REC: INTERVENTIONAL CARDIOLOGY
REVISTA ESPAÑOLA DE CARDIOLOGÍA

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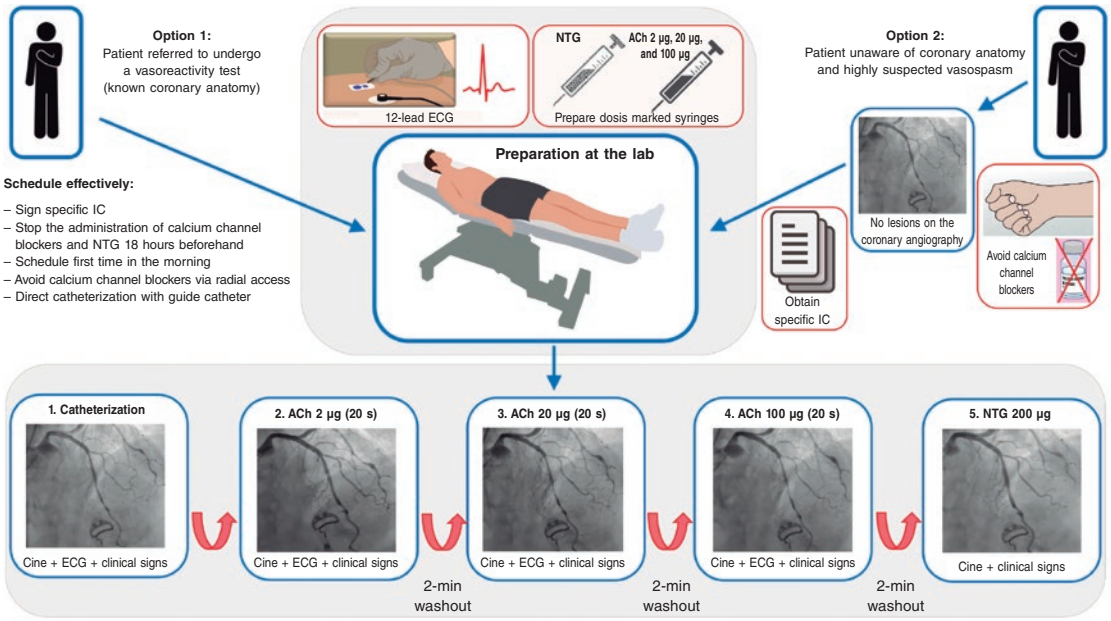

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA
Asociación de Cardiología Intervencionista

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REC publications

REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

CONTENTS

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REC: Interventional Cardiology in the COVID-19 year

REC: Interventional Cardiology en el año de la COVID-19

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Last year's Editor's page discussed the emerging quality of our publication that celebrated its first anniversary at that time. Also, the fast and effective response of the journal at the early and confusing times of the COVID-19 crisis should be noted, publishing—in record time—consensus documents written by the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) in collaboration with other medical societies. A clear example of this was the article describing the effects of the COVID-19 pandemic on the healthcare situation in interventional cardiology in Spain that has been cited numerous times in some of today's most prestigious medical journals.[1]

Over the last year, special articles elaborated by the ACI-SEC or by some of its working groups have been published such as "Update on requirements and equipment in interventional cardiology",[2] and the article on the assessment of endothelial function and spasm provocation test.[3] Both documents are of great interest to the entire cardiovascular community, not only from the clinical but also from the administrative point of view.

The main protagonists of such a satisfactory trajectory have been the authors, both those who have submitted their manuscripts in different formats as well as those invited by the editorial committee to write reviews, editorial comments, debate articles, case comments, clinical trial reviews or news on innovation and technology. Some of these guest authors are nationally and internationally acclaimed experts such as Elazer R. Edelman, Juan F. Granada, Hector Garcia, Bruno Scheller, David Adlam, Nico H.J. Pijls, David Erlinge, and Sanjit S. Jolly, among others.

And if the authors are the most important pieces of our puzzle, our reviewers surely follow as they unselfishly dedicate their time and effort to write very high-quality reviews with exceptional turn-around times.

WHAT DID WE ACCOMPLISH AND CHANGE OVER THE LAST YEAR?

This past year, several milestones have been achieved and changes have been made to improve the performance of the journal whilst essential characteristics have been maintained, like its totally free-of-charge/open-access nature, and bilingual publication (in Spanish and English) followed by an optimal presentation both in the online version and in the limited print edition.

Figure 1 shows many of the changes and advances made along the way to achieve public and institutional recognition in the last year.

Actions and landmarks reached by *REC Interv Cardiol*

Indexing

- Acceptance in Scopus
- Acceptance in DOAJ (Spanish and English versions)
- Acceptance in the Latindex directory and catalogue
- Acceptance in Dialnet

Peer-review

- Granting of CASEC credits to reviewers
- Appointment of elite reviewers
- Systematization of the use of a checklist of ethical questions by the editors

Editorial issues

- Systematic inclusion of the following sections: conflicts of interests, funding, and author's contributions
- More space per issue to the following sections: images in cardiology (3), and scientific letters (4)
- Possibility of spontaneous submission of review articles
- Time limit for the submission of the revised versión of original articles (30 days)
- 2-prize award for original articles, one rewarded with €1500, and the other with €1000

Figure 1. Changes and advances made over the last year.

Over the last 12 months, the process of indexing *REC: Interventional Cardiology* was started. The first milestone in this regard came with the indexation of the journal in the Directory of Open Access Journals (DOAJ), a key player among open-access publications for its quality standards and whose evaluation contributed to improve our journal. Other relevant databases like Scopus, Latindex, and Dialnet followed. Currently, *REC: Interventional Cardiology* is in the evaluation stages in the SciELO, and Embase databases. We should be hearing from them within the next few months. Also, we expect to be accepted by the Committee on Publication Ethics (COPE) shortly.

From the editorial point of view, we have systematized how authors declare the study's ethics committee approval and the availability of patients'/volunteers' informed consent. In response to the publication demand received, the number of images and letters has gone up to 3 and 4 per issue, respectively. Also, the spontaneous submission of review articles is now possible. In addition, it was decided to eliminate the "clinical trial review" section due to the huge

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Online: 14-09-2021.

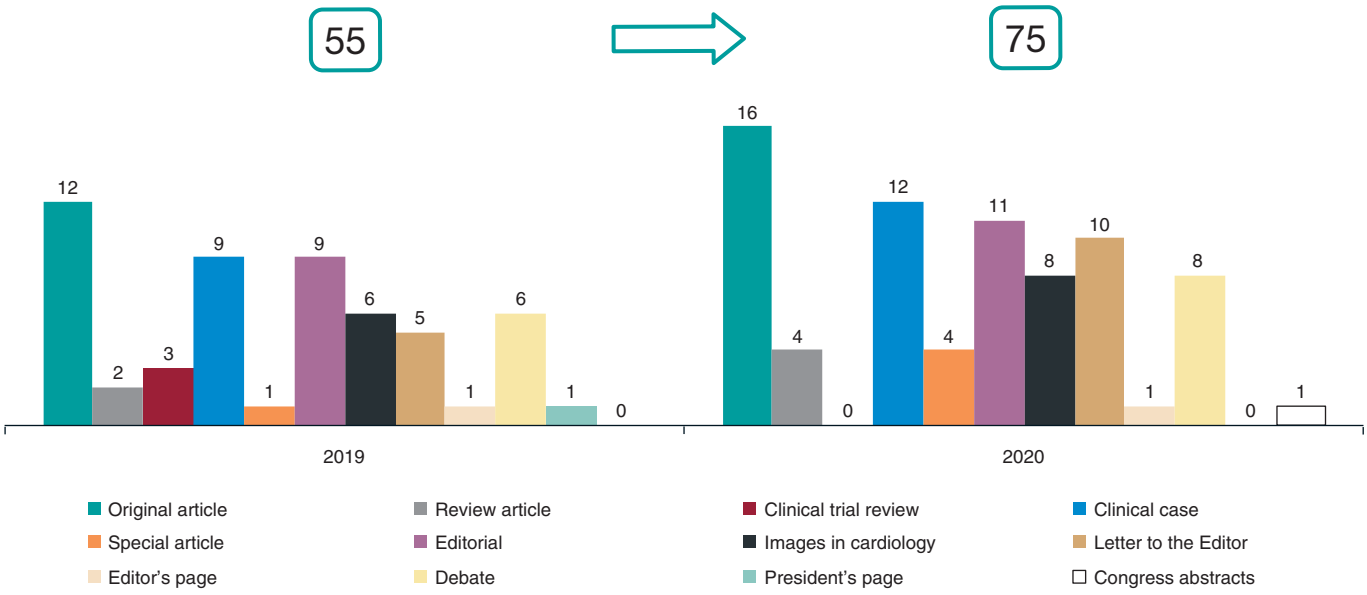


Figure 2. Overall contents published in 2019 and 2020. Abstracts from congresses are counted as 1 unit although a total of 24 abstracts were included. Each clinical case is counted as 3 units since each clinical case includes 3 independent articles: Case presentation, How would I approach it?, and Case resolution.

editorial complexity involved in the publication of these articles in a timely manner.

The number of awards for the best articles of the year has been increased - from 2021, we will grant a first prize, €1500 euros, and a second prize, €1000 euros.)

EDITORIAL ACTIVITY

We will now present the activity of the journal until the present time (data from the period that goes from July 2020 through June 2021).

Firstly, the content published between 2019 and 2020 has increased by 36% (from 55 to 75 manuscripts) as show in figure 2. This increase has occurred in almost all the article formats published in the journal. It was also very satisfactory to publish for the first time the abstracts of the ACI-SEC congress.[4,5] This year's congress abstracts will also be included in the last issue of 2021.

Another rewarding aspect is the international origin of some of the articles submitted. Up to 17% of these manuscripts came from 14 different nationalities, especially from Latin American countries. Most manuscripts are submitted in Spanish, which does not necessarily indicate their origin, but submissions in English are increasing (figure 3).

Original articles

Between the second semester of 2020 and the first semester of 2021 a total of 25 original articles were received without significant variations among the different quarters of the year (figure 3). Within the same period, a total of 14 original articles were accepted for publication (52.8%).

The number of manuscripts received since the the launch of the journal has also gone up; we believe that the tendency of 2021 should be similar to that seen in 2020. As a matter of fact, we anticipate the submission of more than 30 original papers (figure 4).

Currently, our main objective is to increase the number of original articles, which is why we invite the community of interventional cardiologists to submit research papers. In return, *REC: Interventional Cardiology* offers a fast high-quality peer-review process, and maximum exposure of the papers published.

Letters to the Editor

Between July 2020 and June 2021, a total of 16 letters were submitted (figure 5), 70% of which were accepted for publication.

Most of them were received during the third quarter of 2020. However, the number of letters received dropped later (figure 5), a trend also seen in the clinical cases (figure 6) and images in cardiology sections (figure 7). In all cases, the quarterly nature of the journal allowed to complete this content several issues in advance. The editorial committee publicised the situation, which discouraged some authors from submitting articles to these sections.

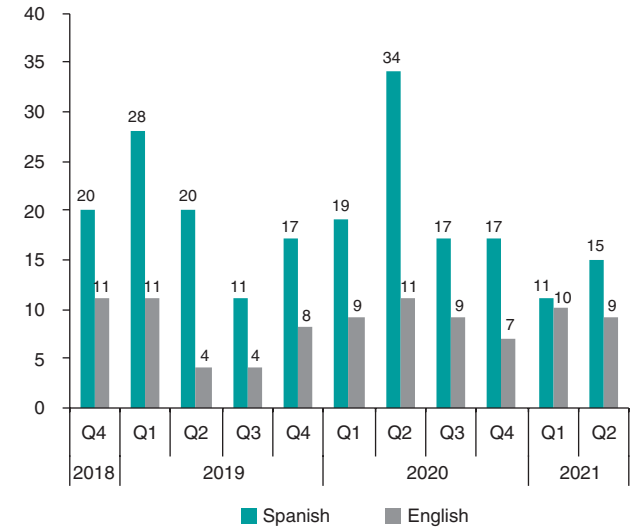
Although the space available for letters has been increased (up to 4 since the last issue of 2020), we still need to find a breakeven point by securing a constant publication demand without generating a large stock whose content could lose momentum regarding print publication.

Clinical cases

As previously mentioned, clinical cases experienced a situation similar to that of the letters: an increase in reception during 2019-2020 was followed by a decrease in 2021 (figure 6).

The explanation seems to be the same. Only 1 case is published per issue—4 cases throughout the natural year—which significantly limits the capacity of acceptance. The stock of cases forced us to be highly restrictive as well, and only 2 of the 6 cases received within the same period were accepted, somehow discouraging submission.

A



B

Origin	2018	2019	2020	2021*
Germany		2		1
Argentina		3	2	
Belgium			1	
Brazil			1	
Canada				1
Chile			1	1
China				1
Colombia		1		
Cuba			2	
Slovakia		1	1	
Spain	28	87	102	33
France		1		1
Iran			1	
Irak			1	
Italy		2	1	2
Mexico	2	3	2	2
The Netherlands		1	2	
Portugal			4	
United Kingdom	1	1	1	3
Dominican Republic		1		
Venezuela			1	
Total	31	103	123	45

Figure 3. **A:** language of the manuscripts received. **B:** origin of the manuscripts received.
* Data from 2021 include the first and second quarter of the year only.

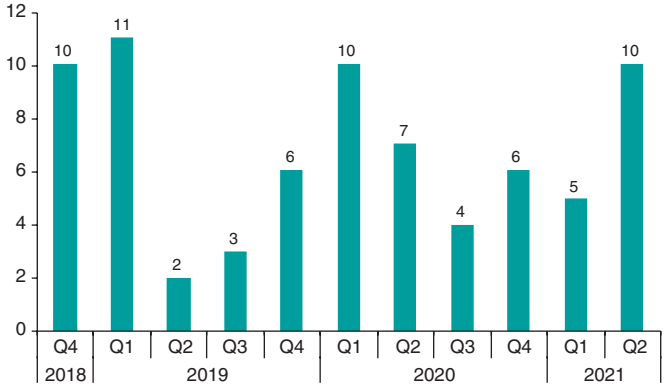


Figure 4. Original articles received since the journal was launched until June 30, 2021, by quarters of the year.

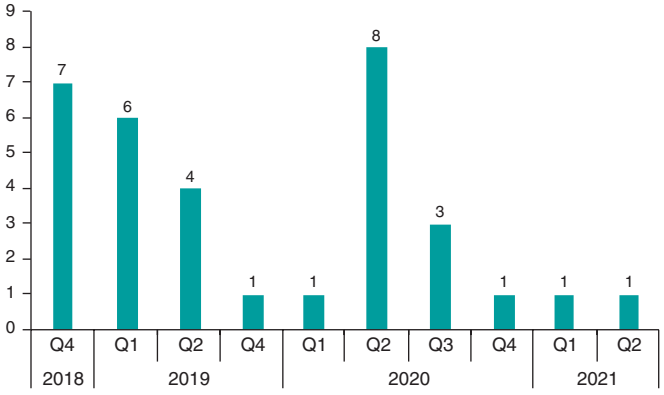


Figure 6. Clinical cases received since the journal was launched until June 30, 2021, by quarters of the year.

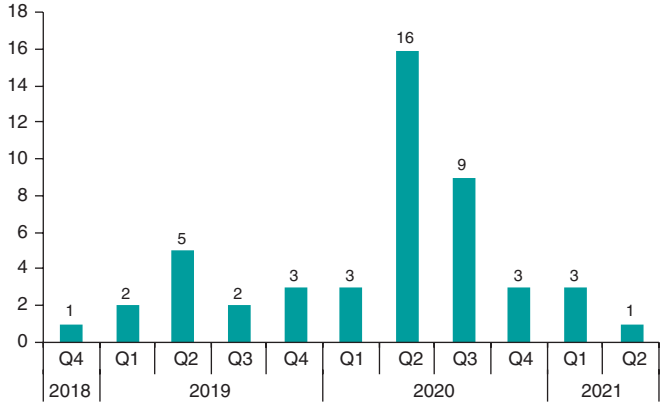


Figure 5. Letters to the Editor received since the journal was launched until June 30, 2021, by quarters of the year.

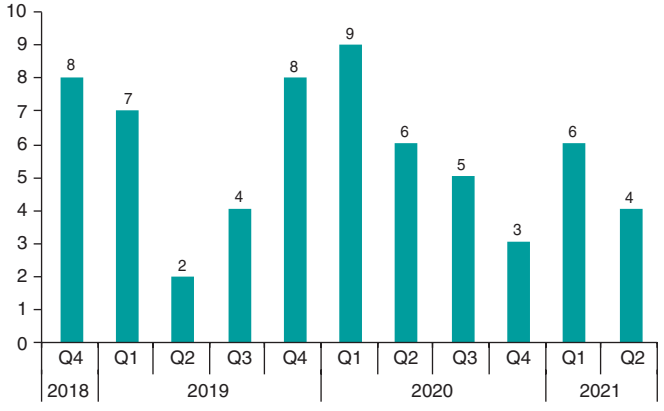


Figure 7. Images received since the journal was launched until June 30, 2021, by quarters of the year.

Images in cardiology

In the interannual period covered by this analysis a total of 18 images were received (figure 7), but only 7 were accepted for publication. The evolution of this type of content is very similar to that of cases and letters: the stock of images pending publication limits the possibility of acceptance, thus discouraging submission. Given these circumstances, over the last year the number of images published per issue was increased from 2 to 3.

CONTENTS TRANSFERRED FROM *REVISTA ESPAÑOLA DE CARDIOLOGÍA*

Our flagship publication, *Revista Española de Cardiología*, has a high impact factor, making it highly attractive for researchers worldwide. This creates an inevitable mismatch between the number of manuscripts received and the number of manuscripts accepted, setting the bar of article rejection quite high despite the undeniable interest of many of the manuscripts. *REC: Interventional Cardiology's* editorial committee evaluates rejected manuscripts within the scope of the journal and offers the authors the possibility of submitting them to our journal.

Over the last interannual period, the authors of 14 manuscripts accepted this referral proposal. We strongly believe that, in time, this alternative will become more attractive and accepted.

THE AUTHORS

The editorial committee wishes to take a moment to write a few words of gratitude to the true architects of this journal, those who have made it possible: the authors of the contents. Our journal is still in its infancy and cannot offer an impact factor to those researchers who decide to publish with us. That is why their contribution is especially appreciated, because it elevates the journal to quality levels that will bring the impact it truly deserves.

This gratitude is not only applicable to the authors who submit their manuscripts spontaneously, but also to those who accept the invitation of the editorial committee to elaborate top quality commissioned contents.

THE REVIEWERS

Last year's Editor's page already discussed the praiseworthy work of our reviewers for their positive response and speedy delivery of their very high-quality evaluations. This year we wish to bring it up again as their response has been the same. Figure 8 includes the evaluation times, and the editorial decision-making times. The performance of our reviewers is simply exceptional. It only takes them an average 8.8 days to evaluate all kinds of contents, and a little over 10.1 days to evaluate original articles. Compared to other journals outside the REC Publications journal family, this is truly remarkable.

For all this, we think all reviewers should be congratulated on their work (table 1). Also, our elite reviewers deserve special credit due to their exceptional evaluations and fast-track responses (table 2). Their work is recognized with CASEC credits.

OUR WEBSITE

Despite our limited print edition, the dissemination of the journal's content in this digital age is predominantly online. The main incoming traffic to our website[6] is organic traffic that grows parallel to the indexing of our contents in database search engines, followed by direct traffic and accesses from other sites: the SEC website,[7] ACI-SEC official website,[8] where the journal has gained visibility, *Revista Española de Cardiología*,[9] *REC: CardioClinics*,[10] Google Scholar,[11] Campus IMAS,[12] websites, etc.

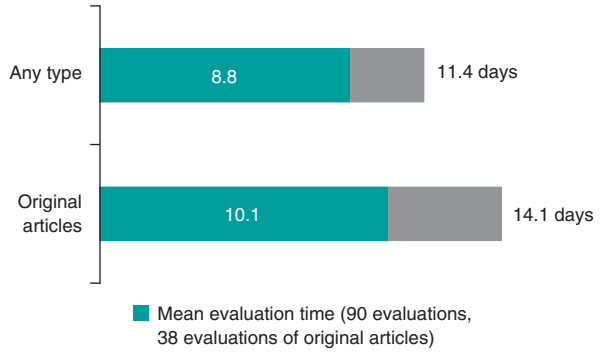


Figure 8. Mean editorial times from July 1, 2020 through June 30, 2021. The mean values reported correspond to 90 evaluations of any type (38 evaluations of original articles).

Table 1. Reviewers of *REC: Interventional Cardiology* who performed evaluations from July 1, 2020 through June 30, 2021

Juan H. Alonso-Briales	Josep Gómez-Lara
Ignacio Amat	Nieves Gonzalo
Eduardo Arroyo	Enrique Gutiérrez-Ibañes
Dabit Arzamendi	Felipe Hernández
Pablo Avanzas	Andrés Íñiguez
Teresa Bastante	Santiago Jiménez-Valero
Salvatore Brugaletta	Alfonso Jurado
Ramón Calviño	Esteban López de Sá
Xavier Carrillo	José R. López-Mínguez
Belén Cid	Ramón López-Palop
Bernardo Cortese	Íñigo Lozano
Ignacio Cruz	Cesar Morís
Javier Cuesta	Soledad Ojeda
José F. Díaz	Manuel Pan
Jaime Elízaga	Armando Pérez de Prado
Rodrigo Estévez-Loureiro	Fernando Rivero
José L. Ferreiro	Oriol Rodríguez
Xavier Freixa	Rafael Romaguera
Guillermo Galeote	Juan M. Ruiz-Nodar
Tamara García-Camarero	José R. Rumoroso
Bruno García del Blanco	Manel Sabaté
Javier Goicolea	Ángel Sánchez-Recalde
Joan A. Gómez-Hospital	Ramiro Trillo

1. Spain	**17552** (34.96%)
2. United States	**5170** (10.30%)
3. Mexico	**3635** (7.24%)
4. Argentina	**2991** (5.96%)
5. India	**1817** (3.62%)
6. Colombia	**1763** (3.51%)
7. Germany	**1715** (3.42%)
8. Peru	**1593** (3.17%)
9. Chile	**1216** (2.42%)
10. Ecuador	**1060** (2.11%)

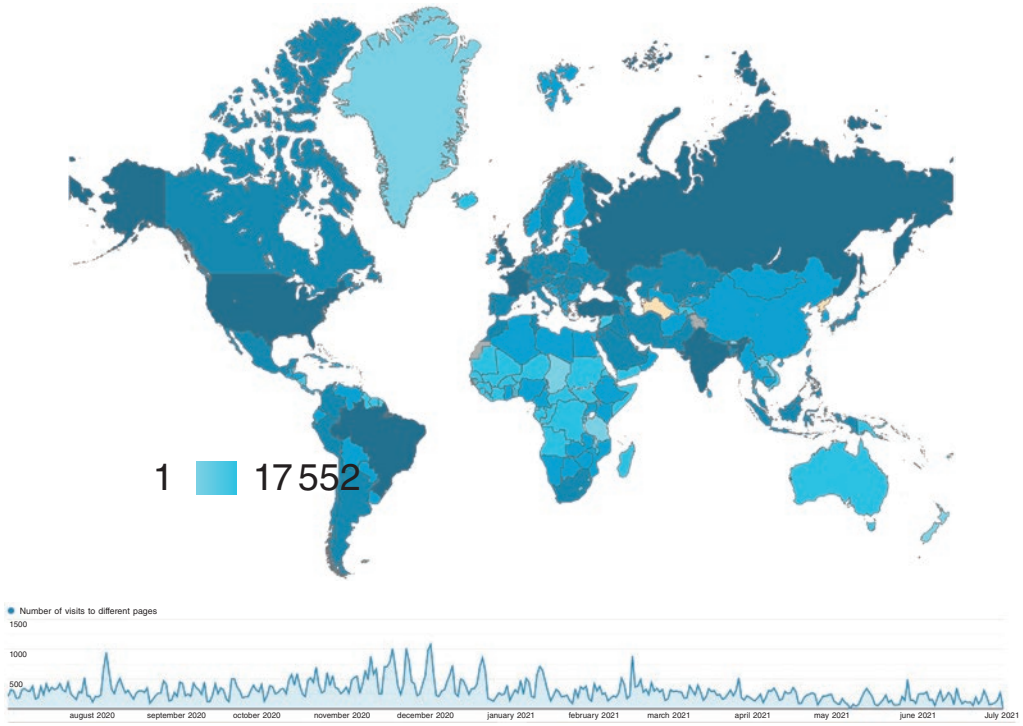


Figure 9. Visits to the electronic edition of *REC: Interventional Cardiology* from July 1 2020 through June 30, 2021.

Table 2. Elite reviewers in 2020

Pablo Avanzas	Alfonso Jurado-Román
Salvatore Brugaletta	Ramón López-Palop
Javier Goicolea	Manuel Pan
Joan A. Gómez-Hospital	Fernando Rivero
Felipe Hernández	Juan M. Ruiz-Nodar
Santiago Jiménez Valero	

We wish to take this opportunity to thank all Latin American scientific societies that have included a hyperlink to our journal in their official websites.

Our journal is read all over the world. The highest number of visits come from Spain, followed by the United States, Mexico, Argentina, and India (figure 9).

Regarding social networks, Twitter is our main source of traffic (62%) followed by Facebook (28%), Instagram (5%), and LinkedIn (2%).

Our homepage, ahead-of-print contents, abstracts, and COVID-19-related contents have been quite visited. Also, we should mention the interest generated by contents such as the special article on the percutaneous management of tricuspid regurgitation, or the review article on TAVI in special indications.[13,14]

Between the end of 2020 and the beginning of 2021, our publishing house, Permanyer Publications Ltd., updated the journal website[6] several times to make it more stable and lay the foundations for its future growth. The site design has not changed since most of these changes are invisible to the user. However, they improve the user navigation experience allowing new possibilities for the growing volume of contents in our journal.

DISSEMINATION

The journal's Editor's videos[15] with author interviews, were consolidated over the last year. Thanks to streaming recordings, the difficulties following the lack of mobility due to the pandemic were overcome. We became more familiar with a new recording format that allows more flexibility and dynamism. Several authors have expressed their appreciation and surprise for the unexpected peaks of visibility that these videos had had for their articles among our scientific community.

In addition, newsletters with a summary of the latest issue published are sent to our subscribers quarterly. The bulletins sent by *Revista Española de Cardiología* include a hyperlink to our contents too. Also, the latest articles published on *REC: Interventional Cardiology* can be found on *Revista Española de Cardiología's* website.

Interviews with the authors of our articles are regularly published in the blog *Cardiología Hoy*[16] on the SEC website. Also, different access windows have become available for the users (homepage, publications section, etc.). *REC: Interventional Cardiology's* articles are disseminated through SEC bulletins. In addition, our journal has its own specific space on SEC News.

REC Interventional Cardiology was also present in discussion forums specifically created for our journal in congresses and scientific meetings held over the last year in Latin American countries, namely Mexico and Venezuela.

AWARD TO THE BEST ARTICLE PUBLISHED ON *REC: INTERVENTIONAL CARDIOLOGY*

As with all our activities, the initiatives to disseminate our journal have been influenced by the COVID-19 pandemic. The first-edition award for the best article published on *REC: Interventional Cardiology*

went to "Quantitative flow ratio in myocardial infarction for the evaluation of non-infarct-related arteries. The QIMERA pilot study".[17] The prize was awarded during the 31st ACI-SEC Congress that was held virtually in 2020. For the second edition, the ACI-SEC has decided to increase the reward and number of prizes awarded to 2 (an overall prize of €2500; first prize, €1500; second prize, €1000).

The COVID-19 year changed the world overnight. Big –and in many cases permanent– changes have occurred. Our journal knew how to face this historic crisis and came up strong. As we mentioned earlier, the trajectory of *REC: Interventional Cardiology* keeps consolidating, growing, and improving to achieve higher levels of recognition. It is the culmination of a dream that a group of Spanish interventional cardiologists had for years. A dream that has become an unquestionable reality today.

ACKNOWLEDGMENTS

So far we have shown our appreciation to authors and reviewers alike for their essential role in our journal. As the editor-in-chief, I also wish to show my profound gratitude for the work done by associated editors Dr. Juan Sanchis, Dr. Fernando Alfonso, and Dr. Raúl Moreno.

Dr. Juan Sanchis has become the editor-in-chief of *Revista Española de Cardiología*, which is a guarantee of success in the future of this publication.

For the last 2 years, Dr. Raúl Moreno has been a member of the editorial team, and the president of ACI-SEC. The incoming new president, Dr. Ignacio Cruz, will also be one of the main pillars of the journal. We should remember that the ACI-SEC is the leading sponsor of our journal, which is essential to guarantee its viability. And speaking of funding, we wish to thank the contribution made from companies in the interventional cardiology field. Thanks to their unconditional co-sponsoring our journal has come to life as ackowledged in the back cover of every issue.

Finally, we wish to express our gratitude to the members of *Revista Española de Cardiología* editorial office including Iria del Río, Eva M. Cardenal, Belén Juan, María González Nogal, and Helena Gómez Lobo, TIC consultant Pablo Avanzas, the SEC TIC working group, and the entire team at Permanyer Publications Ltd. for their excellent work and dedication. The enthusiasm shown at the beginning has not wavered and is now stronger than ever.

The dedication and devotion of all these people have been unconditional and remain an ongoing stimulus for this editorial team.

"To be perfect is to have changed often"

J.H. Newman

FUNDING

None declared.

CONFLICTS OF INTEREST

None reported.

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REC Interv Cardiol. 2021;3(4):245-246
https://doi.org/10.24875/RECICE.M21000228

Editorial

TAVI in nonagenarians, what do we know so far?

El TAVI en nonagenarios, ¿qué sabemos?

Pablo Díez-Villanueva* and Fernando Rivero

Servicio de Cardiología, Hospital Universitario de La Princesa, IIS-IP, Madrid, Spain

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https://doi.org/10.24875/RECICE.M21000220

Transcatheter aortic valve implantation (TAVI) has become a widely used therapeutic strategy to treat symptomatic severe aortic stenosis. Certain randomized clinical trials available have already described the prognostic benefit of this technique in elderly patients with high or very high surgical risk. Also, when implanted via transfemoral access, it has proven non-inferior or even superior compared to surgical aortic valve replacement in low- and intermediate-risk patients. Therefore, the current recommendations support its use in elderly patients with severe aortic stenosis regardless of their surgical risk.[1]

However, since it is an age-related heart valve disease without an effective medical therapy yet, the prevalence of severe aortic stenosis has been growing parallel to life expectancy. As a matter of fact, this disease has huge repercussions in the patients' survival rate and quality of life.[2] Consequently, nonagenarian patients with severe aortic stenosis are a group in continuous expansion, and, to this date, the best way to treat them is still under discussion. Since most of these patients have traditionally been misrepresented in the clinical trials and there are registries with good results but a possible selection bias, the decision to treat these patients with TAVI is still challenging and is made on an individual basis after meticulous assessment of the patients by the heart team.

Data from the STS/ACC TVT registry on the results of 3773 patients ≥ 90 age provide us with relevant information on this clinical setting.[3] Data show a higher mortality rate compared to younger patients at 30 days (8.8% vs 5.9%; $P < .001$) and 1 year (24.8% vs 22.0%; $P < .001$) mainly due to higher rates of in-hospital major bleeding (8.1% vs 6.8%; $P < .001$) and strokes (2.7% vs 2.1%; $P = .021$). Table 1 shows the data from the main international registries on nonagenarian patients treated with TAVI.

In a study recently published on *REC: Interventional Cardiology*, Cepas-Guillén et al. describe the national experience with TAVI in nonagenarian patients with severe aortic stenosis between 2009 and 2018.[10] The findings were compared to those from patients between 75 and 90 years who received the same treatment during the same period of time. A total of 8073 patients—387 nonagenarians and 7686 patients between 75 and 90 years—were included. The authors saw a higher in-hospital mortality rate in nonagenarian patients without significant differences at the 1-year follow-up (although with a tendency towards a higher mortality rate in patients ≥ 90 years). In the multivariate analysis, age was not significantly associated with a higher all-cause mortality rate, but the presence of comorbidities such as atrial fibrillation or worsening renal function. Also, a higher surgical risk was reported.[10] The role of comorbidities in nonagenarian patients was analyzed by a former substudy that included 117 consecutive patients around 90 years old (median age, 91.1 years; 117 women) from the PEGASO (Prognosis of symptomatic severe aortic stenosis in octogenarians) and IDEAS (Influence of the severe aortic stenosis diagnosis) registries conducted in our country.[11] A high comorbidity burden, characterized by scores ≥ 3 in the Charlson comorbidity index, present in a high number of patients, was associated with a high mortality rate at the 1-year follow-up.

Nonetheless, data from the SwissTAVI registry confirmed a tendency towards higher rates of mortality, stroke, and pacemaker implantation in the elderly group (< 70, 70-79, 80-89, and > 90 years) among the 7097 patients treated with TAVI between 2011 and 2018 (median age, 82 ± 6.4 years; 49.6% women) in Switzerland.[4] It is interesting that older age was associated with a lower standard mortality rate compared to the general population of the same group without any differences reported among nonagenarian patients. Same as in the study conducted by Cepas-Guillén et al.,[10] the mean comorbidity rate of nonagenarian patients included in this registry was lower compared to that of patients < 90 years, suggestive that it is a highly selected population, which is unequivocally associated with a better prognosis in the short- and long-term. Despite of this, in this series, vascular complications and major bleeding increased significantly among nonagenarian patients. In the metanalysis conducted by Sun et al.,[12] the rate of major bleeding reported was similar above and below the 90-year mark with a relative risk of 1.17 (95% confidence interval, 1.04-1.32). On the contrary, the rate of vascular complications went up > 90 years, especially when non-femoral access techniques were used. In the Spanish national series, transfemoral access was more frequently used in patients < 90 years. Although no random comparison of the access routes was conducted, most data support the idea that risks are higher when the non-femoral access is used.[13] Also, these data recommend the use of this access in elderly patients whenever possible. Also, a tendency towards better results has been confirmed as heart teams have been gaining experienced in the management of this group of patients, both in the selection and implantation technique used as well as in further approaches with lower rates of complications and 30-day mortality > 50% at the 4-year follow-up.[5] Noteworthy, it would be interesting to have more data on the treatment received by the patients, especially regarding antiplatelet therapy, given these patients' higher risk of bleeding

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Table 1. Data of nonagenarian patients treated with TAVI from the main international registries

Study, year	N (≥ 90 years)	Procedural success	Major bleeding	30-day mortality rate	1-year mortality rate
SwissTAVI,[4] 2021	507	N/A	13%	6.7%	19.7%
Mentias et al.,[5] 2019	13 544	N/A	10%	3.6%	26.6%
Vlastra et al.,[6] 2019	882	N/A	8%	9.9%	N/A
Doshi et al.,[7] 2018	1163	N/A	35%	6.0%	N/A
Elgendy et al.,[8] 2018	5840	N/A	28%	6.6%	N/A
McNeely et al.,[9] 2017	3531	N/A	34%	8.4%	25.4%
STS/ACC TVT,[3] 2016	3773	N/A	8%	8.8%	24.8%

N/A, not available; TAVI, transcatheter aortic valve implantation.

with the use of 2 different antiplatelet drugs, instead of 1,[14] and a longer follow-up too.

Added to all this, we should recognise not only the presence of comorbidities, but also frailty, and other geriatric symptoms—prevalent all of them—that have a significant prognostic impact in elderly patients treated with TAVI.[15] Different scales have been described, some of them very easy to implement and based on easy parameters like the presence of lower-limb frailty, cognitive impairment, anemia, and hypoalbuminemia, which allow us to predict mortality at the 1-year follow-up.[16] The implementation of measures is essential to reverse frailty—if present—and prevent the appearance of delirium and other complications during admission since this improves the prognosis of patients significantly.

Finally, we wish to congratulate the Interventional Cardiology Association of the Spanish Society of Cardiology Association for their remarkable work in this area—in continuous expansion and growth—since the experience and learning gained on this regard will contribute to improve the treatments that we will administer to our patients.

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Editorial

New drug-eluting stents: technological refinement continues

Nuevos stents *farmacoactivos: el refinamiento tecnológico continúa*

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The arrival of drug-eluting stents (DES) nearly 2 decades ago ignited a revolution in the field of interventional cardiology. The addition of antiproliferative drugs to the stent platform reduced the rate of in-stent restenosis significantly and increased the number of patients that, to this date, have benefited from percutaneous revascularization.[1,2] However, its Achilles tendon was initially the higher rate of late stent thrombosis involved. The permanent polymer used in the first generation of DES induced inflammatory and hypersensitivity reactions that delayed endothelization. A health alert followed[3] that made the medical community recommend extended courses of dual antiplatelet therapy and put into question the convenience of DES. Beyond the increased rate of stent thrombosis, the first-generation of this type of stents had additional limitations: they were stainless-steel platforms with up to 140 µm thick struts, worse stent navigability, and fewer crossing capabilities. Also, the stent maximum expansion was limited (3.5 mm in the Cypher stent, Cordis Corp.), which occasionally prevented treating left main coronary artery lesions. With the passing of time, this stent technology has been refined to a point that there has been a major overhaul in its 3 main components: platform, polymer, and antiproliferative drug.

The changes made to the stent platform have been the development of more biocompatible alloys that have reduced strut thickness significantly and, consequently, improved stent navigability. Additionally, radial strength has been preserved to prevent recoil (table 1). Most of the stents commonly used today consist of cobalt-chromium or platinum-chromium alloys. The open-cell design has won the battle over the closed-cell design because it reduces the number of inter-strut links, the degree of jailed side-branch while improving stent navigability and conformability. Also, the new generation of DES have wider overexpansion limits (4.5 mm to 6 mm), which allows us to treat left main coronary artery lesions by adapting the stent area to the corresponding lunimal references without damage to the platform.

Polymers are the reservoir from which the drug is released in a controlled way towards the arterial wall. XIENCE (Abbott), and Resolute Onyx (Medtronic) stents include permanent polymers, but with improved biocompatibility. The XIENCE polymer is highly fluorinated, which minimizes adhesion and platelet activation increasing the safety profile. The Onyx stent uses Biolinx that consists of a mixture of polymers with hydrophilic capabilities that make it biocompatible and hydrophobic for a prolonged and uniform drug release. However, despite the good results reported with the new permanent polymers, some companies have decided to develop bioresorbable polymers (SYNERGY [Boston Scientific], Orsiro [Biotronik], Ultimaster Tansei [Terumo] stents, etc.). The use of a bioresorbable polymer-based coating facilitates degradation after the drug complete release just leaving 1 bare-metal stent behind 3-4 months after implantation, which prevents the remaining polymer from participating in the immune response associated with stent thrombosis. The biodegradable polymer-based SYNERGY stent has shown a rate of stent thrombosis of 0% at the 6-month follow-up, and a rate of target lesion revascularization similar to the one observed with the permanent polymer-based Promus Element stent (Boston Scientific).[4] On the other hand, the biodegradable polymer-based Orsiro stent had a significantly lower rate of target lesion failure compared to the XIENCE stent with permanent polymer.[5] However, the XIENCE stent group had more and longer stents implanted, both factors associated with adverse events at follow-up.

Polymer-free stents stand as an alternative to biodegradable polymer-based stents. The most representative of the former is the BioFreedom (Biosensors). It consists of a stainless-steel platform with micropores that store biolimus for a 1-month release of the drug. The lack of a polymer may potentially allow to shorten the duration of the period on dual antiplatelet therapy down to 1 month, like with bare metal stents. In the LEADERS FREE trial,[6] the BioFreedom was compared to a bare metal stent in patients with high-risk of bleeding and a 1-month course of dual antiplatelet therapy. The outcomes proved that it was superior regarding the primary evaluation criteria for the safety and efficacy profile. Afterwards, almost every company has conducted or started safety and efficacy trials with 1-month courses of dual antiplatelet therapy (table 1).

Therefore, several advances have been made with new generation DES. The clinical impact associated with strut thickness reduction

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Table 1. Characteristics of drug-eluting stents

Stent	Plataform	Polymer/ coating	Drug	Strut thickness (µm)	Maximum expansion (mm)	Studies with 1 month DAPT duration
XIENCE	Cobalt-chromium	Permanent/ circumferential	Everolimus	81	2-3.25 → 3.75 3.5-4 → 5.5	Xience 28 USA (NCT03815175)
SYNERGY	Platinum-chromium	Bioresorbible/ abluminal	Everolimus	74	2.25 → 3.5 3-3.5 → 4.25 4-5 → 5.75	SENIOR (NCT02099617)
Onyx	Nickel-platinum-chronium	Permanent/ circumferential	Zotarolimus	81	2.5-3 → 3.75 3.5-4 → 4.75 4.5-5 → 5.75	Onyx ONE (NCT03344653)
Orsiro	Cobalt-chromium	Bioresorbible/ circumferential	Sirolimus	60	2.5-3 → 3.5 3.5-4 → 4.5	Bioflow-DAPT (NCT04137510)
Ultimaster Tansei	Cobalt-chromium	Bioresorbible/ abluminal	Sirolimus	80	2.25-3 → 4.5 3.5-4 → 5.5	Master DAPT (NCT03023020)
BioFreedom	Stainless-steel	Polymer-free/ abluminal	Umirolimus	112	2.5-3 → 4.76 3.5-4 → 5.96	LEADERS FREE (NCT01623180)
Angiolite	Cobalt-chromium	Permanent/ circumferential	Sirolimus	75-85	2-2.5 → 4 2.75-3.5 → 5.25 4-4.5 → 6	–

DAPT, dual antiplatelet therapy.

or the selection of bioresorbable polymer-based stents vs permanent or polymer-free stents is still under discussion. However, these improvements have had significant repercussions in the stent navigability, overexpansion capabilities, and selection of duration for dual antiplatelet therapy. However, these stent properties highly demanded by interventional cardiologists should always be based on a robust set of trials that confirm the efficacy and safety profile of each stent. Currently, the Angiolite stent (iVascular) is in this stage. It has recently joined the family of DES. This stent is an ultra-thin strut (75 µm to 85 µm) cobalt-chromium platform made from a biostable fluorinated polymer plus sirolimus as the antiproliferative drug. In the ANCHOR trial it showed an excellent degree of endothelization on the optical coherence tomography,[7] with an 83% strut endothelial coverage at 3 months. Afterwards, the ANGIOLITE trial compared it to the standard DES and found a 0.04 mm late luminal loss vs the 0,08 mm of the XIENCE stent, as well as a low rate of events at the 2-year follow-up in both groups[8] (target lesion failure, 7.1% with the Angiolite vs 7.6% with the XIENCE). In an article published on *REC Interventional Cardiology*, Pérez de Prado et al.[9] presented a multicenter real-world registry of patients treated with the Angiolite stent. This registry could be considered the «moment of truth» for this stent. We should remember that the Absorb stent (Abbott) had excellent immediate results and at the 5-year follow-up[10] in the early trials. However, it showed a high rate of stent thrombosis when used in real-world patients. The ANCHOR registry included 646 patients with a 2-year clinical follow-up. A total of 30% of these patients were diabetics. ST-segment elevation myocardial infarction was the clinical presentation in almost 25% of these patients, and nearly 50% of them had multivessel disease. The rate of target vessel failure and the rate of stent thrombosis at the 2-year follow-up were 3.4%, and 0.9%, respectively. In this sense, the stent offers similar results to those obtained with state-of-the-art DES as the table of the supplementary data of the aforementioned article shows.[9] However, these promising results will need to be confirmed at the 5-year follow-up. The behavior of the stent in the most complex lesions like bifurcations or chronic total occlusions associated with worse clinical outcomes—underrepresented in the registry—also needs to be assessed.

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Original article

Outcomes of nonagenarians after transcatheter aortic valve implantation

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ABSTRACT

Introduction and objectives: Nonagenarians are a fast-growing age group among cardiovascular patients, especially with aortic stenosis, but data about their prognosis after transcatheter aortic valve implantation (TAVI) is scarce. The objective of our study is to analyze the baseline characteristics of nonagenarians treated with TAVI and determine whether age ≥ 90 years is associated with a worse prognosis compared to non-nonagenarian patients.
Methods: We included all patients ≥75 years enrolled in the multicenter prospective Spanish TAVI registry between 2009 and 2018. Patients < 75 years were excluded.
Results: A total of 8073 elderly patients (≥ 75 years) from 46 Spanish centers were enrolled in the Spanish TAVI registry; 7686 were between ≥ 75 and < 90 years old (95.2%), and 387 were nonagenarian patients (4.79%). A gradual increase of nonagenarians was observed. The transfemoral access was used in 91.6% of the cases, predominantly among the nonagenarian patients (91.4% vs 95.1%, $P = .01$). Nonagenarians were more likely to die during their hospital stay (4.3% vs 7.0% among nonagenarians, $P = .01$). However, no difference was seen in the all-cause mortality rates reported at the 1-year follow-up (8.8% vs 11.3%, $P = .07$). In the multivariate analysis, age ≥ 90 years was not independently associated with a higher adjusted all-cause mortality rate (HR, 1.37, 95%CI, 0.91–1.97, $P = .14$). The baseline creatinine levels, and the in-hospital bleeding complications were all associated with a worse long-term prognosis in nonagenarians treated with TAVI.
Conclusions: Nonagenarians are a very high-risk and growing population with severe AS in whom TAVI may be a safe and effective strategy. Careful patient selection by the TAVI heart team is mandatory to achieve maximum efficiency in this population where the baseline kidney function and bleeding complications may determine the long-term prognosis after TAVI.

Keywords: TAVI. Aortic stenosis. Nonagenarians. Elderly.

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Pronóstico de pacientes nonagenarios tras implante percutáneo de válvula aórtica

RESUMEN

Introducción y objetivos: Los nonagenarios son un grupo de edad en rápido crecimiento entre los pacientes cardiovasculares, en especial con estenosis aórtica, pero los datos sobre su pronóstico después de la implantación transcatéter de válvula aórtica (TAVI) son escasos. El objetivo de este estudio es analizar las características basales de los nonagenarios tratados con TAVI y determinar si la edad ≥ 90 años está relacionada con un peor pronóstico en comparación con los pacientes no nonagenarios.
Métodos: Se incluyó a todos los pacientes ≥ 75 años inscritos en el registro prospectivo multicéntrico español de TAVI entre 2009 y 2018. Se excluyó a aquellos < 75 años.
Resultados: Se inscribieron en el registro español de TAVI 8.073 pacientes ≥ 75 años de 46 centros de España; 7.686 de > 75 a 90 años (95,2%) y 387 nonagenarios (4,79%). Se observó un aumento progresivo de los nonagenarios. El acceso transfemoral se utilizó en el 91,6% de los casos, predominantemente en los nonagenarios (91,4 frente a 95,1%; p = 0,01). Los nonagenarios tenían más probabilidades de morir durante la hospitalización (4,3 frente a 7,0%; p = 0,01). Sin embargo, no hubo diferencia en la tasa de mortalidad por cualquier causa al año de seguimiento (8,8 frente a 11,3%; p = 0,07). En el análisis multivariable, la edad ≥ 90 años no se asoció de forma independiente con un aumento de la mortalidad por cualquier causa ajustada (HR = 1,37; IC95%, 0,91-1,97; p = 0,14). La creatinina basal y las complicaciones hemorrágicas intrahospitalarias se asociaron a un peor pronóstico a largo plazo en pacientes nonagenarios tratados con TAVI.
Conclusiones: Los nonagenarios son una población creciente y de muy alto riesgo, con estenosis aórtica grave, para quienes la TAVI podría representar una estrategia segura y efectiva. Una cuidadosa selección de los pacientes por un equipo multidisciplinario de TAVI es obligatoria para lograr la máxima eficiencia en esta población en la que la función renal basal y las complicaciones hemorrágicas pueden determinar el pronóstico a largo plazo tras la TAVI.

Palabras clave: TAVI. Estenosis aórtica. Nonagenarios. Ancianos.

Abbreviations

TAVI: transcatheter aortic valve implantation. **AS:** aortic stenosis. **SAVR:** surgical aortic valve replacement.

INTRODUCTION

The development of transcatheter aortic valve implantation (TAVI) has marked a milestone in the management of severe aortic stenosis (AS). Thanks to its minimally invasive approach, TAVI allows us to treat patients with severe AS and inoperable or high surgical risk, thus improving their prognosis and quality of life compared to standard therapy and surgical aortic valve replacement (SAVR), respectively.[1,2] According to trial results, elderly patients have benefited the most due to their high surgical risk. Given the current demographic trend towards aging[3] in developed countries and the increasing prevalence of the corresponding severe AS,[4] it seems reasonable to expect that the number of elderly patients with severe AS who will require TAVI within the next few decades will be on the rise. In this sense, nonagenarians are a fast-growing and high-risk segment of the population on whom scarce data on specific outcomes are available. Given their anticipated short life expectancy and comorbidity burden, TAVI may be an excellent option for them. However, we should mention that the absolute cost of TAVI is high.[5] Therefore, there is an unmet need for "real-world" data before assessing the impact of this beneficial and expensive technique in a growing and high-risk population like nonagenarians. To this end, the objective of our study was to describe the baseline characteristics, assess the clinical outcomes, and identify the characteristics of futility of this high-risk subgroup based on data from the Spanish TAVI registry.[6]

METHODS

Patient selection and follow-up

The Spanish TAVI registry is a multicenter prospective registry that enrolled all consecutive patients with severe AS treated with TAVI in 46 Spanish centers (table 1 of the supplementary data). The Spanish TAVI registry has been promoted by the Interventional Cardiology Association of the Spanish Society of Cardiology. For our analysis, we included all patients ≥ 75 years included in the Spanish TAVI registry from 2009 through 2018. Patients < 75 years were excluded. The baseline characteristics, echocardiographic findings, and procedural results were all recorded. The follow-up protocol included a medical consultation 30 days and 1 year after hospital discharge. The registry complies with the Spanish legislation on data protection and has been approved by a central ethics committee. Center participation in this registry was voluntary and all participants gave their informed consent. All data were included in the registry prospectively and systematically reviewed while looking for inconsistencies or lack of data. The data collected included the patients' demographic characteristics, past medical history, baseline clinical characteristics, echocardiographic findings, procedural characteristics, and in-hospital clinical and follow-up outcomes.

Study endpoints and definitions

Standardized definitions of all patient-related variables, clinical diagnoses, and in-hospital complications and outcomes were used according to the Valve Academic Research Consortium (VARC) definitions.[7,8] The primary endpoint was all-cause mortality occurring within the first year after TAVI between nonagenarians and elderly non-nonagenarian patients. Also, the rates of in-hospital mortality, stroke, myocardial infarction, major or life-threatening bleeding events as defined by the VARC criteria,[8,9] and permanent pacemaker implantation were compared too. High surgical risk was defined as logistic EuroSCORE values > 20% or Society of Thoracic Surgeons (STS) risk model values > 8%. The unadjusted and

adjusted short- (in-hospital) and long-term (within the first year after TAVI) mortality rates were assessed in the general cohort.

Statistical analysis

Categorical variables were expressed as frequencies (percentages), and the differences were assessed using the chi-square test (or Fisher's exact test, when appropriate). Continuous variables were expressed as mean ± standard deviation or as median [interquartile range]. The Kolmogorov-Smirnov test was used to guarantee a normal distribution. Continuous variables were compared using the analysis of variance (ANOVA) test or the Kruskal-Wallis test, when appropriate. Using all follow-up data available survival curves were built for the time-to-event variables using the Kaplan-Meier method. To identify the independent predictors of first year all-cause mortality in the general cohort, the multivariate Cox proportional hazard regression model was used. The proportionality assumption was assessed graphically using log-minus-log plots. Also, the Cox proportional hazard models for the primary endpoint satisfied the proportional hazards assumption. In all analyses, 2-tailed *P* values < .05 were considered statistically significant. Follow-up was scheduled to end on the date of the last follow-up or at the 1-year mark, whichever came first. The analyses were performed using IBM SPSS statistical software (V 19.0, IBM, United States).

RESULTS

Baseline and echocardiographic characteristics

From January 2012 through December 2018, a total of 8073 elderly patients (≥ 75 years) from 46 Spanish centers were enrolled in the Spanish TAVI registry; 7686 (95.2%) were elderly non-nonagenarian patients (≥ 75-< 90 years) while 387 (4.79%) were nonagenarians (≥ 90 years). The patients' baseline characteristics in both groups are shown on table 1. The mean age ± standard deviation of the non-nonagenarian group was 82.6 ± 3.66 years (91.06 ± 1.29 years in nonagenarians). Women were predominant in both groups (55.3% vs 58.4% in nonagenarians; *P* = .23). Nonagenarians had a lower prevalence of diabetes mellitus, peripheral arterial disease or previous myocardial infarction. On the other hand, they showed a lower estimated glomerular filtration rate at baseline, and a higher EuroSCORE model I. There were no differences in the TAVI indications between both groups. Figure 1 shows the number and percentage of nonagenarians treated with TAVI over the years. In absolute terms, there is a gradual increase of nonagenarians from the 11 patients reported in 2011 to the 78 patients reported in 2018.

Procedural characteristics

The post-implantation TAVI echocardiographic findings and procedural characteristics are shown on table 2. Transfemoral access was used in 91.6% of the cases, predominantly among nonagenarians (91.4% vs 95.1%; *P* = .01). No differences were seen in the type or size of valve used. The device implantation success achieved was high in both groups (94.9% vs 95.6%; *P* = .55).

Clinical outcomes

A comparison of clinical outcomes between the non-nonagenarian group and the nonagenarian one is shown on table 3. Compared with the non-nonagenarian group, nonagenarians were more likely to die during their hospital stay (4.3% vs 7.0% among nonagenarians; *P* = .01) and have major or life-threatening bleeding events (1.2% vs 3.1%; *P* < .05). No differences were found in stroke, myocardial infarction, vascular complications, permanent pacemaker implantation or acute kidney injury. The median follow-up was 308 days (31-365). At the 1-year follow-up, a total of 719 patients had died (8.9%). The unadjusted risk of all-cause mortality at the 1-year follow-up was similar among nonagenarians compared to the non-nonagenarian group (8.8% vs 11.6%; *P* = .07) (figure 2).

The multivariate Cox proportional hazard models identified independent predictors of all-cause mortality in the cohort (table 4). Age ≥ 90 years was not independently associated with a higher adjusted all-cause mortality rate (hazard ratio [HR], 1.37; 95% confidence interval [95%CI], 0.91–1.97; *P* = .14). The baseline creatinine levels prior to the procedure (HR, 1.28; 95%CI, 1.15–1.44; *P* < .001), dyspnea as the predominant symptom of severe AS (HR, 1.49, 95% CI 1.14–1.3, *P* < .01), surgical risk assessment as high-risk or inoperable (HR, 1.34; 95%CI, 1.01–1.79; *P* = .04), and atrial fibrillation (HR, 1.37; 95% CI, 1.09–1.73; *P* = .008) were independently associated with a higher adjusted all-cause mortality rate. On the other hand, the body mass index (HR, 0.97; 95%CI, 0.95-0.99; *P* = .02), the use of femoral access (HR, 0.68; 95%CI, 0.51–0.92; *P* = .02), and the device implantation success rate (HR, 0.18; 95%CI, 0.13–0.23; *P* < .001) were associated with a lower adjusted all-cause mortality rate at the follow-up.

Table 2 of the supplementary data shows differences in the baseline characteristics, echocardiographic findings, and procedural characteristics between the nonagenarian patients who died at the follow-up and those who did not. The nonagenarians who died after TAVI had higher baseline creatinine levels (1.16 ± 0.42 vs 1.34 ± 0.56; *P* = .02), and more in-hospital complications: vascular complications (12.2% vs 35.7%; *P* = .001), major or life-threatening bleeding events (0.9% vs 21.4%; *P* < .001), and acute kidney injury (5.2% vs 19.0%; *P* = .004).

DISCUSSION

There are 3 main findings in our study. First, the absolute number of nonagenarians treated with TAVI has been growing gradually over time. Secondly, age ≥ 90 years was not independently associated with a higher adjusted all-cause mortality rate. Thirdly, both the baseline kidney function and in-hospital complications have been associated with the prognosis of nonagenarians treated with TAVI.

The number of nonagenarians treated with TAVI has been growing gradually over time

Aortic stenosis is a slowly progressive heart disease associated with dismal outcomes within a few years after symptom onset if it goes untreated. Surgical aortic valve replacement (SAVR) has been the only effective treatment of severe AS for many years. This has resulted in a high percentage of patients with severe AS going untreated because the risks of this surgical procedure outweigh its possible benefits. Over the last few years, the development of minimally invasive TAVI has changed the decision-making process regarding valvular procedures.[10] Initially introduced as a 'bailout' therapy for inoperable patients with severe AS, TAVI is currently a feasible option for high- and intermediate- risk patients,[11] which widens the spectrum of patients with severe AS who get treated and moves away from the poor outcomes associated with the standard treatment (an all-cause mortality risk at 5 years of nearly 93%).[1] The great beneficiaries are elderly patients who used to be considered noneligible for SAVR as confirmed by the CURRENT AS (Contemporary outcomes after surgery and medical treatment in patients with severe aortic stenosis) registry.[12]

Table 1. Clinical characteristics

Variable	All patients (N = 8073)	Elderly < 90 y (N = 7686)	Nonagenarians (N = 387)	*P*
Demographics				
Age, years	82.9 ± 4.01	82.6 ± 3.66	91.1 ± 1.29	< .001
Women	4476 (55.5%)	4250 (55.3%)	226 (58.4%)	.23
Body mass index (kg/m²)	27.8 ± 4.60	27.9 ± 4.70	26.3 ± 4.20	< .001
Medical history				
Hypertension	6572 (82.9%)	6259 (83.0%)	313 (81.9%)	.59
Hyperlipidemia	4502 (59.7%)	4313 (59.2%)	189 (49.7%)	< .001
Diabetes mellitus	2660 (34.5%)	2586 (35.3%)	74 (19.3%)	< .001
Smoker	1254 (20.4%)	1207 (20.6%)	47 (15.9%)	.05
Peripheral arterial disease	972 (12.9%)	943 (13.2%)	29 (8.4%)	.01
Chronic kidney disease				
Hemodialysis	98 (1.4)	98 (1.5)	0	.02
Baseline estimated glomerular filtration rate (mL/min)	54.0 ± 27	54.5 ± 27	44.5 ± 21	< .001
Previous stroke	847 (11.1%)	805 (11.1%)	42 (11.1%)	.99
Heart disease				
Previous ischemic heart disease	4553 (57.9%)	4346 (59.9%)	207 (55.3%)	.08
Previous myocardial infarction	935 (12.6%)	904 (12.8%)	31 (8.8%)	.03
Previous percutaneous coronary intervention	1563 (20.6%)	1508 (20.9%)	55 (14.9%)	.006
Percutaneous coronary intervention 1-month before	1888 (24.8%)	1816 (25.0%)	72 (19.5%)	.02
Previous coronary artery bypass grafting	539 (7.30%)	536 (7.6%)	3 (0.9%)	< .001
Previous heart valve surgery				
Aortic	227 (2.9%)	223 (3.0%)	4 (1.1%)	.03
Mitral	115 (1.5%)	113 (1.5%)	2 (0.5%)	.12
Atrial fibrillation	2169 (27.9%)	2075 (28.1%)	94 (24.9%)	.19
Previous pacemaker or ICD	582 (7.50%)	552 (7.50%)	30 (8.00%)	.73
Risk scores				
Logistic EuroSCORE, %	16.72 ± 11.6	16.54 ± 11.6	20.31 ± 11.9	< .001
Clinical presentation				
Angina	578 (7.30%)	559 (7.40%)	19 (4.90%)	.06
Dyspnea	5000 (67.0%)	4730 (66.7%)	270 (72.4%)	.02
Echocardiographic characteristics				
LVEF, %	57.4 ± 15.4	57.4 ± 15.5	58.8 ± 11.8	.47
Mean gradient, mmHg	48.2 ± 15.0	48.1 ± 14.9	51.0 ± 15.1	< .001
Peak gradient, mmHg	78.9 ± 22.9	78.7 ± 22.8	83.8 ± 23.0	< .001
Aortic valve area, cm²	0.66 ± 0.2	0.66 ± 0.2	0.62 ± 0.2	.06
Moderate or severe mitral regurgitation	469 (6.9%)	444 (6.9%)	25 (7.8%)	.57
Moderate or severe aortic regurgitation	151 (3.1%)	143 (3.0%)	8 (3.3%)	.79
Pulmonary artery systolic pressure, mmHg	46.55 ± 18.0	46.24 ± 13.6	46.56 ± 18.2	.83
Diameter of the aortic annulus, mm	23.90 ± 2.8	23.07 ± 2.8	22.70± 2.7	.08
TAVI indication				.10
Contraindication	1656 (29.3%)	1584 (29.5%)	72 (25.3%)	
High risk	2379 (42.0%)	2242 (41.7%)	137 (48.1%)	
Intermediate risk	1626 (28.7%)	1550 (28.8%)	76 (26.7%)	

ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.
Data are expressed as no. (%) or mean ± standard deviation.

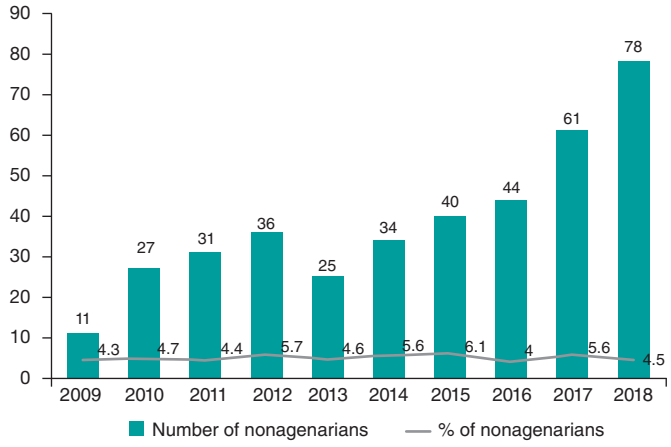

Figure 1. Absolute number and rate of nonagenarians treated with TAVI by year. The bar chart and line graph respectively express the number and rate of nonagenarian patients with severe aortic stenosis treated with TAVI from 2009 to 2018. TAVI, transcatheter aortic valve implantation.

Table 2. Procedural characteristics

Variable	All patients (N = 8073)	Elderly < 90 y (N = 7686)	Nonagenarians (N = 387)	*P*
Procedural characteristics				
Balloon-expandable valve	3663 (45.7%)	3477 (45.6%)	186 (48.1%)	.34
Self-expanding valve	4356 (54.3%)	4155 (54.4%)	201 (51.9%)	
Valve size				.82
< 23	2126 (28.3%)	2017 (28.3%)	109 (29.1%)	
24-28	3146 (41.9%)	2987 (41.9%)	159 (42.5%)	
< 29	2236 (29.8%)	2130 (29.9%)	106 (28.3%)	
Transfemoral access	7360 (91.6%)	6993 (91.4%)	367 (95.1%)	.01
Predilatation	2617 (49.9%)	2508 (50.2%)	109 (44.0%)	.06
Postdilatation	1671 (22.4%)	1593 (22.3%)	78 (22.7%)	.86
Device implantation success	7666 (95.0%)	7296 (94.9%)	370 (95.6%)	.55
Procedural duration, min	104.2 ± 48	103.9 ± 48	109.7 ± 51	.05
Post-TAVI echocardiographic characteristics				
Mean gradient, mmHg	10.1 ± 5.5	10.1 ± 5.5	9.5 ± 4.3	.18
Peak gradient, mmHg	18.9 ± 9.9	18.9 ± 10.0	18.0 ± 8.3	.14

LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.
Data are expressed as no. (%) or mean ± standard deviation.

Table 3. Outcomes

Variable	All patients (N = 8073)	Elderly < 90 y (N = 7686)	Nonagenarians (N = 387)	*P*
Procedural				
Conversion to open-heart surgery	54 (0.7%)	51 (0.7%)	3 (0.8%)	.74
In-hospital				
Death	357 (4.4%)	330 (4.3%)	27 (7.0%)	.01
Stroke	148 (1.8%)	144 (1.9%)	4 (1.0%)	.23
Myocardial infarction	99 (1.2%)	94 (1.2%)	5 (1.3%)	.81
Vascular complication	976 (12.1%)	919 (12.0%)	57 (14.7%)	.10
Major/life-threatening bleeding	108 (1.3%)	96 (1.2%)	12 (3.1%)	.002
Permanent pacemaker implantation	1213 (15.0%)	1155 (15.0%)	58 (15.0%)	.98
AKI > 1	466 (5.8%)	440 (5.5%)	26 (6.7%)	.41
Follow-up				
Median 1-year follow-up	308 (31-365)	306 (31-365)	362 (19-365)	.60
1-year all-cause mortality rate	719 (8.9%)	674 (8.8%)	45 (11.6%)	.072

AKI, acute kidney injury.
Data are expressed as no. (%) or mean ± standard deviation.

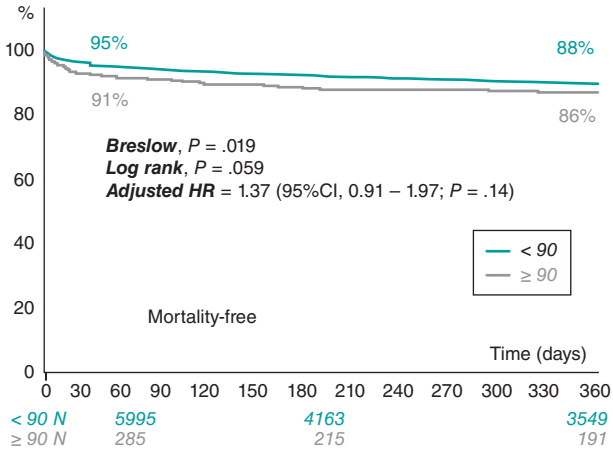

Figure 2. Kaplan-Meier survival estimates for the 1-year all-cause mortality and survival rates. 95%CI, 95% confidence interval; HR, hazard ratio.

In our study, we saw an increase in the absolute number of nonagenarians treated with TAVI from only 11 cases reported before 2009 to 78 cases reported back in 2018 (figure 1). The gradual increase in the number of nonagenarians referred for TAVI can be explained by the greater knowledge gained on this technique, the excellent early results reported,[6] the higher number of TAVIs performed, and the gradual aging of the population, which is a global phenomenon. The aging of the population is a global phenomenon. There were 703 million people ≥ 65 years in the world in 2019. The number of elderly people is projected to double to 1.5 billion by 2050.[3] It has been predicted that, in Spain, by 2040, life expectancy will exceed 85 years of age in both sexes.[13] Other study claims that chances are over 50% that by 2030, female life expectancy will break the 90-year barrier, a level deemed unattainable by some at the turn of the 21st century. South Korea would have the highest projected female life expectancy followed by France, Spain, and Japan.[14] Taking these data into consideration, the natural evolution of valvular heart disease, the advances made

Table 4. Independent predictors of all-cause mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age ≥ 90 years	1.59 (1.16-2.18)	.007	1.37 (0.91-1.97)	.14
Women	0.94 (0.80-1.11)	.49	–	–
Body mass index (kg/m^2)	0.97 (0.95-0.98)	< .001	0.97 (0.95-0.99)	.02
Peripheral vascular disease	1.34 (1.07-1.68)	.06	–	–
Baseline creatinine levels (mL/min)	1.22 (1.11-1.34)	< .001	1.28 (1.15-1.44)	< .001
Atrial fibrillation	1.28 (1.07-1.52)	.008	1.37 (1.09-1.73)	.008
Previous pacemaker or ICD	0.70 (0.49-1.01)	.05	–	–
LVEF, %	0.99 (0.98-0.99)	.007	–	–
Moderate or severe mitral regurgitation	1.39 (1.02-1.89)	.05	–	–
Moderate or severe aortic regurgitation	1.49 (0.88-2.56)	.16		
Dyspnea	1.26 (1.04-1.52)	.02	1.49 (1.14-1.93)	.002
High-risk/inoperable	1.57 (1.23-2.00)	< .001	1.34 (1.01-1.79)	.04
Transfemoral access	0.61 (0.48-0.78)	< .001	0.68 (0.51-0.92)	.02
Device implantation success	0.19 (0.15-0.23)	< .001	0.18 (0.13-0.23)	< .001

95%CI, 95% confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.
Hazard ratios and their 95% confidence intervals were calculated using the multivariate Cox regression analysis.

with TAVI devices, and the results associated with this procedure,[15] a higher number of nonagenarians with severe AS should be expected in the coming future. This should lead to more routine assessments of these patients by the heart team on the possibility to perform TAVI.

Being a nonagenarian is not associated with a higher adjusted all-cause mortality rate in TAVI

Over the last decade, healthcare spending has been gradually rising at a higher speed than the gross domestic product, which challenges the sustainability of healthcare systems.[16] A number of factors have been identified as contributors to increasing spending, among them, the aging of the population and the development of new medical technologies.[17] Both are implicated in our study. Given the economic implications of TAVI,[18] identifying the patients in whom TAVI would likely be futile, as defined by the composite endpoint of death and/or absence of functional improvement at the postoperative short-term follow-up (6 months to 1 year),[19] must be a priority. In our study, age ≥ 90 years was not independently associated with a higher adjusted all-cause mortality rate. This may be due to the fact that nonagenarians treated with TAVI are a highly selected population with a healthier clinical profile compared to younger patients. This is a selection bias introduced by the heart team that selects the healthiest nonagenarians to perform TAVIs while looking for the highest benefit possible, which is seen in the preferential use of femoral access. Our results are consistent with other cohorts of nonagenarians treated with TAVI.[20,21] In addition, several studies have shown that the benefit of the procedure goes beyond a higher survival rate, thus improving the quality of life.[22,23] This is a remarkable aspect in the elderly setting: the so-called idea of "adding life to years" rather the "adding years to life". Nevertheless, we should be cautious when interpreting the results reported: we found that 1 in 10 nonagenarians treated with TAVI died within the first 30 days.

Prognosis in this high-risk population can improve if TAVI is performed in advance in asymptomatic patients with severe AS. Detecting the early signs of symptoms can be challenging in many sedentary and deconditioned elderly patients in whom irreversible left ventricular decompensation may have appeared when detected. This strategy is supported by evidence from the recently published RECOVERY trial (The randomized comparison of early surgery versus conventional treatment in very severe aortic stenosis).[24] It was designed to compare the long-term clinical outcomes of early surgical aortic valve replacement and the outcomes of a conservative strategy in asymptomatic patients with fairly severe aortic stenosis (transvalvular velocity ≥ 4.5 m per second) based on the current clinical practice guidelines. It was found that the rate of the composite endpoint of procedural mortality or cardiovascular death at the follow-up was significantly lower in those treated with early aortic valve replacement surgery compared to those treated conservatively [1% vs 15%, HR 95%CI, 0.009 (0.001–0.67)]. The performance of TAVI as a less invasive procedure compared to surgery can be easily justified as a preventive measure in nonagenarians instead of having to wait for the development of early symptom to trigger this valve procedure. Two randomized controlled trials, the EARLY-TAVR (Evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis; NCT03042104) and the EVoLVeD (Early valve replacement guided by biomarkers of left ventricular decompensation in asymptomatic patients with severe aortic stenosis) trials[25] are currently recruiting asymptomatic patients with AS to study if an early therapeutic approach may actually improve the outcomes compared to the current standard of care. These trials have the potential to change clinical practice and reduce the threshold for the procedure.[26]

The finding on mid-term futility characteristics in nonagenarians

This is the third and last point we would like to underline. In our cohort, we identified several characteristics associated with a worse prognosis (table 2 of the supplementary data), and their recognition may help clinicians select the eligible nonagenarians for TAVI. Among them, 2 deserve special attention: the presence of chronic kidney disease and a bleeding event as in-hospital complications. Chronic kidney disease is widely known as one of the worst prognostic factors among patients treated with SAVR,[27] and similar results have been reported in TAVI.[28] In our study, higher baseline creatinine levels at admission were associated with a worse long-term prognosis. Our results are consistent with those from different registries that found that the presence of chronic kidney disease has been consistently associated with poorer outcomes after TAVI.[7] Yamamoto et al[29] studied the prognostic value of an impaired renal function based on a chronic kidney disease classification in very elderly patients treated with TAVI. They found that, in stage 4 patients (eGFR < 30 mL/min/1.73 m^2), the 30-day, 1-year, and cumulative 2-year mortality rates were 26.2%, 47.8%, and 68.2%, respectively. On the other hand, something that would explain the higher in-hospital mortality rate of nonagenarians is the presence of major or life-threatening bleeding compared to younger patients. Patients treated with TAVI have a high baseline risk of bleeding: peripheral vasculopathy, chronic kidney disease, acquired and reversible von Willebrand disease, and acquired thrombocytopenia[30]

increase the risk of bleeding events.[31] Age has been associated with bleeding events after TAVI immediately after the procedure or later on,[32] along with chronic kidney disease and comorbidities. Age and comorbidities are non-modifiable variables, which means that modifiable variables associated with bleeding like vascular access[33] and antithrombotic therapy should be controlled. In this regard, intensive antithrombotic regimens with dual antiplatelet therapy with aspirin plus clopidogrel have been the standard antithrombotic therapy at discharge after TAVI.[34] This could have a higher negative impact on nonagenarians since age is one of the major predictors of bleeding when on dual antiplatelet treatment.[35] The recently published POPular TAVI trial[36] showed that, among patients treated with TAVI without an indication for anticoagulation, aspirin alone was associated with fewer all bleeding and nonprocedural-related bleeding complications compared to aspirin and clopidogrel. The adoption of a single antiplatelet therapy regime after TAVI instead of dual antiplatelet therapy may reduce the number of major bleeding events in this high-risk population, thus improving the efficacy and long-term prognosis of TAVI in this population. Regarding the predictive ability of the surgical risk score, the STS-PROM is the only surgical risk score to accurately predict mortality risk in nonagenarians.[20] Finally, although the presence of atrial fibrillation is less common among patients who died at the follow-up compared to those who survived, we think this correlation to be spurious given the results shown in other series of nonagenarian patients treated with TAVI that revealed the presence of atrial fibrillation associated with a worse prognosis.[21]

Study limitations

The main limitation of this study is its observational design, which implies an inherent selection bias. Also, it is difficult to capture and control all potential confounders such as the time trend of the technique used and the type of patients.[15] Our data come from a voluntary registry whose data have not been externally audited and does not include all Spanish TAVI-capable centres. This limits the external validity of our results. In addition, the sample size may be lacking the statistical power to detect other statistically significant differences in the outcomes reported and does not allow us to develop a multivariate analysis to assess independent predictors of all-cause mortality in a cohort of nonagenarian patients. The lack of antithrombotic therapy at discharge does not allow us to determine its actual impact on this population. Also, we are lacking data on quality of life at the follow-up—a remarkable aspect in the elderly setting—and the prognosis of the procedure > 1-year follow-up. The inclusion of nonagenarians in large, well-designed, randomized clinical trials is needed to fully clarify the actual potential benefit of TAVI in this high-risk cohort of patients.

CONCLUSIONS

Nonagenarians are a growing very high-risk population with severe AS for whom TAVI may be a safe and effective option. Careful patient selection by the TAVI heart team is required to achieve maximum efficiency in this population where baseline kidney function and bleeding complications may determine the long-term prognosis after TAVI.

FUNDING

The Interventional Cardiology Association of the Spanish Society of Cardiology sponsored the maintenance and exploitation of the database.

AUTHORS' CONTRIBUTIONS

P. L. Cepas-Guillén, X. Freira, and M. Sabaté designed the study. A. Regueiro, D. Sanmiguel Cervera, R. Blanco Mata, J. F. Oteo, I. Amat-Santos, F. Ten, J. M. Nogales, E. Fernández-Nofrerías, V. Mainar, G. Lasa-Larraya, L. Andraka, J. A. Baz-Alonso, M. Cruz Ferrer, E. Pinar, R. Romaguera, C. Cuellas Ramón, F. Alfonso, C. A. Urbano-Carrillo, S. García-Blas, A. Piñero, A. Albarrán, R. Ruíz-Salmerón, J. Moreu, Ó. Gil-Albarova, J. M. Melero, and T. Heredia-Cambra supervised the data mining, recruited the participating centers and patients, and managed the data. P. L. Cepas-Guillén, A. Regueiro, and M. Sabaté provided statistical counselling on the study design and analyzed the data. P. L. Cepas-Guillén, M. Sabaté, and X. Freira drafted the manuscript, and all authors contributed substantially to its revision. P. L. Cepas-Guillén, and M. Sabaté take full responsibility for this manuscript entirely. The authors submitting the manuscript accept full responsibility for its content as defined by the International Committee of Medical Journal Editors.

CONFLICTS OF INTEREST

M. Sabaté declared having received personal fees from Abbott Vascular, and Ivascular outside the setting of this manuscript.

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WHAT IS KNOWN ABOUT THE TOPIC?

- Nonagenarians are a fast-growing age group among cardiovascular patients, especially with aortic stenosis.
- Due to its minimally invasive approach, TAVI allows us to treat patients with severe aortic stenosis who are inoperable or at high surgical risk, which improves their prognosis and quality of life compared to standard therapy.
- Given their anticipated short life expectancy and comorbidity burden, TAVI may be an excellent alternative for nonagenarians with severe aortic stenosis, but the data on their prognosis after TAVI are still scarce.

WHAT DOES THIS STUDY ADD?

- This is the first study to assess the prognosis of the nonagenarian population after TAVI in our setting.
- A progressively increase of nonagenarians was observed and because of the aging of the population, a higher number of nonagenarians with severe aortic stenosis will be expected in the coming future.
- Being a nonagenarian is not associated with a higher adjusted all-cause mortality rate in TAVI; instead, careful patient selection is essential to achieve maximum efficiency in this high-risk population.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000220.

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Original article

Real-world registry of the durable Angiolite fluoroacrylate polymer-based sirolimus-eluting stent: the EPIC02 – RANGO study

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ABSTRACT

Introduction and objectives: After the positive pre-clinical and clinical results with Angiolite, a cobalt-chromium sirolimus-eluting stent, we decided to analyze its performance in a non-selected, real-world population: the RANGO registry.
Methods: We conducted an observational, prospective, multicenter registry of patients with different clinical indications. All consecutive patients treated with percutaneous coronary intervention with, at least, 1 Angiolite stent and who gave their informed consent were included. The registry primary endpoint was the occurrence of target lesion failure (TLF) at 6, 12, and 24 months defined as cardiovascular death, myocardial infarction (MI) related to target vessel, and clinically driven target lesion revascularization. The secondary endpoints were the individual components of the primary endpoint, major adverse cardiovascular events (MACE: all-cause mortality, any MI, or any revascularization), and stent thrombosis. We describe the 2-year clinical results of the RANGO study in the entire population, in those who only received Angiolite stents, and in 2 predefined subgroups: diabetics and patients with small-vessels (≤ 2.5mm).
Results: 646 patients (426 of them only received Angiolite stents) with a high-risk profile were recruited: prevalence of previous MI (18.4%), previous coronary revascularization (23.4%), clinical presentation as ST-segment elevation MI (23.1%), and multivessel disease (47.8%). At the 2-year follow-up, the rates of TLF, MACE, and stent thrombosis were 3.4%, 9.6%, and 0.9%, respectively. Similar results were observed among patients treated with Angiolite stents only: TLF, 3.1%; MACE, 8.0%; thrombosis, 0.7%. The rates were not significantly different for the diabetic (TLF, 3.0%; MACE, 14.1%; thrombosis, 1.0%), and small-vessel subgroups (TLF, 4.3%; MACE, 12.1%; thrombosis, 0%).
Conclusions: In conclusion, the results of this observational registry on the use of Angiolite in a real-world population, including a high-risk population, corroborate the excellent results observed in previous studies, up to a 2-year follow-up. An extended 5-year follow-up is planned to discard the occurrence of late events.

Keywords: Sirolimus-eluting-stent. Durable fluoropolymer. Observational study. Efficacy. Safety. Stent thrombosis.

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Registro prospectivo del stent liberador de sirolimus con polímero estable de fluoroacrilato Angiolite: estudio EPIC02 – RANGO

RESUMEN

Introducción y objetivos: Para confirmar los resultados observados en análisis preclínicos y clínicos del *stent* liberador de sirolimus Angiolite se diseñó el registro observacional de vida real RANGO.
Métodos: El registro prospectivo multicéntrico incluyó pacientes con distintas indicaciones clínicas que recibieron al menos 1 *stent* Angiolite para tratar su enfermedad coronaria y que dieron su consentimiento informado. El objetivo primario fue la incidencia de fracaso del tratamiento de la lesión (FTL) a 6, 12 y 24 meses, definido como muerte de causa cardiaca, infarto de miocardio en relación con el vaso tratado o nueva revascularización de la lesión tratada. Los objetivos secundarios fueron los componentes individuales del objetivo primario y las incidencias de eventos cardiacos mayores (MACE) y de trombosis del *stent*. Se presentan los resultados del registro RANGO a 2 años en la población global, en los pacientes que recibieron *stent* Angiolite y en 2 subgrupos predefinidos de diabéticos y vasos pequeños (≤ 2,5 mm).
Resultados: Se seleccionaron 646 pacientes (426 solo recibieron *stents* Angiolite) con un perfil de riesgo elevado: infarto previo (18,4%), revascularización coronaria previa (23,4%), presentación clínica como infarto agudo con elevación del segmento ST (23,1%) y enfermedad multivaso (47,8%). A los 2 años, la incidencia de FTL en el grupo global fue del 3,4%, la de MACE fue del 9,6% y la de trombosis del *stent* fue del 0,9%. En el grupo tratado solo con *stents* Angiolite, los resultados fueron similares (FTL 3,1%, MACE 8,0% y trombosis 0,7%). Los resultados no fueron significativamente diferentes en los diabéticos (FTL 3,0%, MACE 14,1% y trombosis 1,0%) y en los pacientes con vasos pequeños (FTL 4,3%, MACE 12,1% y trombosis 0%).
***Conclusiones*:** Los resultados del registro observacional RANGO a los 2 años en población de vida real con perfil de riesgo elevado confirman los excelentes resultados del *stent* Angiolite observados en estudios previos. Se plantea un seguimiento clínico a 5 años para descartar eventos muy tardíos.

Palabras clave: *Stent* liberador de sirolimus. Fluoropolímero estable. Estudio observacional. Eficacia. Seguridad. Trombosis del *stent*.

Abbreviations

DES: drug-eluting stents. **MACE:** major adverse cardiovascular events. **PCI:** percutaneous coronary intervention. **TLF:** target lesion failure. **TLR:** target lesion revascularization. **TVR:** target vessel revascularization.

INTRODUCTION

Drug-eluting stents (DES) are one of the greatest advances in the percutaneous treatment of coronary artery disease. These devices have consistently shown lower rates of revascularization of the treated vessel in a wide range of clinical situations, and have become the treatment of choice.[1] However, the risk of late and very late stent thrombosis arose with first-generation DES,[2] and, to this date, it is still a matter of concern.[3] This phenomenon has been associated with side effects to the drug (impairing the proliferation of new endothelial cells), the polymer, the stent platform or a combination of them on the vessel wall, leading to delayed or incomplete endothelialization, persistent inflammatory reactions, and the development of neo-atherosclerosis. New DES have been developed with superior efficacy in terms of abolishing the need for revascularization, but with the reassurance of much lower rates of stent thrombosis, the most dreadful clinical manifestation of suboptimal vessel healing. The Angiolite stent (iVascular, Spain) is a thin-strut cobalt-chromium sirolimus-eluting stent with biostable coating made of 3 layers: acrylate to ensure adhesion to the metal surface, fluoroacrylate loaded with sirolimus (1.4 µg/mm^2), and a top layer of fluoroacrylate for drug release control (> 75% elution within the first month).

The Angiolite stent was initially tested in a pre-clinical model with very promising results,[4] with an equivalent antiproliferative response, and a better healing pattern compared to the XIENCE stent (Abbott Vascular, United States). Subsequently, a first-in-human study[5] (ANCHOR study) proved a powerful inhibition of neointimal hyperplasia as seen on the OCT: The Angiolite stent efficiently inhibited the proliferative response (vessel area stenosis, 4.4% ± 11.3%), in- stent late lumen loss at 6 months (0.07 mm ± 0.37 mm), and had a low rate of strut malapposition (1.1% ± 6.2%). Finally, the ANGIOLITE study,[6] a randomized clinical trial, compared the Angiolite stent to the XIENCE stent in 223 patients (randomization with a 1:1 allocation ratio). In this study, the primary endpoint, the 6-month in-stent late lumen loss, was non-inferior in the Angiolite group (0.04 mm ± 0.39 mm) compared to the XIENCE group (0.08 mm ± 0.38 mm). The stent received the CE marking (*Conformité Européenne*) for its routine use. Therefore, we designed the present observational, prospective, registry to endorse the previous results in the routine clinical practice, with wider indications for use.

METHODS

Study design

The EPIC02-RANGO study was designed as a prospective, single-arm, multicenter, observational registry for the evaluation of the safety and efficacy profile of the Angiolite stent in unselected patients representative of the routine clinical practice. The study design was approved by all investigators and the sponsor as well. A reference ethics committee approved the protocol and the informed consent forms; local ethics committees were informed that this study would be conducted in their centers in compliance with the national legislation. The study was conducted and monitored by an independent contract research organization. The authors of this original manuscript independently conducted the data final analysis, interpreted

the study results, and drafted/wrote this original manuscript. The sponsor was informed on the status of the study and the final results, but had no further participation.

Selection of the study population

To be enrolled in the study, subjects should met all the 3 following inclusion criteria: ≥ 18 years-old; treated with percutaneous coronary intervention (PCI) with at least 1 Angiolite stent; and have received proper information and signed the corresponding informed consent.

To guarantee a real-world population, non-stringent exclusion criteria were applied. Subjects were only excluded from the study if they met any of the following exclusion criteria: contraindication to dual antiplatelet therapy; established cardiogenic shock; unlikely to complete the scheduled follow-up; or formal refusal to participate in the study.

The PCI (predilatation, invasive imaging, postdilatation, planning, and final performance) was left at the discretion of the operator, and was indicative of the real-world use of the stents. Medical treatment during and after the procedure, including antiplatelet regime and duration, also followed the standard local practices; however, we suggested the investigators to follow the guidelines available on the management of these patients.[1,7]

Endpoints

The primary endpoint was target lesion failure (TLF) at 6, 12, and 24 months defined as cardiovascular death, target vessel myocardial infarction or clinically driven target lesion revascularization.

The secondary endpoints were:

- Target vessel failure defined as cardiovascular death, target vessel myocardial infarction or target vessel revascularization.
- Major adverse cardiovascular events (MACE) defined as all-cause mortality, any myocardial infarction or any target vessel revascularization.
- Stent thrombosis (definite or probable, as defined by the ARC criteria[8]).

In all cases, myocardial infarction refers to spontaneous infarction only. Two subgroups were predefined: patients with diabetes, and patients with Angiolite stents placed in small vessels (stent diameter ≤ 2.5 mm).

Sample size calculation

We conducted an exploratory analysis that rendered a population of 640 patients (with an estimated loss to follow-up of 10%). This sample size produces a 2-sided 95% confidence interval with a precision equal to 1.75% when the TLF rate is 4.86%. This value was obtained from the data published from different contemporary stents[9-17] (table 1 of the supplementary data).

Population analysis

The primary safety and efficacy analysis considered all patients who received the Angiolite stent only except for those who withdrew their consent. The secondary analysis was performed on all patients included in the study who received, at least, 1 Angiolite stent plus another different stent except for those who withdrew their consent.

Clinical events committee

An independent data and safety monitoring board reviewed the cumulative safety data to safeguard the well-being of the participants. All events were remotely monitored by a contract research organization. The clinical events committee reviewed, adjudicated, and classified all adverse events. The 5 members of the clinical events committee were not affiliated to the centers that participated in the study.

A total of 90 random patient audits (14% of the global population) were conducted at 4 centers, including the top 3 recruiters. The result of these audits detected 9 unreported events, most of them corresponded to scheduled procedures that required admission (non-cardiac surgeries and 2 scheduled PCI cases). None of the events associated with these audits corresponded to events classified as primary or secondary endpoints.

Descriptive statistics

All continuous variables were summarized using the following descriptive statistics: n (based on the number of recorded data values for each parameter), mean, standard deviation, 95% confidence interval for the mean, median, interquartile range [Q1, Q3], maximum, and minimum. The frequency and percentages (based on the number of recorded data values for each parameter) of the observed values are reported for all categorical measures. In general, all data are listed, and sorted by study site, and subject.

Statistical methods

Regarding the continuous variables, results were expressed as mean ± standard deviation. Variables were compared using an independent t test or the Mann-Whitney test, when applicable. Categorical variables are expressed as counts and percentages and compared using the chi-square test or Fisher's exact test. Variables were compared between patients with only the Angiolite stent versus patients with other stents in addition to the Angiolite one. The clinical variables at 6, 12, and 24 months were expressed as counts and percentages. Time-to-event hazard curves were expressed as Kaplan-Meier estimates.

These methods were applied for the entire cohort and the 2 predefined subgroups, when appropriate: patients with diabetes, and patients with small vessel lesions (stent diameter ≤ 2.5 mm).

The statistical software SAS Version 9.4 was used for all statistical analyses, listings, tabulations, and figures.

RESULTS

A total of 654 patients were recruited from 16 academic medical centers in Spain and Portugal from June 2017 through July 2018. A total of 8 patients were excluded for not meeting the selection criteria (2 in whom the Angiolite stent was not intented to be used, 5 duplicated patients with staged, planned, procedures, and 1 patient without any data available). Therefore, the population analyzed consisted of 646 patients (figure 1); a total of 426 patients were treated with Angiolite stents only (primary analysis).

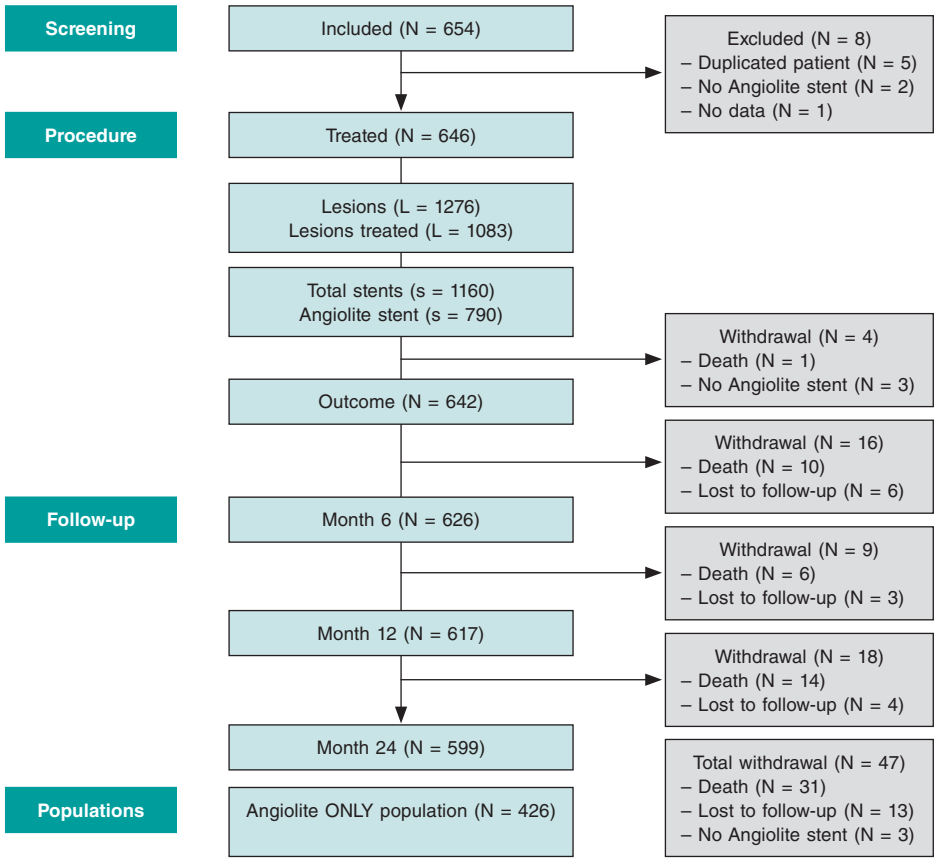

Figure 1. Flow chart of the study.

The baseline characteristics and clinical data, as well as the angiographic and procedural features are shown on table 1 and table 2, respectively. Noteworthy, the population has a high-risk profile with a remarkable prevalence of previous myocardial infarction (18.4%), previous coronary revascularization (23.4%), clinical presentation as ST-segment elevation myocardial infarction (23.1%), and multivessel disease (47.8%).

The mean ± standard deviation number of lesions per patient was 1.98 ± 1.2, the mean number of treated lesions per patient was 1.68 ± 0.9 with a mean number of stents per patient of 1.80 ± 1.1. These numbers were significantly lower among patients treated with the Angiolite stent and consistent with the different patient profile. Table 3 summarizes the characteristics and treatment of each individual lesion. Interestingly, Angiolite stents were more frequently used to treat the infarct-related artery compared to other stents in our population. Subsequently, lesions with thrombus were more common in the group treated with Angiolite stents only while severe calcification was more prevalent in the entire group. Procedural complications occurred in 10 patients, 7 of them associated with Angiolite stents: 1 uncrossable lesion, 1 guidewire-related distal perforation, 1 severe no-reflow phenomenon, and 4 cases of dissection, 2 of them treated with additional stents. The procedural and device success rates were 99.7% and 99.2%, respectively. In more complex anatomic scenarios, specifically lesions with moderate/severe calcification, the procedural and device success rates stayed high (99.6% and 99.3%, respectively). Those rates were 100% in the subgroup of lesions at bifurcations or at left main coronary artery level.

The 6-month and 1-year follow-ups were good, with only 9 (1.4%) and 12 (1.9%) patients lost to follow-up, respectively. At the 1-year follow-up, 368 patients (59.6%) were still on dual antiplatelet therapy; this rate dropped to a 15.5% at the 2-year follow-up. During the established follow-up period (2 years for all patients), only 13 patients (2%) were lost. In the global population, at 2 years, the rates of TLF, target vessel failure, and MACE were 3.4%, 4.3%, and 9.6%, respectively. Two of the 9 cases of TLF were not associated with Angiolite stents but with other stents implanted. The rate of definite/probable stent thrombosis was 0.9%; all patients were on dual antiplatelet therapy when the event occurred. Interestingly, 4 cases appeared during the first week of follow-up, 1 case within the first month, and only 1 case of stent thrombosis after 6 months (268 days). Table 4 and figure 2 summarize the individual event rate and timing.

In the primary analysis population (patients treated with Angiolite stents only) at 2 years, the rates of TLF, target vessel failure, and MACE were 3.1%, 4.0%, and 8.0%, respectively. The rate of definite/probable stent thrombosis was 0.7%. No cases of stent thrombosis were found beyond the first 6 months. Table 5 and figure 3 summarize the individual event rate and timing.

The subgroup analysis rendered 2-year results that were slightly worse that those observed in the global population:

- The diabetic subgroup showed rates of TLF, target vessel failure, and MACE of 3.0%, 4.5%, and 14.1%, respectively. The rate of stent thrombosis was 1.0%: 2 cases among 199 diabetic patients; only 1 of these cases appeared in the primary analysis of patients treated with the Angiolite stent only. Supplementary data give a description of the event rate (table 2 of the supplementary data).

- The patients with stents placed in small vessels (≤ 2.5 mm) showed rates of TLF, target vessel failure, and MACE of 4.3%,

Table 1. Baseline and clinical characteristics

	Total N = 646	Angiolite only population N = 426
Age (years old)	66.41 ± 11.93	65.72 ± 11.98
Male sex	495 (76.6%)	320 (75.1%)
Cardiovascular risk factors & history		
Hypertension	402 (62.2%)	254 (59.6%)
Dyslipidemia	385 (59.6%)	251 (58.9%)
Diabetes mellitus*	199 (30.8%)	119 (27.9%)
Current smoker	182 (28.2%)	127 (29.8%)
Chronic kidney disease	46 (7.1%)	25 (5.9%)
Peripheral vascular disease*	44 (6.8%)	23 (5.4%)
Previous stroke	28 (4.3%)	17 (4.0%)
Previous myocardial infarction	119 (18.4%)	73 (17.1%)
Previous coronary surgery	20 (3.1%)	13 (3.1%)
Previous PCI	131 (20.3%)	78 (18.3%)
Atrial fibrillation	34 (5.3%)	20 (4.7%)
Heart failure	46 (7.1%)	32 (7.5%)
Valvular heart disease ≥ grade III	16 (2.5%)	7 (1.6%)
PCI indication		
NSTEMI	220 (34.1%)	141 (33.1%)
STEMI	149 (23.1%)	112 (26.3%)
Stable angina	120 (18.6%)	68 (16.0%)
Unstable angina (negative biomarkers)	72 (11.1%)	51 (12.0%)
Silent myocardial ischemia	32 (5.0%)	19 (4.5%)
Other	53 (8.2%)	35 (8.2%)

NSTEMI, non-ST-elevation acute myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
* Significant differences between patients with the Angiolite stent only vs patients with any stents in addition to the Angiolite, $P < .05$.
Data are expressed as no. (%) or mean ± standard deviation.

Table 2. Angiographic and procedural features

	Total N = 646	Angiolite only population N = 426
Coronary angiography		
Radial approach	585 (90.6%)	396 (93.0%)
Extension of the disease		
*No. of diseased vessels**		
1	337 (52.2%)	289 (67.8%)
2	198 (30.7%)	92 (21.6%)
3	111 (17.1%)	45 (10.6%)
Left main coronary artery*	29 (4.5%)	12 (2.8%)
Proximal LAD disease	179 (27.7%)	110 (25.8%)
Diffuse disease*	128 (19.8%)	63 (14.8%)
*No. of lesions per patient**	1.98 ± 1.24	1.51 ± 0.90
*No. of treated lesions per patient**	1.68 ± 0.95	1.25 ± 0.53
*No. of stents per patient**	1.80 ± 1.11	1.24 ± 0.55
Index procedure		
Revascularization		
Complete	489 (75.7%)	331 (77.7%)
Functional	84 (13.0%)	51 (12.0%)
Intravascular imaging		
IVUS	15 (2.3%)	5 (1.2%)
OCT	12 (1.9%)	7 (1.6%)
*Staged revascularization**	85 (13.2%)	26 (6.1%)

IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; OCT, optical coherence tomography.
* Significant differences between patients with the Angiolite stent only vs patients with any stents in addition to the Angiolite, $P < .05$.
Data are expressed as no. (%) or mean ± standard deviation.

6.0%, and 12.1%, respectively. No stent thrombosis was found. Supplementary data give a description of the event rate (table 3 of the supplementary data).

DISCUSSION

The results of the current real-world registry of the Angiolite coronary stent show an outstanding safety and efficacy profile as the ANCHOR[5]–first-in-human study–and the ANGIOLITE[6] randomized clinical trial comparison with the XIENCE stent showed. The clinical profile shows a relatively high-risk population with a prevalence of diabetes mellitus of 30.8%, 17.6% on anticoagulation with oral drugs, 18.4% of patients diagnosed with previous myocardial infarction, and 23.4% with previous coronary revascularization. Also, a high rate of complex coronary artery disease was found in the recruited population: significant multivessel disease was diagnosed in 47.8%, compromised left main coronary artery in 4.5%, and diffuse coronary artery disease in 19.8% of the patients. Therefore, the mean number of significant lesions (1.98 ± 1.24), treated lesions (1.68 ± 0.95), and stents implanted per patient (1.8 ± 1.11) was relatively high. The ST-segment elevation myocardial infarction clinical setting of the PCI in around a quarter of the cases also shows the all-comer, real-world nature of the study.

The registry was designed to include all the patients in whom an Angiolite stent was intended to be used. Therefore, we may distinguish 2 different populations: those in whom ONLY the Angiolite stent was intended (primary analysis) and those who received different stents to treat other lesions on top of the Angiolite stent (secondary analysis). These populations have some significant differences: Angiolite ONLY-patients were more prone to have single vessel disease, few significant lesions, few treated lesions, and few stents implanted. Reasonably, this population with lower atherosclerotic burden showed less diffuse disease and fewer staged procedures. However, not all the characteristics of this group were so favorable since the presence of thrombus and the target lesion as the infarct-related artery were more common in the Angiolite ONLY stent group.

The primary endpoint, TLF at 1-year was consistently low both in the Angiolite ONLY population (primary analysis), 2.3%, and in the

Table 3. Characteristics and treatment of each individual lesion

	Total L = 1083 (84.9% of all lesions)	Angiolite only population L = 531 (82.5% of all lesions)
Vessel		
Left anterior descending territory	459 (42.4%)	236 (44.4%)
Right coronary territory	327 (30.2%)	172 (32.4%)
Circumflex territory	273 (24.9%)	112 (21.2%)
Left main coronary artery	19 (1.8%)	5 (0.9%)
Other	5 (0.7%)	6 (1.1%)
*AHA/ACC Classification**		
A	95 (8.8%)	68 (12.8%)
B1	355 (32.8%)	193 (36.3%)
B2	429 (39.6%)	185 (34.8%)
C	204 (18.8%)	85 (16.0%)
Lesion characteristics		
Thrombus*	145 (13.4%)	91 (17.1%)
Stent at the infarct-related artery*	366 (33.8%)	249 (46.9%)
Severe calcification*	85 (7.8%)	22 (4.1%)
Restenotic lesion treated	37 (3.4%)	22 (4.1%)
Chronic total coronary occlusion	37 (3.4%)	20 (3.8%)
Lesion at bifurcation	108 (10.0%)	47 (8.9%)
Severe tortuosity	142 (13.1%)	62 (11.7%)
Vessel diameter (mm)	2.91 ± 0.55	2.91 ± 0.53
Lesion length (mm)*	19.47 ± 9.80	17.56 ± 8.26
*Pre-dilatation**	786 (72.6%)	363 (68.4%)
Scoring balloon	45 (4.2%)	11 (2.1%)
Cutting balloon	28 (2.6%)	8 (1.5%)
Rotational atherectomy	27 (2.5%)	9 (1.7%)
Thrombectomy*	75 (6.9%)	48 (9.0%)
Stents implanted	S = 1160	S = 529
No. of stents per lesion	1.07 ± 0.45	1.00 ± 0.35
*Characteristics of the stent**		
Type = Angiolite stent	784 (67.6%)	529 (100.0%)
Stent diameter (mm)	2.99 ± 0.51	2.99 ± 0.46
Stent length (mm)	21.38 ± 8.51	20.34 ± 7.03
Maximum pressure (atm)	14.61 ± 2.48	14.69 ± 2.46
Stent crossing the lesion at the 1st attempt	1067 (98.5%)	527 (99.2%)
Lesions at bifurcation	104 (96.3%)	45 (95.7%)
Moderate or severe calcification	268 (97.1%)	75 (97.4%)
Left main coronary artery	19 (100%)	5 (100%)
Postdilatation	284 (26.2%)	149 (28.1%)
Balloon diameter (mm)	3.24 ± 0.62	3.25 ± 0.53
Type of balloon, non-compliant	186 (67.4%)	112 (76.7%)

ACC, American College of Cardiology; AHA, American Heart Association; L, lesions; S, stents.
* Significant differences between patients with the Angiolite stent only vs patients with any stents in addition to the Angiolite, $P < .05$.
Data are expressed as no. (%) or mean ± standard deviation.

Table 4. Outcomes in the global population

Total population (N = 646)	6-month follow-up	1-year follow-up	2-year follow-up
Death	11 (1.7%)	17 (2.6%)	31 (4.8%)
Cardiovascular death	6 (0.9%)	8 (1.2%)	11 (1.7%)
Myocardial infarction	11 (1.7%)	16 (2.5%)	20 (3.1%)
Target vessel myocardial infarction	6 (0.9%)	8 (1.2%)	8 (1.2%)
Definite/probable device thrombosis	5 (0.8%)	6 (0.9%)	6 (0.9%)
Revascularization	13 (2.0%)	22 (3.4%)	32 (5.0%)
Target lesion revascularization	6 (0.9%)	8 (1.2%)	9 (1.4%)
Target vessel revascularization	7 (1.1%)	11 (1.7%)	15 (2.3%)
Non-target vessel revascularization	6 (0.9%)	11 (1.7%)	17 (2.6%)
Target lesion failure[a]	13 (2.0%)	18 (2.8%)	22 (3.4%)
Target vessel failure[b]	14 (2.2%)	21 (3.3%)	28 (4.3%)
MACE[c]	25 (3.9%)	41 (6.3%)	62 (9.6%)

MACE, major adverse cardiovascular events.
[a] Target lesion failure defined as cardiovascular death, target vessel myocardial infarction, and clinically indicated target lesion revascularization.
[b] Target vessel failure defined as cardiovascular death, target vessel myocardial infarction, and target vessel revascularization.
[c] MACE defined as all-cause mortality, any myocardial infarction, any revascularization.

entire population (secondary analysis), 2.8%. Target vessel failure, a wider safety variable, was also noticeably low (3.1% and 3.3%, respectively). To confirm these results, MACE (including all-cause mortality too), a clinically oriented variable, was also very low (5.3% and 6.3%, respectively). An overview of the TLF results of different stents tested in registries and RCTs is shown on table 1 of the supplementary data. In these studies, the TLF mean value at 1-year is 5.4%, higher that the rate seen in this study.

The 2-year follow-up confirmed the very low rate of unfavorable cardiac events seen at the early 1-year period. The rate of new cardiac events, both device- and patient-oriented, within the second follow-up year was about half of the observed rate during the first year.

Both the ANCHOR FIH[5] and the ANGIOLITE RCT[6] pointed out an extraordinary antiproliferative efficacy of the Angiolite stent, with a mean late luminal loss < 0.05 mm. Consequently, we thought it was mandatory to assess the safety of this stent through the rate of stent thrombosis. The real-world use of the Angiolite stent is associated with a low rate of such a catastrophic complication (0.7% in primary analysis, 0.9% in secondary analysis), which guarantees the safe use of this powerful DES. The studies published showed a mean rate of stent thrombosis from 0.4% to 4.9% at the 2-year follow up (table 1 of the supplementary data). Also, the very low rate of definite/probable stent thrombosis beyond the first week (only 2 cases, 1 within the first month and the other 268 days later) restates this safety profile. We should mention that the use of dual antiplatelet therapy was high in this population (59.6% at the 1-year follow-up), which is indicative of the prevalence of acute coronary syndrome as the patients' clinical presentation (68.3% of the patients).

The predefined subgroup analysis rendered interesting results. Diabetic patients showed TLF and stent thrombosis rates at 2 years, similar to the overall rate (3.0% vs 3.4%, and 1.0% vs 0.9%, respectively), while the rate of MACE was higher (14.1% vs 9.6%).

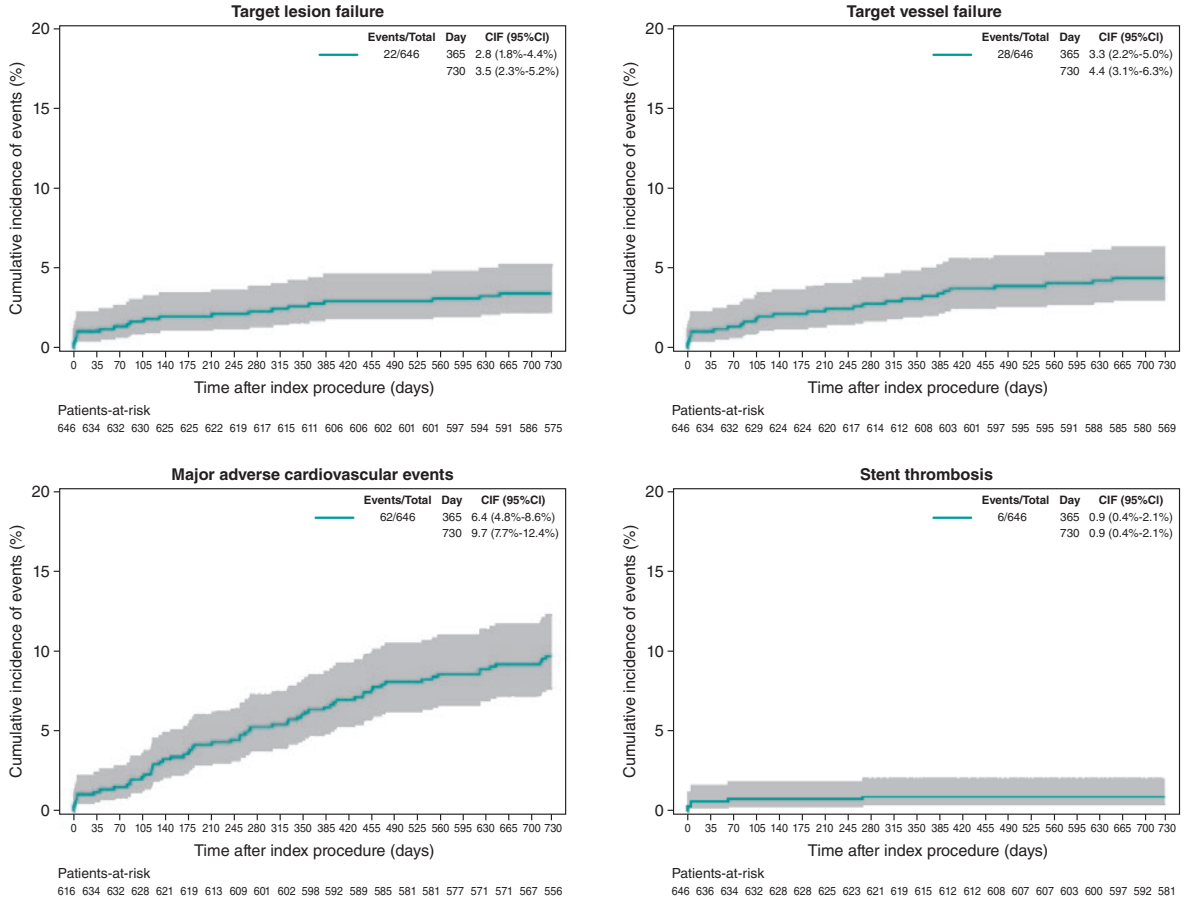

Figure 2. 2-year cumulative incidence of events in the entire population (N = 646).

This finding may show the worse clinical prognosis of diabetic patients, not necessarily associated with the lesion treated but with the remaining coronary artery disease. Our results are consistent with previous data published on the EVOLVE II substudy on diabetes[13] that showed a 2-year TLF rate of 11.2% and a definite/probable stent thrombosis of 1.1%.

As expected, the subgroup of small vessel disease (≤ 2.5 mm) showed slightly higher rates of 2-year TLF and MACE (4.3% and 12.1%, respectively) than the global population (3.4% and 9.6%, respectively). The lack of definite/probable stent thrombosis cases could be indicative of detection bias as the thrombosis of these vessels may have a milder clinical expression. The results of this subgroup are usually hard to compare with other data as the definition of small vessel is highly arbitrary, from 2.25 mm to 3.0 mm. However, the results of our study are consistent with those reported in the Basket Small[18] trial.

Limitations

The limitations of this study are the well-known issues of real-world observational registries: potential selection bias, reporting biases, and losses to follow-up (not in this case though, with a 98% of the follow-up period completed). However, the results are similar to previously reported data and are consistent with the results of previous studies with this stent. In the global population (patients who received other stents besides Angiolite stents), endpoints like probable stent thrombosis or cardiovascular death cannot be clearly attributed to a certain stent.

Table 5. Outcomes in the primary analysis population: patients treated with the Angiolite stent only

Angiolite only population (N = 426)	6-month follow-up	1-year follow-up	2-year follow-up
Death	5 (1.2%)	10 (2.3%)	18 (4.2%)
Cardiovascular death	3 (0.7%)	5 (1.2%)	7 (1.6%)
Myocardial infarction	5 (1.2%)	5 (1.2%)	10 (2.3%)
Target vessel myocardial infarction	4 (0.9%)	4 (0.9%)	4 (0.9%)
Definite/probable device thrombosis	3 (0.7%)	3 (0.7%)	3 (0.7%)
Revascularization	7 (1.6%)	11 (2.7%)	18 (4.2%)
Target lesion revascularization	3 (0.7%)	4 (0.9%)	5 (1.2%)
Target vessel revascularization	4 (0.9%)	7 (1.6%)	9 (2.1%)
Non-target vessel revascularization	3 (0.7%)	4 (0.9%)	9 (2.1%)
Target lesion failure[a]	7 (1.6%)	10 (2.3%)	13 (3.1%)
Target vessel failure[b]	8 (1.9%)	13 (3.1%)	17 (4.0%)
MACE[c]	13 (3.2%)	22 (5.3%)	34 (8.0%)

MACE, major adverse cardiovascular events.
[a] Target lesion failure defined as cardiovascular death, target vessel myocardial infarction, and clinically indicated target lesion revascularization.
[b] Target vessel failure defined as cardiovascular death, target vessel myocardial infarction, and target vessel revascularization.
[c] MACE defined as all-cause mortality, any myocardial infarction, any revascularization.

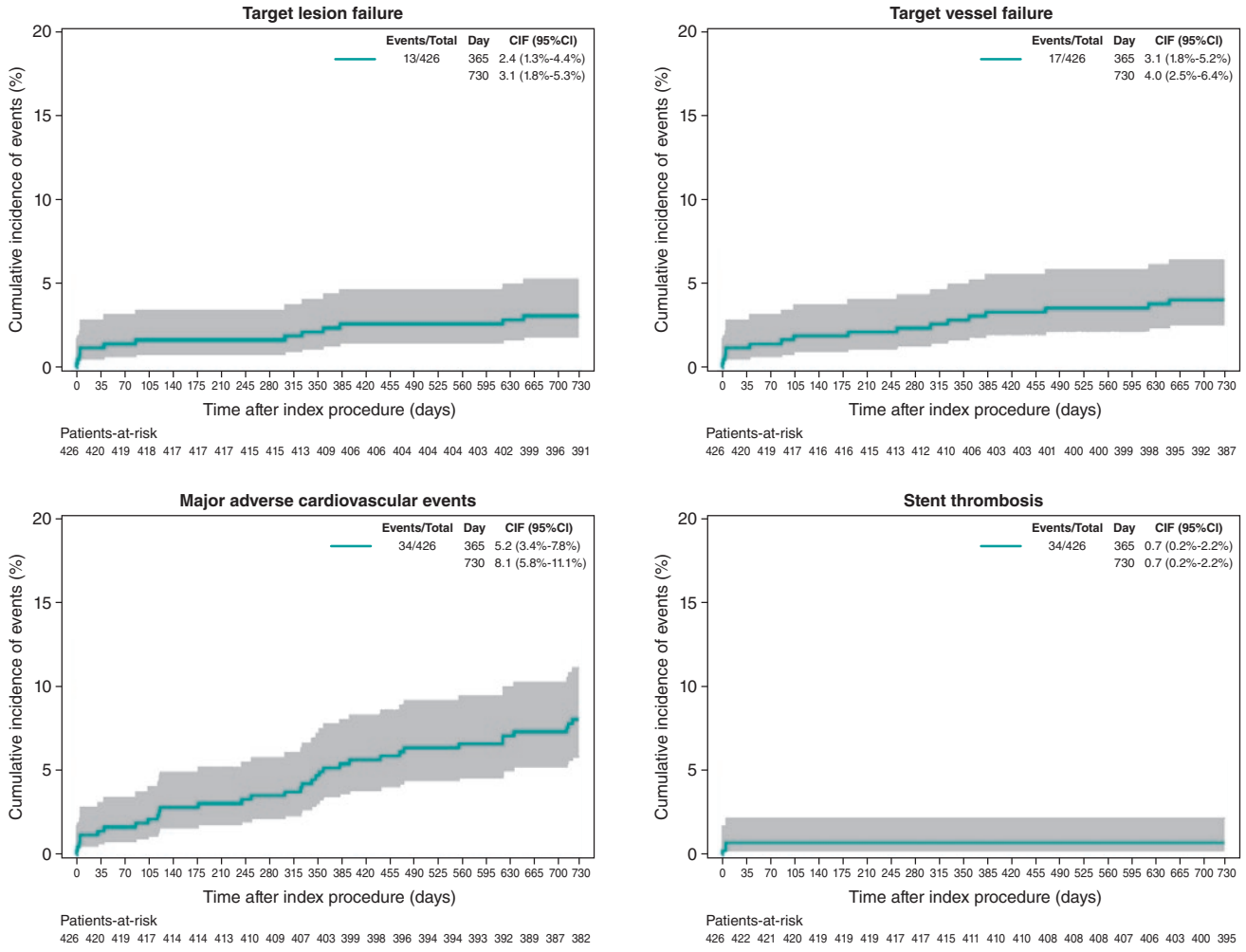

Figure 3. 2-year cumulative incidence of events in the primary analysis population of patients treated with the Angiolite stent only (N = 426).

To minimize potential errors and reinforce the safety message, the steering committee has decided to extend the follow-up period up to 5 years.

CONCLUSIONS

In conclusion, the results of this observational registry on the use of the Angiolite DES in a real-world population confirm the excellent efficacy and safety profile seen in previous studies at the 2-year follow-up. An extended 5-year follow-up is planned to discard late events.

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This study was conducted with financial support from Cardiva S.L. Data management and analysis were performed by an independent CRO. The final draft and the manuscript were wrote by investigators without any participation from the sponsors.

AUTHORS' CONTRIBUTIONS

Idea and design: A. Pérez de Prado, F. Lozano Ruiz-Poveda, J. Moreu Burgos, B. García del Blanco, E. Pinar, V. Peral, J.R. Rumoroso, and R. Trillo Nouche. Data acquisition: A. Pérez de Prado, R. Ocaranza-Sánchez, F. Lozano Ruiz-Poveda, J. Moreu Burgos, R. Álvarez Ramos, A. Rodrigues, L. Fernández González, P. Aguar, B. García del Blanco, E. Pinar, V. Peral, F. Sainz Laso, J.R. Rumoroso, A. Torres, M. Sabaté, and R. Trillo Nouche. Statistical analysis and manuscript writing: A. Pérez de Prado, F. Lozano Ruiz-Poveda, J.R. Rumoroso, and R. Trillo Nouche. Provision of critical feedback to the manuscript and final content approval: A. Pérez de Prado, R. Ocaranza-Sánchez, F. Lozano Ruiz-Poveda, J. Moreu Burgos, R. Álvarez Ramos, A. Rodrigues, L. Fernández González, P. Aguar, B. García del Blanco, E. Pinar, V. Peral, F. Sainz Laso, J.R. Rumoroso, A. Torres, M. Sabaté, and R. Trillo Nouche.

CONFLICTS OF INTEREST

A. Pérez de Prado, and M. Sabaté received consulting honoraria and research grants from iVascular, and Cardiva S.L. F. Lozano Ruiz-Poveda received honoraria for his lectures from Abbott and Medtronic. All authors have declared payments to their centers from Cardiva S.L.

WHAT IS KNOWN ABOUT THE TOPIC?

– Current DES offer superior efficacy in terms of reducing restenosis with very low rates of stent thrombosis. The Angiolite stent (iVascular, Barcelona, Spain) is a thin-strut

cobalt-chromium sirolimus-eluting stent with biostable coating of thrombus-resistant fluoroacrylate loaded with sirolimus. This stent has been comprehensively tested in preclinical studies, in a first-in-human study (ANCHOR study), and in a randomized clinical trial (compared to a cobalt-chromium everolimus- eluting stent) with consistent positive results. We designed an observational, prospective, and registry to endorse the previous results in our daily routine practice.

WHAT DOES THIS STUDY ADD?

– The results of this observational registry on the use of the Angiolite stent in a real-world, high-risk population confirm the excellent results seen in previous studies at the 2-year follow-up. Both the rate of device-related outcomes (target lesion and vessel failure) and patient-related outcomes (MACE) were lower compared to former data.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000223.

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Original article

Long-term results of a primary angioplasty program in patients over 80 years of age

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ABSTRACT

Introduction and objectives: There is scarce information available on the long-term outcomes of primary angioplasty (PA) in patients over 80 years of age. Our objective was to analyze the characteristics and results of PA in these patients and recognize the prognostic factors and long-term survival.
Methods: Observational and retrospective single-center study of consecutive patients over 80 years of age treated with PA between January 2013 and September 2019. A long-term clinical follow-up was performed (mean follow-up of 29 ± 25 months).
Results: The study included 133 patients (mean age 85.3 ± 3.8 years and 57 women [43%]). Seventeen percent of the patients were in Killip class III-IV at admission. The mean Charlson Comorbidity index was 2.3 ± 1.6. During the hospitalization, almost half of the patients developed heart failure and mortality rate was 18%. The overall mortality rate at the follow-up was 23%, yet 97.2% of the deaths were due to non-cardiac causes. The independent predictors of overall mortality at the follow-up were chronic kidney disease (HR, 5.7; 95%CI, 1.29-25.5; *P* = .022), and a Charlson Comorbidity index > 2 (HR, 2.57; 95%CI, 1.07-6.18; *P* = .035).
Conclusions: Patients over 80 years of age treated with PA have high in-hospital and long-term mortality rates. Comorbidities and chronic kidney disease were the only independent predictors of long-term mortality.

Keywords: Elderly. Myocardial infarction. Primary angioplasty.

Resultados a largo plazo de un programa de angioplastia primaria en pacientes mayores de 80 años

RESUMEN

Introducción y objetivos: Existe poca información sobre los resultados a largo plazo de la angioplastia primaria (AP) en pacientes mayores de 80 años. Nuestro objetivo fue analizar las características y los resultados de la AP en estos pacientes, y valorar los predictores pronósticos y la supervivencia a largo plazo.
Métodos: Estudio observacional, retrospectivo y unicéntrico de pacientes mayores de 80 años consecutivos sometidos a AP entre enero de 2013 y septiembre de 2019. Se efectuó un seguimiento clínico a largo plazo (media de 29 ± 25 meses).
Resultados: Se incluyeron 133 pacientes (57 [43%] mujeres) con una edad media de 85,3 ± 3,8 años. El 17% se encontraban en clase Killip III o IV. El índice de Charlson medio fue de 2,3 ± 1,6. En cuanto a la evolución hospitalaria, casi la mitad de los pacientes desarrollaron insuficiencia cardiaca y un 18% fallecieron durante el ingreso. La mortalidad total en el seguimiento a largo plazo fue del 23%, siendo el 97,2% de las muertes de causa no cardiaca. Los predictores independientes de mortalidad total en el seguimiento a largo plazo fueron la enfermedad renal crónica (*hazard ratio* [HR] = 5,7; intervalo de confianza del 95% [IC95%], 1,29-25,5; p = 0,022) y el índice de Charlson mayor de 2 (HR = 2,57; IC95%, 1,07-6,18; p = 0,035).
Conclusiones: Los pacientes mayores de 80 años sometidos a AP tienen una elevada mortalidad hospitalaria y en el seguimiento a largo plazo. La comorbilidad y la enfermedad renal crónica resultaron ser los únicos predictores independientes de mortalidad a largo plazo.

Palabras clave: Anciano. Infarto de miocardio. Angioplastia primaria.

Abbreviations

PA: primary angioplasty.

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INTRODUCTION

The current estimates reveal the population gradual aging, which will be more evident in the coming years.[1] Based on these estimates, by the year 2050, our country will become one of the oldest worldwide with more than 4 million people over 80 years of age. This means that the percentage of patients treated with primary angioplasty (PA) is on the rise in our setting.

Although old age is associated with worse prognoses, PA is still the best reperfusion strategy for these patients.[2-5] This segment of the population has a high prevalence of comorbidities, is often recommended fewer treatments, and has a higher risk of complications during revascularization procedures. Also, these patients are often misrepresented in the clinical trials, meaning that there is little scientific evidence available on the clinical characteristics, results, and long-term prognosis after PA.[6]

The objectives of this study were to analyze the characteristics, results, mortality, and prognostic predictors of patients > 80 treated with PA in our center.

METHODS

Single-center, retrospective, and observational study. All patients > 80 treated with PA in our center from January 2013 through September 2019 were included. Different clinical and epidemiological variables like age, sex, cardiovascular risk factors, presence of comorbidities, and the total ischemic time were prospectively registered in the unit database. The Charlson Comorbidity was retrospectively obtained at admission to stratify the patients' overall comorbidities.[7,8] This study was approved by *Hospital Universitario Fundación Alcorcón* ethics committee and waiver of informed consent was accepted.

Catheterization and treatment

Most cases were treated with percutaneous coronary intervention using the standard technique via radial access. The contrast agents used in all the cases were iohexol (Omnipaque 350, and Omnipaque 300), and iodixanol (Visipaque 320). The number of main vessels damaged seen on the coronary angiography, the access route, the dose of contrast used, the x-ray image time, and the number and type of stent use were recorded. Angiographic success and the presence of complications during the procedure were recorded as well. The operator chose the type of stent he would use during the procedure, although the local protocol recommended the use of conventional stents preferably. Drug-eluting stents were spared for situations of high risk of restenosis.

Follow-up and endpoints

Follow-up data were obtained after reviewing our hospital electronic health records. Also, phone calls to the patient or his family were made followed by a standard survey when appropriate. The endpoints studied were in-hospital mortality and complications, cardiovascular events, and cardiac death at the long-term follow-up.

Definitions

Left ventricular systolic function was estimated on the echocardiogram. The presence of a left ventricular ejection fraction < 45% was considered moderate-to-severe left ventricular dysfunction. Cardiogenic shock was defined as systolic arterial pressure < 90 mmHg for, at least, 1 hour followed by tissue hypoperfusion that required inotropic support and/or intra-aortic balloon pump implantation. Cardiac deaths were due to acute coronary syndrome, heart failure or ventricular arrhythmia. Angiographic success was defined as the presence of TIMI grade ≥ 2 flow in the absence of residual stenosis > 50%. The glomerular filtration rate was estimated using the simplified modification of diet in renal disease (MDRD) equation.[9] Chronic kidney disease was defined as a glomerular filtration rate < 60 mL/min/1.73 m^2 at admission. Bleeding complications associated with vascular access were classified based on the Bleeding Academic Research Consortium (BARC) definitions.[10] BARC type > 2 hemorrhages were considered major bleeding. Target lesion revascularization was defined as the need for a new revascularization procedure (whether percutaneous or surgical) of the coronary segment with stenting in the presence of angiographic restenosis (stenosis > 50%) and symptoms or signs of myocardial ischemia.

Statistical analysis

The statistical software package SPSS version 20 was used for the analysis of data. Quantitative variables were expressed as mean ± standard deviation. The categorical ones were expressed as absolute value and percentage.

Univariate and multivariate modified Poisson regression analyses were conducted to determine the independent prognostic factors of in-hospital mortality. The variables included in the multivariate analyses were those considered of the greatest clinical relevance: Killip Class > I at admission, age > 85, chronic kidney disease, Charlson Comorbidity index > 2, and presence of moderate-to-severe left ventricular dysfunction. Results were expressed as relative risks and their 95% confidence interval (95%CI).

Univariate and multivariate Cox regression analyses were conducted to determine the independent predictors of overall mortality at the long-term follow-up. The variables included in the multivariate analyses were those associated with a higher mortality rate in the univariate analysis and also those of the greatest clinical relevance: Killip Class > I at admission, age > 85, chronic kidney disease, Charlson Comorbidity index > 2, and presence of moderate-to-severe left ventricular dysfunction. Results were expressed as hazard ratios (HR) and their 95%CI. *P* values < .05 were considered statistically significant. The inter-group overall mortality-free survival rates based on the presence of chronic kidney disease and a Charlson comorbidity index > 2 were compared using the Kaplan-Meier Curves (log-rank test).

RESULTS

Clinical characteristics and of the interventional procedure

A total of 1269 PAs were performed in our center from January 2013 through September 2019. A total of 10.5% were ≥ 80 years old at admission. The study group included 133 patients (57 women [43%]) with a median age of 85.3 ± 3.8 years treated with PA. The study population had a high prevalence of cardiovascular risk factors. A total of 66.2% of the patients had chronic kidney disease. The anterior was the most common location of the infarction. A total of 16.6% of the patients were Killip Class III-IV. In 28.5% of the cases delays of more than 6 hours between the beginning of pain and reperfusion were reported. The mean Charlson Comorbidity index used to assess the comorbidities of the patients included in our series was 2.3 ± 1.6 (table 1).

Regarding the angiographic and procedural data, the radial access was used in 80.5% of the patients of whom 47.4% had multivessel

disease. Almost half of the patients were released from the hospital with incomplete angiographic revascularizations. Thrombus aspiration was performed in one fourth of the patients and drug-eluting stents were implanted in 30.8% of these patients (table 1).

Patient progression at the hospital setting

Regarding patient progression at the hospital setting, 63 patients (49%) developed heart failure and 24 patients (18%) died during admission. Two patients (1.5%) had stent thrombosis during their hospital stay. The cause of death of 21 of the dead patients (87.5%) was cardiovascular. There was a statistically significant higher in-hospital mortality rate in patients with Charlson comorbidity indices > 2 (28.9% vs 13.7%, $P = .039$), Killip Class > I (51.5% vs 7%; $P < .001$), and worse ventricular (26% vs 4.3%, $P = .003$) and renal functions (23.9% vs 6.7%; $P = .031$). The Killip Class-based mortality rate based was 7% for Killip Class I, 27.3% for Killip Class II, 57.1% for Killip Class III, and 66.7% for Killip Class IV (figure 1).

In the multivariate modified Poisson regression analysis, the only independent prognostic factor of in-hospital mortality was the Killip Class at admission (relative risk, 6.5; 95%CI, 2.01-20.36; $P = .001$) (table 2).

Long-term follow-up

A long-term follow-up was conducted of the 109 survivors. The median clinical follow-up was 24.3 months (interquartile range, 6.9-49.4 months) with 3 patients (2.8%) lost to follow-up. The clinical events occurred at the follow-up are shown on table 3. The overall

Table 1. Clinical angiographic, and interventional procedure data

Patients	N = 133	Patients	N = 133
Age (years)	85.3 ± 3.8	*Killip Class*	
Sex (woman)	57 (43%)	I	100 (75.1%)
Diabetes mellitus	46 (34.6%)	II	11 (8.3)
Dyslipidemia	77 (57.9%)	III	7 (5.3)
Arterial hypertension	110 (82.7%)	IV	15 (11.3)
Active smoking	4 (3%)	*Total ischemic time > 6h*	37 (28.5%)
Charlson Comorbidity index	2.3 ± 1.6	*Median of total ischemic time (min)*	268 [177-406]
Body mass index	26.4 ± 3.3	*Median of time from symptom onset until arrival at the PA-capable center (min)*	203 [124-330]
Previous infarction	23 (17.3%)	*Median of time from the arrival at the PA-capable center until guidewire passage (min)*	50 [37-77]
Previous angioplasty	18 (13.5%)	*X-ray image time (min)*	16.6 ± 13
Previous coronary artery bypass surgery	3 (2.3%)	*Volume of contrast (mL)*	173 ± 72
Atrial fibrillation	31 (23.3%)	*Radial access*	107 (80.5%)
LVEF echocardiogram	47.1 ± 11	*Number of diseased vessels*	
LVEF < 50%	61 (45.8%)	1	70 (52.6%)
Creatinine levels at admission (mg/dL)	1.25 ± 0.44	2	39 (29.3%)
GFR-MDRD (mL/min/1.73 m²)	52.2 ± 18.5	3	24 (18%)
*Chronic kidney disease**	88 (66.2%)	*Number of stents implanted*	1.04 ± 0.2
Location of the infarction		*Thrombus aspiration*	34 (25.6%)
Anterior	62 (46.6%)	*Glycoprotein IIb/IIIa inhibitors*	17 (12.8%)
Inferior	48 (36.1%)	*Drug-eluting stent*	41 (30.8%)
Lateral	11 (8.3%)	*PCI of NC lesions in the acute phase*	4 (3%)
Undetermined	9 (6.8%)	*PCI of NC lesions in another procedure at admission*	11 (8.3%)
Cardiac arrest	3 (2.3%)	*Complete revascularization*	69 (51.9%)
		Angiographic success	127 (95.5%)
		In-hospital mortality	24 (18%)

GFR-MDRD, glomerular filtration rate (Modification of Diet in Renal Disease); LVEF, left ventricular ejection fraction; NC, non-culprit; PA, primary angioplasty; PCI, percutaneous coronary intervention.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].
*Defined as a glomerular filtration rate < 60 mL/min/1.73 m².

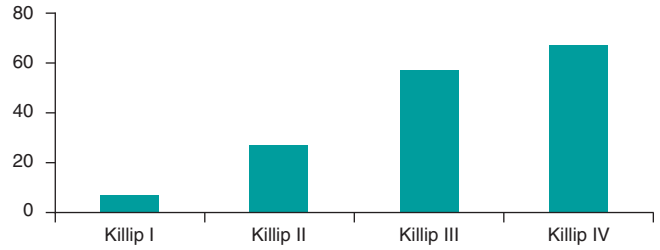

Figure 1. In-hospital mortality based on Killip Class.

Table 2. Factors associated with a higher in-hospital mortality rate. Univariate and multivariate modified Poisson regression analyses

	RR	95%CI	*P*
Univariate analysis			
Age	1.06	0.8-1.15	.135
Sex (woman)	1.58	0.76-3.27	.221
Diabetes Mellitus	1.35	0.65-2.81	.42
Killip Class > I	**7.36**	**3.34-16.22**	**< .001**
Moderate-to-severe left ventricular dysfunction	**6.07**	**1.81-20.28**	**.003**
Total ischemic time (hours)	1.05	0.98-1.22	.163
Atrial fibrillation	1.65	0.78-3.48	.193
Charlson Comorbidity index > 2	**2.12**	**1.04-4.31**	**.039**
Chronic kidney disease	**3.58**	**1.12-11.41**	**.031**
Anterior location	1.60	0.77-3.36	.211
Multivessel disease	1.49	0.70-3.17	.297
Incomplete revascularization	1.38	0.67-2.86	.383
Drug-eluting stent	1.1	0.43-2.82	.846
Mulivariate analysis			
Age	1.1	0.99-1.21	.074
Killip Class > I	**6.5**	**2.01-20.36**	**.001**
Chronic kidney disease	1.23	0.26-5.96	.793
Charlson Comorbidity index > 2	2.2	0.9-5.38	.083
Moderate-to-severe left ventricular dysfunction	3.05	0.95-9.81	.062

95%CI, 95% confidence interval; RR, relative risk.
Statistically significant results are highlighted in **bold**.

mortality rate at the long-term follow-up was 23% with 97.2% of deaths due to noncardiac deaths.

In the univariate Cox regression analysis, the variables associated with a higher overall mortality rate were Killip Class > I (HR, 4.26; 95%CI, 2.38-7.62; *P* = .001), chronic kidney disease (HR, 7.24; 95%CI, 1.7-30.8; *P* = .007), and a Charlson Comorbidity index > 2 (HR, 2.74; 95%CI, 1.18-6.36; *P* = .019) (table 4). Patients with chronic kidney disease had a higher percentage of cases with Charlson Comorbidity indices > 2, but this difference was not statistically significant (19% vs 28,4%; *P* = .27).

Table 3. Events at the long-term follow-up

Patients	N = 106
New acute coronary syndrome	10 (9.2%)
Target lesion revascularization	4 (3.7%)
Stent thrombosis	3 (2.8%)
BARC bleeding type > 2	19 (17.4%)
Stroke	9 (8.3%)
Overall mortality	25 (22.9%)
Cardiovascular mortality	3 (2.8%)
Infection	6 (5.5)
Neoplasm	6 (5.5)
Respiratory failure	5 (4.6)
Unknown	5 (4.6)

BARC, Bleeding Academic Research Consortium.

In the multivariate Cox regression analysis, the only independent predictors of overall mortality were chronic kidney disease (HR, 5.7; 95%CI, 1.29-25.5; *P* = .022), and a Charlson Comorbidity index > 2 (HR, 2.57; 95%CI, 1.07-6.18; *P* = .035) (table 4).

Patients with chronic kidney disease had lower survival rates at the long-term follow-up (56 ± 4.4 months vs 75 ± 3 months; *P* = .002) (figure 2). Patients with Charlson comorbidity indices > 2 also had lower survival rates at the long-term follow-up (45.5 ± 5.9 months vs 65.8 ± 3.3 months; *P* = .015) (figure 3).

DISCUSSION

Information on the results of PA in elderly patients and its long-term prognosis is scarce because this group of patients is often misrepresented in clinical trials.[6] Our study emphasizes these patients' high mortality rate (mainly due to cardiac causes)—both in-hospital and at the long-term follow-up—with a significant contribution from noncardiac mortality and comorbidities as prognostic predictors.

This segment of the population has special characteristics that pose an added risk. These are patients with a high prevalence of comorbidities and worse renal function.[5] Diagnosis is not always easy because of the atypical symptoms reported and possible presence of previous changes on the EKG, factors that contribute to delaying reperfusion therapy.[11] Finally, these are patients with a higher risk of bleeding and other complications during PA.[12]

Regarding the clinical profile of patients > 80 treated with PA in our center we should mention the higher percentage of women (43%) compared to other series from the general population, and the high prevalence of chronic kidney disease (66%), delays of more than 6 hours (29%), and advanced Killip Class (17%). All these characteristics are consistent with what has already been described by former studies in this population.[5,13]

Regarding the procedural aspects, the radial access was used in 80.5% of the cases. Elderly patients, especially women, have higher rates of failure with this access, but at the same time, these patients have the highest risk of bleeding with the femoral access. Rodríguez-Leor et al.[14] reported on the possibility of achieving radial access in 95.1% in a population of patients > 75 treated with PA.

Table 4. Factors associated with a higher mortality rate at the long-term follow-up. Univariate and multivariate Cox regression analyses

	HR	95%CI	*P*
Univariate analysis			
Age	1.1	0.99-1.23	.076
Sex (woman)	1.66	0.71-3.91	.244
Diabetes Mellitus	1.98	0.89-4.41	.094
Killip Class > I	**4.26**	**2.38-7.62**	**.001**
Moderate-to-severe left ventricular dysfunction	2.16	0.97-4.84	.06
Total ischemic time (hours)	1.05	0.98-1.12	.159
Atrial fibrillation	1.54	0.61-3.9	.361
Charlson Comorbidity index > 2	**2.74**	**1.18-6.36**	**.019**
Chronic kidney disease	**7.24**	**1.7-30.81**	**.007**
Anterior location	1.36	0.77-2.40	.287
Multivessel disease	1.43	0.81-2.53	.214
Incomplete revascularization	1.590	0.898-2.817	.112
Drug-eluting stent	0.949	0.46-1.957	.887
Multivariate analysis			
Age	1.07	0.95-1.21	.258
Charlson Comorbidity index > 2	**2.57**	**1.07-6.18**	**.035**
Chronic kidney disease	**5.7**	**1.29-25.5**	**.022**
Killip Class > I	0.96	0.31-2.98	.943
Moderate-to-severe left ventricular dysfunction	1.77	0.77-4.04	.177

95%CI, 95% confidence interval; HR, hazard ratio.
Statistically significant results are highlighted in **bold**.

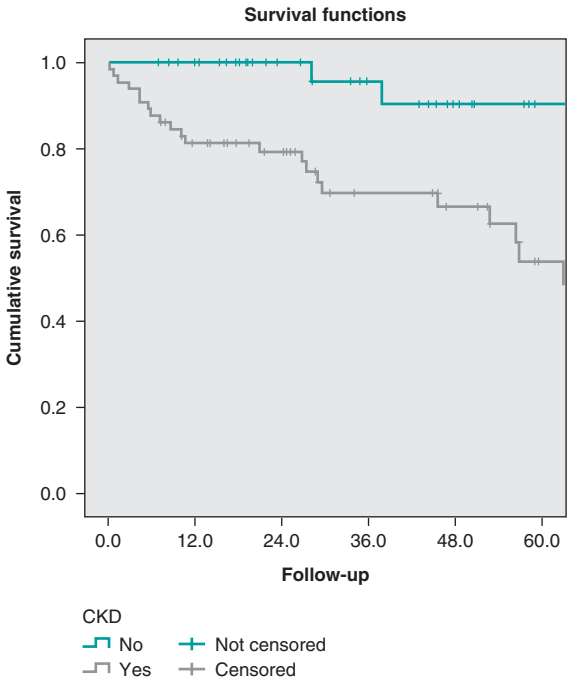

Figure 2. Survival curves at the long-term follow-up stratified based on the presence of chronic kidney disease (log rank test, *P* = .002). ERC, chronic kidney disease.

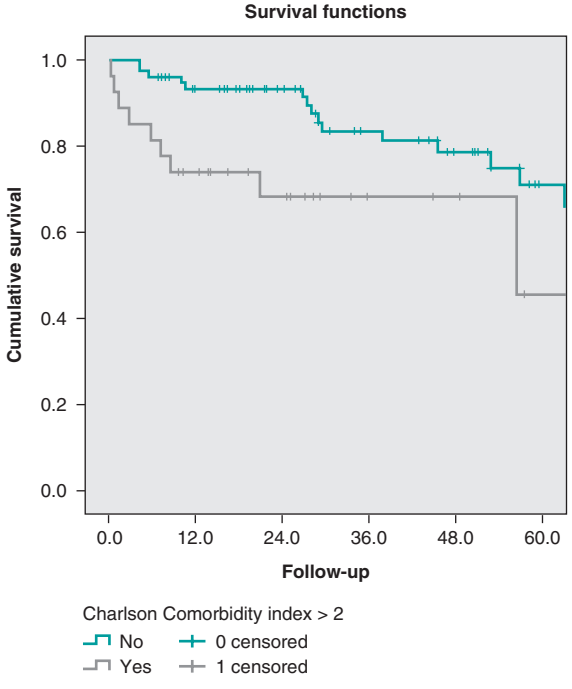

Figure 3. Survival curves at the long-term follow-up stratified based on the presence of Charlson comorbidity indices > 2 (log rank test, *P* = .015).

The in-hospital mortality seen in our study (18) is obviously higher to that of the general population, but not significantly different from that reported by other registries of elderly patients.[12-17] In a group of 34 80-year-old patients treated with PA Sim et al.[5] reported an in-hospital mortality rate of 18%. However, it went up to 37% in patients with ST-segment elevation acute coronary syndrome not treated with PA. In their prospective registry of 496 patients > 80 who received invasive treatment, Kvakkestad et al.[12] reported an in-hospital mortality rate of 13%. In our series the main prognostic factor during admission was the patient's hemodynamic situation measured using Killip Class. It is a well-known prognostic factor that has been widely described in PA studies.[18]

The mortality rate at the long-term follow-up was 23% with a striking contribution from noncardiac mortality, which is a differential factor with respect to series from the general population. This lower rate of adverse cardiovascular events in elderly patients who survive a myocardial infarction was found in other registries and may be due to the high early selection during the acute phase.[13,17] In the aforementioned registry of Kvakkestad et al.[12] the mortality rate at the 3-year follow-up was 29%. In the Swedish registry of 80-year-old patients treated with PA from 2001 to 2010, the annual mortality rate reported was 25%.[17] In our series, the fact that mortality at the long-term follow-up was mostly noncardiac contributed to the fact that the main prognostic predictors at the long-term

follow-up are extracardiac factors like renal function and the Charlson Comorbidity index. These factors may be understudied at the follow-up after PA.

The effect of comorbidities in the prognosis of patients is often quantified using the Charlson Comorbidity index.[7,8] This index assigns a given score to a series of comorbidities based on the risk of mortality of every comorbidity. The overall score is associated with a given mortality risk. Over the last few years, interest has been growing on the analysis of comorbidities and other variables associated with age. However, data are still scarce on their prognostic influence on patients with infarction treated invasively. The existing growing heterogeneity among 80-year-old patients with infarction requires prognostic indices to stratify these patients into risk groups based on uniform criteria. Using a tool to guide us in the long-term prognosis of these patients may help us decide what the most suitable follow-up is. Several studies have proven the utility of the Charlson Comorbidity index in the acute coronary syndrome as a predictor of mortality. Núñez et al. determined the prognostic predictive value of this index in patients with myocardial infarction mostly treated conservatively.[19] They found that the comorbidities present at admission were associated with higher rates of mortality or reinfarction at the 30-day and 1-year follow-up. In our series of invasive management, we found that a Charlson Comorbidity index > 2 was an independent predictor of mortality at the long-term follow-up. However, it is not a predictor of patient progression at the hospital setting where the most important thing is the patient's hemodynamic situation. Therefore, in this population the Charlson Comorbidity index can help us plan their long-term follow-up.

Glomerular filtration rate impairment is a powerful predictor of mortality in different conditions including myocardial infarction.[20] Same as it happens with the Charlson Comorbidity index, in our series of patients, renal function impairment was also an independent predictor of long-term mortality. This confirms that a more comprehensive assessment of 80-year-old survivors of a PA including an accurate assessment of comorbidities and renal function can optimize the management of this population after hospital discharge.

Risk stratification and decision-making are especially complex in 80-year-old patients with myocardial infarction because these a highly heterogeneous patients in whom chronological age may not reflect their actual biological situation. In view of our study findings we believe that in elderly patients it is important to include the measurement of the glomerular filtration rate and, above all, the assessment of comorbidities in the decision-making process at the long-term follow-up after PA. The close follow-up of these patients with several comorbidities can help diagnose potential decompensations (both cardiac and noncardiac) to prevent new hospitalizations. On the other hand, comorbidities determine a high use of drugs which favors the appearance of adverse events, interactions, and therapeutic compliance mistakes. The best thing to do would be to maximize compliance in this population, specify the benefits expected, and minimize the risks associated with the therapy used. Also, optimizing the management of noncardiac diseases can be the key to stabilize coronary artery disease. For all this, keeping a close collaboration with geriatric units after the hospital discharge of 80-year-old patients treated with PA improves their prognosis.

Limitations and strengths

Although the demographic, clinical, and angiographic data were collected prospectively, this was a retrospective analysis with the corresponding limitations of this type of studies. The size of the sample may have limited the statistical power of our study to detect the statistical significance of some associations. Also, the low number of events may have limited the reliability of the multivariate analysis regarding in-hospital mortality and mortality at the long-term follow-up since it included 5 variables in each of these 2 analyses. Since this was a single-center study, results may not be generalizable to other settings.

One of the strengths of the study is that results are based on a thorough and consecutive registry of patients from our setting who were hospitalized after a PA. Also, that a great deal of clinical, analytical, and angiographic information was obtained during their hospital stay and several evolutionary variables were registered at the very long follow-up.

CONCLUSIONS

Patients over 80 treated with PA have a high in-hospital mortality rate (18% in our series). The only independent predictor of in-hospital mortality was Killip Class. Over the next 2 years, mortality is still very high (23%), but is basically associated with noncardiac problems. The independent predictors of overall mortality at the long-term follow-up were chronic kidney disease and a Charlson Comorbidity index > 2

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None.

AUTHORS' CONTRIBUTIONS

L. Hernando Marrupe and J. Botas Rodríguez had the study idea. L. Hernando Marrupe, J. Botas Rodríguez, C. Marco Quirós, and R. Gayoso Gayo designed the study. L. Hernando Marrupe, C. Marco Quirós, R. Gayoso Gayo, V. Espejo Bares, V. Artiaga de la Barrera, C. Jiménez Martínez, R. Del Castillo Medina, and A. Núñez García collaborated in the study data mining. L. Hernando Marrupe, and E. Pérez Fernández conducted the statistical analysis. L. Hernando Marrupe, C. Marco Quirós, and R. Gayoso Gayo interpreted the results and wrote the manuscript first draft. L. Hernando wrote the manuscript final version, and J. Botas conducted the manuscript critical review.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- Primary angioplasty has been considered the best reperfusion strategy in patients with ST-segment elevation myocardial infarction for years. However, elderly patients have special characteristics that pose an added risk. Also, they are misrepresented in the clinical trials. Risk stratification and the decision-making process are especially complex in 80-year-old patients with myocardial infarction because this is a highly heterogeneous population.

WHAT DOES THE STUDY ADD?

- In 80-year-old patients treated with PA it seems that the main prognostic factor of in-hospital mortality is the patient's hemodynamic situation at admission. However,

if the patient survives the index event his prognosis is more associated with the presence of comorbidities. Our study proved that measuring the glomerular filtration rate and Charlson Comorbidity index can help us treat these patients more effectively at the long-term follow-up.

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Original article

Long-term (> 12 months) single-center registry of Magmaris implantation in the acute coronary syndrome setting

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ABSTRACT

Introduction and objectives: The results of Magmaris implantation in the acute coronary syndrome setting is uncertain and more studies will be needed to assess the long-term safety profile of these devices. The objective of this work was to conduct an observational study to analyze the clinical safety profile of Magmaris implanted in a single hospital center in the acute coronary syndrome setting beyond 12 months.
Methods: Registry of 36 patients with Magmaris devices implanted between November 2016 through November 2018 with a diagnosis of acute coronary syndrome included consecutively. The primary endpoint was considered the device-oriented composite endpoint of target vessel myocardial infarction, target lesion failure, and cardiac death. Secondary endpoints included Magmaris related thrombosis.
Results: Regarding the device-oriented combination, no target vessel myocardial infarction was observed, 0 cases (0%), while target lesion failure was seen in 2 cases (5.6%). There were no cases of Magmaris thrombosis at the follow-up and only 1 case of cardiac death (2.8%) was found 36 months after Magmaris implantation. The cause of death could not be determined since no autopsy was performed.
Conclusions: Our results with long-term follow-up confirm that Magmaris has a favorable clinical profile in the acute coronary syndrome complex setting.

Keywords: Magmaris. Acute coronary syndrome. Bioresorbable scaffold thrombosis.

Registro unicéntrico a largo plazo (> 12 meses) del implante de Magmaris en el síndrome coronario agudo

RESUMEN

Introducción y objetivos: Los resultados del Magmaris en el síndrome coronario agudo son controvertidos y se necesitan más estudios para evaluar su seguridad a largo plazo. El objetivo del trabajo fue analizar mediante un estudio observacional la seguridad clínica más allá de 12 meses de los Magmaris implantados en un único centro hospitalario en pacientes con síndrome coronario agudo.
Métodos: Se registraron de manera consecutiva 36 pacientes con Magmaris implantados entre noviembre de 2016 y noviembre de 2018 con diagnóstico de síndrome coronario agudo. Para el objetivo primario se consideró el combinado orientado al dispositivo de infarto de miocardio del vaso diana, fracaso de la lesión diana y muerte de causa cardiovascular. Como objetivo secundario se incluyó la trombosis del dispositivo.
Resultados: En cuanto al combinado orientado al dispositivo no se observó infarto de miocardio del vaso diana (0%), en 2 casos (5,6%) se observó fracaso de la lesión diana y se constató 1 caso de muerte cardiaca (2,8%) a los 36 meses del implante del Magmaris, sin poder conocer la causa por no disponer de autopsia. Con respecto a los objetivos secundarios, no hubo casos de trombosis del Magmaris durante el seguimiento.
Conclusiones: Nuestros resultados, con un seguimiento a largo plazo, apoyan que los Magmaris presentan un perfil clínico favorable en el escenario complejo del síndrome coronario agudo.

Palabras clave: Magmaris. Síndrome coronario agudo. Trombosis armazón bioabsorbible.

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INTRODUCTION

Magnesium-based bioresorbable scaffolds (Magmaris) are safe devices with good results in the long run like the BIOSOLVE II[1] and BIOSOLVE III[2] clinical trials show where no device thrombosis was seen at the long-term 12- to 24-month follow-up. Despite this fact, the device own limitations (ill-advised in cases of calcified complex coronary anatomy or in long lesions) have reduced its use significantly in the routine clinical practice to the point that only 224 procedures with bioresorbable devices were performed in Spain in 2019 (0.2% of the total number of devices implanted).[3]

As already mentioned, the good results reported in long-term follow-ups have turned the Magmaris (Biotronik, Germany) into the only bioresorbable metal scaffold to receive the CE marking (Conformité Européenne).[4]

The role Magmaris plays in the acute coronary syndrome setting is not widely known and further studies will be needed before its safety profile can be assessed. The objective of this work was to analyze—through an observational study in the routine clinical practice—the long-term (> 12 months) clinical safety of Magmaris scaffolds implanted in patients with acute coronary syndrome in the cath lab of a single center.

METHODS

Consecutive observational registry of patients diagnosed with acute coronary syndrome implanted with magnesium-based bioresorbable scaffolds between November 2016 and November 2018. The study was approved by the hospital ethics committee and all patients gave their signed written informed consent to participate in the study. The study primary endpoint was a composite of target vessel myocardial infarction, target lesion failure, and cardiovascular death. The study secondary endpoint included the device thrombosis. The PSP strategy (predilation, sizing, and postdilation) derived from the GHOSTEU registry was used in all the cases.[5] In 100% of the patients the optical coherence tomography was used for the right characterization of the lesion and size of the vessel.

RESULTS

A total of 36 patients (29 males, 80%) were included with a median age of 59.61 ± 9.74 years. The follow-up period was 1001 days with an interquartile range of 342 days. Table 1 summarizes the baseline clinical characteristics of the sample as well as the main angiographic characteristics.

Table 1. Baseline clinical characteristics and angiographic parameters of the patients

	N (%)		N (%)
Family history of ischemic heart disease	11 (30.6)	*AHA classification of coronary lesions:*	
Arterial hypertension	19 (52.8)	Type A	16 (44.5%)
Diabetes mellitus	7 (19.4)	Type B	12 (33.3%)
Dyslipidemia	23 (63.9)	Type C	8 (22.2%)
Smoker	23 (63.9)	*Immediate success after device implantation*	36 (100%)
Type of acute coronary syndrome:		*Drug-eluting stent implantation*	12 (36%)
NSTEACS	23 (63.9)	*Normal LVEF*	26 (72.2%)
STEACS	8 (22.2)	*Antiplatelet therapy at discharge:*	
Unstable angina	5 (13.9)	Acetylsalicylic acid	36 (100%)
Number of diseased vessels:		Ticagrelor	29 (80.6%)
1 vessel	16 (44.4)	Clopidogrel	6 (16.7%)
2 vessels	15 (41.7)	Prasugrel	1 (2.8%)
3 vessels	5 (13.9)	*Prolonged DAPT > 12 months*	14 (38.9%)
Location of the lesion treated with Magmaris:		*Statins*	36 (100%)
LAD	27 (75%)	*Beta-blockers*	31 (86.1%)
RCA	10 (27.8%)		
LCX	4 (11.1%)		

Angiographic parameters	Length (mm)	Diameter (mm)	Peak inflation pressure (atm)
Target lesion	29.2 ± 13.4	3.4 ± 0.2	
Predilation (noncompliant balloon)	16.8 ± 2.9	3.2 ± 0.4	20.2 ± 1.2
Magmaris	22.5 ± 3.05	3.4 ± 0.2	15.9 ± 0.9
Postdilation (noncompliant balloon)	21.4 ± 1.5	3.7 ± 0.3	21.4 ± 1.5

AHA, American Heart Association; DAPT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; NSTEACS, non-ST-segment elevation acute coronary syndrome; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome.

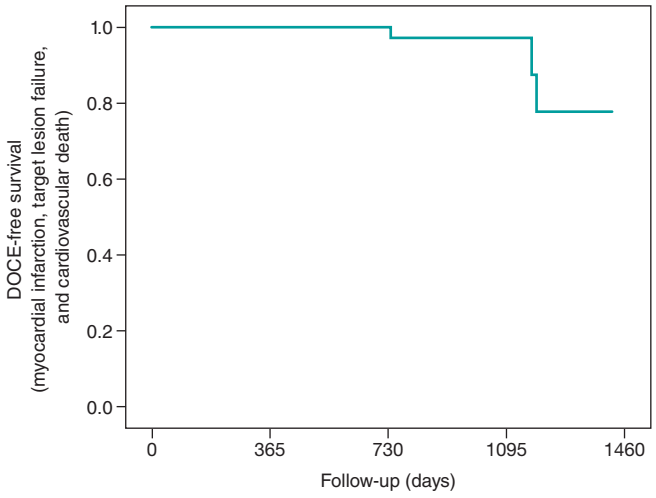

Figure 1. Kaplan-Meier survival curve with respect to the study primary endpoint: a device-oriented composite endpoint of target vessel myocardial infarction, target lesion failure, and cardiovascular death. DOCE, device-oriented composite endpoint.

Table 2. Primary (device-oriented composite endpoint) and secondary clinical events of the patients at the follow-up (N = 36, 100%)

Event	Patients	Percentage
Target lesion failure	2	5.6 %
Target vessel myocardial infarction	0	0 %
Cardiovascular death*	1	2.8 %
Magmaris device thrombosis	0	0 %

* 1084 days after Magmaris implantation.

A total of 100% of the patients received a Magmaris device in the target lesion causing the study acute coronary event. Drug-eluting stents were implanted at the discretion of the operator in 12 of the 36 patients (33.3%), and in 1 patient only (2.8%) the implantation of the stent and the Magmaris scaffold overlapped. However, in the remaining patients they were not implanted in the target vessel.

Only 1 Magmaris scaffold was used in 15 patients (41.7%), 2 in 12 cases (33.3%), 3 in 2 cases (5.6%), 4 in 3 cases (8.3%), 5 in 3 cases (8.3%), and a maximum of 6 Magmaris devices in 1 single patient (2.8%). In 20 patients (55.6%) the stent and the Magmaris device implantation overlapped.

Regarding the device-oriented composite endpoint, 0 cases of target vessel myocardial infarction occurred (0%). However, 2 cases of target lesion failure were confirmed (5.6%), and 1 noncardiovascular death (2.8%) was reported at the 36 months following Magmaris implantation. However, the cause remained elusive for the lack of an autopsy (figure 1). Regarding the secondary endpoints, no Magmaris thrombosis was reported at the follow-up (table 2).

A total of 11 admissions were reported at the follow-up (30.6%). Among these, 8 were due to recurrent angina (22.2%), 2 to heart failure or de novo atrial fibrillation (5.6%), and 1 to atrioventricular block that required pacemaker implantation (2.8%).

The coronary angiography was repeated in 10 cases (27.8%), the absence of lesions was confirmed in 3 patients (8,3%), stent restenosis was reported in 1 patient 2.8%), Magmaris restenosis in 2 (5.6%), and de novo lesions in 4 patients (11.1%).

When the cases of Magmaris restenosis were studied across time it was found that all of these occurred after the 24-months follow-up (1 case after 737 days and the other after 1189 days). The cardiovascular death reported in 1 patient occurred 1084 days after implantation.

DISCUSSION

The magnesium-based bioresorbable scaffold (Magmaris) is a highly successful device when implanted following the recommendations made by the manufacturer[6] including the right predilation and optimization of the lesions using intracoronary imaging modalities. A study proved that an optimal PSP technique was not associated with a lower rate of the device-oriented composite endpoint. However, patients with optimal PSP-3 had numerically fewer episodes compared to patients without optimal PSP-3 (0.5% vs 2.9%, $P = .085$, and 0.5% vs 1.8%, $P = .248$, respectively).[7]

The real-world 12-month follow-up results of a cohort registry with Magmaris have recently been published. These results have confirmed the Magmaris safety profile and its low rate of events (target lesion revascularization in 4.7%) and lack of thrombosis.[8]

Also, the use of magnesium-based bioresorbable scaffolds has been studied in a group of 50 patients with non-ST-segment elevation acute coronary syndrome. This device reached angiographic success in 100% of the cases. One case of failed target vessel revascularization was reported the day after the procedure that required the implantation of a bare-metal stent. No device-related events were reported at the 6-month follow-up.[9]

The Magmaris scaffold and the sirolimus-eluting stent were compared in a controlled, randomized, blinded, multicenter study of patients with ST-segment elevation acute coronary syndrome. This study proved that in 150 patients the primary endpoint of a greater vasomotor response to medication was better in the Magmaris group at the 1-year follow-up. However, the Magmaris scaffold was associated with a worse angiographic progression and a greater late luminal loss compared to the bare-metal stent. It was also associated with a higher rate of target lesion revascularization without a significantly higher number of thrombotic events being reported.[10]

In our registry, the immediate rate of successful device implantation was 100%. Device overlapping occurred in 55.6% of the cases with a high frequency of treatment of 2 and 3 vessels (55.4%). Despite the complexity of the lesions, device restenosis was only reported in 2 cases (5.6%) at the > 3-year follow-up. The rate of thrombosis at the follow-up was 0 cases and the rate of cardiovascular death—considering 1 case with the devices implanted 36 months beforehand (and without necropsy or previous clinical assessment)—was 2.8%. In our study of real-world clinical practice this confirms the device safety profile in the short and mid-term in the acute coronary syndrome setting. The results of the BIOSOLVE IV registry reported a target lesion failure rate of 4.3%,[11] similar to the one seen in our registry—5.5%—despite our patients' profile of higher ischemic risk (all of them with acute coronary syndrome and an average lesion length of 29.17 mm ± 13.39 mm with Magmaris overlapping in 55.6% of the cases).

Limitations

Our study main limitation is its small sample size, which shows the low penetration of resorbable scaffolds in our hospital setting. Another limitation is the registry observational nature with an

inherent selection bias, without defined inclusion and exclusion criteria, and the use of second-generation drug-eluting stents in 33.3% of the patients outside de target vessel except for 1 case where the stent and the Magmaris device overlapped (2.8%).

Another limitation was the lack of an independent clinical event adjudication committee. However, 100% of the patients were followed-up (through electronic health records and phone calls) by the research working team.

CONCLUSIONS

In our registry of patients with acute coronary syndrome who received the Magmaris scaffold the primary endpoint of target lesion failure or target vessel myocardial infarction did not increase compared to registries previously published. No cases of scaffold definitive thrombosis were reported at the follow-up, and only 1 cardiovascular death was reported 36 months after implantation without knowing the definitive cause. Considering the aforementioned limitations, our results confirm that Magmaris scaffolds could have a favorable clinical profile in the complex setting of acute coronary syndrome.

FUNDING

No external funding has been received.

AUTHORS' CONTRIBUTIONS

All authors contributed equally during the collection of clinical data and the performance of the interventional procedures including the follow-up of all of the patients.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- Magnesium-based bioresorbable scaffolds (Magmaris) have proven safe and effective in former studies and registries.
- Despite the recent studies published on the acute coronary syndrome setting, the long-term safety of these devices has still not been confirmed yet.

WHAT DOES THIS STUDY ADD?

- A real-world registry with a very long-term follow-up showing a low rate of device-related events.
- Further multicenter registries with a high number of patients will be needed before solid conclusions can be drawn.

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Original article

Patient-specific flow simulation analysis to predict device-related thrombosis in left atrial appendage occluders

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ABSTRACT

Introduction and objectives: Left atrial appendage occlusion (LAAO) can be an efficient treatment to prevent strokes in patients who suffer from atrial fibrillation, especially those at risk of bleeding. A non-negligible number of patients treated with LAAO develop device-related thrombosis (DRT) after device implantation. Our study aimed to identify the key blood flow characteristics leading to DRT using patient-specific flow simulations.
Methods: Patients treated with LAAO between 2014 and 2019 at a single center with preoperative and follow-up computerized tomography images and ultrasound imaging (US) were used to create patient-specific flow simulations. Amulet LAAO devices were implanted in the study patients. Flow simulations were blindly assessed to discard the presence of DRT in the follow-up imaging.
Results: A total of 6 patients were processed in this pivotal study, half of them with DRT at the follow-up according to the imaging analysis. After a comprehensive analysis of the simulations, the most relevant in silico indices associated with DRT were the presence of stagnant blood flow, recirculation with low flow velocities (< 0.20 m/s) next to the device surface, and regions with high flow complexity combined with low wall shear stress.
Conclusions: Patient-specific flow simulations of LAAO were successfully used to predict blood flow patterns with different device configurations. The results show the potential of the present modelling and simulation approach to recommend optimal settings capable of minimizing the risk of DRT.

Keywords: Device-related thrombosis. Flow simulation. Left atrial appendage occlusion. Patient-specific.

Análisis de la formación de trombo después del cierre de orejuela utilizando simulaciones de flujo personalizadas

RESUMEN

Introducción y objetivos: El cierre de la orejuela izquierda (COI) puede ser una alternativa de tratamiento eficaz para prevenir eventos cardiovasculares en pacientes con fibrilación auricular, en especial en aquellos con alto riesgo de sangrado. Sin embargo, algunos de estos pacientes en los que se realiza COI desarrollan trombosis relacionada con el dispositivo (TRD). Este estudio presenta las características del flujo sanguíneo que son clave en la formación de TDR, a partir de simulaciones personalizadas para cada paciente.
Métodos: Para crear las simulaciones personalizadas se incluyeron en el estudio pacientes intervenidos de COI entre 2014 y 2019 en un único centro, de quienes se disponía de imágenes de tomografía computarizada previas al procedimiento y de seguimiento, así como de control ecocardiográfico. Para el COI se utilizaron los dispositivos Amulet. Las simulaciones se analizaron de forma ciega al diagnóstico de TRD.
Resultados: En total se estudiaron 6 pacientes, de los que la mitad presentaban TRD según las imágenes del seguimiento clínico. Tras analizar los resultados de las simulaciones, los índices hemodinámicos asociados con TRD fueron la presencia de flujo estancado, las recirculaciones de sangre a velocidades bajas (< 0,20 m/s) cerca de la superficie del dispositivo y las regiones con alta complejidad de flujo y baja tensión de cizallamiento en la pared.
Conclusiones: Las simulaciones de flujo personalizadas en pacientes con COI predijeron correctamente el diagnóstico clínico de TRD en todos los casos analizados. Los resultados obtenidos demuestran el potencial de los modelos personalizados para recomendar configuraciones óptimas del dispositivo y minimizar el riesgo de TRD.

Palabras clave: Trombosis relacionada con el dispositivo. Simulaciones de flujo. Cierre de la orejuela izquierda. Personalización del paciente.

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Abbreviations

AF: atrial fibrillation. **CT:** computed tomography. **DRT:** device-related thrombosis. **ECAP:** endothelial cell activation potential. **LAAO:** left atrial appendage occlusion.

INTRODUCTION

Former randomized trials have shown that percutaneous left atrial appendage occlusion (LAAO) can be an efficient strategy to predict cardioembolic events in selected patients with non-valvular atrial fibrillation (AF) as an alternative to lifelong oral anticoagulation (OAC).[1,2] However, device-related thrombosis (DRT) has become a major concern due to its incidence rate (2% to 5%)[3] and the increased rate of associated strokes.[4] Despite the use of different antithrombotic therapies, the rate of DRT has not changed.[5] Arguably, adding or intensifying anticoagulant therapy has proven to be capable of reducing effectively the thrombotic burden in patients diagnosed with DRT.[6] However, in these high-risk patients, intensive antithrombotic therapies may translate into a higher risk of bleeding. Therefore, identifying the predictors of DRT appears to be essential to individualize suitable antithrombotic treatments post-LAAO and identify those patients who would need a closer follow-up.

Several clinical variables (age, AF at time of implantation, congestive heart failure, CHA_2DS_2-VASc score) have been associated with a higher risk of DRT mainly due to their impact on hypercoagulability.[7] Other factors such as peri-device leaks and uncovered pulmonary venous ridge have been suggested as potential factors for DRT, although the data published on this regard are still controversial.[8] Remarkably, only scarce data have been reported on the impact of blood stasis around the device, although the characteristics of blood flow largely influence thrombus formation.[9-11]

Acquiring reliable imaging data characterizing the complex 4D behaviour of blood flow patterns in the left atrium is a challenge. However, patient-specific computational models of the heart, also known as 'Digital Twin' models are emerging as a valuable technology in clinics to back up clinical decisions and contribute to interventional planning, diagnosis, and device optimization.[12-14] Several studies analysing blood flow patterns in the LA and LAA with flow-related computational models have been proposed,[15,16] but most of them have been applied to a very limited set of patient-specific clinical data without follow-up. Furthermore, only a couple of studies have considered LAAO implantation.[11,17] As a matter of fact, only 1 study has analyzed the direct impact of flow dynamics on the generation of DRT with computational models.[11]

This manuscript is a proof-of-concept study that describes our early experience evaluating a computational workflow to assess the risk of DRT through personalized flow simulations after LAAO implantation. Our objective was to identify patients who would need closer follow-ups after the intervention due to a higher risk of DRT.

METHODS

General overview

We developed a computational methodology to build patient-specific models and drew personalized in silico indices from clinical data standardly available in patients treated with LAAO implantation. Figure 1 shows a scheme of the proposed methodological workflow. To test this workflow, a retrospective, single-centre study was performed including 6 patients (3 with DRT, and 3 without DRT, respectively) referred for LAAO implantation, post-implantation cardiac computerized tomographic (CT) imaging of the whole atrium, and ultrasound imaging (US) of the mitral valve (MV). The study protocol was approved by the Hospital de la Santa Creu i Sant Pau ethics committee, and all patients gave their informed consent.

Clinical data

CT images were acquired at least twice between months 1 and 3, and between months 3 and 6, respectively after LAAO implantation. A prospective cardiac-gated computed tomography angiography was performed with a Phillips Brilliance iCT scanner (Philips Healthcare, The Netherlands). A biphasic contrast injection protocol was used: 40 cc of iodinated material (Iomeprol 350 mg/mL, Bracco, Italy) were infused through an 18-gauge cubital catheter at a rate of 5 mL/s followed by a saline flush of 40 mL.

The bolus-tracking method was used for the arterial phase images being the region of interest on the ascending aorta with a 100 HU threshold. A volumetric scan from heart to diaphragm (14 cm to 16 cm) was acquired. Cardiac phase reconstruction was performed at 30% to 40% of the interval between the QRS complex. Digital image post-processing and reconstruction were performed using the Brilliance Workstation to assess the LAAO device positioning and presence/location of the DRT (defined as a CT hypodensity on the device left atrial extremity): *a)* unexplained by imaging artefacts, *b)* inconsistent with normal healing, *c)* visible in multiple CT planes, and *d)* in contact with the device. Patient data were anonymized prior to any computational processing. None of the patients showed leaks after assessing the CT following the methodology and the definition provided by Linder et al.[18]

A 2D Doppler echocardiography was performed within 7 days from CT follow-up acquisition. Transmitral flow velocities as seen on the pulsed-wave Doppler echocardiography were recorded from the apical 4-chamber view with the Doppler samples placed between the tips of the mitral leaflets. Four out of the 6 patients were diagnosed with permanent AF and 2 with paroxysmal AF. One patient from the latter group was in sinus rhythm when the US images were acquired. Since these patients did not have A waves, the measurement of velocity curves corresponded to the mean of the measurements of their E waves over 3 or 5 beats.

3D model construction and simulation experiments

A personalized geometrical model of the whole left atrium was constructed for each patient from the CT images through semi-automatic segmentation. The Slicer 4.10.1 software was used. The geometry and position of the LAAO device implanted were also extracted from the post-procedural CT scans. The thrombi were segmented as a part of the LA. Therefore, the modeller was blind and did not know whether there was a thrombus when he received the 3D model segmented. The segmented regions were then built on 3D mesh models for computational fluid dynamics simulations.

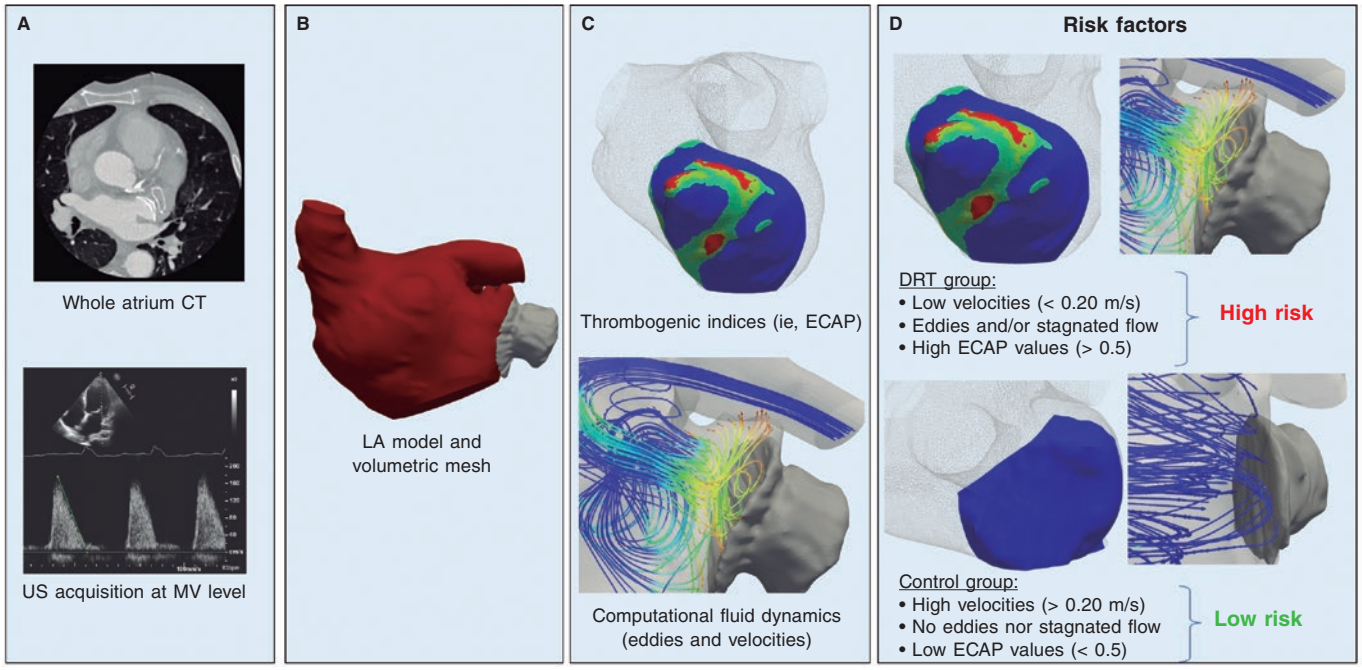

Figure 1. Scheme of the patient-specific computational workflow to predict the risk of device-related thrombus (DRT) formation after left atrial appendage occluder (LAAO) implantation. **A:** computerized tomography (CT) scan acquisition of whole left atrium (LA) and ultrasound (US) study with Doppler measurements at mitral valve (MV) level. **B:** 3D LA segmentation and model generation where finite volume analysis was performed. **C:** blood flow velocities and in silico indices like endothelial cell activation potential (ECAP) estimated from personalized computational fluid dynamics simulations. **D:** the risk factors predicting the presence of DRT were low velocities (< 0.20 m/s), and stagnated flow next to the device surface as well as high ECAP values (indicative of complex blood flow patterns and low wall shear stress).

The velocity curves at the mitral valve were obtained from the Doppler ultrasound imposing patient-specific boundary conditions in terms of outflow during the left atria flow simulations. All simulations used a generic pressure wave from a patient with AF at pulmonary vein level. The movement of the mitral valve annular plane was defined according to the medical literature available,[19] and distributed through the whole LA thanks to a dynamic mesh approach. Flow simulations were performed using the computational fluid dynamics solver Ansys Fluent 19 R3 (ANSYS Inc, United States). Post-processing and visualization of simulation results were performed using ParaView 5.4.1 (Sandia National Laboratories, Kitware Inc., Los Alamos National Laboratory, United States). More details on the 3D construction modelling and computer simulation pipeline are shown on the supplementary data.

Patient-specific flow simulations allowed the local analyses of the following in silico indices: *a)* the presence of swirling flows (eg, eddies) or stagnated flow next to the device surface; *b)* the velocity magnitude averaged over the whole cardiac cycle within the area outlined between the pulmonary ridge and the device surface (see figure 2); low velocity values (< 0.20 m/s) were defined as a strong indicator of thrombus formation[20]; and *c)* regions with complex flow patterns and low wall shear stress were characterized using the endothelial cell activation potential (ECAP) index[21] (ECAP > 0.5).

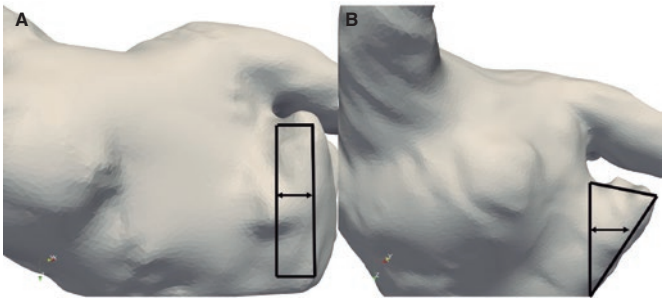

Figure 2. Two examples: patient #2 **(A)** and patient #6 **(B):** region (black rectangle and triangle, respectively) where velocities are estimated from flow simulation between the perpendicular line towards the pulmonary ridge and the device edge.

RESULTS

Patient characteristics

Six patients treated with LAAO with the Amulet device were selected from the overall LAAO database based on the availability of complete CT imaging at the follow-up including the whole atrium anatomy and an echocardiography study with mitral flow analysis. Three cases with diagnosed DRT and 3 controls (without DRT) were included for patient-specific computational fluid dynamics analyses.

The indication for LAA closure was motivated by a history of major bleeding in 5 patients and high bleeding risk in the remaining one. The patients' baseline characteristics are shown on table 1 and table 2 (DRT and control groups, respectively). Antithrombotic treatment post-LAAO was prescribed for a minimum of 3 months (table 1 and table 2). No cardioembolic strokes occurred during a minimum clinical follow-up of 12 months.

Analysis of the simulated flows to predict the risk of DRT

Swirling flows or eddies (figure 3, column 2, red markers) due to blood stagnation and recirculation near the LAAO device surface

Table 1. Characteristics of patients with device-related thrombus

	Patient #1	Patient #2	Patient #3
Age, years	83	86	75
Sex	Male	Male	Male
LVEF, %	68%	47%	62%
Indication for LAAO	Intracranial bleeding	GI bleeding	High bleeding risk
Creatinine, mmol/L	121	122	71
Atrial fibrillation	Permanent	Permanent	Permanent
Diabetes	No	No	No
Current smoker	No	No	No
Arterial hypertension	Yes	Yes	No
History of stroke/TIA	Yes	No	No
CHA_2DS_2VASc score	6	4	3
HAS-BLED score	4	1	4
Device size, mm	31	28	22
Time after LAAO, CT thrombus detection, in weeks	12	22	15
Therapy at time of thrombus detection	Clopidogrel	No treatment	No treatment

CHA_2DS_2VASc score (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 74, sex); CT, computerized tomography; GI, gastrointestinal; HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly); LAAO, left atrial appendage occlusion; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

Table 2. Characteristics of patients without device-related thrombus (control group)

	Patient #4	Patient #5	Patient #6
Age, years	66	64	65
Sex	Male	Male	Male
LVEF, %	77	29	29
Indication for LAAO	GI bleeding	GI bleeding	GI bleeding
Creatinine, mmol/L	75	170	147
Atrial fibrillation	Permanent	Paroxysmal	Paroxysmal
Diabetes	No	Yes	No
Current smoker	No	Yes	No
Arterial hypertension	Yes	Yes	Yes
History of stroke/TIA	No	No	No
CHA_2DS_2VASc score	3	4	4
HAS-BLED score	3	2	3
Device size, mm	28	28	22
Time after LAAO, CT performed in weeks	25	5	38
Therapy at time of thrombus detection	DAPT	Acenocumarol	Acetylsalicylic acid

CHA_2DS_2VASc score (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 74, sex); CT, computerized tomography; GI, gastrointestinal; HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly); LAAO, left atrial appendage occlusion; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

were found in all patients except for patient #5. The areas with flow recirculation in the simulations matched exactly the location where thrombi were found in the post-CT follow-ups (figure 3, column 1) of patients with DRT. In addition, the magnitude of blood velocities near the device surface, averaged over the whole beat, were different in the DRT group compared to the control cases: around 0.15 m/s for the DRT group, and > 0.20 m/s for the control cases. Table 3 shows the estimate average blood velocities at systole, diastole, and over the whole cardiac cycle. These velocities were generally higher during ventricular diastole. Remarkably, patient #5 who suffered severe mitral regurgitation had particularly high flow velocities (2-3 m/s during the E wave), according to simulations (0.87 m/s on average) in the LAAO region and Doppler data. On the contrary, patient #2 had the smallest average velocity value at 0.10 m/s.

ECAP values ≥ 0.5 Pa^{-1} were found near the device surface in all patients with DRT (see table 3 for peak and average ECAP values). The peak ECAP values in patients #1 and #2 (figure 3, column 3, red areas) allowed us to clearly locate the specific areas where simulations predicted the formation of DRT, which was later compared to the post-CT imaging analyses. For instance, the spatial location of the ECAP highest values in patient #2 (figure 3, row 2) on the device upper region next to the pulmonary ridge matches the location of the thrombus in the follow-up images. However, the ECAP map of patient #1 suggested an inferior thrombogenic area whereas the real thrombus also formed on the device upper region. In patient #3, ECAP values were more homogeneously distributed over the entire device surface, yet the peak values were still found where the thrombus was formed (lower device region). Regarding the control group, ECAP results were very low except for those of patient #4. In any case, the threshold of 0.5 was not reached, and the follow-up confirmed that this patient did not develop DRT.

DISCUSSION

Early diagnosis, and even prediction, of DRT seems essential to reduce further complications after LAAO implantation like stroke or systemic embolism. It would also contribute to individualize optimal antithrombotic therapies, on which there is still not consensus in the medical community. In this study, the combination of several in silico indices successfully predicted the presence or lack of DRT in all simulated cases (3 controls and 3 patients with DRT diagnosed with follow-up CT imaging). The computational pipeline developed basically required the 3D reconstruction of the whole LA anatomy, obtained with regular cardiac CT imaging acquisition plus a standard US study, already routinely acquired for LAAO candidates, which allowed us to define patient-specific boundary conditions (such as the mitral flow velocity profile from Doppler data). Each patient-specific simulation extended for 48 hours on average. These requirements make the proposed tool particularly suitable for clinical use, and the estimates indicated that an early diagnosis of DRT within 72 hours following device implantation is possible.

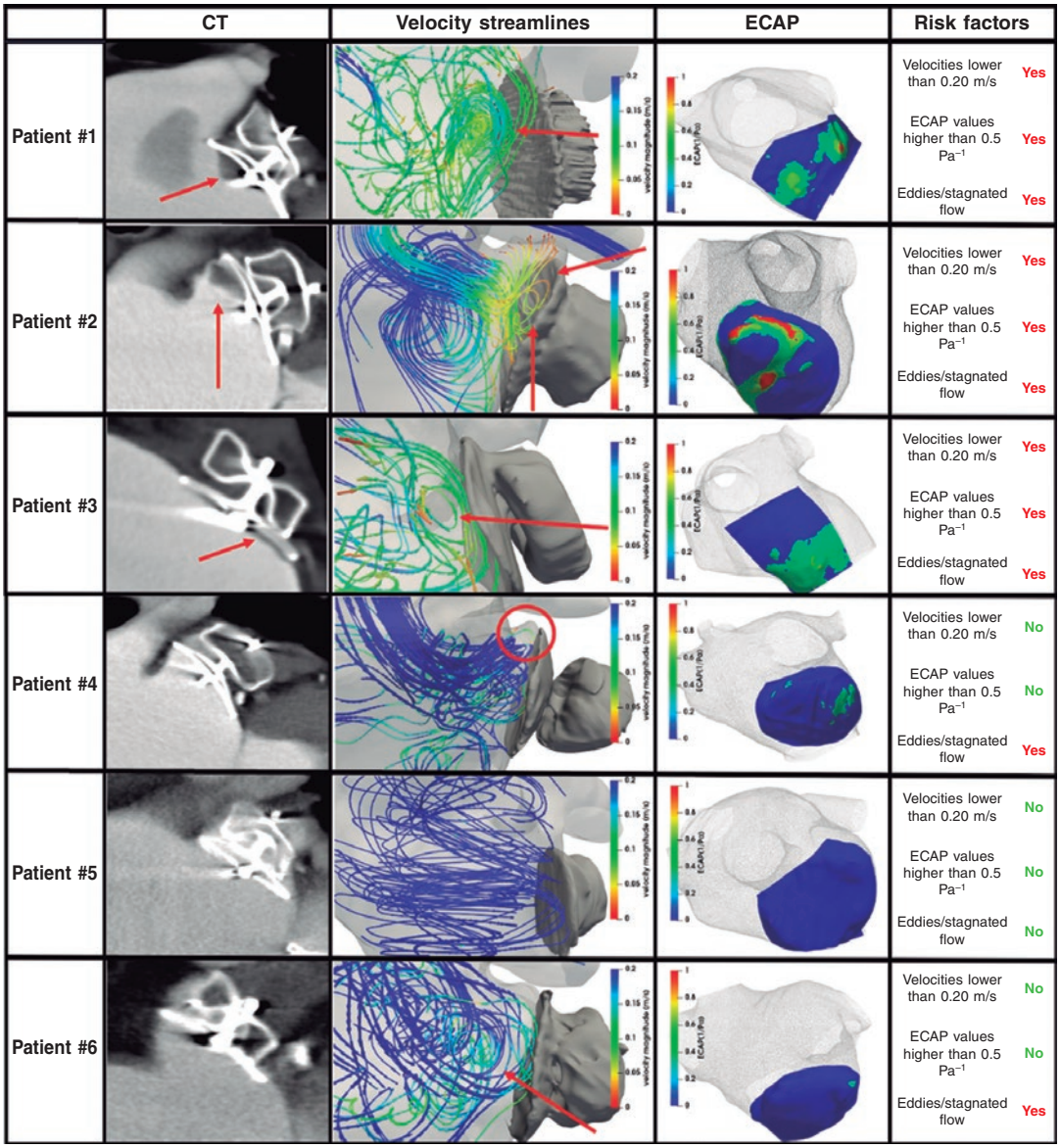

Figure 3. Results of the computational modelling analysis to predict device-related thrombogenesis (DRT). CT column: computerized tomography (CT) scan, red arrows indicate where the thrombus was found at the follow-up imaging analysis. Column with velocity streamlines: simulated blood flow patterns colored by velocity magnitude (blue, high values; red, low values), red arrows indicative of stagnated flow or recirculation. ECAP column: map of the endothelial cell activation potential (ECAP) in silico index near the device surface indicative of high and low DRT risk (red and blue, respectively). Column of risk factors: list of simulation-based risk factors for developing DRT.

Table 3. Blood flow velocities and ECAP near the device surface

	Vel-syst (m/s)	Vel-diast (m/s)	Vel-whole (m/s)	Max-ECAP (Pa^{-1})	Mean-ECAP (Pa^{-1})
Patient #1 (DRT)	0.07 ± 0.02	0.27 ± 0.08	0.16 ± 0.11*	1.23*	0.23 ± 0.14
Patient #2 (DRT)	0.11 ± 0.03	0.09 ± 0.02	0.10 ± 0.03*	1.50*	0.24 ± 0.26
Patient #3 (DRT)	0.10 ± 0.03	0.19 ± 0.07	0.14 ± 0.07*	0.61*	0.25 ± 0.11
Patient #4 (control)	0.13 ± 0.03	0.24 ± 0.13	0.20 ± 0.12	0.45	0.10 ± 0.08
Patient #5 (control)	0.28 ± 0.10	1.6 ± 0.77	0.87 ± 0.83	0.07	0.01 ± 0.01
Patient #6 (control)	0.08 ± 0.02	0.37 ± 0.17	0.29 ± 0.19	0.30	0.03 ± 0.04

diast, diastole; ECAP, endothelial cell activation potential; max, maximum; syst, systole; vel, velocity (average ± standard deviation); whole, whole cardiac cycle.
* Velocity values averaged across the whole cardiac cycle < 0.20 m/s and ECAP values were > 0.5 since they are indicators of high risk of device-related thrombogenesis.

This is the first study to validate the ECAP index with a clear clinical endpoint and assess its performance in patients treated with LAAO. The ECAP index could differentiate between DRT and non-DRT cases based on the characteristics of flow complexity. However, it could not robustly predict the exact location of thrombus formation in all of the cases as it wrongly suggested the formation of an inferior thrombus in patient #1 in whom a superior thrombus was identified clinically. Even though the cohort was small, the results suggested that if thrombotic risk after LAAO needs to be studied, the ECAP index alone is not enough, and needs to be combined with other variables.

The velocity results obtained in our in silico analysis are consistent with studies on low velocities with thrombus formation since they could favour the stagnation of flow and consequently trigger the inflammatory process.[11,20] Velocity results during systole were more similar among the patients compared to results during diastole that varied more. Point velocity measurement was allocated near the device surface, and it was very close to the MV. Therefore, in general, during ventricular systole when the valve is closed, the velocities in that region tend to be low and differences are difficult to see. Once the MV is open the velocities increase. Also, the mean velocity of the entire cardiac cycle (table 3, column 3) showed that patients who developed DRT had lower velocities in all the beats compared to the control group. However, the process through which blood stasis triggers the inflammatory cascade is not fully understood. For instance, the spatial proximity of the left atrial appendage to the MV makes blood flow into the LAA be quite dependent on the dynamics of the MV as it occurred with patient #5. The unusual hemodynamic behaviour of this patient (eg, very high blood velocities) was due to mitral regurgitation, an effect that was captured by the simulations thanks to the patient-specific US-based boundary conditions. Remarkably, these observations are consistent with studies that hypothesize about a certain degree of protection against flow stagnation and thrombus formation in patients with mitral regurgitation due to a better blood washout of the LAA.[22]

The areas of flow recirculation at low velocities could indicate potential regions with risk of thrombus formation, but its precise localization depends on the patient's LA anatomy and the LAAO device final deployment. Our flow simulations revealed the device upper region with an uncovered pulmonary ridge (PR) as the preferred area for eddies as shown on figure 3. This finding was consistent with the literature available on pulmonary ridge uncovering and a higher risk of DRT: 82% of DRT cases with uncovered left upper pulmonary venous ridge.[4,8,11] However, we showed that pulmonary ridge uncovering could increase the risk of DRT only if flow velocities are low and the whole pulmonary ridge area cannot be properly washed out. Therefore, covering the pulmonary ridge, which is often not possible due to anatomical constraints (eg, proximity of a circumflex to other structures) would only be critical if blood flow velocities are not high enough.

Limitations

The main limitations of our study were the reduced number of patients to confirm our simulation-based factors, the different anticoagulant therapies used in the DRT group, the differences reported between the acquisition time of the follow-up CT imaging among the different patients, the lack of a unified protocol at the follow-up, and the differences seen between the stroke risk stratification scores. The need for follow-up CT images of the entire left atria and patient-specific MV velocity profiles as seen on the echocardiography, both essential to run flow simulations, confirmed that only a few patients were eligible for this study. Hence, our computational fluid dynamics-based descriptors for DRT prediction should be viewed as novel potential biomarker candidates accessible through digital twin technologies. Fortunately, CT imaging is increasingly becoming accepted as a key technology for LAAO planning and follow-up analysis,[23] thus facilitating more extensive studies in the next future. More specifically, the requirement of having a whole LA CT image at the follow-up for the computational model would not substantially change the clinical protocol in centers with access to this imaging technique. Also, the examination can be performed within 72 hours after LAAO implantation. Additionally, in the near future, the constant improvements in spatial and temporal resolution of echocardiographies would make it possible to build patient-specific models based on 3D reconstructions of the LA anatomy from these images. Hence, achieving a larger cohort of prospective cases is possible and will allow more rigorous analyses and validations of the candidate factors and thresholds (in both velocities and the ECAP index) to confirm the performance of the proposed in silico indices to predict the risk of DRT after LAAO implantation.

There is not a clear consensus on the optimal boundary conditions to model LA hemodynamics in a realistic way. On the one hand, we used a velocity profile as outlet in the mitral valve since such profile can be obtained from standard echocardiography images routinely acquired on LAAO candidates. On the other hand, a generic pressure waveform of a patient with AF from a former study was applied in the pulmonary veins as an inlet model while coping with the fact that patient-specific pressure measurements would require invasive catheterization, which is not usually performed in these patients. Similarly, in our study, the movement of the LA wall was extrapolated from the passive movement of the mitral valve annular plane, imposed by the left ventricle, which was extracted from the medical literature available. Whereas our patient-specific approximations of the boundary conditions uniquely allowed simulating mitral regurgitation effects, a more realistic left atrial wall dynamics may be extracted from temporal imaging sequences.

Simplifications are intrinsically associated with the concept of modelling, which was applied in the present study. Still, the integration of relevant patient-specific structural and functional information in our modelling and simulation workflow provided boundary conditions that were realistic enough to achieve accurate estimations of the risk of DRT after LAAO implantation.

CONCLUSIONS

In this proof-of-concept study we present a description of an in silico modelling workflow capable of integrating patient-specific data and simulating hemodynamics within the LA while predicting the risk of DRT after LAAO device implantation. The model was used to study 6 patients retrospectively: 3 patients with DRT and patients 3 without DRT. The simulations reproduced the flow dynamics inside the LA and showed that patients with DRT had low velocity blood flow recirculation with complex patterns next to the device surface. The combination of several in silico indices representing pro-thrombotic factors that cannot be measured in situ, in clinics, could detect differences and distinguish patients with DRT from those of the control group. Here we showed a first proof-of-concept study with in silico indices from personalized models capable of identifying potential complications of LAAO device implantation and individualizing follow-up therapies to minimize the rate of unfavorable clinical outcomes. Nevertheless, future studies should focus on validating the computational workflow developed in a larger cohort of cases.

FUNDING

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AUTHORS' CONTRIBUTIONS

J. Mill: study idea, methodology, investigation, and writing; V. Agudelo: study idea, methodology, and investigation; C. H. Li: data curation; J. Noailly: formal analysis, supervision, and methodology; X. Freixa, and D. Arzamendi: study idea, supervision, and validation; O. Camara: supervision, writing, validation, and study idea.

CONFLICTS OF INTEREST

D. Arzamendi has received personal grants for proctoring for Abbott, and Boston Scientific. X. Freixa has received personal grants for proctoring for Abbott, and Lifetech. The remaining authors have not declared any other conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- DRT has become a major concern, because of its incidence rate (2% to 5%) and the increased rate of associated strokes. Despite the use of different antithrombotic therapies, the rate of DRT has not changed.
- Following Virchow's triad, 3 factors are thought to contribute to thrombus formation: hypercoagulability, endothelial injury, and blood stasis.
- Factors such as peri-device leaks and uncovered pulmonary venous ridge have been suggested as potential factors for DRT, but the data published are still controversial.

WHAT DOES THIS STUDY ADD?

- Patient-specific flow models correctly predicted the formation or lack of device-related thrombus after LAAO implantation in all studied cases.
- The most relevant in silico indices to predict DRT after LAAO implantation were the presence of flow stagnation, low velocity values next to the device surface, and the ratio between (high) flow complexity and (low) wall shear stress.
- Patients treated with LAAO implantation could have more individualized DRT risk assessments and follow-up antithrombotic therapies using personalized simulations built from the patient's postoperative CT scans and ultrasound imaging.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000224.

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Special article

Assessment of the endothelial function and spasm provocation test performed by intracoronary infusion of acetylcholine. Technical report from the ACI-SEC

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ABSTRACT

Coronary vasoreactivity testing is a key diagnostic procedure in patients with suspected coronary spasm and research procedures intended to assess the coronary endothelial function. We should mention that coronary spasm has been observed in > 40% of the patients with angina and non-obstructive coronary stenosis. Also, that its dedicated treatment has proven to reduce ischemic symptoms and improve these patients' quality of life. This technical report elaborated by the Working Group on Intracoronary Diagnostic Techniques of the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) summarizes the indications, preparation, performance, and interpretation of the vasoreactivity testing performed by intracoronary infusion of acetylcholine.

Keywords: Spasm provocation test. Coronary endothelial function.

Valoración de la función endotelial y provocación de vasoespasmo coronario mediante infusión intracoronaria de acetilcolina. Documento técnico de la ACI-SEC

RESUMEN

Las pruebas de vasorreactividad coronaria con infusión de acetilcolina son una prueba diagnóstica fundamental para pacientes con sospecha de enfermedad cardiaca secundaria a vasoespasmo y en procedimientos de investigación en los que se valora la función endotelial coronaria. Se calcula que más del 40% de los pacientes con angina y ausencia de lesiones coronarias presentan vasoespasmo como causa fundamental de los síntomas, y su tratamiento específico ha demostrado mejorar la calidad de vida en estos pacientes. El Grupo de Trabajo de Técnicas de Diagnóstico Intracoronario de la Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC) ha elaborado el presente documento técnico que expone de manera práctica las indicaciones, la preparación, la realización y la interpretación de dichas pruebas.

Palabras clave: Prueba de provocación de vasoespasmo. Función endotelial coronaria.

Abbreviations

DS: diameter stenosis. **INOCA:** ischemia with no obstructive coronary arteries. **MINOCA:** myocardial infarction with non-obstructive coronary arteries.

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INTRODUCTION

Coronary vasoreactivity testing performed by intracoronary infusion of acetylcholine is basically used with 2 goals in mind: for endothelial function assessment and as a vasospasm provocation test in clinically suspicious cases. Although these tests have been known and used for decades, its use is not yet fully consolidated in our setting. This is mainly due to a scarce suspicion of myocardial ischemia due to micro or vasomotor disorders that has eventually lowered the demand for these tests. In addition, the lack of test standardization and training, the off-label use of acetylcholine, and the doubts surrounding these tests safety profile have not encouraged their widespread use in the routine clinical practice.

Over the last few years, this scenario has changed dramatically thanks to the growing evidence on the importance of diagnosing the causes of myocardial ischemia not directly related to fixed stenoses. Currently, invasive coronary spasm provocation tests are formally recommended by the European Society of Cardiology in its clinical practice guidelines on the management of chronic coronary syndromes, non-ST-segment elevation acute coronary syndromes, and ST-segment elevation acute coronary syndromes.[1-3] The most common indications are to treat patients with angina or ischemia but without non-obstructive coronary lesions (ANOCA, INOCA—in this document, both coined under the term INOCA—), myocardial infarction with non-obstructive coronary arteries (MINOCA), persistent angina after coronary revascularization, obstructive coronary artery disease with clinical suspicion of associated angina of microvascular origin, and finally, patients with recovered sudden death of undetermined causes.[1-3] Table 1 summarizes all clinical indications and level of recommendation to perform vasospasm provocation testing. Although this paper focuses on coronary vasoreactivity testing, we should remember that its use is often recommended simultaneously with other coronary functional testing performed using pressure guidewires like coronary flow reserve and microcirculation resistance measurements.[1-5] The specific diagnosis of functional damage to coronary arteries and its targeted therapies have both improved the quality of life of patients with INOCA.[6] The treatment recommended for coronary vasospasm is calcium channel blockers, nitrates, and nicorandil.[6,7]

Based on the current clinical practice guidelines, the objective of the Working Group on Intracoronary Diagnostic Techniques of the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) is to facilitate and standardize the use of coronary vasoreactivity testing. Thus, this paper has been drafted to expose all technical steps in a practical way to encourage the performance and interpretation of these tests in our setting.

NORMAL ENDOTHELIAL FUNCTION OF CORONARY ARTERIES

The modulatory function of vascular endothelium in the blood flow towards the myocardium is intrinsically associated with its metabolic characteristics. Compared to the skeletal muscle, the heart has pretty high oxygen needs (some 20 times higher). The way this oxygen supply is achieved is through very high tissue extraction at baseline: at rest the myocardium extracts approximately 70% to 80% of the oxygen transported by hemoglobin compared to 30% of the skeletal muscle. This explains why, unlike other organs, the

Table 1. Clinical indications for the coronary vasospasm provocation test performed by intracoronary infusion of acetylcholine

Class	Indication	Clinical specifications
Class I (highly recommended)	Clinical suspicion of vasospastic angina without objective documentation of ischemia or obstructive coronary artery disease in patient with chronic symptoms	– Vasospastic angina can occur predominantly at rest (35%), during exertion (30%), as a mixed pattern (30%) or dyspnea (5%)[4] – The epicardial and microvascular function assessment in maximum hyperemia with a pressure guidewire is advised
	Acute coronary syndrome without presence of culprit lesions on the coronary angiography	– Carefully review the angiography to discard embolisms and radiolucent images consistent with thrombus or coronary dissections – The use of intravascular imaging (intracoronary ultrasound or optical coherence tomography) for this type of lesions is advised – Exclude other causes for high troponin levels (like myocarditis) through segmental assessments (ventriculography or echocardiography) and magnetic resonance imaging
	Recovered inexplicable sudden death	– After excluding structural and/or arrhythmic heart disease
	Study of syncope preceded by thoracic pain	– After excluding structural and/or arrhythmic heart disease
	Recurrent angina despite revascularization	– First assess the pressure guidewire to exclude epicardial functional disease and microcirculation disorders in maximum hyperemia
Class IIa (recommended)	Clinically documented vasospastic angina in a spontaneous event or on the non-invasive provocation test that is unresponsive to medical therapy	– Patients unresponsive to therapy with calcium channel blockers and nitrates or nicorandil – Epicardial and microvascular function assessment in maximum hyperemia with a pressure guidewire is advised
Class IIb (debatable)	Clinically documented vasospastic angina or on the non-invasive provocation test that responds to medical therapy to know the type and degree of vasospasm	– The specification of the macro/microvascular spasm and whether it causes the occlusion of the artery can be relevant for the patient's prognosis – Epicardial and microvascular function assessment in maximum hyperemia with a pressure guidewire is advised
Class III (ill-advised)	Asymptomatic patients	Asymptomatic patients
	Patients with ejection fractions < 35%	Patients with ejection fractions < 35%
	Significant epicardial coronary artery disease (left main coronary artery and/or 3 vessels)	Significant epicardial coronary artery disease (left main coronary artery and/or 3 vessels)

Adapted with permission from the consensus document elaborated by the COVADIS Working Group (Coronary Vasomotion Disorders International Study).[5]

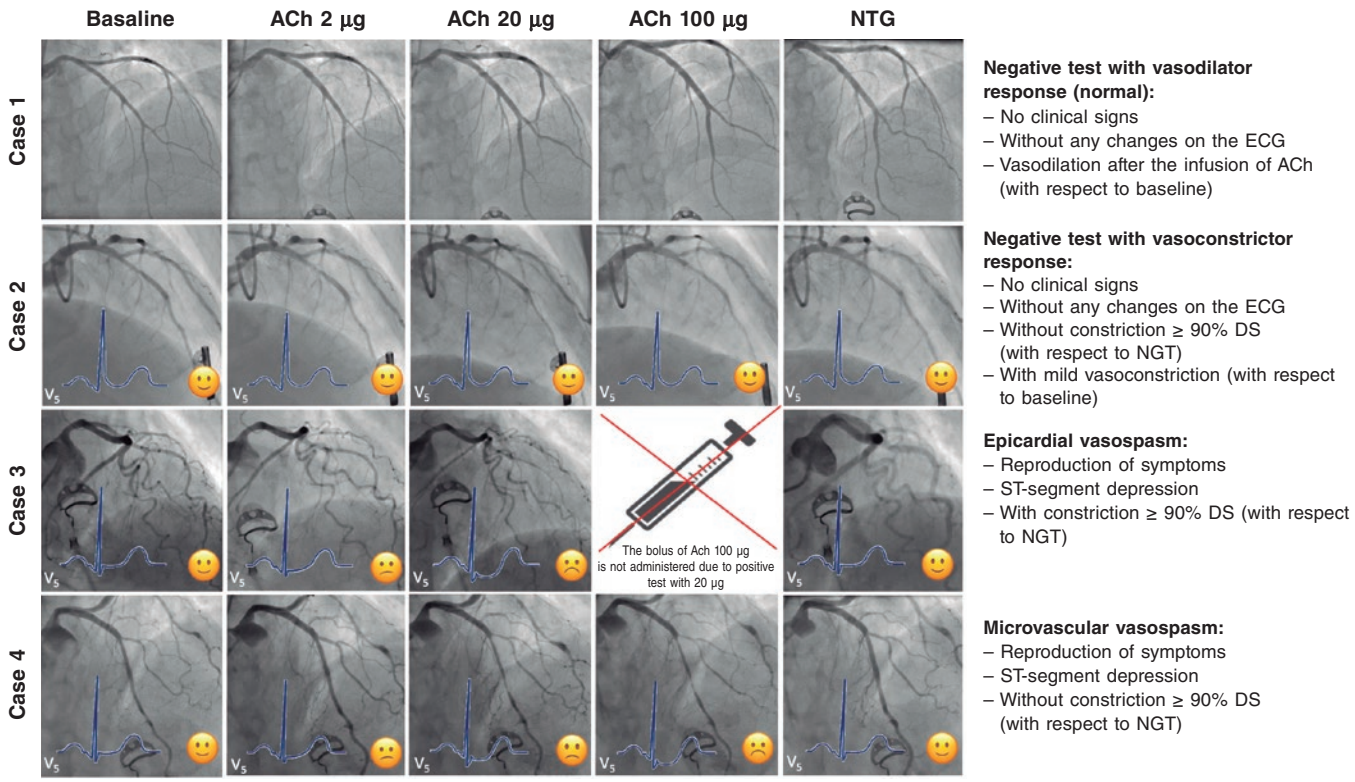

Figure 1. Possible results of the vasospasm provocation test with acetylcholine. Case 1: physiological response (vasodilator response to acetylcholine). Case 2: endothelial dysfunction with vasoconstriction with respect to baseline that does not meet the criteria for micro or macrovascular spasm. Case 3: macrovascular spasm with significant vasoconstriction of the left coronary tree. Case 4: microvascular spasm due to moderate vasoconstriction of the left tree meeting the clinical and ECG criteria for ischemia. ACh, acetylcholine; DS, diameter stenosis; NTG, nitroglycerin.

mechanism through which the heart regulates oxygen supply to the myocardium changing metabolic needs is fast regulation and constant blood flow into the coronary system.[8]

Microcirculation (arteries and arterioles < 400 µm) is basically responsible for regulating coronary blood flow. Although regulation is complex and includes metabolites, hormones, neurotransmitters, and other factors, the main protagonist is the vascular endothelium that produces nitric oxide—a powerful vasodilator—in response to different stimuli. Also, other vasodilator factors—like the hyperpolarizing endothelial factor—and vasoconstrictor factors like endothelin. Endothelium-dependent vasodilation can be stimulated through different ways, but the most commonly used one is the infusion of acetylcholine.

In normal conditions, an artery with a healthy endothelium responds to acetylcholine by releasing nitric oxide that translates into vasodilation. In the presence of artery denudation from the endothelium or if the action of the nitric-oxide synthase enzyme is blocked, the artery responds to acetylcholine with vasoconstriction due to the stimulation of smooth muscle muscarinic receptors not counteracted by the nitric oxide of endothelial origin. Therefore, the infusion of acetylcholine can be used to assess endothelial function: if normal, vasodilation becomes evident. If not, vasoconstriction kicks in. The macrovascular compartment endothelial function (epicardial) can be assessed on an angiography. However, to assess the endothelium-dependent response in microcirculation, blood flow should be measured using a Doppler guidewire or thermodilution. From the macrovascular point of view, visually evident epicardial vessel vasoconstriction in response to acetylcholine is considered endothelial dysfunction. Figure 1 shows examples of vasodilation (physiological) and vasoconstriction responses (suggestive of endothelial dysfunction) to the administration of acetylcholine. From the microvascular point of view, flow reductions or increases < 50% in response to the administration of acetylcholine are considered anomalous.[9] Figure 2 shows examples of microvascular function assessment using the Doppler technique or intracoronary thermodilution.

CORONARY VASOSPASM PROVOCATION TESTING

Different stimuli can be used to provoque epicardial or microvascular coronary spasm. Non-pharmacological stimuli like hyperventilation or coming into contact with cold are associated with an excessive number of false negatives for clinical use. Non-invasive coronary vasospasm assessment (based on changes on the ECG or the echocardiography through the IV administration of ergonovine) is associated with a risk of causing nitrate-resistant flow-limiting coronary spasm.[4] For this reason, to this date, invasive studies based on the intracoronary administration of drugs are considered the single most sensitive and safe method. Actually, to this date, it is the method recommended by European guidelines and consensus docments.[2,7] The direct administration of drugs allows us to use lower doses and establish a time correlation between the development of coronary spasm followed by symptom onset and changes on the ECG. Also, it facilitates immediate treatment through the direct administration of nitrates.[4,10] The use of acetylcholine vs ergonovine is advised too since the former acts on a specific pathway (by stimulating cholinergic receptors only), and its safety profile is good because its half-life is shorter. Also, because it responds faster to nitrates in case of vasoconstriction.[11] Also, acetylcholine allows us to assess the vascular endothelial response specifically, which is an additional advantage. The studies that compared

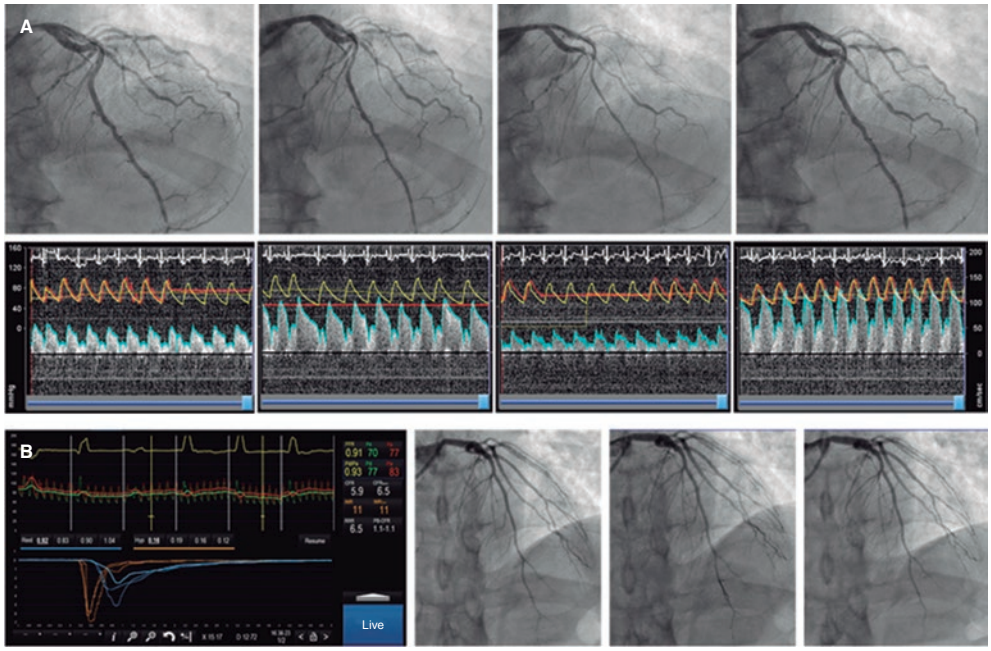

Figure 2. Combined assessment of macro and microvascular function. **A:** pressure-Doppler guidewire study (Combowire, Philips, The Netherlands). After the angiography and measurement of baseline flow velocity, growing doses of acetylcholine are injected. After the second dose, moderate vasoconstriction of the left anterior descending coronary artery occurs followed by an occlusive spasm at circumflex artery level plus a slower flow velocity in the left anterior descending coronary artery indicative of microvascular vasoconstriction. The spasm is solved with intracoronary nitroglycerin followed by the adenosine non-endothelium-dependent assessment of microvascular function. The patient shows macro and microvascular endothelial dysfunction and a normal non-endothelium-dependent microvascular function. **B:** macrovascular endothelial function assessment appears normal; adenosine non-endothelium-dependent assessment with thermodilution guidewire (Pressurewire X, Abbott, United States). Coronary flow reserve is 5.9, and the index of microcirculatory resistance is 11, which is suggestive of a normal microvascular function. In conclusion, physiological examination without any relevant findings.

the results of vasospasm provocation testing with acetylcholine vs ergonovine found similar sensitivity and high matching (94%) between the two. Therefore, in the presence of a negative acetylcholine test no additional studies with different drugs are advised.[12]

ACETYLCHOLINE

Acetylcholine is a neurotransmitter largely found in the nervous system (central, autonomous, and peripheral). It is used in the neuromuscular junction, in all synapses of the parasympathetic autonomous system, and in the first synapsis of the sympathetic nervous system. The muscarinic receptor of acetylcholine has 5 different subtypes; among them, subtype M2 is largely found in the myocardium where it reduces the heart rate and the cardiac conduction system; subtype M3 is found in the coronary arteries both in the endothelium and the smooth muscle. In the coronary arteries, the M3 receptor stimulates the contraction of the vascular smooth muscle (vasoconstriction). Also, it stimulates the endothelial production of nitric oxide that spreads into the smooth muscle reducing the concentration of calcium, and causing relaxation (vasodilation).[13,14] Acetylcholine is rapidly hydrolyzed in both the neuromuscular junction and blood by the action of cholinesterases. When infused intracoronary in the doses described here, no systemic effects occur, and its cardiac effects only last a few minutes.

ACETYLCHOLINE-INDUCED ENDOTHELIAL DYSFUNCTION AND CORONARY VASOSPASM

Endothelial dysfunction is associated with the number of cardiovascular risk factors and is a well-known precursor of atherosclerosis.[15] Also, the presence of endothelial dysfunction has been associated with the appearance of ischemia in the ischemia exercise test, heavier calcification and presence of necrotic and lipidic content in the vascular wall, and more cardiovascular adverse events in the long run.[16-18] The prevalence of a vasoconstrictor response to the intracoronary infusion of acetylcholine, therefore, similar to an epicardial endothelial dysfunction, is variable depending on the characteristics of the patients being more common among males.[19] In the studies conducted in patients with INOCA, the prevalence of endothelial dysfunction is somewhere between 45% and 75%.[19,20]

Although, to this point, no cut-off value has been universally accepted, it has been confirmed that moderate degrees of vasoconstriction (20% to 50%) with respect to the artery baseline diameter after the intracoronary infusion of acetylcholine have an important prognostic impact.[18,21,22] Quantitative coronary angiography studies consider the variability of the technique when measuring changes in the mean luminal diameter of a segment with respect to the different doses of acetylcholine (usually the dose with the highest vasoconstriction with respect to the baseline one). Small imaging variations due to respiratory movements in every cine coronary arteriography, different limits of the study segment in the different measures taken, the analysis of diameters at different times of the cardiac cycle between the baseline image and maximum vasoconstriction, and the operator's variability are the reasons why vasoconstriction can only be confirmed after variability is excluded from this measuring process. Several studies have established this variability (2 times the standard deviation of the percent difference) somewhere between 3% and 6%. Therfore, endothelial dysfunction is defined as a vasoconstrictor response that is greater than this variability.[23,24]

The pathophysiological factors of vasospastic angina, both in their macro and microvascular manifestations are less known and, also,

probably multifactorial. Vasospastic angina has been associated with the presence of coronary plaques, vascular smooth muscle cell hyperreactivity, a high baseline vagal tone, hyperreactivity to sympathetic stimulation, and finally, to a significant degree of endothelial dysfunction.[10] Vasospastic angina, both macro and microvascular, is more common among women.[4] The traditional criteria to define vasospastic angina of macrovascular origin have been described by the Coronary Vasomotion Disorders International Study Group (COVADIS).[5] In their document they describe the diagnostic criteria of this disease that go beyond the traditional definition of variant angina described by Prinzmetal et al.[25]. We should mention that, unlike the definition of endothelial function where baseline angiography is used as the reference, to define macrovascular spasm the COVADIS group recommends assessing the coronary spasp in the segment with the greatest constriction of all after the administration of acetylcholine and then compare it with the diameter of the same segment after the infusion of nitroglycerin.[4] Also, this group recommends the use of drug provocation testing performed by intracoronary infusion of acetylcholine given its high sensitivity and specificity values (90% and 99%, respectively).[26] Based on former studies and the traditional definition, the prevalence of epicardial coronary artery vasospasm, whether associated with microvascular spasm or not, occurs in 30% to 40% of the patients with INOCA.[6,27]

Fewer consensus documents have been published on the definition and diagnosis of microvascular spasm.[28,29] Over the last few years, the appearance of thoracic pain and changes on the ECG suggestive of ischemia in response to acetylcholine and in the absence of macrovascular spasm have been accepted for the diagnosis of microvascular spasm (located in the arterioles). By this definition, 25% of the patients with INOCA meet the microvascular spasm criteria.[27]

TEST PERFORMED BY INTRACORONARY INFUSION OF ACETYLCHOLINE

Preparing the patient

The best way to prepare patients eligible for the coronary vasoreactivity test with acetylcholine is still under discussion. Historically, these procedures used to be performed in a dedicated procedure while avoiding and withdrawing all kinds of vasodilator drugs (like calcium channel blockers and nitrates) for, at least, 18 hours before the infusion of acetylcholine.[27,30,31] However, after the publication of the randomized clinical trial CorMicA and the consensus document of the European Association of Percutaneous Coronary Interventions (EAPCI) on the study of patients with INOCA, conventional wisdom has changed.[6,7] Currently, the use of intracoronary functional testing is recommended including the vasoreactivity test to acetylcholine within the same diagnostic procedure where the coronary angiography is performed.

This brings greater comfort to the patient, uses cath lab resources more efficiently, and alleviates the pressure of the hospital agenda. In any case, this procedure should be fully adapted to the needs and possibilities of every cath lab; in polymedicated patients with vasodilators or in inexperienced centers using this test the scheduled procedure should be used.

If radial access is used in patients eligible for a coronary vasoreactivity test the administration of calcium channel blockers to prevent radial spasm is ill-advised. In these cases, the administration of low doses of nitroglycerin through the introducer sheath (100 µg to 200 µg) can be considered. However, its effect will probably mostly be gone by the time acetylcholine is infused. Also, the coronary vasoreactivity test can be performed after studying microvascular function with a pressure guidewire (with the corresponding administration of intracoronary nitroglycerin before advancing the guidewire).[6,7] In this case, a 2- to 3-min washout period should be observed before the infusion of acetylcholine.[6,7]

Finally, a specific informed consent should be obtained before running any vasoreactivity tests. Also, 12-lead ECG monitoring is required to assess the results. The use of radiotransparent wiring and electrodes is advised here to avoid interfering with the cine-fluoroscopy images obtained for each of the doses infused during coronary angiography. Figure 3 shows a schematic sample of how to prepare a patient before running a coronary vasoreactivity test with intracoronary acetylcholine.

Regarding the use of beta-blockers, certain groups also recommend their cessation before running the test to avoid any possible vasoconstrictor effects. Until more scientific data become available, the opinion of this group is that beta-blockers do not affect the results of the test significantly and in no way give false negative results.

Preparing the acetylcholine

The acetylcholine available in Spain is a preparation for the intraocular injection of 20 mg of acetylcholine chloride (powder) for its dilution in a 2 mL vial of physiological saline solution. After the solution has been prepared, the drug is still unstable, which is why the best thing to do is to prepare it right before the test; if several consecutive tests are going to be performed, the same preparation can be used. Figure 4 summarizes the way to prepare the acetylcholine solutions suggested for the test. An important safety tip is to identify correctly every solution of acetylcholine we will be using; saline solution systems and color syringes for every dose can be useful.

Intracoronary infusion protocol

Over the last 30 years, different protocols on the administration and doses of intracoronary acetylcholine have been used. Table 2 shows the different protocols used in landmark studies.[6,10,19,29,30,32-34] There are differences regarding the routes of administration (manual infusion through guide catheter or controlled selective infusion into an artery through an infusion pump and microcatheter), the number of doses infused (from 2 to 4), the amount of acetylcholine used (from 0.3 µg to 200 µg), and the infusion time (from 20 seconds to 3 minutes). Below we will be seeing the most widely accepted protocols based on the objective pursued (endothelial function assessment or vasospasm provocation) followed by a proposal according to the last consensus documents published to this date.

Endothelial function assessment

Growing doses of acetylcholine are used for endothelial function assessment. If this procedure is performed by selective drug infusion into 1 of the main coronary vessels with a microcatheter (usually the left anterior descending coronary artery), the concentrations used are 10 moL/L to 6 moL/L, 10 moL/L to 5 moL/L, and 10 moL/L to 4 moL/L. Considering the left anterior descending coronary artery flow (some 80 mL/min), it is estimated that the drug reaches concentrations that are 100 lower in coronary microcirculation. Using the microcatheter these dilutions are injected the into the proximal left anterior descending coronary artery or into the artery to be interrogated at a rate of 1 mL/min for 3 minutes or 2 mL/min for 2 minutes through an infusion pump.[24,35] Infusion starts with the least concentrated dilution and, if no complications or overt vasospasm are reported the next infusion should start 2 to

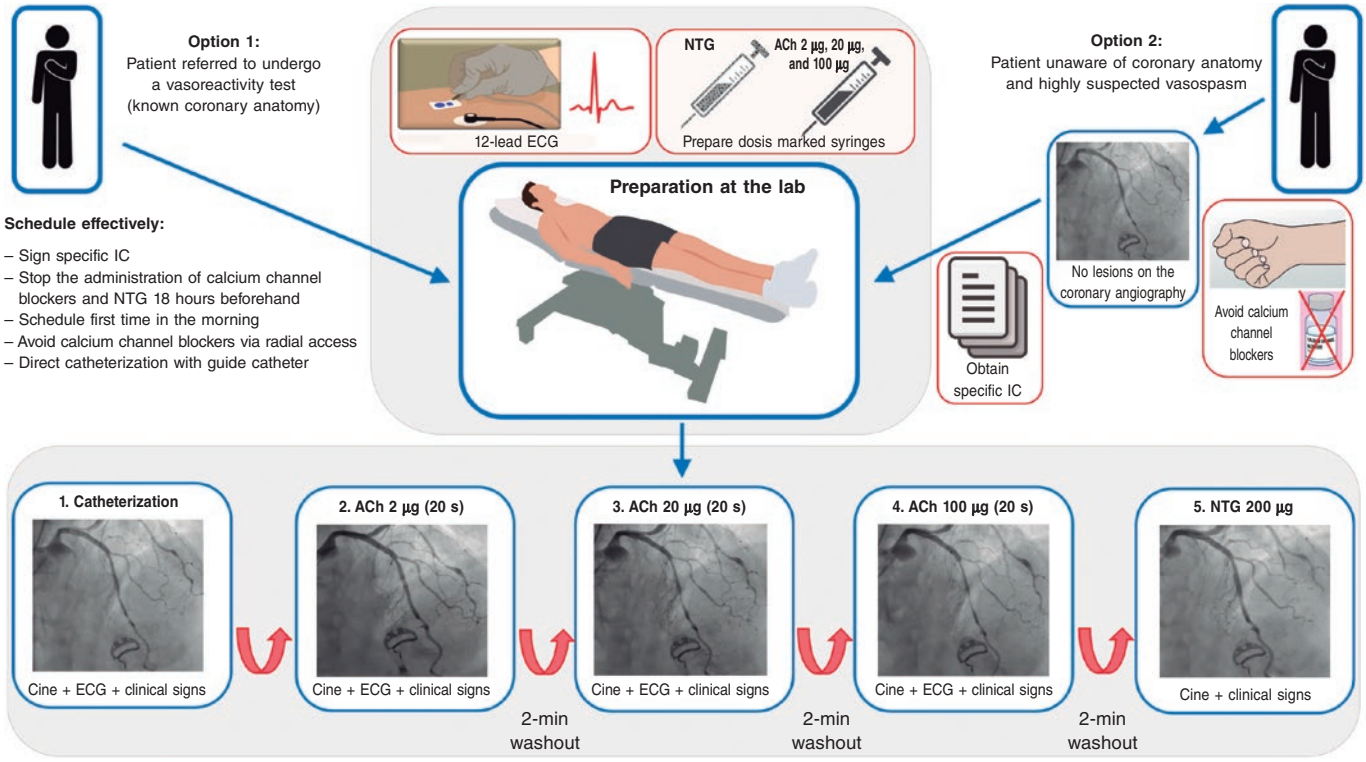

Figure 3. Preparation of the patient before running any vasoreactivity tests. ACh, acetylcholine; Ca, calcium; Cine, cine coronary arteriography; IC, informed consent; NTG, nitroglycerin.

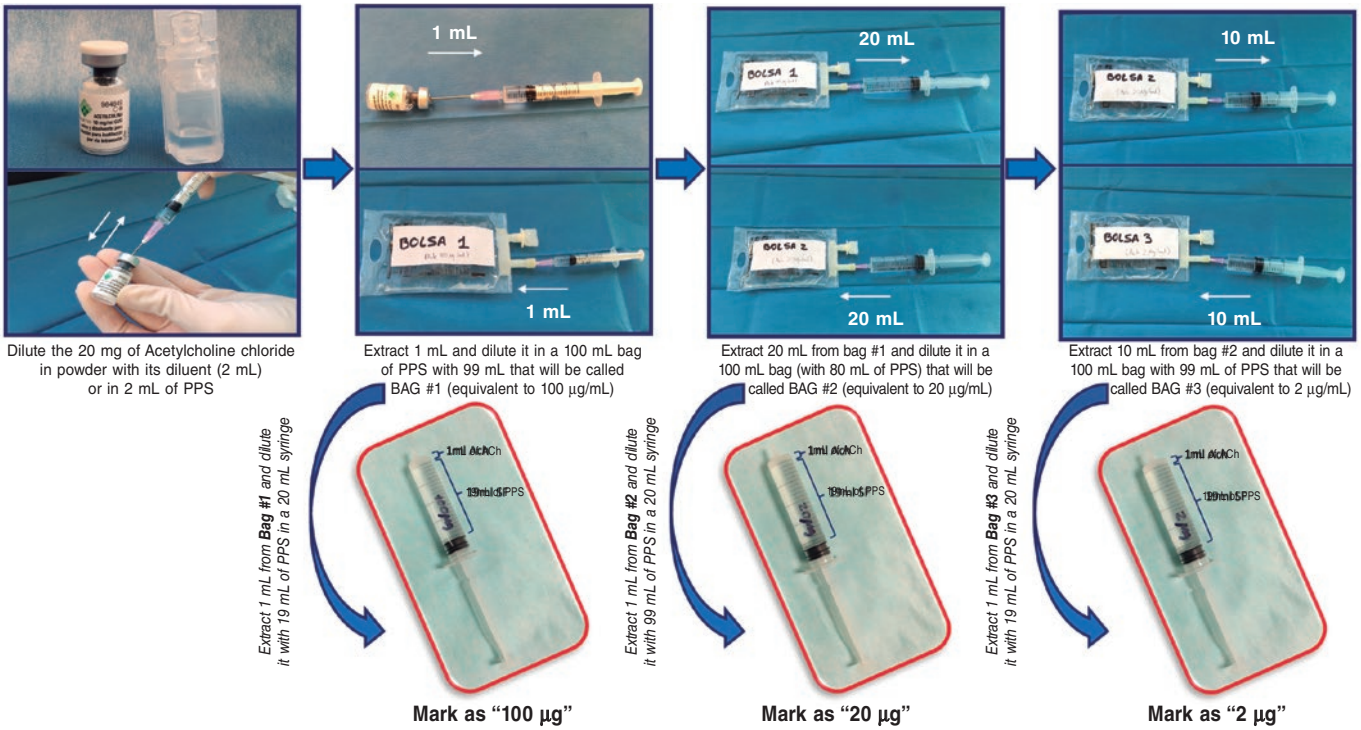

Figure 4. Preparation of growing doses of acetylcholine. ACh, acetylcholine; DS, diameter stenosis; PSS, physiological saline solution.

Table 2. Comparison of the different protocols of coronary vasoreactivity to acetylcholine

Group	Infusion method	Doses used	Infusion time per dose	Comments
Harvard Working Group[30]	Infusion through microcatheter and infusion pump	4 dilutions of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} per liter (infusion at a rate of 0.8 mL/min) into the LCA	2 minutes	– Designed for endothelial function assessment – A final concentration of 10^{-9}, 10^{-8}, 10^{-7}, and 10^{-6} is estimated (equivalent to a selective total dose per artery of 0.03 µg, 0.3 µg, 3 µg, and 30 µg) – It is performed on the LCA
Mayo Clinic[32]	Infusion through microcatheter and infusion pump	3 dilutions of 10^{-6}, 10^{-5}, and 10^{-4} per liter (infusion at a rate of 1 mL/min) followed by a bolus of 100 µg (through the same catheter)	3 minutes (final bolus for 20 to 30 seconds)	– Mixed protocol for endothelial function assessment (equivalent to a selective total dose per artery of 0.5 µg, 5 µg, and 50 µg) and vasospasm assessment with a bolus of 100 µg – It includes the functional assessment of microcirculation with Doppler guidewire during the infusion of acetylcholine – It is performed on the LCA
Korea Working Group[33]	Manual infusion through guide catheter	3 doses of 20 µg, 50 µg, and 100 µg into the LCA	1 minute	– It is performed on the LCA
Japanese Circulation Society[10]	Manual infusion through guide catheter	3 doses of 20 µg, 50 µg, and 100 µg into the LCA In the absence of vasospasm 2 doses of 20 µg and 50 µg into the RCA are advised	20 seconds	– Vasospasm provocation test on the LCA and RCA – The implantation of an electrode catheter to perform it is advised
Standford Working Group[19]	Manual infusion through guide catheter	4 doses of 20 µg, 50 µg, 100 µg, and 200 µg into the LCA	1 minute	– It is performed on the LCA
Stuttgard Working Group[34]	Manual infusion through guide catheter	4 doses of 2 µg, 20 µg, 100 µg, and 200 µg into the LCA In the absence of vasospasm into the LCA an 80 µg dose into the RCA is advised	20 seconds	– It studies both the LCA and the RCA
The CorMicA trial and the COVADIS Working Group[6,29]	Mixed pump and manual infusion	3 growing doses of 0.18 µg/mL, 1.82 µg/mL, and 18.2 µg/mL administered using an infusion pump through the guide catheter The procedure is completed with a manual bolus of 100 µg (50 µg into the RCA)	2 minutes for every growing dose, and 20 seconds for the final bolus	– It is performed on the LCA after microcirculation assessment with adenosine through a pressure guidewire – It assesses the endothelial function and the vasospasm provocation test in the same procedure
Protocol of the ACI-SEC (present document)	Manual infusion through guide catheter	3 doses of 2 µg, 20 µg, and 100 µg into the LCA In case of suspected vasospasm into the RCA the test should be started in this artery with doses of 2 µg, 20 µg, and 50 µg	20 seconds	– For endothelial function assessment purposes, the doses should be infused more slowly for 2 to 3 minutes – It is performed on the LCA

ACI-SEC, Interventional Cardiology Association of the Spanish Society of Cardiology; RCA, right coronary artery; LCA, left coronary artery.

3 minutes later. In practice, this method injects 0.5 µg, 5 µg, and 50 µg of acetylcholine in each of the doses. As already mentioned, in the presence of a non-dysfunctional vascular endothelium, the physiological response is the vasodilation of major epicardial vessels.

The procedure described, although widely used in clinical trials, is somehow complicated and expensive, which is why easier and more practical alternatives have been developed for macrovascular endothelial function assessment. The most important one that has already become the standard may be the one used in the ENCORE trials (Evaluation of nifedipine and cerivastatin on recovery of coronary endothelial function)[36,37] consisting of the infusion of growing doses of 2 µg, 20 µg, and 100 µg directly into the left main coronary artery for 3 minutes each followed by the performance of an angiography after every dose. Also, it consists of the assessment of the arterial diameter compared to the one measured on the baseline angiography. If macrovascular endothelial function needs to be assessed, the recommendation is to follow this infusion pattern. As we will be seeing, this protocol has already been widely adopted in recent publications and, with minor changes, has become the go-to protocol for the diagnosis of coronary vasospasm although with a faster infusion of the doses.

Microvascular endothelial function can also be assessed using dedicated guidewires for the simultaneous measurement of coronary flow. In general, this procedure is performed using a Doppler guidewire (Combowire, Philips, The Netherlands),[9] although the assessment can also be performed through thermodilution with thermistor-based temperature measuring guidewires (Pressurewire, Abbott, United States).[38,39] Figure 2 shows 2 examples of this procedure.

Coronary spasm provocation testing

Although there are different protocols on doses and infusion times, the protocol recommended here for vasospasm provocation has

Table 3. Complications associated with the intracoronary infusion of acetylcholine

Complication	Percentage	Comment	Treatment
Bradycardia and/or transient atrioventricular block	3.23%	More common in high doses and when infused fast, especially into the RCA	Stop the infusion for a few seconds until going back to rhythm. Study the possibility of going on with the test at a slower infusion rate
Appearance of atrial fibrillation	2.38%*	It is often self-limiting, but also fast, and its clinical tolerance is poor. It is a reason to stop the test whose outcome will be undetermined	If hemodynamic tolerance is good, use antiarrhythmic drugs; if poor, study the possibility of electrical cardioversion
Ventricular fibrillation, ventricular tachycardia or need for resuscitation	1.00%	Due to acute ischemia following flow-limiting vasospasm	Nitroglycerin and defibrillation
Shock and/or myocardial infarction	0.07%	Due to flow-limiting spasm at multivessel or left main coronary artery level	Nitroglycerin plus inotropic support +/– ventricular support
Transient hypotension	0.05%	It is often unsignificant	Stop the infusion for a few seconds until going back to rhythm. Study the possibility of going on with the test at a slower infusion rate
Coronary artery dissection	0.02%	Catheter-induced coronary artery dissection	Stenting
Air embolism	0.02%	Operator-dependent complication; it is more common when infusion is performed through a microcatheter. It can be serious if not treated fast	Administer oxygen at 100% and wash the artery with saline serum multiple times (after making sure there is no more air). Inotropic and/or ventricular support (or both) may be needed
Catheter-induced spasm	0.02%	More common in the RCA	Try to avoid nitroglycerin in the absence of flow lost. It is often a transient phenomenon

The percentages disclosed were estimated based on 6183 procedures reported in 9 different studies.
* According to the CorMicA trial, the rate of atrial fibrillation with the fastest doses infused was 6%.[6]
RCA, right coronary artery.
Adapted with permission from Ciliberti et al.[40]

been widely accepted by the most experienced groups. In addition, there are data available on its safety profile in many patients and is the protocol backed by the EAPCI in its recent consensus document.[7]

Three doses of 2 µg, 20 µg, and 100 µg are used in the left coronary artery, and 3 doses of 2 µg, 20 µg, and 50 µg in the right coronary artery. If the test is negative or inconclusive and the previous doses are well-tolerated, a 200 µg or a 80 µg dose can be used in the left or right coronary artery, respectively, if suspicion runs high.

Regarding the infusion time, a slow 20 second-bolus can be administered, although this is based on clinical tolerability. The highest doses, especially in the right coronary artery, often require infusions at a slower rate to avoid sinus arrest-induced bradycardia or atrioventricular block. It is important to carefully and slowly wash the guide catheter with a saline solution to avoid the sudden injection of the remaining drug into the catheter by the time the cine-fluoroscopy imaging is acquired. After every dose both the symptoms and the repolarization and angiographic changes should be assessed while paying special attention to the appearance of epicardial spasms or significant reductions of coronary flow velocity. At the end of the test, intracoronary nitroglycerin is infused (200 µg to 300 µg) and spasm is solved within a few seconds.

Safety and complications

Before indicating the test, the presence of factors that may be correlated with a risk of complications associated with the intracoronary infusion of acetylcholine should be discarded. The test should be carefully performed in patients with a past medical history of asthma or bronchospasm and serious disorders of automaticity and cardiac conduction.

Although safe in experienced hands, coronary vasoreactivity tests to acetylcholine are not stranger to potentially serious complications. These tests should always be performed paying extra care by trained personnel and ready to face the possible complications that may arise. In a metanalysis of different studies with over 6000 procedures, the rates of major (eg, ventricular arrhythmias, need for cardiopulmonary resuscitation or infarction), and minor complications (symptomatic bradycardia, transient atrioventricular block, appearance of ventricular arrhythmias or air embolism) were 1% and 6%, respectively.[40] We should mention that no death was reported in this metanalysis.[40] Table 3 shows the most common complications and their corresponding treatments.

During the infusion of acetylcholine, sinus bradycardia, sinus arrests or episodes of atrioventricular block are common. This is often associated with too fast infusions, especially in the right coronary artery. If these complications occur, infusion should stop for a few seconds and restarted at a slower velocity. Atrial fibrillation can sometimes occur, but it often solves spontaneously; the most persistent cases often solve after the administration of amiodarone or other antiarrhythmic drugs. If bradyarrhythmias make a comeback, the test should stop immediately or be performed with a transient pacemaker in very selected cases where the test is considered indispensable.

An unwanted effect of the test is flow-limiting vasospasm that is not well-tolerated. In general, the consequences depend on the time elapsed between the occurrence of the vasospasm and the infusion of intracoronary nitrates to reverse it. The ischemia originated can cause hypotension and ventricular fibrillation that should be treated with nitroglycerin and immediate defibrillation. To stop this from going unnoticed, the patient's blood pressure should be checked halfway into the infusion of acetylcholine, especially after the highest doses have been infused and when injected into a dominant left

coronary branch. Under no circumstance a growing dose of acetylcholine should be infused if a significant or flow-limiting spasm or any other important complication have been spotted after the infusion of lower doses. Also, we should remember that, at the end of the infusion, the guide catheter still contains 2 mL of acetylcholine dilution that should be slowly pushed with a saline solution to stop it from entering the bolus with the injection of contrast. Same as it happens with any other invasive coronary procedures, and especially in this test, preloaded nitroglycerin should be available and ready to be infused. In most of the cases its infusion causes vasodilation, and fast flow recovery without needing further doses. On the other hand, atropine is a cholinergic receptor antagonist that can be used as an antidote when necessary.

Some operators perform the vasoreactivity test using the pressure guidewire inside the coronary artery as a safety measure. This brings more stability to the catheter, provides better selective infusion of dilutions, and allows us to monitor distal pressure (that can decrease in the case of flow-limiting spasm). Also, it controls the velocity of manual infusion in case of a long infusion without a pump (temperature or velocity changes are indicative that infusion is happening too fast). However, we should remember that the passage of the guidewire itself can cause vasospasm. Actually, it can simulate pseudo-spasms in tortuous arteries due to curve rectification.

INTERPRETING THE CORONARY VASOSPASM PROVOCATION TESTING

General concepts

Interpreting this test rests on 3 basic pillars:

1. The reproduction of the patient's common symptoms that motivated the test. With the last dose of acetylcholine patients often experience changes of rhythm (eg, P-wave block or bradycardia) that can cause symptoms. These disorders should be distinguished from the patient's usual angina symptoms.

2. The presence of changes on the ECG suggestive of ischemia, especially if accompanied by the angina symptoms that motivate the study. This assessment is often performed a few seconds after the infusion of each dose of acetylcholine. We should remember that in the presence of epicardial spasm with decreased blood flow in some of the epicardial arteries, the ST-segment does not need to be elevated or more changes on the ECG need to be present. That is so because patient's safety is a priority at all time. Also, we should remember that, sometimes, the same injection of contrast or saline solution causes changes on the ECG. That is why serial ECGs (or collections of registries) should be performed a few seconds after the infusion of acetylcholine and before the cine coronary arteriography required (with the corresponding infusion of contrast).

3. The presence of angiographic coronary spasm (macrovascular) as seen on the serial registries (with cine-fluoroscopy) after every dose of acetylcholine. Spasm is defined as an obstruction with ≥ 90% stenosis with respect to the diameter of the artery in this segment after the infusion of nitroglycerin. Diameter stenosis (DS) can be determined visually or using a quantitative coronary angiography. The DS is measured by obtaining the minimal luminal diameter after the dose of acetylcholine with greater vasoconstriction (MLD_ACh) with respect to the reference vessel diameter calculated after the infusion of nitroglycerin (RVD_NTG) with the following formula:

$$DS = 100 - [(MLD\_Ach / RVD\_NTG) \times 100]$$

In practice, it is better to use the quantitative coronary angiography on the proximal segments of major arteries than in more distal segments where the reference diameter is often small and, according to the formula described above, could underestimate the DS.

Possible test results

Figure 1 shows the 4 results that can be obtained from a vasospasm provocation test performed by the infusion of intracoronary acetylcholine:

1. *Negative test with vasodilator response (with respect to baseline).* The presence of vasodilator response without symptom onset or changes on the ECG is suggestive of a normal endothelial function at epicardial level.

2. *Negative test with vasoconstrictor response (with respect to baseline).* The presence of epicardial vasoconstriction after acetylcholine without criteria of epicardial or microvascular vasospasm (defined by the lack of symptoms, changes on the ECG or significant vasoconstriction) is indicative of endothelial dysfunction, especially if vasoconstriction is confirmed after the infusion of the first few doses. Since the vasospasm provocation test has not been designed to assess the endothelial function (that requires a slower infusion rate) a certain degree of vasoconstriction is often seen with the highest dose due to the acetylcholine-induced direct stimulation of the vascular smooth muscle, which is not necessarily suggestive of epicardial endothelial dysfunction.

3. *Positive test for epicardial spasm.* The diagnosis of epicardial vasospasm requires the 3 following simultaneous findings:

   - Reproduction of symptoms after the infusion of acetylcholine.

   - Changes on the ECG suggestive of ischemia, usually in the ST-segment (whether depression or elevation > 0.1 mV). The appearance of negative U-waves has been described too.

   - Spasm with a ≥ 90% diameter stenosis with respect to the same segment after the infusion of nitroglycerin that can be flow-limiting, focal, multisegmental or diffuse.

4. *Positive test for microvascular spasm.* Microvascular spasm has been defined as the reproduction of common angina symptoms plus the finding of changes on the ECG indicative of ischemia (basically, ST-segment depression or elevation > 0.1 mV) in the absence of coronary spasm with a ≥ 90% diameter stenosis (with respect to nitroglycerin).

LEGAL ASPECTS PERTAINING TO THE USE OF INTRACORONARY ACETYLCHOLINE

The use of drugs in off-label indications different from those approved in their instructions for use and outside the clinical trial setting like intracoronary acetylcholine for diagnostic purposes requires the approval of local pharmaceutical committees. Because the Spanish Agency of Medicines and Medical Devices accepts the use of these drugs under very particular circumstances no general consensus has been achieved and local approvals are still required.

Also, in observance of Royal Decree 1015/2009 of 19 June,[41] the use of a drug through a route of administration different from the one described in the drug labeling requires the provision of information as well as the patient's written informed consent prior to its administration. For that reason, some centers also require the

Why?	Because the acetylcholine test allows us to assess both the vasospasm and the endothelial function. This has diagnostic, prognostic, and therapeutic implications in several groups of patients. Large series with thousands of cases and consensus documents support its utility and safety profile
To whom?	Patients with INOCA, MINOCA, sudden death without an etiological diagnosis, and seizures with chest pain.
How?	We recommend performing an invasive test with direct and slow infusion of growing doses of 2 µg-20 µg-100 µg into the left coronary artery followed by symptom monitoring, ECG, and angiography after every dose
What for?	To categorize into epicardial vasospasm, microvascular vasospasm or negative test. In the presence of vasospasm, stop the administration of beta-blockers and use vasodilators

Figure 5. Key takeaways of this document. ECG, electrocardiogram; INOCA, ischemia with non-obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries.

signing of a specific informed consent to be able to use intracoronary acetylcholine. These documents are available on the center intranet or the hospital pharmacy.

CONCLUSIONS

Figure 5 summarizes the key takeaways of this document. In conclusion, vasoreactivity testing with acetylcholine is an essential part of the assessment of patients with non-obstructive coronary artery disease and symptoms or ischemia. The result of this assessment allows us to target specific therapies and has proven effective in the routine clinical practice. Cath labs should be prepared to perform this kind of tests, and computers should be ready to use and interpret them.

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E. Gutiérrez and J. Gómez-Lara equally contributed to the manuscript first draft, and to the figures, and tables. The remaining authors performed a thorough revision of the paper and made comments and changes to its content and form.

CONFLICTS OF INTEREST

None reported.

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Review article

Ongoing large randomized clinical trials on complex percutaneous coronary interventions: intravascular imaging-guided trials

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ABSTRACT

Percutaneous coronary intervention of complex coronary artery disease remains challenging and is still associated with suboptimal cardiovascular outcomes. Over the years, different strategies and technologies have been developed to improve these results. Particularly, the development and evolution of intravascular imaging modalities to guide the procedure have improved lesion assessment and preparation, and stent optimization. However, whether these advantages are beneficial in this particular setting is still under discussion. In this article we intend to briefly summarize previous imaging-guided trials and give an outline on the ongoing large trials that are being conducted on imaging-guided interventions in complex coronary disease.

Keywords: Complex percutaneous coronary intervention. Optical coherence tomography. Intravascular ultrasound.

Ensayos clínicos aleatorizados en desarrollo en intervencionismo coronario complejo: estudios guiados por imagen intravascular

RESUMEN

El intervencionismo coronario complejo es aún un escenario desafiante que todavía se asocia con resultados subóptimos. A lo largo de los años han surgido diferentes estrategias y tecnologías con el objetivo de mejorar dichos resultados. En concreto, el desarrollo y la evolución de herramientas de imagen intravascular para guiar el procedimiento han permitido perfeccionar la evaluación de la lesión y su preparación, y asegurar su optimización. No obstante, los posibles beneficios de su uso en este escenario particular son aún objeto de estudio. En este artículo, el objetivo es resumir brevemente los principales estudios realizados previamente con estas técnicas, así como los ensayos que en la actualidad están en marcha en intervencionismo coronario complejo guiado por imagen.

Palabras clave: Intervencionismo coronario complejo. Tomografía de coherencia óptica. Ecografía intravascular.

Abbreviations

IVUS: intravascular ultrasound. **OCT:** optical coherence tomography. **PCI:** percutaneous coronary intervention.

INTRODUCTION

Percutaneous coronary interventions (PCI) of complex coronary artery disease namely heavily calcified coronary lesions, bifurcations (including left main coronary artery bifurcations), in-stent restenosis, chronic and acute total coronary occlusions, and long lesions is still associated with suboptimal long-term cardiovascular outcomes. Whether the advances made in stent technology and intracoronary imaging modalities can help reduce this risk is still under discussion. We provide a brief historical overview of intracoronary imaging-guided trials, and large ongoing randomize clinical trials.

After 4 decades of angiography being the mainstay of balloon angioplasty and stent implantation procedures, the evolution of intravascular ultrasound (IVUS), and optical coherence tomography (OCT) on the wake of the availability of new-generation drug-eluting stents and

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bioresorbable scaffolds has prompted the gradual adoption of both intravascular imaging modalities for PCI guiding purposes. Over the years, several clinical trials and systematic reviews have compared the results and long-term outcomes of angiography vs intracoronary imaging-guided PCI with significant findings.[1-12] The latest clinical practice guidelines recommend both imaging modalities to guide stent implantation in a selected subset of patients only (IVUS guidance–Class IIa, and OCT guidance–Class IIb).[13,14] This opens new opportunities to set up more contemporary clinical trials in high-risk populations who may benefit the most from these interventions.

Although reports including multicenter trials and systematic reviews have shown the benefits of intravascular imaging-guided PCI compared to angiography-guided PCI, different variations have been observed in the findings reported possibly due to differences in: *a)* patients and lesion types included in the studies; *b)* the definition of a specific optimization criteria based on intravascular imaging guidance and differences in those criteria across various studies; *c)* the length of follow up; and *d)* the study endpoints. Invariably, the omission or misrepresentation of certain groups of angiographically complex lesions in former studies has triggered the need for trials to focus on this direction.[2,3,7,9,15-20]

Table 1 shows brief details of former imaging guidance studies and the findings reported.

Table 1. Key former studies on PCI imaging guidance

Study (N.), NCT	Year	Guidance criteria	Modality	Endpoints	Key findings
MUSIC (N = 161) NCT N/A	1998	Complete stent apposition over its entire length against the vessel wall; MLA: in-stent MLA ≥ 90% of the average reference lumen area or ≥ 100% of the reference segment with the lowest lumen area; in-stent MLA of proximal stent entrance ≥ 90% of the proximal reference lumen area. If in-stent MLA is > 9.0 mm^2, in-stent MLA ≥ 80% of the average reference lumen area or ≥ 90% of the reference segment with the lowest lumen area; in-stent MLA of proximal stent entrance ≥ 90% of the proximal reference lumen area; symmetric stent expansion defined by the minimum lumen diameter divided by the maximum lumen diameter ≥ 0.7	IVUS	Death, MI, coronary artery bypass surgery, and TLR, and clinically and/or angiographically documented (sub)acute thrombotic stent occlusion 30 days after stent implantation	6-month angiographic outome in IVUS-guided implantation arm, a TLR of 5.7%, and a restenosis rate of 9.7% with the largest MLD 2.12 ± 0.67
AVID (N = 800) NCT N/A	2000	MSA should be ≥ 90% of the distal reference vessel lumen cross-sectional area; stent fully apposed; dissections covered by stent	IVUS	The study primary endpoint was the rate of TLR at 12 months determined by the clinical follow-up without having to repeat the angiography	The 12-month follow-up results revealed a TLR rate of 10.1% in the angiography group vs a 4.3% rate in the IVUS group (P = .01; 95%CI, −10.6% to −1.2%)
SIPS (N = 269) NCT N/A	2000	Complete apposition against the vessel wall of the entire stent; MLA ≥ 90% of the average reference lumen area or ≥ 100% of the lumen area of the reference segment with a MLA > 9.0 mm^2; MLA ≥ 80% of the average reference lumen area or ≥ 90% of the reference segment lumen area with the lowest lumen area. Symmetric stent expansion	IVUS	The study primary endpoint was the 6-month angiographic MLD. Secondary endpoints included acute MLD, acute and chronic cost, quality of life, composite clinical event rates, and clinically driven TLR	The clinical follow-up (602 days ± 307 days) showed a significant decrease in clinically driven TLR in the IVUS group compared to the standard guidance group (17% vs 29%, respectively; P = .02)
MAIN-COMPARE (N = 975) NCT N/A	2009	Specific criteria for IVUS guidance not provided	IVUS	The study primary endpoint was mortality. Secondary endpoints were MI, target vessel revascularization (TVR) or a composite of events	IVUS guidance, especially during drug-eluting stent implantation, may reduce the long-term mortality rate for unprotected left main coronary artery stenosis compared to conventional angiography guidance
HOME DES (N = 210) NCT N/A	2010	Good apposition; apposition of all stent struts to the vessel wall; Optimal stent expansion (with a MSA = 5 mm^2) or a cross-sectional area > 90% of the distal reference lumen cross-sectional area for small vessels/and no edge dissection (5 mm margins proximal and distal to the stent)	IVUS	MACE (death, MI, and reintervention)	No significant differences were reported between the groups at the 18-month follow-up regarding MACE (11% vs 12%; P = NS)
CLI-OPCI (N = 670) NCT N/A	2012	Stent underexpansion was defined based on established IVUS criteria of optimal stent expansion (eg, in-stent minimal lumen area ≥ 90% of the average reference lumen area or ≥ 100% of the reference segment lumen area with the lowest lumen area)	OCT	Primary endpoint was the 1-year rate of cardiovascular death or MI	The OCT group had a significantly lower 1-year risk of cardiovascular death (1.2% vs 4.5%; P = .010), cardiac death or MI (6.6% vs13.0%; P = .006), and a composite endpoint of cardiac death, MI or new revascularization (9.6% vs 14.8%, P = .044)

(Continues)

Table 1. Key former studies on PCI imaging guidance *(continued)*

Study (N.), NCT	Year	Guidance criteria	Modality	Endpoints	Key findings
AVIO (N = 284) NCT N/A	2013	Final MSA of, at least, 70% of the hypothetical cross-sectional area of the fully inflated balloon used for post-dilatation. The optimal balloon size for post-dilatation is the average of the media-to-media diameters of the distal and proximal stent segments as well as at the sites of maximum in-stent narrowing. The value is rounded to the lowest 0.00 mm or 0.50 mm. For values ≥ 3.5 mm the operator could downsize the diameter of the balloon based on his best clinical judgment	IVUS	The primary study endpoint was the postoperative lesion minimal lumen diameter. The secondary endpoints were a composite of MACE, TLR, target vessel revascularization, MI, and stent thrombosis at 1, 6, 9, 12, and 24 months	IVUS optimized DES implantation as seen on the complex lesions in the postoperative minimal lumen diameter. No statistically significant differences were found in MACE at the 24-month follow-up.
RESET (N = 1574) NCT N/A	2013	Specific criteria for IVUS guidance not provided	IVUS	MACE, including cardiovascular death, MI or target vessel revascularization at the 1-year follow-up after DES implantation in short-length lesions	There were no statistically significant differences regarding the MACE outcome between the IVUS-guided and the angiography-guided groups
AIR CTO (N = 230) NCT N/A	2015	Good apposition, MSA > 80% of the reference vessel area, symmetry index > 70%, and no > type B dissection	IVUS	The primary endpoint was in-stent late lumen loss at the 1-year follow-up	The in-stent late lumen loss in the IVUS-guided group was significantly lower compared to the angiography-guided group at the 1-year follow-up (0.28 mm ± 0.48 mm vs 0.46 mm ± 0.68 mm; *P* = .025) with a significant difference of the "in-true-lumen" stent restenosis between the 2 groups (3.9% vs13.7%; *P* = .021)
CTO IVUS (N = 402) NCT01563952	2015	*a)* MSA ≥ distal reference lumen area; *b)* stent area at CTO segment ≥ 5 mm^2 vessel area permitting; and *c)* complete stent apposition	IVUS	The primary endpoint was the occurrence of cardiovascular death. The secondary endpoint was MACE defined as a composite of cardiovascular death, MI or target vessel revascularization at 12 months	The IVUS-guided CTO intervention did not reduce cardiovascular mortality significantly. The occurrence of MACE was significantly lower in the IVUS-guided group compared to the angiography-guided group (2.6% vs 7.1%)
IVUS-XPL (N = 1400) NCT01308281	2016	MLA greater than the lumen cross-sectional area at the distal reference segments post-PCI	IVUS	The primary outcome measure was a composite of MACE, including cardiovascular death, target vessel MI or ischemia-driven TLR at the 1-year follow-up analyzed by intention-to-treat	IVUS-guided stent implantation was associated with a significant 2.9% absolute reduction, and a 48% relative reduction in the risk of MACE at the 1-year follow-up compared to angiography-guided stent implantation
ILUMIEN III (N = 450) NCT02471586	2016	MSA: achievement of, at least, acceptable stent expansion (a minimum stent area of, at least, 90% in both the proximal and distal halves of the stent relative to the closest reference segment) Acceptable stent expansion: the MSA of the proximal segment is ≥ 90% and < 95% of the proximal reference lumen area, and the MSA of the distal segment is ≥ 90% and < 95% of the distal reference lumen area	IVUS, OCT	The primary efficacy endpoint was the post-PCI minimum stent area as seen on the OCT at a masked independent core laboratory after completing recruitment in all randomly allocated participants with primary outcome data available. The primary safety endpoint was procedural MACE	OCT guidance was non-inferior to IVUS guidance (one-sided 97.5% lower confidence interval, –0.70 mm^2; *P* = ·001), but not superior either to IVUS-guidance (*P* = .42) and angiography guidance (*P* = .12). There were no significant differences in the MACE outcome
OPINION (N = 800) NCT01873222	2016	In-stent MLA ≥ 90% of the average reference lumen area; complete stent apposition over its entire length against the vessel wall; symmetric stent expansion defined by minimum lumen diameter/maximum lumen diameter ≥ 0.7; no plaque protrusion, thrombus or edge dissection with potential to provoke flow disturbances	IVUS, OCT	The primary endpoint was TVF defined as a composite of cardiovascular death, target vessel MI, and ischemia-driven target vessel revascularization 12 months after the PCI	TVF occurred in 21 (5.2%) out of the 401 patients undergoing OFDI-guided PCI, and in 19 (4.9%) out of the 390 patients undergoing IVUS-guided PCI, which proved the non-inferiority of OFDI-guided PCI with respect to the IVUS-guided PCI (hazard ratio, 1.07; upper limit of one-sided 95%CI, 1.80; *P* value for non-inferiority = .042)
ULTIMATE (N = 1448) NCT02215915	2021	*a)* In-stent MLA > 5.0 mm or 90% of the MLA at the distal reference segments; *b)* plaque burden 5 mm proximal or distal to the stent edge is < 50%; and *c)* no edge dissection involves the media with a length > 3 mm	IVUS	The primary endpoint was the risk of TVF at the 3-year follow-up	IVUS-guided DES implantation was associated with significantly lower rates of TVF and stent thrombosis at the 3-year follow-up among all-comers

95%CI, 95% confidence interval; CTO, chronic total coronary occlusion; DES, drug-eluting stent; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MLA, minimum lumen area; MI, myocardial infarction; MLD, minimum lumen diameter; MSA, minimum stent area; NA, not available; NS, not significant; OFDI, optical frequency domain imaging; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVF, target vessel failure.

Table 2. Ongoing studies on PCI imaging guidance

Study, NCT	Modality	Study design	Study objective	Imaging criteria	Clinical endpoints
IMPROVE, NCT04221815	IVUS vs angiography	Prospective multicenter, international, single-blind clinical investigation No. of subjects: approximately 2500-3100 randomized subjects Follow-up period: 2 years	To demonstrate the superiority of an IVUS-guided stent implantation strategy compared to an angiography-guided stent implantation strategy achieving larger post-PCI lumen dimensions, and improving the clinical cardiovascular outcomes of patients with complex angiographic lesions	Optimal stent deployment is considered to have been achieved if the following 3 criteria are met on the final IVUS: MSA > 90% of the distal reference lumen area. No edge dissection involving the media with an arc ≥ 60° and length ≥ 3 mm Absence of geographic miss defined as plaque burden > 50% within 5 mm from the proximal or distal stent edge or both	Target vessel failure outcomes at 12 months defined as a composite of cardiovascular death, target vessel MI or clinically indicated target vessel revascularization
IVUS-CHIP, NCT04854070	IVUS vs angiography	Randomized, controlled, multicenter, international, event-driven, post-marketing study. A total of 2020 patients will be randomized in a 1:1 fashion to the IVUS-guided PCI vs the angio-guided PCI	To demonstrate the superiority of IVUS guidance compared to angio guidance regarding target vessel failure	Final MSA > 5 mm^2 or MSA < 90% of distal reference lumen Plaque burden < 50% within 5 mm from the proximal or distal stent edge No edge dissection involving the media and > 3 mm in length	Target vessel failure defined as a composite of cardiovascular death, target vessel MI or clinically indicated target vessel revascularization
OPTIMAL, NCT04111770	IVUS vs angiography	Randomized, controlled, multicenter, international study	To demonstrate the superiority of IVUS- vs angiography-guided stent implantation in patients with LMCA disease, and also improving the clinical outcomes	MSA > 5 (LCX), > 6 (LAD), > 7 (bifurcation point), > 8 (LMCA) Malapposition < 0.4 mm Absence of edge dissection defined as ≥ 60° and ≥ 2 mm in length Plaque burden at the edge of the stent < 50%	Patient-oriented composite endpoint (POCE): a composite of all-cause death, any strokes, any MIs, any clinically indicated revascularizations at the 2-year follow-up
ILUMIEN IV, NCT03507777	OCT vs angiography	Prospective, multicenter, randomized, controlled clinical trial No. of subjects: between 2490 and 3656 Follow-up period: 2 years Expected study duration: approximately 2 years	To demonstrate the superiority of OCT- vs angiography-guided stent implantation in the patients' clinical outcomes	To achieve: Acceptable stent expansion (an MSA of, at least, 90% in both the proximal and distal segments of the stent relative to the closest reference segment). Both proximal/distal reference segments have a minimal lumen area ≥ 4.5 mm^2 Absence of a major edge dissection defined as ≥ 60° of the vessel circumference at the dissection site and ≥ 3 mm in length	Target vessel failure, a composite of cardiovascular death, target vessel MI or ischemia-driven target vessel revascularization
DKCRUSH VIII NCT03770650	IVUS vs angiography	Randomized, controlled, multicenter trial Sample size: 556 patients Allocation 1:1	To assess superiority of IVUS-guided vs angiography-guided DK Crush stenting in complex bifurcations.	For LMCA: MSA ≥ 10mm2 (LM), 7mm2(LAD), 6 mm^2 (CX) Stent expansion index ≥ 90% (of distal reference lumen area in LCX) Symmetry index > 0.8 For non-LMCA: MSA ≥ 6 mm^2 in the main vessel, and ≥ 5 mm^2 in the ostial side branch Stent expansion ≥ 90% of distal reference lumen area Symmetry index > 0.8	The primary outcome is the rate of 12-month target vessel failure: Cardiac death, target vessel myocardial infarction, clinically driven target vessel revascularization
OCTOBER, NCT03171311	OCT vs angiography	Randomized, investigator-initiated, multicenter trial. The calculated sample size is 1200 patients in total allocated in a 1:1 fashion	To show the superiority of OCT-guided stent implantation compared to standard angiographic-guided implantation in bifurcation lesions	Adequate vessel and stent expansion (> 90%) Full stent apposition Optimal lesion coverage	The primary outcome measure is a 2-year composite endpoint of cardiovascular death, target lesion myocardial infarction, and ischemia-driven target lesion revascularization
CTIVUS NCT03394079	OCT vs IVUS guided PCI	Multicenter, randomized, controlled trial. "All-comer" population Sample size:2000 patients Allocation 1:1	To compare the clinical efficacy and safety of OCT-guided and IVUS-guided PCI	Optimization criteria by IVUS or OCT: Stent expansion > 80% by average reference lumen area Absence of large dissections (> 60°, > 2 mm length, flap extending to media or adventicia) Absence of malapposition Avoidance of a landing zone in a plaque burden < 50% or lipid-rich tissue at stent edge Distal lumen reference based (0.25 mm up-round) or EEM reference based (0.25 mm down-round)	The primary outcome is target vessel failure: cardiac death, target vessel myocardial infarction or ischemia-driven target vessel revascularization at 1 year

IVUS, intravascular ultrasound; LAD, left anterior descendent coronary artery; LCX, left circumflex artery, LMCA, left main coronary artery; MI, myocardial infarction; MSA, minimum stent area; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Patient/Lesion characteristics included in ongoing intracoronary imaging-guided PCI studies							
	Left main coronary artery (LMCA) 	Bifurcation lesions 	Chronic total coronary occlusions 	In stent restenosis 	Calcified lesions 	Long lesions 	Special considerations 
IMPROVE trial	Protected LMCA only Any type of anatomy	Any Medina classification involving any major coronary artery branch disease with a side branch ≥ 2.0 mm	Any	Any	Severe	≥ 28 mm in length	Excluded
IVUS CHIP trial	Not included	True bifurcation lesions involving side branches > 2.5 mm	Any	Any	Severe	≥ 28 mm in length	Ostial lesions & PCI for any lesions and requiring elective mechanical circulatory support assisted PCI
OPTIMAL rial	De novo LMCA lesion (ostial, shaft or distal) where PCI is considered appropiate and feasible by the heart team*	All left main coronary artery bifurcations according to the Medina classification 100, 110, 101, 011, 010, 111, 001 (and LMCA equivalent)	Not included	Not included	Not included	Not included	Not included
ILUMIEN IV: OPTIMAL PCI	Not included	Intended to be treated with 2 planned stents (eg, in both the main vessel and the side branches), and where the planned side branch stent is ≥ 2.5 mm in diameter	Any	Diffuse or multi-focal pattern	Severe	≥ 28 mm in length	Medication-treated diabetes mellitus, STEMI, and NSTEMI
OCTOBER trial	Included	Angiographic inclusion criteria: De novo bifurcation lesion of native coronary artery* More than 50% diameter stenosis in the main vessel (MV) More than 50% diameter stenosis in the side branch (SB) within 5 mm of the ostium. Reference size at least 2.75 mm in the main vessel (MV) and ≥ 2.5 mm in the SB	Not included	Not included	Any	Any	1-stent techniques, 2-stent techniques, LMCA bifurcation subgroup, single-vessel disease, multivessel disease, long and short SB disease, optimal and suboptimal angiographic results, stable angina pectoris and acute coronary syndrome (ACS), diabetes, sex, calcified lesions, and SYNTAX score > 11 which are depicted in a forest plot
DK CRUSH VIII	Included	Medina 1, 1, 1 or 0, 1, 1 and sidebranch diameter ≥ 2.5 mm DEFINITION CRITERIA (1 major and 2 minor criteria)	Not included	Not included	Any	Any	DEFINITION criteria: Mayor: LMCA bif: SB diameter stenosis ≥ 70% and SB lesion length ≥ 10 mm Non LMCA bif: SB diameter stenosis ≥ 90% and SB lesion length ≥ 10 mm Minor: Moderate to severe calcification Multiple lesions Bifurcation angle 45-70° Thrombus containing lesions MV lesion length > 25 mm MV reference vessel diameter < 2.5 mm
OCTIVUS	Included	Included	Any	Any	Any	Any	

Figure 1. Main patient and lesion characteristics included in these ongoing large intracoronary imaging trials.
* Functional inclusion criteria: functional significance of the main vessel lesion or documented ischemia of the main vessel territory or other objective documentation of lesion significance. Objective evidence of ischemia is required for all target lesions except for those with > 80% diameter stenosis that may be considered significant.
PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non—ST-segment elevation myocardial infarction; SB, side branch.

Subsequently, new ongoing studies are assessing the effect of PCI imaging guidance on the clinical outcomes over longer follow-up periods and the value of guiding interventions with imaging modalities when treating specific lesion subsets like in-stent restenosis, calcified lesions, and long lesions. Table 2 highlights the ongoing PCI guidance trials.

ONGOING CLINICAL TRIALS ON INTRAVASCULAR ULTRASOUND GUIDANCE

The IMPROVE (Impact on revascularization outcomes of IVUS-guided treatment of complex lesions and economic impact, NCT04221815) trial,[17] a multicenter, prospective, single-blind 3100 patient study, aims

to demonstrate the superiority of IVUS-guided stent implantation over the angiography-guided stent implantation strategy in complex lesions (including chronic total coronary occlusions, calcified lesions, long lesions, bifurcations, and in-stent restenosis) based on the different post-PCI minimum stent area, and target vessel failure outcomes reported at 12 months defined as a composite endpoint of cardiovascular death, target vessel myocardial infarction, and ischemia-driven target vessel revascularization (table 2 and figure 1).

The IVUS-CHIP trial (Intravascular ultrasound guidance for complex high-risk indicated procedures, NCT04854070) is a randomized, controlled, multicenter, international, event-driven, post-marketing study. A total of 2020 participants with complex coronary lesions (angiographic heavy calcifications, ostial lesions, true bifurcation lesions, left main coronary artery lesions, chronic total coronary occlusions, in-stent restenosis, long-lesions) or requiring elective mechanical circulatory support assisted PCI will be randomized in a 1:1 fashion to receive IVUS-guided PCI vs angio-guided PCI. The study aims to demonstrate the superiority of the IVUS guidance strategy in terms of the primary endpoint, target vessel failure, defined as a composite endpoint of cardiovascular death, target vessel myocardial infarction or clinically indicated target vessel revascularization (table 2 and figure 1).

The OPTIMAL (Optimization of left main PCI with intravascular ultrasound, NCT04111770) study is a randomized, controlled, multicenter, international study. A total of 800 patients will be randomized in a 1:1 fashion to receive IVUS-guided PCI vs qualitative angiography-guided PCI. Patients with a de novo left main coronary artery lesion (ostial, shaft or distal) eligible for a PCI according to the heart team will be included. All left main coronary artery bifurcations according to the Medina classification 100, 110, 101, 011, 010, 111, 001 (and LMCA equivalent) can be included. Patients with a previous coronary artery bypass graft and no patent bypass on the left main coronary artery can be included too. The study primary endpoint is a patient-oriented composite endpoint: a composite of all-cause mortality, any strokes, any myocardial infarctions, and any clinically indicated revascularizations at the 2-year follow-up (table 2 and figure 1).

The DK CRUSH VIII trial (NCT03770650)[19] is a randomized, controlled,multicenter study that aims to assess the superiority of IVUS-guided versus angiography-guided DK crush stenting in 556 patients with complex bifurcation lesions based on DEFINITION criteria. Its primary endpoint is the rate of cardiac death, target vessel failure, target vessel myocardial infarction or target vessel revascularization at 12 months (table 2 and figure 1).

ONGOING CLINICAL TRIALS ON OPTICAL COHERENCE TOMOGRAPHY

In the past, the ILUMIEN III study (NCT02471586), that reported on the non-inferiority of OCT compared to IVUS (minimal stent area; one-sided 97.5% lower confidence interval, −0.70 mm²; $P = .001$) proved the superiority of the OCT-guided stent implantation strategy compared to the angiography-guided stent implantation strategy achieving larger post-PCI lumen dimensions, and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics and/or high-risk angiographic lesions. The ILUMIEN IV (NCT03507777) trial that has completed recruitment (3600 patients initially planned) intends to demonstrate the superiority of an OCT-guided stent implantation strategy over an angiography-guided stent implantation strategy achieving larger post-PCI lumen dimensions, and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics like diabetes and/or high-risk angiographic lesions. The result of both studies and their similar endpoints will be shedding light on the role played by intravascular imaging guidance especially for the management of complex coronary lesions (table 2 and figure 1).

Another OCT clinical trial is the European trial on optical coherence tomography optimized bifurcation event reduction (OCTOBER, NCT03171311), a randomized, investigator-initiated, multicenter trial aimed at showing the superiority of OCT-guided stent implantation compared to standard angiographic-guided implantation in bifurcation lesions. Stratified randomization: *a)* left main or non-left main coronary artery disease, and *b)* upfront planned 1-stent technique with kissing balloon inflation or a 2-stent technique[18].

A direct comparison of OCT and IVUS is planned in the OCTIVUS trial (NCT03394079), a multicenter, controlled trial of an all comers population that will be randomized to either OCT-guided PCI or IVUS-guided PCI[20]. The primary endpoint is death, target vessel myocardial infarction and ischemia-driven target vessel revascularization at one year (table 2 and figure 1).

CONCLUSIONS

Undoubtedly, intravascular imaging plays a role optimizing stent implantation, the extent of which remains to be fully grasped particularly in complex populations and lesion subsets. Based on previous reports that showed overwhelming evidence in favor of intravascular imaging-guided PCI, it is expected that these large 4 contemporary randomized clinical trials will show a reduction of major adverse cardiovascular events and, therefore, favor the use of intracoronary imaging in these populations and lesion subsets. One may also predict a significant increase in the use of IVUS/OCT based on the positive results, increased reimbursements, and hopefully a change in the societal guideline recommendations.

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AUTHORS' CONTRIBUTIONS

H.M. Garcia-Garcia is responsible for the study design and draft of the manuscript. E. Fernández-Peregrina, K.O. Kuku, and R. Diletti also drafted the manuscript and gave their critical review.

CONFLICTS OF INTEREST

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Debate: Minimalist approach to TAVI as a default strategy

A debate: Abordaje minimalista para los procedimientos de TAVI como estrategia por defecto

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Question: For starters, what is the minimalist approach to transcatether aortic valve implantation (TAVI)?

Answer: After the first case described by Cribier et al.[1] back in 2002, the management of aortic stenosis through TAVI has consolidated and become a safe and effective therapy that is based on a well-established and standardized procedure. Although it is a complex procedure due to the characteristics of patients and devices and the fact that experienced operators are needed, the growing number of cases reported, and the technological advances made with the devices have improved processes and reduced complications significantly. This has prompted that, over the last few years, certain experienced groups[2] have modified certain steps of the procedure and introduced strategies before and after the intervention to simplify and make TAVI more efficient. Also, to promote faster recoveries in the patients. This set of modifications is described as minimalist approach to TAVI. Two of the most significant aspects here are suppressing balloon dilatation and reducing hospital stays. However, there are simplifying strategies that can be divided into 3 parts: previous assessment and case analysis, valve implantation, and postoperative care. During the previous assessment part, the objective is to speed up the study circuits of the patients and reduce the waiting lists. Also, the decision between surgery or TAVI should not be made on the surgical risk but on the risk-benefit ratio based on the patient's age, comorbidities, functional status, frailty, anatomical characteristics, family support, and on the experience and results of the treating center. Regarding valve implantation, the simplifying strategies are applied in different settings:

- Healthcare professionals and setting. Procedures can be performed in a cath lab by experienced interventional cardiologists. In cases of transfemoral access, the heart team often includes 2 interventional cardiologists, 2 nurses, and 1 patient care technician. The nurse or the technician is in charge of preparing the device. The presence of 1 anesthesiologist and 1 expert cardiologist in imaging modalities or 1 echocardiographist is advised. With highly selected patients—complex access sites or different from the femoral access, etc.—or if certain complications occur the collaboration of a cardiovascular surgeon may be required.

- Anesthesia. It is one of the main changes of this minimalist approach. Although the presence of an anesthesiologist during the procedure is advised, general anesthesia is often substituted for local anesthesia and sedation. This avoids intubation and ventilation, minimizes risks, and reduces the hospital stay. General anesthesia would be spared for patients of a higher risk of complications who cannot tolerate the procedure or with high chances of conversion to surgery.

- Arterial access. In the primary access, the femoral access is often the one used for valve implantation and has given the best results of all. However, there are other alternatives available when it is not feasible. Puncture should be angiography- or ultrasound-guided and percutaneous closure is often performed with devices like Prostar (Abbott Vascular, United States), Perclose Proglide (Abbott Vascular, United States) or Manta (Teleflex, United States). Although the femoral access site is the preferred one in some cases for a direct control of hemostasis, with these devices, percutaneous puncture is a less invasive option that has good results. Regarding secondary arterial access, another arterial access site is often required, usually the contralateral femoral artery, for pigtail catheter insertion to perform the aortography. When inserted into the non-coronary sinus it serves as the reference for implantation. This access site also allows us to advance the protection guidewire inside the artery through which the access occurs in such a way that, if vascular closure is incomplete or fails, on top of providing compression, a balloon can be advanced to occlude the flow and a covered stent can be implanted. To this point, everal minimalist approaches have been suggested: *a)* use the radial access as the secondary access; *b)* simplify it by performing a more distal puncture preferably in the common femoral artery

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2 cm further down or in the superficial femoral artery. Through 4-Fr or 5-Fr introducer sheath a protection guidewire would be advanced to perform selective injections, and *c)* with the smaller size of today's sheath some even suggest inserting a protection guidewire.

- Echocardiogram. Using transthoracic echocardiography during implantation is considered enough because it avoids the problems associated with the transesophageal echocardiogram and allows us to assess fundamental aspects such as LV contractility, the position of the guidewire, and the outcome of valve implantation. Also, complications like cardiac tamponade, aortic regurgitation, etc can be discarded.

- Transient pacemaker. Rapid ventricular pacing is required for balloon-expandable valve and certain self-expandable valve implantation. Balloon-tipped electrode catheters should be used to reduce the risk of perforation. To avoid the problems associated with catheterizing that venous route, a metal guidewire placed in the left ventricle can be used for pacing purposes. After placing a subcutaneous 22G needle close to the sheath, the clips are connected to the needle (positive) and the ventricle metal guidewire (negative) isolated with a catheter or a valve placed close to the annulus. If there is no AV block (transient or permanent) or QRS widening > 160 m the pacemaker is removed in the cath lab after analyzing the electrocardiogram. If a definitive pacemaker is required, it should be implanted within the next 72 hours to avoid unnecessary longer the hospital stays.

- Avoid balloon predilatation. With some of the new valves available it is possible to perform direct valve implantation, thus reducing the risks derived from aortic valvuloplasty.

- Avoid urinary catheterization. It reduces hospital complications—infections, hematuria—and the hospital stay.

Regarding the third part, postoperative care, it is necessary to monitor the patient closely within the first few hours by closely assessing his hemodynamic status and the vascular access routes. Follow-up blood tests should be performed to detect blood losses. Also, the heart rhythm should be monitored to rule out the presence of cardiac conduction disorders or new-onset arrhythmias. A control echocardiogram is required the next day and, in the absence of complications, the patient should regain mobilization soon.

Q.: What advantages does deep sedation have over general anesthesia and how do you think it should be performed?

A.: The presence of an anesthesiologist in the cath lab guarantees closer monitoring and brings comfort to the patient. It also speeds up the procedure in case of complications. This does not necessarily imply using general anesthesia in every case: the use of conscious sedation and local anesthesia allows us to avoid orotracheal intubation, brings greater hemodynamic stability, and shorter procedural and recovery times. Several studies have proven the safety profile of this type of sedation with similar rates of mortality and complications;[3,4] its use has become very popular over the last few years. For example, in France,[5] it was used in 30% of the cases in 2010 up to 70% in 2017. Therefore, general anesthesia would be spared for patients with hemodynamic instability and higher risk of complications who don't tolerate the procedure or have high chances of conversion to surgery.

Q.: How is echocardiographic imaging implemented during TAVI? Always or occasionally? Transthoracic or transesophageal?

A.: Having a cardiologist expert in cardiac imaging modalities performing monitorization tasks through transthoracic echocardiogram brings extra safety, and avoids the problems associated with the transesophageal echocardiogram. This expert can control the position of the guidewire inside the ventricle, confirm the results of implantation by assessing gradients, identify some degrees of aortic regurgitation, and detect rapidly possible complications that may occur like abnormalities in cardiac contractility or the appearance of pericardial effusion. Transesophageal echocardiogram would be spared for cases of poor acoustic window or specific needs.

Q.: There are very different vascular occlusion systems available. Are there significant differences to pick one over the other based on certain characteristics of the patient? Which are the preferences of your heart team?

A.: Different suture-mediated closure devices (Proglide, Prostar) or collagen-based devices (Manta)[6,7] can be used with good results. Some may be used based on the preferences or experience of the heart team since the comparative studies conducted so far do not make any clear differences on this regard. Suture-mediated closure devices may have more problems in femoral arteries with calcium deposits while the Manta collagen-based devices can present complications in small-caliber femoral arteries (< 6 mm) or in very obese patients. Also, we should take into consideration the cost of each one of these devices, and the necessary learning curves. The single or double Proglide device is the most widely used. As a matter of fact, the latter is the common strategy in our center. None of them is infallible and in the presence of bleeding a balloon is required for occlusion purposes and even covered stent graft implantation to contain the bleeding.

Q.: Which is the average hospital stay after TAVI at your center? What do you think of 24 to 48-hour early hospital discharges?

A.: In our center, the average hospital stay is between 3 and 4 days because, although we try to discharge the patients 48 hours after the procedure, their risk profile often requires longer hospital stays. The patient should regain mobility within a few hours if the transient pacemaker has been removed and there are no vascular access complications. Therefore, uncomplicated patients can be discharged in < 72 hours. This early hospital discharge has proven feasible and safe in different studies and even in 1 meta-analysis that confirmed the good results of discharging patients within 3 days.[8] Next-day faster hospital discharges are also possible in highly selected patients without procedural complications.[9] However, a reason for concern in these patients is the possibility of developing AV block, and the need for pacemaker implantation. Although 50% of cardiac conduction disorders occur during implantation, 44% of them occur within the next 3 days.[10] If the 24-hour discharge is decided, it should be performed with a protocol of electrocardiographic monitoring and early detection of patients requiring pacemaker.[11]

Q.: Finally, in your own opinion, what patients would be eligible for minimalist TAVI and when is it ill-advised?

A.: It is going to depend on how experienced the heart team is, on the characteristics of the hospital, and on the situation of the patient always taking into consideration that the primary endpoint here is the safety and effectiveness of the procedure. The minimalist approach is a reasonable option in hemodynamically stable patients with adequate femoral accesses, collaborators, and without additional problems involving a high risk of complications like coronary occlusion. It will be gradually implemented, yet the effectiveness and quality of healthcare should not be compromised. Instead, the procedures should be performed faster, better, and adapted to the needs of the patients to avoid unnecessary tests, maneuvers, and stays.

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CONFLICTS OF INTEREST

None reported

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Debate: Minimalist approach to TAVI as a selective strategy

A debate: Abordaje minimalista para los procedimientos de TAVI como estrategia selectiva

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Question: For starters, what is the minimalist approach to transcatether aortic valve implantation (TAVI)?

Answer: Minimalist TAVI is a recent strategy to simplify the procedure, reduce possible complications, and favor early hospital discharges. This general definition can be explained by 2 keys aspects: what measures should be taken? And what patients should be eligible? Replacing general anesthesia and orotracheal intubation for sedation and local anesthesia are some of these measures. Sedation with the use of a laryngeal mask airway waking up the patient once the procedure is done is an intermediate situation. The type of hospital stay following TAVI is also an important aspect to be considered and it is associated with the type of anesthesia or sedation used: intensive care unit, post-anesthesia care unit or the hospital cardiac care unit. Other minimalist approaches during the procedure would be the access site used and the percutaneous closure, to avoid bladder catheterization, use the femoral venous access, use the radial, and not the femoral, artery for monitorization purposes, and to avoid the transesophageal echocardiogram. After the implantation, promoting early walking and removing IVs as soon as possible may also help. All these measures facilitate early hospital discharges. However, the hospital stays following these minimalist measures vary in the series published. In the first series ever published,[1] the average stay was 3 days including the intensive care unit stay. Recent series[2] report next-day hospital discharges for patients without complications within the first 24 hours. Finally, in the pandemic era of COVID-19 even same-day hospital discharges have sometimes been proposed.[3]

The other key aspect we should analyze is what patients should be eligible for minimalist TAVI, something we will talk about later.

Q.: What advantages does general anesthesia have to offer and what is patient profile is the most eligible of all?

A.: The way I see it, general anesthesia is beneficial for 2 reasons mainly. The first one is that the patient will remain still for the entire procedure, which is very convenient because precision is required when moving and placing the catheters. The second one is that, in case of hemodynamic instability or serious complications, we have one healthcare professional available, the anesthesiologist, in charge of the patient's ventilation and vital signs. This liberates the operator who can devote himself to the implantation technique alone or to solve any of the complications that may have occurred. Still, some issues still need further clarification: first, the difference between general anesthesia and sedation. In non-intubated patients, superficial general anesthesia or deep sedation can be used. These are very similar techniques with some very similar aspects that overlap. The use of the laryngeal mask airway provides versatility to adequate sedation or anesthesia for each case in particular. The anesthesiologist is free to use the technique he likes the most with one condition only, that the patient needs to «come in awake and leave the same way». Most times, laryngeal mask airways are used. They are often removed after implantation to refer the patient to the post-anesthesia care unit while awake and with spontaneous breathing. He will remain in this unit for 2 to 4 hours. Then, he will be transferred to the hospital cardiac care unit for electrocardiographic monitoring. The second aspect to be considered is the availability of the anesthesiologist. Sedation without anesthesia gives more versatility while setting everything up at the cath lab and facilitates the performance of more TAVIs regardless of the anesthesiologist's days available. However, the drawback is that sedation is not that perfect and, in case of hemodynamic instability during the procedure, the operators will have to do 2 things: stabilize the situation, and then proceed with the implantation. Our experience is that having an anesthesiologist available is beneficial because he can provide «a la carte» sedation or anesthesia without extending the hospital stay. Also, the patient is back to the hospital cardiac care unit within a few hours.

Q.: Do you think the transesophageal echocardiography (TEE) brings added value to TAVI? In what cases would it be more indicated during the procedure?

A.: TEE was often used when this technique was born to measure the aortic annulus when the process of sizing the valve was not as standardized as it is today. The computed tomography analyzed by current software provides all kinds of measurements including

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diameters, perimeters, and areas allowing an accurate selection of the device and leaving the indication for TEE obsolete. Another utility of TEE during the procedure is for the early detection of complications. In patients with severe hemodynamic impairment, it facilitates the differential diagnosis of the complication immediately. Therefore, cardiac tamponade, severe ventricular dysfunction, and severe mitral or aortic regurgitation can be identified early, which in turn facilitates the rapid adoption of the necessary measures. Thrombi and aortic damage are other complications that can also be detected with this imaging modality. To this date, except for the early detection of complications, the TEE does not seem of great utility during the procedure. Since complications are rare and difficult to predict, the systematic use of TEE has been losing interest. This, added to the requirement for endotracheal intubation and longer procedural and hospital stay times[4] has put its elective use to an end in most cath labs. The transthoracic echocardiography provides enough information for the decision-making process. Also, in selected cases informs of major complications like severe mitral regurgitation or aortic annulus rupture, the TEE can be used.

Q.: Vascular occlusion systems have variable, yet constant, rates of failure and complications. Do you think there are still indications for minimal access surgery? Where does your heart team stand regarding valvular accesses?

A.: I think there are no indications for minimal access surgery regarding the femoral access. Computed tomography or ultrasound-guided punctures are often used as well as percutaneous closures. Although the latter have some rate of failure, covered stent implantation from the contralateral femoral region would solve most vascular access problems. Femoral surgery is often spared for catastrophic situations only when the problem simply cannot be solved percutaneously. Therefore, from 2019 to this date, 32 failures (13%) have been reported from of a total of 239 cases regarding closures with the suture device that resolved after covered stent implantation from the contralateral femoral region. Also, only in 1 case (0.4%) emergency surgery was required. If possible, our option should always be the femoral access that, as I already said, has always been percutaneous. Elective minimal access surgery has only been used in other access routes different from the femoral one; in our own experience, it has been the subclavian access in patients with severe disease at the femoral iliac territory. Although the percutaneous approach has been described through this access route,[5] we are not as experienced with it since most TAVIs can be performed percutaneously via femoral access. Other access routes that require surgery are the transcarotid and the transaortic ones, but we don't have any experience at all here.

Q.: Regarding patients discharged after TAVI, what is the common practice at your center and what would you recommend?

A.: Ambulatory care patients without femoral complications or conduction disorders find themselves walking the next day. A transthoracic echocardiography is performed after 24-48 hours, and they are often discharged after 2 days. The causes that can delay hospital discharge are severe heart failure prior to TAVI, access site complications (whether homolateral or contralateral), the presence of fever, kidney failure, and conduction disorders. In the latter, delaying the hospital discharge is due to the decision on whether to implant a definitive pacemaker or keep the patient hospitalized while waiting for a definitive resolution of the possible intermittent disorders. A panel of experts has proposed 5 different algorithms depending on the type of conduction defect reported in baseline conditions and after the procedure.[6] The goal is to standardize both the indications for definitive pacemaker implantation and the monitorization time necessary for the decision-making process. Thus, the decision to implant a definitive pacemaker cannot be made within the first 24-hours in most patients. My recommendation on hospital discharge following TAVI is to simplify procedure and convalescence as much as possible and try hospital discharge after 48 hours. When the aforementioned complications occur, the right thing to do is wait until they are solved. The algorithms mentioned[6] are useful to make the decision, as soon as possible, on whether to implant a definitive pacemaker or not.

Q.: Finally, in your own opinion, what patients would be eligible for minimalist TAVI and when is it ill-advised?

A.: Although the Vancouver 3M[7] criteria are wide enough to include patients in the minimalist approach to TAVI I think it should only be eligible for patients scheduled for TAVI without severe heart failure with good femoral access, no kidney failure or respiratory failure or anemia. However, it would be ill-advised in hospitalized patients with heart failure and hemodynamic instability, depressed ejection fraction or who don't meet the aforementioned criteria. In patients with previous conduction disorders, the algorithms proposed by the panel of experts should be followed.[6] As I have already said, in the presence of complications, the minimal approach to TAVI strategy should be changed and hospital discharged delayed until the complication has resolved, and the patient has fully recovered. In this context, as Albert Einstein used to say: «everything should be made as simple as possible, but no simpler».

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CONFLICTS OF INTEREST

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Short and long-term prognosis of chronic kidney disease in patients undergoing primary angioplasty

Impacto pronóstico a corto y largo plazo de la insuficiencia renal en pacientes tratados con angioplastia primaria

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To the Editor,

Coronary artery disease due to sustained inflammation and the effects of calcification promoters is the leading cause of morbidity and mortality in patients with chronic kidney disease.[1,2] When seen on the optical coherence tomography, the atheromatous plaques of these patients show features of vulnerability.[3] The prevalence or kidney disease (KD) in patients with acute coronary syndrome is up to 30% and is an independent predictor of both ischemic and hemorrhagic adverse events.[1] However, the evidence available on the prognostic impact of KD in patients with ST-segment elevation acute myocardial infarction treated with a primary angioplasty is scarce.[4-8]

Our objective was to assess the long-term and in-hospital prognosis (5-year follow-up) of a single-center, retrospective cohort of patients who underwent a primary angioplasty between 2007 and 2014. We assessed the frequency of the composite endpoint of dead, stroke or non-fatal acute myocardial infarction and major bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5). It was based on the presence of KD defined as an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and taking the serum creatinine levels obtained immediately before the current admission as reference values.

The Student *t* test was used for mean comparison purposes and the chi-square test was used to compare proportions. The variables predictive of the composite endpoint with *P* values < .05 in the univariate analysis (age, sex, arterial hypertension, smoking, and previous ischemic heart disease) were included in a multivariate logistic regression analysis with likelihood-ratio test. Patients gave their verbal consent for the use of data derived from hospitalization and follow-up for teaching and scientific purposes.

A total of 826 out of 1622 primary angioplasties were included (51% without previous creatinine levels). A total of 21.8% had KD and follow-up was completed in 567 patients (222 were lost to follow-up). The baseline characteristics are shown on table 1 (how patients with KD actually had a higher risk profile and more comorbidities). Stent thrombosis was the leading cause of acute myocardial infarction (5% vs 1.1%; *P* = .01).

During the admission and the long-term follow-up, patients with KD more often showed the composite endpoint and a higher mortality rate, mainly cardiovascular. Also, KD was associated with the occurrence of major bleeding. Similarly, in the multivariate analysis, KD was a strong independent predictor of events in all the periods studied, especially in-hospital. Previous arterial hypertension and ischemic heart disease were also independent predictors of the composite endpoint (table 1 and figure 1).

In their last iteration, the European clinical practice guidelines on the management of coronary heart disease, both chronic and acute, have compared patients with KD to diabetic patients regarding their high cardiovascular risk. However, there are no solid recommendations on this regard since these patients have traditionally been excluded from most clinical trials in this field. In the primary angioplasty setting, KD affects 1 out of 5 patients,[4-8] with an up to 9 times higher in-hospital mortality rate and a 5 times higher 3-year mortality rate.[4] Different causes for this have been postulated: higher comorbidity, metabolic alterations, chronic inflammation, oxidative stress, and endothelial dysfunction as contributors to a greater spread, progression, and complexity of coronary artery disease. Also, the underuse of drugs that have proven capable of increasing survival after an acute myocardial infarction.[1,2] On the other hand, chronic kidney disease is one of the most powerful predictors of bleeding and a known risk factor of stent thrombosis (findings we also saw). This adds more complexity to the antithrombotic management of patients with KD though further research is still needed on this issue.[2]

In a practical way, our observations show that the identification of patients with estimated glomerular filtration rates < 60 mL/min based

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Table 1. Baseline characteristics, prognosis, and predictors of adverse events

Baseline characteristics					
		Total (N = 826)	**eGFR ≤ 60 mL/min (N = 180)**	**eGFR > 60 mL/min (N = 646)**	***P***
Age		71.3 ± 8.3	78.2 ± 9.5	62.0 ± 12.5	< .01
Feminine sex		21%	32.2%	17.8%	< .01
Arterial hypertension		60%	80%	54.6%	< .01
Diabetes mellitus		28.6%	31.7%	27.7%	.29
Dyslipidemia		43.5%	44.4%	43.2%	.76
Active smoker		39.8%	11.7%	47.7%	< .01
Atrial fibrillation		9%	18.2%	6.8%	.002
Previous IHD		11.6%	17.8%	9.9%	.004
Peripheral arteriopathy		8.5%	14.4%	6.8%	.001
Previous revascularization		13.6%	23.8%	10.8%	.007
Prognosis KD vs no KD					
		Total	**eGFR ≤ 60 mL/min/1.73 m²**	**eGFR > 60 mL/min/1.73 m²**	***P***
Composite endpoint[a]	Admission	6%	13.9%	3.9%	< .005
	1 year	14.5%	23%	11.9%	.005
	3 years	23%	33.3%	20.5%	.007
	5 years	32.1%	47.8%	28.9%	.001
Overall mortality rate (CV)	Admission	4.5% (3.9%)	10.2% (8.33%)	3% (2.63%)	< .0001 (.05)
	1 year	6% (1.4%)	11.7% (3.5%)	4.4% (0.8%)	.007 (.05)
	3 years	9% (2.1%)	17.4% (6.6%)	7.3% (1.2%)	.004 (.004)
	5 years	23% (5%)	41.8% (15.8%)	19.1% (2.6%)	.001 (.01)
BARC type 3 or 5 bleeding	Admission	3.8%	8.9%	2.5%	< .001
Multivariate analysis[b]					
Variable		**Admission**	**1 year**	**3 years**	**5 years**
Arterial hypertension		1.9 (1.1-3.5; *P* = .02)	1.7 (0.9-3.1; *P* = .06)	1.8 (1.1-3; *P* = .02)	1.9 (1.2-3; *P* = .09)
Previous IHD		3.9 (2.02-7.5; *P* < .001)	3.5 (1.7-7.1; *P* < .001)	2.7 (1.4-5.4; *P* = .03)	1.7 (0.7-3.7; *P* = .18)
KD		5.9 (2.7-12.6; *P* < .001)	1.95 (1.1-3.6; *P* = .03)	2.04 (1.2-3.5; *P* = .01)	2.2 (1.3-3.7; *P* = .03)

BARC, Bleeding Academic Research Consortium; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; KD, kidney disease.
[a] Death, stroke or non-fatal acute myocardial infarction.
[b] Multivariate analysis (odds ratio with 95% confidence interval and Cox model *P* values.

on the last known serum creatinine levels is an easy and effective approach to their risk of poor progression during admission, which extends up to 5 years. This strategy would allow us to take strict precautions like nephroprotection, intensive control of other cardiovascular risk factors, close follow-up, and individual treatments.

As one of the limitations we should mention that 51% of the patients were excluded because their previous creatinine levels were not available, which may have been a selection bias.

We hope future studies will shed light on the optimal treatment for a subgroup of patients on which there are still too many shadows of evidence.

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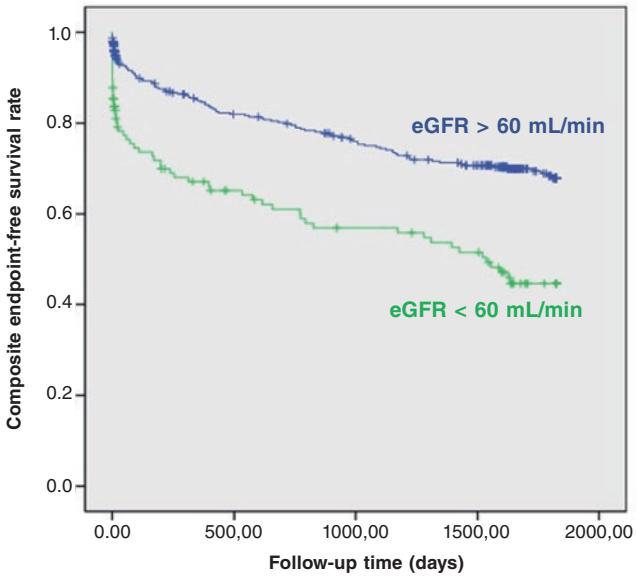

		Admission	1 year	3 years	5 years
GFR < 60 mL/min	At risk	180	131	99	63
	Events	25	30	33	30
GFR > 60 mL/min	At risk	646	436	380	301
	Events	25	52	78	87
	Log-rank (Mantel-Cox)	< .001	.001	.001	.001

Figure 1. Survival curves after 5 years based on the presence or absence of kidney disease. eGFR, estimated glomerular filtration rate.

AUTHORS' CONTRIBUTIONS

The text has been prepared and revised with the participation of all signatory authors.

CONFLICTS OF INTEREST

None.

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Safety and efficacy of the transradial access when performing percutaneous coronary interventions to treat chronic total coronary occlusions

Eficacia y seguridad del acceso transradial en el intervencionismo coronario percutáneo de oclusiones totales crónicas

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To the Editor,

Transradial access has been popularized in percutaneous coronary interventions (PCI). However, the percutaneous management of chronic total coronary occlusions (CTO) is still predominantly via transfemoral access. This study assessed the efficacy and safety profile of a transradial access strategy in a PCI on a CTO and its impact on hospital stay.

A total of 237 consecutive patients treated with PCI on their CTO were included in a single-center registry that compared the results of 2 vascular access strategies used over 2 consecutive periods of time: transfemoral between May 2013 and October 2018, and transradial from November 2018. A total of 40 patients were excluded from the analysis of the transfemoral strategy via transradial access and 9 were excluded from the transradial strategy via transfemoral or mixed radial-femoral access (figure 1). The *Hospital Universitario de Salamanca* clinical research ethics committee approved the study protocol and obtained the patients' informed consent.

The patients who not have any PCI related complications remained in observation at the cardiology day hospital for, at least, 6 to 8 hours. Those who remained asymptomatic and without alterations on their ECGs were discharged from the hospital the same day with outpatient control of their renal function between 48 and 72 hours after the procedure.

In patients hospitalized with acute coronary syndrome, the PCI on the CTO was delayed after completing target and other lesion revascularization with revascularization criteria. In patients treated with multiple catheterization attempts on the CTO, the characteristics of the latest procedure were analyzed. The advanced techniques used were rotablation, re-entry devices, and the CART and CART-REVERSE techniques.

Technical success was defined as the successful recanalization of the CTO with residual stenosis < 50% and TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow. Procedural technical success was defined as the lack of in-hospital mayor adverse cardiovascular events: overall mortality, stroke, acute myocardial infarction, unstable angina or new revascularization. Periprocedural complications included coronary dissections and perforations, pericardial effusion, tamponade, and cardiogenic shock. In-hospital complications included contrast-induced nephropathy, vascular complications, and in-hospital mayor adverse cardiovascular events according to the guidelines. Also, mayor adverse cardiovascular events at the 30-day follow-up were registered.

To adjust the rate of technical success and total in-hospital complications due to the baseline and procedural differences seen between the patients of both strategies, a multivariate binary logistic regression analysis was conducted including variables with *P* values < .10 in the univariate analysis.

The results of 150 patients treated with PCI on a CTO via transfemoral access were compared to those of 38 patients treated via transradial access. Table 1 shows the patients' baseline characteristics, procedural and event-driven data at the follow-up. No significant differences were seen on the baseline characteristic including the score obtained in the J-Chronic Total Occlusion scale.

The PCI on the CTO was successful in 162 patients (86.2%) from the overall sample, and in 50 patients (84.7%) with J-Chronic Total Occlusion scale scores > 2 without differences between both strategies. Transfemoral access was the most commonly used bilateral vascular access and large-caliber guide catheters and a larger volume of contrast were used without any other differences reported in relation to the intervention.

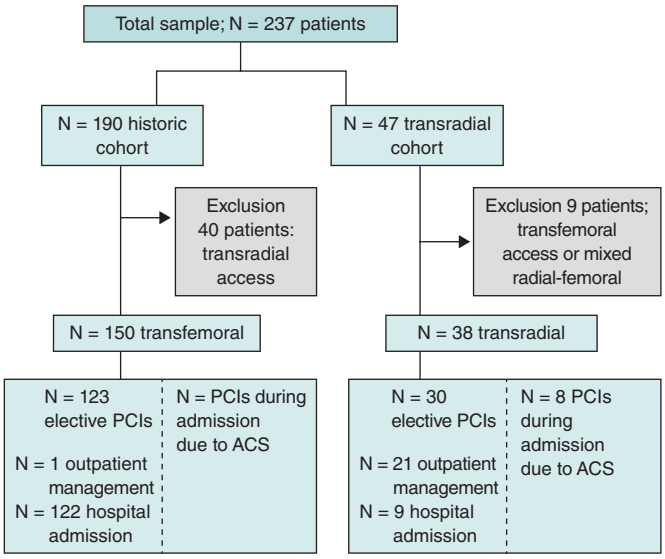

Figure 1. Flow chart of the patients included in the study. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

The percentage of outpatient procedures performed was higher in the transradial strategy (up to 70% of the procedures performed via transradial access in hospitalizations outside the non-acute coronary syndrome setting (figure 2). Consequently, hospital stay was shorter in patients treated via transradial access. No differences were seen in periprocedural or in-hospital complications or in the 30-day follow-up.

In the multivariate analysis, previous surgical revascularizations (odds ratio [OR] = 0.12; 95% confidence interval [95%CI], 0.02-0.87; *P* = .036) were the only independent predictive factor associated with lower chances of technical success in the PCI on the CTO. The past medical history of diabetes (OR = 5.71; 95%CI, 1.65-17.79; *P* = .006), surgical revascularization (OR = 3.96; 95%CI, 1.1513.66; *P* = .029) or previous failed PCI on the CTO (OR = 4.76; 95%CI, 1.46-15.51; *P* = .018) were independent predictors of a higher risk of total in-hospital complications. No differences were seen in the chances of technical success or risk of complications based on the access route.

Recent studies have shown that transradial access in PCIs performed on CTOs reduces bleeding and vascular complications. Also, that efficacy is similar to the one reached via transfemoral access[1]. However, in most of these studies, transradial access was spared for the management of less complex CTOs.

In our study, the PCIs performed on CTOs via transradial access were safe even in outpatients without episodes of contrast-induced nephropathy or late cardiac tamponade. None of the study patients developed late tamponade beyond the first 6 to 8 hours after the procedure. Similarly, transradial access reached a high rate of success comparable to the one reached via transfemoral access even in more complex lesions and with significantly shorter hospital stays. Outpatient treatment was possible in over two thirds of the patients with scheduled procedures, which is consistent with the 63.6% reported by a recent study on complex lesions where CTOs were < 5% of the total lesions.[2]

The impact of a transradial access strategy on hospital stay after a PCI on a CTO has not been studied yet. To this day, the factors associated with outpatient management after performing a PCI on a CTO have only been analyzed in 1 registry.[3] According to this registry, same-day hospital discharges were possible in 41.6% of

Table 1. Baseline characteristics of the patients, and procedural and event characteristics at the follow-up

	Transfemoral strategy (N = 150)	Transradial strategy (N = 38)	Total (N = 188)	*P*
Baseline clinical and angiographic characteristics				
Age (years)	66.8 ± 11.5	64.2 ± 11.1	66.3 ± 11.4	.209
Sex, male (N, %)	131 (87.3)	29 (76.3)	160 (85.1)	.088
Arterial hypertension (N, %)	97 (68.3)	29 (76.3)	126 (70)	.339
Diabetes mellitus (N, %)	55 (36.7)	14 (36.8)	69 (36.7)	.984
Dyslipidemia (N, %)	97 (64.7)	25 (65.8)	122 (64.9)	.387
Chronic kidney disease (N, %)	20 (13.3)	5 (13.2)	25 (13.3)	.501
Peripheral arteriopathy (N, %)	26 (18.8)	3 (8.3)	29 (16.7)	.207
LVEF (%)	51.1 ± 13.1	54.1 ± 10.4	51.7 ± 12.7	.139
Previous coronary surgery (N, %)	19 (12.7)	2 (5.6)	21 (11.3)	.377
Anatomical SYNTAX score	23.1 ± 11.5	22.3 ± 10.6	22.8 ± 11.1	.744
> 1 CTO	25 (16.7)	8 (21.1)	33 (17.6)	.526
Location of the CTO (N, %)				.051
LAD	48 (32)	6 (15.8)	54 (28.7)	
RCA	87 (58)	24 (63.2)	111 (59)	
LCX	15 (10)	8 (21.1)	23 (12.2)	
Previous failed PCI on CTO (N, %)	18 (12)	4 (10.5)	22 (11.7)	.801
J-CTO scale	2.7 ± 0.9	2.5 ± 1.1	2.6 ± 1.0	.466
J-CTO scale > 2 (N, %)	41 (54.7)	18 (64.3)	59 (57.3)	.380
Characteristics of the angioplasty procedure on the CTO				
Contralateral injection (N, %)	129 (86)	27 (71.1)	156 (83)	.029
CTO access route (N, %)				
Antegrade	133 (73.5)	30 (63.8)	163 (71.5)	.142
Retrograde	17 (9.4)	3 (6.4)	20 (8.8)	
Hybrid	31 (17.1)	14 (29.8)	45 (19.7)	
Antegrade guide catheter (Fr)	6.3 ± 0.5	6.0 ± 0.1	6.3 ± 0.5	< .001
Retrograde guide catheter (Fr)	6.1 ± 0.5	5.9 ± 0.3	6.1 ± 0.4	.002
IVUS (N, %)	8 (6.2)	1 (2.7)	9 (5.4)	.685
PCI-CTO advanced techniques (N, %)	36 (24)	10 (26.3)	46 (24.5)	.767
Drug-eluting stent (N, %)	128 (97.7)	33 (100)	161 (98.2)	.380
Stent total length (mm)	83.5 ± 36.5	82.5 ± 33.7	83.3 ± 35.8	.884
Contrast volume (mL)	396.6 ± 229.7	280.9 ± 146.4	373.6 ± 220.3	< .001
Fluoroscopy time (min)	47.0 ± 45.1	43.8 ± 31.9	46.4 ± 42.9	.711
Radiation–Kerma (Gy)	3.5 ± 2.9	3.4 ± 2.9	3.5 ± 2.9	.919
Technical success (N, %)	129 (86.6)	33 (86.8)	162 (86.6)	.893
Procedural success (N, %)	107 (71.3)	29 (76.3)	136 (72.3)	.540
Outpatient PCI (N, %)	1 (0.7)	21 (55.3)	22 (11.7)	< .001
Outpatient elective PCI (N, %)	1 (0.8)	21 (70)	22 (14.4)	< .001

(Continues)

Table 1. Baseline characteristics of the patients, and procedural and event characteristics at the follow-up *(continued)*

	Transfemoral strategy (N = 150)	Transradial strategy (N = 38)	Total (N = 188)	*P*
Hospital stay (days)	3.4 ± 0.4	1.4 ± 0.3	2.0 ± 3.1	< .001
Periprocedural complications and events at the follow-up				
Total in-hospital complications (N, %)	23 (15.3)	5 (13.2)	28 (14.9)	.737
Periprocedural complications (N, %)				
Coronary perforations	4 (2.7)	2 (5.3)	6 (3.2)	.416
Coronary dissections	1 (1.6)	1 (2.6)	2 (1.1)	.364
Cardiac tamponade	1 (1.6)	2 (6.5)	3 (3.3)	.262
Cardiogenic shock	5 (3.3)	0	5 (2.7)	.585
In-hospital complications (N, %)				
Postprocedural AMI	5 (3.3)	1 (2.6)	6 (3.2)	.767
Stroke	1 (0.7)	0	1 (0.5)	.599
Contrast-induced nephropathy	2 (1.3)	0	2 (1.1)	.456
Vascular complications:	9 (6.0)	0	9 (4.8)	.122
Minor (N, %)	4 (2.7)	0	4 (2.1)	.309
Major (N, %)	5 (3.3)	0	5 (2.7)	.254
Cardiac surgery	1 (0.7)	0	1 (0.5)	.599
Pericardial effusion	4 (2.7)	1 (2.6)	5 (2.7)	.707
In-hospital mortality	0	0	0	ND
In-hospital MACE	6 (4)	1 (2.6)	7 (3.7)	.691
Events at the 30-day follow-up				.292
Early stent thrombosis (N, %)	0	1 (2.6)	1 (0.5)	
Unstable angina (N, %)	1 (0.7)	0	1 (0.5)	
MACE at the 30-day follow-up	7 (4.7)	2 (5.3)	9 (4.8)	.311

AMI, acute myocardial infarction; CTO, chronic total coronary occlusion; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NA, not available; PCI, percutaneous coronary intervention; RCA, right coronary artery.

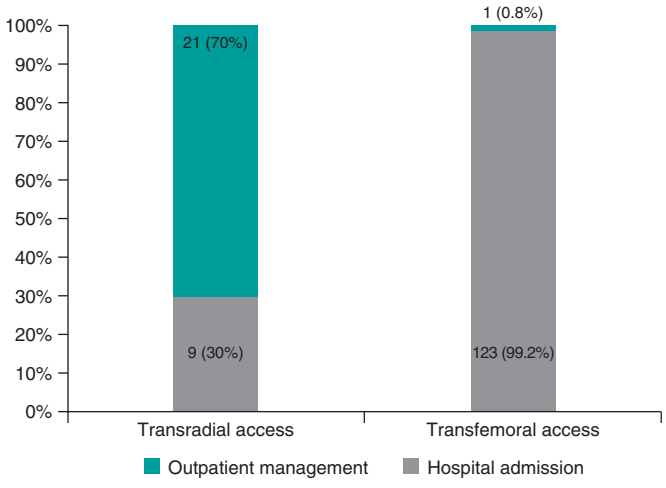

Figure 2. Outpatient management in select patients treated with percutaneous coronary intervention on chronic total coronary occlusions based on the vascular access used.

the patients probably thanks to the use of transfemoral access in most of the cases (90%).

In conclusion, our study provides additional evidence in favor of using transradial access to perform PCIs on CTOs as a safe and effective option to reduce the number and length of hospital stays, which may improve the management of health resources significantly.

FUNDING

No funding was received for this work.

AUTHORS' CONTRIBUTIONS

B. Trejo-Velasco: Design of the study. Collection of information. Statistical analysis and writing of the original manuscript. Graphic design and tables. A. Diego-Nieto: Conception original idea and design of the study. Methodology and statistical analysis. Original manuscript co-writing, manuscript review and correction, and

project supervision. J. C. Núñez: Data collection. Methodology and research. Manuscript review. J. Herrero-Garibi: Data collection. Methodology and research. Manuscript review. I. Cruz-González: Design of the study. Data collection. Methodology and research. Review of the manuscript and supervision of the project. J. Martín-Moreiras: Conception, original idea and design of the study. Methodology and data collection. Revision and correction of the manuscript and supervision of the project.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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Prevention of coronary occlusions during transcatheter aortic valve-in-valve implantation using the BASILICA technique

Prevención de la oclusión coronaria en el implante de prótesis aórtica transcatéter valve-in-valve mediante técnica BASILICA

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To the Editor,

Coronary occlusion is a more common complication after transcatheter aortic valve-in-valve implantation than after transcatheter aortic valve implantation over the native valve. It is due to the displacement of the veil of the surgical valve prior to transcatheter aortic valve implantation until occluding the coronary ostium.[1] The risk is higher with surgical prostheses without stent and with those with veils mounted outside the stent. It also depends on the height of coronary ostia and width of sinuses.[2]

Coronary arteries can be protected by advancing a guidewire or even a stent inside the coronary artery at risk, which creates some sort of chimney to keep the ostium open[3] with unpredictable results especially in the long-term.

Recently, the BASILICA technique (Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction) has been described to avoid coronary occlusions. It consists of lacerating the veil of the surgical prosthesis facing the ostium at risk with an electrified guidewire so that it opens when implanting the new prosthesis while leaving the ostium uncovered.[4]

This is the case of an 89-year-old woman—carrier of a 19 mm Mitroflow bioprosthesis (Sorin Group Inc., Mitroflow Division; Vancouver, Canada) due to severe aortic stenosis since 2010—who was admitted to our center due to heart failure. The echocardiogram confirmed the presence of severe aortic stenosis again due to valve degeneration. The internal area of the aortic annulus according to the coronary computed tomography angiography performed was 230 cm^2 with a 54 mm-perimeter. Coronary arteries originated at the annulus 4 mm to the left and 9 mm to the right and with a 3.5 mm and 4.7 mm distance from the valve virtually implanted to the left and right ostia, respectively.

Given the risk of occlusion of the left coronary ostium, it was decided to approach this case using the valve-in-valve technique with a 23 mm Evolut PRO valve (Medtronic, Minneapolis, Minnesota, United States) using the BASILICA technique with fluoroscopy and transesophageal echocardiography guidance. Thus, via left femoral artery a 23 mm snare was advanced through a 6-Fr multipurpose catheter that crossed the bioprosthesis and allocated in the left ventricular outflow tract. Through this same artery a 0.18 inches pre-shaped guidewire was inserted, in parallel, that remained on the left ventricular apex to stabilize the position of the snare as shown on figure 1. A 14-Fr introducer sheath was used via right femoral artery (after valve implantation) to advance the system to perforate and then tear the veil. This system consisted of a 6-Fr AL 3 guide catheter with a 5-Fr 125 cm internal mammary diagnostic catheter and a 150 cm FINECROSS microcatheter (Terumo, Japan)

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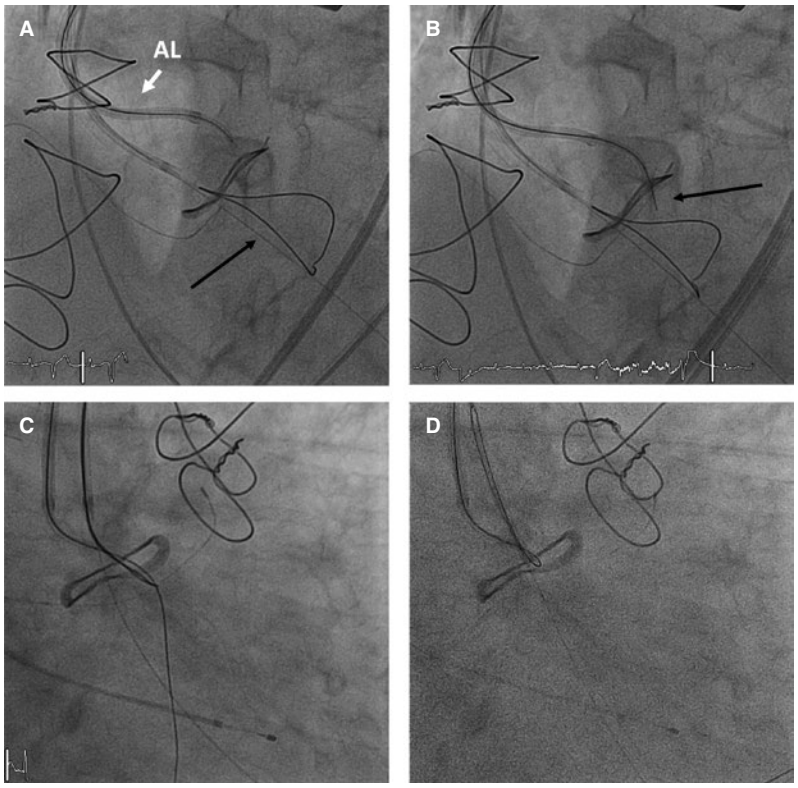

Figure 1. A: AL 3 guide catheter at the base of the left coronary veil of the Mitroflow bioprosthesis with a slightly protruding internal mammary diagnostic catheter. The radiopaque tip of the FINECROSS microcatheter and the Astato guidewire inside the internal mammary catheter can be seen. Snare positioned in the left ventricular outflow tract (arrow). **B:** Astato guidewire already in place in the left ventricle (arrow). **C:** guidrewire captured with the snare. **D:** Astato guidewire inserted into the multipurpose catheter with complete circuit.

with an ASAHI Astato guidewire. The whole process used a telescopic method.

After checking the exact position of the system before perforation on the frontal and lateral projections, the Astato guidewire external border (Asahi, Aichi, Japan) was connected to a 50-Watt electric scalpel. The guidewire—previously peeled with a scalpel blade—was advanced to the left ventricular outflow tract (figure 1). Afterwards, the guidewire was captured using the snare and the circuit was closed. Afterwards, the internal mammary catheter and the microcatheter were retrieved exposing the body of the Astato guidewire to be able to peel a short segment of it to later bend it in V-shape. This V-shape was advanced until the base of the veil that needed to be torn. Then, a high-support guidewire was advanced towards the LV by the 14-Fr introducer via right femoral artery, parallel to the snare, with the prosthesis ready to be implanted. Then the Astato guidewire was connected to the electrical scalpel, and a 70-Watt current was applied. Afterwards, the 2 borders of the circuit were removed to tear the veil.

In our case, after capturing the guidewire with the snare and while the V-shape was being prepared, the patient experienced severe hypotension with both aortic and mitral regurgitation, both severe. Since the transesophageal echocardiography confirmed that the patient was unresponsive to inotropic drugs, external cardiac massage was required that triggered the use of the BASILICA technique and valve implantation under cardiac massage (figure 2). After the implant, the patient stabilized. Compromise of coronary ostium was discarded and a significant aortic gradient was seen (mean gradient, 53 mmHg). Then, it was decided to proceed with postdilatation and fracture the prosthesis with a 20 mm noncompliant ATLAS balloon (BARD Medical, United States) with disappearance of residual gradient (residual 7 mmHg).

Disease progression was good, and the patient was discharged from the hospital after 9 days and following the implantation of a pacemaker due to complete AV block without other complications. She gave oral consent for the publication of the case.

The BASILICA technique is an effective alternative to avoid coronary occlusions and valve-in-valve procedures with high risk of occlusion. However, it is a demanding complex procedure with complications, that requires prior training. The snare can interfere with the mitral valve and cause regurgitation. Also, the tension of the circuit can cause severe aortic regurgitation with hemodynamic collapse.

FUNDING

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AUTHORS' CONTRIBUTIONS

A. Albarrán González-Trevilla participated in the drafting and correction of the manuscript and in the performance of the procedure. J. García Tejada participated in the drafting of the manuscript. F. Sarnago Cebada participated in the correction of the manuscript. J. A. García Robles provided the echocardiogram images and participated in the procedure. M. Velázquez Martín participated in the correction of the manuscript. D. Dvir participated in the correction of the manuscript and the performance of the procedure.

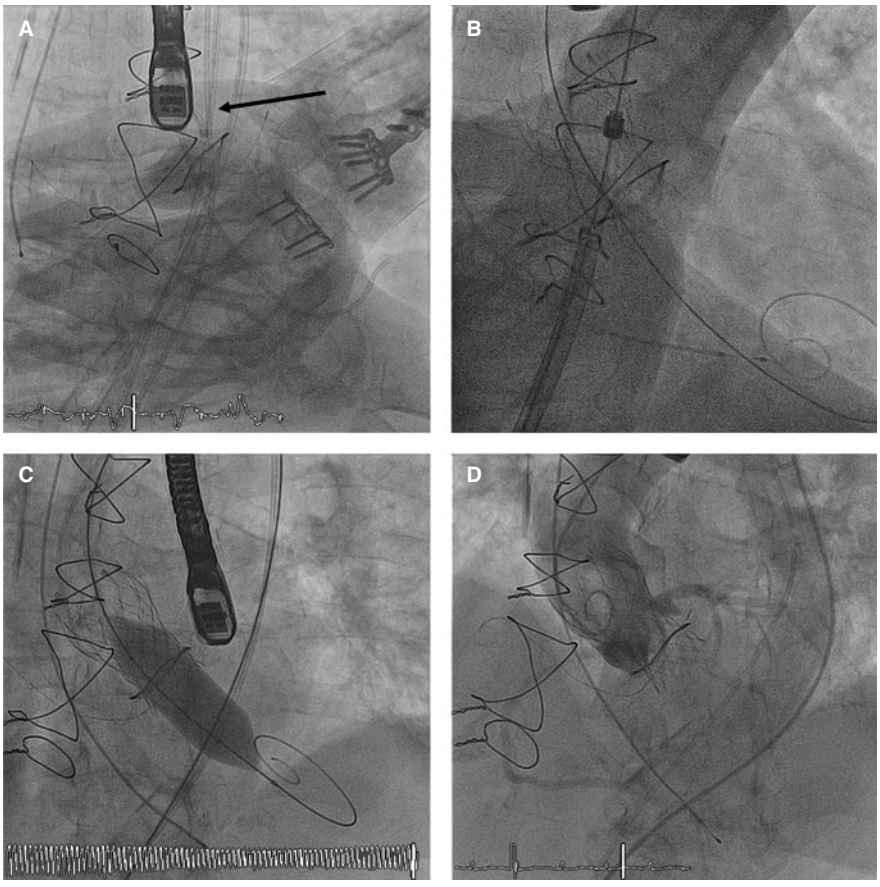

Figure 2. **A:** tear of the veil (BASILICA technique) under cardiac massage. The arrow points at the 2 catheters facing each other with the V-shaped Astato guidewire. **B:** Evolut PRO valve implantation under cardiac massage. **C:** dilatation with ATLAS balloon for fracture purposes. **D:** final aortography.

CONFLICTS OF INTEREST

Nothing to declare.

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Esophagopleural fistula treated with muscular ventricular septal defect occluder

Fístula esofagopleural tratada con un dispositivo de cierre percutáneo de comunicación interventricular muscular

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To the Editor,

Esophageal-pleural fistulas are a rare complication of thoracic surgery. They may occur as the direct result of trauma during surgery or use of a transesophageal device. The management of esophageal-pleural fistulas can be difficult, and they rarely heal spontaneously. Conservative management of esophageal-pleural fistulas are associated with high mortality rates. The traditional treatment of symptomatic patients is surgery. However, this type of surgery has high morbidity and mortality rates; for this reason, many patients are not eligible for surgery. The endoscopic treatment options to repair esophageal fistulas include the injection of glue, covered stents, and endoscopic suture or clipping. After treatment failure, we considered the use of an emerging therapeutic technique as an alternative treatment. In this context, we present a case of a iatrogenic esophageal fistula treated with an Amplazer device.

This is the case of a 72-year-old woman, former smoker with a past medical history of hypertension, chronic atrial fibrillation, and rheumatic mixed mitral valve disease who was admitted due to acute coronary syndrome. A thrombotic occlusion of the left circumflex artery was successfully treated with drug-eluting stent implantation. During her hospital stay, the patient developed bilateral arterial embolism in both lower limbs that was treated with an embolectomy. The transesophageal echocardiography performed confirmed the presence of severe mitral regurgitation, moderate mitral stenosis, left ventricular ejection fraction of 38%, pulmonary artery systolic pressure of 60 mmHg, and left atrial appendage thrombus. The patient underwent mitral valve replacement with a 25 mm ATS heart valve and transesophageal echocardiography guided surgical left atrial appendage closure. After the surgery, the patient developed mediastinitis, recurrent pleural effusions, and an empyema. The contrast computed tomography scan performed revealed the presence of an esophageal perforation that was confirmed by the endoscopy (figure 1A-C). Esophageal surgery was discarded and the endoscopic treatment of the perforation with hemoclips and a covered metal stent was attempted twice; however, both devices migrated to the stomach and had to be removed. A number of hemoclips migrated through the fistula tract into the pleura and were left *in situ*. A gastrostomy was performed to facilitate artificial enteral nutrition. After multiple infections and a 4-month stay at the intensive care unit, we were requested to close

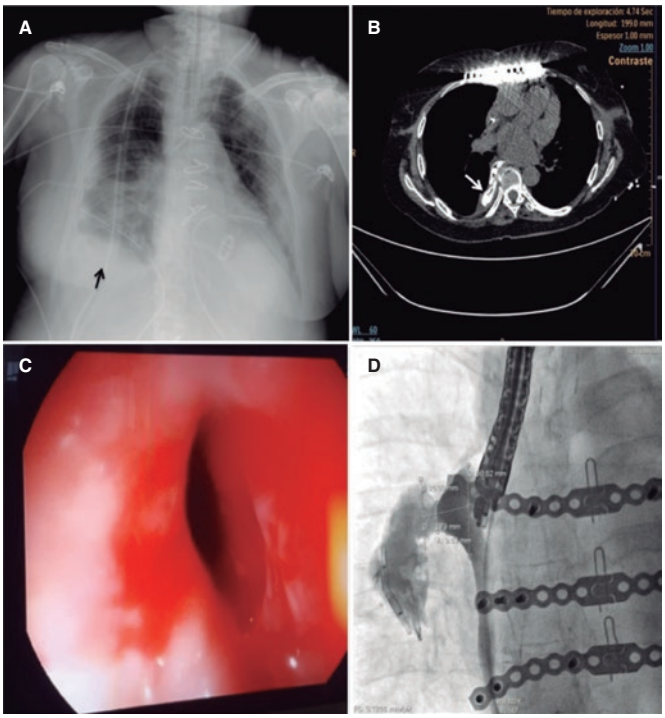

Figure 1. A: X-Ray image showing right pleural effusion (arrow). **B:** computed tomography scan with oral contrast, the axial section shows extravasation of contrast to the pleural space (white arrow). **C:** endoscopic image of the perforation after transesophageal echocardiography. **D:** fluoroscopy with oral contrast showing the morphology and measurements of the esophageal-pleural fistula.

the perforation with an occluder device. To establish the size of the fistula, we injected a fluoroscopy guided contrast medium through the fistula and obtained a perpendicular view that correctly exposed the neck of the fistula for device selection purposes (figure 1D). The implantation was performed in the catheterization laboratory under general anesthesia with endoscopic and fluoroscopic guidance (figure 2A,F). A curved hydrophilic guidewire was introduced through the

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Online: 05-11-2020.

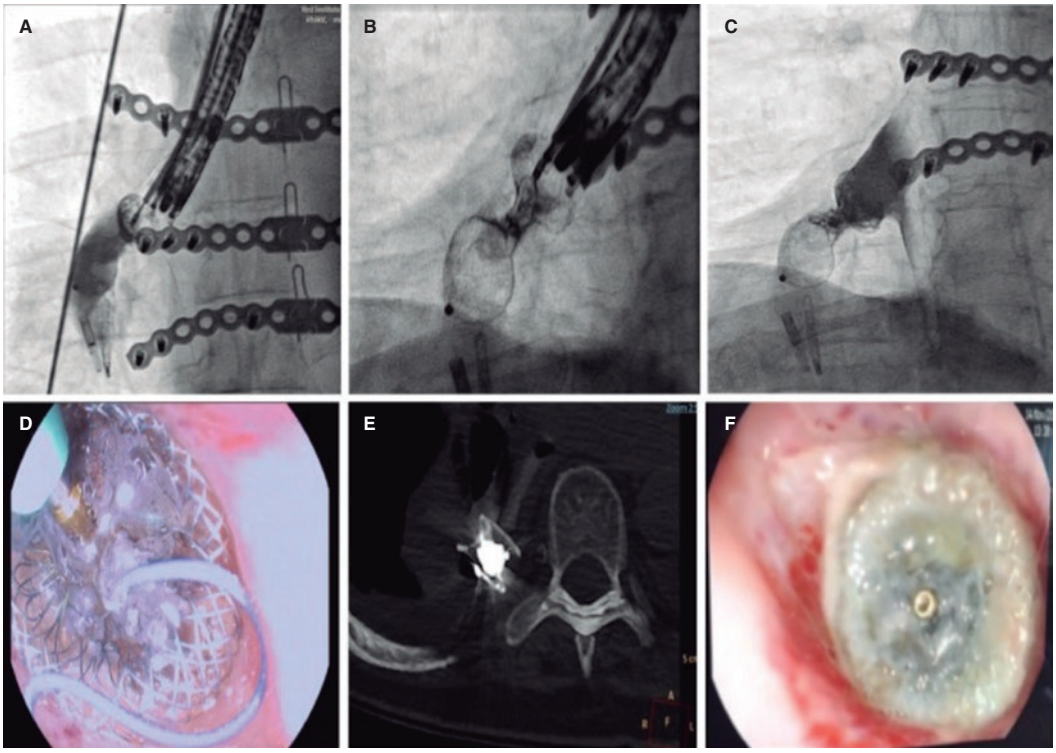

Figure 2. **A:** fluoroscopic projection showing the release of a 14 mm Amplatzer muscular VSD occluder. **B:** administration of the Onyx Liquid inside the neck of the Amplatzer device using a microcatheter (note the device neck turned radiolucent). **C:** contrast injection into the esophagus confirming the immediate sealing of the device. **D:** endoscopic view of the microcatheter during the injection of the embolic sealing liquid. **E:** computed tomography scan showing the device with an embolic sealing agent inside. **F:** endoscopic image of the device after 1-month showing partial endothelization.

endoscope lumen to cross the fistula. Since the endoscope lumen was 4.2 mm and there was no space for further material inside, the endoscopic probe was retrieved followed by its parallel insertion to guide the procedure. A GLIDECATH catheter (Terumo Medical Corporation, NJ, United States) was advanced over the guidewire. A high support guidewire was introduced and a 7-Fr Destination Guiding Sheath (Terumo Medical Corporation, NJ, United States) was advanced. Contrast medium was injected to locate the fistula. A 14 mm Amplatzer Muscular VSD Occluder (Abbott, Illinois, United States) was advanced. The distal and proximal discs were released and a 0.010 in guidewire (Mirage microguidewire, Medtronic, Minnesota, United States) was used to penetrate the device proximal disc. Afterwards, a Marathon microcatheter (Medtronic, Minnesota, United States) was inserted and placed inside the neck of the device to infuse the Onyx liquid embolic system, a radiopaque copolymer that seals in 5 minutes. The administration of contrast confirmed the sealing and the successful final result. After the procedure, no recurrences of pleural effusion or infections were seen. In the subsequent endoscopies and CT scans performed (figure 2D,E), the effective sealing of the esophagus was confirmed and normal feeding was reinstated 1 month later. The 9-month clinical follow-up confirmed the patient was doing well with restored enteral feeding. Family signed a specific informed consent for this procedure.

Endoscopic fistula closure with cardiovascular devices has been tried mainly for the management of bronchopleural fistulas with good clinical outcomes. The evidence for using these devices to close esophageal-pleural fistulas is scarce. To this day, only 3 case reports have been published. The first used an Amplatzer vascular plug, coils, and histoacryl glue. In this case additional coil packing was required for definitive closure.[1] The second case used an Amplatzer atrial septal occluder without a sealing agent. The procedure was unsuccessful due to device migration.[2] In the third case, an Amplatzer ventricular septal occluder was used together with a liquid copolymer leading to an immediate sealing and good clinical outcomes.[3]

Establishing the correct size of the fistula is a critical step, and the techniques used to do this have not been previously described in the medical literature. We think that the use of fluoroscopic measurement using contrast media is a beneficial option that allows the correct selection of the device and a real-time strategy. If the visualization of the defect is suboptimal, a sizing balloon often used to size cardiac defects may be used.

The use of the Onyx sealing agent proved to be one of the key elements that led to therapeutic success. The complete isolation of the pleural space is vital to prevent recurrent infections.[3]

FUNDING

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AUTHORS' CONTRIBUTIONS

R. Vera-Urquiza: performance of the procedure, Critical review of data, drafting the manuscript. J. M. Esteban López-Jamar: performs the procedure, review the manuscript. L. Nombela-Franco: performs the procedure, review the manuscript. M. Vázquez

Romero: performs the procedure, review the manuscript. C. Espejo: clinical follow-up, review the manuscript. P. Jiménez-Quevedo: plans and performs the procedure, Critical review of data, drafting the manuscript.

CONFLICTS OF INTEREST

L. Nombela-Franco is a proctor for Abbott and has participated in and received speaking fees from Edwards Lifesciences. The rest of authors have no conflicts of interest.

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Clinical case

Spontaneous left main coronary artery dissection complicated with vasospasm

Disección coronaria espontánea en el tronco común izquierdo complicada con vasoespasmo

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CASE PRESENTATION

We present the case of a 36-year-old female (informed consent obtained) with a past medical history of childbirth 2 months before being admitted to the emergency room with signs of chest pain with irradiation to her left arm associated with diaphoresis and dyspnea with 1-hour evolution. The electrocardiogram (ECG) performed did not show any alterations, but the blood test confirmed the presence of increased myocardial necrosis markers (troponin I, 1.9 ng/mL; normal < 0.045 ng/mL). The serial ECGs performed revealed progressive alterations, namely T-wave inversion in leads I, aVL, and V_1-V_3. The transthoracic echocardiogram showed good systolic left ventricular function without wall motion alterations. The patient underwent a coronary angiography that revealed an image suggestive of intramural hematoma conditioning a diffuse stenosis of the left main (LMCA) and proximal left anterior descending (LAD) coronary arteries (video 1 of the supplementary data; figure 1A). Due to the patient's high-risk coronary anatomy, it was decided to repeat the coronary angiography 8 days later. However, after cannulating the LMCA (6-Fr JL 3.5), a sudden reduction of the distal LMCA and proximal LAD flow was seen (probable vasospasm) (video 2 of the supplementary data; figure 1B). Consequently, the guidewire was crossed to the distal LAD. The intravascular ultrasound (IVUS) performed on the lesion revealed the presence of an extensive hyperechogenic and heterogeneous area in the tunica media (after the external elastic lamina) with a crescent shape and, in some points, a circumferential shape. This may be consistent with the presence of an intramural hematoma (video 3 of the supplementary data; figure 1C). During the procedure, the presence of a severe vasospasm with flow reduction to the LAD (Thrombolysis in Myocardial Infarction flow grade 1/2) associated with clinical instability—thoracic pain, hypotension- and anterior ST-segment elevation (video 4 of the supplementary data; figure 1D)—was observed. It slowly resolved with the administration of intracoronary nitrates (video 5 of the supplementary data; figure 1E).

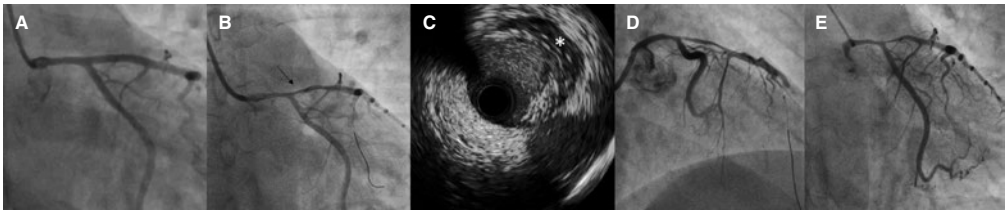

Figure 1. A: diffuse stenosis of the caliber of the left main (LMCA) (50%) and proximal left anterior descending (LAD) (30%) coronary arteries suggestive of the presence of an intramural hematoma. **B:** coronary angiography reassessment (8 days later) showing additional reduction of the distal LMCA and ostial LAD diameters (arrow) associated with a decreased distal flow after crossing the guidewire to the distal LAD. **C:** intravascular ultrasound (IVUS) imaging shows the presence of an intramural hematoma (asterisk). **D:** slow flow (Thrombolysis in Myocardial Infarction flow grade 1) after IVUS imaging due to severe vasospasm. **E:** slow resolution of the vasospasm after the administration of intracoronary nitrates.

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AUTHORS' CONTRIBUTIONS

C. Costa Oliveira was responsible for the analysis of the clinical case and the writing of the article. C. Galvão Braga was the responsible for patient coronary intervention and for revising the article. C. Quina, J.Costa and J. Marques participate in the case resolution and were also responsible for revising the article.

CONFLICTS OF INTEREST

Nothing to declare.

SUPPLEMENTARY DATA

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Spontaneous left main coronary artery dissection complicated with vasospasm. How would I approach it?

Disección coronaria espontánea en el tronco común izquierdo complicada con vasoespasmo. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

Several cases have been published in the medical literature on peripartum spontaneous coronary artery dissection. Its pathophysiology largely remains unknown, although in a significant percentage of cases fibromuscular dysplasia seems to play some sort of role.[1]

We present the case of a 36-year-old woman with spontaneous coronary artery dissection of left main coronary artery (LMCA) and left anterior descending coronary artery (LAD) 2 months after delivery. The patient shows clinical signs of thoracic pain and dyspnea with 1-hour of evolution, T-wave inversion on the electrocardiogram, and elevated cardiac enzyme levels. She remains hemodynamically stable without compromise to the left ventricular function. The coronary angiography performed revealed a suspicious image of diffuse reduction of the blood lumen area on the LMCA and LAD. At an early moment, conservative treatment was administered.

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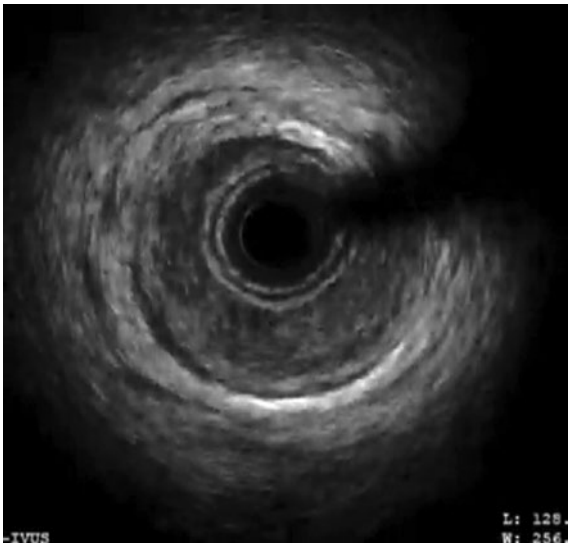

Figure 1. Intravascular ultrasound in the proximal anterior descending coronary artery. Image of a large intramural hematoma in the coronary artery compromising almost the entire vessel lumen.

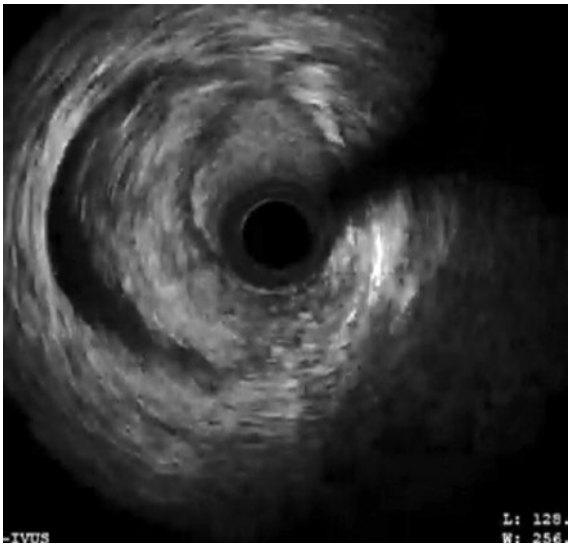

Figure 2. Image of coronary dissection in the distal portion of the left main coronary artery from 6 to 11 hours.

In my opinion, the early treatment was appropriate since, according to the largest series published to this date—Canadian[2]—the in-hospital prognosis is often good and only 3.3% of the patients on conservative treatment required revascularization. This has been confirmed in a study that assessed the infarction size on a cardiac magnetic resonance imaging in patients with spontaneous coronary artery dissection.[3] Our experience is consistent with this study and in patients with hemodynamic stability conservative treatment was prescribed.

Medical therapy has not been clearly established, but since the presence of intraluminal thrombi is scarce in patients who undergo an intravascular ultrasound (IVUS), treatment with acetylsalicylic acid seems to be enough. In the case studied I only miss an IVUS during the first angiography that would have confirmed the dissection and the wall hematoma. Also, to know the exact spread of the disease as the second angiography confirmed. In my opinion the IVUS technique is safer than the optical coherence tomography since the latter requires the intracoronary injection of contrast, which may aggravate the dissection.

The patient remained stable and 8 days after symptom onset a control coronary angiography is performed. According to our own experience, with the standard treatment, this period of time is too short to assess the sealing of the dissection and it is recommended to wait for, at least, 3 to 4 weeks.

A 6-Fr JL 3.5 catheter was used to perform the coronary angiography. It was not specified whether it was a diagnostic or guide catheter since we don't know whether the idea was to perform an intracoronary imaging technique or not. The curve of the catheter guide selected seems appropriate to us because it is less aggressive than other curves like the AL2 or the extra back-up.

After the vessel catheterization reduced the distal LMCA and proximal LAD lumens reduced. The authors attribute this to a vasospasm. Unfortunately, the first angiographic image available shows the blood vessel after worsening luminal narrowing with the angioplasty guidewire inserted, which is why we cannot assess the first injection of contrast. In my opinion, it is unlikely that the worsening luminal narrowing is due to a vasospasm considering that the whole territory has a large intramural hematoma, which is why the contraction mechanism of the coronary artery media layer that causes the vasospasm would not be operative.

It is more likely that the catheterization of the coronary artery or the first injection of contrast increased the wall hematoma, therefore, narrowing the vessel lumen. This significant reduction of the LAD lumen compromises its blood flow. The IVUS shows a large intramural hematoma affecting almost the entire vessel lumen in some segments (figure 1), and a distal LMCA dissection (figure 2).

Consequently, the patient shows hemodynamic instability, thoracic pain, and ST-segment elevation on the electrocardiogram that improves partially with the administration of intracoronary nitrates.

To this point, due to the patient's instability and compromised vessel lumen, in my opinion, an immediate percutaneous revascularization would have been required. Although, according to the angiography and the IVUS, the circumflex artery ostium is not compromised, another angioplasty guidewire should have been inserted to protect that vessel since stent implantation into the LMCA and proximal LAD can displace the hematoma towards the circumflex artery. As a matter of fact, in our own experience, stent implantation into spontaneous dissections often displaces hematoma and dissection towards other vessel segments being necessary to implant several stents into the different segments.

In this context, the best thing to do is to implant a single stent as opposed to several overlapping stents to cover the dissected area. Therefore, I would only implant 1 stent from the LMCA towards the LAD. The IVUS shows the most distal site of the dissection where stent implantation can start. In this case, the IVUS proved that there is a hematoma from the LMCA origin, which means that the vessel

ostium should be covered by slightly protruding the stent towards the aorta. There is no doubt that the use of drug-eluting stents is advisable as well as the selection of stents with a scaffold with significant over-dilatation capabilities to adjust to the size of the vessel and into the LMCA. Checking the results on the IVUS is of paramount importance.

Regarding the circumflex branch that would be jailed by the stent, given the unstable clinical context, I wouldn't prescribe any treatment unless flow or the vessel lumen were compromised. In a different procedure, treatment could be optimized by opening the stent mesh towards the circumflex branch through the simultaneous inflation of 2 kissing balloons.

FUNDING

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CONFLICTS OF INTEREST

No conflicts of interest related to this work.

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Spontaneous left main coronary artery dissection complicated with vasospasm. Case resolution

Disección coronaria espontánea en el tronco común izquierdo complicada con vasoespasmo. Resolución

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CASE RESOLUTION

We decided to end the procedure because the patient (informed consent obtained) became asymptomatic and the ST-segment elevation resolved. After the procedure, the blood test performed revealed a new increase of troponin I levels (4.4 ng/mL). The patient started therapy with dihydropyridine calcium channel blockers due to the observed vasospasm. While in observation, the patient remained asymptomatic. Five days later, she was discharged on dual antiplatelet therapy. One month later, the patient was readmitted to undergo an elective coronary angiography to reassess the lesion. The coronary angiography only revealed the presence of irregularities without further lesions (videos 1 and 2 of the supplementary data). Therefore, the most probable diagnosis was a spontaneous coronary artery

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dissection (SCAD). The management of SCAD is still a matter of great discussion especially regarding left main coronary artery lesions and situations of hemodynamic instability as it is well-known that SCADs can heal spontaneously after 1 month.[1-3] In this case, we decided not to proceed with the percutaneous coronary intervention because the patient became asymptomatic and the electrocardiographic alterations resolved after the administration of intracoronary nitrates and because we were not sure about the etiology of the severe vasospasm (SCAD vs atherosclerotic lesion). The reassessment coronary angiography performed appeared normal and confirmed the most likely diagnosis of SCAD. The patient had multiple risk factors for SCAD: multiparity, a recent delivery, and use of hormonal contraceptives.[1,2] Therefore, after discussion with the gynecology team, the patient was administered lactation suppression medication and hormonal contraception was withdrawn. Autoimmune diseases and fibromuscular dysplasia were excluded. The reassessment transthoracic echocardiogram did not show any alterations. To date, a year has gone by without recurrence.

FUNDING

No funding was obtained for this work.

AUTHORS' CONTRIBUTIONS

C. Costa Oliveira was responsible for the analysis of the clinical case and the writing of the article. C. Galvão Braga was the responsible for patient coronary intervention and for revising the article. C. Quina, J.Costa and J. Marques participate in the case resolution and were also responsible for revising the article.

CONFLICTS OF INTEREST

Nothing to declare.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000195.

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Mechanical thrombectomy with the AVP II device

Trombectomía mecánica con dispositivo AVP II

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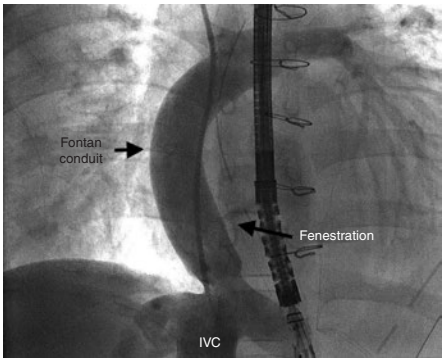

Figure 1.

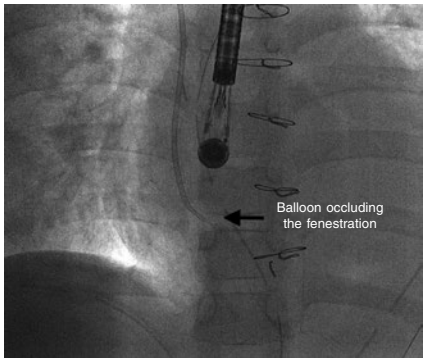

Figure 2.

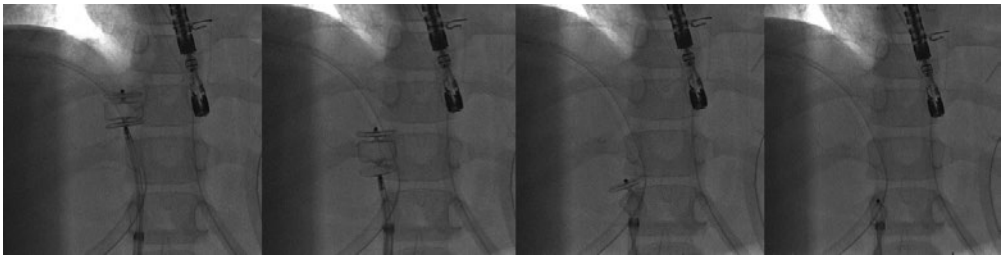

Figure 3.

Seven-year-old male with single ventricle in the postoperative of a fenestrated extracardiac Fontan procedure. The echocardiography performed 7 days after the procedure confirmed the presence of a 20 mm pedunculated thrombus attached to the wall of the inferior vena cava (video 1 of the supplementary data).

Due to the risk of systemic embolism through the Fontan fenestration, the percutaneous extraction of the thrombus was attempted using an Amplatzer Vascular Plug II (AVP II) device (Abbott, United States).

A 6-Fr introducer sheath and a 10-Fr sheath were used for the catheterization of the right jugular vein and right femoral vein, respectively. The fenestration was found in the Fontan conduit using an angiography (figure 1). It was catheterized via jugular access and occluded by inflating the balloon of a 6-Fr Wedge-Pressure Catheter (Arrow, United States) to protect an eventual paradoxical embolism (figure 2). The transesophageal echocardiography performed revealed the location of the thrombus in the inferior vena cava and the diameter of the cava was measured at that level (15 mm). The introducer sheath was advanced via femoral access until it landed right underneath the insertion of the thrombus. Through this sheath a folded 16 mm AVP II device was advanced inside an 8-Fr multipurpose catheter that was advanced until it passed the thrombus distal edge. The AVP II was unfolded in this position and pulled back until it was finally inserted into the sheath located in the inferior vena cava (figure 3 and videos 2, 3, and 4 of the supplementary data). Although the thrombus was never retrieved, it disappeared leaving no trace of pulmonary embolism. The consent of the patient's father was obtained for the publication of the case.

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AUTHORS' CONTRIBUTIONS

All the authors have participated in the writing of this article and have read and approved the final version.

CONFLICTS OF INTEREST

None.

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Incomplete giant aneurysm exclusion due to PK-Papyrus stent shortening

Exclusión incompleta de aneurisma gigante por acortamiento de stent PK-Papyrus

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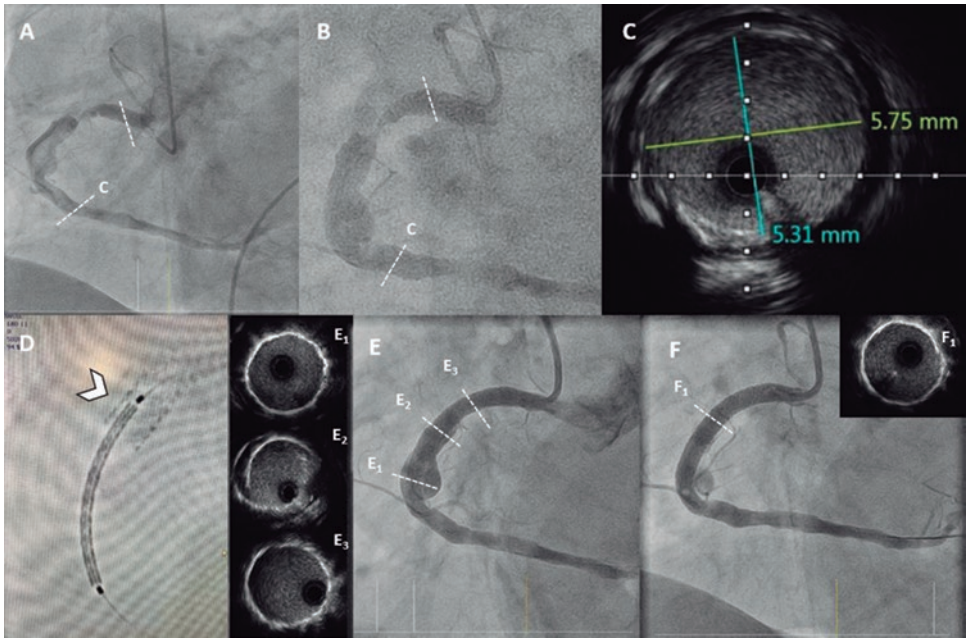

Figure 1.

Seventy-four-year-old male patient admitted with non-ST-elevation acute myocardial infarction. The coronary angiography performed revealed the presence of right coronary artery stenosis with a giant coronary artery aneurysm (CAA) and high thrombus burden (figure 1A). Dual antiplatelet and anticoagulation therapies were recommended for its exclusion in a staged procedure. After confirmation of thrombus reduction (figure 1B), predilatation was attempted and both the length of the CAA (40 mm) and the landing zone were measured on the intravascular ultrasound (IVUS) (figure 1C). From proximal to distal, two 5 mm x 26 mm-PK-Papyrus covered coronary stents (PCS) (Biotronik, Switzerland) were deployed. The overlapping stent zone was confirmed using the StentBoost imaging modality (Philips Medical Systems, Nederland) (figure 1D) and the stent was deployed under fluoroscopic guidance in the absence of any respiratory movements. The subsequent angiography performed revealed an incomplete CAA exclusion (figure 1E) despite postdilatation with a 5.5 mm noncompliant balloon (NCB). The IVUS confirmed the existence of a gap between both stents due to stent shortening (E_2, figure 1E and video 1 of the supplementary data). Another 5 mm × 15 mm PCS was deployed followed by postdilatation with a 5.5 mm NCB. Both the angiography and the IVUS confirmed the complete CAA exclusion (figure 1F and video 2 of the supplementary data). Patient has given his verbal consent for publication of this case report.

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The management of CAAs is still controversial. PCSs designed to treat coronary perforations have also been used to treat CAA exclusions. We described how the significant shortening of these devices, especially when using larger diameters, can cause incomplete CAA exclusion (or perforation). Also, that intracoronary imaging modalities are essential for optimization purposes. As far as we know, this is the first description ever of a Papyrus stent shortening combining angiography, IVUS, and StentBoost.

FUNDING

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AUTHORS' CONTRIBUTIONS

Each person listed as an author has participated to: *a)* Conceive, plan and perform the work leading to the report. *b)* Write the report or reviewed successive versions. *c)* Approve the final version.

CONFLICTS OF INTEREST

R. Moreno is associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

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Coronary embolism due to caseous mitral annular calcification

Embolia coronaria por calcificación caseosa del anillo mitral

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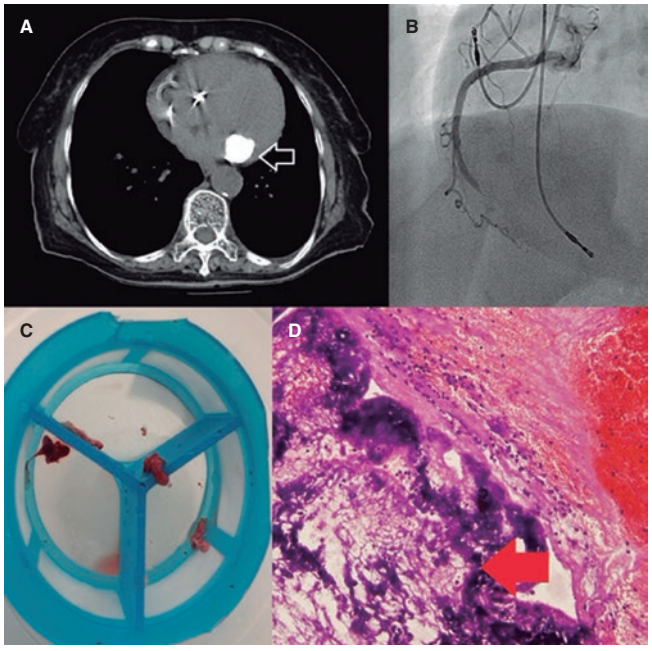

Figure 1.

This is the case of an 84-year-old woman with a past medical history of ST-segment elevation myocardial infarction (STEMI) due to thrombotic occlusion of the right coronary artery treated at a different center with a bare-metal stent. The transthoracic echocardiography and thoracic computed tomography scan performed showed a rounded calcified mass at the posterior portion of the mitral annulus that induced mild mitral regurgitation (figure 1A, black arrow).

A month later the patient was admitted to our center with recurrent inferior STEMI with total occlusion of the right coronary artery (figure 1B). We performed mechanical thrombus aspiration—that resulted in postprocedural TIMI flow grade 3—and obtained a white fibrous substance (figure 1C). We thought the occluding substance was not just a thrombus but rather a caseous degenerative material from the posterior mitral mass. Therefore, we decided to send it to the pathology laboratory.

The pathological examination of the material showed thrombosis and microcalcifications of caseous appearance (figure 1D, red arrow). Therefore, the current STEMI was possibly associated with a coronary embolism due to caseous calcification of the mitral valve (CCMA).

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CCMA is a rare evolution of a calcified mitral annulus due to the caseous transformation of the inner material. It is often an incidental finding when performing cardiac imaging. However, CCMA can become complicated by recurrent systemic embolization: strokes, retinal artery occlusion or acute coronary syndrome as our case showed. In these cases, anticoagulation should be considered; nevertheless, surgery is the definitive treatment. Because of age and comorbidities, a conservative approach was finally decided. The patient's informed consent was obtained.

FUNDING

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AUTHORS' CONTRIBUTIONS

All authors had access to the data and contributed to the writing of this manuscript.

CONFLICTS OF INTEREST

None reported.

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ESC Editors' Network

Heart failure 2019. Insights from the National Society of Cardiology Journals

Insuficiencia cardiaca 2019. Reflexiones de las Revistas de las Sociedades Nacionales de Cardiología

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[h] *Editor-in-Chief of Russian Journal of Cardiology, Russia*
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INTRODUCTION

Most studies on heart failure (HF) management published in 2019 by high-ranking impact factor international journals focus on drug therapy.

This included administration of sacubitril-valsartan with initiation during the index admission and the benefits of SGLT2 inhibitors in reducing cardiovascular mortality and HF. Most of these studies, targeting a broad readership, fail to characterize important local issues.

Improvement in HF management needs to take into account specificities from different European Society of Cardiology (ESC) member countries. This approach may be achieved and disseminated to cardiologists by the National Society of Cardiology Journals (NSCJ). During the ESC Congress 2019, the ESC Editors' Network started an initiative intended to boost dissemination of cardiology research published in the NSCJ by summarizing in a review paper the evidence gathered in selected areas. The ESC Editors Network members decided the first topic of such a review to be publications in the field of HF.

Epidemiology

Inequalities in the prevalence of risk factors, cardiovascular disease burden, cardiovascular mortality, and implementation of some therapeutic methods (coronary interventions, device implantations, and cardiac surgery) among the ESC member countries have recently been shown in the ATLAS study. These shortcomings depend on socio- economic factors and affect more predominantly middle-income than high-income countries. In a single-centre observational study of 1006 patients admitted to a coronary care unit in Egypt, Badran et al.[1] estimated the prevalence of HF by gender and preserved or reduced left ventricular ejection fraction (LVEF). They reported a higher prevalence of HF and a higher incidence of HF with reduced ejection fraction (HFrEF) among women. Female patients were older, more likely to be obese, with more co-morbidities, had less acute coronary syndromes and required fewer coronary interventions, but had a prognosis similar to men.

Nationwide information on mortality and readmissions in HF patients is also of interest. A retrospective analysis from Spain aimed to identify factors associated with in-hospital mortality and readmissions in 77 652 HF patients.[2] In-hospital mortality was 9.2%, rising to 14.5% at 1 year. The 1-year cardiovascular readmission rate was 33%. Risk factors associated with mortality were stroke, metastatic cancer, cardiorespiratory failure, shock, and acute myocardial infarction. Risk-standardized mortality rates were lower among patients discharged from high-volume hospitals. Importantly, the availability of a cardiology department at the hospital was associated with better outcomes.

Specific causes of heart failure

Calcific aortic valve disease (CAVD) is a common disorder which may progress while remaining clinically unrecognized. However, the progression mechanisms remain unknown. In a single-centre study from Bulgaria, Tomova et al.[3] tested the hypothesis that the polymorphism rs10455872 at the lipoprotein(a) (LPa) gene locus increases the risk of CAVD. In a comparison of 108 CAVD patients with 38 controls, they reported that the presence of 2:1 mutant allele of the

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gene was associated with a four-fold greater risk for CAVD. A report from the *Austrian Journal of Cardiology* by Kauffmann et al.[4] demonstrated that the diagnosis of transthyretin-amyloidosis has recently improved significantly with structural screening by magnetic resonance imaging (MRI). The coexistence of CAVD and transthyretin-amyloidosis has substantial implications. The study suggested the value of the electrocardiogram, echocardiography, MRI, technetium radionuclide imaging, and endomyocardial biopsy in these patients.[4] Subclinical myocardial involvement is common in systemic sclerosis (SSc) and is associated with HF and a worse prognosis. In a study of 73 SSc patients from Hungary, Vertes et al.[5] tested the 2D-speckle-tracking-derived global longitudinal strain (GLS) for the detection of early myocardial involvement.

Lower GLS values were found in patients compared with gender- and age-matched healthy controls. GLS values correlated with the duration of the disease from the onset of Raynaud's phenomenon, from the first non-Raynaud symptoms, and with the New York Heart Association (NYHA) functional class.

Pathogenesis

In a prospective Russian study including 297 patients, Lelyavina et al.[6] reported the potential for differentiation, regeneration, and growth of satellite skeletal muscle precursor cells obtained from patients with HFrEF. The studied parameters were similar to those found in healthy donors. This may explain why walking >1.5 h/day induces more physiological reverse myocardial remodelling than aerobic training.

Diagnosis

In another Russian study, Vdovenko et al.[7] compared 80 patients (NYHA Class I–IIa) with chronic HFpEF with 30 healthy controls by using the 6-minute walk-test and echocardiography. All patients had diastolic dysfunction (60 abnormal relaxation patterns and 20 pseudo normal patterns) with reduced global and segmental LV strain. The im- pact of HF on other body organs has been analysed by Ic¸en et al.[8] from Turkey assessing liver stiffness (LS) in HF patients. Liver stiffness estimated using an ElastPQ technique was increased in patients with more advanced NYHA class. A higher LS was associated with higher right ventricular myocardial performance index, regurgitation pressure gradient, NT-proBNP, and aspartate aminotransferase levels. Assuming that the SYNTAX score is not just a measure of the severity but also the complexity of coronary artery disease Öztürk et al.[9] analysed the degree of coronary atherosclerosis, estimated by SYNTAX score and myocardial viability in Turkish patients with ischaemic cardiomyopathy. Patients without viability had a significantly higher SYNTAX score compared with those with viable myocardium.

Treatment

Clinical implications of HF associated with valvular heart disease has been reported by several NSCJ. Transcatheter aortic valve implantation (TAVI) is an alternative to surgical aortic replacement for symptomatic severe aortic stenosis. Indications are now rapidly expanding towards patients at lower surgical risk. Generalization of the transfemoral vascular approach, technological advances, and increased opera- tor skills have resulted in higher rates of procedural success and improved long-term survival. However, data on the incidence of readmission for HF after successful TAVI are scarce.

A French study on 1139 patients, by Guedeney et al.[10] reported that readmission for HF occurs in 1/10 patients after TAVI and suggests a strong risk factor for mortality. The main risk factors for HF readmission were LVEF ≤ 35%, chronic pulmonary disease, chronic kidney disease, diabetes, and atrial fibrillation. Along with international multicentre trials on the percutaneous mitral repair of functional mitral regurgitation associated with HF, national registries provide valuable real-life results in unselected patients which may inform clinical decision making at a local level.

Benak et al. reported a cohort of 30 MitraClip implantations in Czech patients with dilated cardiomyopathy and severe functional mitral regurgitation. Procedural success was 97% with no 90-day mortality. At 1 year, significant improvements in functional class, and quality of life scores were reported, associated with a reduction of LV myocardial mass, an increase in systolic and diastolic arterial pressure and a mortality rate of 10%.

CONCLUSION

Instead of publications in high-ranking impact factor international journals, NSCJ cover a wide spectrum of diagnostic and therapeutic modalities taking into account the national specifics of HF. In contrast, studies published in NSCJ are often single-centre and observational. However, information on HF strategies at a national level are useful in implementing ESC clinical practice guidelines and in optimizing HF patients' care.

CONFLICTS OF INTEREST

None declared.

DISCLAIMER

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