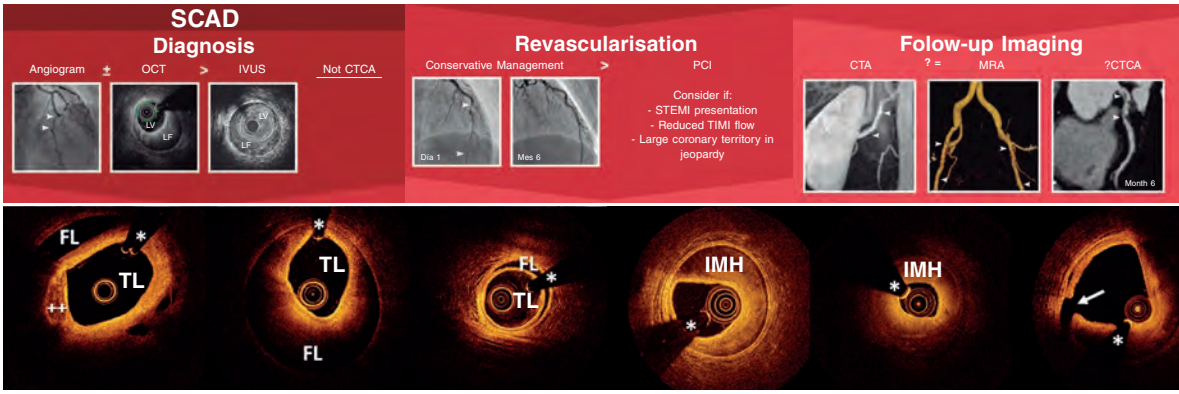
REC: INTERVENTIONAL CARDIOLOGY
REVISTA ESPAÑOLA DE CARDIOLOGÍA

Volume 2, Issue 4 | October-December 2020
ISSN: 2604-7314; e-ISSN:2604-7322



SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA
Asociación de Cardiología Intervencionista

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REC publications

REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

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VOLUME 2, ISSUE 4, OCTOBER-DECEMBER 2020

The first two years of REC: Interventional Cardiology

Primeros dos años de REC: Interventional Cardiology

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Back in May 2019 at the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC), we presented the first issue of *REC: Interventional Cardiology* (figure 1). A dream we had been dreaming for years was finally coming true. And it was coming to life the way we thought was the most suitable one, as a free of charge, open-access, bilingual (Spanish and English) publication with an optimal digital and print presentation.

Since then, 7 issues have been published including original articles, clinical cases, letters, review articles, clinical trial reviews, editorials, debates, and news that have covered all aspects of interventional cardiology both coronary and structural.

The main protagonists of this satisfactory early adventure have been the authors who have submitted their manuscripts in different formats (original articles, cases, letters, and images) and the guests invited by the editorial team to write reviews, editorials, thematic debates, case reports, clinical case reviews or breaking news. Among them, acclaimed national and foreign experts whose names have brought excellence and high-quality to our journal.

We wish to thank the authors who have been submitting their manuscripts to our journal despite the fact that our journal has not been indexed yet or have impact metrics. They have answered our call to bring this journal to life, make it grow, and receive the recognition it truly deserves.

Special articles have been published occasionally as well such as the consensus document published on the requirements and sustainability of primary angioplasty programs for the management of infarction, which is interesting for its important implications.[1]

REACTION TO THE COVID-19 CRISIS

In the trajectory of *REC: Interventional Cardiology* from its origin until the present time we cannot overlook the tremendous health crisis triggered by the COVID-19 pandemic suffered by our country and the entire world this year. As a response to this situation, *REC: Interventional Cardiology* has reacted quickly and effectively. At the initiative of the board of directors of ACI-SEC, and just a few days after the SARS-CoV-2 outbreak, we were already publishing interesting articles on safety issues for the management of patients in such a complex setting.[2-4] We also published articles about the impact of this crisis on the management of infarction in our country,[5] a study that truly resonated with the media.[6]

These articles were the result of consensus papers conducted by members of the ACI-SEC with collaboration from other SEC associations and processed, in record time, by the editorial office and Permanyer Publications within incredibly short time scales. We also published a consensus document by the Mexican Interventional Cardiology Society (SOCIME).[7] That is how the information

Figure 1. Presentation of the journal in 2019. **A:** at the editorial office; from left to right: Iria del Río, María González Nogal, Helena Gómez-Lobo, Belén Juan, and Eva M. Cardenal. **B:** Official Congress of the Spanish Society of Cardiology (2019); from left to right: José M. de la Torre-Hernández, Raúl Moreno, Fernando Alfonso, and Juan Sanchis.

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Online: 16-11-2020.
https://doi.org/10.24875/RECICE.M20000174

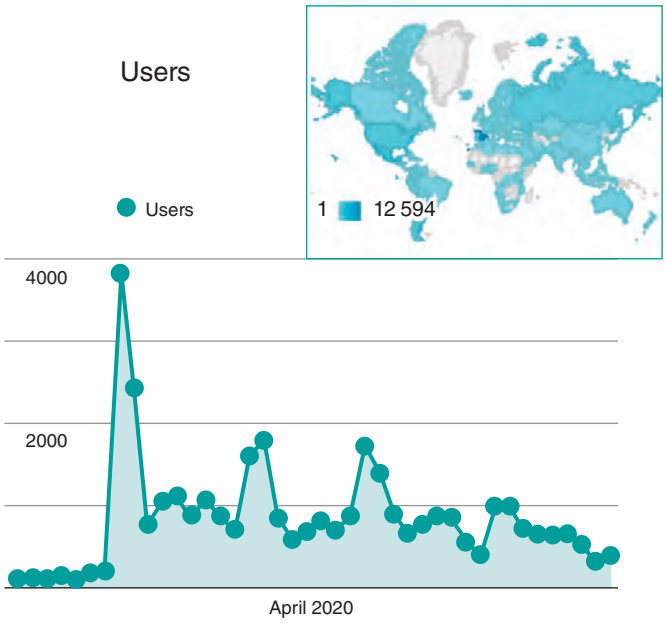

Figure 2. Evolution of the number of users throughout April 2020. The highest peak seen was due to the articles published on COVID-19.

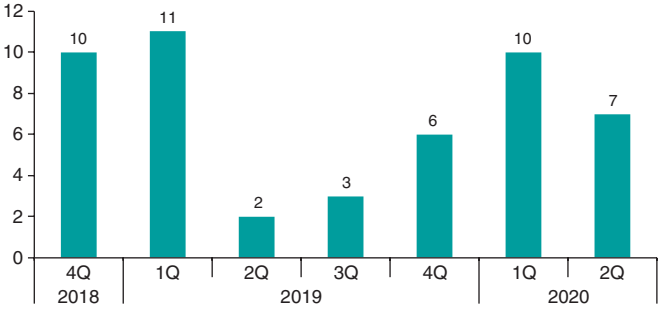

Figure 3. Original articles received since the journal was launched until June 30, 2020. Q, quarter.

Figure 4. Editorial decisions made on the original articles received since the journal was launched until June 30, 2020. Q, quarter.

needs of many interventional cardiologists in Spain and many other countries were met as the visits to our journal website from various places across the world in the days following publication showed (figure 2). We were the first ones to do so and this has had a great impact. The aforementioned article that reported on the effects that the COVID-19 pandemic had on the interventional cardiology care provided in Spain[5] was quoted in medical journals such as the *Journal of the American College of Cardiology*, the *European Heart Journal,* and *Circulation*, among others. The work done by the authors, the editorial office, and Permanyer Publications has been outstanding, actually extraordinary, during thes difficult times.

STATISTICS

Let's now take a look at the journal from the statistical point of view until mid-2020. We should mention that the charts that show article reception and decision-making are not fully comparable since some articles were received at a time when publishing decisions were made at a later point in time.

Original articles

The reception of original article has gone through very different phases (figure 3). Although several articles were received during the last quarter of 2018 and the first quarter of 2019, the number of articles received at the end of the year went down significantly which was somehow disconcerting. There is no doubt that competing with indexed medical journals limits the power of attracting original articles. Despite this huge disadvantage, the reception of articles went up significantly at the beginning of 2020, thus covering the needs of upcoming issues. This situation is highly satisfactory and shows that our journal is becoming more and more popular among researchers. Still, due to its quarterly nature we will have to be even more selective in the process of accepting the papers submitted to us. However, this will increase the quality of the contents published, which is key to increase visibility and recognition. Occasionally, format change will still be an option for original articles that are not of the highest priority, but with contents that are still interesting for our journal.

Forty-nine original articles were received up to June 30, 2020. Thirty-four (69%) of the decisions made during that time were in favor of publication (figure 4). The original articles published were submitted from Spain, but articles from other countries were published as well.

Clinical cases

The publication format of clinical cases includes the discussion of the case by a guest expert. We are glad to say that this section from our journal is very much appreciated by our readers.

Twenty-seven cases were received by the end of the second quarter of 2020 (figure 5). Nine cases (33% of the decisions made on articles of this kind) were accepted during the same period of time (figure 6). Since we only publish 1 clinical case per issue, we have already covered several upcoming issues. This means that in the future we'll have to be much more restrictive when selecting new clinical cases for publication.

Images in cardiology

Images are the most popular content for the authors as the number of articles received clearly shows (figure 7). On the other hand, this is obvious since this content is easier to elaborate. Also, since the use of images is essential for the practice of our medical

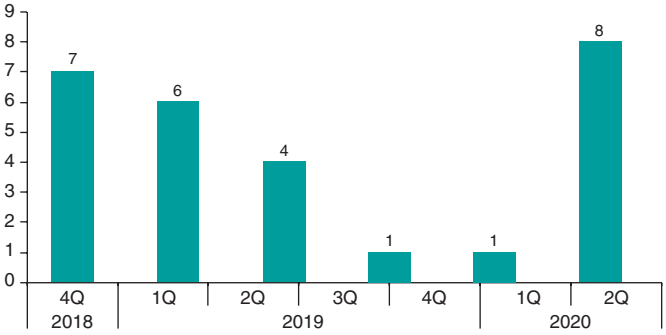

Figure 5. Clinical cases received since the journal was launched until June 30, 2020. Q, quarter.

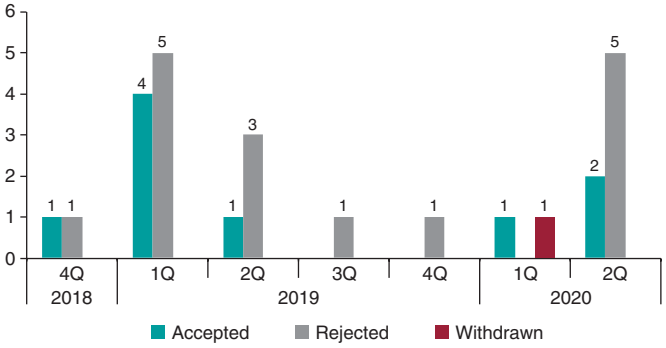

Figure 6. Editorial decisions made on the clinical cases received since the journal was launched until June 30, 2020. Q, quarter.

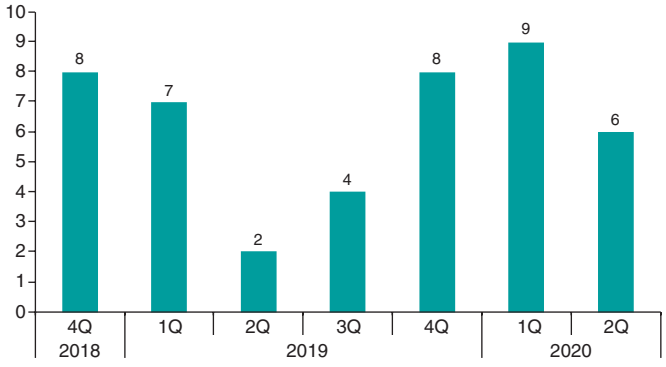

Figure 7. Images in cardiology received since the journal was launched until June 30, 2020. Q, quarter.

specialty to guide diagnosis and to administer interventional treatments, we often come across interesting images. As with original articles and clinical cases, there is a list of images in the pipeline waiting for publication in upcoming issues. Because of how successful this section has actually been, we have decided to publish 3 more images in cardiology per issue starting 2021. Still, we'll need to be more restrictive during the acceptation phase.

Forty-four images in cardiology were received during the second quarter of 2020 (figure 7), 20 of which (46% of the decisions made on articles of this kind) were accepted during the same period of time (figure 8).

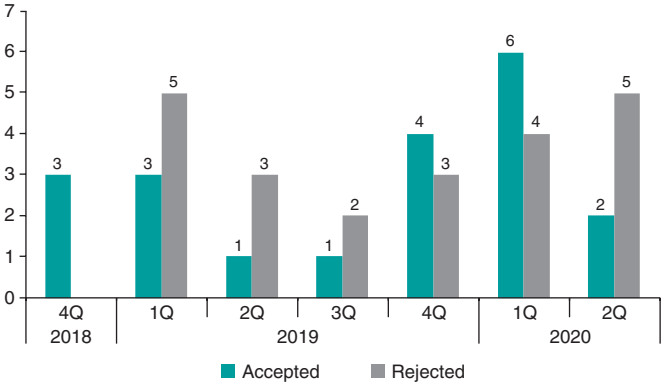

Figure 8. Editorial decisions made on the images in cardiology received since the journal was launched until June 30, 2020. Q, quarter.

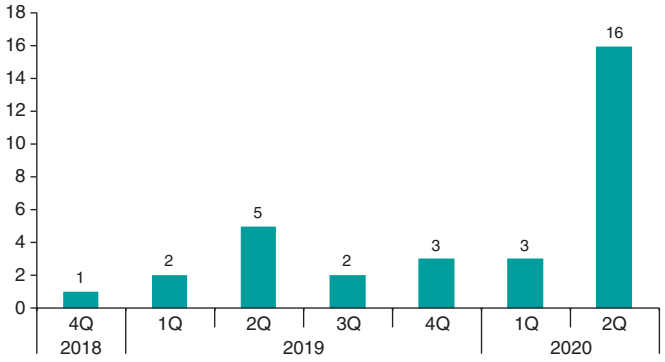

Figure 9. Letters to the Editor received since the journal was launched until June 30, 2020. Q, quarter.

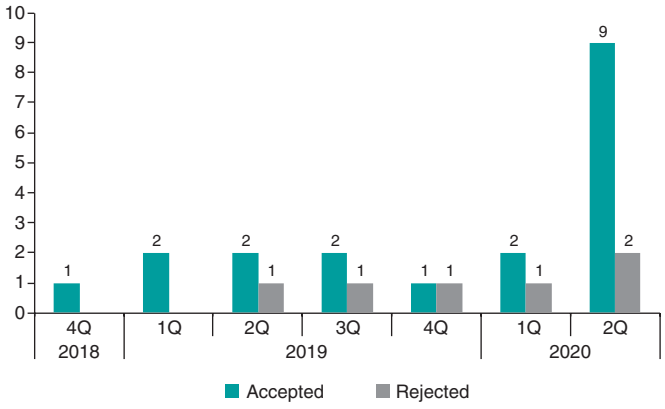

Figure 10. Editorial decisions made on the letters to the Editor received since the journal was launched until June 30, 2020. Q, quarter.

Letters to the Editor

The letters received have been very diverse, both traditional letters to the Editor and brief scientific reports. By June 30, 2020 we had already received 32 letters, a number that went up significantly at the beginning of the second quarter of 2020 (figure 9). Nineteen manuscripts of this type were accepted during this period (49% of the decisions made on articles of this kind) (figure 10).

There was no predefined limit of letters per issue (a couple of them have been published in previous issues), but in light of the growing

number of letters received and accepted we have established a maximum of 4 for upcoming issues.

At times, the letters have been a valid alternative to original manuscripts which, though rejected, were still considered interesting enough by the editorial team to deserve a format change into letters to the Editor.

Submission of manuscripts from *Revista Española de Cardiología*

This matter is of paramount importance. *Revista Española de Cardiología* has an excellent impact factor and, most important of all, is well known. This means it appeals to national and international researchers alike. For this reason, its percentage of manuscript rejection is fairly high. And it is the way it should be with a journal of this level, impact, and quality. Ever since we started this publishing journey and, at the suggestion of the associate editors of *Revista Española de Cardiología*, we have been reviewing the contents rejected by this journal and asked the authors for permission to publish them on *REC: Interventional Cardiology* when appropriate.

The authors have accepted this suggestion of publishing the manuscripts rejected by *Revista Española de Cardiología* relatively well (20%), especially if we consider the gap between both journals at the present time. Fourteen original articles were re-submitted for publication until June 2020, most of which ended up being accepted (figure 11 and figure 12). Images in cardiology was the typology most widely accepted for re-submission (38%) followed by original articles (17%) and letters to the Editor (the other 2 sections most commonly proposed for re-submission). Again, this level of re-submission should be assessed positively. However, it will grow significantly, parallel to the trajectory and visibility of the journal.

In conclusion, the reception of articles has been growing in all sections. Thanks to this we have already completed several upcoming issues. Nonetheless, this should make us more restrictive when accepting manuscripts. And this is not easy to handle because the articles, cases, images, and letters are all interesting to read and all have something valuable to offer. On the other hand, this measure is absolutely necessary due to the space constraints of the journal (4 issues per year) and need not avoid delaying the publication of the manuscripts too long. The indirect effect of this, is we aspire to higher levels in the contents published. Additionally, this situation allows us to give more time to guest authors to write the editorial comments associated with original articles.

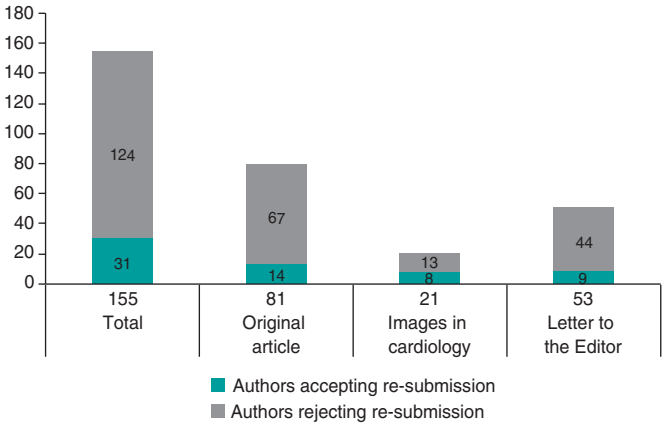

Figure 11. Articles rejected by *Revista Española de Cardiología* and proposed for re-submission to *REC: Interventional Cardiology* between January 1, 2019 and June 30, 2020.

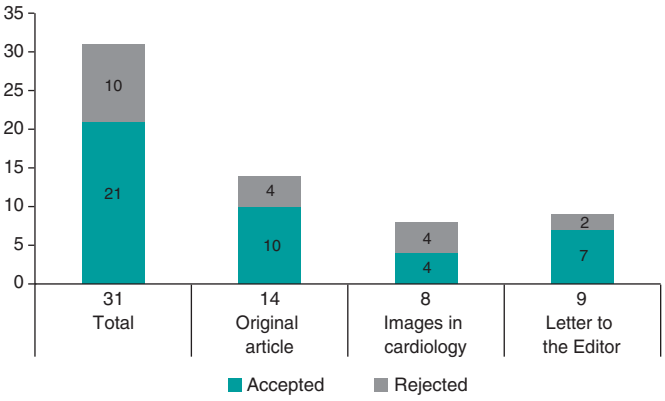

Figure 12. Editorial decisions made on the articles submitted to *REC: Interventional Cardiology* from *Revista Española de Cardiología* between January 1, 2019 and June 30, 2020.

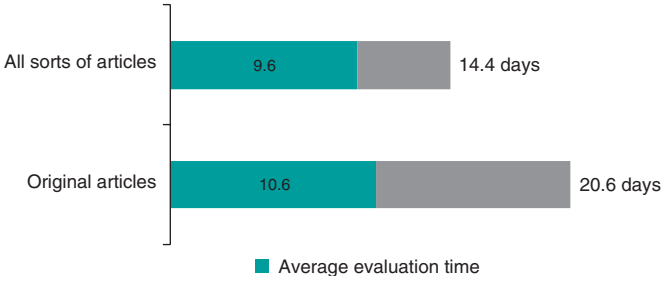

Figure 13. Average editorial times between January 1, 2019 and June 30, 2020. Means correspond to 175 evaluations of any kind (71 evaluations of original articles).

REVIEWERS

Editorial times deserve a special chapter. As figure 13 shows, in general times have been appropriate compared to most medical journals with a mean first decision-making time of 14.4 days. The reviewers deserve a lot of credit because in a very short period of time (mean 9.6 days) they have reviewed the manuscripts submitted (well below the 14 days established in the deadline). The times of the editorial office from manuscript reception have been under 2 days. Still, we think the times of the editorial office handling the manuscripts before and after the evaluation phase can be shorter.

We should not only thank the evaluators for their flexibility and punctuality meeting their deadlines when submitting their reviews, but also give them credit for the quality of their comments and commitment during the entire decision-making process. The evaluators have been able to change their reviews and remarks based on the special characteristics of our journal. Table 1 shows the names of the evaluators who have collaborated with our journal until June 30, 2020.

The evaluators have other commitments with other journals, some of them international and acclaimed medical journals. Still, their commitment with *REC: Interventional Cardiology* has been impeccable so far.

Table 1. Evaluators from *REC: Interventional Cardiology* who have been reviewing articles since the journal was first launched until June 30, 2020

Juan H. Alonso	Felipe Hernández-Hernández
Ignacio J. Amat	Borja Ibáñez
Dabit Arzamendi	Andrés Íñiguez
Pablo Avanzas	Luis J. Jiménez-Borreguero
Teresa Bastante	Santiago Jiménez-Valero
José A. Baz	Alfonso Jurado-Román
Salvatore Brugaletta	Esteban López-de-Sá
Ramón A. Calviño	José R. López-Mínguez
Xavier Carrillo	Ramón López-Palop
Belén Cid	Íñigo Lozano
Ignacio Cruz	Javier Martín-Moreiras
Javier Cuesta	Cesar Morís
José F. Díaz	Luis Nombela
Jaime Elízaga	Soledad Ojeda
Rodrigo Estévez-Loureiro	Manuel Pan
José A. Fernández-Díaz	Armando Pérez de Prado
José L. Ferreiro-Gutiérrez	Eduardo Pinar
Guillermo Galeote	Fernando Rivero
Eulogio García	Oriol Rodríguez
Sergio García-Blas	Rafael Romaguera
Tamara García-Camarero	Gerard Roura
Bruno García del Blanco	Juan M. Ruiz Nodar
Héctor M. García-García	José R. Rumoroso
Arturo García-Touchard	Manel Sabaté
Juan R. Gimeno	Ángel Sánchez-Recalde
Javier Goicolea	Marcelo Sanmartín
Joan A. Gómez-Hospital	Antonio Serra
Josep Gómez-Lara	Ramiro Trillo
Nieves Gonzalo	Beatriz Vaquerizo

DISSEMINATION OF *REC: INTERVENTIONAL CARDIOLOGY*

There are different ways for all of our colleagues to access our journal including SEC and ACI-SEC official websites. REC Publications social media disseminate the contents of our journal under the hashtag *#recintervcardiol*. Additionally, the blog *Cardiología Hoy* publishes interviews with our authors on a routine basis. *REC: Interventional Cardiology* was officially presented at the 30th Annual ACI-SEC Meeting in 2019 and has also been present at the SEC 2019 International Symposium of Cardiovascular Disease and at various other national and international interventional cardiology meetings. We wish to thank our friends in Latin America, especially the Latin American Society of Interventional Cardiology (SOLACI), the National Association of Cardiologists of Mexico (ANCAM), and SOCIME for their warm welcome and dissemination of our journal.

Readers of *Revista Española de Cardiología* can access our latest articles ahead of print from the SEC website and from its newsletters. Also, we have started publishing video-interviews with the authors of the articles chosen in the issues which appeared on 2020.[8]

ACI-SEC AWARD TO THE BEST ORIGINAL ARTICLE PUBLISHED IN 2019

This year we will be giving the very first award to the best article published on *REC: Interventional Cardiology*, a true recognition from SEC with an economic reward granted by ACI-SEC. This will be awarded after deliberation of a jury presided by *REC: Interventional Cardiology* editor-in-chief including the journal associate editors and members from the ACI-SEC board of directors. The jury will take into account the originality, scientific-methodological quality, and significance of the articles for our routine clinical practice. There will be another call for the best original article published in 2020.

A JOURNAL IMPROVING CONSTANTLY AND WITH ASPIRATIONS

Since its inception, our journal has gone through several changes. We have improved different aspects of the editorial process and responded to a working routine based on a continuous cycle of observation, critical review, and improvement.

Ours is a very young publications with much still to learn and with room for improvement. We are open to innovation and change to make the journal easier to work with for authors, readers, and evaluators.

Our next objective is to achieve indexation—a mid-term aspiration. However, we should not forget that our main objective is to achieve scientific prestige and recognition so our journal can be disseminated freely, openly, rigorously, and swiftly to the interventional cardiology scientific community.

CONFLICTS OF INTEREST

None reported.

ACKNOWLEDGEMENTS

We wish to thank all the authors and evaluators for their commitment and impeccable work. The unpleasant part of our job as the editorial team is to reject manuscripts. As authors ourselves we are fully aware of the disappointment and frustration these rejections produce. All, and I mean all manuscripts are interesting and should see the light of a publishing house. Unfortunately, the space of our journal is limited, and we are doing the best we can.

As editor-in-chief I wish to express my most sincere appreciation to my associate editors Juan Sanchis, Fernando Alfonso, and Raúl Moreno. It is my pleasure to work with them.

In his position as president of the ACI-SEC —the sponsors of the journal—Raúl Moreno is key for the economic viability of our journal. And speaking of funding, we should thank the unconditional contribution from all the companies involved in the interventional cardiology setting.

We also wish to thank the excellent work and dedication of REC Publications editorial team: Iria del Río, Eva M. Cardenal, Belén Juan, María González Nogal, and Helena Gómez-Lobo; our ICT

Consultor, Pablo Avanzas, and the entire ICT team at SEC; last but not least, we wish to thank the entire staff at Permanyer Publications led by Ricard Permanyer and directed by Laura Casares as project manager. It is fair to say you would not be reading this journal without their contribution.

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REC Interv Cardiol. 2020;2(4):239-241

Editorial

Spontaneous coronary artery dissection: new insights on diagnosis and management

Disección arterial coronaria espontánea: nuevos conocimientos en diagnóstico y tratamiento

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Over the last decade, understanding of spontaneous coronary artery dissection (SCAD) has progressed from a condition once considered very rare and the subject largely of esoteric case reports to a disease now recognised as a significant cause of acute coronary syndromes, predominantly in young to middle-aged women. Large observational series have been presented, led by groups in the Mayo Clinic, United States and Vancouver, Canada.[1-3] This increased understanding has led to the publication of consensus documents on best practice in both the US and Europe.[4,5] Despite this, SCAD remains a condition devoid of randomised clinical trial data and debate continues over many aspects of what constitutes optimal management.

In a recent article published in *REC: Interventional Cardiology*, Bastante et al.[6] present data on a highly characterised series from a Spanish centre at the forefront of the progressive management of this condition. Their data provide supporting evidence on findings of direct clinical relevance to contemporary clinical practice and provides novel insight, particularly into the relative merits of antiplatelet therapies for this condition.

The Yip-Saw angiographic classification for SCAD[7] coupled with an increased recognition of the central role of intracoronary imaging to aid diagnosis where there is uncertainty, particularly with optical coherence tomography,[8] has greatly enhanced the accurate diagnosis of SCAD in the cardiac catheterisation laboratory. In common with other more contemporary and prospective series where there is likely to be less selection bias,[2,9] Bastante et al. report SCAD occurring in an older (median age 56), predominantly peri- and post-menopausal female population with a risk factor profile more akin to an age matched general population (48% current or ex-smoker, 36% hypertension, 42% hypercholesterolaemia).[6] This further debunks an oft-repeated mantra that SCAD is a disease of pre-menopausal women with few conventional risk factors for ischaemic heart disease. In this and some other studies, only diabetes (6%) seems less prevalent than in the general population. It is interesting to speculate as to whether the adverse vascular effects of diabetes may paradoxically protect against SCAD. Most importantly however, these data remind clinicians not to restrict their consideration of the diagnosis of SCAD to low risk pre-menopausal females.

Accurate diagnosis is the key first management step for SCAD. This paper gives important insights into the diagnostic role of computed tomography coronary angiography (CTCA). It demonstrates that even in a context where the site of SCAD is known from invasive angiography, conventional CTCA missed more than 20% of SCAD locations. This finding confirms that although CTCA is a tempting non-invasive substitute for angiography (particularly given the known increased risk of iatrogenic dissection during invasive angiography in this population[10]), this approach should not be used for the primary diagnosis of SCAD. The inadequate sensitivity and specificity of CTCA for this diagnosis likely arises because SCAD has a predilection for the mid-distal coronary arteries (76% of cases in this series) where coronary diameters approach the effective spatial resolution of current CTCA technologies. Whether CTCA could still be useful in specific clinical contexts, for example to exclude or to follow progression of high-risk proximal-to-mid vessel dissections, remains to be elucidated.

A key difference between the management of SCAD and atherosclerotic acute coronary syndromes is the increased risk of complications during percutaneous coronary intervention following SCAD. This, coupled with high reported rates of complete healing in conservatively managed SCAD has led to a consensus favouring a non-interventional strategy where possible.[4,5] This approach is further supported by the recent demonstration of relatively small infarct sizes in most convalescent SCAD-survivors assessed by cardiac magnetic resonance imaging, with larger infarcts predicted by ST-segment elevation myocardial infarction presentation, reduced TIMI flow and more proximal or extensive dissections.[11] In the paper by Bastante et al. 82% of patients were managed conservatively.[6] This is in keeping with a large recent prospective Canadian series and suggests that in experienced centres, most SCAD can be managed without percutaneous coronary intervention.[2]

Optimal medical management following diagnosis remains unclear. This becomes particularly relevant when considering the optimal long-term antiplatelet treatment strategy after SCAD. Antiplatelet therapies have become a mainstay of treatment for atherosclerotic acute coronary syndromes which are characterised by the formation of luminal thrombus on ruptured or eroded atherosclerotic

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Online: 29-07-2020.
https://doi.org/10.24875/RECICE.M20000146

plaque. However, this paper confirms previous findings[12] that the burden of true luminal thrombus in SCAD is low, leading the authors to adopt a clinical strategy of early aspirin monotherapy in conservatively managed SCAD (only 7/27 such patients were managed with dual antiplatelet therapy). The longer-term justification for maintenance aspirin has also been questioned as it appears somewhat counter-intuitive to use a medication that prolongs bleeding time as prophylaxis for a condition whose primary pathophysiological event seems to be the development of a spontaneous intramural haematoma. The only potentially informative clinical data come from a single Canadian observational series and found no definitive benefit or harm.[1] However, these findings have not yet been validated in other series and whilst this report from Bastante et al.[6] will add further fuel to this debate, clinical trial data are urgently needed to address this question.[13]

The recognition of extra-coronary arteriopathies in SCAD patients[14] has led to a consensus favouring arterial screening by brain to pelvis imaging in all SCAD-survivors.[4,5] However, it is important to demonstrate that imaging has the potential to alter clinical management or prevent vascular events, especially given the associated X-ray dose if computed tomography arteriography is used.

This is particularly relevant as the most frequent arteriopathy in SCAD survivors is fibromuscular dysplasia which although common, seems of little clinical consequence in most cases. Therefore, the report by Bastante et al.[6] of 3 patients in whom intra-cerebral aneurysms identified during screening required closure provides some additional much-needed supportive data that at minimum intracerebral arterial imaging is indeed merited in SCAD-survivors.

Finally and most importantly for patients, Bastante et al. complement data from other series suggesting that although major adverse cardiovascular events (18%) and SCAD recurrence (12%) are significant problems for SCAD-survivors, the disease-related mortality following SCAD is very low.[6] Prevention of SCAD recurrence is therefore the key target for clinical trials targeting improved outcomes in SCAD.

In summary, there has been a paradigm shift in our knowledge of SCAD leading to improved diagnostic accuracy and increasing adoption of a conservative revascularisation strategy (figure 1). However, key questions remain about optimal long-term medical prophylaxis and the best approach to follow-up imaging. International collaboration will be key to generating the data required to definitively address these questions and ensure we continue to improve our approach to the management of this important condition. Recruitment of patients to the new European Society of Cardiology EURObservational Research Programme SCAD registry (CPMS No. 44577, IRAS No. 270314)[15] will provide a key platform for future research.

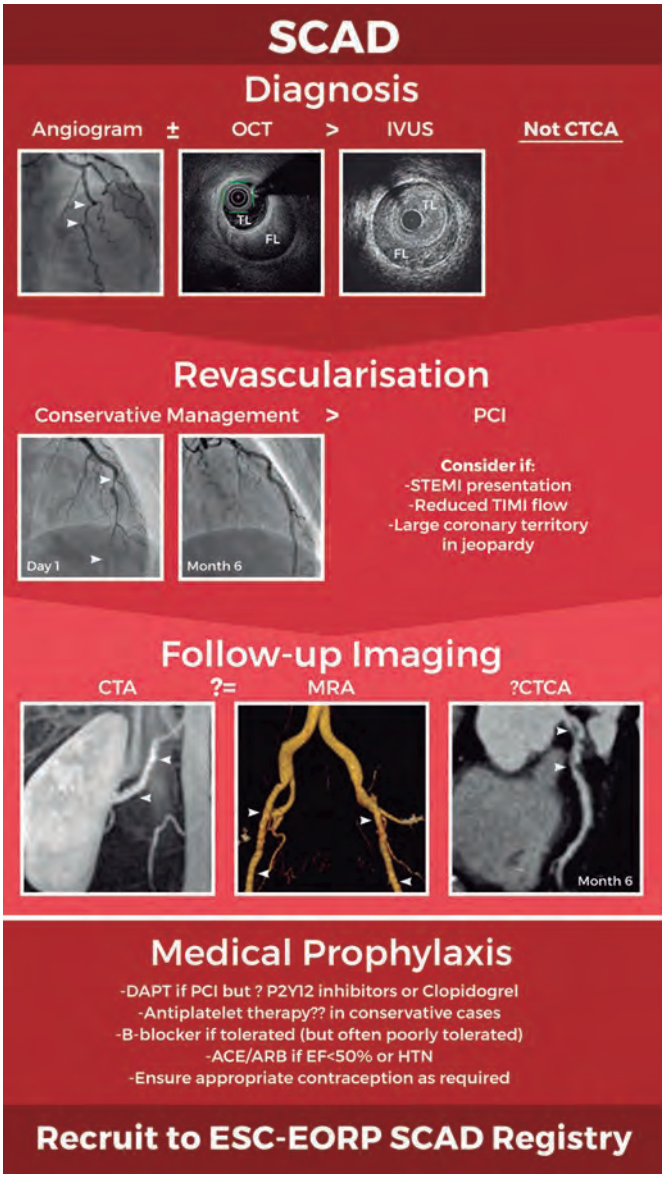

Figure 1. Schematic of current optimal management approach to spontaneous coronary artery dissection (SCAD). Invasive coronary angiography supported by intracoronary imaging if needed remains the diagnostic gold-standard. A conservative approach to revascularisation is favoured except in more extreme presentations. Screening for remote arteriopathies is recommended but the optimal imaging modality and the role of computed tomography coronary angiography remain unclear. Optimal medical management is unknown. All images are from patients from the UK SCAD study (ISRCTN42661582; REC14/EM/0056). ACE/ARB, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists; CTA, computed tomography arteriography; CTCA, computed tomography coronary angiography; DAPT, dual antiplatelet therapy; ESC-EORP, European Society of Cardiology European Observational Research Programme; FL, false lumen; HTN, hypertension; IVUS, intravascular ultrasound; MRA, magnetic resonance angiography; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TL, true lumen.

CONFLICTS OF INTEREST

D. Adlam has received research funds and in kind support from AstraZeneca, including for spontaneous coronary artery dissection research. He has also received an educational grant from Abbott Vascular to support a clinical research fellow and has conducted consultancy for General Electric, Inc. to support research funds. D. Kotecha has no conflicts of interest to declare.

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REC Interv Cardiol. 2020;2(4):242-243

Editorial

Routine endomyocardial biopsy in heart transplantation: in search of lost evidence

Biopsia endomiocárdica rutinaria en el trasplante cardiaco: en busca de la evidencia perdida

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The introduction of endomyocardial biopsy (EMB) for the diagnosis of rejection back in 1972[1] was considered one of the main advances in the history of heart transplant (HT). Ever since, the EMB has been the gold standard for the diagnosis of rejection. However, this is a repetitive, invasive procedure, often described as uncomfortable by patients and associated with sometimes, serious complications. In this context, in a recent article published on *REC: Interventional Cardiology*, Tamargo et al.[2] shared their combined experience from 2 large national HT centers with the use of EMB via brachial access, a route that is relatively less invasive compared to the femoral access or the most common jugular vein. The authors prove that this is a feasible alternative in 94% of the attempts. Brachial access is safer because it is not associated with some of the major complications of central venous access (mainly pneumothorax and arterial puncture). However, brachial access does not affect the main complication of EMB in the mid-long term: traumatic tricuspid regurgitation occurring after repeated biopsies that can be serious and symptomatic enough to require surgical correction.[3] Although brachial access does not reduce procedure time and fluoroscopy time is longer compared to jugular access, it seems evident that this access appears to be more comfortable for patients (although this is based on the testimony of only 19 patients as the authors admit in the limitations section). Therefore, the procedure described is especially appropriate for patients with HT, who represent the largest part of their series and in whom the repeated use of follow-up EMBs is widely accepted as a screening method for graft rejection.

In any case, we should mention that although the EMB still keeps its aura as the gold standard for the diagnosis of rejection, the lack of scientific evidence on this regard is astonishing. In the current era of evidence-based medicine and despite the fact that we have been using this technique for the last 30 years, there is no solid scientific evidence establishing its actual role in the management of patients. In the International Society for Heart and Lung Transplantation clinical practice guidelines,[4] systematic EMB for the detection of rejection has a weak recommendation (level IIa) with the lowest possible level of evidence (class C) and with no back up from scientific references.

Also, the histological interpretation of an EMB is rather subjective, the diagnostic criteria have been changed several times, and there is an alarming inter-observer variability.[5,6] Actually, its sensitivity and specificity are completely unknown. On the other hand, all HT groups have experienced the frustration of obtaining repeated false positives[7] and false negatives[8] to the point that there is often little correlation between the anatomopathological degree of rejection and the functional situation of patient and graft.

Therefore, we are not surprised by the numerous attempts to replace EMB with other non-invasive techniques, mainly echocardiographic. Results have been widely variable and they have never been implemented in the real clinical practice.[9] Over the last few years, sophisticated techniques like gene expression profiles have been introduced. However, they have only been applied to selected patients (low risk of rejection) and relatively late after the HT (> 2 months to 6 months), which in practice excludes most clinically relevant rejection episodes.[10,11]

The main problem of these attempts to replace EMB with non-invasive techniques is that we are comparing these new diagnostic approaches to EMB assuming that EMB is the gold standard. However, this argument is wrong from the beginning because this supposed gold standard is not such. To consider the EMB as the gold standard, the current standards of evidence-based medicine should be applied to undisputedly show that the current practice of systematic follow-up with periodic EMBs and histology-based treatment does actually improves clinical results.

In this context and given the uncertainties due to the frequent false positives and negatives obtained by the EMB, back in the 1990s here at *Hospital Universitario Marqués de Valdecilla* we developed a periodic clinical-echocardiographic follow-up strategy without performing mandatory EMBs.[12] Our strategy is based on this idea: as time goes by after the HT, the episodes of rejection are less aggressive and more spaced-out. Many subside spontaneously, but others may progress until they compromise the function of the graft and are detected either clinically or on the echocardiography. Although we lose diagnostic sensitivity, with this strategy we

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Online: 03-08-2020.
https://doi.org/10.24875/RECICE.M20000131

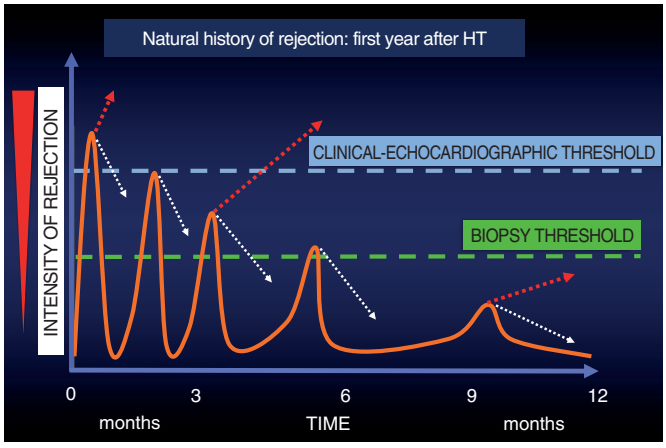

Figure 1. Graphic representation of the natural evolution of rejection within the first year after a heart transplant. The episodes of rejection are less intense and frequent across time. The dotted white arrows indicate spontaneous resolution of rejection thanks to baseline immunosuppression. The dotted red arrows indicate the continuous evolution of rejection.

achieve great clinical specificity because we are only identifying episodes of rejection that do not subside spontaneously (a minority according to experience) and that often respond well to treatment (figure 1).

Therefore, in these periodic reviews we conduct clinical assessments and obtain follow-up echocardiograms without mandatory EMBs that are only performed in suspected cases. Since we are looking for specificity, we only assess "hard" echocardiographic endpoints (relevant changes in wall thickness or a reduced ejection fraction) suggestive of rejection that warrant treatment. We decide not to use other techniques like strain, which is much more sensitive and would make us lose specificity.

After a 30-year experience and some 600 HTs performed, the use of EMB is marginal in our program.[13] The historic mean is 1.24 EMBs per patient, but over the last 10 years it has gone down to only 0.2. In our routine clinical practice we do not perform any EMBs at 1-year follow-up in most patients. Our confidence in this strategy is based on the clinical results that hold a favorable comparison to those of the Spanish Heart Transplant Registry[14] both in the mid and long term. If we exclude the first week after the HT (a time when EMBs are rarely performed), the actual survival rate of *Hospital Universitario Marqués de Valdecilla* is 85% at 1-year follow-up, 75% at 5-year follow-up, and 61% at 10-year follow-up, which is slightly higher compared to that of the Spanish Heart Transplant Registry[14] (84% at 1-year follow-up, 73% at 5-year follow-up, and 58% at 10-year follow-up).

In any case, the brachial vein access suggested by Tamargo et al.[2] is a warmly welcomed proposal, especially by the patients. Following the classic Stanford Protocol[15] a minimum of 14 EMBs should be performed per patient within the first year. This means that the better tolerance shown to this procedure, which is associated with fewer acute complications, can be very relevant for patients given the large number of biopsies they will need to undergo during follow-up.

Several aspects of the current HT management are based on expert opinions and clinical inertia rather than on scientific evidence. Among them, the myth that the EMB is the gold standard should not be accepted given the lack of evidence supporting it. We believe it is important to move forward in this field, but to do so non-invasive alternatives to EMB should change their current approach. Instead of comparing their diagnostic capabilities to those of the EMB (wrong gold standard), they should rather be based on comparing clinical results, which is ultimately what matters. Therefore, we believe that the time has come to design randomized clinical trials comparing clinical results among the different strategies to reduce the use of EMB based on non-invasive methods and review the traditional rule of performing mandatory EMBs.

CONFLICTS OF INTEREST

None reported.

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REC Interv Cardiol. 2020;2(4):244-246

Editorial

Use of cangrelor in percutaneous coronary interventions: a "new" weapon in the antithrombotic therapeutic armamentarium

Cangrelor en el intervencionismo coronario percutáneo: una «nueva» arma del arsenal terapéutico antitrombótico

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During the second half of 2019, cangrelor started selling in our country, a "new" antiplatelet drug with especial pharmacological properties that make it especially appealing for the management of certain clinical situations in the percutaneous coronary intervention (PCI) setting. The adjective "new" is in quotation marks because the clinical trial conducted proved its superiority compared to clopidogrel with ICP. The CHAMPION PHOENIX trial[1] was published in 2013 and it was approved by regulatory authorities back in 2015. This delay has probably caused the scientific evidence to lose relevance and, in consequence this drug might not be widely accepted within the cardiology community. Also, the indication specified in the technical label is only based on the conditions of the clinical trial that prompted its approval—which is mandatory—not on real-world practices. This may be confusing when selecting those patients who may benefit from this drug.[2]

In short, cangrelor is an intravenous reversible, high-affinity antagonist of the platelet $P2Y_{12}$ receptor of adenosine diphosphate to which it binds directly (without need for conversion into an active metabolite). In pharmacodynamic terms, the properties of cangrelor are: *a)* rapid onset of action (3 to 6 minutes); *b)* powerful dose-dependent effect (inhibition > 90% of the $P2Y_{12}$ receptor signaling pathway) in relation to the dose used in the PCI; and *c)* rapid offset of action (shot half-life of 3 to 5 minutes) with recovery of the baseline platelet function in 60 to 90 minutes after infusion.[3]

Given its pharmacological properties, cangrelor may help solve some of the problems posed by other antiplatelet agents. For example, oral $P2Y_{12}$ receptor inhibitors ($iP2Y_{12}$), especially clopidogrel and to a lesser extent prasugrel and ticagrelor, have a delayed optimal platelet inhibition, which is even more significant in the ST-segment elevation myocardial infarction (STEMI) setting, where the bioavailability of oral drugs may be compromised (worse intestinal absorption, vomiting, use of opioids or situations like intubation, therapeutic hypothermia or cardiogenic shock).[3,4] Also, despite their efficacy in reducing thrombotic events, the use of parenteral glycoprotein IIb/IIIa inhibitors, may be associated with a higher risk of bleeding.

The clinical development of cangrelor as a coadjuvant therapy in the PCI setting is based on the CHAMPION program, in which the first 2 studies conducted (CHAMPION PCI[5] and CHAMPION PLATFORM[6]) were prematurely interrupted due to their futility, in part attributed to a restrictive definition of myocardial infarction.[3,7] On the contrary, the CHAMPION PHOENIX clinical trial did prove the superiority of cangrelor vs clopidogrel reducing the main variable of efficacy (a composite of death, myocardial infarction, ischemia guided revascularization or stent thrombosis) after 48 hours in patients who underwent PCI to treat stable angina or any type of acute coronary syndrome (ACS) and who were not eligible for oral $iP2Y_{12}$ pretreatment.[1] We should mention that in a combined analysis of the 3 trials, cangrelor was associated with a slightly higher risk of bleeding mainly at the cost of minor bleeding;[8] this good safety profile is probably due to the fact that the drug is administered over a very limited span of time and its effect rapidly goes away after infusion.

The CHAMPION PHOENIX trial has received 2 important criticisms that may condition its implementation in our routine clinical practice. The first is that cangrelor was never compared to prasugrel or ticagrelor (more powerful and effective than clopidogrel and drugs of choice in patients with ACS). The second is that $iP2Y_{12}$ pretreatment before the PCI was considered an exclusion criterion. We should remember that, although there are serious doubts about its pretreatment benefit in the ACS setting, especially in the non-ST-segment elevation acute coronary syndrome setting,[9] this strategy is widely used in our country. As a matter of fact, the European technical label of this drug specifically says that cangrelor is indicated in association with acetylsalicylic acid in patients "who undergo PCI and have not received an oral $P2Y_{12}$ inhibitor before the PCI, and in whom oral treatment with $P2Y_{12}$ inhibitors is not possible or desired".[2] Still, the pharmacological properties of cangrelor make it especially interesting in situations where not only the aforementioned pretreatment has not occurred, but also in circumstances where it is considered insufficient. Proof of this is the experience published from the Swedish national registry (SCAAR) during the first 2 years of drug use that found an almost exclusive use of cangrelor in patients with STEMI who underwent primary percutaneous coronary intervention; in this real-world study, cangrelor was combined with ticagrelor mainly, although the latter had already been administered in over 50% of the times in the prehospital setting, which is why in such cases the use of cangrelor would be considered an off-label indication.[10]

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Online: 02-10-2020.
https://doi.org/10.24875/RECICE.M20000144

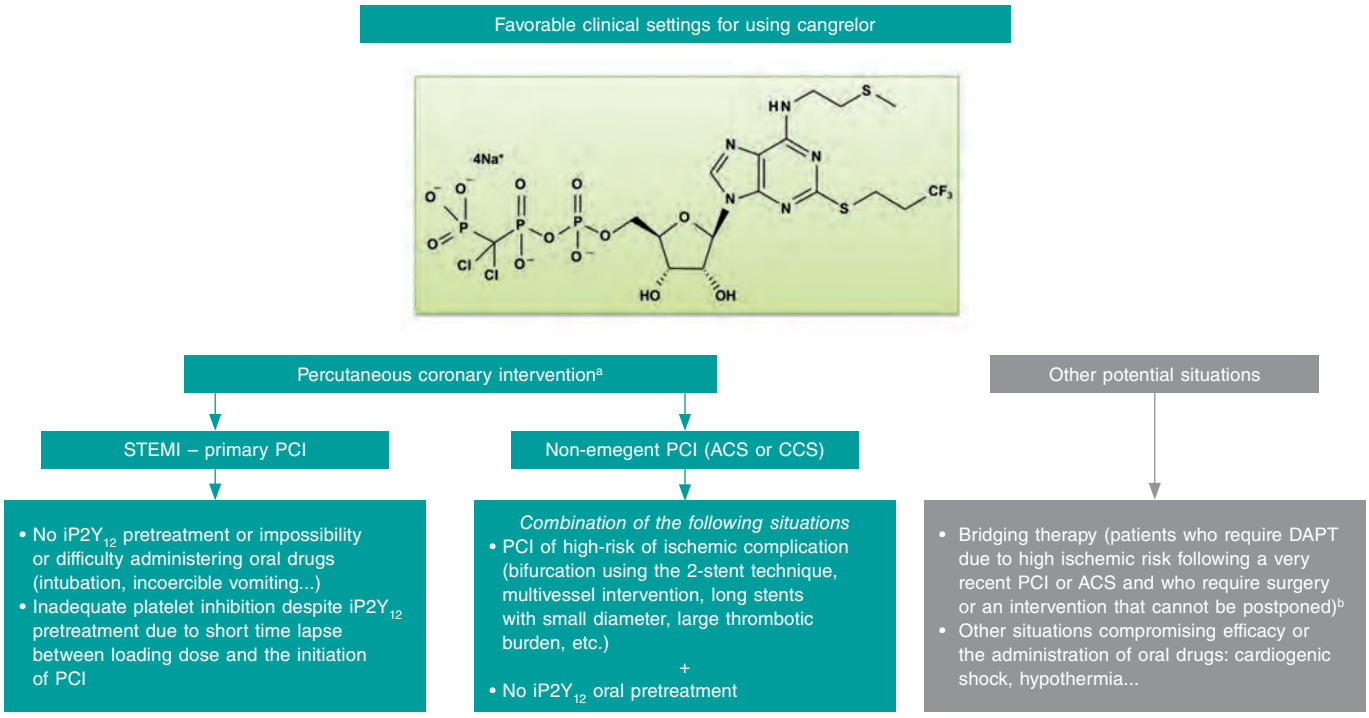

Figure 1. Potential favorable clinical settings for the use of cangrelor. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; iP2Y$_{12}$, platelet P2Y$_{12}$ receptor inhibitors; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation acute myocardial infarction.

[a]The dose in the percutaneous coronary intervention setting should be 30 µg/kg in bolus followed by an infusion at rate of 4 µg/kg/min.
[b]The dose studied in the bridging therapy is an infusion of 0.75 µg/kg/min.

The clinical settings where, in our opinion, cangrelor can be useful both in the PCI setting (most of the cases) and in other situations are shown on figure 1. The most relevant setting would be the primary percutaneous coronary intervention in the management of STEMI, where its use is appropriate in the absence of proper pretreatment with iP2Y$_{12}$ due to the impossibility or difficulty administering oral drugs (intubation or incoercible vomiting); it may also be considered if the loading dose of iP2Y$_{12}$ is ineffective during the procedure (short span of time elapsed from its administration until the PCI is performed). Another acceptable situation (much less common than the latter) would be non-emergent high-risk PCIs (such as bifurcations using the dual stent technique, multivessel interventions, in the presence of great thrombotic load, etc.) in patients without iP2Y$_{12}$ pretreatment. In any case, the drug potential benefit should always be weighed to prevent intraprocedural thrombotic events associated with the procedure and the patient's bleeding risk. Also, we should remember that the use of cangrelor is ill-advised if glycoprotein IIb/IIIa inhibitors are going to be administered.

Other relevant aspects are the duration of infusion that can be reasonably maintained for at least 2 hours after the PCI. According to the drug technical label, it should be started before the procedure and the infusion lasting at least 2 hours or for as long as the procedure lasts, which ever is longer. Still, this may not be enough in situations where the oral drugs early action is delayed. Also, special care is needed when transitioning to oral drugs; in general, the recommendation here is that ticagrelor can be administered at all times (before, during or after infusion) while thienopyridines can be prescribed after infusion (to avoid an interaction that would imply a time lapse without the proper antiplatelet therapy).[3]

Taking all this into consideration, cangrelor should be primarily used in the cath lab in situations of periprocedural high thrombotic risk when oral iP2Y$_{12}$ pretreatment has not occurred, is ill-advised or insufficient. The availability of the drug will probably not change our antiplatelet strategy radically in the short term in the PCI setting. However, in some situations (especially primary percutaneous coronary interventions) its particular pharmacological profile will be very useful. Therefore, its use will probably grow in the interventional cardiology community as we become more familiar with it. In conclusion, cangrelor is an interesting addition to our therapeutic armamentarium in the PCI setting because it can individualize and, therefore, optimize our antithrombotic strategy.

CONFLICTS OF INTEREST

J.L. Ferreiro has declared he has received funds for his lectures for Eli Lilly Co., Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, and Ferrer; also, he has received funds for his counselling for AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Inc., Bristol-Myers Squibb; he has also receive research grants from AstraZeneca. J.A. Gómez-Hospital has declared he has received funds for his counselling for Abbott, Medtronic, Boston Scientific, Terumo, and IHT.

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REC Interv Cardiol. 2020;2(4):247-255

Original article

Contemporary management of spontaneous coronary dissection

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ABSTRACT

Introduction and objectives: Spontaneous coronary artery dissection (SCAD) is a rare but increasingly recognized cause for acute coronary syndrome. The optimal management and treatment of SCAD is still unknown.
Methods: Data analysis of a prospective protocol including centralized care management of a consecutive series of patients with SCAD diagnosed between January 2010 and December 2018. Major adverse cardiovascular events included all-cause mortality, new myocardial infarction, coronary revascularization, ventricular arrhythmia, heart failure or stroke.
Results: A total of 33 consecutive patients were included (41 lesions). Intravascular imaging modalities were used to confirm the diagnosis in 42% patients. None of the patient showed images of thrombus formation in the true lumen. Conservative treatment was the initial approach in most of the cases (82%). No deaths were reported during the index admission, but 15% experienced major adverse cardiovascular events. The coronary computed tomography angiography performed in 58% of patients during the admission identified SCADs in 79% of the patients. Most of the patients managed with conservative treatment received only 1 antiplatelet agent for a limited period of time (17 months [9-35]). During a median clinical follow-up of 33 months [13-49], 82% of patients did not have any adverse events. The angiographic surveillance obtained in 48% of patients at the 6-month follow-up confirmed the complete healing of the SCAD image in 86% of the patients. The screening for extracoronary vascular findings (97% of patients) resulted in a high prevalence of abnormalities (59%).
Conclusions: The unrestricted use of intravascular imaging modalities showed no thrombus in the true lumen of patients with SCAD. In patients managed with conservative treatment, a limited course of antiplatelet monotherapy is safe and provides good clinical outcomes. Performing a coronary computed tomography angiography in the acute phase of SCAD is useful at the follow-up. The screening for extracoronary vascular findings confirmed a high prevalence of abnormalities.

Keywords: Spontaneous coronary artery dissection. Coronary artery disease. Acute coronary syndrome. Optical coherence tomography. Fibromuscular dysplasia.

Manejo contemporáneo de la disección coronaria espontánea

RESUMEN

Introducción y objetivos: La disección coronaria espontánea (DCE) constituye una causa infrecuente, pero cada vez más reconocida, de síndrome coronario agudo. La actitud diagnóstico-terapéutica idónea sigue sin esclarecerse.
Métodos: Análisis del seguimiento prospectivo y centralizado de una serie de pacientes consecutivos diagnosticados de DCE desde enero de 2010 hasta diciembre de 2018. Se definió evento cardiovascular adverso mayor como la aparición de muerte de cualquier causa, reinfarto no mortal, revascularización no planificada, arritmia ventricular, insuficiencia cardiaca o ictus.
Resultados: Se incluyó a 33 pacientes con DCE (41 lesiones). En el 42% se realizó un estudio con imagen intracoronaria para confirmar el diagnóstico, sin identificar trombo en la luz verdadera en ninguno de ellos. En la mayoría de los casos (82%) se

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Received 27 November 2019. Accepted 20 January 2020. Online: 26-02-2020.
https://doi.org/10.24875/RECICE.M20000096

eligió un tratamiento médico conservador. Ningún paciente falleció durante el ingreso, pero el 15% presentó algún evento mayor. En el momento agudo se realizó tomografía computarizada coronaria al 58% de los pacientes y se identificó la DCE en el 79% de los casos. La mayoría de los pacientes con tratamiento conservador recibieron antiagregación simple un tiempo limitado (17 meses [9-35]). Con una mediana de seguimiento de 33 meses [13-49], el 82% no sufrió ningún evento adverso. Al 48% se les realizó control angiográfico a los 6 meses, que mostró resolución en el 86% de los casos. El cribado de anomalías vasculares extracoronarias se realizó en el 97% de los pacientes y se hallaron alteraciones en el 59%, incluyendo 3 pacientes con aneurisma intracraneal.
Conclusiones: En esta serie, con una amplia utilización de imagen intracoronaria, no se ha identificado trombo en la luz verdadera en ningún caso de DCE. En los pacientes tratados de forma conservadora, la monoterapia antiagregante es segura y se asocia a buenos resultados clínicos. La tomografía computarizada coronaria durante el ingreso es útil en el seguimiento. El cribado sistemático de anomalías vasculares extracoronarias revela una alta prevalencia de alteraciones.

Palabras clave: Disección coronaria espontánea. Enfermedad coronaria. Síndrome coronario agudo. Tomografía de coherencia óptica. Displasia fibromuscular.

Abbreviations

ACS: acute coronary syndrome. **EVA:** extracoronary vascular abnormalities. **FMD:** fibromuscular dysplasia. **PCI:** percutaneous coronary intervention. **SCAD:** spontaneous coronary artery dissection.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome (SCA). However, especially in women, it has been identified as the underlying pathophysiological mechanism in a growing percentage of cases. SCAD is defined as the separation of the coronary artery wall layers not associated with trauma, iatrogenesis, atherosclerosis or extension of an aortic dissection.[1] Clinical signs are myocardial ischemia and are due to the coronary flow limitation that alters the arterial parietal structures.

The first description ever reported by Pretty[2] back in 1931 was followed by the description of isolated cases and small series for years. However, we have recently seen a significant increase of information on SCADs lately. Nowadays, clinical profile, diagnostic and therapeutic approach, and prognosis can be found in the SCAD and they vary significantly compared to atherosclerosis—the most common cause of ACS.[3,4] Even the European Society of Cardiology[5] and the American Heart Association[6] have recently published 2 consensus documents on this disease.

In light of the growing evidence and in an attempt to enrich it, back in 2010 our center started a specific program of diagnosis and follow-up of patients with SCAD. The results and conclusions are presented here.

METHODS

All cases of SCAD were collected prospectively since 2010. Diagnosis, treatment, and follow-up were centralized and unified according to the scientific evidence available at the time. Given the length of the study period (9 years) and the extensive medical literature available on this issue over the years, new aspects in the assessment of patients (such as fibromuscular dysplasia [FMD]) have been introduced gradually. This protocol and the data collection book were approved by our center ethics committee and registered in a validated repository (NCT03607981). The patients' informed consents were obtained in all cases.

Clinical information and follow-up

The demographic characteristics, the patients' personal past medical histories, data at admission, and disease progression were collected in the clinical history at admission and follow-up in a SCAD monographic review (T. Bastante). The coronary angiography and intravascular imaging studies were analyzed by 3 expert interventional cardiologists (T. Bastante, M. García-Guimaraes, and F. Alfonso) and the final diagnosis of SCAD was only established if they all agreed unanimously. The use of intracoronary imaging modalities (intravascular ultrasound [IVUS] or optical coherence tomography [OCT]) was left to the operator's discretion. However, it was recommended in cases of suspicious diagnosis (especially type 2 and 3 SCADs according to Saw angiographic classification[7]) or need to perform PCI as long as the segment under study was accessible and in a not overly tortuous artery. When the OCT was used, the intracoronary image was classified as double lumen when the separation of the arterial layers originated true and false lumens, both with lack of refraction due to complete contrast washout. Intramural hematoma was defined as the separation of arterial layers occupied by moderately refracting material with an attenuation consistent with intraparietal bleeding without complete contrast washout. Both the IVUS and the OCT tried to identify the communication between the false and the true lumen and the presence of thrombotic material in the latter (figure 1 shows typical examples). The initial recommended treatment was a wait-and-see conservative approach and the PCI was only performed in cases of clinical instability or symptom persistence. During admission, and as long as it was possible, a coronary computed tomography (CT) scan was performed for a better characterization of coronary lesions. This information was used during follow-up as a comparative pattern in a new coronary CT scan to confirm the healing of the SCAD or in the reappearance of symptoms for reevaluation purposes. Patients with a diagnosis suggestive, but not definitive,

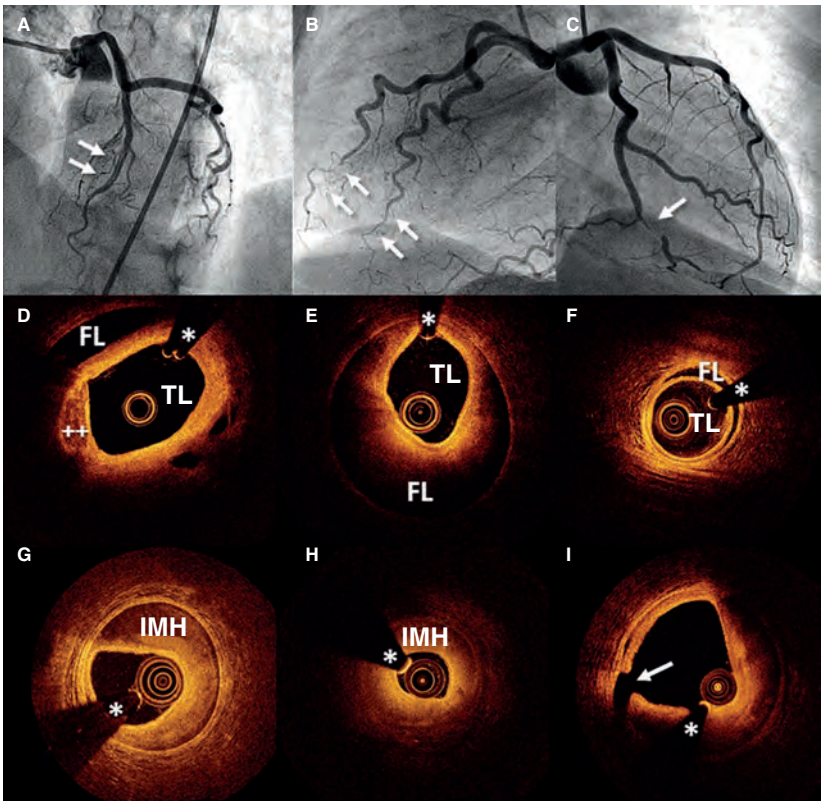

Figure 1. Images of angiography (**A-C**) and optical coherence tomography (OCT) (**D-I**). **A:** type 1 spontaneous coronary dissection (SCAD) in the medial portion of the left anterior descending coronary artery. The arrows point to the characteristic imaging of double lumen with linear intraluminal filling defect outlined by contrast (video 1 of the supplementary data). **B:** type 2 SCAD in distal left anterior descending coronary artery and diagonal branch. The arrows point to the sudden loss of vessel caliber with length > 20 mm (video 2 of the supplementary data). **C:** type 3 SCAD in obtuse marginal artery. The arrows point to focal stenosis with length < 20 mm similar to an atherosclerotic lesion (video 3 of the supplementary data). **D-F:** OCT images showing the double lumen morphology (TL, true lumen; FL, false lumen). Note the unusual image of subintimal calcium displaced with the flap (++). **G-H:** morphology of intramural hematoma (IMH). **I:** entry (arrow) with partially thrombosed false lumen. The asterisk (*) shows guidewire artifact.

of SCAD were scheduled to receive a control coronary angiography within the following months.

Definitions

In order to classify the angiographic patterns of SCAD, the aforementioned specific classification developed by Saw et al.[7] was used (figure 1 shows examples of this). Two different criteria of success were established for cases where a PCI was required. In the first place, conventional procedural success was defined as a final TIMI flow grade 2-3 (Thrombolysis in Myocardial Infarction) with residual stenosis < 30% after stent/scaffold implantation or < 50% after simple balloon angioplasty. Secondly, the PCI-SCAD was considered successful with flow improvements ≥ 1 grade in the TIMI score and a final TIMI flow grade of 2-3.[8] Major cardiovascular adverse events (MACE) at the follow-up included all-cause mortality, reinfarction, unscheduled revascularization, ventricular arrhythmia, heart failure, and stroke.

Screening of extracoronary vascular abnormalities

Since 2013 and as long as it was possible, a selective angiography of both renal and iliac arteries during the diagnostic coronary angiography was performed. Also, 3 to 6 months after the event, the study was completed using the angio-CT scan to examine the floor of the middle cranial fossa up to the femoral arteries (modification of the protocol published by Liang et al.[9]) including intracranial vessels, supra-aortic trunks, the aorta, and mesenteric, renal, and iliac branches. FMD was defined as the presence of focal narrowing separated by dilatation areas with the traditional «pearl necklace» appearance (multifocal shape) or the presence of tubular focal lesions (unifocal shape). Aneurysms were defined as dilatations > 50% with respect to the caliber of the normal, adjacent arterial segment. Dissection was defined as a double lumen morphology in the arterial segment. The screening of extracoronary vascular abnormalities (EVA) was considered complete when the intracranial territories, supra-aortic trunks, the aorta, and the splanchnic, renal, and iliac territories all had been examined (using angiography, angio-CT scan or both).

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median [interquartile range] according to their distribution. Categorical variables were expressed as numbers (percentage). The analysis was conducted using the STATA 12 statistical software package (StataCorp LLC, United States).

RESULTS

Between January 2010 and December 2018 our center performed 12 951 diagnostic coronary angiographies that identified 37 SCADs

Table 1. Baseline characteristics of the patients

	n = 33
Women	32 (97)
Age (years)	56 ± 12
Race	
Caucasian	28 (85)
Other	5 (15)
Cardiovascular risk factors	
Smoking habit	
Current smoker	9 (27)
Former smoker	7 (21)
Hypertension	12 (36)
Hypercholesterolemia	14 (42)
Diabetes	2 (6)
Family history of ischemic heart disease	4 (12)
Family history of SCAD	2 (6)
Relevant findings	
Previous diagnosis of ischemic heart disease	5 (15)
Confirmed diagnosis of previous SCAD	2 (6)
Chronic inflammatory disease	3 (9)
Depressive disorder	5 (15)
Anxiety disorder	9 (27)
History of hypothyroidism	11 (33)
Gynecological/obstetric past medical history	**n = 32**
Menopause	24 (75)
Menopause age (years)	49 ± 4
Hormone replacement therapy	2 (7)
Oral hormonal contraceptive	1 (3)
Intrauterine device	1 (3)
Nulliparous	3 (9)
Multiparous	18 (44)
History of miscarriage	3 (9)

SCAD, spontaneous coronary artery dissection.
Data are expressed as no. (%) or mean ± standard deviation.

(41 lesions) in 33 patients (0.28%). Prevalence among the coronary angiographies performed due to ACS (4185) was 1%, although prevalence among women in this context rose to 3%. If the percentage of patients with a final diagnosis of SCAD in the group of women with ACS under 50 is analyzed, prevalence rose to 12.5%. There are more diagnoses over the years from 1 or 2 patients per year initially to 5-7 annual patients over the last period (figure 1 of the supplementary data).

The baseline characteristics of the patients included in the study are shown on table 1. Most (97%) were middle-aged women (56 ± 12 years). Only 7 women (21%) had no traditional cardiovascular risk factors. Five patients (15%) had a personal past medical history of ischemic heart disease, 2 of them with a confirmed diagnosis of SCAD. A study conducted *a posteriori* confirmed that the remaining 3 patients showed clinical signs consistent with an initially misdiagnosed SCAD (ACS with coronary arteries interpreted as normal, 1 of them in the peripartum).

Table 2 shows the characteristics at hospital admission and during the angiographic assessment. All patients presented with myocardial infarction, most of them (73%) with non-ST-elevation acute myocardial infarction. There was a trigger factor in one third of the cases; the most common was emotional stress (21%) followed by intense physical exercise (9%). Presentation at the peripartum was rare (1 patient only). The artery most frequently compromised was the left anterior descending coronary artery (51%). Eighteen percent of the patients had multivessel disease. Intracoronary imaging modalities (IVUS or OCT) were used in 42% of the cases, mostly OCT (33%). Sixteen lesions in 14 patients were assessed. Those assessed through the OCT confirmed the presence of fenestration between the false and the true lumen in 7 lesions (58%). There were no images consistent with thrombi in the true lumen in any of the cases assessed using intracoronary imaging modalities.

Table 3 shows treatment and the in-hospital disease progression. Initial conservative treatment was the first option in most cases (82%). Only 6 patients were treated with PCI as the initial strategy, 4 of them due to progressive flow worsening with the injections of contrast. The PCI conventional success was reported in 50% of the cases, and the PCI-SCAD success in 67% of the cases. One iatrogenic dissection was reported in the left main coronary artery.

During in-hospital disease progression no patient died or suffered any reinfarctions. However, a new coronary angiography was required in 4 patients with symptoms. Except for the patient with a left main coronary artery iatrogenic dissection initially treated with conservative treatment no case was due to failed initial conservative treatment. The remaining 3 patients had acute stent thrombosis, SCAD of a vessel other than the index, and progression of the SCAD adjacent to the segment treated with the stent. Overall, the rate of in-hospital MACE was 15% and events focused on patients who required PCI. Acetylsalicylic acid (ASA) was prescribed to 94% of the patients at hospital discharge and dual antiplatelet therapy to 14 patients only (42%) of whom 7 required PCI. Fifty-eight percent of the patients received coronary CT scans during admission and images consistent with SCAD were found in 79% of the cases.

Table 4 shows out-of-hospital disease progression. Median follow-up was 33 months [13-49], the overall rate of events was 18%. Two deaths were reported, 1 due to cardiovascular causes (sudden death 6 years after the SCAD) and the other due to non-cardiovascular causes (sepsis in the abdominal postoperative). Only 1 patient required a new revascularization due to restenosis of the stent implanted to treat the SCAD. Three out of the 4 patients (12%) with SCAD relapse had suffered events prior to the index event that were compatible with SCAD; that is, each one of them had presented with, at least, 3 events. Except for 1 recurrence at the 7-month follow-up, most events occurred more than 2 years after the index event (figure 2). Regarding pharmacological treatment, ASA was kept for a median 17 months [9-35] after the event and the second antiplatelet drug was withdrawn early in most of the patients. Of the patients who received conservative treatment, only 25% were still on dual antiplatelet therapy 6 months after the event (median 0 months [0-6]). In those patients who required PCI, dual antiplatelet therapy was keep for a median 5 months [1-7].

Angiography control was performed in 48% of the patients, in 9 of them using coronary CT scan and invasive coronary angiography

Table 2. Characteristics of the patients at hospital admission and in the angiographic assessment

	n = 33
Clinical diagnosis at admission	
STEMI	9 (27)
NSTEMI	24 (73)
Event-triggering factors	11 (33)
Intense physical exercise	3 (9)
Emotional stress	7 (21)
Peripartum	1 (3)
Angiographic characteristics	**n = 33 (41 lesions)**
Access	
Radial	29 (88)
Femoral	4 (12)
Diseased vessel	
Left anterior descending coronary artery	21 (51)
Circumflex artery	10 (24)
Right coronary artery	10 (24)
Diseased segment	
Proximal	10 (24)
Medial	11 (27)
Distal	20 (49)
Secondary branches	18 (44)
Multivessel disease	6 (18)
Multi-segment disease	13 (32)
Saw et al. angiographic classification[7]	
Type 1	6 (15)
Type 2	32 (78)
Type 3	3 (7)
Percentage of stenosis (visual estimate)	77 ± 24
Length of the lesion (mm)	41 ± 28
Initial TIMI flow grade	
0	5 (12)
1	5 (12)
2	1 (2)
3	3 (73)
Intracoronary imaging modality	**n = 14 (16 lesions)**
IVUS	4 lesiones
Fenestration	0
Thrombus	0
OCT	12 lesions
Double lumen	7 (58)
Intramural hematoma	2 (16)
Both	3 (25)
Fenestration	7 (58)
Thrombus	0

CT, computed tomography; IVUS, intravascular ultrasound; NSTEMI, non-ST-elevation acute myocardial infarction; OCT, optical coherence tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
Data are expressed as no. (%) or mean ± standard deviation.

Table 3. Management and in-hospital disease progression of patients

	n = 33
Initial treatment	
Conservative	27 (82)
PCI	6 (18)
PTCA-balloon	2 (6)
Bare-metal stent	2 (6)
Drug-eluting stent	1 (3)
Bioresorbable vascular scaffold device	1 (3)
Results from the PCI group	**n = 6**
Conventional success	3 (50)
PCI-SCAD success	4 (67)
In-hospital disease progression	**n = 33**
Peak troponin T levels (ng/mL)	378 [132-1705]
Peak creatine kinase levels (U/L)	403 [169-1181]
Left ventricular dysfunction [LVEF < 50%]	5 (17)
Segmental abnormalities on the TTE	17 (52)
MACE	5 (15)
Death	0
Reinfarction	0
New coronary angiography	4 (12)
Unplanned revascularization	3 (9)
PCI group (n = 6)	2 (33)
Conservative management group (n = 27)	1 (4)
Ventricular tachycardia/fibrillation	2 (6)
Heart failure	1 (3)
Hospital stay (days)	4 [3-7]
Coronary CT scan at admission	**n = 19 (58)**
SCAD visible on the coronary CT scan	15 (79)
Treatment at hospital discharge	**n = 33**
ASA	31 (94)
Clopidogrel	9 (27)
Ticagrelor	5 (15)
Prasugrel	0
Dual antiplatelet therapy	14 (42)
Anticoagulation	2 (6)
Beta-blockers	28 (85)
ACEI/ARA II	21 (64)
Statins	25 (76)
Nitrates	3 (9)
Calcium antagonists	3 (9)

ACEI, angiotensin-converting enzyme inhibitors; ARA-II, angiontensin II receptor antagonist; ASA, acetylsalicylic acid; CT, coronary tomography; LVEF, left ventricular ejection fraction; MACE, major cardiovascular adverse events; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SCAD, spontaneous coronary artery dissection; TTE, transthoracic echocardiography.
Data are expressed as no. (%) or mean ± standard deviation or median [interquartile range].

Table 4. Out-of-hospital disease progression and follow-up of the patients

	n = 33
Follow-up time (months)	33 [13-49]
MACE	6 (18)
Death	2 (6)
New AMI	3 (9)
Recurrence	4 (12)
New revascularization	1 (3)
Heart failure	1 (3)
Stroke	1 (3)
Time on ASA (months)	17 [9-35]
Time on dual antiplatelet therapy (months)	
Conservative treatment group	0 [0-6]
PCI group	5 [1-7]
Control SCAD	**n = 16 (48)**
Coronary CT scan	9
Planned	6
Due to symptoms	3
Invasive coronary angiography	11
Planned	3
Due to symptoms	8
Screening of EVA	**N = 32 (97)**
Type of screening	
CT scan	18 (56)
Angiography	5 (16)
Angiography + CT scan	9 (28)
Complete screening	28 (88)
EVA data	19 (59)
Type of EVA	
Fibromuscular dysplasia	15 (47)
Aneurysm	5 (15)
Other	1 (3)
Location of EVA	
Renal arteries	9 (28)
Iliac arteries	7 (22)
Supra-aortic trunks	5 (16)
Intracranial	3 (9)
Other	5 (16)

AMI, acute myocardial infarction; ASA, acetylsalicylic acid; CT, computed tomography; EVA, extracoronary vascular abnormalities; MACE, major cardiovascular adverse events; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.
Data are expressed as no. (%) or mean ± standard deviation or median [interquartile range].

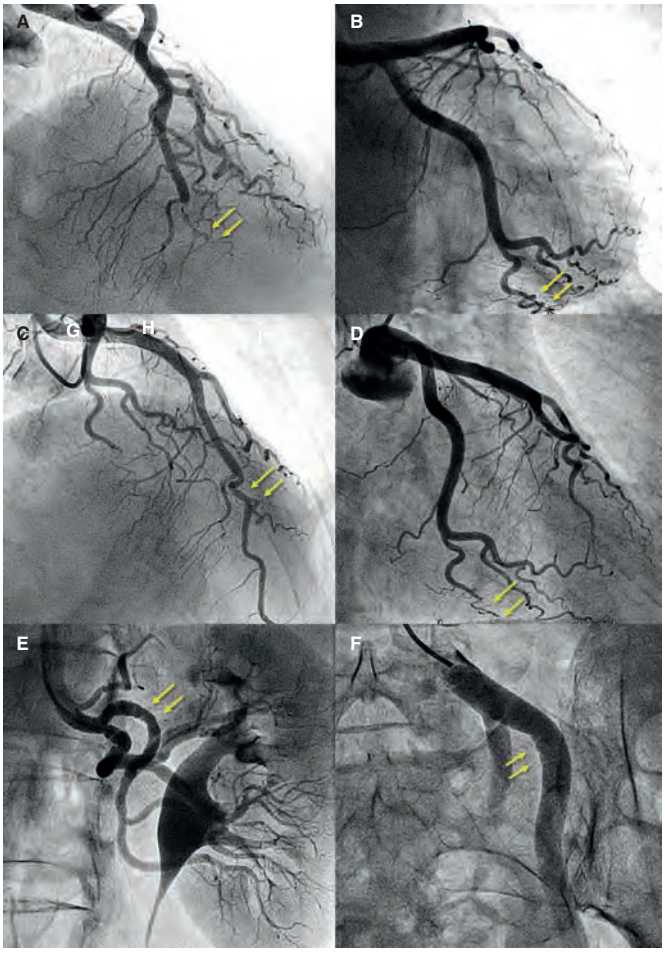

Figure 2. Fifty-five-year old woman with non-ST-elevation acute myocardial infarction (NSTEMI). She had experienced 2 previous acute myocardial infarctions with «normal coronary arteries» according to the coronary angiography. **A:** sudden caliber loss with tapering until the occlusion in the medial-distal portion of the left anterior descending coronary artery compatible with spontaneous coronary artery dissection (SCAD); conservative treatment. **B:** tortuous obtuse marginal artery without evident abnormalities. Two years later new hospitalization due to NSTEMI. **C:** caliber and flow recovery in the anterior descending coronary artery. **D:** obtuse marginal artery with sudden caliber loss and tapering (compare to **B**) compatible with SCAD; conservative treatment. **E-F:** selective angiographies of left renal and left iliac arteries with fibromuscular dysplasia.

in 11 patients. The coronary CT scan was performed in 3 patients in the context of a new episode of chest pain. After comparing it with the previous CT scan performed at the index event, the new SCAD was discarded (figure 3). However, most coronary angiographies were performed in the context of a new cardiac event; only 3 patients received a planned control coronary angiography. Out of the 16 patients on angiographic control, imaging improved with *restitutio ad integrum* in 75% of them. Six months after the SCAD, the documented rate of resolution rose to 86%.

The screening of EVA was performed in 97% of the patients (full screening in 88%). Fifty-nine percent of the patients showed abnormalities that went up to 61% when the screening of EVA was complete. The abnormality most commonly found was FMD (47%) followed by arterial aneurysms (in 5 patients, 3 of which were intracranial aneurysms). The renal and iliac arteries were the most commonly compromised arteries of all: half of the patients studied showed abnormalities in either one of these arteries (examples in

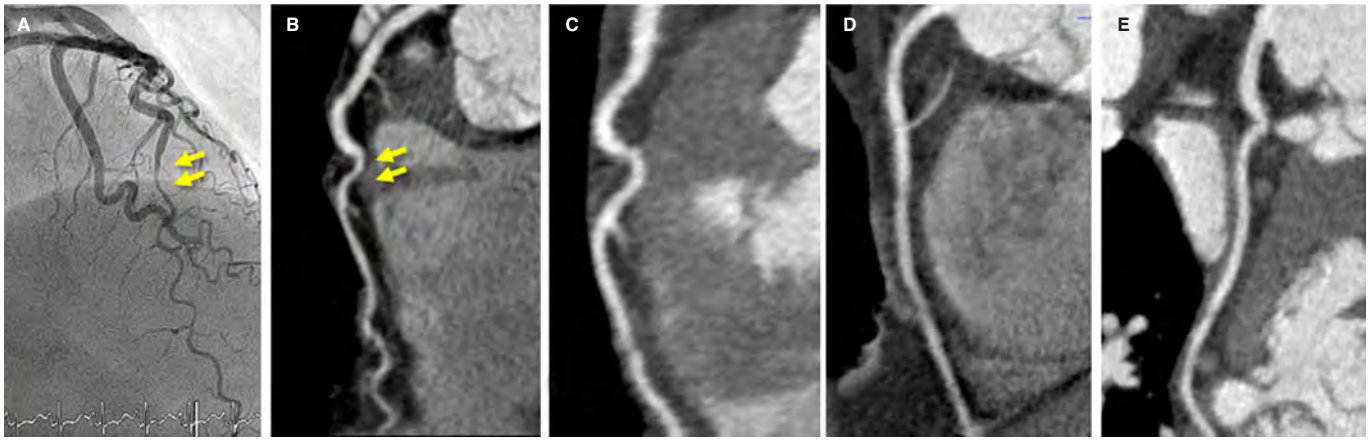

Figure 3. Fifty-three-year old woman with non-ST-elevation acute myocardial infarction. After a tortuous segment, the sudden caliber loss of the left anterior descending coronary artery with vessel tapering can be seen (arrows) on the coronary angiography (**A**) and coronary computed tomography (CT) scan (**B**) compatible with a spontaneous coronary artery dissection (SCAD) at the medial-distal portion of the left anterior descending coronary artery. Four years later, the patient presents to the ER with prolonged chest pain without alterations on the ECG or high markers of myocardial damage. The coronary CT scan shows the coronary arteries without images indicative of SCAD. **C:** left anterior descending coronary artery. **D:** right coronary artery. **E:** circumflex artery.

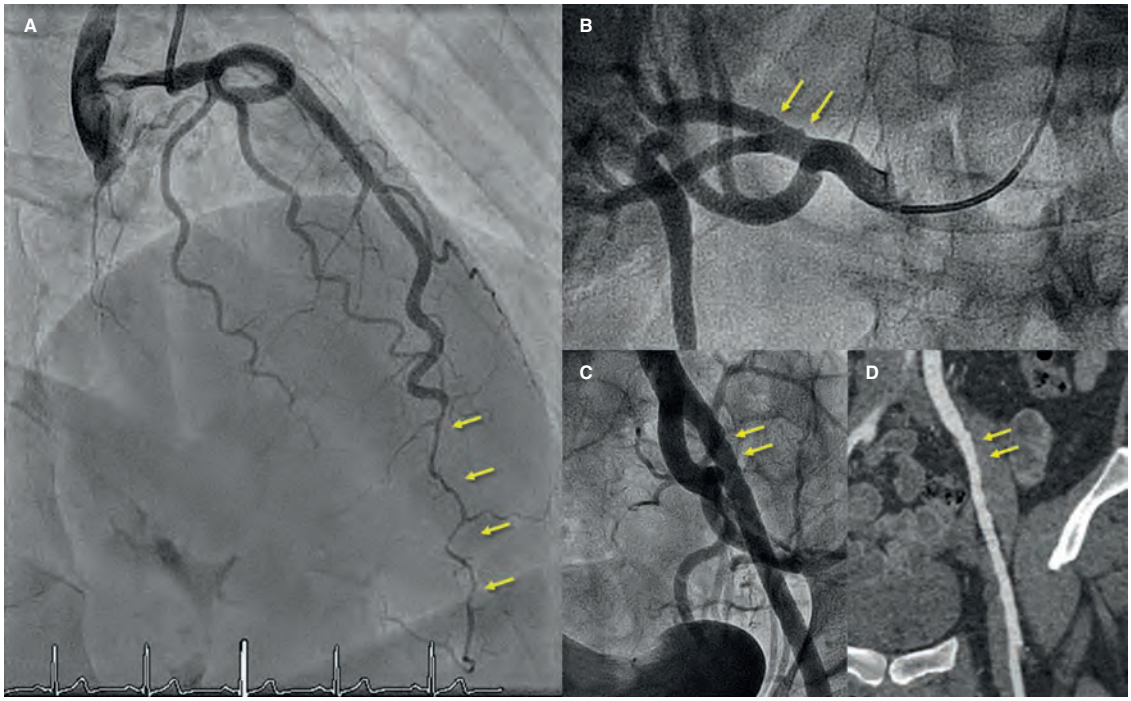

Figure 4. Forty-five-year old woman with non-ST-elevation acute myocardial infarction. The coronary angiography (**A**) shows a spontaneous coronary artery dissection at the medial-distal portion of the left anterior descending coronary artery (arrows). During catheterization the selective coronary angiography performed on the right renal (**B**) and left iliac arteries (**C**) shows wall irregularities compatibles with fibromuscular dysplasia (arrows). **D:** coronary computed tomography angiography at the follow-up with findings compatible with fibromuscular dysplasia on the left external iliac artery (arrows); note the greater sensitivity of coronary angiography (**C**) for the detection of subtle parietal abnormalities compared to coronary computed tomography angiography (**D**).

figure 2 and figure 4). After the study, the stroke team indicated the closure of the 3 intracranial aneurysms.

DISCUSSION

This study prospectively reports on the results of a current series of patients with SCAD with an updated and systematized diagnostic-therapeutic process and prolonged clinical follow-up. The clinical profile is consistent with what it is known about this disease:[3,8,10] middle-aged woman with risk factors and low concomitance of chronic inflammatory disorders, autoimmune diseases or collagen diseases. Both the presentation and the angiographic characteristics were consistent with what has already been described: non-ST-elevation acute myocardial infarction that damaged the medial-distal segments and secondary branches predominantly with a higher incidence reported on the left anterior descending coronary artery. The most common Saw angiographic classification was type 2. Comparatively, in this series, the use of intracoronary imaging modalities was superior to other larger and recent series (42% vs

7.6% and 13% in the series of Saw et al.[10] and Tweet et al.,[8] respectively); this brings high reliability in the inequivocal diagnosis of SCAD. The most important conclusions of intracoronary imaging are: *a)* when OCT was the imaging modality used, the fenestration of both lumens could be identified in half of the lesions; *b)* the presence of mixed patterns (double lumen and intramural hematoma) within the same lesion is not an uncommon finding, which supports the evolutionary theory between both patterns; and *c)* lastly and probably the most important conclusion of all, intraluminal thrombi were not found in any of the lesions studied.

As it has already been described, an initial wait-and-see conservative approach with no interventions seems to bring good results to patients with SCAD.[8,10,11] The rate of in-hospital MACE was low (15%). No deaths were reported, and bailout revascularizations were not necessary in any of the patients who received conservative treatment, except for 1 case due to iatrogenic dissection of left main coronary artery during the initial catheterization. Also, during the patients' initial disease progression, they already showed preserved left ventricular ejection fraction. Similarly, out-of-hospital disease progression was good: 2 deaths were reported (1 due to non-cardiovascular causes) at the 2.7-year median follow-up, and 12% had a new episode of SCAD. These are similar data to those described in a Canadian series[12] (10.4% at the 3.1-year median follow-up) and significantly lower to the rate of recurrence of 27% at the 2.3-years of median follow-up reported by Mayo Clinic.[8]

Unlike the atherosclerosis related ACS, in SCAD the ideal antithrombotic therapy has not been totally established. It seems logical to avoid aggressiveness, especially when 1 of the most plausible etiopathogenic theories is intraparietal bleeding of *vasa vasorum* as the initial event.[13,14] Therefore, given the lack of intraluminal thrombus in a high percentage of patients studied with IVUS and OCT in this series a low-intensity antithrombotic therapy was used. ASA was kept for an average 1.5 years and the second antiplatelet drug was only indicated at hospital discharge in patients who required PCI and for the shortest period of time possible. The satisfactory disease progression reported with rates of out-of-hospital events consistent with those reported in other large series (from 10% to 20%)[1] and the low rate of recurrence suggest that low-intensity antithrombotic therapy can be an excellent option for these patients.

There is very little information on the value of coronary CT scan during SCAD related hospitalizations. It was performed in 58% of patients from this series and SCAD was identified in three fourths of the cases. A more extensive analysis of these findings has been recently published by our group.[15] The current study shows that this information was very useful in the follow-up of 3 patients to discard new episodes of SCAD and avoid the coronary angiography and associated risks for the patients (3.4% of iatrogenic dissections in patients with SCAD).[16] However, in one fourth of the patients the SCAD could not be identified in the acute phase not even with the previous coronary angiography as guidance. Therefore, the value of coronary CT scan as an early diagnostic imaging modality is limited in this context.

Back in 2012 the association between SCAD and FMD[17] was described for the first time, and later studies only not confirmed the high prevalence of this association but also of other EVA (aneurysms, dissections, and thrombosis).[18-20] In the European consensus document recently published the screening of EVA is recommended in patients with SCAD.[5] To our knowledge and up to this day this study shows the results of the most complete screening of FMD and other EVA. With a study in 97% of the patients—complete in 88%—the great presence of EVA (60%) confirms this interesting association. The need to conduct these studies may be put into question since most findings are associated with discrete and typical parietal abnormalities of FMD that do not lead necessarily to significant functional disorders. As a matter of fact, after the long follow-up of patients and despite the high prevalence of EVA, the extracardiac arterial events reported were only 1 stroke. However, there are 3 reasons to support the screening: *a)* in case of suspicious diagnosis, it may be the key to confirm the diagnosis of SCAD;[21] *b)* knowing arterial parietal structural alterations can be useful for the diagnosis and treatment of future extracardiac events; and *c)* the finding of intracranial aneurysms is not negligible (9% in our series, but up to 14% in the Canadian series[16]) and it is relevant due to the risk of intracranial bleeding and secondary morbimortality. As a matter of fact, in 3 of our patients a percutaneous coronary intervention was indicated to seal the intracranial aneurysm.

Limitations

The main limitations of this study are the small size of the sample and the fact that it focused on a single center only. However, this study has a long follow-up with a unified treatment given the centralization of the patients.

CONCLUSIONS

In our center the centralization and protocolization of patients with SCAD systematized both treatment and the performance of additional tests. Intracoronary imaging allows us to confirm diagnosis in angiographically suspicious cases without showing any thrombi in the true lumen whatsoever. A low-intensity antithrombotic strategy with ASA only and for a limited period of time seems to give good results in the management of SCADs with conservative treatment. The high rate of spontaneous resolution of SCAD was confirmed in the 6-month images. Over half of the patients with SCADs show some EVA. Performing a coronary CT scan in the acute phase was useful, comparatively speaking, in new events and scheduled controls.

CONFLICTS OF INTEREST

F. Alfonso is an associate editor of *REC: Interventional Cardiology*; the editorial protocol of the journal was observed to guarantee an impartial manuscript handling.

WHAT IS KNOWN ABOUT THE TOPIC?

- SCAD is a rare disease more commonly regarded as the cause of ACS, especially in women.
- The pathophysiological substrate and prognosis are different from common atherosclerosis as well as the management recommended.
- To this day, the information on SCADs comes from many retrospective series since no randomized, controlled clinical trials have been conducted yet.

WHAT DOES THIS STUDY ADD?

- This was a prospective study with a fairly long follow-up that collected data on a specific diagnostic, therapeutic, centralized, and updated approach based on the new scientific evidence available on the management of SCAD.

– The study presented the results of an almost universal screening of ECA with a high percentage of patients with unequivocal diagnosis of SCAD (thanks to the common use of intravascular imaging modalities) and angiographic control during disease progression.

– Treatment with a very low-intensity antithrombotic strategy (antiplatelet therapy with ASA only and not indefinitely) is safe with excellent results during disease progression.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000096.

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REC Interv Cardiol. 2020;2(4):256-263

Original article

Rotational atherectomy for the management of bifurcation lesions: a pilot randomized study

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ABSTRACT

Introduction and objectives: Coronary bifurcation lesions are a common scenario in our interventional practice and can be challenging for our routine clinical practice. Yet despite the existence of well-defined techniques, side-branch compromise is still the most important problem. Currently, the standard strategy recommended is a 1-stent technique: balloon angioplasty and provisional stenting. Published non-randomized data reveal that in up to 26% of the cases the indication for rotational atherectomy was to preserve the side-branch. A randomized comparison between rotational atherectomy and provisional stenting (RAPS) and standard strategy (SS) for the management of bifurcation lesions is needed at this point.
Methods: We conducted a single center, prospective, randomized pilot study of consecutive patients from our center with bifurcation lesions. We compared the RAPS strategy to the SS. Lesions had to be located in the main vessel only. The bifurcation lesion angle was recorded. The primary endpoint was the need for side-branch therapy.
Results: 148 patients were included: 74 patients (95 rotational atherectomy) were enrolled in the RAPS group and 74 patients in the SS group. The bifurcation lesion most frequently treated was that of the proximal left anterior descending coronary artery. The primary endpoint was lower in the RAPS group compared to the SS group (1.1 vs 31.2%; $P < .001$). Target vessel failure (TVF) was 13.1% and 24.8% ($P = .04$) in RAPS and SS, respectively. Both the primary endpoint and TVF were higher with bifurcation lesion angles < 70° compared to bifurcation lesion angles ≥ 70° ($P = .03$ and $P = .02$) in both groups.
Conclusions: The need for side-branch therapy and TVF was lower when the RAPS strategy was used compared to the SS. Bifurcation lesion angles < 70° are associated with higher side-branch compromise and TVF rates. The SS was associated with a 4.92-fold higher risk of side-branch compromise compared to the RAPS strategy with bifurcation lesion angles < 70°. These data reinforce the idea of the overall clinical relevance of the RAPS strategy regarding the patency of the side-branch.

Keywords: Bifurcation lesion. Rotational atherectomy. Side-branch compromise. Coronary calcification. Bifurcation angle.

Abordaje de las lesiones en bifurcación con aterectomía rotacional: estudio piloto

RESUMEN

Introducción y objetivos: Durante el intervencionismo coronario percutáneo es frecuente observar lesiones coronarias que afectan a las bifurcaciones. El compromiso de la rama lateral es la principal complicación observada con las diversas técnicas descritas para su tratamiento. La estrategia convencional (EC) recomendada en la actualidad es la colocación de un *stent* condicional. Los datos publicados de estudios no aleatorizados muestran que hasta en el 26% de los casos la indicación de la aterectomía rotacional fue el tratamiento de lesiones en las bifurcaciones. Es necesario el desarrollo de un estudio aleatorizado que compare la estrategia de aterectomía rotacional y *stent* condicional (ARSC) frente a la EC.
Métodos: Estudio piloto aleatorizado, prospectivo, de un solo centro, en pacientes con enfermedad coronaria en una bifurcación. Se comparó la estrategia de ARSC con la EC. Se prestó especial atención al ángulo de la bifurcación. El objetivo primario evalúa la necesidad de tratamiento de la rama lateral con ambas técnicas.

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Received 13 January 2020. Accepted 12 May 2020. Online: 02-07-2020.
https://doi.org/10.24875/RECICE.M20000138

Resultados: Se incluyeron 148 pacientes: 74 (95 aterectomías rotacionales) en el grupo de ARSC y 74 en el grupo de EC. El objetivo primario fue menor con la ARSC que con la EC: 1,1% frente a 31,2% (p < 0,001). El objetivo de fallo del vaso tratado (FVT) fue del 13,1% en el grupo de ARSC y del 24,8% en el grupo de EC (p = 0,04). El objetivo primario y el FVT fueron mayores si la lesión era en una bifurcación < 70° en comparación con una bifurcación ≥ 70° en ambos grupos (p = 0,03 y p = 0,02).
Conclusiones: La necesidad de tratamiento de la rama lateral y el FVT fueron menores con la estrategia de ARSC que con la EC. Un ángulo < 70° en la bifurcación aumenta el riesgo de compromiso de la rama lateral y las tasas de FVT. La EC se asoció a un incremento del riesgo de compromiso de la rama lateral de 4,92 veces cuando el ángulo de la bifurcación era < 70°. Estos datos sugieren que el abordaje de lesiones en una bifurcación mediante aterectomía rotacional podría tener un beneficio clínico global.

Palabras clave: Lesión en bifurcación. Ángulo de la bifurcación. Aterectomía rotacional. Compromiso de rama lateral. Calcificación coronaria.

Abbreviations

CBL: coronary bifurcation lesion. **PCI:** percutaneous coronary intervention. **RA:** rotational atherectomy. **RAPS:** rotational atherectomy and provisional stenting. **SS:** standard strategy. **SB:** side-branch.

INTRODUCTION

Over the last few years, the profile of patients referred to undergo a coronary angiography has become worse. Similarly, angiographic findings have become worse as well. Recently, De María et al.[1] published a study on the management of calcified lesions. They provided a nice contemporary overview on the management of calcified lesions in the catheterization laboratory focusing on the technologies available, intravascular imaging, and technical complexities. However, an important marker of procedural complexity was omitted: coronary bifurcation lesions. CBLs are often seen in interventional practice and can be challenging in our routine clinical practice. Yet spite the existence of several well-defined techniques to perform a percutaneous coronary intervention (PCI) on a CBL, side-branch compromise is still the most important problem.[2,3] Currently, the standard strategy (SS) recommended for the management of CBL is a 1-stent technique[2,4] (balloon angioplasty and provisional stenting) since it has proven to be non-inferior to the elective 2-stent technique.[5] It is well-known that rotational atherectomy (RA) is underused during the PCI[6] and no specific randomized data are available regarding its role in the management of CBL. The role of RA in this setting has been suggested in different studies not designed for that purpose. Data published reveal that in up to 26% of the cases the indication for RA was to preserve the side-branch.[7-9] As far as we know, this extended use of RA is an off-label indication that has not been specifically tested in a randomized study. We report the procedural and long-term results of the rotational atherectomy and provisional stenting (RAPS) strategy compared to the SS (balloon angioplasty and provisional stenting) in a randomized pilot study.

METHODS

Study population

We conducted a single center, prospective, randomized pilot study of consecutive patients from our center with bifurcation lesions located only in main vessel (BLMV) and who were screened before being recruited. The angiographic criteria to define the CBLs that were eligible for the study were: *a)* lesions: > 70% located in a major bifurcation point regardless of the length, morphology, and angulation of the bifurcation lesion; *b)* thrombolysis in myocardial infarction (TIMI) flow grade > 2 on both the main vessel (MV) and the side-branch (SB); *c)* MV visual diameter: ≥ 2.5 mm; and 4.0. SB visual diameter: ≥ 2.0 mm. The presence of a heavily calcified lesion was not a prerequisite to enter the study.

The inclusion criteria were patients ≥ 18 years who signed their informed consent with Medina lesions type 1.0.0; 1.1.0 and 0.1.0 and who were eligible to undergo either one of the 2 strategies and with no confirmed or suspected contraindications for prolonged dual antiplatelet therapy.

The exclusion criteria were: *a)* SB < 2 mm; *b)* lesions with thrombus or dissection; *c)* vein graft lesions; *d)* cases of a single main vessel with severe left ventricle dysfunction (EF < 30%); *e)* hemodynamically unstable patients; *f)* contraindication for prolonged dual antiplatelet treatment; *g)* life expectancy < 1 year; and *h)* patient refusal.

Procedures

The random assignment of patients to the different treatment groups was done using the EPIDAT 4.0 software. After obtaining the patients' informed consent they were randomized in a 1:1 ratio to the RAPS group, RA group or SS group. Patients were revascularized according to the current recommendations.[1,10] In the SS group the strategy used was left to the operator's discretion: 1 or 2 wires, previous BA or direct stenting, 1- or 2-stent technique, etc. Everything was decided in each case by the operator. In the RAPS group a single RotaWire was used in the main vessel and only in this vessel rotational atherectomy would be performed (videos 1-7 of the supplementary data).

The baseline clinical data collected include demographics and the patients' cardiovascular past medical history and comorbid conditions. Both the angiographic and PCI data were recorded. The RA technique was performed following the current recommendations.[6] CBLs were classified according to their angles: < 70° or ≥ 70°. Two different operators assessed each individual case.

Endpoints

The primary endpoint was defined as "need for side-branch therapy". This "need for side-branch therapy" was considered in the presence of clinical, ECG or hemodynamic signs suggestive of

TIMI flow ≤ 2 and/or ostial stenosis ≥ 70%.[11] In contrast, "side-branch compromise" was considered when in the presence of impaired SB stenosis or TIMI flow whether severe or not. The secondary endpoints were: *a)* Target vessel failure (TVF): a composite of cardiac death, culprit vessel myocardial infarction, target vessel restenosis, and target bifurcation restenosis at the follow-up (appendix of the supplementary data); *b)* Angiographic outcomes: B.1. Procedural and annual assessment success rate and its correlation with the bifurcation angle. Procedural success was defined as TIMI flow grade-3 in both the MV and the SB and a visual residual stenosis < 20% in the MV; B.2. Angiographic complications rate including stent thrombosis, dissection, occlusion, perforation, no-reflow, target lesion restenosis (TLR), and target bifurcation restenosis at the FUP. *c)* The major adverse cardiovascular and cerebrovascular events (MACCE). Other relevant conditions such as hemorrhages, need for transfusion, and kidney disease were also recorded. All deaths were considered cardiac unless a definite non-cardiac cause was established. Both the bifurcation technique and stent used were left to the operator's discretion.

The periprocedural drugs and laboratory test definitions are shown on in the appendix of the supplementary data. After discharge, the patients' clinical follow-up was conducted through personal interviews or phone calls every 6 months. Patients underwent angiographic control clinically driven only. The monitoring of cardiovascular risk factors, drugs compliance, and blood test controls were left to the discretion of the referring physician.

The aforementioned study has been conducted in full compliance with The Code of Ethics of the World Medical Association Declaration of Helsinki. Also, it has been approved by the hospital local ethics committee. The patients' written informed consent was obtained too.

Sample size

No randomized studies on this subset are available so we could not use the sample size formula. Instead, we used the ARCSIN approximation function and estimated that, at least, 60 subjects should be included in each group to find statistically significant differences (accepting an alpha risk of 0.05 and a beta risk of 0.2 in two-sided tests). A drop-out rate < 1% was anticipated.

Statistical analysis

Data were expressed as means ± standard deviation (SD) for the continuous variables and as frequencies and percentages for the categorical ones. The FUP period was expressed as the median with its interquartile range [IQR]. The chi-square or Fisher's exact tests that assessed the effect and accuracy analyses with the prevalence ratio and 95% confidence interval, when necessary, were used to compare the continuous and categorical variables, respectively. The Mann-Whitney test was used to study the non-parametric variables. Cox regression models were used to perform univariate analyses to estimate the associated hazard-ratio of death and composite endpoints at the FUP. A multivariate analysis was performed as well. The Kaplan-Meier estimates were used to determine the time-to-event outcomes, overall survival rate, and MACCE-free survival rate. We tested the equality of the estimated survival curves using the stratified log-rank test. All analyses were performed using the Statistical Package for Social Scientists (SPSS Inc., 20.0 for Windows). *P* values < .05 were considered statistically significant in all of the tests.

Table 1. Baseline characteristics

Baseline clinical data	RAPS (N = 74)	SS (N = 74)	*P*
Age (mean; SD)	78 (10)	74 (7)	NS
Males (n; %)	60 (81.2)	58 (78.1)	NS
Weight (mean; SD)	73.9 (11.9)	75.4 (11.4)	NS
Height (m) (mean; SD)	1.64 (0.7)	1.66 (0.6)	NS
Body mass index (mean; SD)	27.11 (3.4)	29.24 (11.4)	NS
Current/Previous smoker (n; %)	46 (62.1)	53 (71.6)	NS
Hypertension (n; %)	62 (92.2)	74 (100)	NS
Diabetes mellitus (n; %)	29 (39.1)	30 (40.6)	NS
Dyslipidemia (n; %)	69 (93.2)	62 (83.7)	NS
Left ventricle ejection fraction ≤ 45 (%)	28 (37.8)	14 (18.7)	.03
Previous myocardial infarction (n; %)	42 (56.7)	37 (50)	NS
Previous angioplasty	42 (56.7)	32 (43.2)	NS
Previous Stroke (n; %)	10 (14.1)	18 (24.3)	NS
Peripheral vascular disease (n; %)	16 (21.6)	23 (31)	NS
L-Euroscore (mean; DS)	21.14 (22.15)	13.7 (18.7)	NS
Syntax Score (mean; DS)	34.05 (17.9)	31.57 (17.9)	NS
Clinical onset (n; %)			
Stable angina	14 (19)	20 (27)	NS
NSTEMI	40 (54)	47 (63.5)	NS
STEMI	20 (27)	7 (9.4)	NS
Discarded for cardiac surgery (n; %)	24 (32.4)	20 (27)	NS
NYHA Class ≥ III	8 (9.3)	9 (12.1)	NS
CCS I-II	57 (77)	41 (55.4)	NS
CCS III-IV	17 (23)	32 (44.6)	NS

CCS, Canadian Class Classification angina score; NS, not significant; NSTEMI, non-ST-elevation acute myocardial infarction; NYHA: New York Heart Association; RAPS, rotational atherectomy and provisional stenting; SS, standard strategy; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

RESULTS

One-hundred and seventy-three out of 1028 patients who underwent a PCI between January 2015 and December 2018 were considered eligible to enter the study: 13 refused to participate, 8 patients dropped-out, and 4 patients withdrew their informed consent. Finally, 148 patients were included: 74 patients (95 RAs) were recruited in the RAPS group and 74 patients in the SS group. The inclusion/exclusion flowchart is shown on figure 1 of the supplementary data.

The baseline clinical, angiographic, and procedural data are shown on table 1 and table 2. No sex-based differences were seen. Only the prevalence of a left ventricular ejection fraction ≤ 45% was different between the groups: *P* = .03. No calcification, tortuosity or bifurcation angle differences were reported. The most common bifurcation was found at the first diagonal branch of the proximal left anterior descending coronary artery (D1-LAD) (51%) followed by the distal left main coronary artery (LMCA)/ostial LAD (22.5%) No inter-group differences in single vs staged revascularization were seen.

Table 2. Angiographic and procedural data

Angiographic/procedural data	RAPS (N = 74)	SS (N = 74)	*P*
6-Fr sheath (n; %)	62 (88)	60 (81.2)	NS
Radial Approach (n; %)	29 (39.1)	30 (40.6)	
Femoral approach (n; %)	45 (60.9)	44 (59.3)	
Coadjuvant therapy (n; %)			
Heparin	21 (28.1)	29 (40.6)	NS
Bivaluridin	42 (56.3)	23 (31.2)	.01
Glycoprotein inhibitors	11 (15.9)	23 (31.2)	NS
Right Dominance (n; %)	64 (87.5)	64 (87.5)	NS
Vessel disease (n; %)			
Left Main coronary artery	15 (20.3)	14 (18.7)	NS
Left anterior descending coronary artery	72 (98.4)	57 (78.1)	.02
Left circumflex artery	47 (64.1)	55 (71.8)	NS
Right coronary artery	54 (73.4)	57 (78.1)	NS
Number of diseased vessels (n; %)			
1 vessel	10 (13.5)	13 (17.53)	NS
2 vessels	22 (29.7)	24 (32.4)	NS
3 vessels	34 (45.9)	31 (41.8)	NS
4 vessels	8 (10.8)	6 (8.1)	NS
Multivessel (n; %)	60 (81.2)	53 (71.8)	NS
Coronary calcification (%)			
Mild	28	36	NS
Moderate-severe	72	64	NS
B2C lesions (n; %)	94 (98.4)	60 (81.2)	.048
Medina classification of bifurcation lesions (n; %)			
1.0.0	46 (48.4)	17 (23)	.04
1.1.0	32 (33.6)	22 (29.7)	NS
0.1.0	17 (17.8)	30 (40.1)	.03
Bifurcation angle (n; %)			
< 70º	46 (62)	50 (67.5)	NS
≥ 70º	28 (38)	24 (32.5)	NS
Wire			
Floppy [n (%)]	88 (92.4)	N/A	NS
Directly advanced [n (%)]	84 (88.5)	N/A	NS
Burr size ≤ 1.5 mm	76 (80)	N/A	NS
Speed (rpm) (mean; SD)	134650 (5670)	N/A	NS
Rotational atherectomies performed (% per patient)	95 (1.28)	N/A	NS
Burr-to-artery ratio (mean; SD)	0.55 (.04)	N/A	
Number of balloons per lesion	1.3	4.6	.02
Stent (n)			
Number of stents per lesion	1.6	2.3	.04
Number of stents per patient	2.7	2.33	NS
Bare-metal stent [n (%)]	24 (12.7)	22 (23.2)	NS
Drug-eluting stent [n (%)]	167 (86.9)	72 (76.7)	NS
Stenting technique [n (%)]			
Provisional stenting	64 (100)	41 (55.4)	.04
Two-stent initial approach technique	0	28 (37.8)	< .001
Optimal treatment of the proximal LAD	48 (64.8)	24 (32.4)	< .05
Final kissing balloon technique	1 (1.5)	59 (79.7)	< .001
Final inflation pressure (atm)	18	14	.05
Initial vessel diameter (Me; IQR) (mm)	2.41 (0.34)	2.89 (0.26)	.009
Final vessel diameter (Me, IQR) (mm)	3.1 (1.9)	2.95 (0.37)	NS
Maximum length stented (Me; IQR) (mm)	56 (48)	44 (26.1)	.005
Procedural time (min) (mean; SD)	78.8 (30)	98 (21)	.04
Fluoroscopy time (min) (mean; SD)	13 (7)	29.2 (21)	.02
Contrast media (ml) (mean; SD)	179 (74)	221 (73)	.05
IVUS/OCT	7 (9.4)	11 (14.8)	NS

IVUS, intravascular ultrasound; Me, median; NS, not significant; NYHA, New York Heart Association; OCT, optical coherence tomography; SD, standard deviation.

Long-term follow-up

Both the clinical and angiographic success rates and outcomes were available for the entire population with a median FUP of 4.08 years [IQR: 3.18-4.78 years]. Both the all-cause and cardiovascular mortality rates were similar in both groups. The need for side-branch therapy was consistently lower in the RAPS strategy compared to the SS: 1.1% vs 27% (P < .001) (table 3). TVF was 12.1% and 24.8% (P =.04) in the RAPS strategy compared to the SS, respectively. Also, the statistical analysis confirmed that the use of the RA technique significantly reduced the risk of target vessel restenosis (P = .04), TLR (0.02), target bifurcation restenosis (P = .03), and major adverse cardiovascular events (P = .03). A positive correlation (r = 0.673, P = .03) was seen between the need for SB therapy and CBL angles < 70º. The strongest correlation was observed at the proximal D1-LAD: r = 0.79, P = .03. A weak but positive correlation was seen between the LMCA-LAD arteries angle (r = 0.412, P = .04) and the LMCA-LCx arteries

Table 3. Major adverse cardiovascular events at the follow-up

	RAPS (N = 74)	SS (N = 74)	*P*
Clinical success (%)	98.6	98	NS
Associated cardiovascular mortality (hospitalizations) [n (%)]	3 (4)	2 (2.7)	NS
With procedure	2 (2.7)	2 (2.7)	
With rotational atherectomy	1 (1.3)	N/A	
Angiographic success (%)	96.5	97.5	NS
Angiographic complications [n (%)]			
Unable to advance the wire	1 (1.3)	2 (2.7)	NS
Burr entrapment	0	N/A	NS
Unable to deliver the stent	1 (1.3)	2 (2.7)	NS
Coronary dissection	1 (1.3)	6 (8,1)	.024
*Side-branch compromise**	2 (2.7)	23 (31)	< .001
*Need for side-branch therapy***	1 (1.3)	20 (27)	< .001
Perforation	0	0	NS
Cardiac tamponade	0	0	NS
Stent thrombosis	0	0	NS
Need for pacemaker implantation	0	0	NS
Final flow compromise (TIMI ≤ 2) in SB	0	2 (2.7)	NS
MACCE (4.08 years, ICA: 3.18-4.78)			
GLOBAL: 27 (36.4%)	18 (25%)	30 (40.6%)	.03
Overall death rate	15 (20.3%)	16 (21.8%)	NS
Hospitalization	3 (4%)	3 (4%)	NS
30 days	4 (5.4%)	5 (6.7%)	NS
Cardiac Death	5 (6.7%)	7 (9.4%)	NS
Non-cardiac Death	9 (12.1%)	7 (9.4%)	NS
Stroke	2 (2.7%)	7 (9.4%)	.02
TVF	9 (12.1%)	18 (24.8 %)	.04
TLR	2 (2.7%)	11 (14.8%)	.02
TVR	3 (4%)	7 (9.4%)	.03
TBR	2 (2.7%)	7 (9.4%)	.03
Stent thrombosis	0	0	NS

ICA, interquartile amplitude; MACCE, major adverse cardiovascular and cerebrovascular events; NS, not significant; RAPS, rotational atherectomy and provisional stenting; SS, standard strategy; TBR, target bifurcation restenosis; TLR, target lesion restenosis; TVF, target vessel failure (composite of cardiac death, culprit vessel myocardial infarction); TVR, target vessel restenosis.

* Shift plaque defined as ostial side-branch stenosis > 70% and/or TIMI flow < 3.

** Treatment included: *a)* angioplasty with conventional or drug-eluting balloon; *b)* bare-metal stent or drug-eluting stent.

angle (r = 0.342, *P* = .004). The sum of SS plus CBL angles < 70º was associated with a higher risk of SB compromise and TVF (OR, 4.92; 95%CI, 1.78-14.1; *P* = .03)

DISCUSSION

Main findings

The main findings of this study are: *a)* the RAPS strategy for the management for CBLs minimizes the compromise of the SB, need for SB therapy, and TVF compared to the SS; *b)* There was a strong correlation between the compromise of the SB and acute CBL angles (< 70º); *c)* The SS was associated with a 4.92-fold higher risk of SB compromise compared to the RAPS strategy in CBL angles < 70º.

CBLs are a common thing in our interventional practice and can be challenging in our routine clinical practice. Side-branch compromise is still the most important problem. To our knowledge, this is the first randomized study that addressed this issue and described the role of RA in the management of CBLs. Former studies not specifically designed to address this specific question had already suggested this.[8,9,12,13] We reported sustained short-term benefits of the RAPS strategy at the long-term follow up. Some differences had been previously reported,[14] which is why differences in the primary endpoint could be expected, but still not so significant.

As a hypothesis-generating pilot study we defined a procedural primary endpoint.[11] Selecting a "procedural" primary endpoint at this stage is a reasonable thing to do since the occlusion of large SBs is a serious complication that leads to adverse clinical outcomes.[11,14] We studied whether the RAPS strategy could be as good as the SS for the management of CBL by comparing the compromise of the SB.[15-17] Still, the current clinical practice guidelines minimize the indications for RA to heavily calcified lesions and rigid ostial lesions,[10] although an expert consensus document recently published includes more extensive indications.[6] The real-world use of RA for plaque modification in is nothing new.[9] Actually, in the absence of plaque modification there are more chances of procedural failure, stent underexpansion, in-stent restenosis, and major clinical complications.[2,5,18] Schwartz et al use it in up to 26% of their population.[9]

Percutaneous coronary intervention and bifurcation technique

Only BLMVs were included.[19] Bifurcations are true bifurcations when a significant SB runs the risk of being compromised regardless of whether the disease reaches it or not. Thus, maybe we should rename them as "complex CBLs", that is, those where the SB has baseline disease (1.1.1 in the Medina classification) and "simple CBLs", those without baseline disease (again according to the Medina score). There is wide consensus that the main objective of complex PCIs in the management of CBLs is to keep the patency of both vessels regardless of the PCI technique used and the location of the lesion.[2] For many years we have been focused on the optimization of SB, but clinical events such as TLR mostly occur in the main vessel.[20] In up to 20% of the cases, the SB requires a stent, which means that the proper preparation of the CBL is essential.[3,14,21]

What the best bifurcation technique is for the management of CBL is still under discussion. Currently, the standard strategy recommended for the management of CBL is a 1-stent technique.[2,4] Ideally, the technique selected should provide an easy access for a second stent in the SB even if conventional approach with a 1-stent technique is planned. In our cohort, the RA facilitated this approach. According to cumulative clinical trial data[3] we reported a high rate of provisional stenting in the RAPS strategy that proved non-inferior to the elective 2-stent technique[4,5] and ever better for the management of periprocedural myocardial infarction.[22] The kissing balloon

technique is being systematically used in cases of large territories supplied by the SB or when the SB exhibits flow impairment after MV stenting. Sometimes, in such situations a second stent is implanted in the SB.[23] The differences reported in our population regarding the optimal treatment of the proximal LAD and final kissing balloon and 2-stent technique used are still under discussion. We saw a 4-fold higher rate of the balloon technique in the SS. Maybe these differences were due to the tight lesions described: in the SS there was a need of a step-up ballooning to cross and dilate the lesions and eventually for the final optimization of the stents. Eventually, at least 3 or 4 balloons were needed. Interestingly, as previously reported, when the final kissing balloon technique was used, the optimal treatment of the proximal LAD produced no benefit at all.[24] Maybe this was the case because the stent located in the main vessel is properly expanded after using the kissing balloon technique. We saw a lower need for SB treatment and TVF rates[7,18,25] in the RAPS strategy than previously reported.

Role of rotational atherectomy for the management of bifurcation lesions

The RAPS strategy facilitates the modification of the plaque without SB compromise by extending provisional stenting[2,4] by *a)* minimizing plaque shift, *b)* optimizing plaque modification, *c)* reducing the need for 2 wires/stents and *d)* improving the stent expansion/apposition. Otherwise, certain maneuvers used in other strategies to avoid the occlusion of the SB may cause suboptimal stent expansion/apposition in the MV, which can be a major cause for stent thrombosis and restenosis.[2,14] The bifurcation angle has been suggested as an important issue for the compromise of the SB.[5,11,14] In our population, the LAD was the most commonly affected coronary artery. The LAD is particularly appealing given the angle of the origin of the diagonals. The crux is often at a right angle so it is less of a concern and the circumflex artery only matters when it is dominant. Acute CBL angles (< 70°) have shown to increase the compromise of the SB and, therefore, lead to worse outcomes. In our cohort, "SB compromise", "need for SB therapy", and TVF rates were lower in CBL angles < 70° both in the RAPS and the SS groups. The small size of the sample prevented us from drawing definitive conclusions, but these data were good enough to make us change our daily methodology: with CBL angles < 70° located in the main vessel with a large side-branch we use directly the RAPS technique. Maybe the explanation for the differences seen in the RAPS vs the standard strategy is the underlying mechanism of action of rotational atherectomy. As a matter of fact, this may explain the higher rates of SB compromise and need for SB therapy seen in the SS group: a more controlled plaque modification was achieved with RA that minimized the plaque shift. Unfortunately, our data did not include too many imaging modalities. In our cohort for events assignment, if during the PCI procedure any narrowing occurred adjacent to, and/or involving the origin of a significant SB it was allocated to the selected strategy used. The decision to use the 1-stent or 2-stent technique, the type of stent, etc. was left to the operator's discretion. We should make a few comments on our study population: *a)* although most of the patients were unstable, this did not condition the results in any of the groups; *b)* in the RAPS strategy the use of the jailed wired technique is rare; *c)* CBL angles < 70° between branches facilitate the plaque shift.[26] Thus, if the TIMI flow recorded after stent deployment was < 3 or residual stenosis was > 70% more bail-out balloons and stents were needed, which would explain the different outcomes seen when using the final kissing balloon technique; *d)* in a number of cases where the standard strategy was used it was complemented with the kissing balloon inflation technique at high-pressure balloon inflation instead of the final optimal treatment of the proximal LAD; and *e)* the differences seen in the coronary dissection rate on the angiographic study may be suggestive of micro-dissections due to inadequate balloon assessment through conventional angiography, which could be the underlying mechanism of the endpoint differences reported; performing more intravascular ultrasound/optical coherence tomography studies would provide better assessment here.

Patients were randomized in a 1:1 ratio so the differences seen in the left ventricular ejection fraction and LAD disease were absolutely due to the size of the study sample. Although we saw a lower cardiovascular mortality rate compared to the one published in the medical literature[2,14,15,27] this study was not designed to compare the MACCE results between both groups. Interestingly, the rates of TVF were significantly lower in the RAPS strategy mainly due to fewer culprit vessel myocardial infarctions and target vessel restenoses. In any case, our data underscored the safety profile of the RAPS strategy in unstable patients and patients with left ventricular dysfunction (P = .03)

Limitations

We designed and conducted a single-center pilot study. Small sample sizes have inherent limitations. Our results should be interpreted with caution as a hypothesis-generating pilot study. Several confounding factors and biases could be present, which is why any assessments on this regard should be made with caution too. The study was extremely underpowered to show clinical outcome differences, which is why the clinical findings reported should be considered just exploratory. Our procedural endpoint and inclusion of BLMVs only could be discussed. There is wide consensus that the main objective of complex PCsI for the management of CBLs is to keep both vessels patent regardless of the PCI technique used.[2]

We thought it was the right thing to do to assess the data on the SB compromise by comparing both techniques used. Over thec years we have been focusing on optimizing the SB, but clinical events such as TLR mostly occur in the main vessel.[20] Only BLMVs were included.[19] A bifurcation should be considered as a true bifurcation when a significant SB you do not want to lose is compromised whether it shows coronary stenosis or not. We should mention that in the management of CBLs with the RAPS strategy a low rate of SB stenting is associated with a lower rate of major adverse events and clinically significant rates of restenosis. Therefore, very large numbers of patients are required for the proper assessment of the differences. Some baseline characteristics of coronary lesions vary depending on the interventional strategy used (as in the management of B2C lesions) to the point of impacting the final outcomes. The lack of differences seen in the stent thrombosis and stroke rates may be associated with the size of the study sample.

Although statistical significance was not observed, the percentage of bare metal stents used was numerically higher in the control group compared to the RAPS group. However, this study is not a comparison of drug-eluting stents versus bare-metal stents in bifurcation disease. These findings could be associated with the difference seen in TLR/target vessel restenosis, especially if we take into account that 31.2% of patients from the control group were treated using 2-stent techniques. We saw that RA followed by drug-eluting stents was associated with a low rate of MACCE compared to bare-metal stents. However, this study was not designed to make comparisons like this one. A higher percentage of bivaluridin was intentionally used in the RAPS group, but this did not produce any statistically significant differences. The use of more imaging modalities such as intravascular ultrasound or optical coherence tomography is desirable here. FUP was mostly conducted through phone

calls and it may have underestimated the rate of MACCE. An off-label indication does not necessarily mean a contraindication of our promising, but support for the next step: a large randomized multicenter trial that is about to begin.

CONCLUSIONS

The RAPS strategy for the management of CBL preserves the SB ostium and minimizes the need for SB therapy compared to the SS. The rates of "SB compromise", "need for SB therapy", and TVF were higher with CBL angles < 70º for both the RAPS and the SS groups. Our data reinforce the idea of the overall clinical relevance of the RAPS strategy to keep the SB patent. Although no large clinical trials have taken this approach yet, the results published so far are promising.

CONFLICTS OF INTEREST

J. Palazuelos (corresponding author) is a consultant on the speaker's bureau of Abbott, Boston Scientific, Biotronik, Innovative Health Technologies (IHT) and Medtronic. J. Palazuelos is a proctor for Rotational Atherectomy with a teaching contract with Boston Scientific that has funded this study with a grant. No other relation with the industry regarding this study was declared. He confirms he has had full access to all the study data and holds full responsibility for the decision to submit this manuscript for publication in *Rec: Interventional Cardiology*. The remaining authors have declared no conflicts of interest whatsoever regarding the contents of this manuscript.

WHAT IS KNOWN ABOUT THE TOPIC?

- Over the last few years, the profile of patients referred to undergo a coronary angiography has become worse. Similarly, angiographic findings have become worse as well. With the progressive ageing of the population and the arrival of better technologies, the balance between offer and demand in this field is in continuous expansion. Still, the management of such delicate situations requires profound knowledge of dedicated techniques and accurate clinical judgement. Calcified coronary lesions and bifurcated lesions are a common occurrence that accounts to between 25% and 30% of all PCIs. There are technologies available for the management of these lesions. The older one is rotational atherectomy. Currently, the objective is to modify the plaque since the lack of plaque modification is associated with more procedural failure, stent underexpansion, in-stent restenosis, and major clinical complications. Despite the existence of well-defined techniques for the use of PCI for the management of CBLs, side-branch compromise is still the most important complication.

WHAT DOES THIS STUDY ADD?

- The role of rotational atherectomy for the management of coronary bifurcation lesions has been suggested in different studies not specifically designed for that purpose. Our randomized data support the role of the RAPS strategy for the management of BLMV in a cohort of high-risk patients. The RAPS strategy provided higher SB patency and lower TVF. Still, larger studies are needed to shed light on this question.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000138.

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REC Interv Cardiol. 2020;2(4):264-271

Original article

Endomyocardial biopsy using the brachial venous access route. Description of the technique and 12-year experience at 2 different centers

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ABSTRACT

Introduction and objectives: Recipients of a heart transplant need to receive serial endomyocardial biopsies (EMB) to discard rejection, a procedure that is usually performed through the femoral or jugular vein. Over the last few years, we have developed a technique to perform EMBs using the brachial venous access that we have implemented as the preferential access route. In this article, we describe the technique and the initial clinical experience of 2 different centers.
Methods: Between 2004 and 2016, we developed and implemented a brachial venous access technique. We registered the main clinical and procedural variables of all the brachial biopsies performed in both centers and compared them with a retrospective series of femoral and jugular procedures.
Results: Brachial EMBs were successfully performed 544 of the time with no major complications. The number of brachial procedures per patient rose from 1 to 14. Over the same period of time 1054 femoral and 686 jugular procedures were performed. The total procedural time was similar with different access routes (mean for brachial/femoral/jugular access: 28/26/29 min., $P = .31$) while fluoroscopy time was shorter in jugular procedures (mean 5/5/3 min. respectively; $P < .001$). The brachial procedure was recalled as the least painful procedure of all compared to the jugular or femoral ones (2/8/9 score on a scale from 1 to 10; $P = .001$) with an overall patient preference towards the brachial access.
Conclusions: The venous brachial access route is a good alternative to the central venous one to perform EMBs and is the route of choice in our centers. Also, it has high feasibility and safety and brings additional comfort to patients.

Keywords: Endomyocardial biopsy. Heart transplant. Brachial access.

Biopsia endomiocárdica por vía venosa braquial. Descripción de la técnica y experiencia en 12 años de 2 centros

RESUMEN

Introducción y objetivos: Los pacientes receptores de un trasplante cardiaco necesitan someterse a biopsias endomiocárdicas (BEM) para descartar el rechazo, procedimiento que habitualmente se realiza por acceso venoso yugular o femoral. En los últimos años hemos desarrollado una técnica de biopsia por vía braquial, que hemos implementado como acceso preferente. En este artículo describimos la técnica y la experiencia clínica inicial de 2 centros empleando el acceso braquial.

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Received 5 January 2020. Accepted 25 February 2020. Online: 24-04-2020.
https://doi.org/10.24875/RECICE.M20000110
2604-7322 /

Métodos: Entre 2004 y 2016 desarrollamos e implementamos la técnica de biopsia por vía venosa braquial. Se registraron las principales variables clínicas y del procedimiento de todas las BEM realizadas por vía braquial en ambos centros, y se compararon las características con los procedimientos realizados por vía femoral y yugular.
Resultados: Se realizó la BEM por vía braquial en 544 casos, sin complicaciones mayores. El número de procedimientos braquiales por paciente varió entre 1 y 14. En el mismo periodo se realizaron 1.054 BEM femorales y 686 yugulares. La duración total del procedimiento fue similar por los distintos accesos (mediana braquial/femoral/yugular: 28/26/29 min; p = 0,31), con un menor tiempo de escopia por vía yugular (mediana 5/5/3 min, respectivamente; p < 0,001). Los procedimientos realizados por vía braquial se valoraron como menos dolorosos que los realizados por vía yugular o femoral (2/8/9 en la escala de dolor EVA de 1-10, respectivamente; p = 0,001), y fue la vía de elección por parte de los pacientes.
Conclusiones: La BEM por vía venosa braquial es una buena alternativa a la punción venosa central y la vía de elección en nuestros centros, con altas factibilidad y seguridad, y mayor comodidad para el paciente.

Palabras clave: Biopsia endomiocárdica. Trasplante cardiaco. Acceso braquial.

Abbreviations

EMB: endomyocardial biopsy. **RHC:** right heart catheterization. **RV:** right ventricle.

INTRODUCTION

Endomyocardial biopsy (EMB) is an invasive procedure usually performed using central venous access to obtain samples of the interventricular septum from the right ventricle (RV).[1,2] Its main indication is for heart transplant recipients who need repeated EMBs to discard organ rejection despite immunosuppressive therapy.[3] Less frequently, the EMB is also used as a diagnostic tool with certain heart diseases like myocarditis or suspected infiltrative disease,[4] scenarios where the arterial femoral or radial approach may also be considered to access the left ventricle.[5,6]

EMBs are often performed through central venous access, femoral or jugular access;[2-4] although it is a safe technique, it is associated with a risk of vascular or nerve damage that is inherent to jugular or femoral punctures.[7]

The forearm veins may be a good alternative access route to perform EMBs with the potential advantage of increased vascular safety and more comfort to the patient (figure 1). Basilic and cephalic veins are superficial veins that converge at the subclavian vein, superior cava vein, and ultimately right heart. However, the use of this access route known by the generic term "brachial" to perform EMBs is rare and, to this day, has been reported in one series only.[8]

In our centers we have developed a new technique to perform EMBs through the brachial vein that we have been using since 2004. The main objective of this manuscript is to describe our technique to perform EMBs through brachial venous access, and the feasibility, safety, and efficacy reported by 2 different centers; our secondary objective was to compare the performance of the brachial route to that of conventional femoral and jugular access routes.

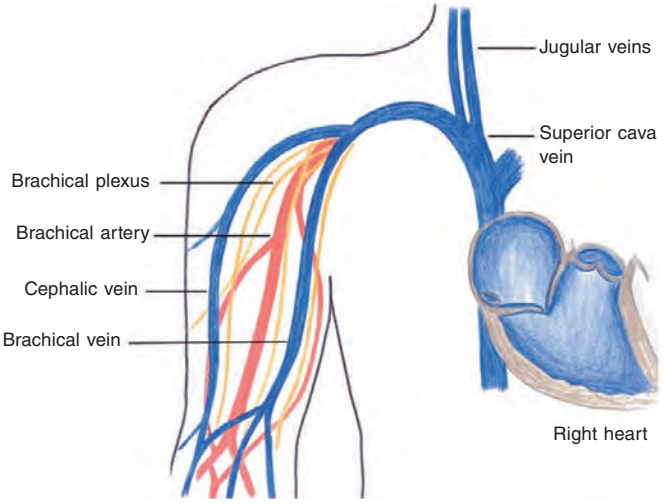

Figure 1. Schematic representation of the anatomy of the superficial veins of the arm, forearm and surrounding structures.

METHODS

Brachial biopsy technique

We have spent over 12 years modifying our technique in 2 different centers since we first described it,[9] and have used different catheters and forceps to overcome the main difficulty we have encountered: the lack of devices specifically developed for this purpose. What follows is a description of the approach that has become predominant in our clinical practice.

After the identification of a large brachial vein, preferably the basilic vein over the cephalic one, we prepare a sterile field and puncture the vein with a regular venous catheter (18 gauge or larger) to allow the insertion of the sheath and guidewire. This first step used to be performed by our nursing team. When a vein was not readily visible or palpable, the physician in charge would perform an ultrasound-guided puncture to select the highest caliber vein. Similarly, when the standard puncture failed or if we knew of failed prior attempts or there were signs indicative that the veins had been punctured multiple times like bruising and scarring we used ultrasound guidance. The addition of ultrasound guidance has been gradual since 2015, and it has significantly increased the percentage of patients considered eligible to receive an EMB through brachial access. Once punctured, the vein is wired using a standard 0.035 in J wire, local anesthetics are administered, and

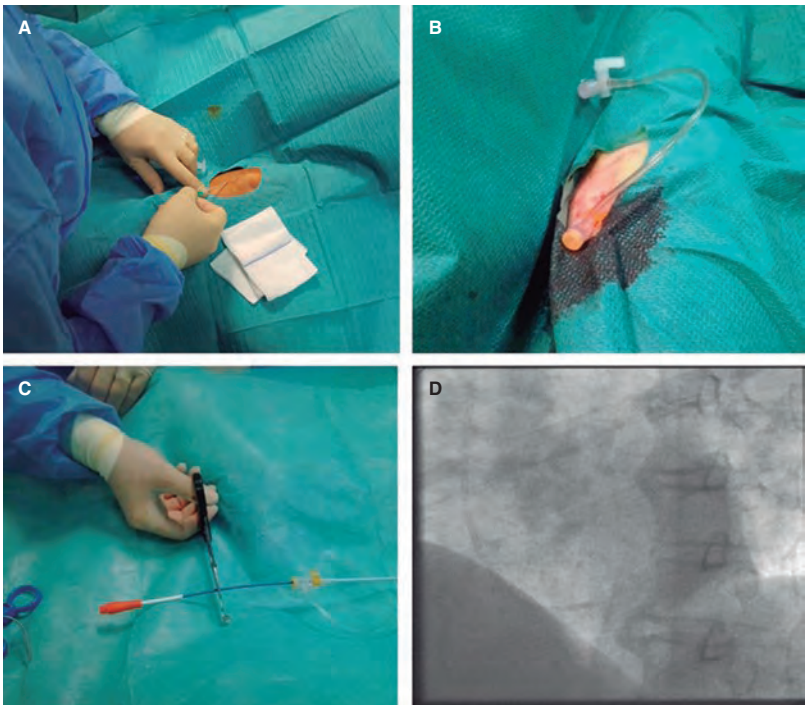

Figure 2. Step-by-step procedure of a brachial endomyocardial biopsy. **A:** a basilic or cephalic vein is identified and punctured with an 18-gauge venous catheter. **B:** the vein is wired for the insertion of a 7 F sheath. **C:** a multipurpose 7 Fr guide catheter is advanced over a J wire and the proximal 5 cm-to-10 cm are cut. **D:** the catheter is inserted into the right ventricle, and its septal orientation is checked through fluoroscopy before inserting the forceps.

a 7 Fr sheath is inserted. Afterwards, a long 0.035 in J wire is advanced and over the wire, a 7 Fr multipurpose guide catheter is positioned towards the right ventricle of the interventricular septum using fluoroscopy guidance. When the J wire could not be advanced easily often due to a venous valve or an occluded or spastic vein, a hydrophilic guidewire or a coronary 0.014 in guidewire was used.

Regarding the biopsy, we used a long forceps (104 cm; Cordis, Johnson & Johnson, United States) that comes in 2 different sizes: 5.5 Fr (142 cases) and 7 Fr (402 cases). Since the guide catheter is longer compared to the biopsy forceps we made it shorter by cutting the proximal 5 cm to 10 cm. To prevent bleeding or air embolism during manipulation, a 7 Fr femoral sheath can be used to seal the proximal end of the catheter. To facilitate the advance of the forceps through the tricuspid valve and prevent it from acquiring caudal orientation we shaped its distal end with a curve. Once the delivery catheter was in place we inserted the forceps, checked the septal orientation with fluoroscopy, and took 3-6 samples as usual. Figure 2 shows the main steps of this technique. The procedure was considered successful when an adequate sample was obtained and no major complications occurred. The inability to advance the J wire or the guide catheter that would eventually lead to change the access route was considered a failure.

After the procedure and only if the patient needed right heart catheterization it was performed through the same vein. If the patient needed an additional coronary angiography, the arterial access route, preferably radial, was canalized. Finally, we extracted both the catheter and the sheath and left a gentle elastic compression for 2 hours. No bed rest was required after the EMB procedure.

Data collection and analysis

We retrospectively collected the demographics, main procedural characteristics, and immediate and 48 h complications of all consecutive patients admitted to our catheterization laboratory to receive EMB from August 2004 through April 2016. Major complications were defined as death, major bleeding, pneumothorax, stroke, and cardiac tamponade. We compared the characteristics of brachial procedures to those of a series of biopsies performed through the jugular or femoral access route. We retrospectively contacted a sample of patients who had received the procedure through 2 different venous routes (brachial and central venous access) and asked them to rate the pain experienced during the procedure on a scale from 1 to 10. Also, to state their preferred venous access for the future.

Statistical analysis was performed using R 3.2.3. Data were expressed as mean ± standard deviation, median (interquartile range) or number (percentage). Inter-group differences were studied using the unpaired Student *t* test, the Wilcoxon rank sum test, Kruskal-Wallis test or the chi-square test as appropriate.

RESULTS

Brachial biopsy population

Between August 2004 and April 2016 we performed a total of 544 brachial EMBs in 118 patients. Mean age of the cohort was 52 ± 13 years; 12% of the patients were female. The reason for the biopsy was post-transplant follow-up in 525 procedures (96.5%) and cardiomyopathy assessment in the remaining patients. The veins used for the procedure were the basilic (90%) and the cephalic (10%) veins; the right arm was more commonly used (74%). The number of brachial procedures per patient rose from 1 to 14 (mean of 5 [1-10]). In 71 cases (13% of the procedures) right heart catheterization (RHC) was performed too, and in 82 cases (15%) a coronary angiography was performed. In these procedures most of the coronary angiographies were performed through the radial or ulnar arteries (92%). Fifty-seven-point-four percent of the cases were outpatient procedures. No major complications were reported.

Table 1. Demographics and baseline characteristics of jugular, femoral and brachial patients

	Jugular (n = 686)	Femoral (n = 1054)	Brachial (n = 544)	*P*
Age (years)	51 ± 13	52 ± 14	52 ± 13	.38
Women	175 (25.5)	257 (24.4)	66 (12.1)	< .001
Hypertension	275 (46.6)	444 (48.8)	253 (52.7)	.14
Hyperlipidemia	218 (36.8)	384 (42.6)	195 (40.9)	.08
Diabetes	152 (31.1)	269 (31.8)	137 (34.7)	.49
Reason for biopsy				< .001
Heart transplant	677 (98.7)	989 (93.8)	525 (96.5)	
Cardiomyopathy	9 (1.3)	65 (6.2)	19 (3.5)	
Patient destination				.017
Outpatient	414 (60.3)	666 (63.2)	312 (57.3)	
Inpatient	253 (36.9)	336 (31.9)	206 (37.9)	
Nonspecific	19 (2.8)	52 (4.9)	26 (4.8)	

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

Table 2. Procedural characteristics

	Jugular (n = 686)	Femoral (n = 1054)	Brachial (n = 544)	*P*
Systolic BP (mmHg)	148 ± 25	147 ± 24	140 ± 24	.01
Diastolic BP (mmHg)	79 ± 14	82 ± 14	77 ± 13	.03
Procedural success	664 (96.7)	1052 (99.8)	511 (93.9)	< .001
Crossover	22	2	33	< .001
Brachial to femoral			19	
Brachial to jugular			14	
Femoral to jugular		2		
Jugular femoral	22			

BP, blood pressure.
Data are expressed as no. (%) and mean ± standard deviation.

The brachial approach failed in 33 cases, always due to the impossibility to wire the vein or advance the catheter so we had to change the access route. Success rate for brachial EMBs was 94%. The percentage of ultrasound-guided procedures varied between both centers; we found that after its routine use in 1 center the brachial approach success rate has gone up up to 98.4% since 2015.

Venous access comparison

A total of 2284 biopsies were included in the registry from August 2004 through April 2016: 1054 femoral, 686 jugular, and 544 brachial. The main reason to perform this procedure was heart transplant in the 3 cohorts ($P < .001$). The patients' clinical characteristics were similar except for brachial procedures that were less common in women (13% vs 26%, $P < .001$). Most of the patients were outpatient cases in all the groups (61% of the total procedures) who did not require hospitalization. The main clinical characteristics are shown on table 1.

Success rate was 96.7% for jugular procedures, 99.8% for femoral procedures, and 93.9% for brachial procedures. Crossover to a different access route was required in 33 brachial cases (19 to femoral and 14 to jugular), 2 femoral cases, and 22 jugular cases ($P < .001$). Patients in whom the brachial access failed were similar to the remaining patients of the cohort: 12% were women with a mean age of 56 years [46-62] and 94% were heart transplant recipients. Seventeen (51.6%) out of the 33 failed procedures occurred during the early experience (between 2004 and 2007). Procedural characteristics are shown on table 2.

We compared total procedural and fluoroscopy times among different venous routes. Total procedural time for biopsy alone was similar among the groups (mean for brachial/femoral/jugular: 28/26/29 min., $P = .31$); however, fluoroscopy time was the shortest of them all in jugular procedures (mean 5/5/3 min., respectively; $P < .001$). Additional RHC or coronary angiography were performed less frequently in the jugular cohort ($P < .001$ in both cases).

Table 3. Procedure and fluoroscopy times grouped by access and procedures

	Jugular (n = 686)	Femoral (n = 1054)	Brachial (n = 544)	*P*
EMB only				
Number of cases	596 (86.9)	738 (70)	394 (72.4)	< .001
Procedural time	29 [20-40]	26 [20-37]	28 [19-40]	.31
Fluoroscopy time	3 [2-5]	5 [3-8]	5 [3-7]	< .001
EMB + RHC				
Number of cases	46 (6.7)	131 (12.4)	69 (12.7)	< .001
Procedural time	43.5 [32.75-63.5]	43.5 [37-54.75]	51 [45-63.5]	.004
Fluoroscopy time	3 [2-5.5]	11 [7.75-15.25]	7 [6-11]	< .001
EMB + CA				
Number of cases	44 (6.4)	185 (17.6)	81 (14.9)	< .001
Procedural time	61 [52-77.5]	59 [46-70]	66 [53-87]	.019
Fluoroscopy time	8 [7-18]	12 [8-17]	14 [10-19]	.003

Data are expressed as median [interquartile range] and no. (%).
CA, coronary angiography; EMB, endomyocardial biopsy; RHC, right heart catheterization.

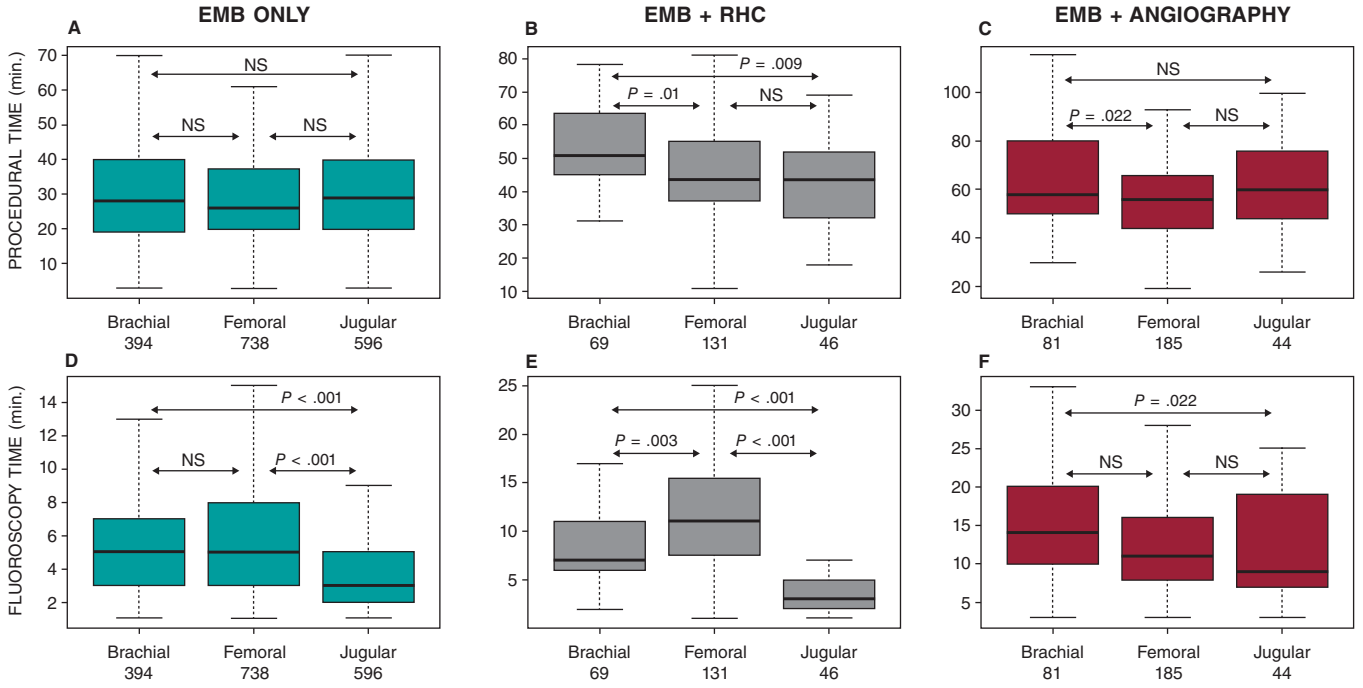

Figure 3. Comparison between the total procedural time (top charts) and fluoroscopy time (bottom charts) according to the different access routes. Inter-group comparisons were conducted using the Kruskal-Wallis and pairwise Wilcoxon tests. RHC, right heart catheterization; NS, not significant.

Together with RHC, the total procedural time was longer in the brachial route compared to the central one (P = .004); however, fluoroscopy time was longer in the femoral cohort compared to both the brachial (P = .003) and the jugular (P < .001) cohorts.

When the EMB was combined with coronary angiography, procedural times were again longer in the brachial group (brachial/femoral/jugular: 66/59/61 min., P = 0.02), but they were only statistically significant with femoral times (P = .022); also, longer fluoroscopy times were required in the brachial compared to jugular access (P = .002), but not in the femoral access (P = .6). Table 3 and figure 3 show the total and fluoroscopy times per procedure alone and combined with RHC or angiography. When we compared our experience with brachial EMBs half way and then over the last half we saw a reduction in the total procedural time (30 min. vs 28 min., P = .366) and total fluoroscopy time (6.6 min. vs 6.0 min., P = .031).

No major complications occurred at the 48-hour follow-up although 9 minor complications were reported: 2 vein dissections and

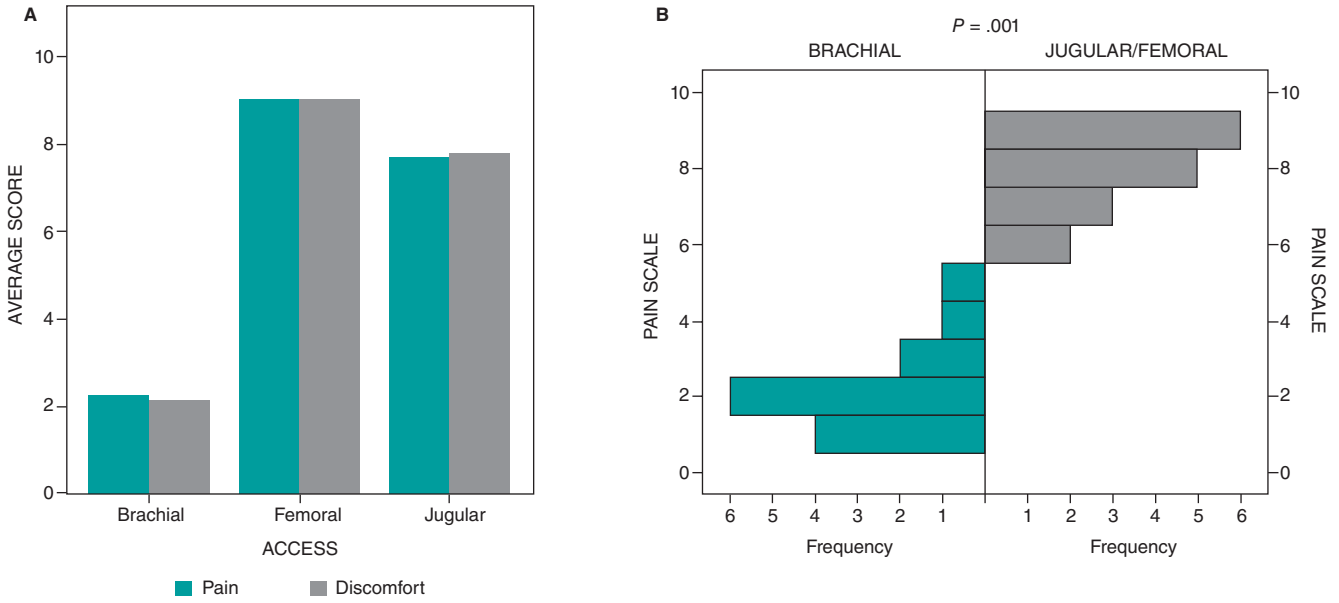

Figure 4. Pain and discomfort perceived during the procedures in patients treated through 2 different access locations (brachial and other). **Chart A** shows the average numeric pain score for each route from 0 (no pain) to 10 (maximum pain). **Chart B** shows the distribution of the pain score for the brachial access (green) vs femoral and jugular accesses combined (gray). Differences are statistically significant (Wilcoxon signed-rank test; $P = .001$).

3 phebitis all in the brachial procedures, and 4 hematomas, 1 in the brachial access and 3 in the jugular one. Bed rest after femoral access extended for 2 hours. However, it was not required after brachial or jugular access, which facilitated shorter recovery time.

We contacted 19 patients who received repeated procedures (64 total) through 2 or 3 different access routes. They all said that the brachial route was less painful compared to the femoral and jugular ones (2/10 vs 9/10 and 8/10, respectively; $P < .001$). When asked about their personal preference regarding future procedures, the brachial access was the preferred access route in all the patients. Figure 4 shows the pain and discomfort reported for each access route.

DISCUSSION

We report the experience of 2 Spanish centers performing EMBs through the brachial veins and the largest series described so far. We showed that it is a feasible and safe alternative that can be used in most patients on a routine basis. Also, we found that in these patients this access route was less painful and uncomfortable compared to the jugular and femoral ones. They also chose it for future prospective procedures.

Experience with the brachial approach

The forearm approach to access the right heart has already been described as a feasible and safe procedure to perform hemodynamic studies in patients with heart failure.[9] Since patients with a heart transplant need to receive repeated EMBs as part of rejection monitoring, it is important to use a technique that brings both safety and comfort and avoids central venous punctures to minimize EMB risks.[10] For this reason, we decided to describe this new peripheral venous access and compared it to the other 2 approaches often used in our centers.

Brachial vein is a good-sized vessel capable of accommodating 7 Fr sheaths. Its superficial location facilitates easy punctures that can be improved using ultrasound-guidance in cases of suboptimal palpation. Because of its straighter path, the basilic vein was mainly used in both traditional and ultrasound-guided accesses. The cephalic vein, although a plausible access too, connects to the subclavian with a pronounced angle that can stop the advance and rotation of the catheters. The technique described here facilitated the performance of EMBs in all but 33 cases where the guidewire or the catheter could not be advanced. We should mention that ultrasound guidance was not recorded on a routine basis and that half of the failures occurred within the first 3 years of using this approach; we think that both the learning curve and ultrasound guidance are major contributors to access failure.

In the absence of specific materials we decided to adapt the ones available in our catheterization laboratories to meet our purposes. Although we did not observe any complications from cutting the catheter (air embolism, bleeding) having better suited devices would have made the procedures safer and easier.

Peripheral versus central venous access

In this manuscript we reported the differences in procedural and fluoroscopy times among brachial, femoral, and jugular access routes. The brachial route did not seem to increase significantly the total procedural time except for when the biopsy was combined with RHC or angiography. Brachial fluoroscopy time was similar to femoral fluoroscopy time although both were longer compared to the jugular one. These differences remained even when the EMB was combined with the RHC or angiography and are consistent with those previously described in the only other series reported so far.[8] The longer total procedural time of brachial procedures may be explained by the longer it took to puncture and wire the peripheral vein; conversely, the femoral vein allows faster punctures, but a more difficult positioning of the catheters–especially the Swan-Ganz–which may explain why fluoroscopy time was longer when using the femoral access in cases that combined EMB plus RHC. Although we did not study operator radiation exposure directly, we think that the radiation the operator may be exposed to is lower in the brachial approach compared to the jugular one. That is so

because the former allows keeping further distance away from the X-ray source and use of radioprotective screens, which is something uncomfortable with jugular procedures where the operator is straddling on the C-arm. We should mention that we found a tendency towards shorter total and fluoroscopy times in procedures performed by more experienced operators.

Although previous reports of RHC revealed more complications in the access site in patients treated with transfemoral procedures,[11] we could not confirm these findings in patients who received EMB. No major complications occurred in any of the groups either. However, rare minor complications were reported more frequently in the brachial access group. Minor complications in other central locations–such as accidental arterial punctures, small hematomas or nerve damage–maybe were underestimated since data were recorded retrospectively and therefore with reporting bias; considering the location of the jugular and femoral access, we still believe that the risk of complications is real.[12,13] Probably, over the next few years ultrasound-guided punctures of central veins will become widely used, which should contribute to increase the safety and comfort of all vascular access routes.

Women had a lower probability of undergoing brachial procedures compared to males. This may be associated with the smaller size of their brachial veins, which may have discouraged the operators from attempting this route.

Regarding the degree of discomfort, patients with brachial access reported significantly lower pain measured through numeric rating scales. Regarding pain and comfort patients with a history of 2 different venous approaches (brachial and another one) preferred the brachial access compared to the femoral or jugular one. Although this cohort was small, these data are consistent with those reported by Harwani et al,[8] where the overall preference was brachial approach. This added to the fact that no bed rest is required, makes the brachial access a good choice for subjects in the outpatient setting mainly.

Limitations

This is a retrospective, observational study from 2 tertiary centers and has certain inherent limitations in the comparison of the different routes mainly. One of the main limitations is the retrospective collection of femoral and jugular procedures, which may have underestimated the real prevalence of vascular complications. In our opinion, brachial access may be safer, but this still needs to be confirmed in prospective series of cases. Also, we have to acknowledge that the use of ultrasound-guidance, the reasons for changing the access route or the need for special material (hyrophilic guidewires, contrast injection) were not recorded on a routine basis. Another major limitation is the small number of patients asked to compare their experience with the different accesses; the small size of the cohort led to lower statistical consistency. Finally, the procedures were performed with equipment not specifically designed for these purposes, so it was not the ideal equipment to use. This may indeed have held our technique back. Also, we believe that the development of a low-profile catheter specifically designed for brachial EMBs may contribute to easier and shorter procedures in the future.

CONCLUSION

EMBs obtained from the arm are highly feasible and safe compared to the standard jugular or femoral access. The arm brings extra comfort to the patients and may become the route of choice in experienced centers.

FUNDING

The study did not receive any specific funding. M. Tamargo has been receiving a grant from IISGM (*Ayuda Intramural PostMIR del Instituto de Investigación Sanitaria Gregorio Marañón*, Madrid, Spain) since 2019. F. Díez-Delhoyo received funds from 2016 to 2019 from Contrato i-PFIS (*Doctorados IIS-Empresa en Ciencias y Tecnologías de la Salud, Instituto de Salud Carlos III*, Ministry of Economy, Industry and Competitivity, Spain). J. García-Carreño has been receiving funds from *Contrato Instituto de Investigación Sanitaria Gregorio Marañón-IISGM*, Madrid, Spain since 2019.

L. Grigorian has been receiving funds from *Contrato CIBERCV* with the project *Retos Colaboración — RTC- 2016-4611-1*, Madrid, Spain since 2016.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest whatsoever.

MAIN POINTS

WHAT IS KNOWN ABOUT THE TOPIC?

- EMB is still the gold standard for rejection monitoring purposes and histological confirmation of myocarditis.
- It is usually performed through a central vein, which is associated with the potential risk of major complications.
- Previous evidence shows that right heart catheterization can be performed through a brachial vein. Still, evidence is scarce regarding the possibility of performing EMBs through this vein.

WHAT DOES THIS STUDY ADD?

- EMB performed through a peripheral vein is a feasible and safe option.
- Basilic and cephalic veins can easily be used to obtain endomyocardial samples using the material available in any catheterization laboratory with results comparable to the femoral or jugular vessels.
- The brachial approach seems less painful and should be considered for patients undergoing EMBs.

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REC Interv Cardiol. 2020;2(4):272-279

Original article

Value of the optical coherence tomography in the diagnosis of unstable patients with non-significant coronary stenosis

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ABSTRACT

Introduction and objectives: The final diagnosis of a myocardial infarction with non-obstructive coronary arteries (MINOCA) is often hard to achieve. Angiographic findings may be suggestive of the presence of unstable plaques although it is common to discharge patients without an etiologic diagnosis. The high spatial resolution provided by the optical coherence tomography (OCT) allows the detection of vulnerable and unstable coronary plaques that are prone to rupture, erosion, and thrombi which may lead to more targeted individual therapies. The objective of this study is to assess the utility of OCT when achieving an etiologic diagnosis in selected patients with MINOCA and high clinical suspicion of atherosclerotic etiology.
Methods: Registry of 27 patients recruited between September 2015 and January 2020 admitted to a single tertiary hospital with acute coronary syndrome and non-significant stenosis in the coronary angiography who underwent OCT. The baseline data of the study population, the angiographic and OCT findings, treatment and follow-up information were all collected.
Results: The OCT imaging showed evidence of unstable plaques (thrombus, plaque erosion or plaque rupture) in 78% of patients, which lead to an etiologic diagnosis of MINOCA. Patients were predominantly males (89%), smokers (63%), middle-aged (median 53 years old) and with a low cardiovascular risk burden. The left anterior descending coronary artery was the most frequently compromised vessel (74%) and 95% of patients ended up receiving coronary stents. The mid-term follow-up was excellent.
Conclusions: In our study, OCT imaging proved to be a valuable tool to achieve an etiologic diagnosis in a large proportion of selected patients with MINOCA which, as a result could lead to more specific and individualized treatments.

Keywords: Optical coherence tomography. Myocardial infarction with non-obstructive coronary arteries. Unstable plaque. Vulnerable plaque.

Utilidad de la tomografía de coherencia óptica en el diagnóstico de pacientes inestables con estenosis coronarias no significativas

RESUMEN

Introducción y objetivos: A menudo resulta complejo diagnosticar a pacientes con infarto agudo de miocardio y estenosis coronarias no significativas en la coronariografía (MINOCA). En ocasiones, la angiografía muestra datos sugestivos de placa inestable, aunque no es infrecuente que estos pacientes acaben sin un diagnóstico etiológico. La tomografía de coherencia óptica (OCT) permite detectar placas vulnerables e inestables con rotura, erosión o trombo gracias a su elevada resolución espacial, lo que podría implicar un cambio en el manejo de estos pacientes. El objetivo de este estudio es valorar la utilidad de la OCT para alcanzar un diagnóstico final en casos seleccionados de MINOCA con alta sospecha de etiología ateroesclerótica.
Métodos: Registro de 27 pacientes desde septiembre de 2015 hasta enero de 2020 en los que se indica OCT en el contexto de síndrome coronario agudo y estenosis < 50% en la angiografía. Se describen las características de la población, los hallazgos en la angiografía y la OCT, la actitud terapéutica y la evolución.

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Received 11 January 2020. Accepted 19 March 2020. Online: 08-06-2020.
https://doi.org/10.24875/RECICE.M20000117

Resultados: La OCT evidenció la presencia de placa inestable con trombo, rotura de placa o erosión de placa en el 78% de los pacientes como causa del MINOCA. Los pacientes fueron predominantemente varones (89%), fumadores (63%), de mediana edad (53 años de mediana), con poca carga de factores de riesgo y afectación principalmente de la descendente anterior (74%). El 95% de los casos en que se detectó placa inestable fueron tratados con *stent*. La evolución a medio plazo fue excelente.
Conclusiones: En nuestra serie de pacientes con MINOCA y alta sospecha de causa ateroesclerótica, la OCT resultó ser una técnica útil para identificar la etiología de la mayoría de ellos, lo que permitió adoptar una estrategia terapéutica más específica.

Palabras clave: Infarto de miocardio con arterias coronarias sin estenosis significativas. Placa inestable. Placa vulnerable. Tomografía de coherencia óptica.

Abbreviations:

MINOCA: myocardial infarction with non-obstructive coronary arteries. **OCT:** optical coherence tomography. **ACS:** acute coronary syndrome.

INTRODUCTION

Patients admitted with a diagnosis of acute coronary syndrome (ACS) with coronary arteries without significant angiographic obstructions (considered as angiographic stenoses < 50% of the lumen of a major epicardial vessel) should be reassessed before re-planning their diagnosis.[1] In general, differential diagnosis is required with other conditions that may trigger acute myocardial damage without an acute myocardial ischemia as the underlying cause (myocarditis, stress cardiomyopathy or other cardiomyopathies, pulmonary thromboembolism, etc.). Only when these are discarded or unlikely the diagnosis of acute myocardial infarction with non-obstructive coronary arteries, also known as MINOCA, can be established.[2]

MINOCA amounts to between 5% and 7% of all acute myocardial infarctions, but even in some series its prevalence reaches 15% of the cases.[3-5] The causes for MINOCA are varied: atherosclerotic plaque disruption (rupture or erosion), vasospasm, microvascular dysfunction, thrombus or coronary embolism, spontaneous coronary dissection or oxygen supply-demand imbalance (like in the tachyarrhythmia or anemia setting). For this reason, treatment varies significantly depending on each particular case.[6] However, some studies have reported that in half of the patients no specific etiological diagnosis was established,[7,8] which may lead to inappropriate treatments.

The optical coherence tomography (OCT) is an intravascular imaging modality based on the use of infrared light to acquire images with very good spatial resolution (approximately between 10 µm and 20 µm), even 10 times better resolution compared intravascular ultrasound (IVUS).[9] For this reason, the OCT allows the detection of vulnerable plaques (those whose characteristics show a higher risk of destabilization) or findings suggestive that the plaque is already destabilized (table 1).[10-12] Therefore, it is a useful imaging modality to establish the etiological diagnosis of MINOCA, especially when there is clinical or electrocardiographic suspicion of ACS due to atherosclerosis and also in cases of spontaneous coronary dissection.

The objective of this study was to assess the utility of the OCT to establish the etiological diagnosis of patients with MINOCA and highly suspected ACS due to atherosclerosis, and describe the profile of the population studied.

Table 1. Pathologic findings on the optical coherence tomography

Vulnerable plaque	Unstable plaque
Type of plaque	Thrombus
Macrophages	Rupture of plaque
Neovessels	Erosion of the plaque
Cholesterol microcrystals	Protruding calcium nodule with presence of thrombus or plaque disruption

METHODS

Study population

This was a prospective registry of selected cases of MINOCA in the reference center of an autonomous community between September 2015 and January 2020 with the following characteristics: *a)* admission with a diagnosis of ACS or recovered sudden death with suspected ACS as the underlying cause; *b)* angiographic coronary stenoses < 50%, and *c)* performance of an OCT on the possible culprit artery causing the event due to suspected angiographic imaging or ECG or segmental alterations on the echocardiogram. When in doubt on which the infarct-related culprit artery was, the vessels considered in each case were assessed using the OCT.

Procedure and analysis

The OCT was performed using the Dragonfly Optis catheter (Abbott, United States) over a pullback length of 55 mm or 75 mm in the segment of interest. The OCT study was performed in the same Ilumien Optis OCT console (Abbott). The angiographic study was performed using the Stenosis Analysis 1.6 software package (GE Healthcare, Advantage Workstation 4.5, United States). The offline analyses of the angiographic and OCT findings were performed by the same operator while the interventional procedure was being performed. This operator made the therapeutic decisions too. Afterwards, 2 expert operators performed an independent, thorough, and retrospective analysis of the angiographic and OCT images in a first reading and, simultaneously, in a second reading to achieve consensus when in the presence of suspected cases or possible discrepancies.

The following qualitative analysis were defined according to the methodology described in the OCT consensus document:[12] vulnerable plaque, presence of thin-cap fibroatheroma (TCFA), macrophages, neovascularization, presence of thrombus, erosion of the plaque, ruptured plaque, and protruding calcium nodule. Unstable plaque is defined as a plaque with a thrombus, ruptured plaque, erosion of the plaque or protruding calcium nodule with thrombus or plaque disruption as seen on the OCT. Quantitative analysis was performed for every 1 mm interval while the software automatically calculated luminal dimension. The results of patients treated with a stent and those who underwent a new OCT after the implant were confirmed by verifying the adequate position, expansion, and lack of large dissections of the borders of the stent.

Statistical analysis

Quantitative variables with a normal distribution were expressed as mean and standard deviation. Those without a normal distribution were expressed as median and interquartile range [IQR]. Finally, qualitative variables were expressed using percentages as the frequency measure.

RESULTS

The registry included 27 patients. A total of 28 arteries through 38 OCT pullbacks were studied. Results are shown on table 2.

The patients' mean age was 53 years [45-64]. Most of them were males (89%). Smoking was the main cardiovascular risk factor (63%). The most common indication for the coronary angiography was non-ST-segment elevation ACS (63%).

The median angiographic stenosis obtained through visual analysis was 40% [30-40]. In 5 cases the stenosis assessed through visual estimation was between 50% to 60%; according to the quantitative coronary angiography the median stenosis was 41.2% [35.5-48.8]. The quantitative coronary angiography showed a 50% to 60% stenosis in 2 cases only. In all of the patients the initial TIMI flow was normal (Thrombolysis in Myocardial Infarction [TIMI] grade 3). The vessel most often damaged was the left anterior descending coronary artery (74%). In most patients the angiographic imaging did not show any signs indicative of an unstable plaque. The angiographic imaging was suggestive of a thrombus and an ulcer in 2 and 3 cases, respectively. No thromboaspiration was performed in any of the patients.

Regarding the OCT findings, the median minimum lumen area was 3.2 mm^2 [2.5-4.9]. In most of the cases different types of vulnerable plaque were found in the form of a TCFA (67%), macrophages (59%), and neovessels (56%). The OCT showed signs of unstable plaque in 21 cases (78%) with thrombus in 70% of the patients. The erosion of the plaque was the main cause for plaque instability (41%) followed by the rupture of the plaque (30%). A decision was made to implant a stent in 20 of the 21 patients (95%) with data of unstable plaque as seen on the OCT. One patient with plaque erosion received medical therapy. The 6 patients without data of unstable plaque on the OCT received medical therapy too. In 75% of the cases with stenting the outcomes were assessed using the OCT; 5 out of the 20 cases were postdilated and an additional overlapping stent was implanted in 1 out of the 20 cases.

Finally, no sudden deaths were reported during the index event. At the median 4-month follow-up only 1 death due to cardiovascular causes was reported.

Figure 1, figure 2, figure 3, and figure 4 show the 4 cases included in the registry together with the images obtained on the coronary angiography and OCT.

DISCUSSION

In some series of patients with MINOCA it has been reported that in up to 50% to 70% of the cases no etiological diagnosis is established. This means that these patients may end up receiving unspecific treatment for their MINOCA.[7,8] For this reason, diagnostic algorithms have been designed by expert consensus including intravascular imaging techniques as useful tools to establish the etiological diagnosis of MINOCA.[2,12,13] Regarding the use of the OCT specifically for these patients, the studies have proven its capacity to detect the mechanism of the infarction in some of MINOCAs.[14,15] However, although its use has been reported in some series of patients with MINOCA[7,8,16] it is still scare (only 0.08% in some registries.)[16] This may be due to the fact that its wide use in this type of patients has not been fully established or to the different availability and training capabilities of each center.

According to different expert consensuses[2,12,13] in our center OCTs are performed on this type of patients (suspected atherosclerotic cause). This registry was started back in 2015 to later study and assess the utility of OCT in these cases since scientific evidence available on this regard is scarce in part due to its low use. Also, it would be advisable to establish a protocol to perform OCTs in most cases of MINOCA even in the absence of suspected atherosclerotic etiology; thanks to its high spatial resolution, the OCT also allows us to detect other causes for MINOCA like thromboembolisms, vasospasms or spontaneous coronary dissections.[12] This was also confirmed by our study that identified 2 cases of hematoma/spontaneous coronary dissection (table 2, figure 3).[12]

The characteristics of this registry were those of a young population of patients (median age, 53 years), which is consistent with what has been reported by former studies. However, most of the patients included were males (89%), which varies significantly from other previous registries or reviews where over half of the patients with MINOCA were women.[3,7,8,15,16] Our interpretation of these data is that our registry studied highly selected cases of MINOCA with a high clinical suspicion of atherosclerotic ACS due, which is more common in males. This would be consistent with the characteristics of the series of ACS previously reported.[17] Also, when the different causes for MINOCA were analyzed, some studies have reported that when it is due to the disruption of the plaque there is a higher prevalence of male sex. However, in the occurrence of MINOCAs due to other causes, female sex is still predominant.[15]

According to several studies, the main clinical presentation of these patients was non-ST-elevation ACS (63%). However, there was a larger number of sudden deaths with MINOCA as the early presentation, which would be indicative of the utility of OCT for the etiological study of recovered sudden death.[7,8,16]

Regarding the coronary angiography findings, although the atherosclerotic cause for MINOCA was suspected, the angiography imaging were inconclusive (non-significant stenosis and scarce cases of images suggestive of plaque instability). This totally justified performing the OCT in all of the cases. The left anterior descending coronary artery was the vessel more commonly damaged, which is consistent with the results reported by other studies.[15]

The OCT findings show that the median minimum lumen area of the patients was 3.2 mm^2. Former studies conducted with IVUS have reported on the minimum lumen area as suggestive of

Table 2. Study results

Demographic and clinical variables of the patients (n = 27)	
Age	53 [45-64]
Female sex	3 (11)
Smoking	17 (63)
Dyslipidemia	12 (44)
Arterial hypertension	10 (37)
Diabetes mellitus	1 (4)
Indication for coronary angiography:	
NSTEACS	17 (63)
STEACS	6 (22)
Sudden death with suspected ACS	4 (15)
Elevation of high-sensitive troponin I levels	20 (74)
LVEF	61 ± 9
Findings of the coronary angiography	
Stenosis as seen on the visual angiographic assessment, %	40 [30-40]
Stenosis as seen on the quantitative coronary angiography assessment, %	41.2 [35.5-48.4]
Suspected vessels on the coronary angiography	
LAD	20 (74)
Cx	1 (4)
RCA	7 (26)
Angiographic characteristics of the lesion	
Irregular lesion	9 (33)
Image of an ulcer	3 (11)
Calcified lesion	3 (11)
Smooth lesion	15 (56)
Angiographic thrombus	2 (7)
Long lesion	6 (22)
Variables of the OCT	
Minimum lumen area, mm2	3.2 [2.5-4.9]
Vulnerable plaque	23 (85)
TCFA	18 (67)
Lipid core > 90% of the vessel area	13 (48)
Protruding calcium nodule	2 (7)
Neovessels	15 (56)
Macrophages	16 (59)
Measure of the TCFA fibrous layer, µm	63 ± 7
Unstable plaque	21 (78)
Thrombus	19 (70)
Rupture	8 (30)
Erosion	11 (41)
Protruding calcium nodule with thrombus/plaque disruption	2 (7)
Variables of the OCT	
Other causes for MINOCA found on the OCT: hematoma/ spontaneous coronary dissection	2 (7)
OCT post-stent implantation	15 de 20 casos (75)
Underexpansion	1 (7)
Malapposition	1 (7)
Dissection of the borders	1 (7)
Therapeutic approach	
Perform PCI after OCT with findings suggestive of plaque	20 de 21 casos (95)
Perform PCI after OCT without findings suggestive of plaque	0 de 6 casos (0)
Progression	
Death during admission	0 (0)
Death during follow-up	1 (4)
Cardiac death	1 (4)
Follow-up, months	4 [1-19]

ACS, acute coronary syndrome; Cx, circumflex artery; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; MINOCA, myocardial infarction with non-obstructive coronary arteries; NSTEACS, non-ST-segment elevation acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome; TCFA, thin-cap fibroatheroma.
Unless specified otherwise, data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

non-significant stenosis for which medical therapy is, therefore, preferred.[18] The study conducted by Gonzalo et al.,[19] that studied the value of OCT to establish the severity of intermediate angiographic stenoses (40% to 70% as seen on the quantitative coronary angiography) in patients with stable coronary artery disease revealed that the minimum lumen area as seen on the OCT to establish the concept of a functionally significant stenosis (fractional flow reserve ≤ 0.80) was 1.95 mm^2. Therefore, our patients showed stenoses on the OCT without compromised coronary flows, which is consistent with the angiographic results that showed non-significant stenoses (median of 40% by visual estimation and 41.2% on the quantitative coronary angiography). However, the OCT detected the instability of the plaque in 78% of registry patients, which is why although no significant stenosis was seen (on the angiography or OCT) a decision was made to implant a stent in 95% of the cases with an unstable plaque as seen on the OCT. There is not enough evidence to support this therapeutic strategy over pharmacological treatment only.[2,6,13,20-22] The EROSION trial[21,22] studied conservative management (pharmacological) in cases of ACS with residual angiographic stenosis < 70% after the aspiration of a thrombus and the erosion of the plaque as the infarction mechanism. At the 1-year follow-up, 92.5% of the patients were still free from any major cardiovascular events. Therefore, conservative treatment may have been an option for a larger percentage of patients from our series. We should mention that the OCT avoided stent implantation in 6 patients in whom no unstable plaque was detected or in whom a different cause for MINOCA was found (hematoma/coronary dissection). It would be advisable to conduct randomized, prospective clinical trials to assess the possible benefit of percutaneous

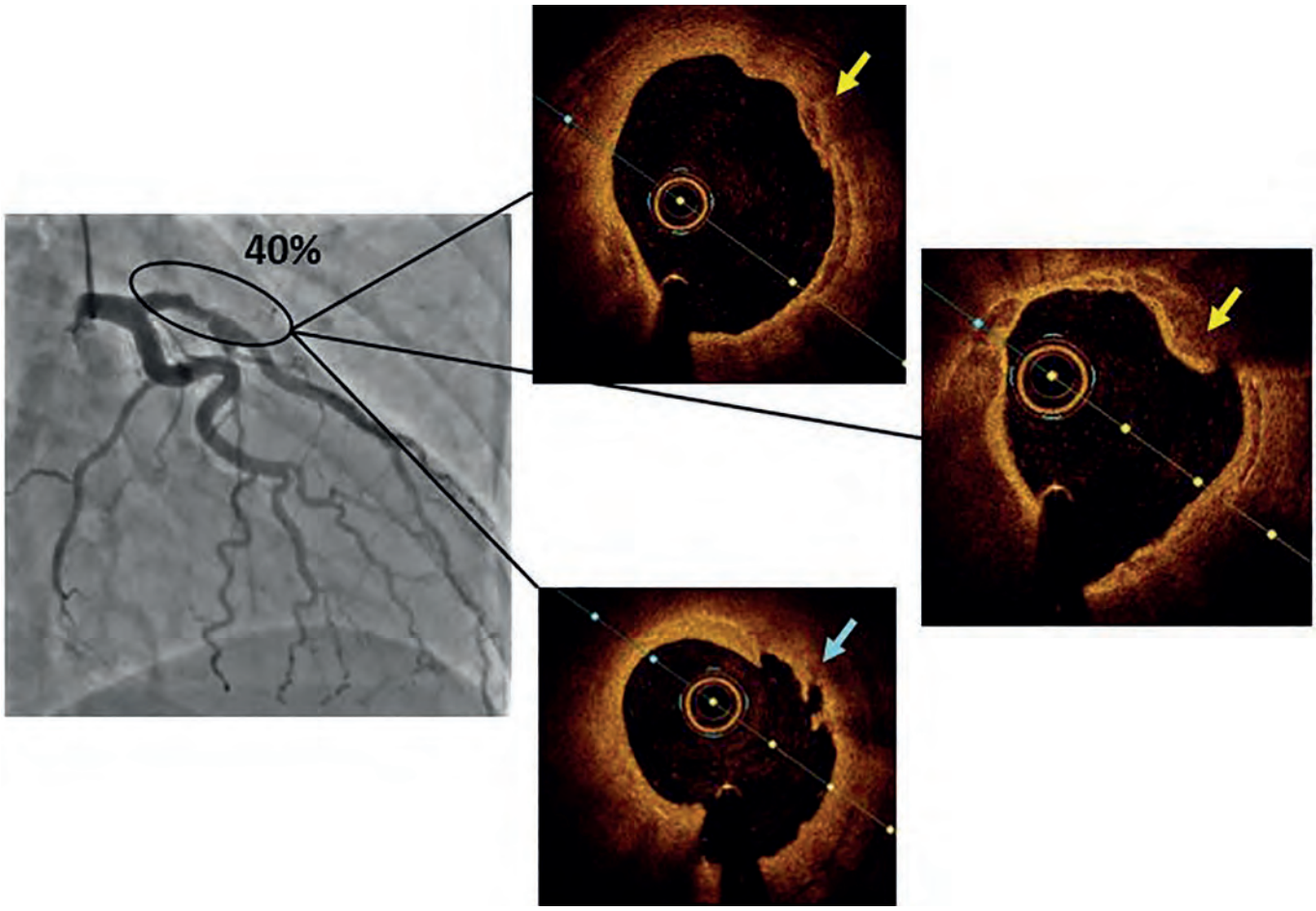

Figure 1. Sixty-nine years-old male patient admitted with a non-ST-segment elevation acute coronary syndrome. Smoking is the only relevant past medical history. High-sensitivity troponin I peak levels of 293 ng/L and preserved left ventricular ejection fraction. The coronary angiography reveals the presence of a non-significant plaque (40%) by visual estimation in the left anterior descending coronary artery. The optical coherence tomography reveals the presence of fibrocalcic plaques with calcium nodules (yellow arrow) protruding into the endovascular lumen to eventually rupture the plaque (blue arrow). Findings of scarce content of white thrombus.

coronary intervention compared to pharmacological medical therapy for the management of patients with plaque disruption as the cause for MINOCA.

Mid-term patient progression was good and consistent with what has been reported by registries.[7] Only 1 patient died of cardiovascular causes at the follow-up (a patient with multiple comorbidities and of an older age compared to the study median age, that is, a patient different from the population studied).

On the other hand, although this trial basically tries to identify the presence of unstable plaques on the OCT, the presence of vulnerable plaques was also studied since they are indicative of high cardiovascular risk. Thus, in most of the patients studied vulnerable plaques were found and they were often thin-cap fibroatheromas. TCFAs are considered as some of the most vulnerable plaques of all because they are made up of a lipid core (also known as lipid-rich necrotic core) covered by a very thin fibrous cap (< 65 µm) that makes them more prone to destabilization. Plaques with calcium nodules protruding towards the vessel lumen also have a higher risk of destabilization due to prospective plaque disruption, but in general they are less common. As a matter of fact, only 2 cases were found in our registry. Other findings of vulnerable plaque are the presence of macrophages (indicative of plaque inflammation), neovessels (they are immature, they can break, and cause intraplaque hemorrhage), and the size of the lipid core. all of these findings were present in over half of the study patients. Findings that are consistent with those reported by former studies.[10,11,14,15]

Finally, we should mention that the registry included very few patients (27) over a 4.5-year period. The largest number of patients included happened over the last 2 years. This is due to the few OCTs performed in our center to this profile of patients at the beginning of the registry with a wider use of this imaging modality after its great utility was confirmed in selected cases (figure 1 of supplementary data). The follow-up of patient was short (median follow-up, 4 months) because over the last 6 months of the registry up to 9 patients (33%) were included and because 7 patients (26%) had a different nationality and were followed in their home countries; overall this amounts to 59% of the patients with a limited follow-up period.

CONCLUSIONS

The OCT is an intravascular imaging modality to establish etiological diagnosis in a large number of patients with MINOCA, which

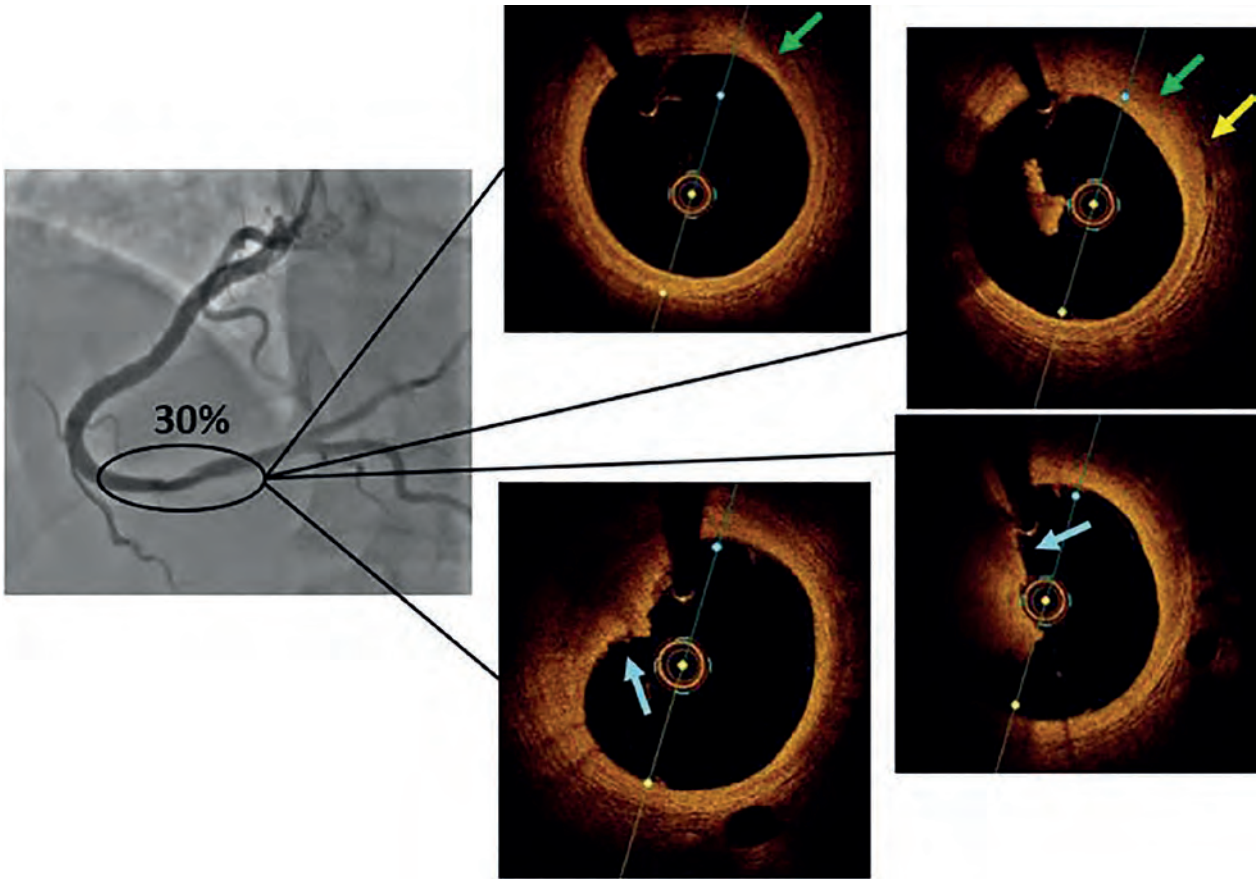

Figure 2. Forty-year-old male patient admitted with an ST-segment elevation acute coronary syndrome. High-sensitivity troponin I peak levels of 5000 ng/L and normal left ventricular ejection fraction. The coronary angiography reveals the presence of a non-significant plaque (30%) in the distal right coronary artery. The optical coherence tomography reveals the presence of vulnerable plaques with the shape of a fibro-lipid plaque (green arrow) and neovessels (yellow arrow). Afterwards, it confirms the presence of a massive amount of thrombus, but the discontinuity of the intima layer cannot be identified (blue arrow) suggestive that it is plaque erosion.

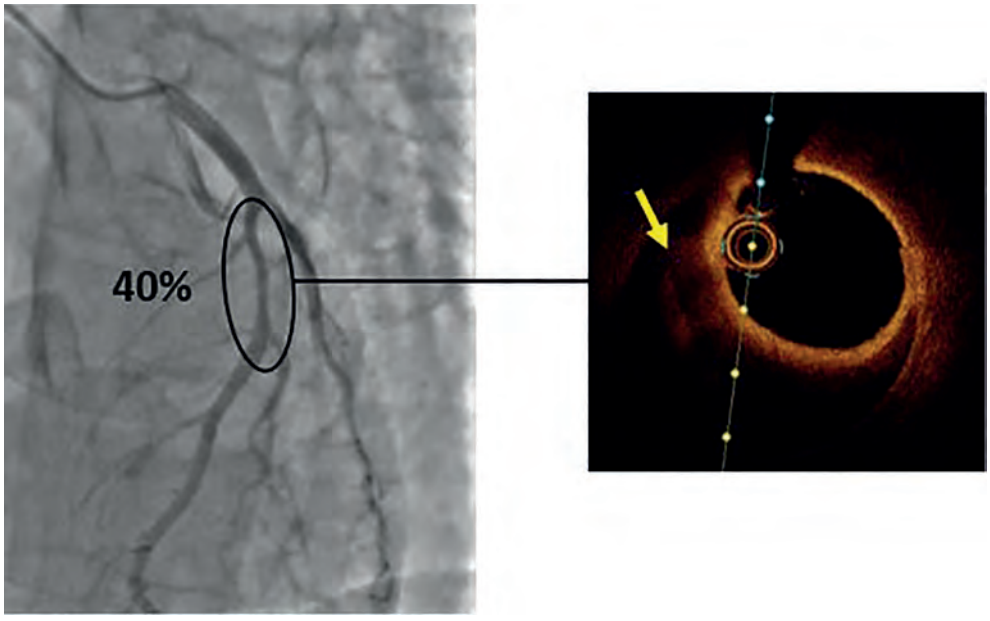

Figure 3. Thirty-five-year-old male patient. He is a smoker who is admitted with a non-ST-segment elevation acute coronary syndrome, high-sensitivity troponin I peak levels of 2796 ng/L, and a normal left ventricular ejection fraction. The coronary angiography reveals angiographic diffuse thinning of the left anterior descending coronary. The optical coherence tomography reveals a very well-established low-signal region surrounding the vessel lumen (yellow arrow) suggestive of hematoma.

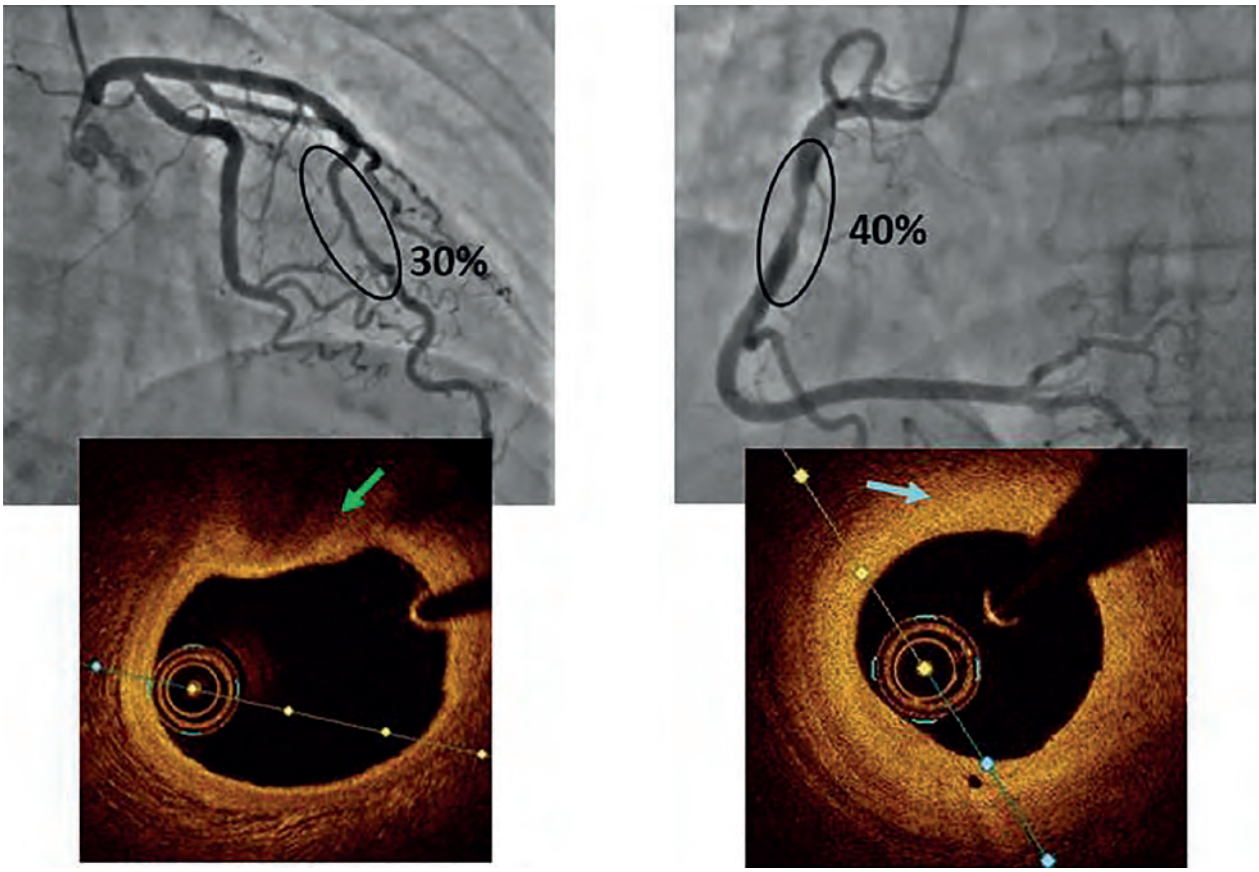

Figure 4. Fifty-nine-year-old female patient admitted with a diagnosis of sudden death of cardiac origin after chest pain. The coronary angiography reveals the presence of non-significant plaques in the left anterior descending coronary artery (LAD) and right coronary artery (RCA). Facing the possibility that either one of them could have destabilized, an optical coherence tomography is performed in both arteries without findings of unstable plaques. A fibro-lipid plaque is seen in the LAD (green arrow) and a fibrous plaque in the RCA (blue arrow). Coronary vasospasm appears as the possible cause, but since the patient was from another country, she was transferred and the study could not be completed in our hospital.

can lead to a better decision-making process with each particular case. Our study confirms the great accuracy of this imaging modality for the detection of unstable atherosclerotic plaques. Yet despite its proven utility and recommendation from expert consensuses, the use of this imaging modality in this type of patients is still scarce. This means that it will be necessary to establish algorithm of common actions in patients with MINOCA to avoid misdiagnosing its different etiologies.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- MINOCAs amount to 5% to 7% of all myocardial infarctions. Different causes can trigger MINOCAs and treatment is different in each of them.
- Although there are different imaging modalities available (magnetic resonance imaging, OCT, IVUS, etc.) and their utility has been proven in the diagnosis of MINOCA, in over half of the patients the etiological diagnosis is never established.
- In part this is due to a scarce use of these imaging modalities, although expert consensuses recommend their use.

WHAT DOES THIS STUDY ADD?

- This study shows the utility of OCT to establish the etiological diagnosis of MINOCA, which reinforces the idea of a wider use of this imaging modality.
- We should mention that OCT findings can change the therapeutic approach.
- The need to conduct more specific studies to assess the best therapeutic strategy for the management of patients with MINOCA and plaque disruption.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000117.

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REC Interv Cardiol. 2020;2(4):280-287

Review article

Left ventricular assist devices in acute cardiovascular care patients and high-risk percutaneous coronary interventions

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ABSTRACT

Percutaneous coronary intervention (PCI) plays a key role in the management of patients with obstructive coronary artery disease. Besides, depending on the patients' clinical presentation, characteristics, comorbidities, and coronary anatomy, an increasing number of patients will undergo a high-risk PCI. Left ventricular assist devices, as the intra-aortic balloon pump, TandemHeart, Impella, HeartMate PHP, and extracorporeal membrane oxygenation are useful tools to provide circulatory support for high-risk PCIs. Some studies and trials have assessed its impact on this clinical scenario with controversial results. This review provides an overview on the scientific evidence available on the use of left ventricular assist devices and their potential role in high-risk PCI.

Keywords: Intra-aortic balloon pump. Left ventricular assist device. High-risk percutaneous coronary intervention. Cardiogenic shock. Right ventricle.

Asistencias ventriculares percutáneas en los pacientes agudos y en el intervencionismo coronario de alto riesgo

RESUMEN

La intervención coronaria percutánea (ICP) desempeña un papel fundamental en el tratamiento de los pacientes con enfermedad coronaria obstructiva. De ellos, un porcentaje significativo se someterán a un procedimiento de alto riesgo, en función de la presentación clínica, las características del paciente y su anatomía coronaria. Los dispositivos de asistencia ventricular izquierda, como el balón intraaórtico de contrapulsación, el dispositivo TandemHeart, el Impella, los dispositivos HeartMate PHP y las técnicas de oxigenación veno-arterial con oxigenador extracorpóreo de membrana (ECMO), son herramientas empleadas para proporcionar soporte circulatorio en la ICP de alto riesgo, con un impacto creciente en la práctica clínica. Existen numerosos trabajos en la literatura científica sobre su empleo en este escenario, con resultados controvertidos. Esta revisión proporciona una visión general de la evidencia disponible sobre el empleo de los distintos tipos de dispositivos, así como de su potencial papel en la ICP de alto riesgo.

Palabras clave: Balón intraaórtico de contrapulsación. Dispositivo de asistencia ventricular izquierda. Intervencionismo coronario percutáneo de alto riesgo. *Shock* cardiogénico. Ventrículo derecho.

Abbreviations

AMI: acute myocardial infarction. **CHD:** coronary heart disease. **ECMO:** extracorporeal membrane oxigenator. **IABP:** Intra-aortic balloon pump. **LMCA:** left main coronary artery. **LVAD:** left ventricular assist device. **PCI:** percutaneous coronary intervention.

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Online: 30-06-2020.
https://doi.org/10.24875/RECICE.M20000130

INTRODUCTION

In the Western world, coronary heart disease (CHD) is a problem of public health. It is estimated that in the US population over 20, 15.5 million people suffer from CHD and nearly 635 000 will suffer from a new acute coronary event each year.[1] The percutaneous coronary intervention (PCI) as the way to treat this condition is still growing exponentially and it is currently the treatment of choice for revascularization purposes,[1-3] except for certain patients with multivessel or highly complex disease.[4,5] The has a class I recommendation for the management of patients with acute coronary events and it is the first-line therapy in 3 clinical settings: refractory angina to medical therapy, cardiogenic shock as a complication of the acute myocardial infarction (AMI), and ST-segment elevation acute coronary syndrome.[3,4]

HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

The criterion to define a PCI as a high-risk PCI is not well-established, but there is a series of characteristics that give it a high periprocedural risk profile that can be divided into 3 groups: patient-specific, lesion-specific, and clinical presentation-specific.[6-9]

Patient-inherent factors are old age, diabetes mellitus, chronic kidney disease, previous myocardial infarction, severe peripheral vascular disease, and the presence of left ventricular systolic dysfunction defined as a value < 30%-35%.[9,10]

The factors dependent on the characteristics of the coronary lesion are left main coronary artery disease (LMCA)—unprotected—, ostial disease or in bifurcations, lesion to the saphenous vein bypass graft, presence of abundant calcification, and chronic occlusions.[11,12] Finally, clinical presentation plays a role in the prognostic of these patients in such a way that those with a cardiogenic shock or hospitalized with an acute coronary syndrome have a higher risk of adverse events during the PCI.[13]

We should mention that cardiogenic shock is the leading cause of death associated with the AMI with a prevalence between 5% and 15%.[13,14] There is growing evidence that the prognosis of patients with AMI complicated with cardiogenic shock could substantially improve with early PCIs and primary angioplasty.[15,16]

PERCUTANEOUS CIRCULATORY ASSIST DEVICES

Left ventricular assist devices (LVAD) are used to provide hemodynamic support during high-risk PCIs. These devices include the intra-aortic balloon pump (IABP), the TandemHeart device (CardiacAssist, United States), the Impella device (Abiomed, United States), the HeartMate PHP devices (St. Jude Medical, United States), and veno-arterial oxygenation techniques with extracorporeal membrane oxygenation (ECMO).[17] Their main characteristic are comparatively described and shown on table 1.

The intra-aortic balloon pump

Since it was first introduced back in the 1970s, the IABP has become a circulatory assist device for several indications

Their capacity to improve coronary flow,[18,19] improve systemic flow by an additional increase of cardiac output of 0.5 L/min,[14,20,21] and reduce the myocardial oxygen consumption[22] recommends it use in all those patients in whom coronary and systemic flow needs to be increased.

Table 1. Comparison of the different type of left circulatory assist devices based on their baseline characteristics

Device	Pump action mechanism	Cardiac chamber of action	Vascular access	Flow
IABP	Counterpulsation	LV	8-9 Fr	1 L/min
ECMO	Centrifugal	Biventricular	Venous (15-22 Fr) Arterial (15-21 Fr)	> 4.5 L/min
TandemHeart	Centrifugal	LV, RV or biventricular	Venous (15-17 Fr) Arterial (21-Fr)	4.5 L/min
Impella 2.5	Axial	LV	12-Fr	2.5 L/min
Impella CP	Axial	LV	14-Fr	3.33 L/min
Impella 5.0	Axial	LV	21-Fr	5 L/min

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricle; RV, right ventricle.

Recently, in the US clinical practice guidelines,[3] the use of IABPs has gone from a class I a to a class II b recommendation in the cardiogenic shock setting as a complication of AMI. The European guidelines[23] give IABPs a class III recommendation. This has to do with the studies that question the value of IABP as a factor worth of prognostic impact.[24] The IABP SHOCK study compared the use of the IABP after PCI and the standard approach with inotropes and vasoactive amines without confirmation of short-term benefits in mortality rate.[25] These findings were backed after the publication of the IABP-SHOCK II study that found no differences in 30-day mortality rate[24] or all-cause mortality rate at the 12-month follow-up[26] in patients with AMI complicated with cardiogenic shock.

A meta-analysis suggests that the preoperative use of IABP reduces preoperative mortality and the 30-day mortality rate in high-risk patients scheduled to undergo elective surgery of myocardial revascularization.[27-32] Other authors think that the use of IABPs does not impact mortality in patients with AMI regardless of whether they show cardiogenic shock or not.[14,33,34]

These contradictory results set the foundations of new research studies.

Current situation in PCI procedures

The IABP has been used over decades in high-risk PCIs thanks to its circulatory support capabilities.[9,35-38] A series of studies compared its elective implantation in this context with its use as a bail-out strategy in stable patients eligible for a high-risk PCI. These studies suggest that the elective implantation of an IABP prior to the procedure is associated with fewer adverse events during the PCI[39,40] with a tendency towards fewer major adverse cardiovascular events. Mishra et al.[38] reported that the prophylactic implantation of an IABP prior to a high-risk PCI was associated with a higher survival rate during the hospital stay and at the 6-month follow-up compared to its implantation as a bail-out strategy due to the development of hemodynamic compromise during the procedure. All of it happened at the expense of a high risk from this group of complications associated with bleeding complications.[41] Although these data are relevant they all come from retrospective studies.

Back in 2010, Perera et al.[39] conducted a prospective, multicenter, randomized, and controlled clinical trial on coronary interventions

assisted with intra-aortic balloon pumps (BCIS-1). This study randomized 301 patients with CHD and a left ventricular systolic dysfunction < 30% to receive, or not, an elective IABP. The primary endpoint was the presence of cardiovascular adverse events at the 28-day follow-up, which occurred in 15.2% of the patients where the IABP was implanted electively compared to 16% of the patients where the IABP was not scheduled. The elective use of the IABP was associated with fewer bleeding and local complications compared to its bail-out use in the group of patients without scheduled implantations. These results are consistent with those of a meta-analysis recently published.[34]

Based on the results from clinical trials, the use of IABPs in high-risk PCIs has been going down.[13,41] At the same time, the development and use of other LVADs in this context has been going up.[42]

TandemHeart

The TandemHeart (figure 1) is an external temporary mechanical circulatory support device capable of supplying a continuous flow 4 L/min.[43] It includes 3 subsystems and it is the only device designed to enter the interatrial septum through a 21-Fr cannula that is allocated in the left atrium. The oxygenated blood is pumped out of the left atrium and then returned through a centrifugal pump that provides continuous flow into the femoral artery (through a 12-Fr cannula) or the iliac artery (through a 5-17-Fr cannula).

A cohort study conducted by Thiele et al.[43] among 18 patients with cardiogenic shock post-AMI confirmed significantly better hemodynamic parameters after IABP implantation at the expense of a series of complications associated with the insertion and maintenance of the catheter with a 44% 30-day overall mortality rate. This study also showed that LVADs can be implanted quickly in less than 30 minutes.

Other studies have compared the efficacy of TandemHeart vs IABP for the management of cardiogenic shock such as the ones conducted by Thiele et al.[42] and Burkhoff et al.[44]. These studies showed the capacity of the TandemHeart device to improve the patients' hemodynamic situation assuming that there is still a risk of complications associated with the device.

Current situation in PCI procedures

The first case ever reported of a TandemHeart device used in a high-risk PCI was documented by Vranckx et al.[45]. Since then, several retrospective studies have been conducted in an attempt to analyze its use. One of them included 9 patients with an LMCA lesion who were not eligible for surgery. This study reached a 100% success rate in the PCI.[46] Four out of these 9 patients developed vascular access complications, 2 of which required vascular surgery due to the presence of lower-limb ischemia. The 6-month survival rate was 88.5% compared to 89.5% in the overall population with LMCA disease in the same hospital.[47,48]

Then, Aragon et al.[49] analyzed the use of the TandemHeart device in 8 patients who underwent a high-risk PCI and found that hemodynamic improvement can be achieved early with angioplasty success rates close to 100% and no immediate complications after the PCI.

Back in 2012, Alli et al.[50] conducted a retrospective study that analyzed 54 patients who underwent a PCI under TandemHeart support between 2004 and 2009 with a PCI success rate of 97% (62% of the patients had multivessel or LMCA disease). The overall 30-day survival rate was 90%, and it was kept for 6 months. However, the rate of vascular complications is significant (13%).[50,51]

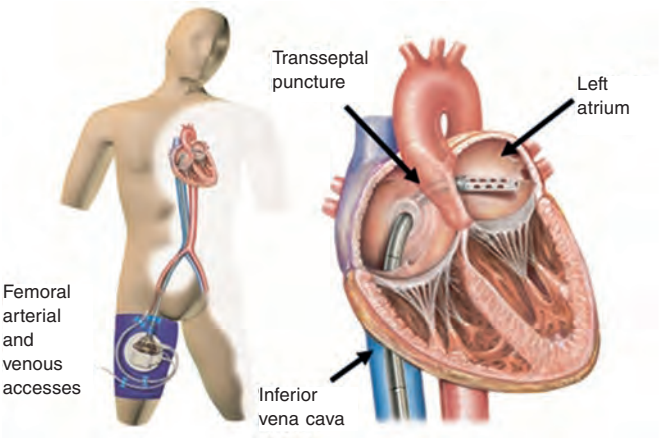

Figure 1. Scheme of the functioning of the TandemHeart device with femoral peripheral access. Oxygenated blood drainage by transseptal puncture of the left atrium that comes back though the femoral artery.

Impella

Impella devices (figure 2) use a catheter via femoral access that crosses the aortic valve that is allocated in the left ventricle where it pumps out oxygenated blood that is then returned to the ascending aorta. There are different models available: Impella 2.5, Impella CP, and Impella 5.0 supplying 2.5, 4, and 5 L/min of flow, respectively.

An early study conducted by Seyfarth et al.[52] that compared the Impella 2.5 device and the IABP in 25 patients with cardiogenic shock post-AMI confirmed that the Impella 2.5 device provided better hemodynamic support compared to the IABP. However, it also had a higher rate of transfusions and hemolysis compared to the IABP, but no differences were seen in the 30-day mortality rate (around 46%). The EUROSHOCK registry[53] included 120 patients with cardiogenic shock post-AMI who received circulatory support with an Impella 2.5 device. This registry confirmed that it is a real option resulting in better plasma lactate concentrations at the expense of a red blood cell concentrate transfusion rate of 24% and a 4.2% need for hemostatic surgery.

In this cohort study, the 30-day mortality rate was 64% and it was attributed to the high percentage of patients with clinical presentations of cardiorespiratory arrest.

Current situation in PCI procedures

Back in March 2015, the US Food and Drug Administration approved the use of the Impella 2.5 device as a LVAD in high-risk PCIs, whether elective or urgent. This followed the results of several studies that back the safety of the device in this context.[54]

The Europella registry[55] included 144 patients who underwent high-risk PCIs under Impella 2.5 support. The primary endpoint was the development of events at the 30-day follow-up: death, major bleeding (requiring transfusion or surgery), AMI, need for urgent revascularization surgery or stroke; it also included safety events associated with the device.

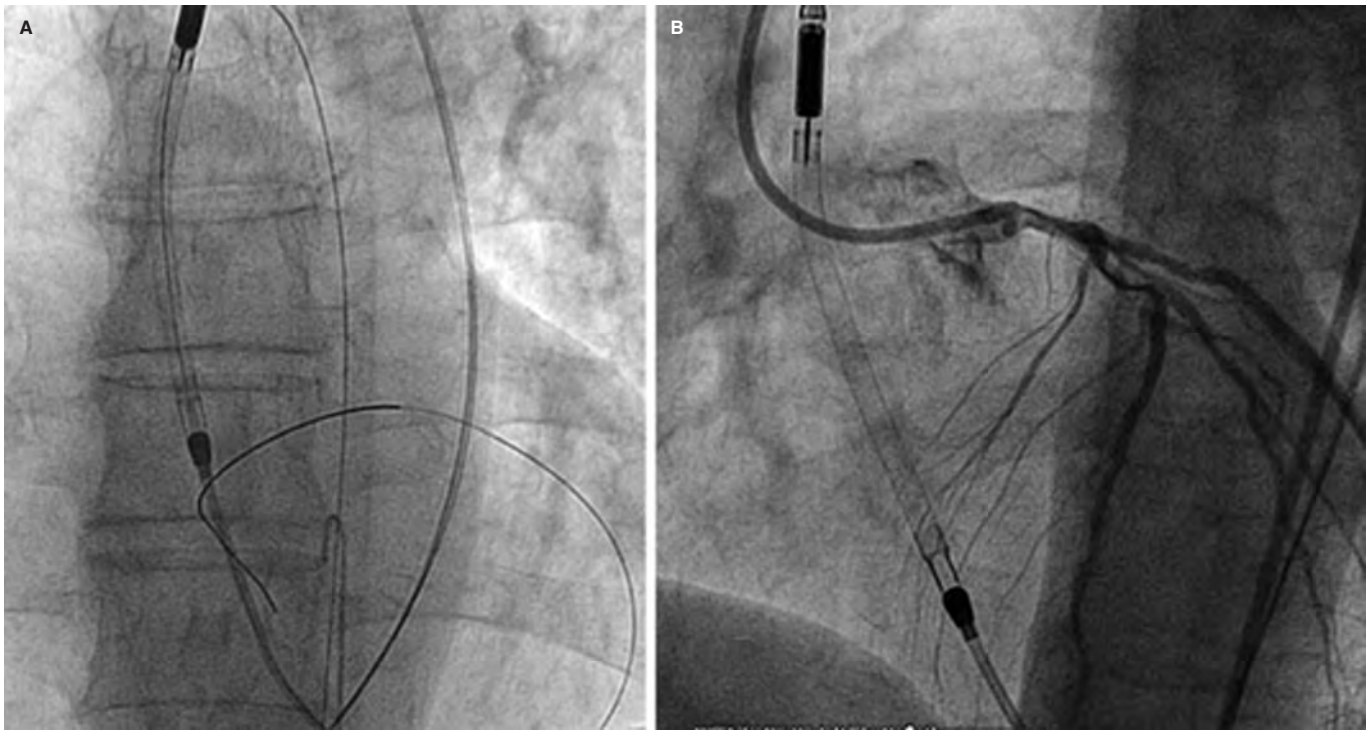

Figure 2. High-risk percutaneous coronary intervention with circulatory support with the Impella 2.5 device. **A** and **B** show the correct location of the device while crossing the aortic valve.

In the American USpella registry[56] of 175 patients with similar endpoints (except for bleeding, that was considered a secondary endpoint), the primary endpoint of death occurred in 7 patients (4%), while in the Europella registry it occurred in 8 (5.5%). Mortality results were better than the ones estimated by the STS score—predictor of surgical mortality—suggestive that support with Impella devices in this type of PCIs is a reasonable option. Complications associated with the removal of the device were reported in 8 (5.5%) and 17 (9.7%) patients, respectively. Transfusions were needed in 1 (0.7%) and 3 (1.7%) cases due to major vascular complications.

The Impella CP device also has a retrospective analysis that was consistent with previous outcomes and found better survival rates in patients with cardiogenic shock due to AMI compared to the Impella 2.5 device.[57]

HeartMate PHP

Same as it happens with the Impella device, the HeartMate PHP uses an axial flow circulatory support system to pump blood out the left ventricle and into the ascending aorta; the main difference here is the existence of a self-expanding cannula that expands itself when it crosses the aortic valve and is implanted via femoral access with a 13-Fr/14-Fr sheath. The cannula is then expanded up to 24-Fr when it reaches the right position through the aortic valve supplying flow of up to 4 L/min.[58] However, since February 2017 its use and the clinical trials that were being conducted like the SHIELD II trial (NCT02468778) have been suspended temporarily due to minor errors in its design.

Extracorporeal membrane oxygenation

ECMO can provide cardiopulmonary support similar to the extracorporeal circulation system used during cardiac surgery. Its use is well documented in the pediatric population in the severe heart or respiratory failure setting.[59,60]

Veno-arterial ECMO includes a circuit with cannulas of venous and arterial blood, a centrifugal pump, and a membrane oxygenator. It can be implanted via peripheral (often femoral) or central access and requires a median sternotomy.

Deoxygenated blood is drained through the venous cannula (20-Fr) from the right atrium towards the membrane oxygenator where gas exchange takes place. Oxygenated blood returns to the patient through the arterial cannula (17-Fr).

Although it is the only device capable of providing full circulatory and respiratory support, it can increase left ventricular afterload and parietal stress (due to several filling pressures), which may have negative consequences for the myocardial oxygen demand.[61-64]

Current situation in PCI procedures

The use of ECMO in the severe heart or respiratory failure setting has gone up 433% during the 2006-2011 period.[65] Still, the experience in its use as a mechanical circulatory support system for high-risk PCIs is limited and only small retrospective studies and series of cases have been published to this day.[66-68]

Back in 1989, Taub et al.[65] documented 7 cases of successful use of ECMO in high-risk angioplasties. The rate of complicated hematomas was high (6 patients of whom 4 required a blood transfusion); we should mention the retroperitoneal hematoma as a complication that caused the patient's death.

In order to study the use of ECMO in high-risk PCIs, Toma-sello et al.[69] published their own experience in a prospective study that included 12 patients with complex of high risk to be surgically revascularized without cardiogenic shock or cardiac arrest with

veno-arterial ECMO implantation prior to the PCI. All patients tolerated the procedure and there was only 1 complication in the vascular access (1 hematoma did not require blood transfusion). No deaths or AMIs were reported at the 6-month follow-up, suggestive that ECMO can be a safe alternative in this context.

IABP vs other LVADs in PCI procedures

Several clinical trials have conducted direct comparisons between the IABP and other LVADs. The PROTECT II trial[11] compared the Impella 2.5 device to the IABP in high-risk PCIs. This was a multicenter, prospective study of 452 patients eligible for a high-risk PCI (defined as LMCA disease and left ventricular ejection fraction < 35% or multivessel disease with left ventricular ejection fraction < 30%). They were randomized to receive circulatory support with the Impella 2.5 device or IABP during the procedure. Patients with recent AMI were excluded from the study. The 30-day primary endpoint was a composite of major cardiovascular events and mortality. The Impella 2.5 device provided better hemodynamic support compared to the IABP without statistically significant differences in the primary endpoint: 35.1% in the Impella 2.5 group and 40.1% in the IABP group (P = .227).

Patel et al.[70] conducted a cross-sectional study during the 2008-2012 period. The study analyzed patients who underwent PCI and received circulatory support with an IABP or other LVADs (Impella, TandemHeart or a combination of IABP plus LVAD) and recorded 18 094 procedures (93% with the IABP, 6% with the Impella o TandemHeart device, and 1% with IABP plus LVAD). In the first place, the patients assisted with a LVAD were older and had more comorbidities (arterial hypertension, diabetes mellitus, renal failure, pulmonary disease) compared to those assisted with the IABP. The overall mortality rate was 19.8% (20.1% with the IABP, 12% with the LVAD, and 41% with the combination of IABP plus LVAD) and the overall rate of complications was 35.5% (36% with the IABP, 26% with the LVAD, and 52% with the combination of IABP plus LVAD). The use of the IABP was associated with a higher rate of cardiovascular (9% vs 4%) and respiratory complications (19 % vs 11%), while the use of other LVADs was associated with a higher rate of vascular complications (8.6% vs 5.5%). A subgroup analysis was conducted based on the presence, or not, of cardiogenic shock or AMI. The main conclusion was that compared to the IABP, the use of the LVAD was a predictor of a lower rate of complications and mortality only in the group of patients without AMI or cardiogenic shock.

Khera et al.[71] conducted a study similar to the previous one in the 2004-2012 period but without patients who received support with both devices (combination of IABP plus other LVADs). A total of 26 556 patients underwent high-risk PCIs under IABP (96%) or LVAD (4%) support. Seven per cent of those who received LVAD support had cardiogenic shock and 2.2%, AMI. Also similar to the previous study, the authors found that patients who received LVAD support were older and had more comorbidities, but a lower rate of AMI, cardiogenic shock, and cardiorespiratory arrest compared to the group of patients who received the IABP; no significant differences were seen in the in-hospital mortality rate.

The IMPRESS trial,[72] published back in October 2016, randomized 48 patients hospitalized due to ST-segment elevation and secondary acute coronary syndrome and secondary cardiogenic shock to receive support with the Impella CP device or the IABP in high-risk primary PCIs; this was the first study ever conducted with characteristics like these ones. No differences were found in the primary endpoint of death and 30-day cardiovascular events (46% mortality rate in the Impella CP group vs 50% in the IABP group; P = .92) or in the all-cause mortality at 6 months (50% in both groups), but there was a higher rate of vascular complications in the group that received support with the Impella CP device (major bleeding: 33% vs 8%) due to the larger caliber of the cannula used by this device (14-Fr vs 7.5-Fr).

The results published by Koen et al. back in 2019 are interesting too.[73] This retrospective, single-center study analyzed the progression and prognosis of patients treated with high-risk PCI during the 2011-2018 period based on whether they received mechanical circulatory support or not. The primary endpoint was a composite of periprocedural mortality (< 24 hours), cardiac arrest, need for vasoactive drugs, need for circulatory support as a bail-out strategy, endotracheal intubation, and peripheral ischemia. One-hundred and ninety-eight patients treated with high-risk PCIs were recruited. Sixty-nine (35%) of these benefited from LVAD support: 18 with the Impella CP device, 25 with the HeartMate PHP device, and 26 with the Pulsecath iVAC 2L device (PulseCath BV, The Netherlands; it is a transfemoral pulsatile ventricular assist device that enables a cardiac output of up to 2 L/min). In this study the rate of the rate for the primary endpoint was 20% in the group of patients without circulatory support compared to 9% in the group that received periprocedural circulatory support.

Amin et al.[74] published a retrospective study including 48 306 patients treated with high-risk PCIs circulatory suppport (43 524 with the IABP and 4782 with the Impella device). This study was conducted throughout a 13-year period (2004- 2016) in 432 hospitals from the United States. A pre-Impella era until 2007 was identified (the Impella 2.5 device was approved by the US Food and Drug Administration to be used in high-risk PCIs in 2008). The use of the Impella device grew exponentially until 2016. In the group of patients received support with the Impella device, the authors saw more adverse events in the form of death, bleeding complications, and strokes. Still, these patients were not in a more critical situation compared to the group of patients that received IABP support.

These findings prompted an interesting discussion. Yet despite the sample size, there are different factors that may explain such results, but they seem insufficient to stop recommending the use of this device in patients treated with high-risk PCIs. In the first place, this was a retrospective study with substantial differences in the experience and volume of cases managed in each center. Similarly, the use of the new antiplatelet therapies—that grew significantly from 2009—may partially justify the higher rate of bleeding complications reported.

On the other hand, the authors did not provide a detailed description of the characteristics of the patients' coronary anatomy (only a higher prevalence of multivessel disease, bifurcation lesions, and chronic occlusions was reported in the Impella group). They did not report either on the rates of PCI success, the patient's clinical and hemodynamic tolerance to the procedure, the main reason for using a LVAD in this context or the causes for the mortality seen. The authors clarify that patients with the Impella device were not more critical since the rate of cardiogenic shock and need for invasive mechanical ventilation was lower compared to patients with the IABP. However, after a thorough review of the results, it stands out that in the Impella group there was a higher prevalence of previous heart failure, chronic obstructive pulmonary disease and chronic kidney disease, comorbidities that may be behind the results seen. Also, we should mention that the average hospital and ICU stays combined were lower in the group that used the Impella device as the LVAD.

For these reasons, taking the above-mentioned limitations into consideration, and yet despite the study sample size and its surprising results, some associated confounding factors were seen,

which is why it may be risky to stop recommending the use Impella devices in the high-risk PCI setting.

Right ventricular failure in patients implanted with a LVAD. Circulatory support devices

Generally speaking, right ventricular (RV) failure occurs in nearly 20% to 50% of the patients after a LVAD implantation procedure.[75] However, no uniform requirements to define RV failure are to be found in the medical literature (table 2). Its pathogenesis is multifactorial. Left ventricular unloading by LVADs induces a loss of septal contribution to the right function (septal contraction represents 60% of the power of RV contractility).[76]

Due to the significant morbimortality associated, the right selection of patients who are eligible for LVAD implantation is key. These are some predictors of RV failure:[77]

- Right atrial pressure prior to implantation > 20 mmHg.
- Transpulmonary gradient prior to implantation > 16 mmHg.
- Sudden drop (> 10 mmHg) of the pulmonary arterial pressure after implantation.
- Central venous pressure/pulmonary capillary wedge pressure ratio > 0.63.
- Tricuspid regurgitation grade > III prior to implantation.
- RV short axis/long axis ratio > 0.6.
- Need for circulatory support prior to LVAD implantation.
- Hypertransaminasemia, hyperbilirubinemia or renal impairment.
- Need for invasive mechanical ventilation prior to implantation.
- *Right ventricular free wall* global *longitudinal* strain < –9.6%.

The management of RV failure is basically preventive. The proper selection of patients eligible for LVADs is key as well as optimizing their RV preload and afterload situation in order to reduce central venous pressure. As general measures, it is essential to perform anti-infective prophylaxis, avoid cardiac arrhythmias, and schedule protective mechanical ventilation towards the RV (with low positive end-expiratory pressure). Dobutamine, adrenaline, and milrinone are the main inotropic agents used to treat RV failure after LVAD implantation and they can be associated with drugs used to reduce pulmonary arterial pressure.

Circulatory assist devices have a role in the clinical setting too. Veno-arterial ECMO—already described in this manuscript—mimics the RV function. Another member of the Impella family is the Impella RP model that has a single 22-Fr cannula that pumps blood out of the inferior vena cava and into the pulmonary artery and supplies flow at a rate of 4 L/min with promising results in the RECOVER RIGHT trial.[78] This study recruited 30 patients with acute RV failure (after LVAD implantation and due to an AMI with right ventricular involvement).

Economic impact of the use of LVADs

The economic impact left by the technical advances made in the percutaneous management of cardiovascular heart disease is growing. An analysis of the costs involved in the healthcare provided in the PROTECT II trial shows that hospitalization related costs were higher in the Impella group compared to the IABP group ($47 667 vs $33 684). A difference that would not only be explained by the cost of the device.[79] In contrast, the costs derived from the hospital stay and rehospitalizations were lower in the Impella 2.5 device group ($11 007 vs $21 834).

Table 2. Definitive criteria for right ventricular failure after left ventricular assist device implantation

Postoperative support with inotropes for over 14 days
Use of inhaled nitric oxide for over 48 hours
Need for inotropic treatment at the hospital discharge
Right circulatory support
2 or more of the following hemodynamic parameters:
Mean arterial pressure < 55 mmHg
Central venous pressure > 16 mmHg
Mixed venous saturation < 55%
Cardiac index (flow supplied by LVAD) < 20 L/min/m^2
Inotropic support score > 20 U

LVAD, left ventricular assist device.

CONCLUSIONS

The future will shed light on the true role of LVADs in the cath lab. All of these devices are used to improve the cardiac output, mean arterial pressure, coronary perfusion by reducing the pulmonary capillary wedge pressure in patients with a reduced cardiac reserve.

Yet despite the controversial results offered by different studies, registries, and clinical trials, the use of LVADs is on the rise in high-risk PCIs allowing us to preserve hemodynamic stability during the procedure.

FUNDING

The authors did not declare any sources of funding while this study was being conducted.

CONFLICTS OF INTEREST

None declared.

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Debate: Intravascular ultrasound and optical coherence tomography in percutaneous revascularization. The IVUS expert perspective

A debate: Ecografía intravascular y tomografía de coherencia óptica en la revascularización percutánea. Perspectiva del experto en IVUS

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Question: Do you think there is enough evidence to indicate the use of intravascular imaging during percutaneous coronary interventions?

Answer: The appearance of intracoronary angiography was a major breakthrough for the management of ischemic heart disease. However, the limitations of this imaging modality became evident right from the start. The arrival of intravascular ultrasound (IVUS) 30 years ago now and then the optical coherence tomography (OCT) brought significant advances regarding diagnosis and percutaneous coronary intervention. Although the independent studied that compared IVUS and angiography showed variable results, several meta-analyses[1] reinforce the use of the former. On the other hand, although the OCT is much newer compared to the IVUS and there is less scientific evidence supporting it, the excellent quality of its images has turned it into the imaging modality of choice for the management of complex plaques, the detection of complications during the procedure, and the assessment of stent implantation both in the clinical practice and clinical studies.

Q.: Which are the anatomical or clinical contexts with more evidence available?

A.: Both imaging modalities have proven their best cost-effectiveness ratio for the management of complex lesions. In this context, both provide very valuable information in calcified lesions. However, each of them has a specific profile with important differences between the 2.

The left main coronary artery disease is the location where the IVUS has proven most beneficial because it can guide the procedure, but also in long lesions and chronic total occlusions. On the other hand, the effectiveness of IVUS in patients with conditions like diabetes or acute coronary syndrome has been confirmed in former studies.

The excellent quality of the images provided by the OCT makes it very attractive especially in 3 scenarios. In the first place, in cases of acute coronary syndrome where the angiography can show non clearly culprit stenoses, the OCT can detect the presence of dissections, eroded or ruptured plaques, small thrombi or vessel wall hematomas. The second scenario is in-stent restenosis, where it can identify underlying mechanisms like underexpansion, hyperplasia and neoatherosclerosis. Finally, it is the imaging modality of choice to study stent endothelization, a very important aspect if it can be relevant enough as to decide on the continuity or not of antiplatelet therapy and, above all, in the context of clinical studies

Q.: Is the IVUS and OCT level of evidence the same?

A.: To this day, and partly due to the fact that IVUS has been with us much longer, its scientific evidence is more solid since the OCT has less often been compared to the angiography and only to IVUS in a clinical trial.[2] As a consequence, the clinical practice guidelines[3] show the current scientific evidence available in the following recommendations and levels of evidence:

- IVUS in selected cases to optimize stent implantation: IIa B.
- IVUS to determine severity and optimize stent implantation in unprotected left main coronary artery disease: IIa B.
- IVUS or OCT to study the underlying mechanism of stent failure: IIa C.
- OCT in selected cases to optimize stent implantation: IIb C.

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Online: 21-09-2020.
https://doi.org/10.24875/RECICE.M20000153

Q.: What are the advantages of OCT with respect to IVUS during percutaneous coronary interventions?

A.: Although the IVUS has 10 times less resolution than the OCT and, therefore, worse image quality, it is superior to the OCT in some aspects. The IVUS has a greater capacity to penetrate soft tissues (5-6 mm vs 1-2 mm of the OCT) and detects the total thickness of the vessel, which is an advantage when having to decide on the diameter of the stent in relation to the size of the vessel. Its second greatest advantage is that it does not require washing the artery to eliminate the red blood cells that complicate the performance of an OCT so much. Finally, in certain patients, especially those with left main coronary artery disease, and since no artery washing is required, both scientific evidence and image quality make IVUS the imaging modality of choice.

Q.: Which cases would be eligible for using IVUS and which for using OCT?

A.: The characteristics of the patient and the lesion condition the use of 1 imaging modality over the other. For example, IVUS is more adequate in cases of:

- Left main coronary artery disease, especially proximal: IVUS is supported by more scientific evidence as shown by the guidelines. On the other hand, in many cases, the arterial washout with contrast cannot be performed properly, which leads to suboptimal image quality with the OCT.

- Aorto-ostial junction, both in the left and right coronary arteries since, as we already mentioned, the OCT does not provide a proper image quality.

- Kidney disease or patients in whom the amount of contrast should to be limited: although a few alternatives to this have been described like the use of dextran to induce less kidney damage, in general, all these agents cause volume overload which is ill-advised in complex procedures. It is estimated that the use of OCT involves some extra 17 mL and 70 mL of contrast per case.

In the remaining scenarios, the superior image quality provided by the OCT is a very significant advantage, which means that it is the imaging modality of choice when the aforementioned situations don't take place.

There is a subgroup of lesions where the OCT has become very popular. I am talking about bifurcations that amount to 15% of all the percutaneous coronary interventions performed these days. The use of intravascular imaging is highly recommended here since they are lesions with an associated higher rate of thrombosis and restenosis. Besides, the latter is difficult to treat, and a top level of excellence is advised in the results obtained that can be optimized with the use of imaging modalities, especially OCT. Having said this, we should always remember the limitation imposed by the use of additional contrast at the end of a complex case. Therfore, despite the fact that the image quality of IVUS is worse compared to OCT, at times it can replace it. The recent advances made in the design of new higher-resolution IVUS catheters can be an alternative to bear in mind when the use of OCT is somehow problematic.

Q.: What studies are necessary to establish the role of these imaging modalities during percutaneous coronary interventions?

A.: Since the left main coronary artery is the location where IVUS performs better and taking into consideration the current class IIa recommendation with grade B level of evidence, it would be very interesting to have studies available that would enable an upgrade to a class I recommendation. Regarding the left main coronary artery disease, these studies can also be very interesting for another reason. For example, the EXCEL and NOBLE clinical trials are no longer producing more evidence on the percutaneous revascularization of these patients. This means that «something new» should come up if we want to show additional benefits to be able to upgrade the levels of recommendations and evidence. Examples of these trials in the pipeline are (ClinicalTrials.gov):

- The OPTIMAL NCT04111770 clinical trial: an international, randomized, controlled, multicenter clinical trial where 800 patients will be randomized in a 1:1 ratio to undergo IVUS or angiography-guided percutaneous revascularization. Patients will be followed for 2 years after the index procedure.

- The INFINITE NCT04072003: a study with a similar design to the previous one with 616 patients with left main coronary artery disease with bifurcation types 1.1.1 or 0.1.1 according to the Medina classification. In the angiography group, patients will be treated with 2 stents and the implantation technique will be left to the operator's criterion. However, in the IVUS group the lateral branch will be treated based on the lumen area as seen on the IVUS (in cases with lumen areas > 4 mm^2 no stent will be implanted).

On the other hand, the situation with the OCT is different. This imaging modality has grown rapidly thanks to its excellent image quality. However, scientific support is not as strong. Added to the studies where this imaging modality is not the study primary endpoint but the tool to show the primary endpoint in subgroups of patients (acute coronary syndrome with or without ST-segment elevation and studies focused on the results of certain stents), it would be interesting to conduct clinical trials on the OCT. These studies primary endpoint would be to improve clinical results to increase the level of recommendation published by the guidelines. An example of this type of studies is the ILUMIEN IV: OPTIMAL PCI NCT03507777 where 3656 patients will be randomized in a 1:1 ratio to compare the result of angiography vs OCT-guided stenting at a 2-year follow-up.

Q.: What technical advances are available today or could be available in the near future regarding the OCT?

A.: Over the last few years, the following advances have been made regarding IVUS, some of them are still in the pipeline.

- High-definition IVUS: of up to 60 MHz and a superior image quality compared to the 20 MHz or 40 MHz IVUS. It is already available for clinical use.

- IVUS-angiography co-registration: this system integrates the information provided by the IVUS and the angiography in such a way that it can locate the artery of each spot analyzed by the IVUS. It is also available for clinical use.

- Dual-element IVUS transducer: one 35 MHz transducer to generate standard IVUS images plus another 70 MHz transducer to receive the second harmonic signals induced by the 35 MHz ultrasound. This dual transducer performs simultaneous analyses of the general anatomy through 35 MHz images and the media and adventitia layers through harmonic signals. It is still in the preclinical phase.

- Hybrid IVUS and OCT single transducer: undoubtedly this is the most advanced project of all by far, and it can acquire IVUS, OCT or OCT-IVUS images of the same spot with high sensitivity (up to 50 MHz for the IVUS). It is also in the preclinical phase.

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Debate: Intravascular ultrasound and optical coherence tomography in percutaneous revascularization. The OCT expert perspective

A debate: Ecografía intravascular y tomografía de coherencia óptica en la revascularización percutánea. Perspectiva de la experta en OCT

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Question: Do you think there is enough evidence to indicate the use of intravascular imaging during percutaneous coronary interventions?

Answer: Currently, there is enough evidence on the benefits provided by intracoronary imaging modalities during percutaneous coronary interventions. Actually, the clinical practice guidelines recommend their use. For the most part, evidence has been collected on the use of these imaging modalities to optimize angioplasty. In this sense, the 2018 guidelines on revascularization published by the European Society of Cardiology give a class IIa recommendation and a grade B level of evidence to the use of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) for the optimization of percutaneous coronary interventions (PCI) in selected patients.[1] In the case of IVUS, these recommendations are based on multiple studies and meta-analyses that compared the results of angiography vs IVUS-guided PCIs and showed fewer events (including death, infarction or need for new revascularization) with the use of intravascular imaging modalities.[2] Guidelines make a specific recommendation on the use of IVUS while performing an angioplasty on the left main coronary artery (class IIa, grade B level of evidence). The other indication for intracoronary imaging modalities established in the guidelines on revascularization is stent failure (class IIa, grade C level of evidence). Several observational studies have proven the utility of IVUS and OCT to detect the causes of thrombosis and restenosis and guide percutaneous treatment.

Q.: Which are the anatomical or clinical contexts with more evidence available?

A.: As I said the clinical context with more evidence available today is the optimization of coronary angioplasty with numerous randomized clinical trials and meta-analyses that confirm the occurrence of fewer events with IVUS-guided PCIs. This effect is especially relevant in the subgroup of patients with complex lesions (including long lesions, bifurcations, and chronic total coronary occlusions) who have a higher risk of events. During the PCI, imaging modalities allow us to determine the size of the stent, optimize its implantation, guarantee its adequate expansion and apposition, and detect possible complications like border dissections.[2]

The second context with more evidence available (in this case from observational studies) is stent failure. Regarding restenosis, imaging modalities can provide information on its causes (neointimal growth, neoatherosclerosis, underexpansion, disease progression in the stent borders) to determine the most appropriate treatment. Regarding stent thrombosis, intracoronary imaging modalities can detect whether stent thrombosis is due to mechanical causes (like stent underexpansion or incomplete apposition). Also, the OCT allows us to determine whether the cause is associated with an inadequate neointimal coverage of the struts or the rupture of a plaque at the borders or inside the stent.

The anatomical location with highest consensus of all regarding the advantages of using intracoronary imaging modalities (IVUS in particular) is the left main coronary artery. Several studies have proven the utility of this imaging modality to determine the severity of stenosis, the need for revascularization, and eventually to optimize angioplasty.

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Online: 21-09-2020.
https://doi.org/10.24875/RECICE.M20000145

Q.: Is the IVUS and OCT level of evidence the same?

A.: Since the IVUS has been used much longer than the OCT, there are more clinical studies available on the use of the former, especially as an angioplasty guided imaging modality (to determine the size of the stent and optimize its implantation). However, 2 studies have proven the non-inferiority of OCT vs IVUS for the optimization of stent implantation. The ILUMIEN III study randomized 450 patients who received an OCT, IVUS or angiography-guided angioplasty. It proved the non-inferiority of OCT vs IVUS regarding the minimum stent area obtained. The OPINION study, conducted in Japan, randomized 829 patients to OCT or IVUS-guided stent implantation and proved the non-inferiority of OCT vs IVUS in the primary endpoint of target vessel failure including cardiac death, treated vessel related infarction or new revascularization on the lesion operated on. This prompted that the latest iteration of the revascularization guidelines published by the European Society of Cardiology to give the same class of recommendation (IIa) to the use of IVUS and OCT for PCI optimization.

Q.: What are the advantages of OCT with respect to IVUS during percutaneous coronary interventions?

A.: The OCT has 10 times more resolution than the IVUS, which allows much more detailed visualizations of the arterial wall and its interaction with the stent. This makes it much more sensitive to detect phenomena like stent incomplete apposition or stent border dissection. In the long-term assessment of the stent it also allows us to study the vessel tissue repair and determine whether the stent is completely covered by tissue. Regarding acute coronary syndromes, the OCT is much more sensitive to detect the presence of thrombi and it can characterize the underlying cause much better. In this sense, the OCT allows us to distinguish in vivo acute coronary syndromes due to the rupture of the plaque from those due to erosions, calcified nodules or non-atherosclerotic causes (such as spontaneous coronary artery dissections or embolizations). This is relevant to guide treatment because it can determine whether it is necessary to operate or just use conservative strategy.[3]

Also, the OCT offers several advantages in the assessment of the causes of stent failure. Regarding in-stent restenosis, it allows us to detect its underlying mechanisms like underexpansion, neointimal tissue growth or disease progressions. Also, the high resolution of this imaging modality has enabled the in vivo detection of neoatherosclerosis as a common cause for restenosis. The analysis of these mechanisms is essential to determine the best therapeutic strategy. For example, in the case of disease progression in the borders of the stent it will be necessary to implant a new stent. However, in cases of stent underexpansion it will be necessary to expand the stent with high pressure dilatations, in some cases, even use plaque modification techniques. If the cause of restenosis is neointimal growth a new stent or a drug-coated balloon can be implanted. Regarding neoatherosclerosis, at the moment there is not enough evidence to determine whether the best strategy is to implant a new stent or use a drug-coated balloon. Still, some data available suggest that both options may be useful.

Regarding stent thrombosis, the OCT allows us to demonstrate in vivo that this is often a multifactor phenomenon and that the cause is not only the lack of stent coverage (as it was initially thought with drug-eluting stents). Instead, it can be due to other factors like neoatherosclerosis with plaques ruptured inside the stent or around its borders, stent underexpansion, incomplete apposition or restenosis. Again, this is an important piece of information to guide the interventional treatment and correct the underlying cause.

Q.: Which cases would be eligible for using IVUS and which for using OCT?

A.: There are 2 anatomical locations where the IVUS is superior compared to the OCT: 1) ostial lesions, due to the impossibility to clean out the blood from the vessel to acquire good images on the OCT; and 2) the left main coronary artery, especially when the ostial segment is involved. Before, the size of the left main coronary artery was a limitation when performing OCT, but with the systems we have today we can see almost all left main coronary arteries unless they are too big. Several studies show the utility of IVUS to assess the severity of the left main coronary artery and for guidance purposes during the angioplasty. At this moment, several studies in the pipeline are assessing the use of OCT while performing angioplasties on the distal left main coronary artery. Probably in the mid and distal left main coronary artery setting, the OCT will be as useful as the IVUS. Maybe even more in the assessment of bifurcations. However, if the ostial segment is involved and we want to see it, we better use the IVUS. Another situation where the IVUS may be preferred over the OCT is to see kidney damage given the need to use contrast for the acquisition of OCT images. In this sense, I should say that the use of contrast can be optimized when performing OCT-guided angioplasties to avoid unnecessary angiographies. A single injection of contrast allows us to perform an angiography and an OCT at the same time. With a single OCT-pullback the reference areas can be selected, and the diameter and length of the vessel can be obtained avoiding the need to perform multiple angiographies.

The OCT is superior to the IVUS and should be the imaging modality of choice to assess stent failure (thrombosis and restenosis) because it is much more precise to determine the underlying mechanism. It is also superior for the assessment of acute coronary syndromes because it is much more sensitive to detect thrombi and distinguish acute coronary syndromes due to plaque rupture from those due to other mechanisms like erosions or non-atherosclerotic causes. The OCT is superior to the IVUS for the assessment of bifurcations because it allows online 3D reconstructions that provide relevant information on the anatomy of the bifurcation and can optimize the angioplasty. An important advantage of the OCT over the IVUS conventional systems is the possibility of a simultaneous registry with an angiography incorporated to the system that does not require the use of any additional software. This facilitates significantly the use of OCT to guide and optimize stent implantation because it offers an online co-registration of the angiographic location of each and every one of the images seen on the OCT.

Q.: What studies are necessary to establish the role of these imaging modalities during percutaneous coronary interventions?

A.: Regarding IVUS, several studies show that its use during the angioplasty can improve the prognosis of patients by reducing the occurrence of events. Regarding the OCT, the primary endpoint of the ILUMIEN IV study, currently in the pipeline, is to show that OCT-guided PCIs can improve stent implantation and reduce clinical events compared to angiography-guided PCIs only. The positive effects of using intracoronary imaging modalities are especially relevant in the subgroup of lesions with higher risk of failure (including long lesions, bifurcations, restenosis, and chronic coronary occlusions). Actually, it is in these patients in whom we should encourage the use of IVUS or OCT.

Beyond the evidence generated in the clinical trials, in order to promote the use of intracoronary imaging modalities, interventional cardiologists need to be trained on how to interpret them. At the same time, imaging systems need to improve to make them easier to use during the procedures. For example, the use of fast systems of image acquisition integrated in the cath lab that allow the operator to use the controls from the table, and co-registration of angiography are some of the tools that can improve the use of these imaging modalities.

Q.: What technical advances are available today or could be available in the near future regarding the OCT?

A.: Among the technical advances currently under research, the most relevant ones have to do with the possibility of estimating and assessing the physiological parameters from OCT acquired 3D reconstructions. This would allow us to use 1 imaging modality only (the OCT) to determine the need to treat and optimize the intervention.

Plaque characterization (especially calcium) using dedicated software is another important field of study. Ultrafast pullbacks will allow us to reduce the amount of contrast needed, and the combination of IVUS plus OCT in the same catheter are other advances being made today.

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REC Interv Cardiol. 2020;2(4):294-297

Clinical case

Embolization of pseudoaneurysm in Dacron subclavian-aortic graft for interrupted aortic arch repair

Embolización de seudoaneurisma en prótesis subclavio-aórtica de dacrón para la corrección de interrupción de aorta

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https://doi.org/10.24875/RECICE.M20000124
https://doi.org/10.24875/RECICE.M20000136

CASE PRESENTATION

This is the case of a 23-year-old male with a past medical history of interrupted aortic arch after left subclavian artery emergency found in the 8th month of the his life. Back in 2004, the surgical correction attempted with a subclavian-aortic graft using a Dacron graft was uneventful. The procedure resulted in an improvement of the arterial blood pressure. The anomalies associated with the initial diagnosis were the anomalous origin of the patient's right subclavian artery with an emergency following the interruption and a bicuspid aortic valve without stenosis or regurgitation. Additionally, in 2015, and due to a significant scoliosis of the spine, the patient underwent surgery with placement of screws and rods.

Back in January 2018, the patient became sick due to a massive hemoptysis that required the use of hemoderivatives. From the start the patient had a total of 17 episodes, the last one of approximately 1 liter with a reduction of hemoglobin levels down to 7 g/dL.

The patient was admitted to our center in October 2019 with a coronary computed tomography angiography performed back in April 2019 (figure 1) and in a period of 5 days. The clinical and CT scan assessment revealed the presence of a pseudoaneurysm in the anastomosis of the left subclavian artery with the Dacron graft possibly due to the dehiscence of the suture and the presence of a fistula between the aorta and the bronchi proximal to the lesion that was causing the hemoptysis. The case was studied by the heart team and the surgical option was discarded. The emergent embolization of the pseudoaneurysm was decided with the resources and equipment available in the cath lab. Pseudoaneurysms in the thoracic aorta that develop in the suture sites between the aorta and the Dacron graft are rare, but potentially lethal; they may be spontaneous, traumatic or associated with a medical procedure and, in general, require emergent surgical treatment. However, the endovascular option can be an alternative in selected cases.

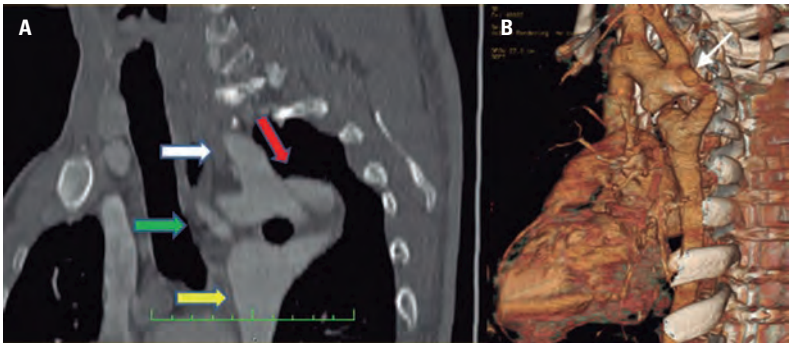

Figure 1. A: sagittal projection showing the left subclavian artery (white arrow), the pseudoaneurysm in the anastomosis of this artery with the Dacron graft (red arrow), the anomalous origin of the right subclavian artery (green arrow), and the descending thoracic aorta (yellow arrow). **B:** 3D volumetric reconstruction of the thoracic aorta revealing the location of the pseudoaneurysm (white arrow).

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Online: 11-06-2020.
https://doi.org/10.24875/RECICE.M20000135

Embolization of pseudoaneurysm in Dacron subclavian-aortic graft for interrupted aortic arch repair. How would I approach it?

Embolización de seudoaneurisma en prótesis subclavio-aórtica de dacrón para la corrección de interrupción de aorta. ¿Cómo lo haría?

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https://doi.org/10.24875/RECICE.M20000135
https://doi.org/10.24875/RECICE.M20000136

HOW WOULD I APPROACH IT?

Pseudoaneurysm is defined as a partial rupture of the arterial wall that originates a fragile aneurysm sac of incomplete wall that communicates with the arterial lumen through the neck. The pseudoaneurysm of this case refers to the so-called anastomotic aneurysms (AA) that occur as a complication after surgery with synthetic valve implantation. The AA is due to the appearance of a dehiscence between the valve and the artery, which allows a pulsatile blood flow that is often contained by the fibrous reaction of surrounding tissues. The AA is not a rare entity and it is more common during the postoperative period to the point that 15 years after implanting the valve it is still present in one third of the patients, as it happened with this case.

Early AAs should lead us to think of an infectious origin. Late AAs are due to valve deterioration (specially Dacron grafts). Sometimes both causes overlap as in the case of AA fistulization towards a contaminated cavity. This is important because in the presence of an infection the endovascular solution is not possible being surgery the right option.

A high percentage of AAs are found when they are symptomatic (in this case due to aortobronchial fistulization), but even with incidental findings and given the unpredictability of the moment of rupture, treatment should be prescribed fast. In most cases this means using the endovascular option because in most cases—especially in emergent situations—surgery is often associated with a high morbimortality rate.

The imaging modality of choice to assess AA is the coronary computed tomography angiography (CCTA). In order to plan endovascular treatment, the following data should be obtained from the angiographic study:

- Location of dehiscence and aneurysm sac: proximal anastomosis, distal anastomosis or both. Relation to surrounding anatomical structures and eventual presence of fistulization. Arterial vascular anatomy in the valve juxtaposed area and, in particular, the presence of nearby bifurcation areas.

- Larger and smaller diameter of the sac; length of the neck.

- Diameter of the valve and vascular segment adjacent to the dehiscence.

The CCTA of the case shows the presence of a proximal AA of an interposed bridge graft between the aortic arch and the descending thoracic aorta. The sac has saccular morphology and discrete size with a possibly well-defined neck. The valve dehiscence is in contact with the origin of the left subclavian artery.

There are 2 endovascular approaches often used to seal a pseudoaneurysm: close the dehiscence by implanting a covered stent or fill the sac with a metal (coil) or chemical (glue) structure. In the second option the intrasaccular administration of thrombin is included too.

Thanks to its efficacy and greater simplicity, the first-line therapy to resolve an AA is often the implantation of a covered stent. The decision between a self-expandable covered stent and a balloon-expandable stent is made on 2 questions basically. The first one is whether the target area to be treated is subject to movements of flexion or a potential extrinsic compression. Nearly 90% of all AAs are found in the groin region. Here self-expandable stent should be used. The second question is the degree of precision required in the implant; balloon-expandable stents are clearly more precise.

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Online: 11-06-2020.
https://doi.org/10.24875/RECICE.M20000124

Covered stents, self-expandable stents, and balloon-expandable stents are available today. They are easy to use technically and they can be used in vessels/valves of up to 12 mm to 13 mm. For larger diameters, the devices require the use of a more complex technique. Aortic endoprostheses are considered as a self-expandable alternative and the covered Cheatham Platinum stent as a balloon-expandable stent.

As a general rule, the anchorage of the covered stent should be delivered among healthy vascular segments (whether arterial or intraprosthetic); in the case of a self-expandable stent the largest diameter of the anchorage is oversized by 1 mm and postdilatation of the stent nominal diameter is advised.

Is it possible to treat this case using a covered stent? It is not, at least it is not easily. To protect the origin of the left subclavian artery the chimney technique would be required (implantation of self-expandable covered stent from the aortic arch to the thoracic aorta with protection of a balloon-expandable stent from the left subclavian artery to the aortic arch) or else build a customized covered self-expandable prosthesis with fenestration towards the subclavian artery. The first option—more available—is limited by the large diameter of the subclavian artery, which would make it difficult to avoid the risk of leak through the self-expandable stent.

In order to consider the possibility of AA filling, the use of glue (cyanoacrylate) an even thrombin (often through percutaneous administration although it can also be administered through a microcatheter, personal experience) has been reported. With both the sac can be sealed immediately. The lack of control during their delivery and, therefore, their potential distal embolization is an important limitation here. In our own experience, these are the perfect agents to occlude pseudoaneurysms in distal vessels or in situation of multiple afferent and efferent vessels to the aneurysm sac, but this was not the case.

«Sac packing» the pseudoaneurysm with a coil can be the best option in this case, especially because the size of the sac is discrete, and the neck seems small. The stability during delivery recommends the use of a telescopic technique (5-6-Fr/90 cm guide catheter, 5-Fr Bernstein diagnostic catheter, and microcatheter). However, the secret for a proper coil embolization is to properly select the first coil: its diameter should be nominal to the sac largest diameter (it is very important to avoid excessive oversizing that may rupture its frail wall) and always larger than the diameter of the neck (to minimize the risk of embolization) with the largest possible length to occupy the maximum volume of the pseudoaneurysm. It is advised that the first coil should be a controlled delivery coil to keep all the repositioning options open. The first coil is followed by others to fill in the holes and complete the packing.

Embolization of pseudoaneurysm in Dacron subclavian-aortic graft for interrupted aortic arch repair. Case resolution

Embolización de seudoaneurisma en prótesis subclavio-aórtica de dacrón para la corrección de interrupción de aorta. Resolución

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https://doi.org/10.24875/RECICE.M20000135

CASE RESOLUTION

The patient was referred to the cath lab. The high left brachial artery access was tried using the dissection technique due to significant stenosis of the distal brachial artery as a consequence of an aortography performed during the patient's childhood with the Sones technique. General anesthesia with selective orotracheal intubation was used. A 6-Fr Cobra-type guide catheter was advanced and entered the pseudoaneurysm. An early injection was used for its catheterization (video 1 and video 2 of the supplementary data) (neck: 8.4 mm; base: 2.9 × 1.5 cm). Three fiber coils (6 mm with 5 turns) were deployed in the base of the pouch (figure 1). Afterwards, a 5 × 4 mm Amplatzer

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Online: 11-06-2020.
https://doi.org/10.24875/RECICE.M20000136

ADO II device was positioned and delivered in the pseudoaneurysm neck. The persistence of the passage of contrast to the pouch was evident and it was decided to deliver another 6.5 mm fiber coil with 3 turns to finish the pseudoaneurysm neck sealing (figure 2, video 3 of the supplementary data). One month after the procedure, the patient had a new episode of hemoptysis. The coronary computed tomography angiography performed confirmed the patency of the pouch in its proximal portion, which is why the patient underwent a second procedure. This time the procedure was performed under local anesthesia using the brachial dissection technique, a 6-Fr Cobra-type guide catheter, and pouch embolization with Interlock 2D coils of 20 and 8 cm. The complete filling of the pseudoaneurysm was secured (figure 3, video 4 of the supplementary data).

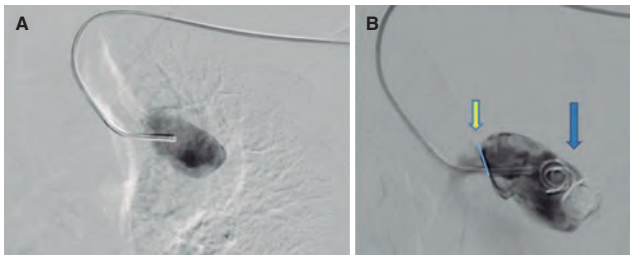

Figure 1. A: anteroposterior projection showing the trajectory of the catheter until it enters the pseudoaneurysm. **B:** right anterior oblique projection at 20º showing 3 fiber coils occupying a third of the base of the pouch (blue arrow); additionally, flowback is seen indicative of the pseudoaneurysm neck (yellow arrow).

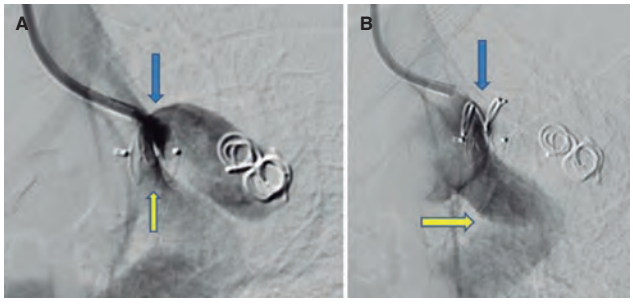

Figure 2. A: right anterior oblique projection at 20º showing the Amplatzer device partially sealing the neck (yellow arrow). An endoleak seen above the device that keeps filling the pseudoaneurysm (blue arrow). **B:** fiber coil sealing the endoleak (blue arrow) and subclavian-aortic bypass with Dacron graft (yellow arrow).

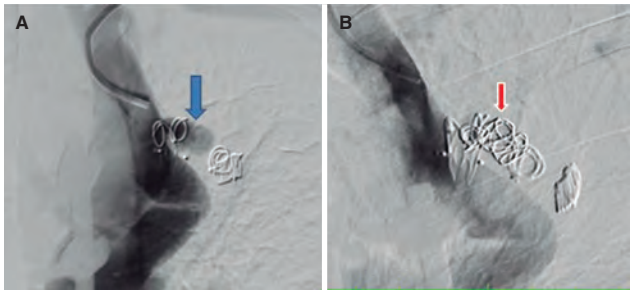

Figure 3. A: left anterior oblique projection at 20º. The blue arrow shows the endoleak partially filling the pouch. **B:** left anterior oblique projection at 30º. The red arrow shows the Interlock coils totally occupying the pouch.

Pseudoaneurysms are due to the rupture of 1 of the layers of the vessel wall that is contained by the remaining layers of the wall and adjacent structures. In general, it is often corrected through surgery. The endovascular resolution of this condition with the use of coils or other devices is not a common thing in the medical literature; however, it is a valid option for selected cases. This time, such technique was decided because of the urgent need to solve the case and considering the material and equipment available at our center. The use of covered stents to correct coarctations of aorta or interruptions of the aortic arch due to nearby aneurysms or pseudoaneurysms has been reported in the medical literature; however, in this particular case, the proximity of both subclavian arteries required a bilateral carotid-subclavian bypass before deploying the endoprosthesis followed by left subclavian artery embolization, which would delay the procedure.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000136.

REC Interv Cardiol. 2020;2(4):298-301

Clinical trial review

The POPular TAVI trial. Antithrombotic therapy following TAVI: towards a minimalist strategy

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ABSTRACT

Antithrombotic therapy following transcatheter aortic valve implantation (TAVI) has evolved empirically with dual antiplatelet therapy (DAPT, aspirin plus clopidogrel) currently recommended in the clinical guidelines. The pilot ARTE trial showed a higher risk of major/life-threatening bleeding events and no reduction of thromboembolic complications with the use of DAPT vs aspirin alone in TAVI recipients. The recently published POPular TAVI trial (NCT02247128) confirmed an increased risk of DAPT (vs. aspirin alone) following TAVI, which was associated with a significant increase in all bleeding events (primary endpoint) and no reduction of ischemic events (stroke, myocardial infarction) or death. Also, DAPT had no effects on the occurrence of clinically apparent valve thrombosis. While ongoing and future studies will have to determine the potential role of anticoagulation (vs antiplatelet) therapy as the antithrombotic treatment of TAVI, the evidence currently available strongly supports the use of single antiplatelet therapy (aspirin) in this setting. Thus, a minimalist approach with aspirin alone should urgently be adopted in the TAVI routine clinical practice and, therefore, implemented in the guidelines.

Keywords: transcatheter aortic valve replacement; antithrombotic therapy; bleeding; stroke.

Ensayo POPular TAVI. Tratamiento antitrombótico tras TAVI: hacia una estrategia minimalista

RESUMEN

El tratamiento antitrombótico tras el implante percutáneo de válvula aórtica (TAVI) ha evolucionado empíricamente, y en la actualidad en las guías clínicas se recomienda el tratamiento antiagregante plaquetario doble (TAPD, ácido acetilsalicílico más clopidogrel). El ensayo piloto ARTE mostró un mayor riesgo de episodios hemorrágicos graves o potencialmente mortales y ninguna disminución de las complicaciones tromboembólicas con el uso de TAPD frente a ácido acetilsalicílico solo en los pacientes receptores de TAVI. El ensayo POPular TAVI recientemente publicado (NCT02247128) ha confirmado los efectos negativos del TAPD (en comparación con el ácido acetilsalicílico solo) tras TAVI, que se asoció con un aumento significativo de todos los eventos hemorrágicos (objetivo principal) y ninguna disminución de los eventos isquémicos (accidente cerebrovascular, infarto de miocardio) ni de las muertes. Además, el TAPD no tuvo ningún efecto sobre la aparición de trombosis valvular clínicamente aparente. Si bien los estudios en curso y futuros determinarán el posible papel de la anticoagulación (frente a la antiagregación plaquetaria) como tratamiento antitrombótico tras TAVI, la evidencia actual apoya firmemente el uso del tratamiento antiagregante plaquetario único (ácido acetilsalicílico) en este contexto. Por lo tanto, en la práctica clínica habitual del TAVI se debe adoptar con urgencia un enfoque minimalista con ácido acetilsalicílico solo, e implementarlo en las guías de práctica clínica.

Palabras clave: Implante percutáneo de válvula aórtica. Tratamiento antitrombótico. Hemorragias. Ictus.

Abbreviations

DAPT: dual antiplatelet therapy. **SAPT:** single antiplatelet therapy. **TAVI:** transcatheter aortic valve implantation.

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Online: 26-10-2020.
https://doi.org/10.24875/RECICE.M20000173

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to conventional surgical valve replacement to treat elderly patients with severe aortic stenosis.[1,2] There have been substantial advances in transcatheter valve technology and periprocedural management of TAVI recipients over the last few years. However, the optimal antithrombotic therapy following TAVI remains to be determined. Back in the 2017, the guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) for the management of patients with valvular heart disease, recommended clopidogrel 75 mg/day for the first 6 months after TAVI plus lifelong aspirin 75-100 mg/day.[3] The 2017 ESC guidelines recommended dual antiplatelet therapy (DAPT) for the first 3 months to 6 months after TAVI followed by lifelong single antiplatelet therapy (SAPT) in patients who did not require oral anticoagulation for other reasons.[4] However, these recommendations were based on expert opinions and not on clinical evidence on the potential benefits of DAPT in this setting.

The ARTE trial was a pilot randomized study that compared DAPT and SAPT (aspirin) for 3 months following TAVI. The study included 222 patients and the main results showed a lower rate of major/life-threatening bleeding events in the SAPT group without any differences in the occurrence of ischemic events (myocardial infarction, stroke) or mortality at the 3-month follow-up.[5] A recent patient-level meta-analysis that included the ARTE trial plus 2 additional smaller randomized trials (a total of 421 patients, 210 and 211 in the DAPT and SAPT groups, respectively) confirmed a higher rate of major/life-threatening bleeding complications at 30 days in the DAPT group (11.4% vs 5.2%; odds ratio = 2.24; 95% confidence interval [95%CI], 1.12-4.46; P = .022) without any differences in the occurrence of stroke events (2.4% in each arm).[6] Therefore, there was strong preliminary evidence towards the harmful effects of DAPT in the TAVI setting.

THE POPular TAVI TRIAL

In the recently published POPular TAVI trial (cohort B) a total of 665 patients undergoing TAVI (and without an established indication for long-term anticoagulation therapy) were randomized to receive clopidogrel (a loading dose of 300 mg followed by 75 mg/day for 3 months) plus aspirin (a loading dose of 300 mg followed by 80-10 mg/day, lifelong) vs aspirin alone (SAPT), lifelong.[7] The 2 primary endpoints were all hemorrhages (minor, major, and life-threatening or disabling) and non-procedural-related bleeding over a 12-month period. The occurrence of death due to cardiovascular causes or ischemic events (ischemic stroke, myocardial infarction) was considered a secondary endpoint. The mean age and median Society of Thoracic Surgeons (STS) score of the study population were 80 years and 2.5%, respectively. The main results showed fewer bleeding and non-procedural-related bleeding events in the SAPT group (all bleeding, 15.1% vs 26.1%; risk ratio = 0.57; 95%CI, 0.42-0.77; P = .001; non-procedural-related bleeding, 15.1% vs 24.9%; risk ratio = 0.61; 95%CI, 0.44-0.83; P = .005) without any differences between the groups regarding the occurrence of death or ischemic events (SAPT, 9.7%; DAPT, 9.9%; P = .004 for non-inferiority). The rate of ischemic stroke at the 12-month follow-up was similar in the SAPT (5.1%) and the DAPT group (5.4%).

Therefore, the POPular TAVI trial provides definite evidence on the adverse events derived from using DAPT in TAVI patients and urges to change clinical practice and the recommendations established by the guidelines regarding the optimal antithrombotic therapy post-TAVI. The considerations below would be important to put the results of this important trial into context and evaluate future perspectives.

Clinical applicability: from the ARTE to the POPular TAVI trial

It should be considered that a significant percentage of TAVI patients exhibit previous conditions (eg, coronary artery disease requiring coronary stenting and DAPT or atrial fibrillation requiring anticoagulation) that would preclude the use of SAPT as the only antithrombotic treatment after the procedure. Unfortunately, the authors of the POPular TAVI trial failed to provide data on the overall number of patients screened and finally excluded from the study. However, based on data from large TAVI registries,[8] the percentage of ineligible patients would be close to 50% in the moderate-to-high risk cohort. Also, the rate of new-onset atrial fibrillation following TAVI is around 10%.[9] As a matter of fact, the occurrence of such complication required a change of the antithrombotic strategy (anticoagulation started) in ~11% of the patients included in the ARTE and POPular TAVI clinical trials. On the other hand, the patients included in the ARTE trial exhibited moderate-to-high surgical risk (mean STS score, 6.3% ± 4.5%) and a high percentage of patients (~30%) underwent TAVI via non-transfemoral approach.[5] However, most of the patients included in the POPular TAVI trial were patients of low surgical risk, and a non-transfemoral approach was used in a minority of the them (~10%). This means that the adverse events of DAPT in TAVI recipients would apply to the entire spectrum of surgical risk patients regardless of the approach used for the TAVI procedure.

Bleeding complications following TAVI

Bleeding events remain as 1 of the most common complications of TAVI, and have been associated with worse outcomes.[10,11] The elderly are often candidates for TAVI and they usually show comorbidities like frailty, renal impairment, anemia or hypertension that elevate the risk of bleeding events.[8,10,11] Also, the use multiple arterial accesses (particularly transfemoral) and large bore catheters during TAVI procedures also contributes to the occurrence of vascular and bleeding complications in this high-risk population.[12,13] Finally, the combination of clopidogrel plus aspirin has already been associated with a higher risk of bleeding events outside the TAVI setting.[14-16] Also, the POPular TAVI trial confirmed that the higher risk of bleeding complications (including major/life-threatening bleeding) was even more important in TAVI patients. As expected, in the ARTE and POPular TAVI trials, most bleeding complications were due to vascular/access site complications. However, a large number of complications were bleeding events not associated with the access site (42% of bleeding events in the ARTE trial were associated with subacute gastrointestinal bleeding within the weeks following the procedure, all of them in the DAPT group). Thus, although further reductions in the size of the catheter and improvements in vascular hemostasis could partially compensate the adverse events of DAPT, the higher bleeding risk would still persist beyond the periprocedural period.

Stroke

The reason for prescribing DAPT to TAVI patients was to prevent ischemic events, particularly stroke, in their acute phase and within the weeks following the procedure. However, the results of a patient-level meta-analysis (prior to the POPular TAVI trial) and the POPULAR TAVI trial showed similar rates of ischemic stroke in both the SAPT and the DAPT groups.[6,7] Although none of these studies was powered to detect inter-group differences regarding ischemic events, no favorable tendency was seen associated with the use of DAPT after including about 1000 patients in randomized trials (DAPT vs SAPT). This made the hypothesis of a possible benefit of DAPT to treat cerebrovascular ischemic events in this setting highly unlikely.

The pathophysiology of cerebrovascular events post-TAVI may partially explain the lack of efficacy of DAPT in this context. Most ischemic stroke events post-TAVI occur within the week following the procedure (over half of them occur immediately after the procedure or within the next 24 hours),[17,18] and seem to be due to the mechanical interaction between the transcatheter valve system and the aorta and the diseased native valve with embolization of multiple debris (calcified material, thrombus, atheromatous debris) during the manipulation of the guidewire and the catheter.[19,20] Also, when considering the occurrence of cerebrovascular events within the first 24 hours following the procedure, a significant percentage of events seem to be associated with the occurrence of atrial arrhythmias,[17,21] against which DAPT has a very limited efficacy. Overall, the pathophysiology of acute and subacute post-TAVI stroke seems to escape the mechanism of action of antiplatelet therapy with thienopyridines.

Valve thrombosis

There have been some concerns about bioprosthetic valve thrombosis within the weeks/months following TAVI. However, the occurrence of clinically relevant valve thrombosis is a rare event (rate < 1%) that does not seem to be influenced by the presence thienopyridine therapy either.[22,23] The POPular TAVI trial confirmed both the very low rate (< 1%) of clinically apparent valve thrombosis and the lack of DAPT effect regarding the prevention of this complication.

More recently, the occurrence of subclinical valve thrombosis post-TAVI has been gaining interest.[24] This occurs to between 10% and 15% of TAVI recipients and may be prevented by anticoagulation therapy but not DAPT.[25]

Anticoagulation vs antiplatelet therapy following TAVI

After establishing the lack of any beneficial effect of DAPT in TAVI recipients, one may wonder whether anticoagulation therapy (vs SAPT) would have a role in this setting. As a matter of fact, the use of short-term anticoagulation therapy (3 months) is suggested by the current AHA/ACC and European Society of Cardiology (ESC) clinical guidelines following surgical aortic valve replacement (IIb and IIa recommendation, respectively).[3,4] Some studies using continuous ECG monitoring post-TAVI have shown a high rate (close to 20%) of silent episodes of atrial fibrillation within the weeks/months following the procedure.[26] The administration of anticoagulation therapy would potentially be more effective to prevent thromboembolic events in such patients. Interestingly, Muntané-Carol et al.[27] recently showed a higher risk of post-TAVI late strokes (> 1 month) in patients who don't receive anticoagulation therapy, suggesting the potential benefit of such a strategy. Additionally, recent data showed the role of anticoagulation therapy to prevent subclinical valve thrombosis as seen on the 4D computed tomography scan.[25,28] Therefore, there would be a mechanistic basis supporting a potential role for anticoagulation therapy in this context. However, the clinical consequences of subclinical valve thrombosis remain to be seen, and the potential clinical benefits of anticoagulation may be counterbalanced by a higher risk of bleeding events compared to SAPT.

The GALILEO clinical trial compared a strategy of systematic anticoagulation post-TAVI (rivaroxaban 10 mg/day plus aspirin for the first 3 months) to prevent death or thromboembolic events.[29] However, the trial ended prematurely due to safety concerns and the results showed a higher risk of death/thromboembolic events and a higher rate of major/life-threatening bleeding with the use of rivaroxaban. The ongoing ATLANTIS clinical trial (Anti-Thrombotic Strategy After Trans-aortic Valve Implantation for Aortic Stenosis; NCT02664649), a 3-arm study that compared apixaban versus DAPT versus SAPT (aspirin) in patients with no clinical indication for anticoagulation, should shed some light (probably definitely) on the actual role of anticoagulation therapy in TAVI recipients.[30]

CONCLUSIONS

In conclusion, the POPular TAVI trial confirmed the harmful effects of DAPT (vs SAPT) following TAVI and stood as a major step forward when it comes to determining the optimal antithrombotic strategy in this context. Future studies will assess whether systematic anticoagulation (together with its duration, short-term?) may be superior to SAPT regarding better outcomes. Of note, clinical events (including bleeding complications), and not subclinical imaging features, should ideally drive the clinical decision-making process regarding the antithrombotic strategy following TAVI. Meanwhile, a minimalist approach with aspirin alone should urgently be adopted in the TAVI routine clinical practice and implemented in the guidelines.

CONFLICTS OF INTEREST

J. Rodés-Cabau declared he had received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific.

ACKNOWLEDGMENTS

J. Rodés-Cabau holds the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions (Laval University, Quebec City, Canada).

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REC Interv Cardiol. 2020;2(4):302-303

Calcified plaques in the radial artery: OCT insight

OCT en placas calcificadas de arteria radial

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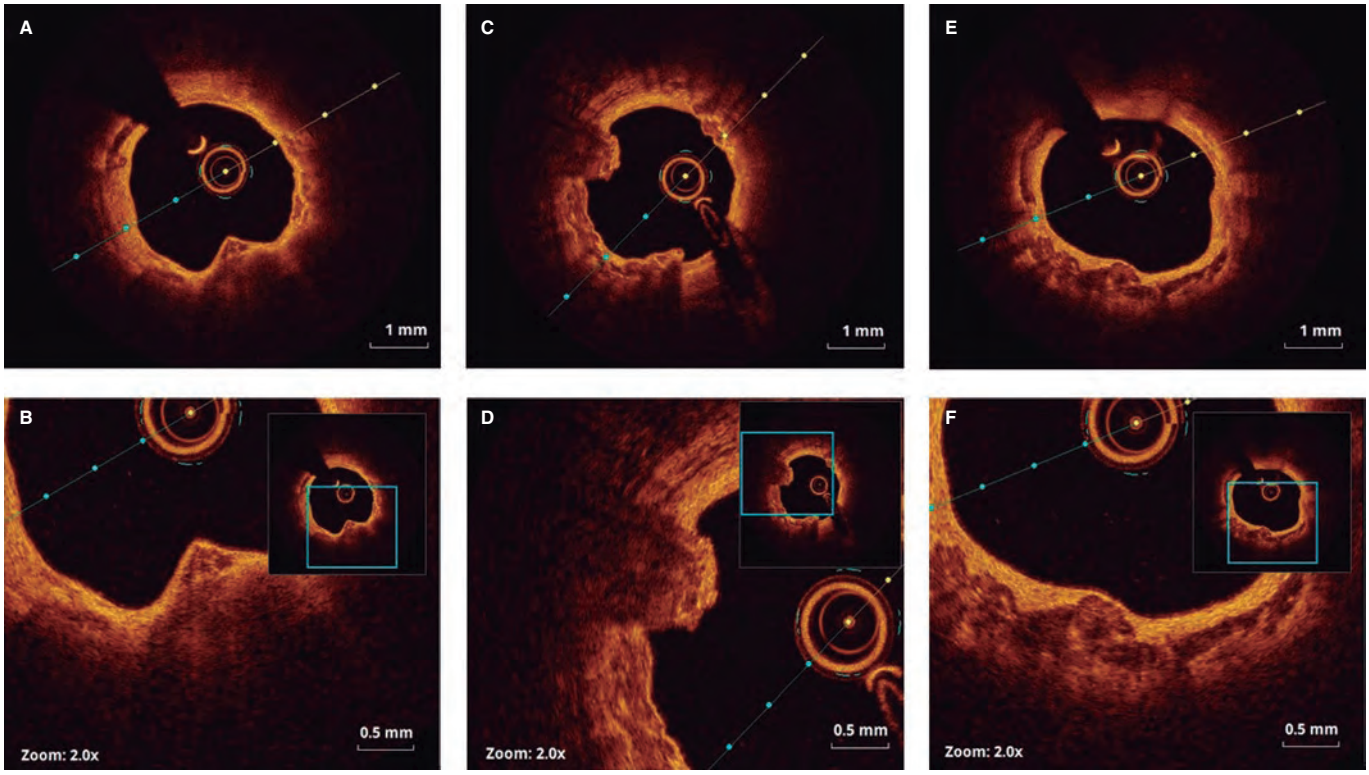

Figure 1.

The calcified nodule has been established as the least common underlying substrate in the acute coronary syndrome; however calcium can be widely present in other acute-common scenarios. In this setting, the optical coherence tomography (OCT) study has identified 3 different types of calcification according to morphology. Former studies have already documented calcified nodules in patients with peripheral artery disease; however the different patterns that exist beyond coronary arteries remain unknown.

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Online: 17-02-2020.
https://doi.org/10.24875/RECICE.M20000094

An 80-year-old patient was referred for coronary angiography following systolic dysfunction. The coronary angiography performed through right radial approach showed a severely calcified vessel (mid portion of the left anterior descending artery) and mitral and aortic calcification. The OCT pullback performed with 6 mL of contrast at 3 mm/seg through the radial artery removed 4 cm of the radial sheath and showed multiple calcified plaques (mid portion of the artery) defined by the presence of superficial, well-established, low-backscattering and heterogeneous regions (video 1 of the supplementary data). The simultaneous angiography co-registration confirmed the presence of ulnar artery occlusion. Three patterns of superficial calcification were identified:

- Calcified protrusion (protruding calcified mass without eruptive nodules [figure 1A,B]).
- Eruptive calcified nodules (cluster of small calcified nodules protruding into the lumen [figure 1C,D]).
- Sheet-like superficial calcified plate (without superficial coating disruption and minimal laminar protrusion [figure 1E,F]).

The types and causes of peripheral calcification described included calcified atherosclerosis, calcific medial vasculopathy, elastocalcinosis, and calcific uremic arteriolopathy. This is the first time that an OCT study describes calcification patterns of atherosclerotic plaques in peripheral artery disease. As previously defined for calcified coronary culprit lesions, 3 types could be identified. The coexistence of ulnar artery occlusion suggests causality, but further studies will be needed to clarify its pathological meaning in the setting of the acute peripheral syndrome.

CONFLICTS OF INTEREST

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

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000094.

REC Interv Cardiol. 2020;2(4):304-305

Alternative approach to advance the Impella CP device

Abordaje alternativo para avanzar el Impella CP

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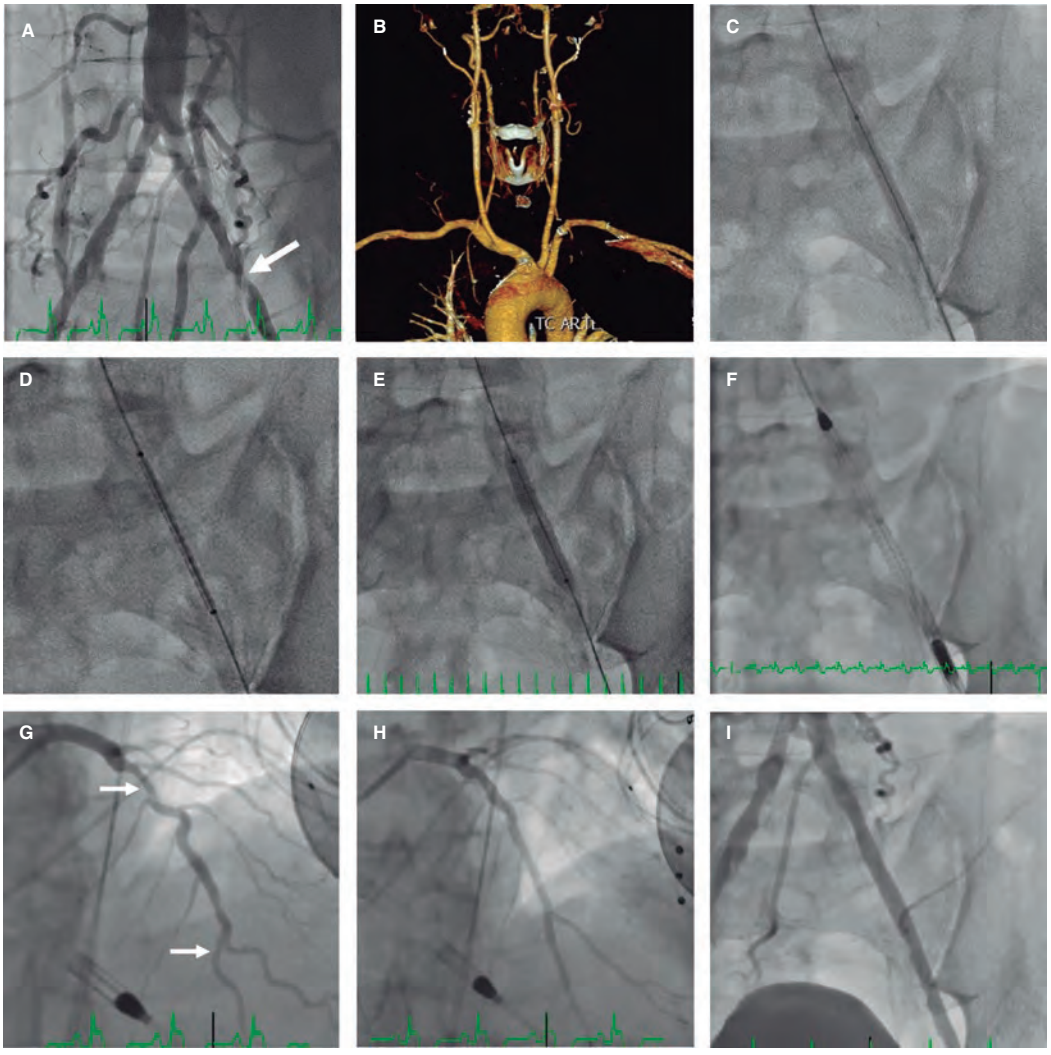

Figure 1.

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Online: 02-03-2020.
https://doi.org/10.24875/RECICE.M20000097

A 59-year old male with severe left ventricular dysfunction, slow ventricular tachycardia and previously treated with cardiac resynchronization therapy was referred for percutaneous coronary intervention (PCI) of the left anterior descending coronary artery (LAD). The patient had 2 severely calcified lesions at mid-LAD level. Because it was a high-risk PCI, the heart team decided to perform this procedure using percutaneous left ventricular support using the Impella CP device (Abiomed, United States). The patient had a past medical history of right femoral-popliteal bypass surgery and a severely calcified stenosis in his left external iliac artery (figure 1A, arrow). The computed tomography performed on the supraaortic arteries revealed subclavian and axillary arteries with diameters < 5mm (figure 1B). The Impella CP device (14-Fr)—that requires a minimal vessel diameter of 5mm—was implanted using the left femoral access after revascularization of left external iliac artery. Predilation was performed using a 5 x 40 mm Mustang PTA balloon catheter (Boston Scientific, United States) (figure 1C); afterwards a 6 x 38 mm balloon expandable covered stent Advanta V12 (Atrium Medical Corporation, United States) was implanted (figure 1D,E). The Impella CP device was advanced through the stent (figure 1F). The PCI of the mid-LAD was performed using 2 drug-eluting stents (figure 1G,H; arrows: lesions at mid-LAD level). After the PCI, the Impella CP device was retrieved; vascular access was closed using Perclose ProGlide (Abbott Vascular Inc., United States). The control angiography showed good results (figure 1I, video 1 of the supplementary data).

The percutaneous revascularization of the iliac artery with a covered stent may be an alternative approach to advance the Impella CP device and facilitate high-risk PCIs when subclavian and axillary accesses are not an option for having small diameters.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000097.

ISCHEMIA trial: a win for the optimal medical therapy in the management of stable coronary artery disease?

Estudio ISCHEMIA: ¿una victoria del tratamiento conservador en la enfermedad coronaria estable?

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To the Editor,

We have read with great interest the results of the ISCHEMIA trial[1] of 5179 patients with moderate or severe ischemia who were randomized to receive an early invasive strategy of angiography plus revascularization, when necessary, or a conservative strategy of early optimal medical therapy and angiography if the medical therapy failed. As already known, the conclusion is that an early invasive strategy does not reduce the risk of cardiovascular ischemic events or all-cause mortality at the follow-up. However, it had beneficial effects because it reduced the occurrence of spontaneous myocardial infarction at the expense of a number of peri-PCI myocardial infarctions. Currently, this observation is under discussion probably because a different result was expected by researchers.

In an interesting article[2] it has been argued that the ISCHEMIA trial did not compare the benefits of coronary revascularization vs medical therapy, but assessed an early strategy of medical therapy vs early invasive treatment with angiography. In this sense, 79.4% of the patients from the invasive group were percutaneous or surgically revascularized vs 21.0% of the patients from the conservative group. A careful review of the supplementary data of the original publication[1] reveals interesting additional data that we wish to share. A total of 667 patients from the early conservative group were referred to undergo a coronary angiography at the follow-up for different reasons including failed medical therapy unable to control the angina (15%) or the appearance of a confirmed adverse event (unstable angina, myocardial infarction, heart failure or reversed cardiac arrest) in 27%. Therefore, in a significant percentage of these patients (n = 387, 14.9% of the overall conservative group) the decision to request the angiography was based on criteria different from the aforementioned including adverse events categorized as «unconfirmed» (n = 177) or less obvious reasons like «noncompliance» to the medication or «other reasons» (n = 210). In other words, overall, in 58% of the patients initially randomized to conservative treatment later referred to undergo an angiography there was not refractory angina or confirmation of the appearance of adverse events that justified such a decision. These patients underwent 477 PCIs, 198 surgical revascularizations and 955 were referred to the cath lab.[1]

A second relevant aspect here is follow-up, which is unusually strange regarding clinical trials. Authors say that the median follow-up was 3.2 years, but interquartile range was 2.1/2.2 years to 4.3 years. This peculiarity of the study, associated with low recruitment rate in most centers,[2] elevates significantly the degree of uncertainty on the comparative analysis of the benefits derived from the 2 strategies and runs parallel to the higher percentage of patients who were censored, that is, as the comparison is conducted beyond the median. However, the article includes comparative data between the different strategies of treatment at the 5-year follow-up when the percentage of individuals «censored» or «not at risk» at that time is already > 75%. Therefore, it is incomprehensible that a more homogeneous follow-up was not available, despite reaching the number of events anticipated, to conduct a more consistent analysis due to the clinical implications of such a relevant trial.

Finally, we wish to emphasize that the population included in the ISCHEMIA trial[1] was a highly selected one as the strict inclusion and exclusion criteria suggest and the fact that only 5179 out of 8518 patients (61% of those potentially recruitable) were included. On this regard, out of the 5 criteria specifically established by the Guidelines on Myocardial Revascularization of the European Society of Cardiology[3] to improve prognosis in this context, only 2 improve prognosis in this context (left main coronary artery disease > 50% and left ventricular systolic function < 35%) and they became exclusion criteria. The pressure guidewire (also considered by the guidelines as a tool to detect patients who may benefit from revascularization) was used in 481 patients only (20.3%). We should remember that the exclusion of patients with chronic kidney disease and an estimated renal clearance rate < 30 mL/min/1.73 m^2, also categorized as patients of «very high cardiovascular risk» by the Clinical Practice Guidelines of the European Society of Cardiology,[4] may have limited the potential prognostic benefit of the early invasive strategy and the corresponding revascularization.

We conclude that, in light of the controversial methodological aspects mentioned above and some others,[2] maybe the practical implications of the ISCHEMIA trial[1] should be «limited» to some selected patients (without serious left ventricular dysfunction or end-stage renal disease) with chronic coronary syndrome and

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Online: 30-07-2020.
https://doi.org/10.24875/RECICE.M20000134

moderate ischemia, and only after left main coronary artery disease has been discarded, in whom the early optimal medical therapy may have a chance. If the patient «prefers» greater symptom relief or wishes to take less medication, the invasive strategy can still be the favorite option.

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Temporal relation between invasively managed acute coronary syndromes and confinement during the current COVID-19 pandemic

Relación temporal entre ingresos por síndrome coronario agudo con tratamiento invasivo y confinamiento durante la pandemia de COVID-19

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To the Editor,

The infection caused by the SARS-CoV-2 virus (COVID-19) has impacted significantly the management of other conditions. In particular, the data from surveys conducted in coronary[1] and interventional cardiology units[2] show fewer admissions due to myocardial infarctions and coronary interventions, respectively.

Although these are observational and retrospective data that cannot be used to establish causal relations, they are valuable information, actually they may be the only information available to this day. Different hypotheses have been proposed to explain this 40% to 50% drop in the number of acute coronary syndromes (ACS) managed at the hospital setting. The first hypothesis is that a true reduction of new cases of ACS (health epidemic) would have been due to the population physical rest and reduction of air pollution.[3] The second one is that it was due to the patients' lower attendance rate on fears of acquiring COVID-19 in the hospital setting and to avoid saturating health services. The third hypothesis is that it was due to the worse quality of care of the healthcare system due to saturated ERs and diagnostic biases from ACS towards COVID-19.

We conducted a study to analyze the impact of SARS-CoV-2 on the new cases of ACS that were managed invasively. Our interventional cardiology database included prospective data until hospital discharge and covered an area of approximately 1 million people (*Hospital Príncipe de Asturias, Hospital Severo Ochoa, Hospital de Fuenlabrada,* and *Hospital Clínico San Carlos de Madrid*). The data provided here go from March 1 until April 30, 2020 and include a total of 118 patients with ACS and cardiac arrest who underwent a coronary angiography. Table 1 shows the clinical characteristics (similar) and angiographic findings (fewer culprit lesions in the group of COVID-19 positive patients).

In the first place, the new cases of ACS were examined in patients in whom a coronary angiography was performed, this number was compared to the same period from 2019, and a significant 40.4% reduction was seen (chi-square goodness of fit test, $P < .001$) in the new diagnoses of ACS (figure 1). These data are similar to the ones obtained in the national surveys conducted in Spain and Italy.[1,2]

When an in-depth temporal analysis was conducted (with data only from 2020 this time), we compared the new cases of ACS that were managed invasively on a weekly basis to the new cases of COVID-19 from our regional registry (figure 2). A negative correlation was seen with the number of new cases of COVID-19 diagnosed in Madrid (official data from the Spanish Ministry of Health dated March 15, 2020[4]) as well as an obvious impact of the mandatory confinement declared in Spain back in March 15, 2020. Afterwards, the cases recovered gradually as the incidence of new cases of COVID-19 decreased. This means that, during confinement, it is

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Online: 21-09-2020.
https://doi.org/10.24875/RECICE.M20000157

Table 1. Clinical characteristics and angiographic findings

	Total (n = 118)	COVID-19 negative (n = 105)	COVID-19 positive (n = 13)	*P*
Clinical characteristics				
Age	66 (56-77)	65 (55-76)	75 (62-77.5)	.158
Feminine sex	35 (29.7%)	33 (31.4%)	2 (15.4%)	.34
Hypertension	76 (64.4%)	68 (66%)	8 (66.7%)	.964
Dyslipidemia	57 (48.3%)	53 (51.5%)	4 (33.33%)	.235
Diabetes	35 (29.7%)	33 (32%)	2 (16.7%)	.273
Former smoker	62 (52.5%)	56 (54.4%)	6 (50%)	.774
Peripheral vascular disease	6 (5.1%)	5 (5%)	1 (8.3%)	.628
Previous stroke	12 (10.2%)	11 (10.9%)	1 (8.3%)	.786
Previous infarction	27 (22.9%)	22 (21%)	5 (38.5%)	.156
Kidney damage	16 (13.6%)	15 (14.9)	1 (8.3%)	.54
Type of ACS				.849
Unstable angina	35 (29.7%)	31 (29.5%)	4 (30.8%)	
Non-ST-segment elevation ACS	48 (40.7%)	42 (40%)	6 (46.2%)	
ST-segment elevation ACS	35 (29.7%)	32 (30.5%)	3 (23.1%)	
Primary angioplasty	25 (21.2%)	23 (21.9%)	2 (15.4%)	.587
Left ventricular function (%)	57 (44.3-60)	56 (45-60)	60 (37-61)	.497
Angiographic findings				
Normal coronary arteries	24 (20.3%)	21 (20%)	3 (23.1%)	.795
Number of vessels with serious disease	1 (0-2)	1 (0-2)	1 (0-2.5)	.844
Culprit angiographic lesion	69 (58.5%)	65 (61.9%)	4 (30.8%)	.032
Revascularization	72 (61%)	67 (63.8%)	5 (35.8%)	.077
Number of vessels treated	1 (0-1)	1 (0-1)	0 (0-1)	.107
Total number of stents	0 (0-1)	1 (0-1)	0 (0-1)	.256

ACS, acute coronary syndrome.
Data are expressed as count (percentage) and median (interquartile range).

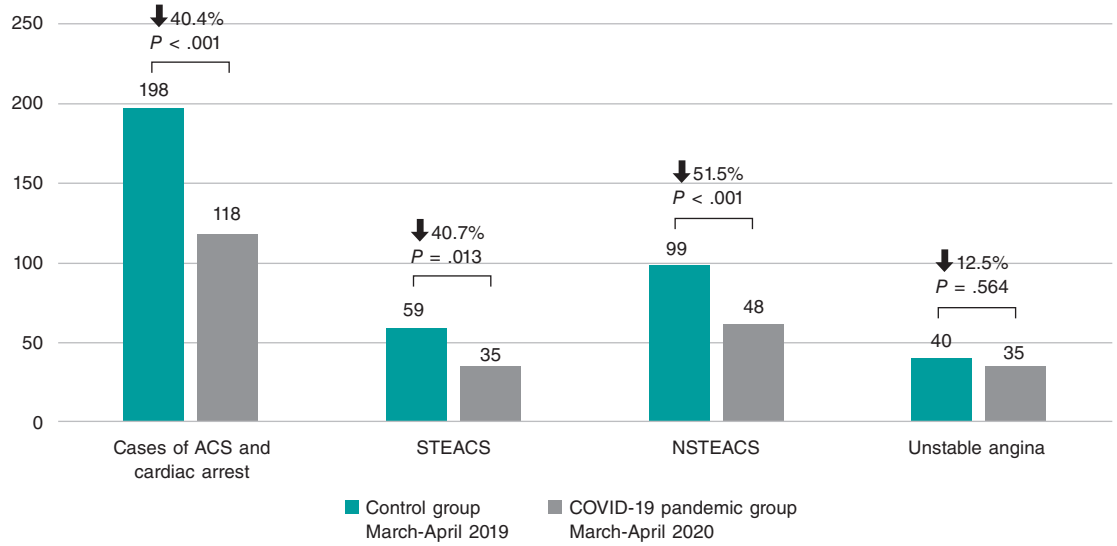

Figure 1. Count of cases of acute coronary syndrome in 2019 and 2020 during the months of March and April. *P* value obtained using the chi-square goodness of fit test. ACS, acute coronary syndrome; NSTEACS: non-ST-segment elevation acute coronary syndrome; STEACS, ST-segment elevation acute coronary syndrome.

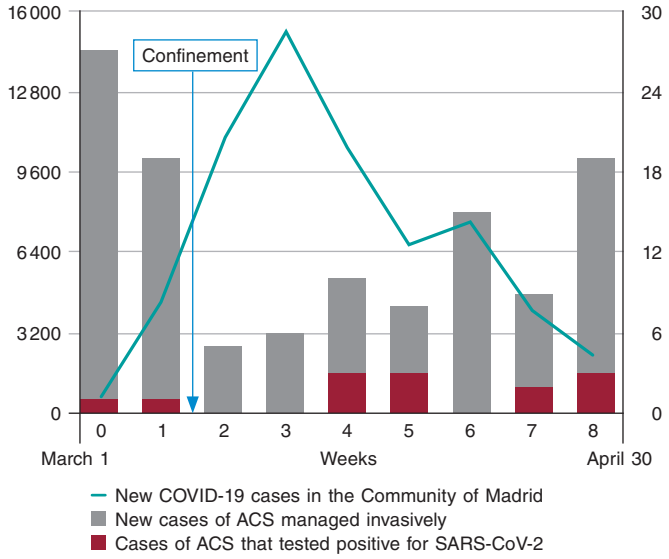

Figure 2. New weekly cases of COVID-19 in the Community of Madrid vs new admissions due to acute coronary syndrome (ACS) between March 1 and April 30, 2020. The left vertical axis shows the number of new cases of COVID-19 found in the province (green line). The right vertical axis shows the count of new cases of ACS that were managed invasively (gray bars) and those cases of ACS with a polymerase chain reaction (PCR) positive test for SARS-CoV-2 (red bars). Week 8 only included 5 days from April 26 to April 30.

possible that these cases changed the normal provision of healthcare and the patients' attendance rate to their doctor's office. By the way, the reduction in the number of cases is not associated with the incidence of COVID-19 in other regions.[2] If there was actually a «health epidemic» with a real reduction in the number of ACSs, this reduction of cases should have been maintained in time since the degree of confinement was exactly the same at the end of the study.

Figure 2 (red bars) shows the cases that tested positive as confirmed by the polymerase chain reaction test during admission due to ACS (13 out of the 118 patients, 11.02%). There were some sporadic cases seen during weeks 4 and 5 (30% and 27% COVID-19 positive, respectively). This rate is consistent with the seroprevalence seen in a pilot study conducted by the Spanish Ministry of Health in our region that revealed that 11.3% (95% confidence interval, 9.8-13.0) of the population of Madrid already has IgG antibodies to SARS-CoV-2 (preliminary results from the ENE-COVID study[19] from March 13, 2020[5]).

This study has the limitations of an observational and retrospective study and does not provide information on patients with ACS who did not undergo a coronary angiography. However, the protocols for the management of ACS did not change substantially.[6]

In conclusion, the temporal analysis on the reduction of new cases of ACS that were managed invasively keeps a negative correlation with the official data of new cases of COVID-19 and a direct correlation with the declaration of confinement. The number of patients who tested positive for SARS-CoV-2 on the polymerase chain reaction test is similar to the seroprevalence estimated in the region.

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Impact of the COVID-19 pandemic on transcatheter aortic valve implantation in Spain

Impacto de la pandemia de COVID-19 en el implante de prótesis valvular aórtica percutánea en España

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To the Editor,

The current COVID-19 pandemic has changed our health system dramatically. The need to have resources available to assist the high volume of patients affected, the healthcare overload, and the need to limit exposure to the virus have led to the implementation of extraordinary measures like delaying the healthcare provided to patients with chronic conditions and the almost total suspension of elective procedures such as the transcatheter aortic valve implantation (TAVI).[1]

The Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) sent a survey to the hospitals included in the Spanish TAVI registry with the following objectives: quantify the temporal damage caused by the COVID-19 pandemic to TAVI procedures in our country, analyze the disease progression of patients not treated because of the pandemic, study the rate and consequences of the infection in patients treated during this period of time, and ultimately assess the number of COVID-19 infections within the medical staff of the cath labs. Forty out of the 46 centers included in the national registry participated in the study (86.9%). The parameters of thid survey are shown on figure 1.

From January 1 to April 30, 2020, 890 TAVIs were performed. Most of them (813 out of the 890, 91.4%) until the first 2 weeks of March, and only 77 (8.6%) since the state of alarm was declared, which is a 95% drop in the activity developed. If we take 2 comparable time periods before and after the declaration of the state of alarm—the month of February and the first 2 weeks of March 2020 vs the second 2 weeks of March and the month of April—the drop is still very significant: 509 TAVIs vs 77 TAVIs (an 86.9% drop) (figure 2). After TAVI, 18 patients (2.0%) died at the hospital, most of them of cardiovascular causes (16/18, 88.9%). During admission, 7 patients (0.8%) contracted the virus, all of them between the months of February and March, and most of these infections occurred before the declaration of the state of alarm (6 vs 7; 85.7%). Two of these patients died. Therefore, in February and within the first 2 weeks of March, the rate of

Hospital:			
Treatment with TAVI during the first half of 2020			
2020	Treated with TAVI	Dead at the hospital*	Nosocomial COVID
1st 2 weeks of January			
2nd 2 weeks of January			
1st 2 weeks of February			
2nd 2 weeks of February			
1st 2 weeks of March			
2nd 2 weeks of March			
1st 2 weeks of April			
2nd 2 weeks of April			
* In patients dead at the hospital during or after TAVI, please specify the cause of death whether cardiovascular (or not) or due to COVID-19 infection (or not).			
Evolution of patients who were not treated			
Patients on the waiting list in March 1, 2020:			
Deaths among patients who were not treated in April 30, 2020:			
COVID-19 related deaths among patients who were not treated:			
Overall number of interventional cardiologists and those with COVID-19:			

Figure 1. Survey sent to the participating centers.

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◊ The annex shows a list of all participating hospitals and principal investigator in each center.

Online: 26-10-2020.
https://doi.org/10.24875/RECICE.M20000165

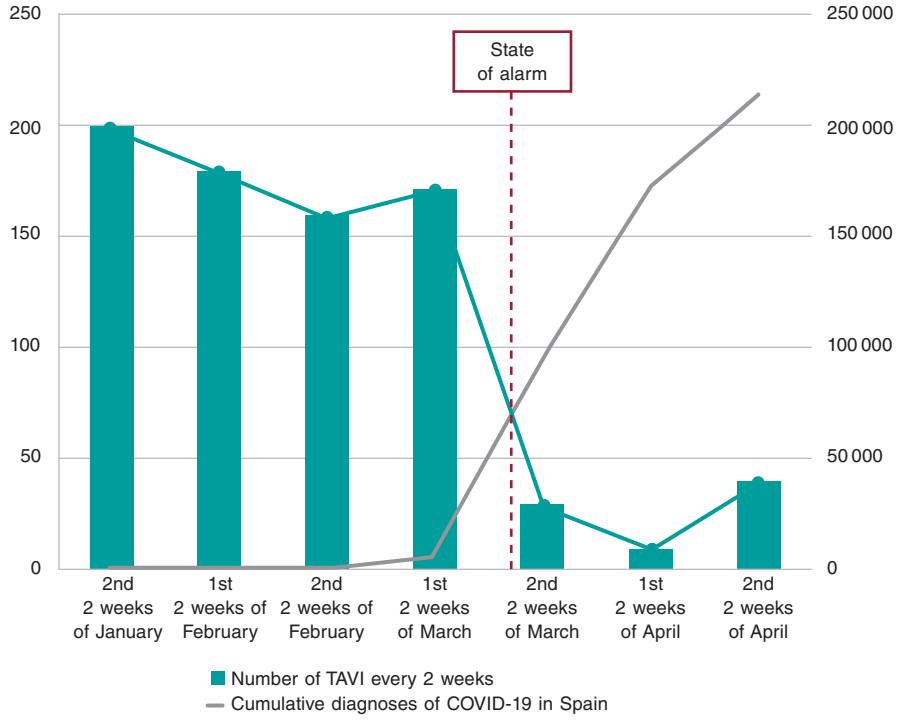

Figure 2. Temporal evolution of transcatheter aortic valve implantation (TAVI) in relation to the incidence of COVID-19 in Spain.

nosocomial COVID-19 was 1.2%, lethality was 33.3%, and mortality rate due to nosocomial COVID-19 was 0.4%. During the state of alarm, only 1 of these 77 patients treated with TAVI had nosocomial COVID-19. This patient ended up dying (rate of nosocomial COVID-19 and mortality rate due to nosocomial COVID-19 of 1.3%). There are data available of the waiting lists of 37 of the 40 participating centers. Back in March 1, 2020, 810 patients were waiting to receive their implants. Twenty-four (2.9%) patients died while on the waiting list within the following 2 months (until April 30). Most deaths (20 out of the 24; 83.3%) were due to aortic valve disease and 4 (16.7%) to COVID-19 infection. Another 4 patients (0.5%) required an emergency TAVI, had no complications, and a favorable progression after the procedure. Therefore, 28 patients (3.5%) died while on the waiting list or required an emergency TAVI. Finally, 15 (6.9%) out of the 217 interventional cardiologists from the cath labs of the participating centers tested positive for COVID-19 in the polymerase chain reaction tests performed.

The national registry shows a significant reduction in the number of percutaneous coronary interventions performed to treat aortic valve disease since the COVID-19 pandemic was declared in our country. The risk of nosocomial infection and healthcare overload added to the risk associated with postponing these procedures[2,3] make it necessary to keep a follow-up and individualized assessment of every patient to be able to prioritize the indications.[4] A practical consequence of these data is that the patients' mortality rate while on the waiting list was clearly higher (3%) compared to the mortality rate due to nosocomial COVID-19 (1.3%). This may lead to the need of having to keep TAVI programs if logistically possible in future pandemics we may encounter. Finally, it is essential to guarantee the adequate protection of patients to avoid nosocomial infections that may be life-threatening and provide individual protection equipment (IPE) to the healthcare professionals who may be exposed to infections.[5]

CONFLICTS OF INTEREST

The authors declared no conflicts of interest in relation to this manuscript. R. Moreno is associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

Annex. Participanting hospitals and principal investigator in each center

Hospital Clínico Universitario de Santiago: Ramiro Trillo-Nouche
Complejo Universitario de Vigo: José Antonio Baz
Hospital Universitario San Carlos: Pilar Jiménez-Quevedo
Hospital Universitario Reina Sofía: Manuel Pan
Hospital Clínico Universitario Virgen de la Arrixaca: Eduardo Pinar
Hospital Universitari de Bellvitge: Rafael Romaguera
Hospital Universitario Virgen de la Victoria: José María Hernández
Hospital Universitario Virgen de las Nieves: Eduardo Molina
Hospital Universitari Vall d'Hebron: Viçens Serra
Hospital Universitario La Fe: Francisco Ten
Hospital Universitario Central de Asturias: Raquel del Valle
Hospital Clínico Universitario de Valladolid: Ignacio Amat
Hospital Ramón y Cajal: Luisa Salido
Hospital Clínic Barcelona: Ander Regueiro
Hospital Gregorio Marañón: Enrique Gutiérrez
Hospital de la Santa Creu i Sant Pau: Dabitz Arzamendi
Hospital General Universitario de Alicante: Vicente Mainar

(Continues)

Annex. *(Continued)*

Hospital La Paz: Raúl Moreno
Hospital Universitario de Gran Canaria Dr Negrín: Pedro Martín
Hospital Universitario Marqués de Valdecilla: José M. de la Torre-Hernández
Hospital Universitario Virgen del Rocío: Manuel Villa
Hospital Germans Trias i Pujol de Badalona: Eduard Fernández-Nofrerias
H. Puerta del Mar: Livia Gheorge
Hospital Universitario de León: Carlos Cuellas Ramón
Hospital Clínico Universitario de Valencia: Sergio García-Blas
Hospital Universitario Miguel Servet: María Cruz Ferrer
Hospital Universitario de Cruces: Roberto Blanco Mata
Hospital Universitario Regional de Málaga: Cristóbal Urbano
Hospital de Basurto: Leire Andraka
Complejo Hospitalario de Navarra: Valeriano Ruiz Quevedo
Hospital Universitario de Badajoz: Juan Manuel Nogales
Hospital Universitario de Salamanca: Ignacio Cruz
Complejo Hospitalario de Toledo: José Moreu
Hospital Universitario de La Princesa: Fernando Alfonso
Hospital Universitario Puerta de Hierro Majadahonda: Juan Francisco Oteo
Hospital Universitario Fundación Jiménez Díaz: Antonio Piñero
Hospital Universitari Son Espases: Vicente Peral
Hospital Universitario Juan Ramón Jiménez: Jessica Roa
Hospital General de Valencia: Alberto Berenguer
Clínica Universidad de Navarra: Miguel Artaiz
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Percutaneous extracorporeal membrane oxygenation during the COVID-19 pandemic. A Spanish multicenter registry

Oxigenador extracorpóreo de membrana con implante percutáneo durante la pandemia de COVID-19. Registro multicéntrico español

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Online: 26-10-2020.
https://doi.org/10.24875/RECICE.M20000169

Table 1. Baseline characteristics, treatment and outcomes of patients with percutaneous ECMO implantation during the COVID-19 pandemic

	Total (n = 14)
Baseline characteristics	
Age (years)	48.79 ± 7.13
Weight (kg)	85.79 ± 18.03
Height (m)	1.73 ± 0.07
BMI (kg/m²)	28.32 ± 5.02
Female sex	3 (21.4)
Hypertension	4 (28.6)
Diabetes mellitus	2 (14.3)
Dyslipidemia	5 (35.7)
Smoker (former or current)	6 (42.8)
Atrial fibrillation	1 (7.1)
Coronary artery disease	2 (14.3)
Congestive heart failure	1 (7.1)
Previous stroke	0 (0)
Chronic liver disease	0 (0)
Chronic kidney disease	0 (0)
Apnea-hypopnea respiratory syndrome	2 (14.3)
Previous cancer	1 (7.1)
Treatment	
Hydroxychloroquine	13 (92.9)
Azythromycin	12 (85.7)
Glucocorticoids	12 (85.7)
Lopinovir/Ritonavir	12 (85.7)
Tozilizumab	9 (64.3)
Remdesvir	4 (28.6)
Antibacterial co-treatment	14 (100)
Cephalosporins	7 (50)
Piperacillin tazobactam	6 (42.9)
Vancomycin	3 (21.4)
Colistin	3 (21.4)
Daptomycin	1 (7.1)
Meropenem	8 (57.1)
Linezolid	7 (50)
Outcomes	
Days on ECMO	12 [9-14]
Days on mechanical ventilation	34 [18-51]
Days at the ICU/CCU	44.5 [19.0-56.0]
Length of hospital stay (total, in days)	62 [27-66]
Death	4 (28.6)
Multiorgan failure	1 (25)
Withholding of live-sustaining therapies	3 (75)

BMI, body mass index; CCU, coronary care unit; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

To the Editor,

Extracorporeal membrane oxygenation (ECMO) has been used as invasive mechanical respiratory support for almost 40 years. Venovenous ECMO makes full use of cardiopulmonary bypass to take over the lungs respiratory function. Venoarterial ECMO provides circulatory support plus oxygenation and is useful to treat cardiogenic shock or refractory cardiopulmonary arrest.[1] The technical advances made on ECMO devices have boosted its use through a fully percutaneous approach, often performed by interventional cardiologists trained in large bore percutaneous access. This, in turn, has led to quicker setups and has reduced time in critical situations and increased the chances of survival.[2]

Since the beginning of the novel coronavirus disease (COVID-19) pandemic, different Chinese centers have reported a high incidence of acute respiratory distress syndrome (ARDS) (17% to 29%) and critical illness (23% to 32%) among hospitalized patients.[3] The management of ARDS includes lung-protective ventilation, adequate fluid strategy, and early initiation of pronation.[4] If these strategies are insufficient, the use of ECMO to treat refractory hypoxemia becomes the only alternative available.[5] Also, important delays in the application of reperfusion therapies in the context of ST-segment elevation myocardial infarction have been observed during the current pandemic, leading to higher mortality rates, mechanical complications, and cardiogenic shock.[6] Finally, patients with advanced chronic heart failure have a greater risk of developing severe COVID-19 symptoms.

ARDS, acute cardiogenic shock, and advanced chronic heart failure are the triple threat of ECMO candidates with COVID-19.

This is a multicenter retrospective registry of percutaneous implantation of ECMO between March 15 and May 15, 2020 in 4 Spanish centers during the COVID-19 pandemic. The official number of COVID-19 cases admitted to the centers that participated in the study period was ~4500. A total of 14 infected patients (0.3%) were treated with an ECMO device. The main baseline characteristics of the patients included in the study are shown on table 1. Ten patients developed ARDS (71.4%), 2 ARDS added to decompensated advanced chronic heart failure (14.3%), and 2 more developed cardiogenic shock due to acute coronary syndrome in the context of SARS-CoV-2 infection (14.3%).

Nine patients (64.3%) were initially admitted to conventional wards and 5 (35.7%) were immediately transferred to the intensive care unit. During admission, different treatments were used as shown on table 1. An echocardiography was performed in all cases; the median

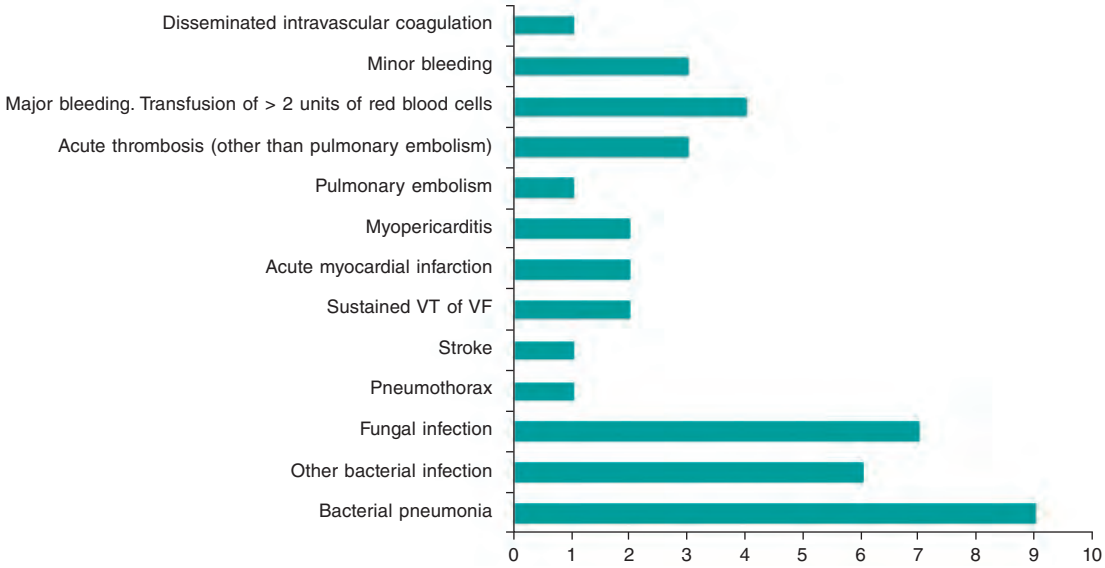

Figure 1. Complications during extracorporeal membrane oxygenation assistance and frequency. VF, ventricular fibrillation; VT, ventricular tachycardia.

left ventricular ejection fraction of patients without previous cardiovascular disease affected by ARDS (10 patients [71.4%]) was 58% [interquartile range (IQR), 51% to 64%] and the tricuspid annular plane systolic excursion was 18.5 mm [17.7 mm to 19.3 mm]. The ECMO device was implanted a median of 7 days from admission through fully percutaneous approach in all cases but one. Based on the ECMO modality used, 2 patients received a venoarterial ECMO (14.3%) and 12 received a venovenous ECMO (85.7%). In 2 patients of the latter group VAV (venoarterial-venous) ECMO conversion was performed (13.3%). Two patients (14.3%) also needed a left ventricular assist device that in both cases was an intra-aortic balloon pump. The complications of these patients are shown on figure 1. Although coexisting infections were the most common problem, we should mention the very high-risk of presenting with thrombotic and bleeding events (4 [28.6%] and 8 [57.1%], respectively) likely due to the ECMO device *per se* but also to the inflammatory and coagulation disorders due to COVID-19. All patients showed, at least, 1 complication. The median time connected to the ECMO device was 12 days [9-14] and the median length of the hospital stay was 62 days [27-66]. Four patients died (28.6%), 1 (25%) due to multiorgan failure and 3 (75%) after withholding limitation of live-sustaining therapies or limitation of the therapeutic effort.

In conclusion, this relatively small registry is nothing but a glimpse of the most advanced therapies used during the current COVID-19 pandemic. It shows that 3 out of 4 patients who required ECMO survived until hospital admission despite the high rate of related complications. We should mention that the rapid and minimally invasive implantation of ECMO devices in critically ill patients has become more and more popular among interventional cardiologists.

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