity	Stainless steel	140 µm	Sirolimus	12.6 µm
Taxus Express	Boston Scientific	Express	Stainless steel	132 µm	Paclitaxel	16 µm
Taxus Liberté	Boston Scientific	Veriflex	Stainless steel	97 µm	Paclitaxel	16 µm
Endeavor	Medtronic	Driver	Chromium-cobalt	91 µm	Zotarolimus	4.1 µm
Resolute Onyx	Medtronic	Integrity	Nickel-chrome + platinum-iridium	81-91 µm	Zotarolimus	4.1 µm
Xience V/Promus	Abbott/Boston Scientific	Multi-link	Chromium-cobalt	81 µm	Everolimus	7.6 µm
Promus Element	Boston Scientific	Omega	Chromium-platinum	81 µm	Everolimus	6.0 µm

Table 4. Drug-eluting stents with biodegradable polymer or polymer-free

Name	Company	Metal	Strut thickness	Polymer	Drug
Biomatrix Flex	Biosensors	Stainless steel	112 µm	Yes	Biolimus A9
Biomatrix Alfa	Biosensors	Chromium-cobalt	84-88 µm	Yes	Biolimus A9
Nobori	Terumo	Stainless steel	112 µm	Yes	Biolimus A9
Ultimaster	Terumo	Chromium-cobalt	80 µm	Yes	Sirolimus
Synergy	Boston Scientific	Chromium-platinum	74-81 µm	Yes	Everolimus
Orsiro	Biotronik	Chromium-cobalt	60-80 µm	Yes	Sirolimus
Biomime	Meril	Chromium-cobalt	65 µm	Yes	Sirolimus
Supraflex Cruz	SMT	Chromium-cobalt	60 µm	Yes	Sirolimus
Coroflex ISAR Neo	Braun	Chromium-cobalt	55-65 µm	No	Sirolimus + probucol
Biofreedom	Biosensors	Stainless steel	112 µm	No	Biolimus A9
Biofreedom Ultra	Biosensors	Chromium-cobalt	84-88 µm	No	Biolimus A9
Cre8	Alvimedica	Chromium-cobalt	70-80 µm	No	Sirolimus + fatty acid

an advantage in terms of reducing the incidence of repeat revascularizations at the target lesion in the long term.[44,45] Nowadays, drug-eluting stents available in the market navigate very satisfactorily and are highly effective. The differences between various models are subtle, and the purported advantages are challenging to demonstrate. The prevalence of direct comparison studies with noninferiority designs reflects this sort of stagnation in progress.[46] Despite this, technological development continues in pursuit of improvements.[41]

Special mention goes to the concept of the bioresorbable stent, which aimed to avoid the drawbacks of leaving a permanent metal scaffold in the coronary artery. In the 1990s, Japanese engineer Keiji Igaki and interventional cardiologist Hideo Tamai developed a platform made from polylactic acid polymer with a 170 µm strut and no drug. It required heating to expand during implantation (using contrast heated to 80º C). Theoretically, the polymer was supposed to begin degrading after 6 months to 2 years, gradually losing its radial strength. Hideo Tamai implanted the first bioresorbable stent in history (the Igaki-Tamai stent, Kyoto Medical) in Japan in 1998. The initial publication reported 15 patients with a 6-month follow-up showing a 10.5% restenosis incidence per treated lesion.[47] However, a 10-year follow-up of 50 patients revealed a 28% incidence of vessel revascularization and 2.4% thrombosis.[48]

In 2006, John Ormiston implanted the first drug-eluting bioresorbable stent, the Absorb Bioresorbable Vascular Scaffold (Abbott Vascular, USA), with everolimus embedded in a polylactic acid polymer matrix and 150 µm struts.[1] Following promising data from pilot studies, the ABSORB II study was initiated, which randomized 501 patients to Absorb BVS vs Xience, aiming for superiority in vasomotor response of the treated segment (theoretical advantage of a resorbable platform) and noninferiority in terms of late lumen loss. Unfortunately, the 3-year analysis presented in 2016 showed failure to achieve either objective, with an added increase in subacute thrombosis (2.8% vs 0%; $P = .03$) and target vessel myocardial infarction (7.1% vs 1.2%; $P = .006$).[49] This was followed by unfavorable long-term results from other randomized clinical trials and meta-analyses,[50] eventually leading Abbott to withdraw its device from the market.

The first bioresorbable drug-eluting stent failed in comparisons with the gold standard Xience, which demonstrated its high reliability. Nonetheless, important lessons were learned for future progress.[51] The Absorb was a device with thick struts (150 µm vs 81 µm of the Xience), which limited its navigability, compromised the side branches even more, had worse endothelialization, and increased thrombogenicity. These issues required improvement for this stent to be more competitive. In additional, Absorb had lower radial strength than bare-metal stents, making optimal implantation

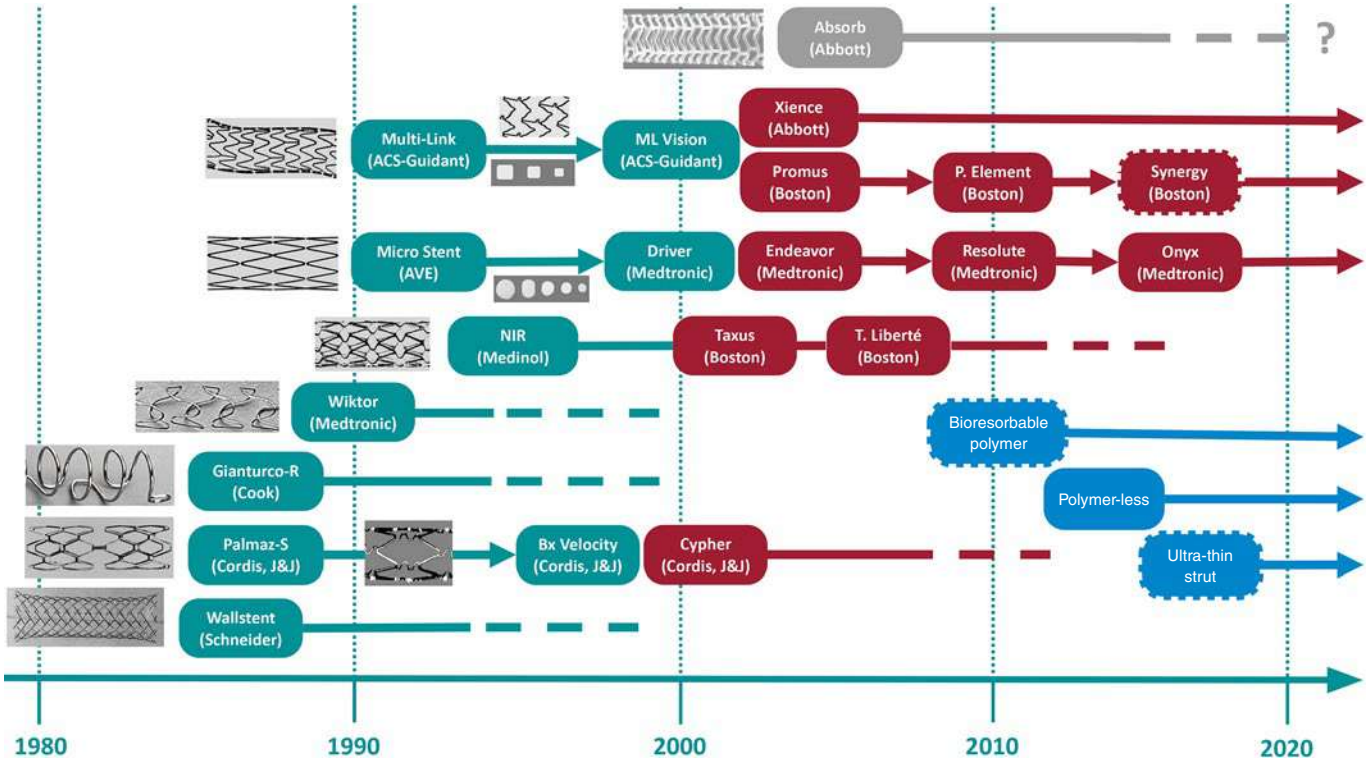

Figure 9. Timeline of milestones in the development of coronary stents. Conventional metal stents are shown in gray; drug-eluting stents in green; bioresorbable polymeric stents in blue; and new drug-eluting stents in orange. The dashed border denotes a resorbable polymer. ACS, Advanced Cardiovascular Systems; AVE, Arterial Vascular Engineering; J&J, Johnson & Johnson.

technique crucial. This included proper plaque preparation, precise vessel measurement using intracoronary imaging guidance, and high-pressure postdilation.[52] These shortcomings became evident in pragmatic postmarketing studies. This project ended partly due to the early (perhaps premature) widespread use of a first-generation device in scenarios of greater anatomical complexity, such as long lesions, small vessels, bifurcations, and even chronic occlusions,[53] which undoubtedly highlighted its disadvantages compared with the standard stent at the time.

Other companies developed bioresorbable polymer platforms,[51] but, unable to overcome the limitations of the Absorb stent, clinical experimentation in this area slowed until the development of new technological advancements. Additionally, clinical practice guidelines advised against the use of the Absorb stent outside research protocols.[54] In contrast, the sirolimus-eluting magnesium bioresorbable stent DREAMS (Biotronik AG, Switzerland) appears to offer a brighter outlook. The new generation features thinner radial struts and increased radial strength achieved by modifying the composition. Data from the first-in-man study—the BIOMAG-I trial—are also promising.[55] However, more safety data will be needed before off-protocol use of this stent is allowed. The combination of technological development and application of the lessons learned from the Absorb stent will undoubtedly provide new opportunities to use this technology in cath labs.[51]

CONCLUSIONS AND FUTURE DIRECTIONS

The invention of the stent has been one of the greatest advances in the history of cardiology and medicine in general. This article recounts the success of the collaboration between innovative minds and the biomedical industry, which invested the necessary resources to develop a much-needed therapy (figure 9). This feat also provided important lessons for research in interventional cardiology. The need to evaluate the safety and effectiveness of successive advancements quickly matured research methodologies and led to the creation of large collaborative networks. The coordination of protocols, data collection and auditing, and subsequent analysis were made possible by the hard work of dedicated researchers and significant funding from companies and academic institutions. As a result, interventional cardiology today benefits from a valuable systematic approach and infrastructure for continued innovation.

The practice of angioplasty has become highly safe and effective, largely due to the modern stent, which incorporates numerous improvements developed over its history. Today, the incidence of stent thrombosis is less than 1% in the acute, late, and very late phases.[56] Due to the safety of these devices and improvements in technique, the use of potent antithrombotic treatment is being minimized.[1] The annual incidence of stent restenosis requiring revascularization is currently 1% to 2% after implantation.[57] Although these figures are very low—considering that millions of stents are implanted annually worldwide—it remains a significant health concern from an epidemiological perspective. There are still issues requiring research attention: patients with a propensity to recurrent restenosis, calcified lesions that prevent optimal outcomes, and the deleterious effect of antiproliferative drugs on endothelial function with the consequent development of neoatherosclerosis.[41] All these challenges present opportunities for innovation in the stent industry. Moreover, the prospect of performing effective angioplasties without leaving a permanent device remains open with the development of bioresorbable stents, alongside the potential widespread use of drug-coated balloons in various clinical and anatomical scenarios where a permanent stent could pose disadvantages.[58]

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

F. Macaya-Ten: conception and design and writing of the first draft. N. Gonzalo: critical review of the manuscript. J. Escaned: critical review of the manuscript. C. Macaya: conception and design, and critical review of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Review article

The role of implant projection in optimizing transcatheter aortic valve implantation

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ABSTRACT

Severe aortic stenosis is the most frequent valve condition requiring surgery, and its incidence is increasing yearly. Transcatheter aortic valve implantation (TAVI) is the first-line treatment for patients at all levels of surgical risk. Nevertheless, modifications to the procedure often appear to improve clinical outcomes. A major concern after TAVI is the higher rate of permanent pacemaker implantation (PPMI) compared with surgical valve replacement. Optimal implantation depth is crucial to reduce the burden of PPMI without causing serious complications such as valve embolization. The classic implantation technique, where the 3 cusps are aligned in the same plane, has been modified to a cusp overlap projection by isolating the noncoronary cusp and superimposing the left and right cusps. This simple modification provides optimal visualization during deployment and helps to achieve the desired implant depth to reduce conduction disturbances and PPMI. Another limitation after TAVI is coronary reaccess due to the frame of the transcatheter valve obstructing the coronary ostia. Commissural alignment of the prostheses with the native valve may facilitate selective cannulation of the coronary arteries after this procedure. This review will discuss the techniques and supporting evidence for these modifications to the deployment and implant projection methods, and how they can improve TAVI outcomes.

Keywords: Cusp overlap projection. Commissural alignment. Transcatheter aortic valve replacement.

El papel de la proyección del implante para optimizar el implante percutáneo de válvula aórtica

RESUMEN

La estenosis aórtica grave es la valvulopatía más frecuente y su incidencia aumenta cada año. El implante percutáneo de válvula aórtica (TAVI) es la primera línea de tratamiento con cualquier riesgo quirúrgico. Una complicación frecuente del TAVI es una tasa más alta de implante de marcapasos permanente (IMPP) en comparación con la cirugía. La profundidad óptima de implante es fundamental para reducir la tasa de IMPP sin generar otras complicaciones, como la embolización de la válvula. La técnica clásica de implante, en la cual las 3 cúspides están alineadas en el mismo plano, se ha modificado a una proyección de superposición de cúspides, aislando la cúspide no coronaria y superponiendo la izquierda y la derecha. Esta modificación proporciona una visualización óptima durante el despliegue y facilita obtener la profundidad deseada para reducir la tasa de IMPP. Otra limitación del TAVI es el reacceso coronario debido a la obstrucción de la válvula a los *ostium* coronarios. La alineación comisural de la prótesis con la válvula nativa facilita la canulación selectiva de las coronarias después del procedimiento. En la presente revisión se comentan las técnicas y la evidencia sobre estas modificaciones de la técnica de liberación e implante, y cómo pueden mejorar el TAVI.

Palabras clave: Alineamiento comisural. Proyección de superposición de cúspides. Recambio valvular aórtico percutáneo.

Abbreviations

CAD: coronary artery disease. **COP:** cusp overlap projection. **ID:** implantation depth. **PPMI:** permanent pacemaker implantation. **TAVI:** transcatheter aortic valve implantation. **THV:** transcatheter heart valve.

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INTRODUCTION

Severe symptomatic aortic stenosis (SAS) is the most frequent valve disease in Europe and North America. This disease has been diagnosed in over 7 million patients and accounts for up to 40% of all native valve interventions.[1] The absolute number of aortic valve interventions has steadily increased yearly, mainly due to the large number of new diagnoses in the aging population. Some projections estimate that the number of significant valve diseases will double by 2050.[2]

The treatment of SAS used to require open heart surgery. However, since the first implant in 2002 and its European approval in 2007, transcatheter aortic valve implantation (TAVI) has transformed the landscape, offering a less invasive treatment for SAS.[3] TAVI was initially restricted to inoperable patients but since the Partner 3[4] trial in low-risk patients and SURTAVI[5] trial in intermediate-risk patients, it has become the first-line treatment for patients at all levels of surgical risk. The latest European guidelines favor transfemoral TAVI as the treatment choice in patients older than 75 years.[4] Moreover, some studies have reported cost-effectiveness analyses favoring TAVI over surgical aortic valve replacement (SAVR),[5] while early discharge and outpatient protocols have proven safe, with encouraging results.[6] From 2019 to 2021, the number TAVI procedures increased in Spain from 90 to 120 per million people.[7] Given this trend, the absolute number of TAVI procedures in both younger and older patients is expected to rise in the coming years.

Considering that the indication for TAVI has been extended, several key aspects may warrant further investigation and might discourage the use of this procedure. First, up to 50% of TAVI patients have significant coronary artery disease (CAD). Since implants are being performed in younger patients with longer life expectancy, it is expected that a large number will develop significant CAD, requiring coronary angiography and treatment.[8] Coronary artery catheterization in patients with a transcatheter heart valve is complex since the prosthesis creates a direct obstacle to the arteries to be engaged. Consequently, strategies to facilitate coronary procedures after TAVI are essential.

Second, compared with SAVR, the number of permanent pacemaker implantations (PPMI) is higher, with rates of up to 17.4% for self-expanding valves and 6.5% for balloon-expandable valves.[9,10] Recent registries report a PPMI rate of 11.3% for all TAVI procedures. Patients requiring a PPMI after TAVI have worse clinical outcomes, longer hospitalizations, and higher mortality rates during follow-up.[11]

To mitigate these risks, newer-generation valves are being developed and special considerations during preprocedural planning and transcatheter heart valve (THV) have emerged. These advancements will be discussed in the following review.

OPTIMAL IMPLANTATION DEPTH

There has been much discussion regarding the optimal implantation depth (ID), particularly its effect on valve performance and ability to modify other clinical endpoints. High THV implantation may lead to dreaded complications, such as valve embolization, coronary obstruction, and paravalvular leak (PVL). Conversely, deep vale implantation increases the risk of PPMI, PVL, and impaired mitral valve function. Therefore, ensuring optimal ID is essential to obtain better results (figure 1).[12]

One of the main reasons ID produces conduction disturbances is its interaction with the membranous septum, a fibrous structure of the interventricular septum located at the base of the triangle of Koch. The conduction system travels within the membranous septum and continues as the left bundle branch superficially as it reaches the muscular septum. This is why left bundle branch block (LBBB) is the most common conduction disturbance after TAVI, depending on the length of the membranous septum and THV depth. An optimal ID has been proven to minimize membranous septum interaction, conduction disturbances, and PPMI rates.[13]

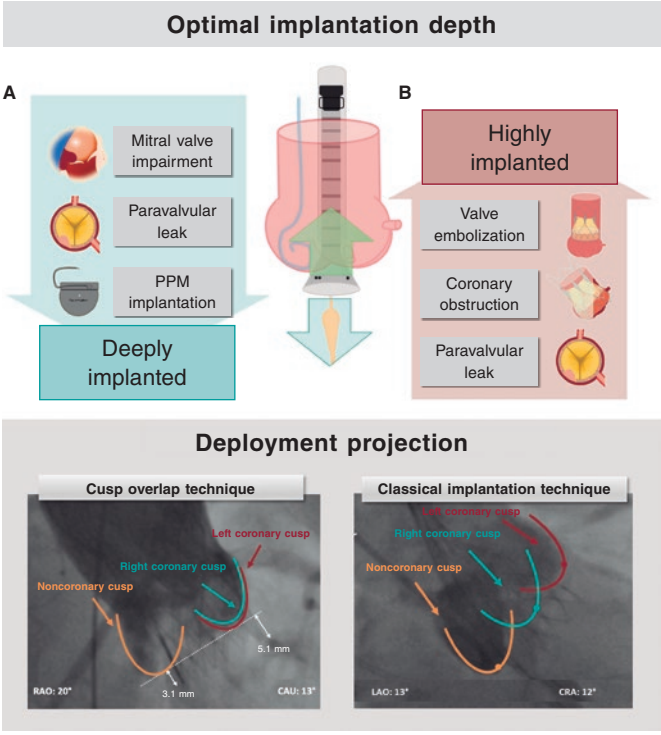

Figure 1. A: achieving optimal implantation depth is fundamental to improving outcomes. A deeply implanted valve may impair mitral valve function, produce paravalvular leaks, and interact with the conduction system, increasing permanent pacemaker rates. In contrast, high valve implantation may produce coronary obstruction, valve embolization, and paravalvular leak. **B:** cusp overlap projection where the left and right cusp overlap on the right side of the screen, isolating the noncoronary cusp, has been shown to optimize implantation depth. CAU, caudal; CRA, cranial; PPM, permanent pacemaker; RAO, right anterior oblique.

DOUBLE S CURVE

The classic implantation technique, which aligns the 3 cusps in the same plane, usually results in the delivery system being foreshortened and eliminates parallax, which deviates the prosthesis from the annular plane. A double S-shaped curve consisting of the intersection point where the annulus and the delivery system are in the optimal position may facilitate a more controlled deployment of the THV.

In a study by Ben-Shoshan et al.,[14] 100 patients underwent TAVI, which was deployed using the double S curve model with the Medtronic self-expanding valve. More than 80% of the patients had a double S curve in the right anterior oblique and caudal quadrant. The authors reported procedural success in 98% of the patients, and the rates of PPMI and other complications were similar to those described in previous studies. They also specified that they did not intend a higher ID. Therefore, PPMI rates were similar to those in previous studies in patients at the same risk. This technique has

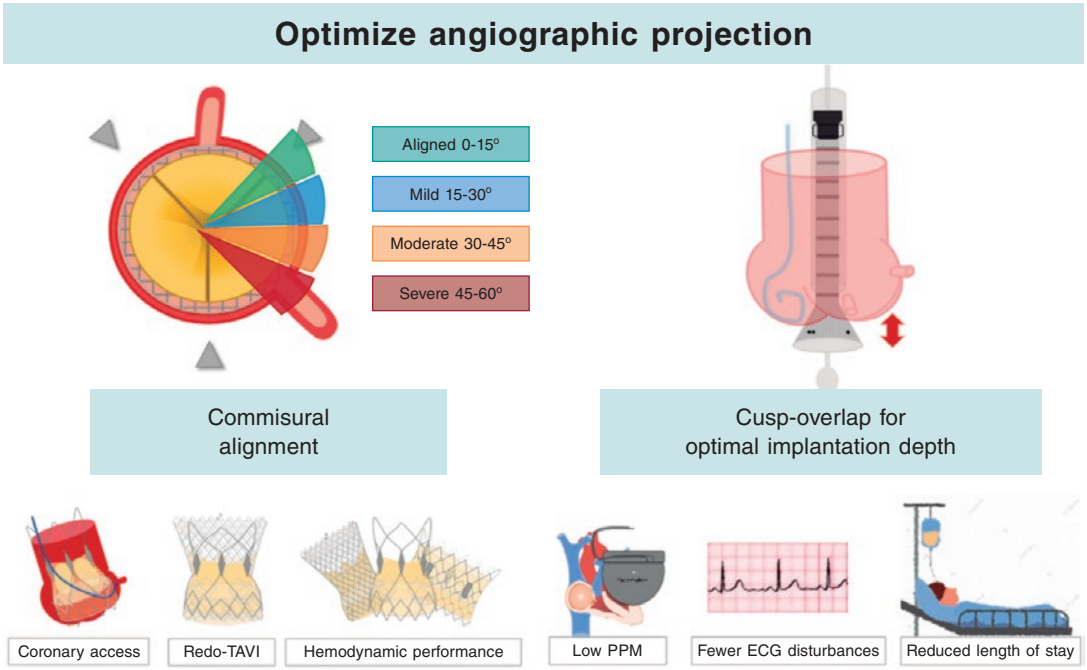

Figure 2. Central illustration. Minor modifications during deployment can achieve commissural alignment (left side of the panel), facilitate coronary access in future procedures, reduce the burden of coronary occlusion in redo-TAVI, and improve valve hemodynamics. A cusp overlap projection (right side of the panel) can improve the implanter's view to help optimize implantation depth, reduce conduction disturbances and permanent pacemaker rates, and subsequently improve outcomes and length of stay. ECG, electrocardiogram; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation.

not been widely adopted because the S curve requires intraprocedural image analysis, which is not available in all centers.[14]

CUSP OVERLAP

The cusp overlap projection (COP) technique was proposed by Tang et al.[15] to optimize the implantation of self-expanding THV using the classic implantation technique (CIT) by overlapping the left coronary cusp and the right coronary cusp, thereby isolating the noncoronary cusp. The angulation required during implantation is predicted by multislice computed tomography (MSCT). This view offers several benefits: it elongates the outflow tract and overlaps the right coronary cusp and left coronary cusp (LCC) along the basal plane of the annulus, isolates the noncoronary cusp (NCC), and centers the right noncommissure in the center of the fluoroscopic view. This allows more controlled deployment, achieving a higher ID.[15] Compared with the double S curve, COP was highly concordant in over 80% of the patients, reducing the need for intraprocedural imaging (figure 1).[14]

A simplified summary of the COP technique is as follows: *a)* a preprocedural MSCT isolates the NCC and overlaps the right and left cusps. In most patients, this results in a right anterior oblique/caudal view; *b)* a high-support wire, such as a Safari (Boston Scientific, USA) or a double-curved Lunderquist (Cook Medical, USA), maintains the position during deployment; *c)* a pigtail catheter is placed in the NCC, and deployment begins by positioning the ring marker in the mid-portion of the pigtail (in the case of the latest Evolut FX [Medtronic Inc, USA] valve, in the lowest portion of the pigtail) to achieve an ID of approximately 3 mm; *d)* when the valve reaches 80% deployment, parallax is eliminated in a left anterior oblique view for depth assessment. The valve should be recaptured and repositioned if the ID is < 1 mm or > 5 mm; and *e)* if the inflow portion of the valve is infra-annular, the valve is slowly released from the delivery catheter (figure 2).[16]

SELF-EXPANDING VALVES

Evolut R, Evolut PRO, Evolut PRO+ and Evolut FX from Medtronic Inc, United States

Most of the available literature on the COP technique has focused on the Medtronic self-expanding valve. In a single-center experience, Pascual et al.[17] evaluated COP with the Evolut R and PRO valves. This center modified all implants from the CIT to COP and compared 226 patients, with 113 in each arm. The results showed that, in patients in the COP group, implant depth was 1 mm lower (4.8 mm ± 2.2 vs 5.7 mm ± 3.1; P =.011) and the PPMI rate decreased from 23% to 12.4% (odds ratio: 0.45; 95% confidence interval [95%CI], 0.21-0.97; P =.043).[17] Although the sample size in this single-center study was relatively small, similar results were obtained in a second analysis involving 2 high-volume centers with a propensity score-matched analysis of 444 patients (175 in the COP group). The analysis demonstrated a mean depth reduction of 1 mm (4.2 mm vs 5.3 mm; P < .001) and lower PPMI rates in the first 30 days (11.8% vs 21.7%; P = .03; relative risk: 0.54; 95%CI, 0.32-0.91) with a similar incidence of other complications.[18] This latter study included patients with the newer Evolut PRO+ generation.

In a 3-center experience, Mendiz et al.[19] analyzed new LBBB and PPMI rates in 257 patients (101 in the COP group). The rates were lower for the COP group, with 12.9% vs 5.8% (P = .05) for new LBBB and 17.8% vs 6.4% (P = .004) for PPMI. Similarly, Maier et al.[20] recruited 759 patients in a single-center from 2016 to 2021 and used a propensity score analysis. The results mirrored those previously mentioned, with a PPMI rate of 8.0% for the COP group vs 16.8% for the CIT (P = .028) and fewer conduction disturbances. Even more interesting is that the reduced PPMI rates led to shorter hospital stay in the COP group (8.4 ± 4.0 vs 10.3 ± 6.7 days; P = .007). A study by Ochiai et al.[21] included 258 patients from 2017 to 2022. Using the COP technique, these authors aimed for a higher ID. New-onset LBBB was numerically lower (4.2% vs 11.3%), and

PPMI rates were significantly lower in patients undergoing COP (0.0% vs 10.8%; $P = .02$).

The newest valve generation from Medtronic (Evolut FX) was designed to improve deliverability, trackability, and deployment accuracy. Merdler et al.[22] included 200 consecutive patients in their study; the first 100 received the Evolut PRO+ while the remaining 100 received the Evolut FX. No significant differences were found in PPMI rates (12% vs 9%; $P = .21$) and clinical outcomes were similar. Another series showed a reduction in PPMI rates from 11.2% to 7% in the first 43 patients, although this difference was not statistically significant ($P = .25$). Given these results and the modifications made to the valve, it is expected that the benefits of the COP technique will be maintained with the latest generation of valves. Therefore, best practice supports the use of the COP technique for this generation as well.[23]

In a meta-analysis including 11 studies with 1464 patients in the COP group and 1743 in the CIT group, the odds ratio for PPMI was 0.48 (95%CI, 0.33-0.70), achieving a higher ID with a mean difference of almost 1 mm (0.83; 95%CI, 1.2 to −0.45; $P < .001$). No statistically differences were found in new rates of LBBB, and similar complication rates were observed for moderate/severe PVL, valve dislocation, need for a second THV, 30-day mortality, stroke, conversion to surgery, coronary obstruction, and post-TAVI mean gradients (mmHg).[24] However, this meta-analysis did not include the most extensive analysis to date by Wieneman et al.[25] These authors recruited 2209 patients from 2016 to 2022, with 1151 patients undergoing the COP technique. The rates of PPMI (17.0% vs 12.3%; $P = .002$) and PVL (4.6% vs 2.4%; $P = .006$) were significantly lower in the COP cohort.

The only prospective analysis currently underway is the Optimize PRO study (NCT04091048), a nonrandomized analysis comparing the safety and efficacy of COP using the Evolut PRO and Evolut PRO+ valves. Preliminary data have been reported by Grubb et al.[26] Among 400 attempted implants, the PPMI rate was 9.8% and decreased to 5.8% if 4 critical steps from the COP protocol were met.[26] The 30-day complication rates were also low, with an all-cause mortality of 0.8%, disabling stroke of 0.7%, hospital readmission of 10.1%, cardiovascular rehospitalization of 6.1%, and no instances of moderate or severe aortic regurgitation at discharge. These promising results should to be confirmed when the final results are published.

Acurate Neo2

Kim et al.[27] compared 901 TAVI procedures using the self-expanding Acurate Neo 2 (Boston Scientific Corporation, United States) valve: 631 using the CIT and 270 with the COP technique. There were no significant differences in the primary combined outcome of PPMI, new-onset LBBB, technical failure, and ≥ moderate PVL (23.1% vs 21.5%; $P = .586$). When PPMI rates were analyzed separately, they were similar among groups (CIT7.3% vs COP 6.3%; $P = .592$) with no differences in ID. The authors point out that initial anchoring of the upper crown limits repositioning of the valve, and ID is not affected by COP. Nevertheless, the projection proved safe and feasible for this valve, and the complication rates were similar for the 2 techniques. To document commissural alignment during the procedure, Meduri et al.[28] used the COP view to confirm that the THV was positioned correctly. Therefore, it is arguably a better projection for this valve since it is equivalent in most aspects but can favor commissural alignment.

Portico and Navitor valves

The Portico valve (Abbott Cardiovascular, United States) with the second-generation FlexNav delivery system was tested in 3 tertiary centers. A total of 85 patients undergoing transfemoral TAVI were recruited, 42 with the COP view. The target depth was 3 to 5 mm from the NCC to the inflow of the heart valve frame. The primary endpoints were ID and a combination of new-onset LBBB and PPMI. COP was associated with a higher ID (4.9mm vs 7.4mm; $P = .005$) and a lower rate of the combined outcome (31.0% vs 58.1%; $P = .012$). However, when the endpoints were analyzed separately, there was only a tendency toward fewer PPMI (14.3% vs 30.2%; $P = .078$).[29] Despite the similarities between the Portico and the Evolut valves, they seems to be a different impact on conduction disturbances while achieving a higher ID. These differences may be explained by the opening force and distribution of the radial force, with lower overall PPMI rates for the Portico system (13.5% vs 19%).[30]

A larger trial by Wang et al.[31] included the Portico valve and its newest generation, the Navitor valve. These authors compared 366 patients and compared deployment using COP vs the standard 3-cusp coplanar projection. They analyzed 183 pairs in a propensity score-matched analysis. The PPMI rate was 12.6% in the COP group vs 18% in the CIT group, but this difference was not statistically significant ($P = .15$). However, like other self-expanding valves, commissural alignment was obtained in the COP projection, and the complication rate was similar in the 2 groups. It is worth noting that after matching, the Portico valve was used in 183 patients in the CIT group, whereas the newest generation Navitor valve was used in 183 of the COP group.

BALLOON-EXPANDABLE VALVES

While cusp overlap was initially developed for self-expanding valves due to the asymmetrical nature of their deployment, Sammour et al.[32] applied the same principles to the Sapien 3 valve (Edwards Lifesciences, United States) using the double S curve and COP technique. In most patients, a right anterior oblique/caudal projection will isolate the NCC and overlap the LCC and right coronary cusp. Following this concept, they developed a high-deployment technique (HDT): the valve is deployed in a right anterior oblique/caudal view, and the parallax of the crimped valve is eliminated. Then, the valve is positioned by aligning the radiolucent line of the crimped valve at the base of the NCC. Finally, a flush catheter is located at the base of the NCC as a marker for the deployment aortogram to confirm stent coverage. The authors recruited 622 patients (60.5%) for conventional deployment, while HDT was used in 406 patients (39.5%). ID was significantly shallower with HDT (1.5 vs 3.2 mm; $P < .001$). The rates of PPMI (5.5% vs 13.1%; $P < .001$), complete heart block (3.5% vs 11.2%; $P < .001$), and LBBB (5.3% vs 12.2%; $P < .001$) were lower with HDT. Multivariable logistic regression showed that HDT was an independent predictor for 30-day PPMI (OR, 0.439; 95%CI, 0.246–0.781; $P = .005$). Complication rates were similar, with 1 case of valve embolization and no cases of coronary obstruction.

The aforementioned study by Ochiai et al.[21] included 258 patients with Sapien 3 THV, 108 with HDT, and 150 with conventional deployment. The results were similar to those of Sammour et al., with fewer conduction disturbances. However, PPMI rates were low in both groups, occurring in only around 2% of the patients. The position of the coronary ostia relative to the THV was assessed using post-TAVI MSCT. There were no differences in the interference of the THV skirt with the coronary ostia. Conversely, the incidence of interference of the stent frame with access to the coronary ostia was significantly higher in the HDT group (97.2% vs 89.3%; $P = .02$).

The most recent analysis by Stephan et al.[33] recruited 280 patients undergoing transfemoral TAVI with the Sapien 3 valve. The authors

used the COP technique in 143 patients, resulting in significantly higher IDs. However, there were no significant differences in new-onset LBBB. Although PPMI rates were numerically lower (7.3% vs 4.9%), the difference was not statistically significant (P = .464).

The evidence on a higher ID for balloon-expandable valves is contradictory. Some studies suggest a reduction in PPMI and conduction disturbances, while more recent analyses show equipoise between HDT and the CIT. However, in most cases, there is at least a tendency toward fewer PPMI, low complication rates, and high success rates with HDT. More extensive prospective studies are warranted to accurately determine outcomes with HDT in this type of prosthesis.

DRAWBACKS OF CUSP OVERLAP AND HIGHER IMPLANTATION DEPTH

The COP is a safe and feasible technique that requires minimal modifications to the standard procedure for most commercially available THVs. This projection facilitates commissural alignment and provides better visual orientation to obtain an optimal ID, reducing conduction disturbances and PPMI. Although most studies have not reported significant differences in complication rates, several considerations must be taken into account. Valve embolization is a potentially severe complication with a risk of < 1%. Operators must be skillful and resourceful in managing this complication by positioning the valve safely in the aorta while preparing a second THV for deployment. In patients with a lower calcium burden and without prior conduction disturbances, which may be the case for younger patients, the benefit of a higher ID must be weighed against the risk of valve embolization. Another risk of a higher ID is that it could hamper proper cannulation of the coronary arteries during subsequent interventions.

Second, a higher ID may complicate coronary access and has been identified as a predictor of unsuccessful cannulation. Although this risk may be mitigated by commissural alignment, there is a potential risk that high valve implantation will cause obstruction of the coronary ostia, where a pericardial skirt covers the inflow of the frame. This poses a risk of occluding native arteries. Furthermore, in younger patients, who may require a valve-in-valve TAVI procedure in the future, high deployment may preclude a second procedure because the leaflets of the first valve could create a neoskirt that potentially obstructs the coronary ostia.[35]

In addition, patients with previous aortic valve replacement have a lower risk of PPMI after redo-TAVI but a significantly higher risk of coronary obstruction, especially those with narrow sinuses of Valsalva and lower coronary ostia. In these patients, aiming for a higher ID may not enhance outcomes.

COMMISSURAL ALIGNMENT

One of the main concerns in expanding the indication of TAVI to younger and low-risk patients is the feasibility of coronary access post-TAVI, mainly due to the potential need for percutaneous coronary intervention. This underscores the practical importance of achieving commissural alignment (CA). Additionally, considerations of durability and the potential for redo-TAVI are crucial when contemplating the expansion of indications to younger patients.[35]

The concept of CA has gained prominence in recent years, leading to improvements in the design of the newest valve generations to facilitate its achievement.[35] MSCT data from studies without intentional CA technique show that approximately 80% of patients undergoing TAVI experience commissural misalignment.[36] In low-risk patients who underwent balloon-expandable TAVI, approximately 13% had a commissural post obstructing the coronary ostium. Commissural misalignment is as high as 16% with self-expanding TAVI.[37] In the RE-ACCESS study, Barbanti et al.[38] showed that only 7.7% of patients underwent unsuccessful coronary cannulation after TAVI.

The ALIGN-TAVI consortium defined CA based on the angle between the native and new valve commissures. The definition of CA was established among different categories: aligned (angle deviation < 15°), mild commissural misalignment (CMA) (15°-30°), moderate CMA (30°-45°), and severe CMA (> 45°) (figure 3).[39]

Commissural alignment in self-expanding valves

Evolut R, Evolut PRO, Evolut PRO+, Evolut FX Medtronic valves

The optimal technique for CA starts with a preprocedural MSCT analysis to select a patient-specific fluoroscopic projection. The most commonly used technique for the Medtronic self-expanding valve begins with the flush port positioned at 3 o'clock. The hat marker band must be placed toward the outer curvature when the valve is advanced in the descending aorta. During deployment, the gantry must be placed in the COP, with the left and right commissures of the THV appearing on the right side of the screen and the hat marker facing the NCC (in some cases, it may face center front). In the newest generation Evolut FX valve, there are 3 markers in the inflow portion of the skirt of the valve, corresponding to each commissure. These marks enhance the fluoroscopic view and are associated with fewer cases of CMA (figure 3).[39]

ACURATE neo2

The technique for CA in the ACURATE neo2 platform varies. The insertion must be made with the flush port positioned at 6 o'clock. The THV has 3 radiopaque posts that mark each commissure. Correct CA can be ensured with fluoroscopy by torquing the delivery catheter counterclockwise. In the COP, 2 posts should overlap in the major curvature of the aorta and the last post on the lesser curvature. Using the CIT, one post should be viewed in the middle of the aortic annulus and the other 2 on each side (figure 3).[40,41]

Commissural alignment in balloon-expandable valves

There is very little reliable evidence on the topic, but extended methods exist to obtain CA with balloon-expandable THV. A small study by Santos-Martínez et al.[42] evaluated the feasibility of CA with the Myval THV (Meril Life Sciences Pvt. Ltd, India). A preprocedural MSCT-simulated TAVI in a silico model predicted the optimal rotation of the valve for achieving CA using a self-developed script. The Myval devices were then crimped in the rotation predicted by the silico model to avoid CMA. This strategy was tested in 10 patients, with only 4 showing minor CMA and none showing moderate-severe CMA. The mean CMA angle was 16.7°. Although the results are promising, the need for a silico model before the procedure limits the usage of this technique.

CORONARY REACCESS

Recent studies on coronary reaccess after TAVI in patients without CA have shown that the rate of unsuccessful selective coronary reengagement is approximately 7.7%.[38] Tarantini et al.[43] compared Sapien valves with aligned and nonaligned supra-annular

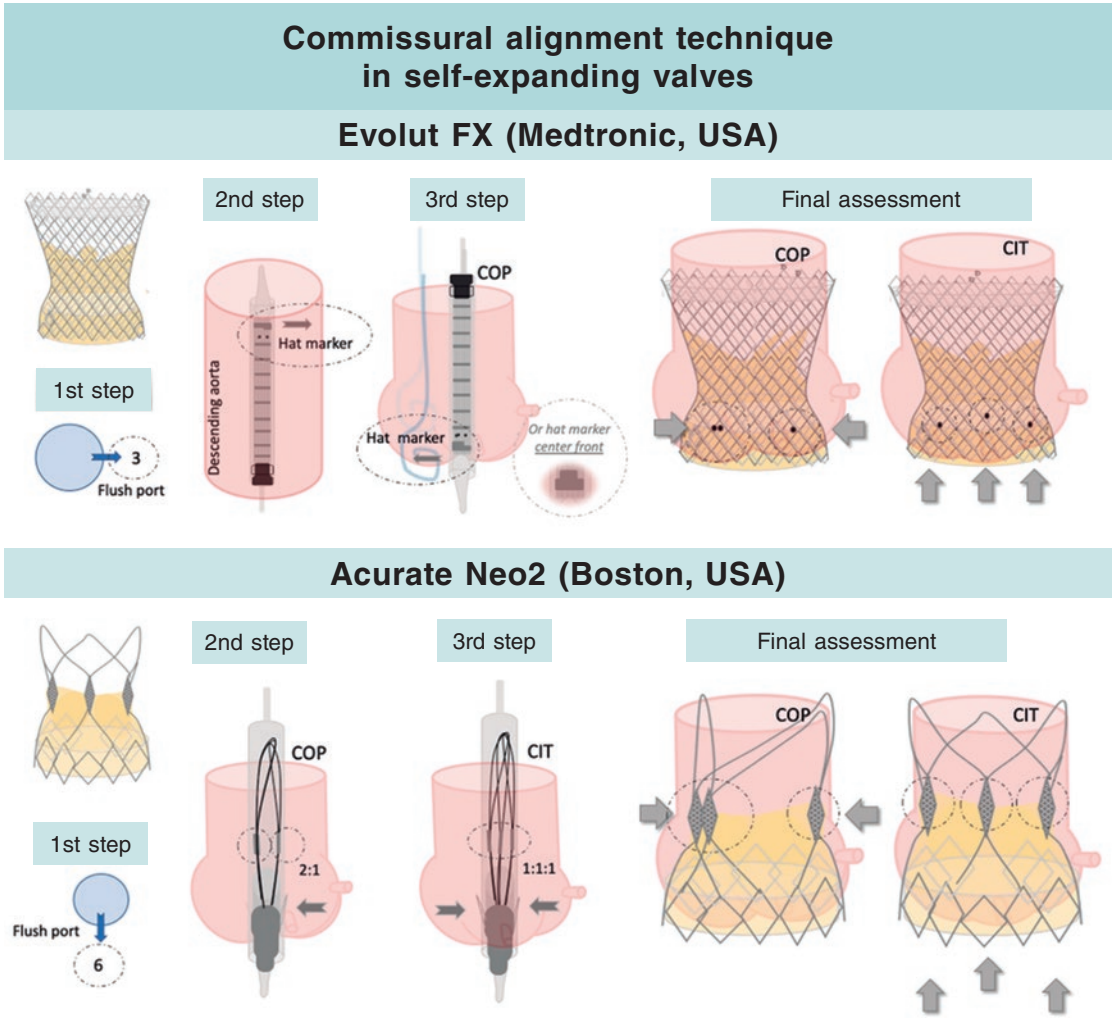

Figure 3. Step-by-step tutorial for commissural alignment in self-expanding valves. **A:** Evolut FX valve. First, the flush port is positioned at 3 o'clock. The hat marker band must be placed toward the outer curvature when advancing the valve in the descending aorta. Second, during deployment, the hat marker faces the NCC. Finally, 2 of the radiopaque markers of the Evolut FX valve should be viewed on the left side of the screen and the other marker on the right. **B:** Acurate Neo2 valve. First, insert the valve with the flush port positioned to 6 o'clock. Second, torque the delivery catheter counterclockwise. Finally, during valve deployment, 2 radiopaque posts should be viewed in the major curve of the aorta and 1 on the other side. Using the classic implantation technique, 1 post should be viewed in the middle of the aortic annulus and the other 2 on each side. CIT, classic implantation technique; COP, cusp overlapping projection.

self-expanding valves (Evolut R/PRO and ACURATE Neo). These authors found that only 5% of patients receiving Sapien 3 valves had nonselective coronary access, and no patients had unfeasible coronary access. However, with self-expanding THVs, the group undergoing the nonaligned commissural technique showed a 43% rate of nonselective access, and 11% had unfeasible access. Conversely, in the group with CA, only 3% had unfeasible access, while 26% had nonselective access.[43]

The most frequent predictors of unsuccessful coronary access are patient anatomy (narrow sinus of Valsalva), THV type (self-expanding valves), and TAVI technique (higher ID). Regarding patient anatomy, cusp symmetry and coronary ostial eccentricity are fundamental in predicting the feasibility of CA and potential coronary reaccess.[38] Despite the achievement of commissural alignment, some patients show coronary eccentricity or cusp asymmetry, in which commissural alignment does not prevent obstruction of the coronary ostium by the THV post. This is most frequently observed in patients with bicuspid valves. Consequently, the concept of coronary alignment has emerged (figure 4).

In a study evaluating 1851 computed tomography scans of patients undergoing TAVI evaluation, virtual valves were placed, simulating CA and coronary alignment in the aortic root to evaluate moderate and severe coronary overlap from the THV post. The findings revealed that severe CMA is rare when CA is used and that coronary alignment only improved the right ostium overlap (coronary 0.52% left, 0.52% right; commissural 0.30% left, 3.27% right). The incidence of no overlap with the left coronary ostium was lower in the CA group than in the coronary alignment group. This was due to the higher prevalence of eccentricity of the right coronary ostium; intentional alignment with the right coronary ostium may increase the risk of overlap with the left coronary ostium. The prevalence of coronary asymmetry and eccentricity was low.[44]

VALVE HEMODYNAMICS: PERFORMANCE AND DURABILITY

Better hemodynamic results are important, as the indications for TAVI are broadened to include low-risk and younger patients. Fuch et al.[45] compared surgical aortic valves with TAVI and conducted a

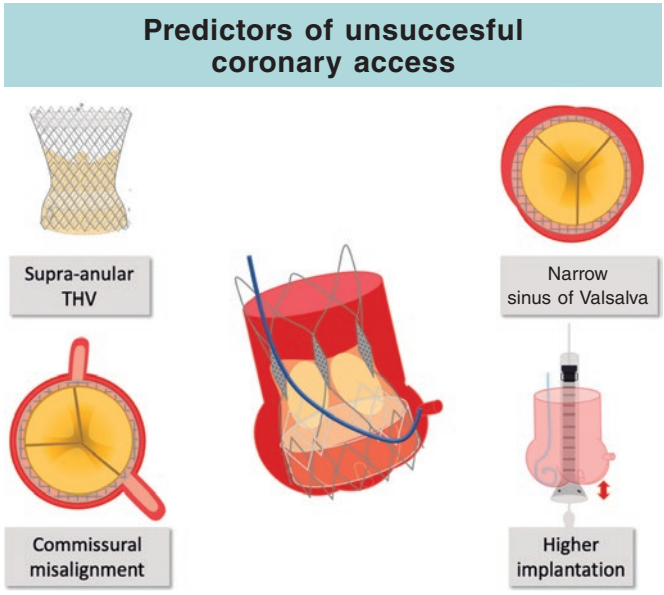

Figure 4. Major predictors of impaired coronary reaccess. THV, transcatheter heart valve.

computed tomography (CT) study after TAVI. These authors divided the participants into groups based on CA and observed no differences in transvalvular gradients, coronary filling, or PVL. However, they showed a significant increase in central aortic regurgitation.

A retrospective study included 324 patients who underwent random implantation of a balloon-expandable THV. Post-TAVI MSCT was performed to define CMA as deviations of more than 30°. Among these patients, CMA was present in 52.8%. At the 30-day analysis, there were no differences among patients with and without CMA regarding aortic regurgitation rates, transvalvular gradients, or significant residual gradients. Similarly, the incidence of PPMI and long-term clinical outcomes—including death and stroke—did not vary between the 2 groups.[46]

CMA has been associated with changes in flow patterns and increased leaflet stress, leading to an increased risk of leaflet thrombosis. Consequently, detection of hypo-attenuated leaflet thickening (HALT) in CT studies has gained attention in recent studies, as it is a marker of subclinical leaflet thrombosis and may predict valve durability.[39] A case-control study comparing CA in patients with and without HALT (85 patients per group) showed that severe CMA was present in 32% of the patients with HALT and in only 17.2% of those without HALT.[47]

REDO-TAVI

The indications for TAVI have expanded, particularly in low-risk and younger patients. However, data on TAVI-in-TAVI procedures are scarce. According to the landmark analysis of the EXPLANTORREDO-TAVR registry, 30-day and 1-year mortality were lower in redo-TAVI patients, with no differences in mortality at 4 years. Arguably, SAVR will be reserved for specific situations, such as PVL or unfavorable anatomy for redo-TAVI, whereas TAVI-in-TAVI will grow exponentially in the coming years.[48]

The main problem with redo-TAVI is the risk of coronary occlusion and the potential difficulty of coronary reaccess after the procedure. Predictive models based on CT studies suggest a higher risk of coronary occlusion in patients without CA. Buzzati et al.[49] reported that 10% to 20% of redo-TAVI procedures carry an increased risk of coronary occlusion, and more than 50% have impaired coronary access. Another study using CT data post-TAVI with Evolut and Sapien valves predicted that 45.5% of Evolut patients and 2% of Sapien patients were at risk of coronary obstruction due to sinus sequestration. The risk was predicted based on the distance between the valves and the sinotubular junction.[21]

Experience with valve-in-valve procedures is derived from THVs implanted within previously placed surgical valves with CA. Conversely, most degenerated THVs were implanted without accounting for CA. Aggressive techniques like BASILICA, which enable leaflet modification to reduce the risk of coronary obstruction, are less effective than those performed in surgical valves.[22]

CONCLUSIONS

In summary, the role of implant projection in optimizing TAVI can help reduce the most common drawbacks of this procedure. There is abundant evidence supporting the potential benefits of the COP technique in reducing conduction disturbances and PPMI by making a small modification during deployment without increasing the risks compared with the CIT.

The risk of conduction disturbances and PPMI is a significant obstacle after TAVI. Careful MSCT evaluation and preprocedural planning are required to select the correct strategy for each patient. Ultimately, the risk-benefit of a higher ID using the COP technique should be tailored to patient-specific characteristics. The technique should be favored in patients at high risk for PPMI and discouraged in those at high risk of coronary obstruction and a higher burden of coronary disease. However, in most patients, especially when self-expanding valves are used, it should be classified as the standard deployment projection.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Debate: ECMO in patients with cardiogenic shock due to myocardial infarction. A researcher's perspective

A debate: El ECMO en pacientes con shock *cardiogénico por infarto de miocardio. Perspectiva del investigador*

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Acute myocardial infarction-related cardiogenic shock (AMI-CS) carries a dismal prognosis. Short-term mortality is in the range of 40% to 50%.[1] Until recently, only percutaneous coronary intervention of the culprit lesion reduced mortality within randomized controlled trials (RCT).[1] More recently, the active microaxial flow pump showed a mortality reduction at 6-month follow-up in the Danish German Shock trial (DanGer-Shock).[2] However, this RCT was performed in a highly selected group of patients with ST-elevation myocardial infarction only and excluded patients with possible hypoxic brain injury.[2] In addition, it remains unclear whether the positive results were influenced by: *a)* device design (loading vs unloading of the left ventricle), *b)* patient selection, and *c)* treatment bias.[3] High expectations have also been placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO), and its use has risen exponentially by up to 40 times in the last decade despite a lack of relevant evidence from RCTs.[4]

In contrast to microaxial flow pumps, the concept of VA-ECMO is to provide temporary complete circulatory and respiratory support during the critical first days as a bridge-to-recovery, bridge-to-decision, bridge-to-durable left ventricular assist device (LVAD), or bridge-to-transplantation.

Question: What evidence exists for the use of ECMO in cardiogenic shock due to a myocardial infarction?

Answer: The evidence is relatively robust and is discussed in more detail below.

- Evidence regarding efficacy. Evidence regarding percutaneous VA-ECMO in AMI-CS is relatively robust with 4 RCTs (ECLS-SHOCK I: n = 42 patients; EURO SHOCK: n = 35; ECMO-CS: n = 117; and ECLS-SHOCK: n = 420).[5-8] The only study powered for a mortality difference is the ECLS-SHOCK trial, which included 420 randomized patients with AMI-CS.[8] By study design, the included patients had more advanced CS, as a lactate level of > 3 mmoL/L was an inclusion criterion. There was no difference in 30-day mortality (49.0% in the control group vs 47.8% in the VA-ECMO group; relative risk 0.98; 95% confidence interval [95%CI], 0.80-1.19; P = .81).[8] The neutral results in the primary endpoint were further supported by a lack of effect on secondary endpoints, such as lactate clearance, renal function, and catecholamine use and duration.

  The evidence for the lack of benefit of VA-ECMO is further supported by an individual patient data (IPD) meta-analysis incorporating results from all 4 RCTs.[9] There was no significant 30-day mortality benefit for AMI-CS patients receiving routine VA-ECMO (45.7%) in comparison with the control group (47.7%), (odds ratio [OR], 0.92; 95%CI, 0.66-1.29).[9]

- Evidence regarding safety. VA-ECMO use was associated with a 23.4% rate of moderate to severe bleeding vs 9.6% in the control group (relative risk, 2.44; 95%CI, 1.50-3.95) in ECLS-SHOCK.[8] This finding has been confirmed in the IPD meta-analysis (OR, 2.44; 95%CI, 1.56-3.84).[9] Since bleeding is known to be associated with worse outcomes,[10] these results indicate that VA-ECMO may even be harmful for those experiencing this complication.

Another typical drawback of VA-ECMO is peripheral ischemic complications. Although a high rate (> 95%) of prophylactic antegrade perfusion cannulae was applied in ECLS-SHOCK, ischemic complications occurred with an OR of 2.86 (95%CI, 1.31-6.25), which was further aggravated in the IPD meta-analysis (OR 3.53; 95%CI, 1.70-7.34).[8,9] VA-ECMO modifications to enable left ventricular (LV) unloading, such as VA-ECMO + Impella or VA-ECMO + intra-aortic balloon pump, should be further scrutinized, as despite potential benefits for LV recovery, they may increase bleeding risks even more.

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Another problem with VA-ECMO was the prolongation of mechanical ventilation time and intensive care unit stay by roughly 2 days, which may also have caused more harm than benefit.[8]

Q.: In relation to the ECLS-SHOCK trial, what are the implications of its results on clinical practice and what do you consider the possible limitations of the study in this regard?

A.: When considering the implications of VA-ECMO on clinical practice, with evidence showing no mortality benefit but higher complications, guidelines usually classify this as a Class III A recommendation, advising against the routine use of VA-ECMO. However, the limitations or gaps in the evidence need to be discussed before final conclusions can be drawn.

On the limitations of the current evidence, negative or neutral trials often trigger discussions, particularly when the results do not concur with general perceptions, ie, VA-ECMO reduces CS mortality. A typical reflex is then to argue, using registry data, that RCTs are not valid.[11]

- *Inclusion of resuscitated patients.* The high rate of patients with successful resuscitation prior to randomization (>70%) in ECLS-SHOCK may have limited the VA-ECMO results since hypoxic brain injury cannot be positively influenced by mechanical circulatory support. Shock/hypotension and elevated lactate after resuscitation may not be directly associated with prolonged decreased cardiac output to a similar extent as in CS without cardiac arrest. This patient selection may be supported by the positive results of the DanGer-Shock trial.[2] Notably, evidence for reduced cardiac output was not required in ECLS-SHOCK. As a result of the risk enhancement for inclusion, this resuscitation rate was higher than in previous RCTs in AMI-CS. Interestingly, mortality in resuscitated patients was numerically even lower than in those without resuscitation.[8] In the IPD meta-analysis, the number of resuscitated patients was lower and no benefit was observed.[9] Importantly, exclusion of resuscitated patients would lead to any trial result being less generalizable to all CS-like patients.

- *VA-ECMO timing.* Results from an observational meta-analysis for AMI-CS (IABP: n = 956; Impella: n = 203; VA-ECMO: n = 193) suggest that initiation of VA-ECMO prior to percutaneous coronary intervention reduces mortality.[12] However, this was refuted in ECLS-SHOCK and the IPD meta-analysis.[8,9]

  There are also other timing aspects to consider. In ECLS-SHOCK, VA-ECMO was started routinely after randomization. It remains unclear whether there is any clinical benefit to a watch and wait strategy and to decide for or against VA-ECMO only if there is further clinical and hemodynamic deterioration.

Q.: Is there any subgroup that may benefit from ECMO in this setting?

A.: In addition to the inclusion of resuscitated patients and timing aspects, the ECLS-SHOCK trial included patients with more advanced shock severity based on signs of tissue hypoperfusion. The SCAI shock classification was not in place at the start of the study and the definition is dynamic, which usually does not allow immediate staging.[13] The distribution of the SCAI stages was therefore made retrospectively in ECLS-SHOCK using a modified post hoc definition.[8] Some argue, therefore, that SCAI C patients were not sick enough to benefit from VA-ECMO or, in contrast, that SCAI stage E patients were in a futile situation. Irrespective of these considerations, no SCAI stage showed a benefit from VA-ECMO.

The question remains whether specific patient subgroups in AMI-CS benefit from VA-ECMO, as current guidelines do not mention patient selection.[14] Importantly, there was no signal for a survival benefit of VA-ECMO in any of the subgroups analyzed.[8,9]

Q: Do you think there is a need for a new trial on the subject?

A.: Through its mode of operation, VA-ECMO increases afterload. Multiple unloading strategies have been developed but these also increase invasiveness and possibly complications. In ECLS-SHOCK, unloading criteria were predefined, leading to a relatively low 6% rate of active unloading. However, more patients in the VA-ECMO group were treated with dobutamine, indicating medical unloading by increasing ventricular inotropy. When evaluating evidence for active unloading, it is also important to note that potential benefits were generated from retrospective observational studies only.[15,16] A recent RCT comparing routine LV unloading by a transseptal left atrial cannula vs VA-ECMO alone showed no effect on mortality.[17] This evidence suggests that further rigorous investigation is needed before the approach of using both VA-ECMO plus Impella for routine unloading can be adopted. Regarding the low use of durable LVADs or heart transplantation, in ECLS-SHOCK—similar to previous RCTs—the rate of patients receiving a durable LVAD or heart transplantation was < 2%. Advanced heart failure specialists often argue that VA-ECMO is mainly considered as a bridge-to-LVAD or transplantation and therefore that the trial was doomed to failure.[11] Patients included in RCTs in AMI-CS are often older and not eligible for such treatment strategies. In addition, many of these patients have high rates of concomitant inflammation or infections precluding these advanced therapies.

In conclusion, for the vast majority of patients with AMI-CS, routine immediate VA-ECMO should be avoided. Future RCTs should define whether any subgroup can be identified and whether treatment modifications that reduce bleeding and limb ischemia complications or routine LV unloading strategies may alter the outcomes. In addition, currently evidence is only available for AMI-CS and not other causes of CS.

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CONFLICTS OF INTEREST

None.

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Debate: ECMO in patients with cardiogenic shock due to myocardial infarction. A clinician's perspective

A debate: El ECMO en pacientes con shock *cardiogénico por infarto de miocardio. Perspectiva del clínico*

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Question: In your center, which patients with cardiogenic shock due to myocardial infarction are currently considered candidates for extracorporeal membrane oxygenation (ECMO)?

Answer: Several factors influence the decision to use an ECMO-type mechanical circulatory support device in patients admitted for acute myocardial infarction (AMI) complicated by cardiogenic shock. When we're dealing with shock, we can quantify its severity through a detailed clinical assessment and by analyzing various hemodynamic parameters. These can be easily obtained at admission using straightforward imaging techniques like echocardiography, even at the bedside. Key factors such as mean arterial pressure, lactate levels, and urine output are crucial here. ECMO support can make a real difference in these cases, acting as a bridge therapy until we can treat the underlying cause, see improvement, or until we move to long-term ventricular assist devices or heart transplantation.

However, it's important to remember that some factors cannot be modified by mechanical circulatory support devices. These include the patient's biological age, overall frailty, severe comorbidities, and the depth of coma following cardiac arrest. These elements should be assessed as objectively as possible because they play a significant role in determining the patient's overall prognosis.

In clinical practice, if we could focus purely on high hemodynamic risk, it would be reasonable to conclude that, at this point, it's difficult to justify escalating to ECMO—with all its associated complications—in patients at stage C of the SCIA (Society of Cardiovascular Angiography and Interventions) classification. This is especially true if we´ve already successfully treated the triggering cause (for example, percutaneous revascularization of an ST-segment elevation myocardial infarction). At stage C, the patient is typically stable and well-perfused on fixed doses of usually just one drug. So, why take on additional risks?

While we still have a lot to learn, ECMO can be a game-changer for patients who worsen after early first-line therapy, particularly in stages D/ E of the SCAI classification. This is especially the case when there's a delay in resolving the underlying cause or we can't correct it—like a myocardial infarction with onset more than 12 to 24 hours previously, a final Thrombolysis in Myocardial Infarction (TIMI) flow of 0-1, or no-reflow phenomena.

Finally, when we're dealing with patients in SCAI stages D/ E who've been resuscitated from cardiac arrest and are admitted in a comatose state, they're automatically at high hemodynamic and neurological risk. Given that post-anoxic encephalopathy is the leading cause of death in these patients, it wouldn't be reasonable to ignore factors related to survival with good neurological outcome (Cerebral Performance Category 1-2) when we're considering whether to escalate therapy. In these situations, our approach should probably resemble the strategies used in ECMO-assisted CPR for refractory cardiac arrest. The key here is to avoid futile interventions by sticking to strict criteria and protocols.

At our center, with our extensive experience in managing cardiac arrest and postresuscitation care, we consider ECMO implantation for patients in shock after an AMI in SCAI stages D/E, but under specific conditions. We're talking about patients whose cardiac arrest was witnessed, ideally with immediate resuscitation—or if not, with no-flow times under 5 minutes—a nontraumatic cause, and an initial shockable rhythm, especially in out-of-hospital arrests. We also pay close attention to indicators of the quality of resuscitation efforts, like initial pH levels and end-tidal CO_2. Now, if the predictors of neurological recovery are unfavorable, we usually stick to the classic approach for managing shock, at least initially. Because these patients are at high risk for postanoxic encephalopathy, we make sure our postresuscitation efforts carefully adhere to international guidelines, which currently include temperature control. But if, after the immediate period, we start to

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see signs that suggest a benefit from escalating therapy—like a return of consciousness or low suppression rates on cerebral monitoring in the first 6 to 24 hours[1]—and if the patient is still in shock at SCAI stage D/ E, we would then reopen the discussion about ECMO implantation.

As you can see, this process is much more complex and demands significantly more time and resources. Sure, it might be easier to place ECMO without considering all these factors, but what would be the point? Are we just looking at the potential for organ donation?

So, to sum up, at our center, we take a case-by-case approach to patient selection. We reserve ECMO for those who don't respond significantly and rapidly to shock treatment—like primary angioplasty—in SCAI stages D/E, and who don't have other short-term poor prognostic factors.

Q: Has your strategy changed after the results of the ECLS-SHOCK trial?[2]

A: The ECLS-SHOCK trial has reinforced our routine practice. We've never been an "ECMO for all" center because ECMO isn't without its risks and certainly shouldn't be the first-line treatment for all patients with an AMI complicated by cardiogenic shock. What this study has done is push us to continue emphasizing a tailored approach through our multidisciplinary Shock Team, which has expertise in both clinical care and mechanical circulatory support. A characteristic that adds quality to our process is the team's 24/7 availability. These cases often don't follow a 9-to-5 schedule—they can occur at any time, including late at night or on nonworking days. Delays in diagnosing and treating the underlying cause or in stabilizing the patient can significantly impair outcomes. That's why, in managing cardiogenic shock after an AMI, we've been adopting strategies similar to primary angioplasty, such as aiming to achieve a less than 90-minute interval from the first medical contact to ECMO implantation.

We believe it's not just ECMO alone but the combination of all the elements involved in the decision-making and treatment process that can truly change the course in patients in shock after an AMI. An example of this is the in-hospital mortality rates reported by the National Shock Initiative in the United States, which are around 25% to 30%.[3] These numbers are much lower than the 40% to 50% 30-day mortality rates reported by many centers, even tertiary hospitals, that don't have a specific focus on managing cardiogenic shock.

Q: We would like to know your overall view on the most positive and, also, most controversial aspects of this study.

A: Just a few of the factors that make it difficult to generate evidence through randomized trials in acute cardiac care are the patients' clinical status, the cost of treatment, and the ethical implications of not offering all available resources to someone on the brink of death. Very few authors are willing to undertake such studies, and even fewer actually see them through to completion. So we really have to give credit to those who do. That said, the study in question is negative, and we need to carefully interpret the information we've got. There are several limitations that we can't ignore when evaluating its results and applying them to our routine clinical practice.

Recruiting a sample of that size for a complex disease within a reasonable timeframe sometimes requires some leeway. In fact, randomized clinical trials often end up sacrificing some of the more "clinical" aspects to ensure the studies are feasible. For instance, Thiele et al.[2] have tried to show the benefits of early and nonselective ECMO use in patients with shock after an AMI who are scheduled for revascularization. But does this really address the core question we need to answer to improve patient outcomes? Are all patients truly eligible for ECMO?

In my opinion, this "ECMO for all" mindset goes against all the work we've been doing for years to identify the patients who might benefit the most from ventricular assist devices. Why have we developed so many concepts related to etiology, phenotypes, metabolism, risk stratification scales, and modifying factors? What's the point of having Cardiac Shock Centers—those top-tier facilities with the best resources and expertise—unless it's to improve the care of these patients? The aim of the study is, to say the least, surprising, especially considering that the lead author is part of the key working groups focused on this area.[4]

The main weaknesses of the study are that it didn't consider the type of AMI—over 40% of the patients had non-ST-elevation acute coronary syndrome. Also, half of the patients were in SCAI stage C and were still considered for ECMO, but in clinical practice, it's rare to implant ECMO in this group. Neurological death is undoubtedly a competing risk in patients who have recovered from a cardiac arrest (77.7% in this study), so it's surprising that there is only one exclusion criterion related to neurological issues (duration > 45 minutes) and that it's somewhat arbitrarily defined. Since postanoxic encephalopathy wasn't considered in patient selection, high-quality postresuscitation care should have been a priority, but it wasn't. Lastly, the high rate of vascular complications, the percentage of ventricular unloading, and the limited access of a younger population with shock after an AMI to therapies such as long-term assist devices or heart transplantation, make one wonder about the experience of the participating centers in managing these patients (47 centers were involved but included only 44 patients, with 61.4% being tertiary centers).

Q: Do you think a new study on this topic is needed?

A: Absolutely. Cardiogenic shock is still the most serious unresolved issue in the context of AMI, and circulatory support, in this case ECMO, has a very sound rationale. Even with the overall negative results of this study, we cannot stop research in this area.

The next study should avoid some of the possible causes of failure, such as by: *a)* selecting the best candidates, as patients with shock are a widely heterogeneous group; *b)* minimizing the delay time before treatment; *c)* ensuring that participating hospitals have greater experience with the technique and, possibly, better outcomes; *d)* increasing the sample size, as has been necessary in the vast majority of clinical trials that have demonstrated clear benefits and have had an impact on reducing mortality—from more than 30% in the early days of coronary care units to about 5% today, which undoubtedly requires adequate funding; *e)* reducing or avoiding crossover (in this case, more than 27% switched to ECMO or other types of support); *f)* ensuring that participation and teamwork are concentrated in a single study; and *g)* if the study selects the best candidates and shows positive results, then it would be time to consider expanding the indications. Until we get all of this right, we should avoid the widespread use of ECMO in cardiogenic shock after an AMI.

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DECLARATION ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this article.

CONFLICTS OF INTEREST

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Scientific letter

Practical concepts of catheter-directed aspiration thrombectomy in ECMO-supported patients

Aspectos prácticos de la trombectomía pulmonar mediante aspiración en pacientes soportados con ECMO

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To the Editor,

The use of extracorporeal membrane oxygenation (ECMO) circulatory support devices in patients with cardiac arrest, shock, or refractory respiratory failure due to pulmonary thromboembolism is increasingly recognized as a safe and effective therapy.[1-3] With the aim of improving the hemodynamic and respiratory status of these patients, the adjuvant use of transcatheter pulmonary thrombectomy through thrombus aspiration is increasingly common.[4-6] However, combining these two therapies requires careful consideration of technical issues to ensure procedural success and prevent additional risks.

ECMO consists of a centrifugal pump that rotates at high speed to create negative pressure in the central axis, allowing blood to be aspirated through the venous insertion cannula (figure 1 of the supplementary data). Subsequently, after passing through the ECMO, the blood is pumped through a second cannula—arterial or venous—to be reintroduced into the patient's circulatory system.

Sealing refers to the quality of a system or compartment being isolated from the rest, without transfers. Under normal conditions, the vascular system is considered sealed, with no blood losses or entries of other elements. However, its integrity is compromised if a vessel is punctured, creating a shunt with the exterior. When the puncture orifice is closed, the vascular system regains its seal either by closing the catheter or by connecting the catheter or a cannula to another closed system (such as the ECMO circuit). Thus, after cannulating the accesses and connecting them to the ECMO circuit, both the patient's vascular system and the ECMO system form a common sealed circuit, which is compromised only if openings occur at any point in the system.

Transcatheter thrombus aspiration devices consist of 1 or several usually large-bore catheters, which are inserted through a vein and guided toward the thrombotic material, usually in the main or segmental pulmonary arteries (figure 2 of the supplementary data).

Once the catheter is in position, the thrombus is removed using various techniques, such as manual or automatic aspiration, etc. During the procedure, different valves of the system usually need to be opened or even removed for device reinsertion, which may interfere with ECMO in a patient requiring combined therapy.

When thrombus aspiration is performed in a patient connected to a pump system that creates negative pressure in the venous line, various special situations should be considered to prevent complications or dysfunctions resulting from the interaction of these devices. Although veno-arterial ECMO is the most widely used system in this context, other systems that create negative pressure, such as veno-venous ECMO, may lead to similar complications, which can be prevented in the same way, as they all stem from the aspiration generated by the venous cannula. The most frequent complications are outlined below.

The most common and potentially serious complication is air embolism. When any of the valves or taps of the thrombus aspiration catheters are opened, the patient-ECMO system loses its seal. If this occurs while ECMO is running, the negative pressure created by the pump in the venous system (ideally up to −60 mmHg) generates a pressure difference with the ambient air (1 atm = 760 mmHg), leading to air movement or aspiration from the outside into the venous system, causing venous air embolism. To prevent this complication, we need to clamp the ECMO arterial cannula or reduce the revolutions when performing any of these operations: *a)* introducing or extracting the dilators or introducer sheaths/catheters; *b)* opening the valves that make up the catheters or the introducer sheaths (figure 1); *c)* entering or removing the devices through the introducer sheath.

Since the patient is supported by the device, meticulous coordination between the interventional cardiologist and the ECMO operator is required to minimize support reduction or clamping times (less than 2-4 seconds in experienced groups).

Another potential complication is obstruction of the ECMO venous cannula due to embolization of thrombotic material, which can cause the system to stop. The obstruction of the venous cannula is a consequence of thrombus embolization from the thrombus aspiration catheter (figure 2). This usually occurs when the thrombus aspiration catheter is obstructed by a large thrombus and requires manual extraction outside the patient's vein. As the catheter

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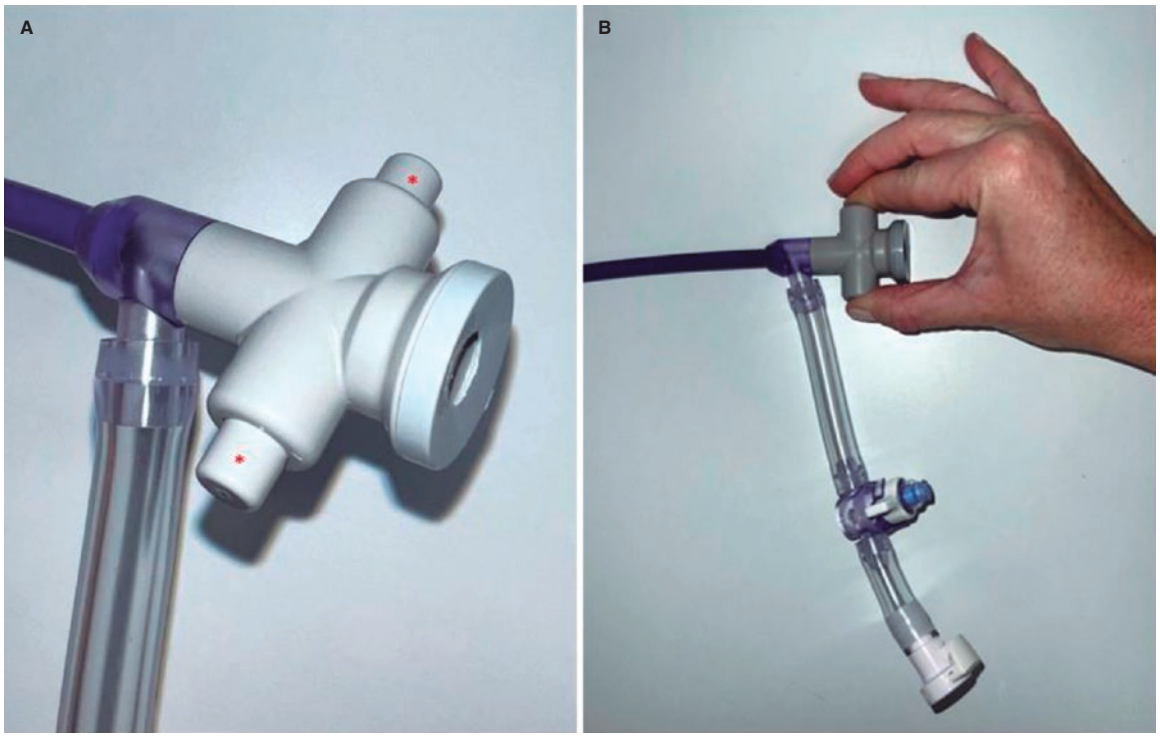

Figure 1. **A:** valve of a large-bore thrombus aspiration catheter. The asterisk shows the 2 buttons that, when pressed, allow the valve to open. **B:** opening of the valve by pressing the 2 buttons. Support needs to be reduced or stopped before opening this or any other valve in patients on extracorporeal membrane oxygenation (ECMO).

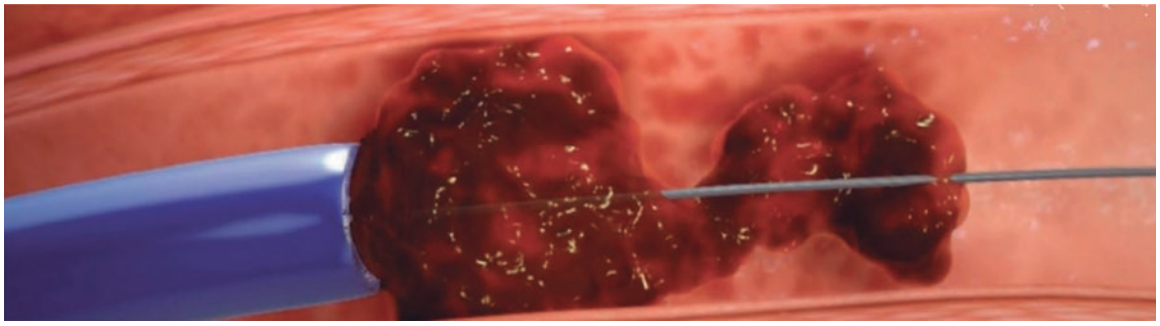

Figure 2. Graphic representation of the obstruction of a thrombus aspiration catheter by a large thrombus, which becomes lodged at the tip of the catheter. Extracorporeal membrane oxygenation (ECMO) flow reduction and rapid catheter withdrawal while on negative pressure reduce the risk of embolization to the ECMO venous cannula.

advances toward the exterior, it approaches the distal end of the venous cannula, which is when the risk of embolization is highest. Precautions during thrombus removal include the following: *a)* maintaining negative pressure in the thrombus aspiration catheter; *b)* decreasing the ECMO flow to reduce the suction power of the venous cannula; *c)* quickly and continuously removing the thrombus aspiration catheter.

Finally, another complication is venous suction. The continuous blood suction generated by the system in the venous line reduces both the volume and velocity of blood flow reaching the pulmonary arteries, thus decreasing the suction pressure that the catheter can create, along with its effectiveness. Although not imperative, in cases of failed aspirations, we recommend reducing ECMO flow during aspiration to increase efficacy, reduce the duration of the procedure, and minimize blood loss.

In conclusion, pulmonary thrombectomy through thrombus aspiration in patients with high-risk pulmonary embolism who require ECMO support is feasible and can improve the patient's clinical status. Considering some technical aspects can facilitate the procedure and prevent the risk of complications. Adequate team communication and coordination are essential to ensure the success of the procedure.

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affiliations, knowledge, or beliefs) in the topic or materials presented in this article.

ETHICAL CONSIDERATIONS

Informed consent or validation by an ethics committee was not deemed necessary since no patients were included in this study. Possible biases of sex and gender were taken into consideration while drafting this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools have been used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

All authors significantly contributed to the drafting of this work.

CONFLICTS OF INTEREST

R. Moreno is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedures to ensure the impartial processing of the manuscript have been followed. The remaining authors declared no conflicts of interest related to this work.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000453.

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Scientific letter

Therapeutic approach to patients with severe aortic stenosis undergoing orthopedic traumatological surgery

Abordaje terapéutico de los pacientes con estenosis aórtica grave sometidos a cirugía traumatológica ortopédica

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To the Editor,

The perioperative risk associated with aortic stenosis during noncardiac surgery (NCS) depends on the presence of symptoms, the severity of aortic stenosis, concomitant cardiovascular diseases, and the risk associated with noncardiac comorbidity. Severe symptomatic aortic stenosis is a major risk factor for postoperative heart failure and a predictor of 30-day and long-term mortality after noncardiac surgery; therefore, an appropriate perioperative strategy is essential in patients undergoing intermediate- or high-risk noncardiac surgery.[1,2] Hip and vertebral fractures, which are highly prevalent in the elderly population, are usually due to accidental falls and considered intermediate-risk interventions.[3] Nonetheless, these patients are characterized by their advanced age and the presence of concomitant diseases, which increases their surgical risk. In this context, the management of aortic stenosis is associated with reduced morbidity and mortality rates in patients undergoing intermediate or high-risk noncardiac surgery.[4,5] The perioperative management of patients with severe symptomatic aortic stenosis requiring uncertain trauma surgery is challenging.

We present a series of 4 consecutive patients with a past medical history of severe symptomatic aortic stenosis with a trauma emergency, 3 of them due to hip fracture and 1 due to vertebral fracture, all after accidental falls, in whom perioperative management of aortic stenosis was optimized by transcatheter aortic valve implantation (TAVI). The study was conducted following the ethical principles for medical research of the Declaration of Helsinki and was approved by the ethics committee of our center. Table 1 lists the patients' baseline characteristics. Two of the patients were octogenarians and the other 2 were nonagenarians, with a high comorbidity index (Charlson ≥ 7), severe aortic stenosis, and in New York Heart Association functional class II-III. Initially, we evaluated the risk associated with the surgical intervention required, and we considered it to be intermediate-high risk. Regarding waiting time, we considered the procedures to be a priority, which needed to be performed as soon as possible. In this context, we evaluated the patients' clinical risk, the presence of symptomatic aortic stenosis with echocardiographic repercussions (decreased left ventricular ejection fraction or pulmonary hypertension), and comorbidity, and considered aortic valve replacement as a high-risk procedure. Furthermore, we analyzed the patients' quality of life and observed that they could all undertake most activities of daily living, with acceptable mobility. The Heart and Outer Teams both made their assessment and decided to optimize the perioperative period of noncardiac surgery by definitively treating aortic stenosis through TAVI, which was accepted by the patients and their families. All patients underwent previous anatomical studies (echocardiography, angiography, computed tomography, or 3-dimensional transesophageal echocardiography). We selected transfemoral access, opting for the unaffected lower limb in the case of hip fracture, with extra radial access support, due to the presence of a certain external rotation and shortening of the affected limb. The implanted valve was self-expandable according to the experience of the center and availability.

We successfully performed TAVI, with a median of 3 days, and only 1 complication, an acute anterior myocardial infarction due to embolization during implantation, which was resolved by direct stenting of the left anterior descending coronary artery. We performed the orthopedic trauma surgery during admission, between 2 and 3 days after TAVI, without any cardiac complications being reported during or after the intervention, with good tolerance to blood volume and favorable clinical and hemodynamic parameters.

In our series of patients with various degrees of surgical risk and a need for intermediate-high risk noncardiac surgery with priority status, we opted for definitive treatment through TAVI, after establishing inter- and multidisciplinary consensus between an Outer Team and the Heart Team. To date, the approach has been the strict control of blood volume or performing aortic valvuloplasty as a bridge therapy. However, after the consolidation of TAVI, it can be considered an appropriate therapeutic option to facilitate perioperative treatment and reduce mortality.

Based on our results and the clinical outcomes of the patients in our series, as well as the European clinical guidelines,[3] we developed an algorithm to evaluate perioperative management (figure 1). The risk of noncardiac surgery must be assessed and stratified as low, intermediate, or high. Furthermore, the Outer Team must establish the waiting time for surgery, categorizing it as emergent, urgent, elective prioritized, or elective. Subsequently, the heart team must evaluate the risk of aortic stenosis based on severity,

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Table 1. Patients' clinical, biochemical, and echocardiographic characteristics, and clinical events

Variables	1	2	3	4
Age. years	89	94	80	91
Sex	Male	Female	Male	Female
STS Score (%)	9.89	6.23	2.18	10.73
Charlson Index	12	7	8	8
PROFUND Index	11	9	3	8
Activities of daily living	Independent (lives alone)	Partial (walks alone + caregiver)	Independent (lives alone)	Partial (walks with cane + caregiver)
Cognitive status	Normal	Normal	Normal	Normal
Coronary heart disease	Yes	No	No	No
Clinical event	Right pertrochanteric femur fracture	Left pertrochanteric femur fracture	Vertebral fracture	Left intertrochanteric and distal radius and left styloid apophysis fracture
Cardiovascular symptoms	FC II dyspnea	FC II-III dyspnea	FC II dyspnea	FC III dyspnea
BNP/NT-proBNP pre-TAVI (pg/mL)	938 / NA	320 / 1130	NA / 2235	935 / 4951
BNP/NT-proBNP post-TAVI (pg/mL)	536 / NA	96 / 638	NA / 698	406 / 1066
Hb pre-TAVI (g/dL)	9.8	8.8	10.8	11.2
Hb post-TAVI (g/dL)	9.1	11.7	9.9	9.8
Creatinine pre-TAVI (mg/dL)	2.39	1.59	0.84	1.79
Creatinine post-TAVI (mg/dL)	2.12	2.43	1.15	2.1
High creatinine (mg/dL)	1.71	1.23	1.34	1.5
Red blood cell transfusion	After surgery	After TAVI	After surgery	After TAVI and surgery
Echocardiographic parameters				
Peak gradient (mmHg)	69	84	51	66
Mean gradient (mmHg)	47	52	34	42
Area (cm^2)	0.8	0.68	0.88	0.64
AR	None	Moderate	None	None
LVEF (%)	60	61	55	60
sPAP (mmHg)	36	40	32	80
Anatomic parameters of the aortic annulus (CT and 3D-TEE)				
Perimeter (mm)	70	66	83.7	73
Area (mm^2)	380	336	540	389
Annular diameter (mm)	21.5	20.7	26.6	22.7
Days event-TAVI	3	3	2	3
Permanent pacemaker	Yes	No	No	No
TAVI access	Transfemoral	Transfemoral	Transfemoral	Transfemoral
Transcatheter closure	Double ProGlide	Double ProGlide	Double ProGlide	Double ProGlide
Type of valve	Accurate Neo 2 S	Evolut Pro + 26 mm	Evolut Pro 34 mm	Accurate Neo 2 S
Echocardiographic parameters post-TAVI				
Peak gradient (mmHg)	18	12	7	26
Mean gradient (mmHg)	11	7	4	13

(Continues)

Table 1. Patients' clinical, biochemical, and echocardiographic characteristics, and clinical events *(continued)*

Variables	1	2	3	4
AR	None	None	None	None
LVEF (%)	63	52	53	65
sPAP (mmHg)	NA	32	28	74
Days TAVI-surgery	2	3	2	3
Events				
Heart failure	No	No	No	No
Myocardial infarction	No	Yes, during TAVI	No	No
Vascular complications	No	No	No	No
Stroke	No	No	No	No
De novo atrial fibrillation	No	No	No	NA
Ventricular arrhythmias	No	No	No	No
Mortality	No	No	No	No
Cardiovascular mortality	No	No	No	No
Others	UTI	UTI, membranous colitis	UTI	UTI
Antiplatelet/anticoagulant therapy				
Pre-TAVI	Aspirin + clopidogrel	Aspirin	Acenocumarol*	Apixaban
Post-TAVI	Aspirin + LMWH	Aspirin + LMWH	LMWH	LMWH (bemiparin)
Discharge	Aspirin + clopidogrel	Aspirin + clopidogrel	Acenocumarol	Apixaban
Follow-up	Deceased at the 11-month follow-up due to urothelial cancer	Alive at the 19-month follow-up	Alive at the 20-month follow-up	Deceased at the 3-month follow-up due to pneumonia

3D-TEE, 3-dimensional transesophageal echocardiogram; AR, aortic regurgitation; BNP, B-type natriuretic peptide; CT, computed tomography; FC, New York Heart Association functional class; Hb, hemoglobin; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; UTI, urinary tract infection.
* Oral anticoagulation for pulmonary embolism.

symptoms, and hemodynamic repercussions. Then, the patient's frailty indices[6] need to be evaluated, supported by their quality of life; in our series, one of the markers that allowed us to make decisions was the extent of dependency and the ability to walk, with or without assistance, and the absence of cognitive impairment. Finally, perioperative TAVI should be considered as the treatment of aortic stenosis if the risk of the transcatheter procedure, including anatomical criteria and the experience of the center, does not entail excessive morbidity and mortality (transfemoral access). We prioritized a bridge therapy such as aortic valvuloplasty in patients requiring emergency surgery because of time constraints, mainly for organizational reasons; nevertheless, TAVI has been reported in patients in cardiogenic shock with encouraging results. In fact, for interventions such as that presented in our series, perhaps definitive treatment (TAVI)—compared with a bridge therapy that also carries risks—can minimize cardiac complications and better address blood volume in surgical interventions requiring transfusions.

Therefore, in our small series, the strategy for treating severe symptomatic aortic stenosis with transfemoral TAVI as a minimally invasive procedure in the perioperative approach of patients requiring intermediate-high risk trauma surgery with priority status, is a safe and feasible approach, without postoperative cardiac complications.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The present study complies with the criteria of the Declaration of Helsinki and was approved by the ethics committee of our center. Patients signed their informed consent forms for procedures and the use of their data for registration. SAGER guidelines have been followed.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used.

AUTHORS' CONTRIBUTIONS

M. Muñoz-García: project management, data collection, and manuscript drafting. R. Rivera López, J. Sánchez Gila, and E. Molina Navarro: project management, data interpretation, and supervision. R. Parrilla Linares and J.M. Romero León: data interpretation and

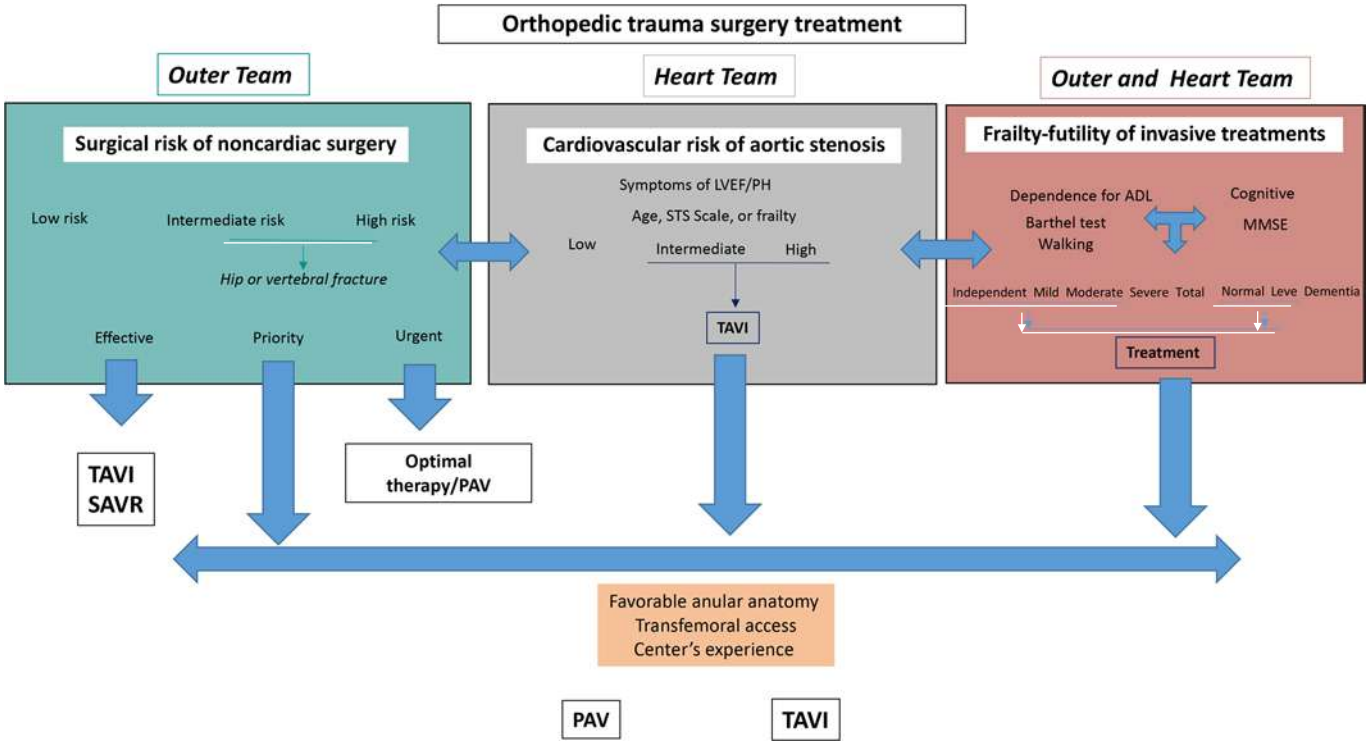

Figure 1. Therapeutic decision-making algorithm in patients with aortic stenosis requiring noncardiac surgery. ADL, activities of daily living; LVEF, left ventricular ejection fraction; MMSE, Mini-Mental State Examination; PAV, percutaneous aortic valvuloplasty; PH, pulmonary hypertension; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

manuscript review. All authors have substantially contributed to the design, formal analysis, research, and critical review of the study, and given their final approval.

CONFLICTS OF INTEREST

None declared.

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Scientific letter

Donor artery in coronary total occlusion recanalization: QFR versus FFR

Arteria donante en recanalización de oclusión coronaria crónica: CFC frente a RFF

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To the Editor,

Revascularization of a coronary chronic total occlusion (CTO) is indicated in patients with refractory angina, after treatment of non-CTO lesion.[1] Observational studies have suggested that when intermediate stenosis is present in an artery providing collaterals to a CTO ("donor artery"), its fractional flow reserve (FFR) value increases after percutaneous coronary intervention (PCI) of the CTO.[2] Quantitative flow ratio (QFR) has demonstrated excellent correlation with FFR in several settings.[3,4] The purpose of this study was to determine the ability of QFR to predict the severity of intermediate lesions in donor arteries as compared to its value after CTO-PCI and, also, as compared to FFR.

A retrospective analysis of a prospective registry was performed. Patients who underwent successful CTO-PCI and had a

Table 1. Main characteristics of the atients included in the study

Variable	N = 33	Variable	N = 33
Baseline characteristics		*Location of chronic total occlusion*	
Age, years	69.3 ± 11.7	Circumflex artery	3 (9.1)
Gender, male	21 (63.6)	Left anterior descending artery	10 (30.3)
Hypertension	26 (78.8)	Right coronary artery	20 (60.6)
Diabetes mellitus	19 (57.6)	*Location of donor artery*	
Dyslipidemia	27 (81.8)	Left anterior descending artery	23 (69.7)
Smoking	16 (48.5)	Right coronary artery	10 (30.3)
Prior myocardial infarction	6 (18.2)	**Procedural characteristics**	
Prior percutaneous coronary intervention	4 (12.1)	*Successful recanalization technique*	
Prior coronary bypass grafting	3 (9.1)	Antegrade dissection - reentry	7 (21.2)
Left main disease	0 (0)	Antegrade wire escalation	17 (51.5)
Left anterior descending disease	14 (42.4)	Retrograde wire escalation	9 (27.3)
Circumflex disease	11 (33.3)	*Fluoroscopy time (min)*	42.6 ± 16.7
Right coronary artery disease	26 (78.8)	*Contras dose (cc)*	322.9 ± 134.1
		Radiation dose (Gy)	2.8 ± 1.1
		Successful recanalization of the chronic total occlusion	33 (100)

Data are expressed as mean ± standard deviation or absolut number (number and percentage).

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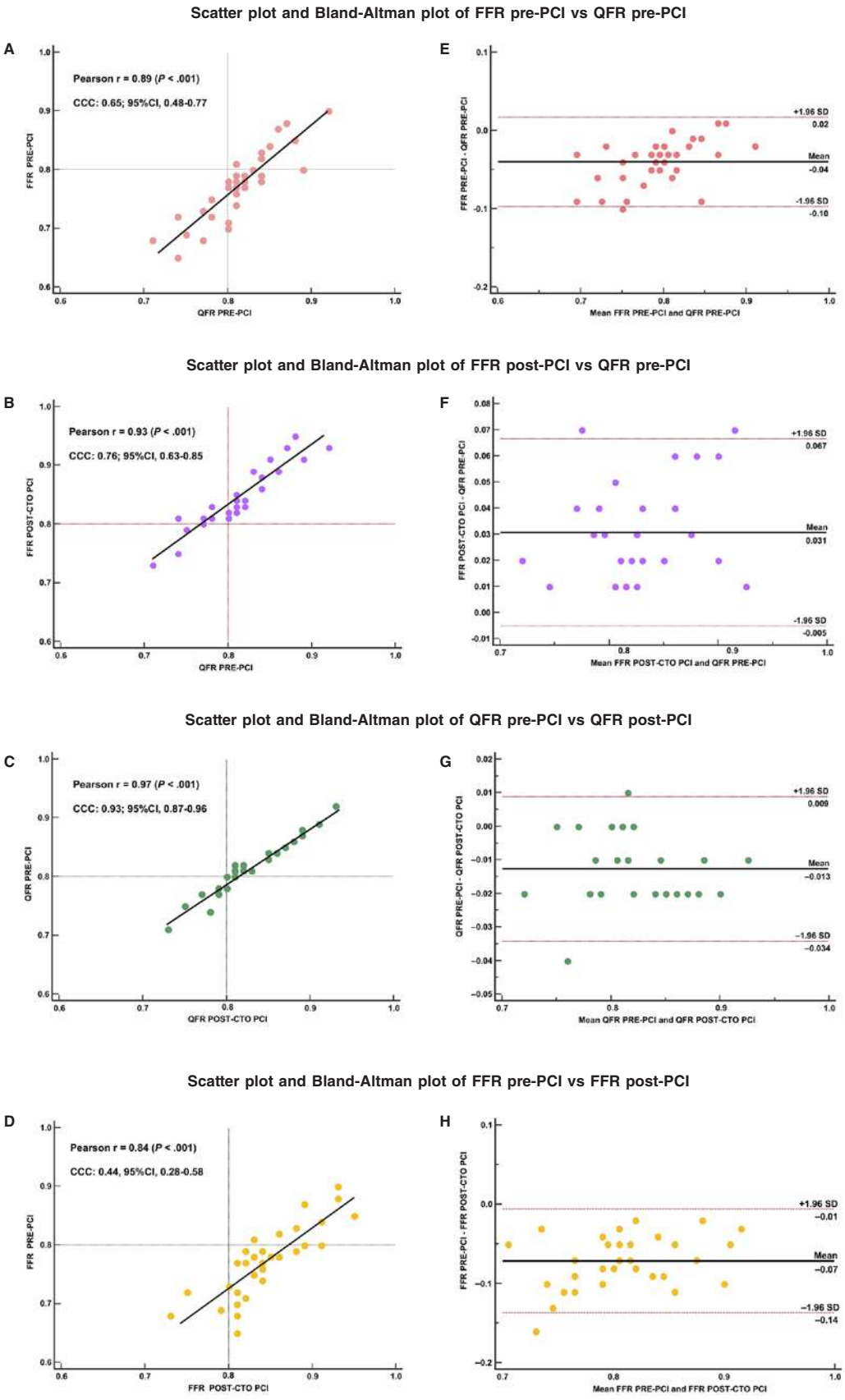

Figure 1. Correlation between QFR and FFR values in the donor artery of a CTO before and after a percutaneous coronary intervention of the CTO. Scatter (A,B,C,D) and Bland-Altman (E,F,G,H) plots showing the strong correlation between QFR estimated before CTO-PCI and FFR estimated after CTO-PCI demonstrating the potential of QFR as a predictive tool due to its independence from the revascularization. 95%CI, 95% confidence interval; CCC, concordance correlation coefficient; CTO, chronic total occlusion; FFR, fractional flow reserve; QFR, quantitative flow ratio; PCI, percutaneous coronary intervention; SD, standard deviation.

concomitant intermediate stenosis (between 30% to 70% on visual estimation) in the donor artery were included. FFR measurements, obtained according to standard protocol before starting and after completing CTO-PCI, were available for all participants, and the index of microcirculatory resistance (IMR) was available in 72.7% of the patients. Intracoronary adenosine was used to induce hyperemia. QFR was calculated retrospectively based on angiographic acquisitions before and after CTO-PCI and was feasible in all cases. To ensure reproducible results, QFR measures were performed starting within the sensor of the pressure wire. QFR computation was performed by a blinded technician using the QAngio XA 3D/QFR (Medis Medical Imaging Systems, the Netherlands). FFR and QFR < 0.80 were considered positive. Patients whose intermediate lesions in donor artery were ostial or presented any contraindication for adenosine administration were excluded from the study. One-month and one-year clinical follow-up were available for all patients. Categorical variables were presented as counts and percentages, while continuous variables were expressed as mean ± standard deviation. The agreement and correlation between QFR and FFR were evaluated using the Bland-Altman plot, Lin's concordance correlation coefficient (CCC) and Pearson's test. The Shapiro-Wilk was used to ensure the normal distribution of data. All analyses were conducted using the statistical software R, version 4.2.0 (R Project for statistical computing).

A total of 33 patients were analyzed. Baseline patient and procedural characteristics are presented in table 1. The most common CTO location was the right coronary artery (RCA), 60.6%, followed by the left anterior descending coronary artery (LAD), 30.3%, and the circumflex (Cx) 9.1%. Conversely, LAD was the most common donor artery (69.7%), followed by RCA (30.3%). The mean donor vessel's pre-procedural FFR was 0.773 ± 0.059 with 75.8% of the patients showing a positive FFR, and the baseline QFR was 0.813 ± 0.446 (36.4% positive). Post-CTO-PCI, FFR increased to 0.844 ± 0.049 (12.1% positive) and QFR to 0.825 ± 0.044 (27.3% positive). The mean change of post-PCI FFR was + 0.067 (LAD occlusion), + 0.073 (Cx) and + 0.08 (RCA). Figure 1 summarizes the main results of the study. Moderate agreement was observed between pre-CTO-PCI FFR and QFR measurements (CCC: 0.65; 95% confidence interval [95%CI], 0.48-0.77). A stronger agreement emerged between pre-CTO-PCI QFR and post-CTO-PCI FFR (CCC: 0.76; 95%CI, 0.62-0.85), as well as between QFR values measured before and after PCI (CCC: 0.93; 95%CI, 0.87-0.96). However, the correlation between pre- and post-PCI FFR values was comparatively weaker (CCC: 0.44; 95%CI, 0.275-0.58). IMR demonstrated a significant improvement (from 43.1 ± 5.6 to 31.5 ± 8.2 mmHg/s, $P < .001$) as estimated immediately post CTO-PCI.

This post-angioplasty microvascular resistance assessed values are consistent with those previously described in the literature during the acute phase following revascularization, where slight variations are found.[5]

Our findings align with previous observations showing an increase in FFR within the donor artery. This might result from the donor artery's decreased absolute total perfused coronary territory flow and microvascular resistance after normal flow is restored.[2] The minimal variation in QFR values pre- and post-PCI could be attributed to the software's processing of angiography images and coronary territories, which may not fully consider the physiology of microvasculature and the actual total territory perfused by the donor artery. These limitations may diminish the role of QFR in assessing donor arteries intermediate lesions as compared to FFR and therefore require further validation.

Despite the limitations of the study due to its retrospective nature and the small sample, the hypothesis-generating findings suggest lower impact of microvascular index on QFR than on FFR assessment of donor arteries in patients with CTOs. Further prospective studies are required to confirm these findings.

FUNDING

None.

ETHICAL CONSIDERATIONS

The protocol was approved by the ethics committee and informed consent was obtained from the patients. SAGER recommendations were followed.

STATEMENT ON THE USE OF ARTIFICIAL INGELLIGENCE

Artifical intelligence was not used during this investigation.

AUTHORS' CONTRIBUTIONS

I.J. Amat-Santos and L. Scorpiglione designed the manuscript. I.J. Amat-Santos, C. Cortés-Villar, A. Gutiérrez and A. Fernández Cisnal collected the data. L. Scorpiglione and J. Ruiz Ruiz analyzed the data and drafted the manuscript. All authors have read and approved the sending of this manuscript.

CONFLICTS OF INTEREST

None to declare.

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Transcaval access for mechanical circulatory support in cardiogenic shock

Acceso transcava para soporte circulatorio mecánico en shock *cardiogénico*

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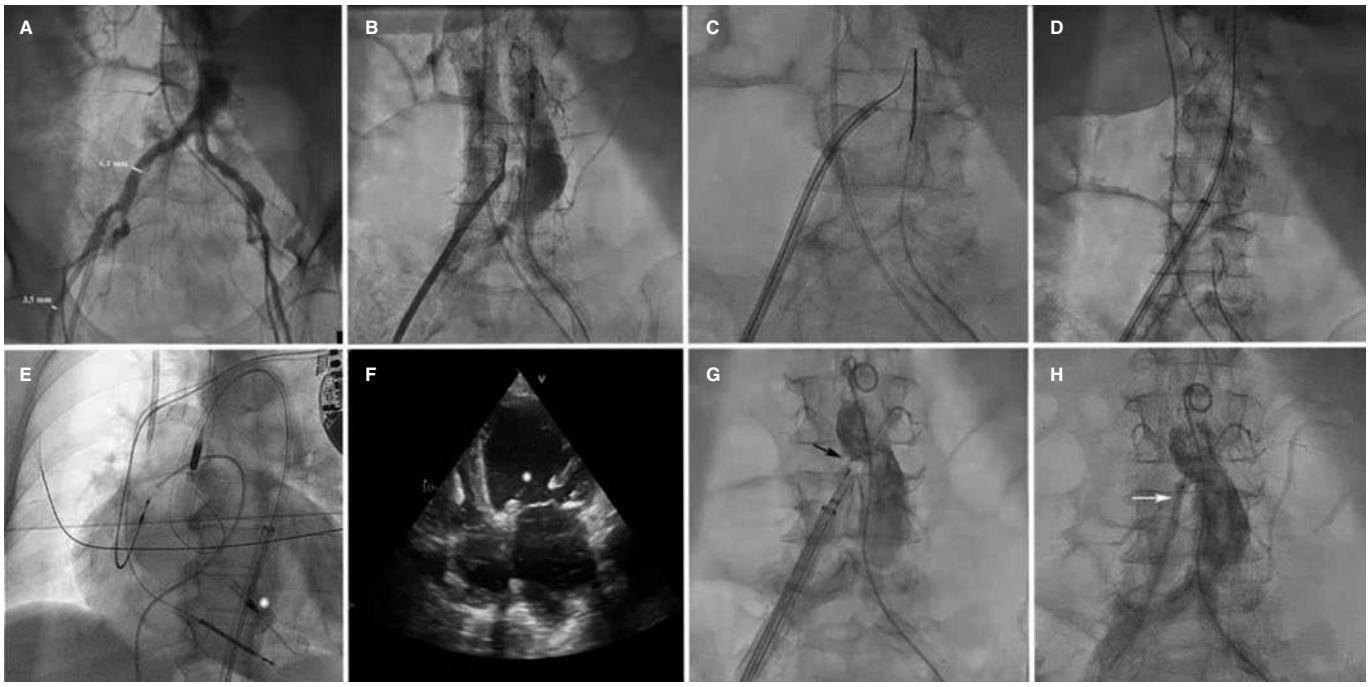

Figure 1.

We present 2 cases which required transcaval access for mechanical circulatory support device implantation.

Case #1 is a 65-year-old woman with ischemic dilated cardiomyopathy and severe ventricular dysfunction who was admitted due to cardiogenic shock (SCAI D, SOFA 15, vasoactive-inotropic score 55, and lactate levels of 5.7 mg/dL). An Impella-CP device (Abiomed, United States) was implanted via transcaval access due to the lack of femoral (figure 1A) and subclavian access. To identify the appropriate projection angle for incision, 2 pigtail catheters were overlapped in the aorta and vena cava. The incision was performed through electrification of a heavyweight guidewire that eventually crossed the aorta (figure 1B, C, and video 1 of the supplementary data). The guidewire was exchanged for a 0.35 mm extra-stiff guidewire, and a 16-Fr × 65 cm GORE DrySeal introducer sheath was advanced (Gore, United States) (figure 1D and video 1 of the supplementary data), on which the Impella device was implanted (figure 1E, F; asterisk: Impella inlet). The Impella device was removed 7 days later, and the transcaval incision was closed (figure 1G, arrow, and video 2 of the supplementary data) leaving an untreated minimal residual leak behind (figure 1H, arrow), which was not visualized on follow-up angiography performed 3 weeks later.

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Case #2 is a 59-year-old man with peripheral vascular disease who was admitted due to Killip IV myocardial infarction with left main coronary artery occlusion. Despite revascularization and use of an intra-aortic balloon pump, the patient remained in shock (SCAI E, SOFA 18, vasoactive-inotropic score 170, and lactate levels of 15.7 mg/dL). Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was implanted using the technique described above (video 3 of the supplementary data) with a 17-Fr × 55 mm arterial cannula that was inserted directly after dilatation. VA-ECMO was removed 5 days later with good patient progress (video 4 of the supplementary data). There were no complications associated with either one of the 2 procedures.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This study was approved by Hospital Universitari Vall d'Hebron research ethics committee. The corresponding informed consent forms were obtained from both patients for publication.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

All the authors participated in the design, drafting, and review of this manuscript.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000431.

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Cyanosis after surgical closure of atrial septal defect

Cianosis tras cierre quirúrgico de comunicación interauricular

Viviana Arreo del Val,* Enrique Balbacid Domingo, and Ángela Uceda Galiano

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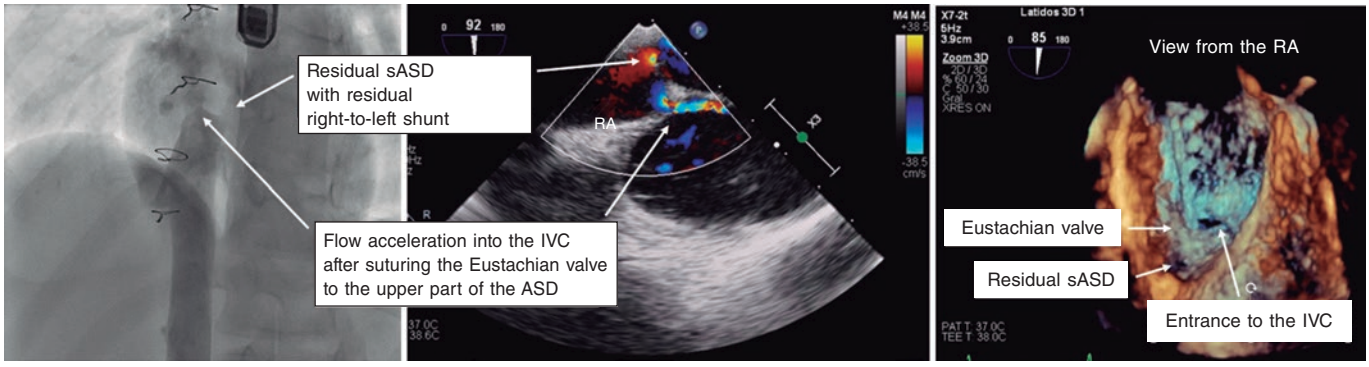

Figure 1.

We present the case of a 12-year-old boy treated for a secundum atrial septal defect (sASD) at the age of 2 years who was referred due to dyspnea, cyanosis with digital clubbing, and oxygen desaturation of 75%.

Transthoracic echocardiogram showed an acceleration of flow of the inferior vena cava (IVC) inside the right atrium (RA) due to an iatrogenic suture between the Eustachian valve and the upper part of the ASD, with residual right-to-left shunt.

Subsequently, a transesophageal echocardiogram and cardiac catheterization (figure 1, arrows) with cavogram revealed the severe obstruction of the IVC drainage into the RA through a 6 mm orifice, with a 12 mm IVC diameter, and a residual 5 mm ASD, leading to a right-to-left shunt (videos 1-3 of the supplementary data).

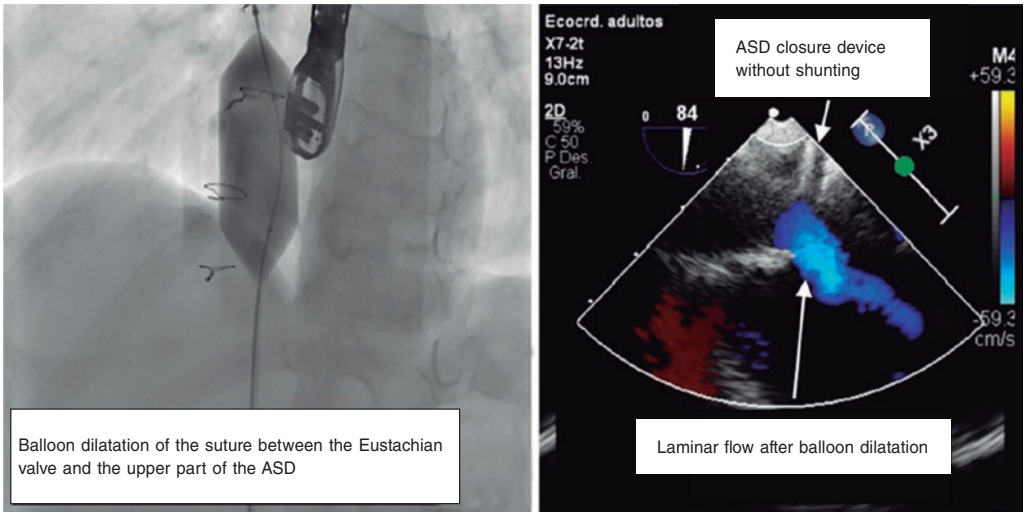

Figure 2.

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The cava axis was catheterized, and the stenosis area was sequentially dilated with balloons of up to 22 mm. Color Doppler echocardiography confirmed the absence of flow acceleration, and a hemodynamic gradient of 1 mmHg between the IVC and the RA. A 4 mm occlusion device was implanted to close the ASD without residual shunting after its release (figure 2, arrows), resulting in the restoration of normal oxygen saturation.

The partial deviation of the IVC into the RA can occur iatrogenically after surgical closure of an sASD by suturing the Eustachian valve to the upper part of the ASD. The standard of care for this complication is usually surgical reintervention. This is the first case ever reported of an obstruction treated with balloon dilatation.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This article abides by the international recommendations on clinical research. Considering the content of the article, it was not deemed necessary to account for potential sex and gender biases. The patient's prior written informed consent form was obtained for publication.

DECLARATION ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools have been used.

AUTHORS' CONTRIBUTIONS

All authors were physicians of the patient and contributed to the drafting of this article.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000432.

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Making matters worse with Impella

Rizar el rizo en el soporte con Impella

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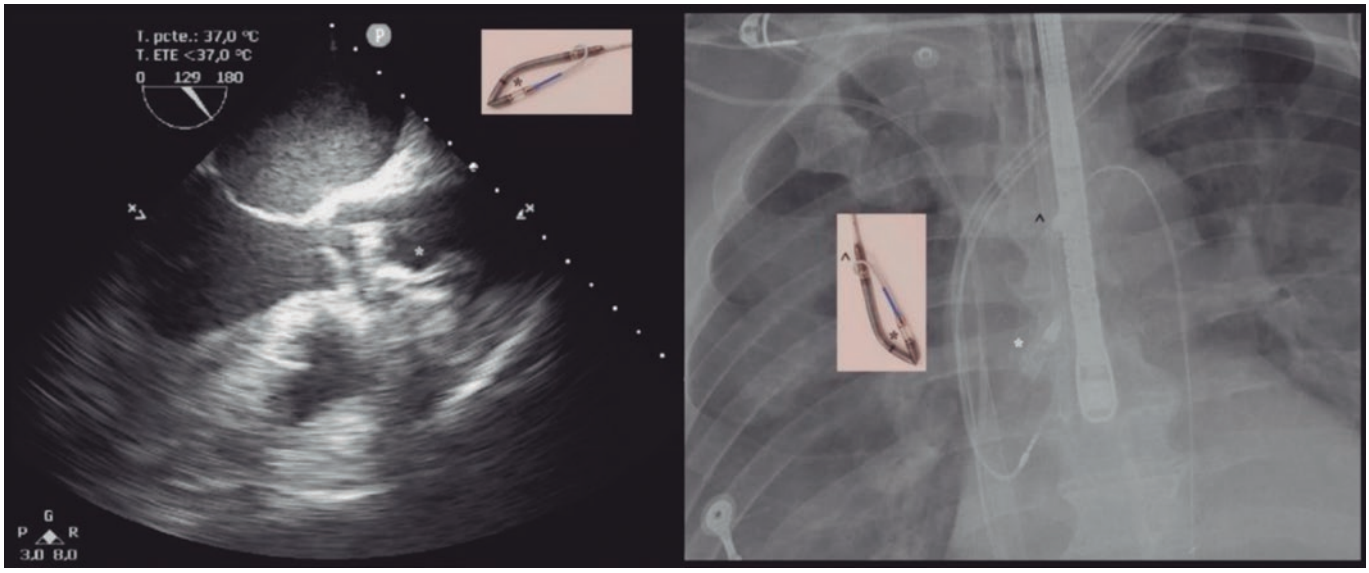

Figure 1.

A 53-year-old man was treated with extracorporeal cardiopulmonary resuscitation with the controlled automated reperfusion of the whole body (CARL) system (Resuscitec, Germany) after a refractory in-hospital cardiac arrest following an arrhythmic storm in the setting of an episode of inflammatory cardiomyopathy. The patient required Impella-CP device implantation (Abiomed, United States) via femoral access due to insufficient unloading with the intra-aortic balloon pump. Catheter malapposition was suspected after several suction alarms were triggered. Despite repeated attempts at repositioning, flow rates remained < 1 L/min. Transesophageal echocardiography and thoracic x-ray (figure 1) confirmed that the catheter had bent in upon itself (asterisk in the figure), and the pigtail had been caught in the outlet (figure 2) following the multiple attempts at repositioning. The catheter migrated toward the descending aorta and urgent removed was decided. An attempt to unscrew the pigtail through femoral manipulation proved unsuccessful (figure 3A and video 1 of the supplementary data). A 7-Fr Amplatz Super-Stiff guidewire (Boston Scientific, United States) was advanced through the Impella loop via left radial access, and traction on the catheter from the femoral access successfully disengaged the pigtail from the outlet (figure 3B). Concurrently, a 12 mm × 20 mm EN-Snare loop (Merit Medical, United States) was inserted to capture the tip of the pigtail (figure 3C). The guidewire was removed and traction was applied simultaneously to the Impella device and the pigtail tip, which extended the Impella (figure 3D and video 2 of the supplementary data) and allowed its extraction through its introducer. We decided not to restart the device due to the risk of thrombosis in its interior, and chose to remove it using a 14-Fr transaortic pigtail catheter through the Impella access.

A deep understanding of medical devices is of paramount importance to recognize rare complications and optimize outcomes.

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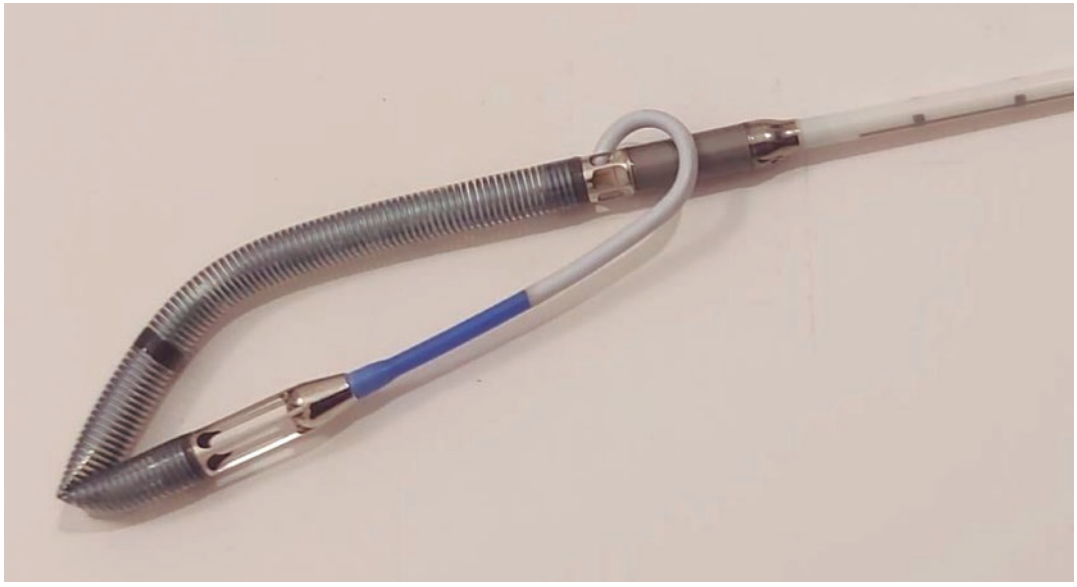

Figure 2.

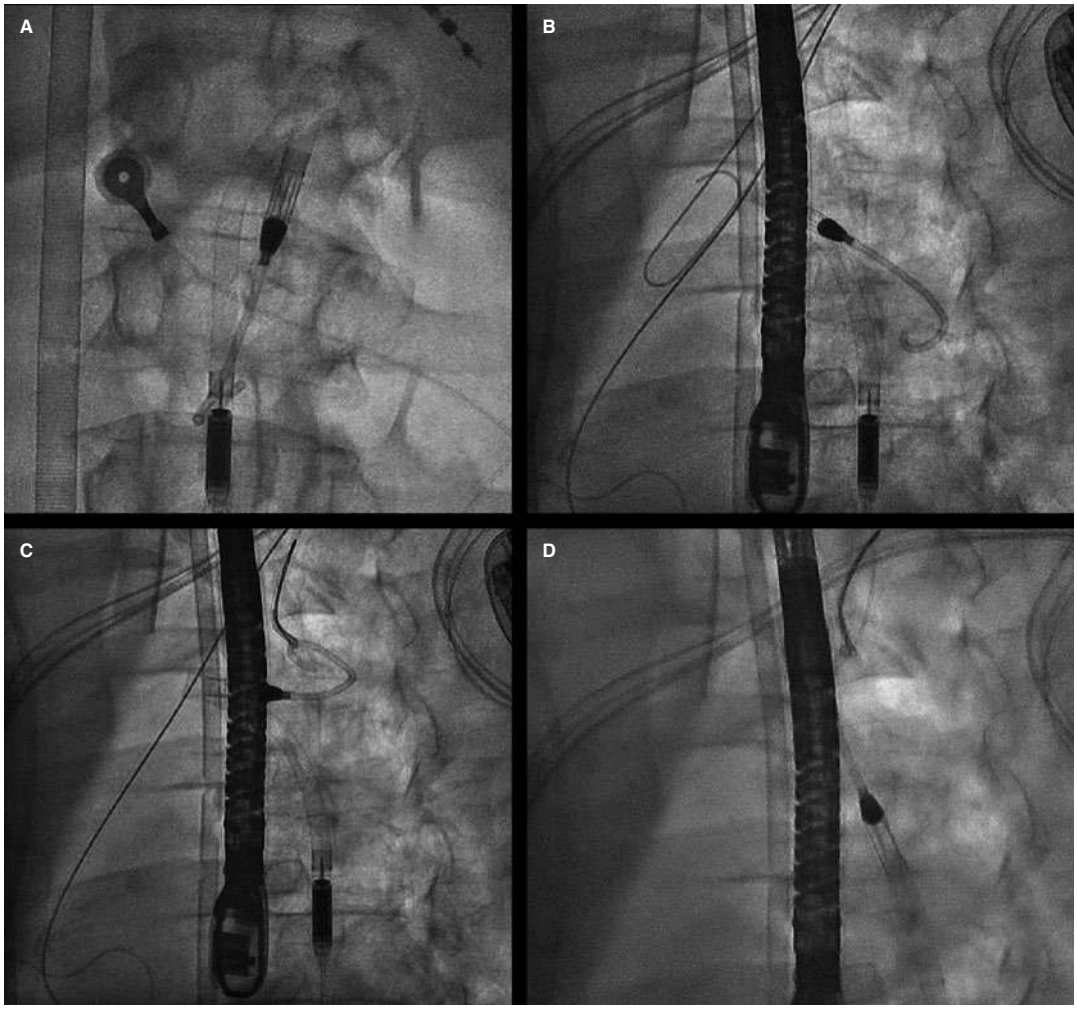

Figure 3.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The authors declared to have obtained the prior written informed consent the patient for publication, reproduction, and disclosure in print and online through *REC Interventional Cardiology*. The work was conducted in full compliance with the international recommendations on clinical research set forth in the Declaration of Helsinki.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The authors declare they did not use artificial intelligence in the preparation of this article.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the preparation of the article.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000435.

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Correction

Correction in article by Freixa-Benavente et al. "Cardiac catheterization activity in pediatric cardiac transplantation. Can catheterization needs be predicted?", *REC Interv Cardiol.* 2024;6:97-105

Corrección en el artículo de Freixa-Benavente et al., «Actividad de hemodinámica cardiaca en trasplante cardiaco pediátrico. ¿Es posible predecir las necesidades de cateterismo?», REC Interv Cardiol. 2024;6:97-105

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Our publisher has identified a formatting error in the article "Cardiac hemodynamic activity in pediatric heart transplantation. Is it possible to predict catheterization needs?" In table 2, values of 0 incorrectly appear in the column corresponding to *P*-values.

The correct table is:

Table 2. Data on pretransplant cardiac catheterizations

Pretransplant procedures	Cardiomyopathy (n = 39)	Congenital heart disease (n = 22)	*P*
Patients with previous CC	17 (43.59%)	18 (81.82%)	.282*
1 CC	12	6	
2 CC	2	1	
3 CC	2	5	
4 CC	1	1	
5 or more CC	0	5	
CC per person; median (IQR)	0 (0-1)	2.5 (1-3.75)	.014*
Number of previous procedures	60	82	
Number of therapeutic interventional procedures (n)	15	35	
Balloon atrioseptostomy	2	0	
Atrioseptostomy with stent	5	3	
Coronary angioplasty with stent	3	0	
Interatrial stent redilatation	2	0	
Balloon coronary angioplasty	2	0	
IVUS	1	0	
Collateral artery closure	0	9	
Pulmonary branch angioplasty with stent	0	9	
Cavopulmonary anastomosis balloon angioplasty	0	2	
Cavopulmonary anastomosis angioplasty with stent	0	1	
Aortic valvuloplasty	0	3	
Ventricular septal defect closure	0	2	
Coronary fistula embolization	0	2	
Pulmonary trunk angioplasty with stent	0	1	
Superior cava vein balloon angioplasty	0	1	
Iliac stent dilatation (previous migration)	0	1	
Fontan fenestration (failure)	0	1	
Diagnostic procedures (percentage of total procedures)	45 (75.0%)	47 (57.3%)	.029*
Coronary angiography	8	4	
Endomyocardial biopsy	10	0	
Diagnostic catheterization	27 (45.0%)	43 (52.4%)	.380

CC, cardiac catheterization; ECLS, extracorporeal life support; IVUS, intravascular ultrasound.
Qualitative data are expressed as absolute numbers and percentages and quantitative variables as median the and interquartile range.
* Statistical significance.

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