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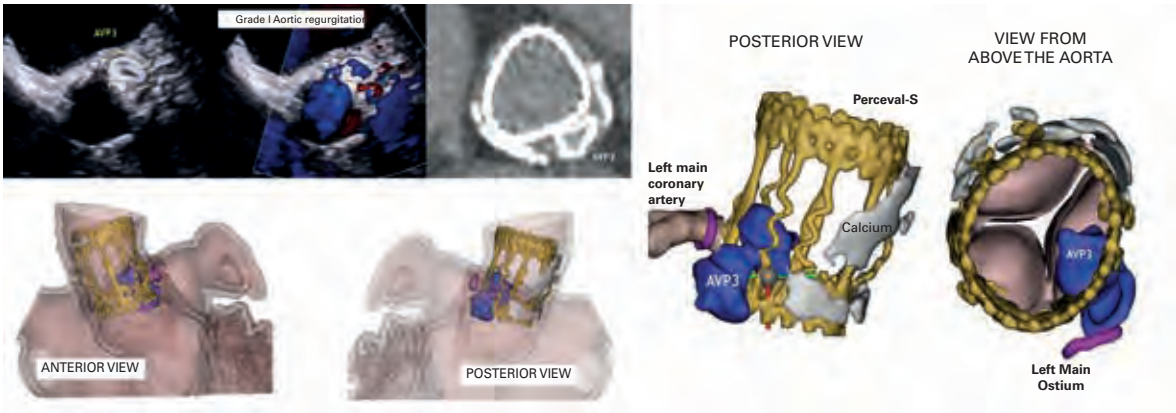

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REC: INTERVENTIONAL CARDIOLOGY

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Editorial

Primary angioplasty programs. Should we redirect the Stent for Life initiative 10 years later?

Programas de angioplastia primaria: ¿debemos redireccionar la iniciativa Stent for Life 10 años después?

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Spain was inducted in the European initiative Stent for Life in a ceremony hosted by the General Assembly of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) back in 2009. As president of the Hemodynamics and Interventional Cardiology Section of the Spanish Society of Cardiology (SEC), Dr. Fina Mauri signed the declaration of commitment with this initiative aimed to improve the access of patients to reperfusion by the increasing use of primary percutaneous coronary interventions (pPCI) as the optimal treatment in the management of ST-segment elevation myocardial infarction (STEMI).

The Stent for Life initiative was born the previous year (September 2008) as an alliance among the Spanish Society of Cardiology, EAPCI, and Eucomed.[1] In Europe the situation of reperfusion in the management of infarction was under discussion. They came to the conclusion that there was a great heterogeneity among the different countries with an overall scarce penetration of pPCI as the treatment of choice.[2] These differences were not related to gross domestic product (GDP): countries with relative low GDPs (Czech Republic, Hungary, Slovakia, Slovenia, Poland, Lithuania) performed many more pPCIs per million inhabitants compared to other countries with higher GDPs like Spain.[2] For this reason, Spain was among the 6 countries asked to participate in this initiative together with Turkey, France, Greece, Bulgaria, and Serbia. All performed less than 200 pPCIs per million inhabitants (in 2008 only 165 PCIs per million inhabitants were performed in Spain). The objectives established at that time are shown on table 1; they were numerical objectives of implementation and penetration of this technique in the management of STEMI with the implicit creation of acute myocardial infarction networks.

Back in 2008, there were only 4 well-structured infarction networks across in Spain: Murcia, Galicia, Balearic Islands, and the Chartered Community of Navarre performed between 200 and almost 400 pPCIs per million inhabitants. However, eventually only 12.8% of the entire Spanish population benefited from these 4 networks. In the remaining autonomous communities, the pPCIs were performed erratically with numbers lower or closer to 100 pPCIs per million inhabitants. Regions like the Community of Valencia, the Principality of Asturias, and Andalusia performed 61, 78, and 106 pPCIs per million inhabitants).[3] Like Europe, these regional differences were not related to the GDP of the different Spanish autonomous communities. Therefore, the creation of a myocardial infarction network with full hospital infrastructure, trained professionals, and a system of medical emergencies in a developed country like ours became a purely organizational matter. In October 2010 and with the explicit support from the SEC and its affiliate sections Hemodynamics and Interventional Cardiology, Ischemic Heart Disease, and Coronary Units the different scientific societies of the autonomous communities signed the declaration of membership to the Stent for Life initiative (figure 1). From that moment on, the focus was on 3 different levels for the progressive and gradual implementation of infarction networks. In the first place, there was a political and media approach to the different health administrations involved. The publication of the comparative results from the different autonomous communities in the media (figure 2) contributed effectively to their involvement in this issue. Parallel to this and thanks to scientific publications and cardiology meetings, professionals became aware on the clinical need to implement these infarction

Table 1. Objectives of the Stent for Life initiative from 2008

Define regions/countries with unmet medical needs for the implementation of the optimal management of acute coronary syndrome
Implement an action program to increase the access of patients to pPCIs: a) Increase the percentage of pPCIs performed in > 70% of STEMI patients b) Achieve pPCI rates > 600 per million inhabitants/year c) Offer a 24/7 service in all necessary angioplasty centers for the full coverage of the region/country

pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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Figure 1. A: induction ceremony of the scientific societies of the different autonomous communities into the Stent for Life initiative (Madrid, October 4, 2010); **B:** certificate of membership to the Stent for Life initiative of an affiliate society (Society of Cardiology of Castile and León).

networks.[4-7] Finally, patients were approached through commercial campaigns and media announcements with positive short-term results.[8] Everything was mostly funded with the unconditional support from the industry. After 10 years of many people working for the Stent for Life initiative it can be said that it has contributed to the implementation of infarction networks nationwide. In 2018, 21 261 pPCIs were performed (13 395 back in 2008) with an average rate of 416 pPCIs per million inhabitants. This rate is considered adequate given the prevalence of ischemic heart disease in our country without great differences among the different autonomous communities.[9] At this point, what challenges will the next decade bring? The survey of a paper recently published by Rodriguez-Leor et al.[10] in *REC: Interventional Cardiology* may have some of the answer to this question. The current objectives should focus on both the patient and the healthcare provider. At this point it is not about opening new centers or programs anymore, but about designing the procedures required for each center to keep quality outcomes. The satisfaction of well-trained professionals built on adequate retributions, regulating the rest periods, and the correct sizing of staff based on the healthcare needs are all key issues to take into consideration at the infarction centers. Similarly, generational replacement should occur while keeping the quality of the entire process. The Administration should consider payment to centers based on results and make sure that these payments reach the treating physician. On the other hand, very complex cases like STEMI patients complicated with cardiogenic shock should be referred to specialized centers capable of performing advanced ventricular assist techniques, heart surgery, and transplants. In this type of patients, mortality rate is still very high (around 50%). Therefore, each infarction network should be able to identify its shock centers for the adequate management of these patients.

In conclusion, the objectives of the Stent for Life initiative in our country should look at the new clinical and professional challenges ahead with the patient as the protagonist of all clinical actions.

Figure 2. Examples of news published by the media on comparative results among different autonomous communities on the management of ST-segment elevation myocardial infarction.

CONFLICTS OF INTEREST

M. Sabaté was the national coordinator of the Stent for Life initiative in Spain between 2009 and 2013. No other conflicts of interest have been reported.

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Editorial

Women and STEMI: a shared responsibility

Mujer e IAMCEST: una responsabilidad compartida

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The sex-based differences in approach and mortality in the management of patients with acute coronary syndrome (ACS) have been known for a while now. Back in 1991 the *New England Journal of Medicine* published an editorial[1] on this matter. In this article Healy coined the term "the *Yentl Syndrome*" to refer to the invisibility of women in the studies of cardiovascular disease. She argued that women should behave according to the masculine clinical standards to receive the same care; otherwise they were misdiagnosed and mistreated resulting in healthcare of a lower quality and effectiveness.

Over the last few decades, cardiovascular mortality has decreased thanks to the advances made in the prevention, diagnosis, and treatment of ischemic heart disease. This improvement has benefited women as well. According to the RESCATE II registry,[2] between 1992 and 2003, in-hospital mortality after a first acute myocardial infarction decreased 25% in women. In spite of this, unlike what happens with males, circulatory system diseases are still the leading cause of mortality among women.[3] In the study presented by Anguita et al.[4] in the last European Congress of Cardiology, female sex was still an independent predictor factor of mortality in ST-segment elevation acute myocardial infarction (STEMI) in Spain. In this study, the authors retrospectively analyzed the Minimum Basic Data Set of the Spanish Ministry of Health from 2005 through 2015. They identified 325 017 patients with STEMI of whom 38.8% were women, and concluded that in-hospital adjusted mortality is still high in this group. It should be mentioned that odds ratio dropped from 1.28 in 2006 to 1.14 in 2014, which may indicative of better care to women with STEMI.

The article by Tomassini et al.[5] recently published on *REC: Interventional Cardiology* is an in-depth analysis of primary angioplasty and mid- and long-term mortality in patients with STEMI based on sex differences. It is a retrospective analysis of all patients with STEMI presenting with < 12 h of chest pain who underwent a primary angioplasty at their center from March 2006 to December 2016; in total, 1981 patients (24.4%, women). According to other registries,[6] compared to males, women are older (mean age 71.3 ± 11.6 vs 62.9 ± 11.8 years), have a higher prevalence of traditional cardiovascular risk factors, longer total ischemic times, and worse Killip functional class at admission. Oddly enough after matched propensity score analysis, with the same percentage of multivessel coronary artery disease (5.3% vs 4.7%) and stent implantation (82.9% vs 83.9%), the success of the procedure and ST-segment resolution were significantly lower in women (90.2% vs 94.4% and 47.5% vs 54.1%, respectively). The authors suggest that this is probably due to the different pathophysiology of acute myocardial infarction in women, but they do not say anything about the time elapsed from the first medical contact until guidewire crossing or subsequent medical therapy, variables that have a direct impact on the prognosis of patients.

As interventional cardiologists we have a hard time thinking that there may be different system delays because when the infarction code goes off, the most important thing is to find the ST-segment elevation on the EKG, the timeline of disease progression, and the patient's clinical signs and hemodynamic status (not always in this order). In any case, we should not forget that treatment starts before and after our intervention.

A study conducted in Portugal[7] revealed that delays from the first medical contact to radial access were 15 minutes longer among women. This is not an isolated datum. Huded et al.[8] analyzed variability during management and the results of the STEMI care network from Cleveland Clinic (Ohio, United States). They observed worse quality of care in women, longer door-to-balloon times, and medical therapies inconsistent with the guidelines in a higher percentage of cases. The implementation of an adapted protocol improved these parameters, especially among women (the percentage of women who received medical therapy as recommended by the guidelines rose to 98%, and system delays were reduced in 20 minutes). Overall, in-hospital mortality decreased 43%. This makes us think that maybe the variability seen in the management of STEMI is something generalized, that the reduction of discrepancies is possible, and that it can reflect the quality and maturity of care networks.

It is noteworthy to discuss the atypical nature of symptoms in women as the cause for these delays. The VIRGO clinical trial[9] interviewed 2009 women and 976 males between 18 and 56 years of age admitted due to an STEMI. In both groups, the main symptom was chest pain defined as pain, pressure, tension or discomfort (87% vs 89.5%). Also, women had more accompanying symptoms (58.5% showed more than 3 additional symptoms compared to 46.2% of males). These data are reproduced in another prospective study conducted at an ER that interviewed 1941 patients with suspected ACS. The study confirmed that 92%

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of women and 91% of males reported chest pain as the main symptom.[10] When women were asked why did not they look for help earlier,[11] most of them thought it was not an STEMI and they did not want to be called hypochondriacs if it was not serious after all. And they may be right. According to the VIRGO trial, 53% of women who previously sought medical attention were told that it was not an acute coronary event. Maybe as Healy used to say[1] women do not belong in the medical and social category of ACS.

For all this, although the management of STEMI in women has improved over the last few decades, articles like Tomassini et al.'s[5] are a friendly reminder that there is still work to be done. Not only clinical trials, but also daily gestures like rising the awareness of society and healthcare providers that STEMI affects everyone, women included.

CONFLICTS OF INTEREST

None declared.

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Editorial

The challenge of integrating Ibero-America through research and scientific publications

El desafío de integrar Iberoamérica a través de la investigación y las publicaciones científicas

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Undertaking the project *REC: Interventional Cardiology*, a bilingual journal published in English and Spanish and devoted to interventional cardiology seems a gigantic task to implement, which is why we wish to thank the editors for their entrepreneurial spirit and also *Revista Española de Cardiología* for making space for this new project. A unique opportunity for developing agreements and team work for the entire Spanish-speaking cardiological community that often feels the imposing presence of English-speaking scientific journals.

Combining the organizational and academic trajectory and leadership of the Spanish Society of Cardiology and the vitality, thrust, and enthusiasm of the Latin American interventional cardiology community may be the beginning of a huge agreement of productivity and novelty. This may, in turn, help the communication network between the Spanish vision planted at the very heart of Europe and the Latin American one that influences over 600 million people, thereby exponentially increasing the opportunities of communication for members of scientific societies and the possibilities of providing relevant scientific information. Talent is universal, opportunities are not.

Although European and American clinical practice guidelines on evidence-based medicine have tremendous exposure and each country publishes its own guidelines, we have been unable to integrate these concepts in regional or intersociety guidelines or approved documents. Yet at the Latin American Society of Interventional Cardiology (*Sociedad Latinoamericana de Cardiología Intervencionista,* SOLACI) we have tried to integrate the interventional guidelines established by the Society for Cardiovascular Angiography and Interventions and the American College of Cardiology. *REC: Interventional Cardiology* could well serve as a forum for all interventional cardiology guidelines and consensus documents of our region.

We should also mention that several clinical trials, series, and clinical cases studied in Latin America, especially those including international collaborations or inter-society agreements, should be published in this journal.

Although most multicentric randomized evidence-based clinical trials that are conducted in the United States and Europe are published in English, many significant advances made in cardiovascular medicine such as saphenous vein grafts used in coronary artery bypass graft surgery, stents, and stent-grafts have come from doctors within our region, such as R.G. Favaloro, J. Palmaz, and J.C. Parodi. However, even though these advances may speak Spanish, they have been implemented by English-speaking countries, which is the main reason why cooperation and integration should be our guiding spirit. The goal of this journal is to contribute, not to compete.

Needless to say that the success of this project depends entirely on us; all interventional cardiologists in Ibero-America should convince ourselves that we are capable of producing quality educational material that is attractive, not only to us, but also to our colleagues in other specialties, both in Latin America and the rest of the world. We are convinced that this will be so.

80% of the teachers predict that by 2026 digital content will replace print. In this sense, the educational resources that turn learning into a videogame, such as virtual reality or gaming, and that are patrimony of the digital world[1], will make learning a more interactive experience. The digital format of *REC: Interventional Cardiology*, with its tremendously dynamic character and adaptability to the user, will help amplify its educational purpose, making it an addictive yet healthy experience.

In the battle to conquer everyone's attention, sensationalist tabloid-style material seems to have replaced academic writing. The focus should be on getting the attention of the specialists through an updated informative model that never loses its primary educational purpose.

Sitting talent and different visions at the same table multiplies the options of creativity. *REC: Interventional Cardiology* is a golden

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opportunity for generating knowledge, healthy controversy, and pushing the Latin American interventional medical practice to the limit, under the mentoring of *Revista Española de Cardiología* in an effort to make a useful and enriching difference in the final result published.

This will be a privileged stage for exchange and academic contribution for the Ibero-American interventional cardiology communities. Congratulations and best wishes!

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever regarding this manuscript.

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Original article

Survey on the needs of primary angioplasty programs in Spain

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ABSTRACT

Introduction and objectives: ST-segment elevation myocardial infarction (STEMI) regional networks pose great organizational differences that may compromise their results. The Working Group on Hemodynamics and Interventional Cardiology has carried out a survey among its members on the level of satisfaction and the state of primary angioplasty programs in Spain.
Methods: On-line, open and anonymous survey, among the Hemodynamics and Interventional Cardiology Working Group members conducted between May 22 and June 5, 2018 on the necessities of the aforementioned programs and the degree of satisfaction of the professionals involved.
Results: Answers were obtained from 172 professionals with representation from 75 centers and 17 autonomous communities. The number of angioplasties performed in the STEMI setting per year and per center was 259 ± 110. The degree of satisfaction of the professionals with the application of the Infarction Code and the degree of personal satisfaction scored 7.2 ± 2.2 and 7.2 ± 2.4 points out of 10, respectively, although with significant regional differences. The main areas of concern detected were logistics issues, insufficient paycheck compensations and lack of rest. A 55% were inclined to leave their on-call duties when possible.
Conclusions: The survey has revealed a high degree of satisfaction by the professionals involved in STEMI treatment, although with notable differences among different autonomous communities and has allowed detecting logistical, structural and paycheck disturbances that can put primary angioplasty programs in situations of vulnerability.

Keywords: Infarction Code. ST-segment elevated myocardial infarction. Survey. Satisfaction. Primary PCI.

Encuesta sobre las necesidades de los programas de angioplastia primaria en España

RESUMEN

Introducción y objetivos: Las redes regionales de atención al infarto agudo de miocardio con elevación del segmento ST presentan grandes diferencias en términos de organización que puede llegar a comprometer sus resultados. La Sección de Hemodinámica y Cardiología Intervencionista ha realizado una encuesta entre sus miembros sobre el grado de satisfacción y la situación de los programas de angioplastia primaria en España.
Métodos: Se realizó una encuesta *online*, abierta y anónima, entre los miembros de la Sección de Hemodinámica y Cardiología Intervencionista entre los días 22 de mayo y 5 de junio de 2018, sobre las necesidades de los programas y el grado de satisfacción de los profesionales.

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Resultados: Se obtuvieron 172 respuestas de profesionales, con representación de 75 centros y 17 comunidades autónomas. El número de angioplastias en el infarto agudo de miocardio con elevación del segmento ST por año y por centro fue de 259 ± 110. El grado de satisfacción de los profesionales con la aplicación del Código Infarto, así como el grado de satisfacción personal, obtuvieron una puntuación de 7,2 ± 2,2 y 7,2 ± 2,4 puntos sobre 10, respectivamente, aunque con diferencias regionales significativas. Las principales áreas de preocupación detectadas fueron las limitaciones logísticas, la retribución insuficiente y la falta de descanso. Si fuera posible, un 55% estaría dispuesto a dejar las guardias.
Conclusiones: La encuesta ha puesto de manifiesto un alto grado de valoración del sistema por parte de los profesionales, aunque con diferencias notables entre las comunidades autónomas, y ha permitido detectar disfunciones logísticas, estructurales y retributivas que pueden poner a los programas de angioplastia primaria en situación de vulnerabilidad.

Palabras clave: Código Infarto. Infarto con elevación del segmento ST. Encuesta. Satisfacción. Angioplastia primaria.

Abbreviations

PPCI: primary percutaneous coronary intervention. **SHCI:** Working Group on Hemodynamics and Interventional Cardiology. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

The ST-segment elevation acute myocardial infarction (STEMI) is one of the leading causes of cardiovascular morbimortality. Primary percutaneous coronary intervention (pPCI) or primary angioplasty is the recommended reperfusion therapy for the management of STEMI since it reduces mortality and major ischemic events compared to pharmacological reperfusion therapy. This benefit is only evident when the pPCI is performed in adequate centers (infarction centers) by experienced professionals and ideally within the first 2 hours after the patient first medial contact contact with the healthcare system.[1] These conditions require a huge organizational effort in order to guarantee early diagnoses, quick transfers of patients to the infarction centers, and the availability of a team capable of performing the procedure swiftly and 24/7.[2-4]

Over the last few years Spain has seen the gradual arrival of regional networks for the management of STEMI that, in most cases, have spread nationwide. The heterogeneity implicit in the structures of the different healthcare systems has produced great organizational differences in these networks from programs created exclusively by healthcare providers with almost no institutional support to programs where the Administration has been involved providing detailed analyses of subdivisions, logistics, infrastructure, and all necessary resources.[5,6] The particular characteristics and specific requirements of pPCI programs can put them in a scenario of vulnerability which can gradually make very difficult to keep their sustainability while limiting the favorable prognostic impact they have on patients with STEMI.

In order to study the current situation of pPCIs in Spain, detect vulnerabilities in the system, and establish minimum requirements from the point of view of organization, infrastructure, and outcome assessment, the Working Group on Hemodynamics and Interventional Cardiology (SHCI) of the SEC promoted the creation of the SHCI Infarction Code Working Group. This paper shows the results of a survey on the actual situation of primary angioplasty programs in Spain, and the degree of satisfaction of the interventional cardiologists involved.

METHODS

Study population

A survey was conducted online through a website and a mobile app. The survey was open and anonymous and was carried out among SHCI members. The respondents received an invitation through a link sent directly to their e-mail accounts and through direct access from the SHCI official website.

Data mining

The survey was conducted from May 22 through June 5, 2018. It included 4 different sections: personal data from respondents (while keeping their anonymity), information from the corresponding center, characteristics of the pPCI program, and opinions on this program. This last section included a blank box to write areas for improvement, grouped into 3 sections for analysis: issues related to improving logistics, changes in the rate pay model and changes in the resting hours model. Table 1 shows the survey questions. Answering these questions took no more than 5 minutes.

Analysis

The descriptive variables are expressed as means ± standard deviations, the continuous variables as ranges, and interquartile ranges (between square brackets), and the discrete variables are expressed as a numbers (percentage of frequency).

All analyses were conducted using the STATA 15.1 statistical software package (StataCorp, College Station, Texas, United States).

RESULTS

Study population

Out of the 823 invitations sent, 172 interventional cardiologists and SHCI members (21%) from 75 hospitals (71 public and 4 private) of the 17 Spanish autonomous communities responded to the survey. Figure 1 shows the location of the hospitals. Ninety-five-point-six percent of participants were part of infarction teams that remained available on a 24/7/365 basis, and 26% of them were the directors of their corresponding interventional cardiology unit (in 59% of participating centers, the person who responded to the survey was the director of the unit). The mean age of respondents was 45 ± 8 years (range, 28-66 years), [39-50 years]. The years of experienced performing primary angioplasty procedures were 9.5 ± 5.7 (range, 0-21), [5-13].

Annex 1 shows the participating centers by autonomous communities

Table 1. Questions asked in the survey

Personal data
Center (optional)
Autonomous community
Age (N)
Sex (male/female)
Years performing pPCI (N)
Data from the center
Type of hospital management (public/private)
Human resources of the center (professionals participating in the pPCI program): Number of interventional cardiologists (N) Number of nurses (N) Number of assistant nurses (N)
Annual number of pPCI performed per STEMI at the center (N)
Specifics of the center pPCI program
Possibility of rest after the pPCI while on-call duty (Yes/No)
Type of rest after the pPCI while on-call duty (next day/some other day)
Hours of rest after being activated while on-call duty (N)
Distribution of the calls (in weeks/days)
Number of professionals within the on-call duty program: Number of interventional cardiologists (N) Number of nurses (N) Number of assistant nurses (N) Number of technicians (N)
Type of payment per on-call duty: Payment of on-call duty only (Yes/No) Payment of on-call duty plus payment of physical presence during activation hours (Yes/No) Payment of on-call duty with physical presence in case of activation only (Yes/No) Payment per procedure (Yes/No) On-call daily double list (Yes/No) On-call double list during the weekend (Yes/No) Payment per monthly on-call duty (Yes/No)
Opinion on the center pPCI program
Would you say that the implementation of the Infarction Code initiative carried out by your center was satisfactory? Score from 1 to 10
Do you think that the management of STEMI patients can be improved at your center? (Yes/No)
In your professional opinion, not in the patient's opinion, and regarding the management of ST-segment elevation acute coronary syndrome, are you satisfied with your job? Score from 1 to 10
Would you say that the pay received per activation is fair? (Yes/No)
In your opinion, can you have sufficient rest after being activated? (Yes/No)
Would you say that there is enough personnel to handle all on-call duties (Yes/No)
In your opinion, how many doctors should your cath lab have to be able to handle all hemodynamic on-call duties? (N)
In your opinion, the implementation of the Infarction Code initiative has improved the management of patients with ST-segment elevation acute coronary syndrome? (Yes/No)
Would you say that the responsibility that your job requires receives the recognition it deserves? (Yes/No)
Would you consider leaving the on-call mandatory program once you are not eligible anymore? (Yes/No)
Write all possible areas with room for improvement. What kind of rest would you need? What about the pay? And what about your numbers? (free writing)

N, number; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation acute myocardial infarction.

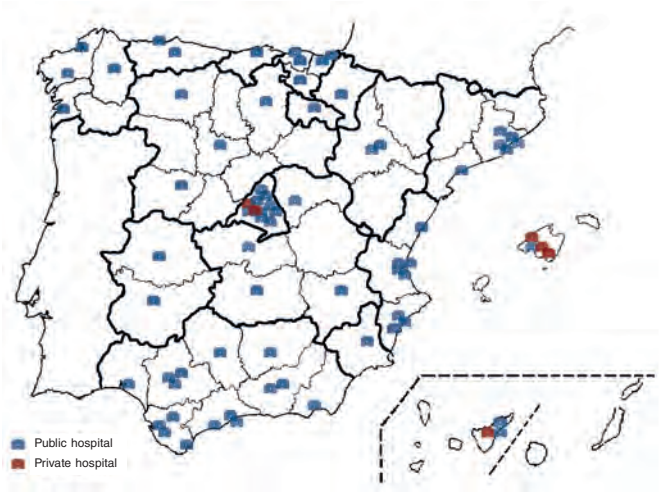

Figure 1. Map with the distribution of centers represented in the survey. Blue shows public hospitals and red shows private centers. Eight respondents did not tick the working center box and, therefore, are not represented on the map.

Specificities of pPCI programs

Regarding the management of STEMI, the number of annual pPCIs performed per center (considering the data provided by hospitals to the 2017[7] SHCI Registry) was 239 ± 112 (range, 14-587), while the number of angioplasties performed per STEMI per center (primary angioplasty, bailout angioplasty, and early angioplasty after effective thrombolysis) was 259 ± 110 (range, 15-596) per year.

On average there were 5 ± 1 interventional cardiologists (range, 2-9) and 8 ± 3 nurses (range, 2-25) per center as part of the infarction team.

Infarction Code calls were available at all time. The distribution of the calls was mostly throughout days (82%), whereas in 18% of the cases, the period of continuous call spanned throughout 7 days/week. Seventy-two percent of respondents claimed to not have rest hours after being on call. Figure 2 shows the distribution of the number of hours of rest after performing a procedure while being on call; when there is a possibility of rest (which only happens in 54% of the cases), it occurs the next day.

Figure 3 shows how on-call pay rates are arranged. There is a heterogeneous pattern but in almost two thirds of the cases, the pay rate is only location based regardless of the number of procedures performed. If pay rate from centers with the largest volumes of procedures performed while on call (> 300) is analyzed, we will see that these pay rates vary slightly: 58% to 45% for on-call duty, 19% to 25% for on-call physical presence, 8% to 10% for on-call daily double list, and from 13% to 16% for pay per procedure.

Opinions on the pPCI program

Figure 4 shows the distribution of the score attributed to the degree of satisfaction of the professionals involved in the Infarction Code initiative of their center on a scale from 0 to 10. Fourteen percent of respondents gave scores < 5 points, whereas 33% of respondents gave scores between 9 and 10 points.

Figure 5 shows the distribution of the scores given to the question of the degree of satisfaction with the job done from the professional and not the patient's point of view regarding the

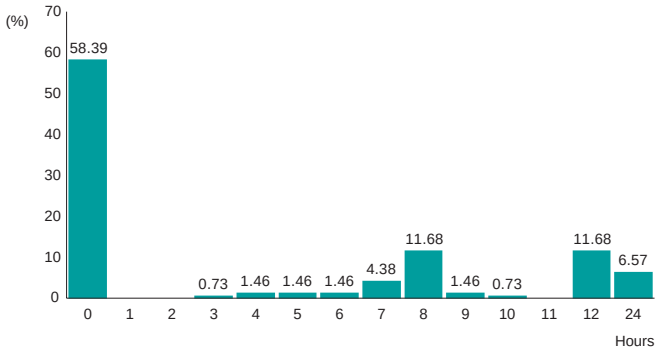

Figure 2. Distribution of the number of hours of rest agreed after performing one procedure while on on-call duty.

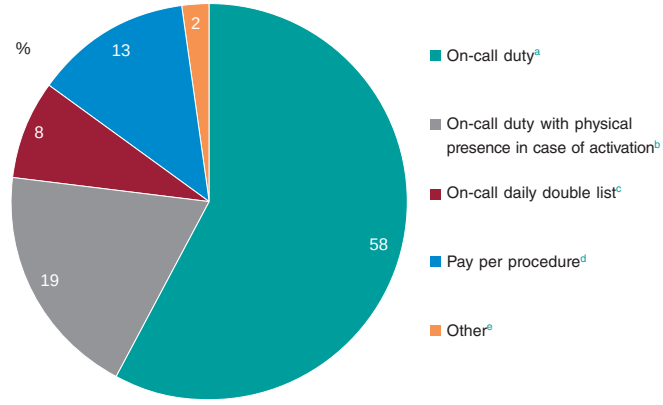

Figure 3. Pay per on-call duty within the Infarction Code initiative.
[a] Payment on an on-call duty basis only regardless of the activity performed.
[b] Payment on an on-call duty basis that in case of activation turns into payment on an on-call duty basis plus physical presence.
[c] Payment on an on-call duty basis with two interventional cardiologists on call.
[d] Payment per every procedure performed.
[e] Others includes 2 cases (1.2%) of payment on an on-call duty basis with 1 interventional cardiologist available during business days and 2 interventional cardiologists available during public holidays, plus payment of hours of physical presence per procedure performed, and 1 case (0.6%) of monthly payment on an on-call duty basis.

management of STEMI. Twelve percent of respondents gave scores < 5 points and 31% of respondents gave scores between 9 and 10 points. In this sense, 86% of respondents answered "yes" to the question «Do you think the management of STEMI patients can be improved? Table 2 shows the score attributed to the degree of satisfaction with the implementation of the Infarction Code initiative, and the score attributed to degree of professional satisfaction on the management of STEMI distributed across all autonomous communities.

With respect to the perception of working conditions, 76% of respondents said that they did not rest enough after being activated while on call, 32% claimed that the personnel in charge of the calls is shorthanded, 63% thought that the responsibility involved in this procedure does not receive the recognition it deserves, and 85% of respondents agreed that the on-call pay rate is not right.

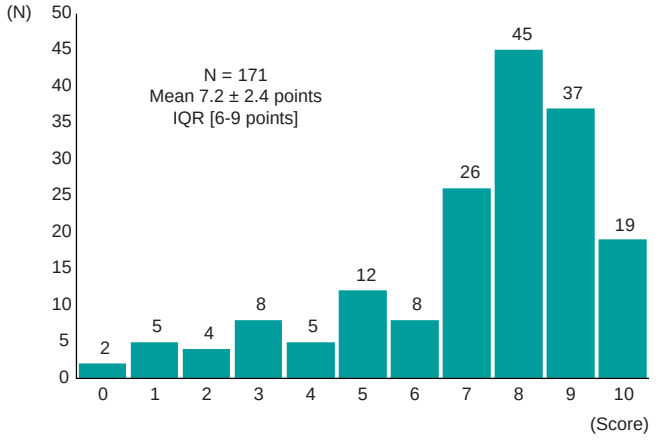

Figure 4. Distribution of the score given on the degree of professional satisfaction after the implementation of the Infarction Code initiative (on a scale from 0 to 10). IQR, interquartile range.

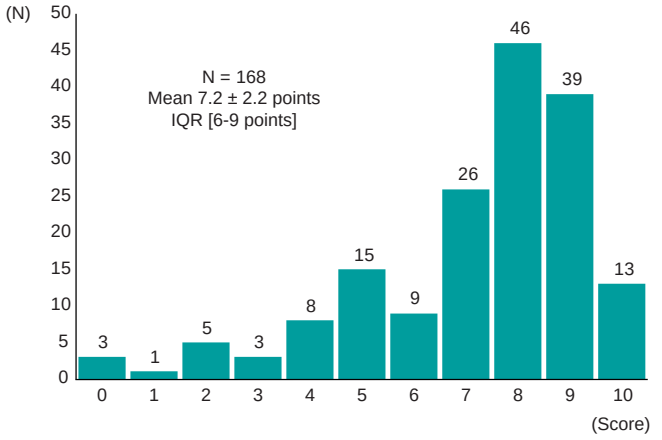

Figure 5. Distribution of the score given on the degree of satisfaction with the job done from the professional and not the patient's point of view on the management of ST-segment elevation acute myocardial infarction. IQR, interquartile range.

The survey included a blank box where the professional could list areas for improvement as part of the primary angioplasty program: 132 respondents (77%) wrote on this box and the answers given were about improving logistics (32%), pay rates (53%) or the hours of rest (47%).

Lastly, 55% of professionals said they would consider leaving these on-call mandatory programs once they were not compulsory anymore.

DISCUSSION

The survey on the needs of pPCI programs in Spain conducted among interventional cardiologists involved in these programs with a sample representative of all autonomous communities has shown 4 basic aspects: *a)* the assessment given to the Infarction Code initiative in terms of patients' benefits and professional satisfaction is high; *b)* there are significant local and regional differences in how professionals perceive their own degree of

Table 2. Scores given to the questions on the degree of satisfaction after the implementation of the Infarction Code initiative from the professional point of view and itemized by autonomous community

	Would you say that the implementation of the initiative carried out by your center was satisfactory? (0-10)	When it comes to the initiative, are you satisfied with your job in the professional aspect? (0-10)	Difference in the mean score given between the first and the second question
Andalusia	6.2 ± 2.6 (31)	6.4 ± 2.4 (29)	+0.2
Aragon	6.6 ± 2.2 (7)	7.1 ± 2.4 (7)	+0.5
Canary Islands	6.8 ± 1.5 (5)	8.2 ± 0.8 (5)	+1.4
Cantabria	9 ± 1.2 (5)	7.2 ± 3.1 (5)	−1.8
Castile and León	5.1 ± 2.8 (11)	6.1 ± 1.9 (11)	+1
Castile-La Mancha	7.4 ± 2.5 (16)	6.9 ± 3.2 (8)	−0.5
Catalonia	8 ± 2.3 (21)	7.6 ± 2.2 (21)	−0.4
Chartered Community of Navarre	7 ± 1.8 (4)	5.2 ± 3.6 (4)	−1.8
Valencian Community	6.9 ± 2.8 (16)	7.2 ± 2.1 (16)	+0.3
Community of Madrid	7.2 ± 2.5 (25)	7.3 ± 2.3 (24)	+0.1
Extremadura	6.5 ± 0.7 (2)	7 ± 1.4 (2)	+0.5
Galicia	7.9 ± 1.7 (9)	7.7 ± 1.2 (9)	−0.2
Balearic Islands	8.2 ± 0.8 (5)	8.4 ± 0.5 (5)	+0.2
La Rioja	7 ± 0 (2)	6 ± 2.8 (2)	−1
Basque Country	8.7 ± 0.8 (10)	8.3 ± 0.5 (10)	−0.4
Principality of Asturias	8.6 ± 0.9 (8)	8.8 ± 1 (8)	+0.2
Region of Murcia	8 ± 0 (2)	7.5 ± 0.7 (2)	−0.5
Total	7.2 ± 2.4 (177)	7.2 ± 2.2 (168)	0

The score given to each question is expressed as mean ± standard deviation. The numbers shown in brackets are indicative of the number of professionals who answered the question.

satisfaction; *c)* there is a general feeling that there is room for improvement in 3 different fields in terms of patient care/infrastructure, hours of rest after activation, and pay per on-call duty; and *d)* over half of the respondents are seriously considering leaving these on-call mandatory programs once they become of an age when they are not compulsory anymore.

The identification of a series of deficiencies and shortfalls may put these pPCI programs in a situation of vulnerability that may eventually jeopardize their own sustainability. This has been one of the main goals of SHCI Infarction Code Working Group. One study analyzed the impact that the presence of infarction care networks had on mortality in the management of STEMI in Spain between 2003 and 2012 and showed significant differences among the different autonomous communities in the implementation of pPCI programs such as significant differences in hospital mortality among the different autonomous communities.[6] However despite the improvements made over the last few years, these differences still stand.[8] In this sense, up to 86% of respondents believe that there is still room for improvement in the management of heart attacks. Since 2012 there has been a growth of regional pPCI programs to the extent that to this day almost every single Spanish autonomous community has implemented a pPCI program for the management of STEMI .

The overall average score in the assessment of the Infarction Code initiative in terms of benefits for the patient and degree of professional satisfaction is high: 7.2 points scored by both items. However, when the different autonomous communities are studied separately, the scores of these two items change dramatically. Thus, the degree of satisfaction with how the Infarction Code initiative works varies significantly from the 5.1 points of Castile and León to the 8.7 points of the Basque Country. The degree of professional satisfaction varies as well from the 5.2 points of the Chartered Community of Navarre to the 8.8 points of the Principality of Asturias. The scores given to both questions also vary depending on the autonomous community. For example, the score given by the Canary Islands (1.4 points) to the degree of professional satisfaction, which is higher than the degree of professional satisfaction with the Infarction Code initiative, or the score given by Cantabria (1.9 points), which is lower. There is no question that these differences show heterogeneity in the way these programs have been implemented by each autonomous communities. Analyzing the causes in each autonomous community is not an easy task and cannot be done with the present survey. Still, overall, there are factors that may justify the results obtained.

On the one hand, the implementation of pPCI programs occurred with partial or incomplete prior analyses, limited official support, and poor resources. The implementation of the Infarction Code initiative has had a great impact on daily care since 30%-45% of all emergencies occur within business hours[9] altering the normal functioning of the daily agenda and eventually leading to the cancellation of cases (hospitalized patients, scheduled cases or scheduled cases from other centers) or to unforeseen extensions of working hours to avoid these cancellations.

On the other hand, this survey shows that the sizing of the personnel involved in these Infarction Code initiatives is not right in many centers. The correct amount of professionals is required to take care of significant volumes of pPCIs during night time, and also to carry on with the activity scheduled by the unit for the next day and to make sure that these professionals get the hours of rest they need. In this sense, it is significant that up to 72% of respondents said that they did not have enough hours of rest after performing one procedure while on-call, and that on many occasions, these hours of rest were based on the actual healthcare possibilities and not on the needed rest *per se*. Performing these elective interventional procedures under conditions of lack of sleep and rest has been associated with a higher rate of suboptimal results.[10]

In this context it should be mentioned that many pPCI programs in Spain are not categorized as individual speciality programs. Therefore, the pay of these healthcare providers is no different from the pay of other providers who deal with urgent performances of lower complexity much less frequently and with low or no risk patients and that can often be scheduled with several hours in advance.

Even though the overall assessment of the pPCI programs made by professionals is high, the structural limitations found by this survey can have a negative impact on the teams and eventually lead to lack of motivation in many of the professionals involved with these programs. It comes as no surprise that this can also impact the degree of excellence provided that should be the goal of all pPCI programs, especially if we take into account the special profile of the patients who benefit from these programs. The fact that over half of the respondents are already thinking about leaving these on-call mandatory programs once they become of an age when they won't be eligible anymore can jeopardize the sustainability of these pPCI programs and put them in a situation of vulnerability. Ironically, this moment will come when these professionals are at their best and when they would have the best results. Eventually this may lead to a lack of recognition of these professionals from different points of view. In this sense, in each autonomous community, the ongoing monitoring and data measurement should include healthcare information, medical information, and the needs of all the professionals involved with the healthcare process in terms of which areas can be improved. The local and regional administrations should make sure that these pPCI programs are sustainable and certainly in our country they have shown a good cost-effective profile[11] when the right investment has been made.

Limitations and strengths

The present study has some limitations. First, the number of participants is relatively low compared to the overall amount of SHCI members. However, the sample seems representative enough since not all SHCI members are involved with pPCI programs and because 75 centers from all autonomous communities were represented in the survey. Also, a 21% participation rate is clearly higher compared to the participation rate from another similar online survey where only 14% of all the possible candidates responded.[12] Also, according to data published in the last SCHI registry, the number of active registered interventional cardiologists today is 390[7] which amounts to a 44% participation rate. Secondly, the observational and cross-sectional nature of the study is a limitation *per se*.

The strength of this study is the fact that all Spanish autonomous communities were represented and with the anonymous nature of the survey that guarantees honest answers from respondents.

CONCLUSIONS

The survey on the needs of pPCI programs in Spain shows a high degree of satisfaction in the assessment of the system made by professionals, although with significant local and regional differences among the different autonomous communities. This survey has also allowed us to detect logistical, structural, and payment dysfunctions that may jeopardize the integrity of pPCI programs.

CONFLICTS OF INTEREST

R. Moreno is an Associate Editor of *REC: Interventional Cardiology*.

WHAT IS KNOWN ABOUT THE TOPIC?

- Over the last few years, several regional infarction care networks have been implemented in Spain with heterogeneous structure and functioning.
- There is no information on the professional perspective on how these networks work or on the degree of professional and personal satisfaction of the interventional cardiologists involved with these procedures.

WHAT DOES THIS STUDY ADD?

- The assessment of the Infarction Code initiative in terms of benefits for the patient and professional satisfaction is fairly good, although there are significant regional differences in the way professionals perceive this satisfaction.
- There is generalized feeling that there is room for improvement in terms of patient care and infrastructure, hours of rest after activation, and pay per on-call duty.
- Under the actual conditions, over half of the respondents said they would consider leaving these on-call mandatory programs once they become of an age when they won't be eligible anymore.

ANNEX 1. LIST OF PUBLIC HOSPITALS PER AUTONOMOUS COMMUNITY (INFORMATION ON THE WORKING CENTER WAS NOT PROVIDED IN 8 SURVEYS)

- Andalusia: *Hospital Universitario Virgen Macarena, Hospital Universitario Virgen del Rocío, Hospital Universitario Virgen de las Nieves, Hospital Universitario de Jerez, Hospital Universitario Reina Sofía, Hospital Punta de Europa, Hospital Regional de Málaga, Hospital Universitario San Cecilio, Hospital Costa del Sol, Hospital Juan Ramón Jiménez, Hospital Universitario de Jaén, Hospital Universitario Puerta del Mar, Hospital Universitario Puerto Real, Hospital Universitario Virgen de Valme, Hospital Universitario Virgen de la Victoria,* and *Hospital Universitario Torrecárdenas.*
- Aragon: *Hospital Universitario Miguel Servet*, and *Hospital Clínico Universitario Lozano Blesa.*
- Canary Islands: *Hospital Universitario Nuestra Señora de Candelaria,* and *Hospital Universitario de Canarias.*

- Cantabria: *Hospital Universitario Marqués de Valdecilla.*
- Castile and León: *Hospital de León, Hospital Clínico Universitario de Valladolid, Hospital Clínico Universitario de Salamanca,* and *Hospital Universitario de Burgos.*
- Castile-La Mancha: H*ospital Virgen de la Salud, Hospital General Universitario de Ciudad Real, Hospital General Universitario de Albacete,* and *Hospital Universitario de Guadalajara.*
- Catalonia: *Hospital Universitari de Bellvitge, Hospital Universitari Germans Trias i Pujol, Hospital del Mar, Hospital Universitari Mútua Terrassa, Hospital de la Santa Creu i Sant Pau, Hospital Clínic de Barcelona, Hospital Universitari Joan XXIII,* and Hospital *Universitari Vall d'Hebrón.*
- Chartered Community of Navarre: *Complejo Hospitalario de Navarra.*
- Valencian Community: *Hospital de Alzira, Hospital General Universitari de Castelló, Hospital Clínic Universitari de València, Hospital Universitari i Politècnic La Fe, Hospital de Manises, Hospital Universitari Sant Joan d'Alacant, Hospital General Universitari d'Alacant*, and *Hospital Universitari de Torrevieja-Elche-Vinalopó.*
- Community of Madrid: *Hospital Universitario 12 de octubre, Hospital Universitario Fundación de Alcorcón, Hospital Clínico San Carlos, Hospital Universitario Fundación Jiménez Díaz, Hospital General Universitario Gregorio Marañón, Hospital Universitario La Paz, Hospital Universitario de La Princesa, Hospital Universitario Puerta de Hierro, Hospital Universitario Ramón y Cajal,* and *Hospital Universitario de Torrejón.*
- Extremadura: *Hospital Universitario Infanta Cristina*, and *Hospital Universitario de Cáceres.*
- Galicia: *Hospital Clínico Universitario de Santiago, Hospital Universitario de A Coruña, Hospital Universitario Lucus Augusti,* and *Hospital Álvaro Cunqueiro.*
- Balearic Islands: *Hospital Universitari Son Espases.*
- La Rioja: *Hospital San Pedro.*
- Basque Country: *Hospital Universitario Basurto, Hospital Universitario Cruces, Hospital Universitario Araba,* and *Hospital Universitario Donostia.*
- Principality of Asturias: *Hospital Universitario Central de Asturias,* and *Hospital Universitario de Cabueñes.*
- Region of Murcia: *Hospital Clínico Universitario Virgen de la Arrixaca.*

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Original article

Gender-related differences among patients with STEMI: a propensity score analysis

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ABSTRACT

***Introduction and objectives*:** Female sex is believed to be a significant risk factor for mortality among patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary interventions (pPCI).
Methods: We collected data on all consecutive STEMI patients treated with pPCI within 12 hours and compared the males vs the females. The primary endpoint was long-term mortality one month after hospital discharge. The secondary endpoint was 30-days mortality.
Results: From March 2006 to December 2016, 1981 patients underwent pPCI at our hospital, 484 (24.4%) were females. Compared with men, women were older (mean age 71.3 ± 11.6 vs 62.9 ± 11.8 years, $P < .001$), less smokers (26.7% vs 72.7%; $P < .001$), more diabetic (28.0% vs 22.3%; $P < .002$), more hypertensive (69.6% vs 61.3%; $P < .001$), presented more often with shock at baseline (13.2% vs 9.0%; $P = .006$), had longer symptoms-to-balloon time frames (5.36 ± 3.97 vs 4.47 ± 3.67 hours; $P < .001$). Also, women were less likely to receive glycoprotein IIb-IIIa inhibitors (59.5% vs 71.4%; $P < .001$) and stents (79.5% vs 86.6%; $P = .01$). During the 30-day and long-term follow-up (mean 4.9 ± 3.2 years) the female sex was associated with a higher mortality rate (8.9% vs 4.0%, $P < .001$ and 23.8% vs 18.4%, $P = .01$, respectively). After propensity score matching, 379 men and 379 women were selected. Female sex continued to be associated with a higher death rate at 30 days (9.5% vs 5.5%; $P = .039$) but not in the long term among survivors (25.6% vs 21.4%; $P = .170$).
Conclusions: Compared to men, women with STEMI undergoing pPCI had higher 30-day mortality rates. However, among survivors, the long-term mortality rate was similar. Even if residual confounding cannot be ruled out, this difference in the outcomes may be partially explained by biological sex-related differences.

Keywords: ST-segment elevation myocardial infarction. Primary angioplasty. Sex differences. Outcomes.

Diferencias relacionadas con el sexo en pacientes con IAMCEST: análisis por puntuación de propensión

RESUMEN

Introducción y objetivos: El sexo femenino se considera un importante factor de riesgo de mortalidad en el infarto agudo de miocardio con elevación del segmento ST (IAMCEST) tratado con intervención coronaria percutánea primaria (ICPp).
Métodos: Se analizó a todos los pacientes consecutivos con IAMCEST tratados con ICPp dentro de las primeras 12 horas, y se compararon varones y mujeres. El objetivo principal fue la mortalidad a largo plazo en los supervivientes después del primer mes del alta, y el objetivo secundario fue la mortalidad a los 30 días.

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Resultados: Desde marzo de 2006 hasta diciembre de 2016 se trató con ICPp 1.981 a pacientes, de los cuales 484 (24,4%) eran mujeres. En comparación con los varones, las mujeres tenían mayor edad (edad media 71,3 ± 11,6 frente a 62,9 ± 11,8 años, p < 0,001) y la frecuencia de fumadoras era más baja (26,7 frente a 72,7%; p < 0,001), mientras que era más alta la frecuencia de diabetes (28,0 frente a 22,3%; p < 0,002), hipertensión arterial (69.6 frente a 61,3%, p < 0,001) y *shock* al ingreso (13,2 frente a 9,0%; p = 0,006), y más largo el tiempo desde el comienzo de los síntomas hasta la intervención con balón (5,36 ± 3,97 frente a 4,47 ± 3,67 horas; p < 0,001). Además, la frecuencia de tratamiento con inhibidores de la glucoproteína IIb-IIIa (59,5 frente a 71,4%; p < 0,001) y *stent* (79,5 frente a 86,6%, p = 0,01) fue inferior. Tanto a los 30 días como a largo plazo (media 4,9 ± 3,2 años), el sexo femenino se asoció con una mortalidad más alta (8,9 frente a 4,0%, p < 0,001, y 23,8 frente a 18,4%, p = 0,01, respectivamente). Se seleccionaron 379 mujeres y 379 varones emparejados por puntuación de propensión. Se mantuvo la asociación entre sexo femenino y mayor mortalidad a los 30 días (9,5 frente a 5,5%; p = 0,039), pero no a largo plazo (25,6 frente a 21,4%; p = 0,170).
Conclusiones: En comparación con los varones, las mujeres con IAMCEST tratadas con ICPp tuvieron mayor mortalidad a los 30 días. Sin embargo, entre los supervivientes, la mortalidad a largo plazo fue similar. Aunque no puede descartarse el efecto de variables residuales de confusión, las diferencias en el pronóstico podrían explicarse en parte por diferencias biológicas relacionadas con el sexo.

Palabras clave: Infarto agudo de miocardio con elevación del segmento ST. Angioplastia primaria. Diferencias por sexo. Pronóstico.

Abbreviations

pPCI: primary percutaneous coronary interventions. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Primary percutaneous coronary interventions (pPCI) have proven superior to fibrinolytic therapy for the management of patients with ST-segment elevation myocardial infarction (STEMI)[1-3] becoming the treatment of choice in this field.[4] However, the question of whether there are any prognostic differences between women and men is still under discussion. Yet despite the fact that in recent studies women exhibit higher mortality rates,[5] it is not clear if these differences are associated with worse risk profiles or with a sex-related frailty. Indeed, some studies have not shown any significant relationships between sex and mortality in STEMI, even after adjusting for age and other risk factors.[6] Actually, only a limited number of studies have described medium or long-term mortality outcomes and differences in the inclusion criteria (ie, the entire acute coronary syndrome spectrum or only the STEMI subset) and in the therapeutic strategies (ie, medical or interventional) might explain these different findings. The goal of this large, single-center registry was to assess whether in consecutive patients with STEMI undergoing pPCI there were any differences between men and women in the clinical, angiographic, procedural characteristics, and clinical outcome at 30 days or in the long-term.

METHODS

All consecutive patients admitted to our center between January 2006 and December 2016 with a diagnosis STEMI treated with pPCI within 12 hours of symptom onset were recruited. The baseline features (age, sex, burden of cardiovascular risk factors, time from symptoms onset to balloon) were collected along with the procedural characteristics (target vessel, site and type of lesion, pharmacological treatment, thrombus aspiration, type of stent). All interventions were performed following the actual standards of PCI, and the treatment choice was left at the discretion of the operator who performed the procedure. All patients were routinely treated with aspirin (325 mg upon arrival, and then 100 mg daily indefinitely), and an IV bolus of unfractionated heparin (5000 IU). The use of bivalirudin (0.75 mg/kg and 1.75 mg/kg/h at least to the end of the procedure), or unfractionated heparin (100 U/kg or 60 U/kg if abciximab was used) or abciximab was left at the operator's discretion. When used, the infusion of abciximab was extended for another 12 hours after the procedure. A loading dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) was administered before or immediately after the PCI, unless patients were already on chronic maintenance therapy, and then followed by a maintenance dose of clopidogrel (75 mg once a day), prasugrel (10 mg once a day), or ticagrelor (90 mg twice a day) for 12 months when possible. Repeated revascularization was only performed in the presence of symptom recurrence or proven ischemia related to the treated lesion.

Data on the 30-day follow-up were available for all patients at our center database. Information beyond the first month was collected through outpatient visits, telephone calls or by reviewing any available medical records to obtain the longer follow-up for each patient. All data were entered into a dedicated database.

The men vs women outcomes before and after the propensity score matching were compared. The primary endpoint was long-term mortality after hospital discharge. The secondary endpoint was 30-day mortality rate, 30-day and long-term Bleeding Academic Research Consortium bleeding type ≥ 2.[7] Long-term events were evaluated starting from day 31 after discharge until the longer available follow-up. The rate of procedural efficiency (defined a Thrombolysis in Myocardial Infarction [TIMI] III grade flow and residual stenosis < 30%) and ST-segment resolution of more than 50% 60–90 minutes after the PCI was also collected and reported.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median (Q1-Q3), according to the normality of their distribution. Qualitative variables were expressed as frequencies and percentages. The Fisher's exact test or the chi-square test were used for qualitative variables while the Student's t test or the Mann-Whitney U test were used for quantitative variables as appropriate. Survival data were represented and analyzed using the Kaplan-Meier curves and the Cox regression analysis. All statistical tests were 2-sided. Results were considered significant if *P* values < .05. Given the baseline differences between female and male patients and in order to reduce selection bias, we used propensity score matching. The logistic regression model was used based on the baseline and peri-percutaneous coronary intervention characteristics. Thus, *P* values < .20 were defined to include the selected variables in the final model. The selected variables were

Table 1. Baseline features

		Raw			Matched		
	Overall (n = 1981)	**Female (n = 484; 24.4%)**	**Male (n = 1497; 75.6%)**	***P***	**Female (n = 379)**	**Male (n = 379)**	***P***
Age	65.0 ± 12.3	71.3 ± 11.6	62.9 ± 11.8	< .001	68.5 ± 11.9	69.2 ± 11.6	.43
Age > 80 years	262 (13.2)	134 (27.7)	128 (8.6)	< .001	69 (18.2)	75 (19.8)	.58
Diabetes mellitus[a]	469 (23.7)	135 (27.9)	334 (22.3)	.002	63 (16.6)	74 (19.5)	.29
Hypertension[b]	1254 (63.3)	337 (69.6)	917 (61.3)	.001	227 (59.9)	240 (63.3)	.33
Dyslipidemia[c]	742 (37.5)	182 (37.6)	560 (37.4)	.93	134 (35.4)	142 (37.5)	.54
Obesity[d]	307 (15.5)	113 (23.3)	194 (13.0)	< .001	64 (16.9)	66 (17.4)	.85
Chronic kidney failure[e]	53 (2.7)	17 (3.5)	36 (2.4)	.19	23 (6.1)	23 (6.1)	1.00
Smoking (current or former smoker)	1217 (61.4)	129 (26.7)	1088 (72.7)	< .001	129 (34.0)	129 (34.0)	1.00
Cardiogenic shock at presentation	198 (10.0)	64 (13.2)	134 (9.0)	.006	56 (14.8)	43 (11.3)	.16
Oral intubation	116 (5.9)	31 (6.4)	85 (5.7)	.56	26 (6.9)	23 (6.1)	.66
Cardiac resuscitation at presentation	21 (1.1)	8 (1.7)	13 (0.9)	.14	7 (1.8)	8 (2.1)	.79
Left ventricular ejection fraction (%)	48.4 ± 10.0	46.8 ± 10.0	48.5 ± 10.0	.007	47.5 ± 9.4	47.3 ± 9.6	.83
Left ventricular ejection fraction < 35%	202 (10.2)	69 (14.3)	133 (8.9)	.001	43 (11.3)	44 (11.6)	.91
Total ischemia time	4.7 ± 3.8	5.4 ± 4.0	4.5 ± 3.7	< .001	4.4 ± 3.7	4.6 ± 4.0	.13
Anterior wall infarct location	877 (44.3)	217 (44.8)	660 (44.1)	.82	165 (43.5)	165 (43.5)	1.00

[a] American Heart Association Guidelines definition.
[b] Arterial systemic pressure ≥ 140/90 mmHg.
[c] Total cholesterol ≥ 200 mg/dL; low density lipoproteins ≥ 130 mg/dL; triacylglycerol ≥ 175 mg/dL.
[d] Body mass index > 30.
[e] Dialysis o serum creatinine > 2 mg/dL.
Values are expressed as mean ± standard deviation or frequencies (percentages).

age, smoking habit, hypertension, dyslipidemia, diabetes mellitus type 2, obesity, severe chronic renal failure, shock at presentation, cardiac resuscitation at presentation, ejection fraction < 35%, anterior wall myocardial infarct location, femoral access, use of bivalirudin, use of glycoprotein IIb-IIIa inhibitors, percutaneous transluminal coronary angioplasty on the left main coronary artery, use of counterpulsation, thrombectomy, use of drug-eluting stents and total ischemic time. Using these covariates, propensity score was calculated for each patient. Each female patient was matched using 1:1 nearest neighbor matching with a patient from the control group (male) with the same propensity score. The maximum difference (caliper) in the match propensity scores was < 0.15. The standardized mean differences were estimated before and after the matching and balance between both matched cohorts was assessed using the Hotelling T-squared test. Using this technique, 2 comparable groups of 379 patients each were obtained for final analysis. All standardized mean differences after matching were below 10%. Calibration was tested using the Hosmer-Lermeshow test and accuracy was assessed using the area under the ROC curve. Statistical analyses were performed using SPSS 21 statistical software package (IBM software). Propensity score matching was performed using the MatchIt package of R software (version 3.0.2).

RESULTS

From March 2006 to December 2016, among the 1981 patients who underwent pPCIs at our hospital, 484 (24.4%) were females (table 1). Compared to men, women were older (mean age 71.3 ± 11.6 vs 62.9 ± 11.8 years; $P < .001$), there were fewer female smokers (26.7% vs 72.7%; $P < .001$), they were more diabetic (28.0% vs 22.3%; $P < .002$), more hypertensive (69.6% vs 61.3%; $P < .001$), and they presented more frequently with cardiogenic shock at admission (13.2% vs 9.0%; $P = .006$). They also had longer symptoms-to-balloon time (5.36 ± 3.97 vs 4.47 ± 3.67 hours; $P < .001$) and lower left ventricular ejection fractions (46.8 ± 10% vs 48.5 ± 10%; $P = .007$). Also, as shown on table 2, women were less likely to be treated with glycoprotein IIb-IIIa inhibitors (59.5% vs 71.4%; $P < .001$), thrombus aspiration devices (48.3% vs 58.0%, $P < .001$) and stents (79.5% vs 86.6%; $P = .01$). Procedural efficiency and ST-resolution were significant lower in the female cohort (93.0 vs. 97.1%, $P < .001$ and 60.0 vs 65.8%, $P = .033$, respectively, and table 3).

At the 30-day and long-term follow-up (mean 4.9 ± 3.2 years, completed in 1634, 82.5% patients) the female sex was associated with a higher mortality rate (8.9% vs 4.0%, $P < .001$ and 23.8% vs 18.4%, $P = .01$, respectively) and a higher rate of major bleedings at 30 days (4.5% vs 1.4%; $P = .002$).

After propensity score matching, 379 men and 379 women were selected. The baseline and peri-procedural characteristics of the propensity-matched pairs were identical (table 1, table 2, figure 1, figure 2, and table 1 and table 2 of the supplementary data). In this cohort, female sex continued to be associated with a lower procedural efficiency (94.4% vs 90.2%; $P = .039$) and a higher rate of major bleedings and death at 30 days (9.5% vs 5.5%, $P = .039$ and 4.2% vs 1.6%, $P = .007$). Conversely, in the matched

Table 2. Angiographic and periprocedural features

		Raw			Matched		
	Overall (n = 1981)	Female (n = 484; 24.4%)	Male (n = 1497; 75.6%)	*P*	Female (n = 379)	Male (n = 379)	*P*
Multivessel disease	1055 (53.3)	259 (53.5)	796 (53.2)	.90	194 (51.2)	195 (51.5)	.94
Graft disease	6 (0.3)	2 (0.4)	4 (0.3)	.62	1 (0.3)	2 (0.5)	.56
Radial access	371 (18.7)	82 (16.9)	289 (19.3)	.25	58 (15.3)	57 (15.0)	.92
Use of GP IIb-IIIa	1357 (68.5)	288 (59.5)	1069 (71.4)	< .001	251 (66.2)	242 (63.9)	.49
Bivalirudin	210 (10.6)	61 (12.6)	149 (9.9)	.12	35 (9.2)	45 (11.9)	.24
Multivessel PCI	93 (4.7)	25 (5.2)	68 (4.5)	.57	20 (5.3)	18 (4.7)	.74
PCI on left main coronary artery	64 (3.2)	17 (3.5)	47 (3.1)	.69	13 (3.4)	13 (3.4)	1.00
Aortic counterpulsation	251 (12.7)	69 (14.3)	182 (12.2)	.23	57 (15.0)	49 (12.9)	.40
Thrombus aspiration	1102 (55.6)	234 (48.3)	868 (58.0)	< .001	203 (53.6)	193 (50.9)	.47
Stent implantation	1682 (84.9)	385 (79.5)	1297 (86.6)	.01	314 (82.9)	318 (83.9)	.58
Drug-eluting stent implantation	832 (42.0)	194 (40.0)	658 (43.9)	.09	148 (39.0)	152 (40.1)	.77

GP, glycoprotein; PCI, percutaneous coronary intervention.
Values are expressed as mean ± standard deviation or frequencies (percentages).

Table 3. Outcomes

		Raw			Matched		
	Overall (n = 1981)	Female (n = 484; 24.4%)	Male (n = 1497; 75.6%)	*P*	Female (n = 379)	Male (n = 379)	*P*
Procedural efficacy	1903 (96.1)	450 (93.0)	1453 (97.1)	< .001	342 (90.2)	358 (94.4)	.039
ST-segment resolution > 50%	1086 (64.4)	243 (60.0)	843 (65.8)	.033	180 (47.5)	205 (54.1)	.07
30-day BARC bleeding type ≥ 2	27 (2.1)	22 (4.5)	21 (1.4)	.002	16 (4.2)	6 (1.6)	.007
Long-term BARC bleeding type ≥ 2	41 (2.1)	21 (4.3)	20 (1.3)	< .001	13 (3.4)	7 (1.8)	.257
30-day mortality rate	103 (5.2)	43 (8.9)	60 (4.0)	< .001	36 (9.5)	21 (5.5)	.039
Overall mortality at long-term follow-up	390 (19.7)	115 (23.8)	275 (18.4)	.01	97 (25.6)	81 (21.4)	.170

Values are expressed as frequencies (percentages).
BARC, Bleeding Academic Research Consortium.

cohort no significant differences were found in the long-term mortality rate among survivors (25.6% vs 21.4%, *P* = .170, table 3; and log-rank *P* = .23, figure 3). The multiple Cox regression analysis revealed that age (hazard ratio [HR], 1.09; (1.06 – 1.12); *P* < .001), cardiogenic shock at presentation (HR, 6.82 (3.84 – 12.12); *P* < .001), the left ventricular ejection fraction < 35% (HR, 1.98 (1.11 – 3.54); *P* = .022) and procedural efficacy (HR, 0.46 (0.23 – 0.89); *P* = .022) have an effect on mortality when included together with female sex (HR, 0.68 (0.42 – 1.09); *P* = .106), which is not significant as stated before (table 4).

Main outcome analysis was performed based on a 2-time period (2006-2010 and 2011-2016) without underlining any differences among the groups (table 2 of the supplementary data).

DISCUSSION

Our large single-center registry showed that in a high PCI volume center, women admitted with STEMI undergoing pPCI have a higher 30-day and long-term mortality rate compared to men. This difference persists after propensity score adjustment regarding the 30-day mortality.

A drop in cardiovascular mortality has been observed over the

Table 4. Multiple regression analysis

	HR (95%CI)	*P*
Female sex	0.68 (0.42 – 1.09)	.106
Age	1.09 (1.06 – 1.12)	< .001
Cardiogenic shock at presentation	6.82 (3.84 – 12.12)	< .001
Left ventricular ejection fraction < 35%	1.98 (1.11 – 3.54)	.022
Procedural efficacy	0.46 (0.23 – 0.89)	.022

95%CI, 95% confidence interval; HR, hazard ratio.
Cox proportional hazard model for overall mortality at long term follow-up.

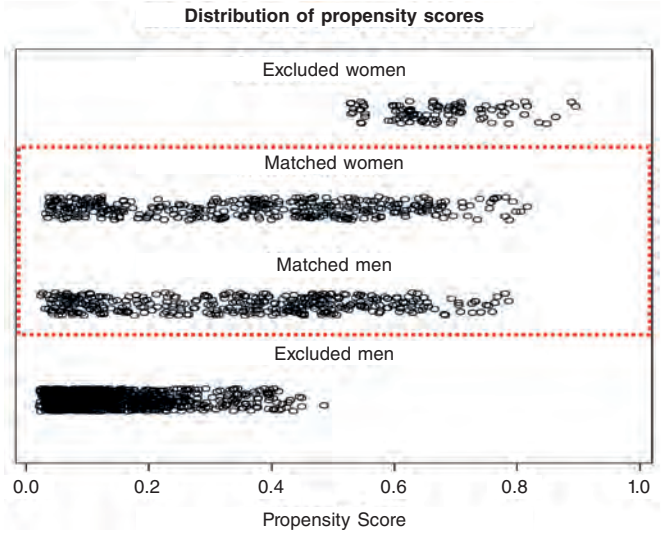

Figure 1. Distribution of propensity scores. Propensity score goes between 0 and 1 and several variables are included in its estimation. It serves as a tool for measuring the similarities among patients. Therefore, matched female and male patients show similar distributions of propensity scores and a wide range, covering all types of patients. Unmatched propensity score units lay on opposite extremes, as expected.

last few decades, but cardiovascular disease is still the leading cause of mortality in women worldwide. Cardiovascular mortality remains higher in women compared to men.[5] So far, the reasons of this difference have been mainly justified by the higher prevalence of traditional risk factors (higher mean age, hypertension, diabetes, and renal failure) in the female cohort.[6] Also, women who experience myocardial infarction often present with atypical symptoms like dyspnea, fatigue, nausea/vomiting and atypical chest pain, which can lead to delayed diagnosis and treatment.[8]

Another factor associated with a higher mortality rate to be taken into account is represented by bleeding and mechanical complications, more common in women compared to men.[9-11] Our study confirmed all these data: in our population, women were significantly older, with more traditional risk factors (except for smoking), longer ischemic time frames and higher-risk presentations. Also, they had a significantly higher rate of bleeding and mechanical complications.

After propensity score adjustment, out study showed that female sex was independently associated with 30-day but not long-term mortality. These findings are similar to those of a recent large meta-analysis led by Conrotto et al.,[12] that included 98 778 patients (73 559 men and 25 219 women) and could be explained, at least in part, by the different pathophysiology of coronary disease in women: the rupture of the plaque surface, the leading cause of coronary occlusion in men, happens only in around 50% of women,[13] the remaining percentage being represented by the erosion of the plaque,[14] coronary spasm leading to thrombus generation,[15] and spontaneous coronary artery dissection.[16] Particularly spontaneous coronary artery dissection seems to play an important role in younger women (< 60 years of age) and is associated with a high rate of major adverse cardiac events.[17] Therefore, these findings may explain why, in our population, women had lower rate of thrombus aspiration, use glycoprotein IIb-IIIa inhibitors, and stent implantation, which in turn may justify, along with the clinical features, the lower procedural success and ST-segment resolution observed in our study. These factors, associated with the higher rate of bleedings and mechanical complications and other psychological factors, like depression, more prevalent in women compared to men in the general population,[18,19] may be phenotypes of a higher frailty in the female sex, and may definitely explain the worse outcomes, at least in the short-term. At long-term, other factors, like the lower in-stent restenosis rate and the resulting lower need for target vessel revascularization observed in women, and already shown in some studies,[20-23] may explain the similar outcomes observed in the propensity score analysis.

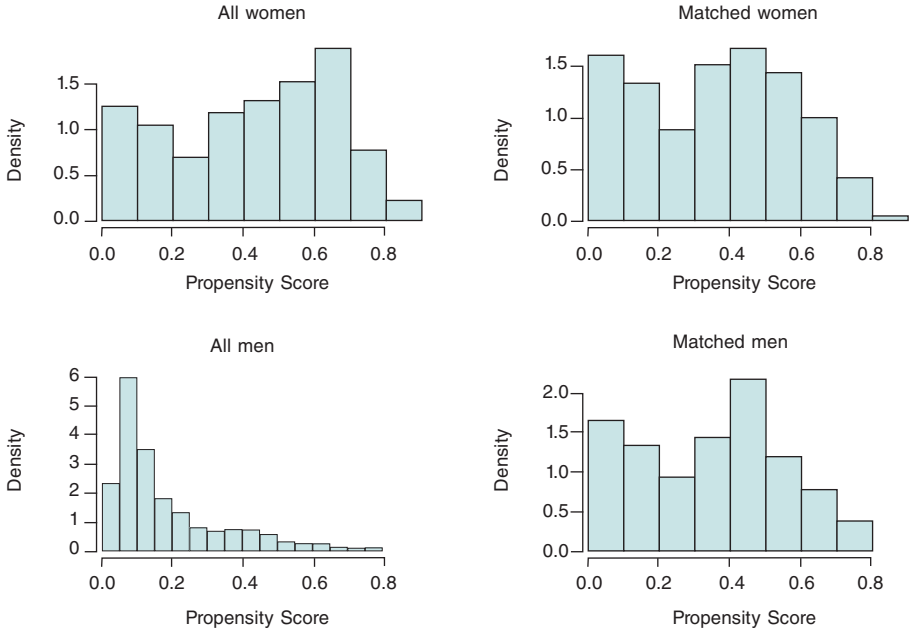

Figure 2. Distribution of propensity score before and after the matching.

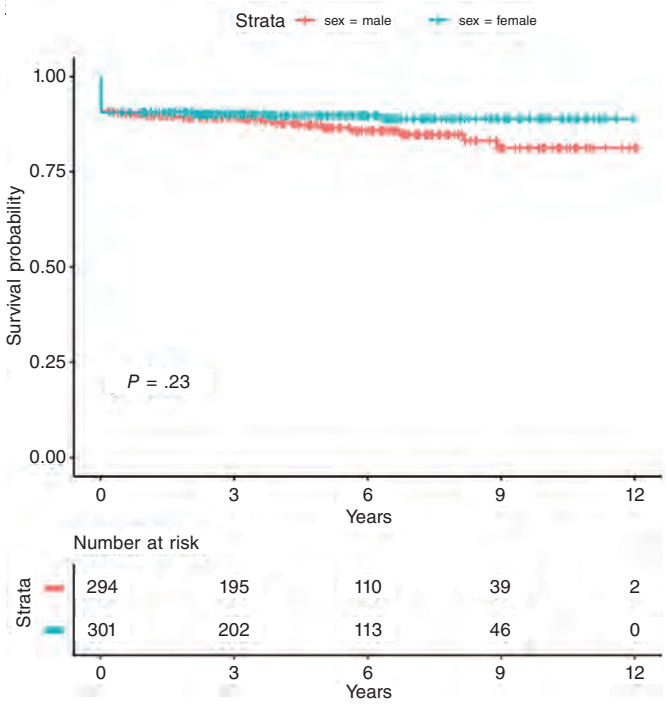

Figure 3. Kaplan-Meier curve for long-term mortality based on sex. There is no difference on the long-term mortality rate between female and male patients in the matched population.

Limitations

This study has some important limitations; first, even though is a retrospective analysis, it is based on a prospective and dedicated database with propensity score matched analysis. Secondly, data are derived from a single center, which limits their applicability. For example, the use of drug-eluting stents was lower than it is actually is, mainly because the time frame of the study is wide. Actually, from 2006 to 2010 the percentage of drug-eluting stents was about 15% while during the second period (2011-2016), we found 65% of cases with drug-eluting stent implantation. Finally, due to the time frame of the data collection, most procedures were performed via femoral artery access, so we can assume that radial access could have lowered the rate of access bleeding complications, but we need further randomized studies targeted at the female population before being able to validate this hypothesis. However, this is probably a representative sample of an all-comers STEMI population who undergo pPCI in the real world.

CONCLUSIONS

In conclusion, in our single-center cohort of patients and after propensity score adjustment, women with STEMI undergoing pPCI seem to have a higher 30-day mortality rate but similar long-term outcomes after discharge compared to men. Even if residual confounding cannot be ruled out, this difference in the outcomes may be partially explained by biological sex-related differences.

CONFLICT OF INTERESTS

None of the authors have declared any conflicts of interests related to the present article.

WHAT IS KNOWN ABOUT THE TOPIC?

- Women have a higher ACS-related mortality rate but there is no consensus on whether to consider female sex as a risk factor of poor outcomes. This is due to the fact that many authors explain this sex difference by the atypical onset of symptoms in women and the lower recurrence to cath. lab procedures and angioplasties performed in females. However, only a limited number of studies have reported medium or long-term mortality results and even fewer studies have had clear inclusion criteria (ie, the entire acute coronary syndrome spectrum or only the STEMI subset) or reported on the treatment strategies used.

WHAT DOES THIS STUDY ADD?

- Our large single-center registry showed that in a high PCI volume center, women admitted with STEMI to undergo pPCI have a higher rate of 30-day and long-term mortality compared to men. This difference persisted even after propensity score adjustment on the the 30-day mortality, which may be justified by the higher frailty of the female sex, which could in turn explain the worse outcomes seen, at least, in the short-term.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000061.

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Original article

Functional assessment of intermediate lesions of collateral donor artery in chronic total coronary occlusions

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ABSTRACT

Introduction and objectives: The strategy of the percutaneous treatment of patients with multivessel disease associated with chronic total coronary occlusion (CTO) lesions is not well defined. Also, the functional significance of lesions located in the collateral donor artery has not been fully addressed. Using the fractional flow reserve (FFR) the objective was to evaluate the amount of ischemia related to the angiographically intermediate stenosis of collateral donor vessels before and immediately after successful percutaneous coronary intervention (PCI) of a CTO. Also, to assess any changes operated in the amount of ischemia using cardiovascular magnetic resonance imaging prior to the PCI and at 1-month follow-up.
Methods: Prospective pilot study including 14 patients with stable angina and a CTO receiving collateral circulation from a blood vessel with intermediate stenosis (50%-70% diameter stenosis measured using quantitative angiography). In order to indicate recanalization by PCI all patients were referred for magnetic resonance assessment of the presence of myocardial viability.
Results: Seven (50%) of the 14 patients included showed FFR values ≤ 0.80 before the PCI. FFR measures of the donor artery significantly increased after the revascularization of the CTO (0.75 [0.73-0.78] vs 0.83 [0.81-0.84]; *P* = .017). Eventually, only 3 patients showed hemodynamically significant FFR values after the recanalization of CTO requiring further revascularization. There was a tendency towards a reduction of the number of ischemic segments (2.5 [0-4] vs 0 [0-0.25]; *P* = .066) assessed using magnetic resonance imaging before and after the PCI. No major adverse cardiovascular events were reported at the 2-year follow-up.
Conclusions: Our data suggest that FFR measurements in intermediate stenoses of collateral donor vessels of a CTO may be misleading. Therefore, the strategy of focusing primarily on the revascularization of the CTO and then on the assessment of the intermediate lesion in a collateral donor vessel may be recommended.

Keywords: Chronic total coronary occlusion. Collateral donor vessel. Fractional flow reserve. Cardiovascular magnetic resonance imaging.

Evaluación funcional de lesiones intermedias en arterias donantes de colaterales en oclusiones totales crónicas

RESUMEN

Introducción y objetivos: La estrategia de tratamiento percutáneo de los pacientes con enfermedad multivaso y oclusión total crónica (OTC) no está bien definida. La importancia funcional de las lesiones localizadas en arterias donantes de colaterales no se ha abordado por completo. Nuestro objetivo fue evaluar mediante reserva fraccional de flujo (RFF) la cantidad de isquemia dependiente de una lesión angiográfica intermedia en un vaso donante de colaterales antes y después de la recanalización de la OTC, y valorar el cambio en la cantidad de isquemia por resonancia magnética cardiaca (RMC) antes y 1 mes después de la recanalización.
Métodos: Estudio piloto prospectivo en 14 pacientes con angina estable y una OTC que recibía circulación colateral de un vaso con una estenosis intermedia (50-70% por angiografía coronaria cuantitativa). Para indicar la revascularización, todos los pacientes presentaban viabilidad miocárdica por RMC.
Resultados: De los 14 pacientes, 7 (50%) evidenciaron una RFF ≤ 0,80 antes de la recanalización. Los valores medios de RFF de la arteria donante aumentaron significativamente tras la revascularización de la OTC (0,75 [0,73-0,78] frente a 0,83 [0,81-0,84]; p = 0,017). Solo 3 pacientes mostraron valores de RFF hemodinámicamente significativos después de la recanalización de una OTC que requirió revascularización adicional. Hubo una tendencia hacia una reducción del número de segmentos isquémicos (2,5 [0-4] frente a 0 [0-0,25]; p = 0,066) evaluados por RMC antes y después del intervencionismo. No se observaron eventos cardiacos adversos mayores durante el seguimiento de 2 años.

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Conclusiones: Las mediciones de RFF en estenosis intermedias de vasos donantes de colaterales de una OTC pueden ser engañosas. En estos casos podría plantearse la estrategia de centrarse primero en la revascularización de la OTC y después en la evaluación de la lesión intermedia del vaso donante.

Palabras clave: Oclusión total crónica. Reserva fraccional de flujo. Resonancia magnética cardiaca. Vaso colateral donante.

Abbreviations

CMR: cardiovascular magnetic resonance imaging. **CTO:** chronic total coronary occlusion. **FFR:** fractional flow reserve. **PCI:** percutaneous coronary intervention.

INTRODUCTION

The prevalence of chronic total coronary occlusions (CTO) is around 16% to 52% in patients with significant coronary artery disease on the angiography.[1] In the presence of a CTO, collateral blood supply is often enought to maintain resting perfusion and contractility in the collateral-dependent myocardium.[2] Restoration of antegrade flow by the percutaneous coronary intervention (PCI) of a CTO is associated with a rapid reduction in the collateral supply received in the treated vessel.[3]

Randomized trials support the use of fractional flow reserve (FFR) to guide the PCI with an established treatment threshold of ≤ 0.8.[4-8] Although the FFR is reported to be independent of hemodynamic changes,[9] it is intimately related to total coronary flow through a stenosis, which in turn is related to perfused myocardial mass.[10] In keeping with this, there have been several reports of normalization of FFR values from collateral donor vessel after successful recanalization of a CTO.[11] By removing nutrient flow to the collateralized territory by CTO recanalization, the collateral network almost immediately increased its resistance, thus favoring flow to the donor territory during maximal hyperemia.[12]

In patients with Rentrop grade-2 or grade-3 collateral flow, the FFR value of the donor artery increased at least 0.10 after revascularization of the recipient artery. However, the FFR value did not change significantly in patients with Rentrop grade-0 or grade-1 collateral flow following revascularization. This suggests that well-developed collateral circulation might overestimate the FFR value in the donor artery with mild stenosis.[13]

The assessment of myocardial-perfusion through cardiovascular magnetic resonance imaging (CMR) is a noninvasive imaging modality for the detection of coronary artery disease with a high degree of concordance with the FFR for ischemia detection.[14-16] Also, the CMR has emerged as robust and reproducible method to assess the ischemia and viability of the myocardium related to the CTO.[17-19] The MR-INFORM trial showed that in patients with stable angina and risk factors for coronary artery disease, the CMR of myocardial perfusion was associated with a lower incidence of coronary revascularization compared to the FFR and was noninferior to the FFR regarding major adverse cardiovascular events (all-cause mortality, non-fatal myocardial infarction or target-vessel revascularization) at 12 months.[20] However, it is uncertain whether opening a CTO can modify the amount of ischemia related to an angiographically intermediate lesion of the collateral donor vessel. It could also be possible to diagnose microvascular dysfunction using CMR.[21]

Therefore, in this pilot study, using the FFR we assessed changes in the amount of ischemia related to the angiographically intermediate stenosis of collateral donor vessel before and immediately after the successful PCI of a CTO. We also tried to determine any changes in the amount of ischemia using the CMR prior to the PCI and 1 month after recanalization.

METHODS

In this prospective pilot study, we included patients with stable angina and CTO with collateralization of the distal vascular bed, and collateral donor vessel with a single angiographically intermediate lesion (50%-70% diameter stenosis by quantitative coronary angiography). In order to indicate recanalization through PCI all patients were referred for CMR evaluation to assess the presence of myocardial viability. During the procedure, the FFR of the donor vessel was measured before the PCI of the CTO (figure 1). Only with FFR values ≤ 0.80, the measure was reassessed after the procedure (figure 2). A second CMR was performed 1 month after the index PCI. All patients gave their informed consent, the local ethics committee approved the study, and all procedures were performed in accordance with the Helsinki Declaration. The study population was clinically followed for 2 years. The rate of major adverse cardiovascular events was established. This was defined as a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI), clinically-driven target vessel revascularization or rehospitalization due to unstable or progressive angina according to Braunwald Unstable Angina Classification. The exclusion criteria were: prior IAM; failed recanalization of the CTO, inability to obtain signed written informed consents; severity of valvular heart disease; acutely decompensated chronic heart failure; asthma or obstructive sleep apnea; high risk of bleeding; known hypersensitivity or contraindication to aspirin; nursing subjects; patients with pacemakers/implantable cardioverter-defibrillators.

The percutaneous coronary intervention

The PCI was performed using bilateral femoral artery access and 7-Fr sheaths and guide catheters. Anticoagulation was achieved with 100 U/Kg of unfractionated heparin to maintain activated clotting times of 250-300 msec. All the procedures on the CTO were performed using the antegrade wire escalation technique. All patients were treated with drug-eluting stent implantation. The J-CTO score was calculated for each CTO lesion and assessed taking the following parameters into consideration: occlusion

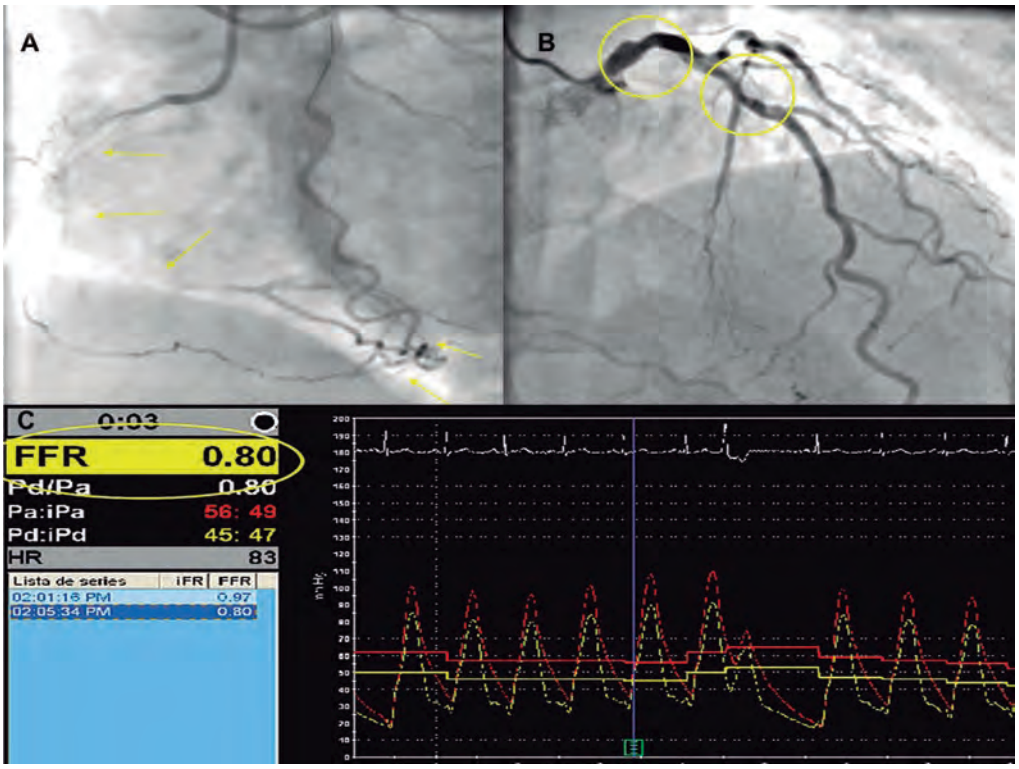

Figure 1. Example of chronic total coronary occlusion (CTO) of right coronary artery (**panel A**, yellow arrows) with collateralization of distal vascular bed, and left main and left anterior descendent artery (LAD) as the collateral donor vessel shows an angiographically intermediate lesion (**panel B**, yellow circles). During the procedure, the fractional flow reserve (FFR) of the donor vessel was measured before the percutaneous coronary intervention of the CTO **(panel C)**.

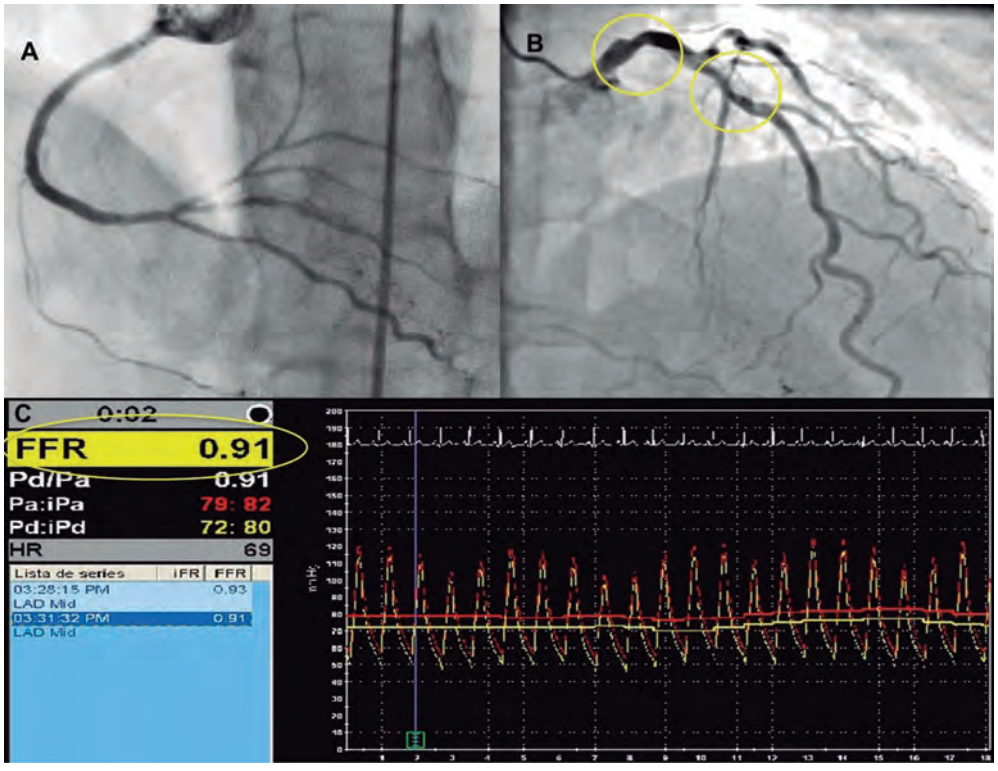

Figure 2. Example of the recanalization of chronic total coronary occlusion (CTO) of the right coronary artery **(panel A)** with left anterior descendent artery (LAD) as the collateral donor vessel shows an angiographically intermediate lesion (**panel B**, yellow circles). **Panel C:** after the CTO repermeabilization, the fractional flow reserve (FFR) value of the LAD increased (FFR value = 0.91).

length, stump morphology, presence of calcification, presence of tortuosity and prior attempt to open the CTO.[22] Collateral flow was graded in accordance with Rentrop collateral flow classification.[23] Procedural success was defined as achievement of residual post-PCI stenosis < 30% in the target lesion associated with TIMI grade-3 flow without mortality, IAM or new lesion revascularization during the index hospitalization.

Assessment using fractional flow reserve

To measure FFR in the intermediate coronary lesions a 0.014-inch pressure-monitoring guidewire (Prime Wire Volcano Therapeutics, Inc, Rancho Cordova, CA, United States) was used. After calibration of both the aortic and wire pressures, the FFR wire was advanced until the tip of the guiding catheter. Equalization of both pressures was performed. Then, the wire was advanced and positioned distally at least 15 mm from the stenotic lesion followed by the administration of 0.2 mg of nitroglycerin to avoid any form of epicardial vasoconstriction. Maximal hyperemia was induced through the IV infusion of adenosine (180 µg/kg/min). After reaching the steady state we measured the FFR as the ratio between mean distal coronary pressure and mean aortic pressure. Values < 0.80 were considered significant from the hemodynamical standpoint. After FFR measurement and under maximal hyperemia, the pressure wire was pulled back until the sensor was close to the tip of the guiding catheter to make sure that no drift had occurred.

Cardiovascular magnetic resonance imaging

All CMR studies were performed using a General Electric Signa HDxt 1.5-T scanner equipped with an 8-channel coil and cardiac-dedicated software. Perfusion studies were conducted using a gradient-echo turbo-field sequence prescribed in the left ventricular short-axis orientation, at the basal, mid-ventricular and apical levels after 4 min of IV administration of adenosine (Atepo-din) at a dose of 180 µg/kg/min and simultaneous administration of 0.1 mmol/kg of gadobutrol (Gadovist, Bayer Hispania) at a 5 mL/s rate. The functional and volumetric assessment of the left ventricle (LV) was conducted using the conventional Steady State Free Precession (SSFP) cine sequence, prescribed in sequential short-axis slices, and encompassing the entire LV and the 2-, 3-, and 4-chamber views. The typical temporal and in-plane spatial resolution of these images was 40 ms and 1.4 × 1.4 mm, respectively. Rest perfusion images were obtained at least 10 min after the stress perfusion study using the same sequence, location, and contrast injection protocol. Ten minutes after administering the dose of gadolinium for the rest perfusion study, late gadolinium-enhanced images were obtained using a segmented inversion-recovery spoiled gradient echo sequence in the same location and identical spatial resolution as the cine images. To calculate left ventricular ejection fraction (LVEF), the LV mass and left ventricular end-systolic and end-diastolic volumes, the endocardial and epicardial borders were manually traced at end-systole and end-diastole in the cine short-axis images using a dedicated software package (ReportCard, GE). The regional wall motion analysis was performed by visual grading of the cine images according to the 17-segment model proposed by the American Heart Association.[17] The pre- and post-PCI image analysis was conducted by 2 independent experienced operators masked to the patient's coronary anatomy and the PCI results; the disparities in their evaluation were resolved by consensus with a third independent operator. The appropriate allocation between the involved myocardial segments and the correspondent coronary anatomy in each case was evaluated according to previously reported criteria.[18]

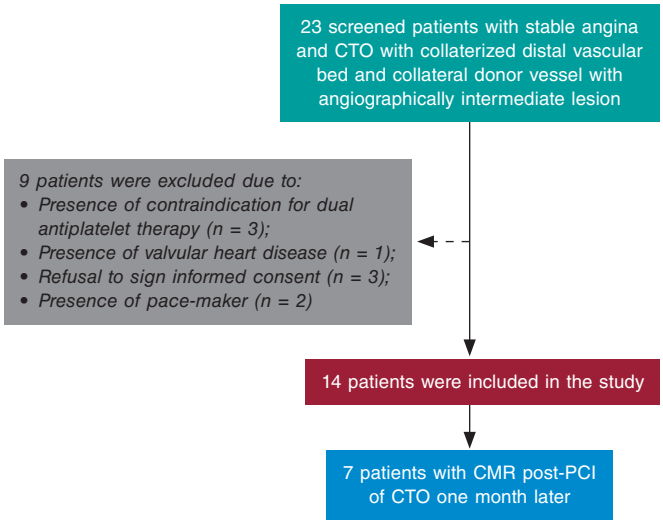

Figure 3. We screened 23 patients with stable angina and chronic total occlusion (CTO) with collateralization of distal vascular bed, and collateral donor vessel with angiographically intermediate lesion; 9 of them were excluded after meeting the exclusion criteria. In particular, 3 contraindications for dual antiplatelet therapy, 1 valvular heart disease requiring surgery, 3 refusals to sign the informed consent, and 3 pacemakers. CMR, cardiovascular magnetic resonance; PCI, percutaneous coronary intervention.

Statistical analysis

The distribution of continuous variables was assessed by visual inspection of frequency histograms and using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) when they followed a normal or non-normal distribution, respectively. The continuous variables were compared using the unpaired Student *t* test or Mann–Whitney *U* test and the categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Correlations between variables were conducted using the Pearson test. The software SPSS 17.0 (SPSS Italy, Florence, Italy) was used for statistical analyses.

RESULTS

We screened 23 patients with stable angina and CTO with collateralization of distal vascular bed, and collateral donor vessel with angiographically intermediate lesion. We excluded 9 patients who showed some exclusion criteria. Fourteen patients were finally included in the study (figure 3). The clinical characteristics and angiographic details are shown on table 1. Seven intermediate lesions (50%) of the collateral donor vessels showed FFR values ≤ 0.80 before the recanalization of the CTO. On average, FFR measures significantly increased after CTO revascularization (0.75 [0.73-0.78] vs 0.83 [0.81-0.84]; P = .017) (table 2 and figure 4). Four patients normalized their FFR values, while in the other 3 the FFR remained hemodynamically significant and required subsequent PCI. There was a tendency towards a reduction of the number of ischemic segments assessed through CMR before and after the recanalization of the CTO (2.5 [0-4] vs 0 [0-0.25]; P = .066). No differences were found in other parameters including the number of hypokinetic segments, left ventricular ejection fraction, left ventricular end-diastolic and end-systolic volumes; left ventricular mass; and necrotic mass before and after the PCI (table 2). In addition, the number of ischemic segments did not significantly correlate with the FFR values before or after PCI (R^2 = -0.31, P = .328; R^2 = -0.68, P = .20, respectively). Finally, no major adverse cardiovascular events were reported during the 2-year follow-up.

Table 1. Clinical and angiographic characteristics

Clinical characteristics	Patients (n = 14)
Age, years	67.44 ± 12.9
Male	12 (85)
Hypertension	6 (42.8)
Smoking	2 (14.3)
Hyperlipidemia	10 (71.4)
Diabetes Mellitus	5 (35.7)
Renal failure	2 (14.3)
Prior CABG	1 (7.1)
Medical treatment	
Beta-blockers	5 (35.7)
Calcium antagonist	2 (14.3)
ACE inhibitor	4 (28.5)
Statins	10 (71.4)
Angiographic characteristics	
CTO vessel	
LAD	2 (14.3)
LCX	1 (7.1)
RCA	11 (78.6)
Calcification	7 (50%)
Bending > 45 degrees	2 (14.3)
Tapered	8 (57.1)
Occlusion length, mm	24.6 [6-43.3]
Rentrop > 1	13 (92.8)
J-CTO score > 2	3 (21.4)
Collateral donor vessel	
LAD	7 (50)
LCX	4 (28.6)
RCA	3 (21.4)
Stenosis degree	52 [50-55]

ACE, angiotensin converting enzyme; CABG, coronary artery bypass grafting; CTO, chronic total occlusion; IQR, interquartile range; JCTO, Japanese CTO; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
Data are expressed as n (%), mean ± standard deviation or median [interquartile range].

Table 2. FFR and CMR measures in the study population

	Before PCI (n = 7)	After PCI (n = 7)	*P*
Pd/Pa	0.93 (0.88-0.96)	0.91 (0.89-0.93)	1.00
FFR	0.75 (0.73-0.78)	0.83 (0.81-0.84)	.017
IS	2.5 (0.0-4.0)	0.0 (0.0-0.25)	.066
HS	1.0 (0.0-4.75)	0.0 (0.0-0.50)	.15
LVEF, %	60.5 (55.0-63.25)	63.5 (54.0-65.25)	.41
LVEDV, ml	111.3 (102.7-451.1)	109.0 (100.6-139.2)	.50
LVESV, ml	41.1 (38.6-65.17)	38.9 (35.2-81.4)	.49
LV mass, gr	83.4 (56.4-92.1)	88.5 (69.1-110.2)	.50
NM, gr	0.83 (0.3-2.3)	0.92 (0.4-1.5)	1.0

CMR, cardiovascular magnetic resonance imaging; FFR, fractional flow reserve; HS, hypokinetic segments; IS, ischemic segments; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NM, necrotic mass; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; PCI, percutaneous coronary intervention.
Data expressed as median (interquartile range).

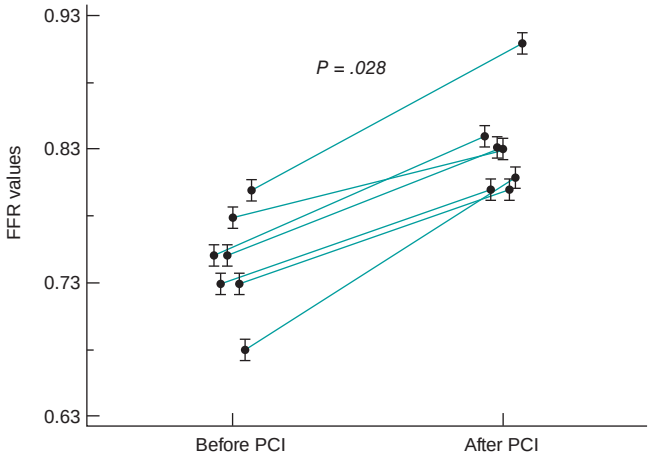

Figure 4. Fractional flow reserve (FFR) values of 7 angiographically intermediate lesions in the collateral donor vessels before and after the percutaneous coronary intervention (PCI) of a chronic total coronary occlusion.

DISCUSSION

These are the main findings of the study: *a)* functional assessment of intermediate lesions located in the collateral donor artery showed significantly lower FFR values than it would have in the absence of collateralized CTOs; *b)* after the recanalization of the CTO, the FFR values of the collateral donor artery normalized in most of patients; *c)* the amount of ischemia assessed through CMR used to decrease after successful CTO recanalization; *d)* no major adverse cardiovascular events were reported in our population at the long-term follow-up.

The FFR is a method used to assess the functional significance of coronary stenosis while taking in account the following parameters: severity of stenosis, myocardial territory and viability, and collateral perfusion.[19] Results from the FAME trial showed that FFR-guided PCI was superior to the angiography-guided PCI at 1 and 2 years in terms of death or AMI and AMI alone.[5,11] In the FAME 2 trial, the FFR-guided PCI reduced the rate of major adverse cardiovascular events compared to medical therapy alone.[6] To this day, physiology has been proposed to outline which stenoses should be treated in the context of multivessel disease.[24] However, there is uncertainty around what the waiting time is before performing an accurate pressure wire assessment of donor arteries after the successful recanalization of a CTO. Several studies have shown that full collateral regression does not happen immediately after the successful revascularization of a CTO.[3] During embryonic development, collaterals derive either from capillary sprouting or pre-existing arteriolar connections.[25] Collateral growth occurs through 2 major processes: arteriogenesis and

angiogenesis. The former, stimulated by physical forces, consists of the growth, positive remodeling, and expansion of preexisting collateral vessels. The latter, induced by hypoxia, is the de novo growth of new capillaries by sprouting or intussusception from pre-existing vessels.[26] Although once established, coronary collaterals are believed to persist and can be re-recruited, this process does not happen immediately. Well-developed collateral vessels close when the pressure gradient across the collateral network disappears. Also, the time needed to reopen the closed collaterals after reestablishing the pressure gradient seems to be directly related to the time interval between coronary occlusions.[27] Recently, Mohdnazri et al. have showed that the successful recanalization of a right coronary artery CTO resulted in a modest but statistically significant and immediate increase of instantaneous wave-free ratio (iFR) in the predominant donor vessel following the recanalization of the CTO. At 4 months, both the FFR and the iFR showed significant improvement compared to pre-PCI values together with a concomitant reduction of collateral function.[28] Ladwiniec et al. showed that the recanalization of a CTO resulted in a modest FFR increase of the predominant collateral donor vessel associated with a reduced coronary flow, of a similar magnitude at baseline and maximal hyperemia.[29] Few patients of our study did not show this improvement. The persistence of non-angiographically visible collateral circulation, the presence of microcirculation dysfunction and type of prior collateral circulation grade,[30] and distal embolization or myonecrosis following PCI recanalization may be potential causes of this lack of improvement. In this regard, in a recent study, measurements repeated shortly after the PCI of a CTO showed transient procedural-related changes like microvascular dysfunction secondary to distal embolization, catecholamine release, left ventricular stunning or hyperemic stimulus related to side-branch occlusion.[29]

Our data suggest that in the setting of CTOs and an angiographically intermediate lesion of the collateral donor vessel, it seems like the FFR measurement may be misleading. Therefore, it seems advisable to postpone the assessment of intermediate stenoses until achieving the successful recanalization of the associated CTO. This approach should avoid overtreating patients who only require the revascularization of their CTOs. On the contrary, if the recanalization of the CTO fails, treating the intermediate stenosis in the donor artery may be necesary to reduce ischemia in this territory. It also still is a good practice to try to re-open the CTO prior to performing any interventions on the donor vessel, due to the risk of extensive acute ischemia in case of troublesome PCIs.

Moreover, we did not find any correlations between the amount of ischemia assessed through CMR and the FFR values before or after the PCI. As far as we know, this is the first comparison between CMR and FFR assessment of an angiographically intermediate lesion in a collateral donor vessel related a CTO. Former studies have suggested that the CMR underestimates or that the FFR overestimates the number of ischemic segments in multivessel disease.[31-32] This discrepancy seems to highlight the poor accuracy of the FFR method in the presence of collaterals involving territories that are from the target lesion to be assessed.

Finally, after treating the patients according to the FFR measures obtained after the PCI of a CTO, no major adverse cardiovascular events were detected at the 2-year follow-up.

Limitations

Several limitations should be acknowledged. First, due to the small size of the sample our findings should be, at best, hypothesis-generating findings. Secondly, we only used FFR as hyperemic index; other indices (eg. iFR, IMR, etc.) were not assessed. Similarly, we could not assess the influence of microcirculation through CMR or hyperemic microvascular resistance. Third, we did not assess whether collateral circulation originated from a segment proximal or distal to the target stenosis under study. Fourth, in patients with negative FFR before the recanalization of their CTO we did not repeat the FFR after the PCI. Finally, no follow-up CMRs were performed in patients with negative FFR prior to recanalization.

CONCLUSIONS

The FFR assessment of intermediate stenoses in a collateral donor vessel of a CTO may overestimate the severity of the lesion by increasing the territory at risk. Therefore, the strategy of first focusing on the revascularization of the CTO and then re-assess the intermediate lesion in a collateral donor vessel may be recommended to overcome this pitfall.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

- In patients with CTOs, collateral circulation supplied by donor vessels is often seen.
- The progression of atherosclerosis in donor vessels may compromise the coronary circulation of several territories.
- Angiography is not a reliable technique to assess the hemodynamic compromise of an intermediate lesion located in a vessel that provides collateral circulation to a chronically-occluded vessel.

WHAT DOES THIS STUDY ADD?

- Patients with positive FFR of donor vessels before the recanalization of a CTO may show significant increases of FFR values (even normalization in most of them too) after successful revascularization of the CTO.
- Also, the revascularization of the CTO may lead to a reduction in the number of ischemic segments assessed through CMR before and after the PCI of the CTO.
- These findings support the strategy of recanalizing the CTO first and then performing the functional assessment of donor artery with intermediate lesions.

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Original article

Prognostic impact of early coronary angiography in patients with non-ST-elevation acute myocardial infarction

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ABSTRACT

Introduction and objectives: According to the recommendations of the latest clinical practice guidelines, non-ST-elevation acute myocardial infarction (NSTEMI) patients should undergo an invasive coronary angiography. However, the best moment to perform this coronary angiography has not been stablished yet. Our main objective was to see if performing an early angiography (within the first 24 h) in NSTEMI patients was associated with better prognosis compared to delayed angiography (beyond the first 24 h).
Methods: From January 2014 to June 2016, 447 consecutive patients were admitted to the acute cardiac care unit of a tertiary hospital with a diagnosis of NSTEMI. They all underwent catheterization. We classified them into 3 groups depending on the moment when the coronary angiography was performed (within the first 24 h after diagnosis, 24 h to 72 h later, and > 72 h after diagnosis).
Results: Coronary angiography was performed within the first 24 h in 285 patients (63.8%). There were no differences among the groups regarding gender, distribution of cardiovascular risk factors, past medical history of coronary disease or presence of other comorbidities. We found no differences among the 3 groups in variables with known prognostic impact. The cardiovascular events and 1-year mortality at follow-up were similar among the 3 groups.
Conclusions: In our study, in the whole spectrum of NSTEMI, early coronary angiography (within the first 24 h) did not show any clinical benefits regarding survival or fewer major adverse cardiovascular events.

Keywords: Acute coronary syndrome. GRACE score. Early angiography. Prognosis. Mortality.

Impacto pronóstico de la realización de una coronariografía precoz en pacientes con infarto de miocardio sin elevación del segmento ST

RESUMEN

Introducción y objetivos: Las guías clínicas recomiendan la realización de una coronariografía en los pacientes con infarto agudo de miocardio sin elevación del segmento ST (IAMSEST). Sin embargo, no está claramente establecido el mejor momento para hacerla. Por ello, el objetivo del presente trabajo fue analizar si practicar un cateterismo precoz (durante las primeras 24 h) se relaciona con un mejor pronóstico, en comparación con hacerlo de manera diferida (más allá de las 24 h).
Métodos: De enero de 2014 a junio de 2016 ingresaron en la unidad de cuidados agudos cardiológicos de un hospital terciario 447 pacientes consecutivos con diagnóstico de IAMSEST a los que se hizo una coronariografía. Se clasificó de forma retrospectiva a los pacientes en 3 grupos en función del momento de realización del cateterismo: durante las primeras 24 h, entre las 24 y las 72 h tras el diagnóstico, y después de las primeras 72 h.
Resultados: El cateterismo se llevó a cabo en las primeras 24 h en 285 pacientes (63,8%). No se identificaron diferencias entre los grupos en cuanto a sexo, prevalencia de factores de riesgo cardiovascular ni presencia de comorbilidad. Tampoco se encontraron diferencias en las variables pronósticas analizadas ni en la mortalidad. En el seguimiento a los 12 meses, la incidencia de eventos cardiovasculares y la mortalidad fueron similares entre los grupos.
Conclusiones: En el presente estudio, la realización de una coronariografía precoz (en las primeras 24 h) a los pacientes ingresados por IAMSEST no mostró beneficio clínico en términos de supervivencia o reducción de eventos cardiovasculares.

Palabras clave: Síndrome coronario agudo. GRACE *score*. Cateterismo precoz. Pronóstico. Mortalidad.

Abbreviations

CA: coronary angiography. **NSTEMI:** non-ST-elevation acute myocardial infarction.

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INTRODUCTION

Coronary angiography (CA) is a key step in treatment of patients with non-ST-elevation acute myocardial infarction (NSTEMI). CA reduces mortality and the rates of new cardiovascular adverse events compared to the conservative approach.[1,2] Therefore, the current European clinical practice guidelines on the management of NSTEMI recommend an invasive strategy to treat these patients.[1]

The appropriate time to perform the CA in NSTEMI patients is still under discussion. Early CA (within the first 24 h after diagnosis) is still recommended in patients with high-risk NSTEMI defined as a GRACE score > 140. However, the potential benefit of this approach has not been completely established yet.[3]

The objective of our study was to assess the prognostic impact of an early CA (within the first 24 h after diagnosis) in patients NSTEMI compared to a delayed CA strategy (after 24 h).

METHODS

This is a retrospective, observational cohort study. From January 2014 to June 2016, data from 447 patients with NSTEMI admitted to a tertiary referral hospital who underwent an invasive coronary angiography were consecutively collected.

NSTEMI was defined according to the guidelines and all patients were treated following the recommendations established by these guidelines.[1]

Data from all the cases were included prospectively in a continuous multipurpose database. The collection of data included detailed past clinical histories, physical examinations, pulse oximetry measures, 12-lead electrocardiograms, continuous electrocardiogram monitoring, blood tests, echocardiographies, and CAs. The Global Registry of Acute Coronary Events (GRACE) and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) scores were calculated for each patient.[1]

Patients were classified into 3 groups according to the time to CA (figure 1): catheterization within the first 24 h after diagnosis (group 1, n = 285 patients), 24 h to 72 h later (group 2, n = 102 patients) and after 72 h (group 3, n = 60 patients). The decision on when to perform the CA was made by the treating physician in each case. After being discharged from the hospital, the 12-month follow-up of patients was performed in a dedicated clinic.

The primary endpoints of our study were mortality and major adverse cardiovascular events (stroke, new acute coronary syndrome, new revascularization) during hospitalization and depending on the time to CA in patients with NSTEMI. The secondary endpoints were mortality and the rate of major cardiovascular events at the 1-year follow-up, and bleeding events according to the BARC criteria.[4] We also analyzed the antiplatelet treatment prescribed at discharge and its correlation with MACE at follow-up.

Statistical analysis

Continuous variables are described as mean and standard deviation or median and interquartile range [IQR] when appropriate. The Kolmogorov-Smirnov test was used to assess the variables normal distribution. Regarding quantitative variables, the groups were compared using the 2-tailed Student *t* test or the Mann-Whitney *U* test when necessary. Categorical variables were expressed as frequency and percentage, and compared using the chi-square test or Fisher's exact test when appropriate. No variable had losses > 15%.

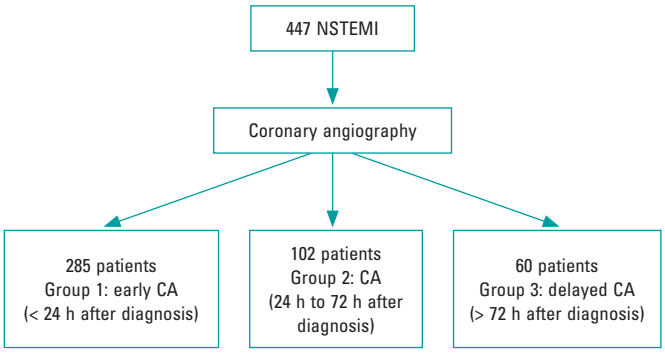

Figure 1. Flowchart. CA, coronary angiography; NSTEMI, non-ST-elevation acute myocardial infarction.

A multivariate logistic regression analysis was performed to assess the potential impact of the CA timing on in-hospital mortality. The model included all variables that were statistically significant in the univariate analysis regarding mortality and time to CA. Adjusted odds ratios (OR) with 95% confidence intervals (95%CI) were calculated for each variable. Regarding the secondary endpoint of 1-year mortality, a Cox regression analysis was performed to assess any potential prognostic factors.

All tests were 2-tailed and the differences were considered statistically significant with *P* values < .05. The statistical analysis was performed using the statistical software package IBM SPSS Statistics V 22.0.

RESULTS

Table 1 shows the baseline characteristics of the patient population. Patients in group 1 were younger (66.5 ± 13.5 years vs 71.1 ± 12.7 years in group 2, and 70.7 ± 13.5 in group 3, *P* = .016). There were no gender differences among the groups (*P* = .565). The cardiovascular risk factors, previous coronary artery disease (*P* = .314), and presence of other comorbidities were similar among the groups (table 1).

A CA was performed within the first 24 h in 285 patients (63.8%). Surprisingly, we noticed that the patients from group 1 showed lower GRACE scores [157.67 (44.9) points vs 170 (39.5) points in group 3, (*P* = .041)] and similar CRUSADE scores compared to the other 2 groups (*P* = .251).

There were no significant differences among the groups in the Killip class at admission (table 1). The left ventricular ejection fraction and the peak values of cardiac biomarkers were similar among the groups. The presence of multivessel disease was similarly in the 3 study groups (table 1). There were no significant differences in the primary endpoint among the 3 study groups (table 2). During hospitalization, strokes and bleeding events occurred similarly in the 3 groups (table 2). It is important to emphasize here the low rate of bleeding events (5 patients with BARC 2 and 2 patients with BARC 3 events in group 1, and 3 patients with BARC 2 and 2 patients with BARC 3 events in groups 2 and 3, with no fatal events). At the 1-year follow-up, cardiovascular adverse events and 1-year mortality were similar among the 3 groups (table 2).

Table 1. Baseline characteristics among the 3 study groups and antiplatelet therapy at discharge

	Group 1 (n = 285)	Group 2 (n = 102)	Group 3 (n = 60)	*P*
Age (years)	66.5 (13.5)	70.7 (13.5)	71.1 (12.7)	.016
Sex (male)	78.9%	80.2%	73.3%	.565
Diabetes	34.9%	37.6%	35.0%	.880
Hypercholesterolemia	63.4%	54.5%	55.9%	.195
Hypertension	71.1%	71.3%	73.3%	.942
GRACE score	157 (44.9)	161 (45.7)	170 (39.6)	.041
CRUSADE score	32.8	34.8	36.4	.251
GFR	72	69.8	66	.118
Peak CK levels	659.9	479.4	590	.623
LVEF at discharge	49.6	54.2	52	.229
Killip class				.604
I	194 (71.3%)	75 (72.7%)	37 (62.7%)	
II	32 (11.8%)	15 (15.2%)	9 (15.3%)	
III	23 (8.5%)	7 (7.1%)	8 (13.6%)	
IV	23 (8.5%)	5 (5.1%)	5 (8.5%)	
Mechanical ventilation	29 (10.7%)	6 (6.1%)	5 (8.3%)	.636
Number of vessels with severe stenosis				.488
1	133 (46.8%)	45 (44.6%)	23 (38.6%)	
2	77 (27.1%)	23 (22.8%)	22 (36.7%)	
3	68 (23.9%)	29 (28.7%)	14 (23.3%)	
Successful revascularization	211 (89.8%)	70 (92.1%)	42 (91.3%)	.930
Antiplatelet therapy at discharge				
Ticagrelor	154 (54%)	52 (50.9%)	29 (48.3%)	.154
Clopidogrel	105 (36.8%)	40 (39.2%)	24 (40%)	.358
Prasugrel	26 (9.2%)	10 (9.9%)	7 (11.7%)	.469

CK, creatine kinase; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.
Group 1: coronary angiography within the first 24 h after diagnosis; group 2: 24 h to 72 h later; group 3: coronary angiography > 72 h after diagnosis.

Regarding medical treatment at discharge, a similar percentage of patients received clopidogrel, prasugrel and ticagrelor in the 3 study groups (table 1). In our cohort, antiplatelet therapy was not associated with differences in the rate of major adverse cardiovascular events and mortality at the 12-month follow-up.

The multivariate logistic regression analysis performed to predict mortality revealed that hypertension, Killip class IV at admission, left ventricular ejection fraction, and myocardial damage (defined as peak creatine kinase levels) were independently associated with higher in-hospital mortality rates. The time to CA was not an independent predictor of in-hospital mortality after the multivariate adjustment (table 3).

Regarding 1-year mortality, the Cox regression analysis showed similar results. The time to CA was non-significant in the multivariate analysis. Hypertension, age, left ventricular ejection fraction, and Killip class at admission were independently associated with higher mortality rates at 1 year (table 4).

DISCUSSION

Our study included a large cohort of 447 consecutive patients with NSTEMI that were retrospectively analyzed. Our results showed that early CAs (defined as a CA performed within the first 24 h after diagnosis) in NSTEMI patients did not improve the prognosis of this cohort of patients compared to delayed CAs. No differences were seen among the 3 groups regarding the time to CA in the in-hospital cardiovascular adverse event rate, mortality rate or at the 12-month follow-up either.

Early CA, within the first 24 h after diagnosis, is currently recommended by the clinical practice guidelines for the management of patients with NSTEMI. However, this recommendation is based on the results of relatively old clinical trials and a meta-analysis.[4-8] Several recent trials have explored the prognostic impact of the CA timing on NSTEMI patients in order to find stronger evidence in this clinical setting.[9,10]

Table 2. In-hospital and follow-up rate of adverse events and mortality (expressed as percentage) among the 3 groups

	Group 1 (n = 285)	Group 2 (n = 102)	Group 3 (n = 60)	*P*
In-hospital events				
Heart failure	74 (25.9%)	26 (25.4%)	21 (36%)	.246
Non-fatal AMI	3 (1%)	4 (3.9%)	3 (6%)	.371
Acute kidney injury	47 (16.5%)	18 (17.6%)	15 (25%)	.334
Stroke	3 (1%)	2 (1.9%)	2 (3.3%)	.548
Bleeding events	20 (7%)	6 (5.8%)	6 (10%)	.213
In-hospital mortality	19 (6.6%)	7 (6.8%)	2 (3.4%)	.358
Events at the 1-year follow-up				
Death	17 (5.9%)	5 (4.9%)	5 (8.3%)	.114
Stroke	3 (1.05%)	3 (2.9%)	1 (1.6%)	.271
Major bleeding	7 (2.45%)	6 (5.8%)	4 (6.6%)	.427
Myocardial infarction	16 (5.6%)	5 (4.9%)	4 (6.6%)	.907

AMI, acute myocardial infarction.
Group 1: coronary angiography within the first 24 h after diagnosis; group 2: 24 h to 72 h later; group 3: coronary angiography > 72 h after diagnosis.

Table 3. Multivariate logistic regression analysis to predict in-hospital mortality

Variable	Odds ratio (95%CI)	*P*
CA after 72 h	reference	
CA within the first 24 h	0.98 (0.26-3.74)	.978
CA 24 h to 72 h later	1.33 (0.28-6.24)	.716
Hypertension	6.25 (1.09-33.3)	.04
Age (per year)	1.03 (0.98-1.08)	.292
Successful revascularization	0.51 (0.12-2.21)	.371
Peak CK levels (per pg/mL)	1.00 (1.00-1.01)	.010
LVEF	0.93 (0.90-0.97)	< .001
Killip class at admission		
I	reference	.026
II	3.39 (0.98-11.75)	.054
III	3.24 (0.92-11.36)	.067
IV	15.34 (2.19-107.58)	.006

95%CI, 95% confidence interval; CA, coronary angiography; CK, creatine kinase; LVEF, left ventricular ejection fraction.

Table 4. Multivariate Cox regression analysis to predict 1-year mortality

Variable	Hazard ratio (95%CI)	*P*
CA after 72 h	reference	
CA within the first 24 h	0.96 (0.46-2.03)	.919
CA 24 h to 72 h later	0.82 (0.33-2.07)	.677
Hypertension	3.64 (1.30-10.3)	.014
Age (per year)	1.04 (1.01-1.07)	.022
Successful revascularization	0.94 (0.41-2.13)	.876
Peak CK levels (per pg/mL)	1.00 (1.00-1.01)	.198
LVEF	0.96 (0.94-0.98)	< .001
Killip class at admission		
I	reference	
II	2.83 (1.32-6.08)	.008
III	2.78 (1.27-6.09)	.010
IV	2.91 (0.83-10.2)	.096

95%CI, 95% confidence interval; CA, coronary angiography; CK, creatine kinase; LVEF, left ventricular ejection fraction.

The results of the TIMACS study (Timing of Intervention in Acute Coronary Syndromes) showed that an early CA was associated with a reduction in the composite endpoint of death, myocardial infarction or refractory ischemia compared to a delayed CA strategy.[11]

A retrospective cohort study that included 19 704 propensity score-matched patients hospitalized with a first acute coronary syndrome conducted between January 1, 2005 and December 31, 2011 showed that the use of an early invasive treatment strategy was associated with a lower risk for cardiovascular mortality and re-hospitalization due to myocardial infarction compared to a conservative invasive approach.[12] However, it is important to emphasize the retrospective nature of this study and the fact that patients were followed for 60 days only.

However, a meta-analysis that combined data from 83 229 patients did not show any significant differences regarding mortality, myocardial infarction or major bleeding events between the 2 strategies.[13]

Another meta-analysis that included 8 randomized controlled trials (n = 5324 patients) with a median follow-up of 180 days [180-360] and compared an early invasive group of NSTEMI patients to a delayed strategy showed that the early invasive

strategy did not reduce mortality in all NSTEMI patients including high risk patients with GRACE score > 140 points.[14]

Similarly, a recent meta-analysis that combined the results of 10 clinical trials did not find any differences in mortality, myocardial infarction or major bleedings among NSTEMI patients based on the CA timing. Nevertheless, the early CA strategy was associated with less recurrent angina and shorter hospital stays.[15]

The LIPSIA-NSTEMI study randomized patients with NSTEMI to undergo CA within the first 2 h after randomization (immediate CA strategy), 10 h to 48 h after randomization (early CA), and the so-called "selectively invasive" arm, in which patients initially received medical treatment without showing any differences in the infarct size among the 3 study groups.[16]

A recent randomized controlled trial conducted by a Kofoed et al., the VERDICT trial, included a total of 2147 patients of which 1075 were allocated to very early invasive evaluation (within the first 12 h after diagnosis), and 1072 to receive standard invasive care (CA 61.6 h after randomization).[17] The primary endpoint was a composite of all-cause mortality, nonfatal recurrent myocardial infarction, refractory myocardial ischemia-related hospital admission or heart failure-related hospital admission. In this trial, the very early invasive coronary evaluation strategy did not improve overall the long-term clinical outcome compared to the invasive strategy performed within 2 to 3 days in patients with non-ST-segment elevation acute coronary syndrome. However, in patients with the highest risk, the very early invasive therapy improved long-term outcomes[17] which is consistent with the results shown by the TIMACS trial.

Despite all these data, there is still controversy on what the best timing is to perform a CA in patients with NSTEMI.

An important limitation of previous studies is heterogeneity in the definition of early and late CA, and the differences seen in the primary endpoints.[4-14] The lack of uniform criteria makes it difficult to compare the results. The definition of NSTEMI has changed over time. Thus, old clinical trials used a different criterion for the definition of NSTEMI and included different patients from those of current studies. We should try to identify what patients with the highest risk would benefit from an early invasive strategy. In this sense, previous studies did not use risk grading systems to classify patients. However, in our study we calculated the ischemic and bleeding risks of all patients. As our objective was to assess the potential benefit of an early invasive strategy among NSTEMI patients, the GRACE risk score was estimated in the entire study population. However, despite the high ischemic risk of our patients, no significant differences were found between the 2 strategies (early or delayed CA) regarding mortality or adverse events.

Limitations

Our study has several limitations that should be considered when interpreting the results. Although we included a large number of NSTEMI patients with a collection of high quality data, this is an observational, retrospective, single center study with the limitations of this type of study. Besides, the current clinical practice guidelines recommend the PRECISE-DAPT score to assess bleeding risk in this clinical setting. In our study bleeding risk at admission was classified according to CRUSADE score.

CONCLUSIONS

The results of our study show that the early CA strategy did not improve prognosis or reduce mortality in NSTEMI patients. However, larger studies are still needed to clarify which group of patients may benefit from early CA strategies.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Early CA is recommended by the current clinical practice guidelines in patients with a high-risk suffering from non-ST-elevation acute myocardial infarctions.
- To this day, clinical trials and meta-analyses show contradictory results without clear prognostic differences between the early CA strategy and delayed catheterization.

WHAT DOES THIS STUDY ADD?

- A large cohort of consecutive NSTEMI patients was retrospectively studied. We assessed in-hospital progression and cardiovascular events and mortality at the 1-year follow-up.
- The results of our study show that the early CA strategy did not imporive prognosis or reduced mortality in NSTEMI patients.
- No differences among the 3 groups were seen based on the CA timing regarding cardiovascular adverse events and mortality during the hospital stay or at the 12-month follow-up.
- However, larger studies are needed to clarify which group of patients may benefit from an early CA strategy.

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Review article

Percutaneous revascularization of coronary bifurcation lesions

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ABSTRACT

In this article, we analyse the changes occurred over the last 20 years in the percutaneous treatment of bifurcation lesions based on our own experience. We also analyse the more relevant papers recently published, as well as the strategies and guidelines recommended for the percutaneous management of bifurcation lesions. Technical aspects are relevant in this field and, for this reason, a significant section of this manuscript is dedicated to the technique used together with some tips and tricks also provided here. The technical advances made over the last years have significantly increased the success rate in the management of these complex lesions. At the same time, the technique of treatment has been standardized allowing the management of all type of bifurcations including distal left main disease.

Keywords: Coronary heart disease. Coronary bifurcation lesions. Stents. Percutaneous treatment.

Revascularización percutánea de las lesiones en bifurcación

RESUMEN

En este artículo se revisan los cambios acaecidos durante los últimos 20 años en el tratamiento percutáneo de las lesiones en bifurcación bajo la perspectiva de nuestra experiencia. También se analizan los estudios más relevantes en este campo, así como las estrategias y las recomendaciones actuales. Los aspectos técnicos son fundamentales en el tratamiento de las lesiones en bifurcación, por lo que parte de la revisión se dedica a ellos. Las mejoras técnicas aparecidas en los últimos años han sido determinantes en el aumento de la tasa de éxito del tratamiento de este tipo de lesiones complejas. Al mismo tiempo, la estrategia terapéutica ha sido reglada y estandarizada, de modo que actualmente podemos abordar con seguridad todo tipo de lesiones en bifurcación, incluida la enfermedad del tronco común de la arteria coronaria izquierda.

Palabras clave: Enfermedad coronaria. Lesiones coronarias en bifurcación. *Stents*. Tratamiento percutáneo.

INTRODUCTION

Bifurcation lesions are a common group of lesions (20%-30%) we usually see at the cath. lab.[1] Although they fall within the category of complex lesions, the management of these lesions has improved favorably over the last few years in such a way that today there is a new generation of stents and co-adjuvant techniques to angiography available that are very effective in the management of such lesions. At the same time, the therapeutic strategy has been standardized and regulated,[2] with success rates that are higher compared to years ago. Thus, to this day it is possible to approach all sorts of bifurcations including bifurcations of the left main coronary artery disease.[3] However, it has been a long 20-year-old road before reaching the actual standards of management that we have today.

HISTORIC PERSPECTIVE

The percutaneous management of bifurcations started in the era of balloon angioplasty that was available before the arrival of coronary stents. At the time, there were already specific techniques available such as the use of two 8 Fr guiding catheters through which guidewires and balloons would be inserted independently in the main branch (MB) and side branch (SB) to proceed with simultaneous inflation (figure 1). However, the turning point in the percutaneous management of bifurcations came with the arrival of the Palmaz-Schatz stent. The was the first technique ever to describe a simple balloon dilation of the SB through the stent cells.[4] After that, we would see a never-ending cascade of techniques for the management of both vessels using 1 or 2 stents. With the arrival of drug-eluting stents, all coronary procedures

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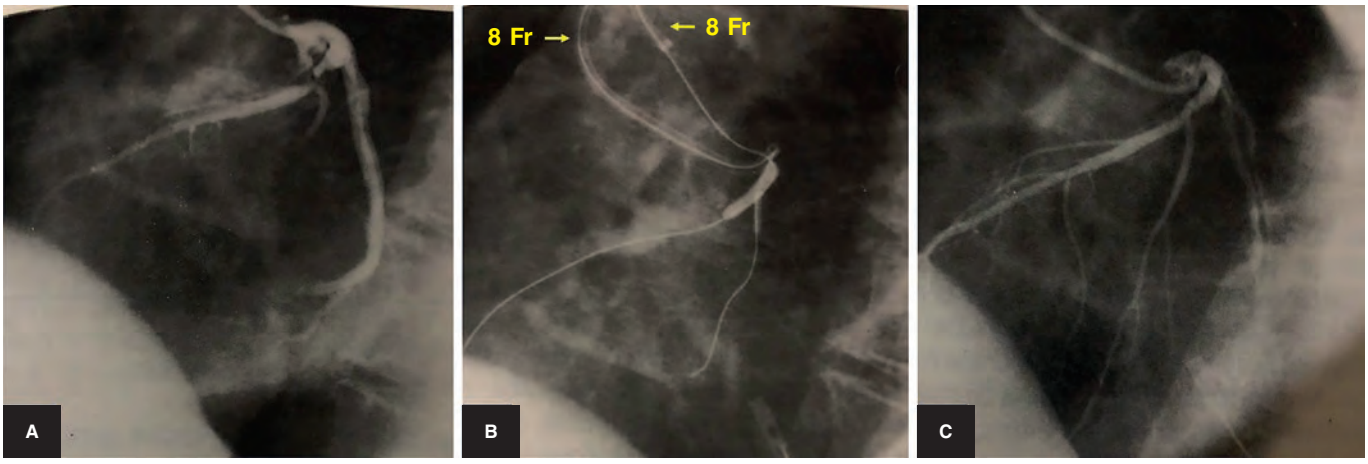

Figure 1. Bifurcation in the anterior descending artery/diagonal branch branch. Percutaneous treatment prior to the era of stents. **A:** baseline angiography. **B:** balloon dilation of the anterior descending and diagonal arteries. Two 8 Fr femoral guiding catheters with guidewires and independent balloons for simultaneous balloon dilation (kissing balloon). **C:** final outcome.

improved. When it comes to the management of bifurcations, the experience acquired during the era of bare-metal stents contributed to the development of new and complex techniques: the crush technique and its variants, the TAP (T with protrusion), and the simultaneous kissing stent (SKS) techniques.

DEFINITION OF BIFURCATION LESIONS

Coronary bifurcation lesions are lesions adjacent to the division of one major pericardial artery. The definition of significant SB is arbitrary and totally depends on the interventional cardiologist´s subjective criteria.[5] Although in the very definition we can see the lack of consensus on what is considered significant and what is not, most studies talk about bifurcations with SB > 2.2 mm. The differential characteristic of these lesions compared to conventional lesions is that when we act on the MB, we can compromise the SB due to the displacement of the carina or the atherosclerotic plaque. That is why we need specific strategies to solve this situation.

CLASSIFICATION OF BIFURCATION LESIONS

Several classifications have been proposed to define the baseline characteristics of bifurcations, some of them during the era of bare-metal stents. However, the most widely accepted of all is the classification established by Medina[6] (figure 2). Its success is due to its simplicity when it comes to memorizing it. This classification was first accepted back in 2005 during the first congress held by the European Bifurcation Club in Bordeaux, France (figure 2). Here the authors of the Massy classification rejected their own classification for the adoption of the new one[6] as the only proposal made by this group. This extraordinary event, the bith of a classification, was published in *Revista Española de Cardiología* and reached a record number of citations (actually it is the most cited article to this day).

PERCUTANEOUS MANAGEMENT OF BIFURCATION LESIONS

Over the last few years, a great number of different techniques have appeared for the management of coronary bifurcation lesion with the use of stents. In an attempt to systematize them all, the

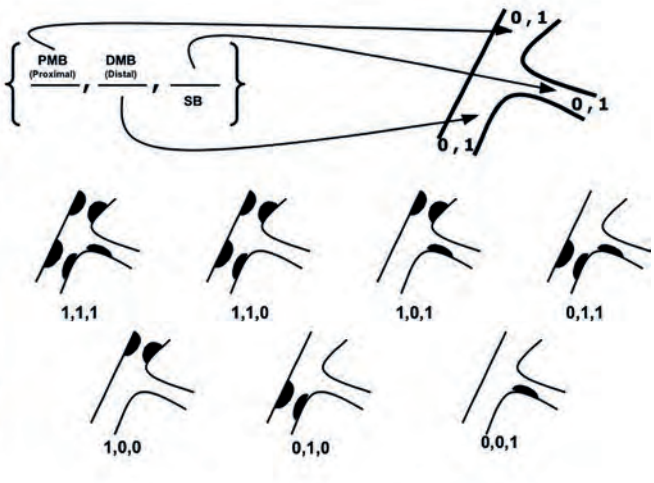

Figure 2. To the left: Bordeaux congress from September 2005, where the Medina classification was established as the only accepted classification by the European Bifurcation Club. To the right: Medina classification reproduced with permission from Medina et al.[6] DMB, distal main branch; PMB, proximal main branch; SB, side branch.

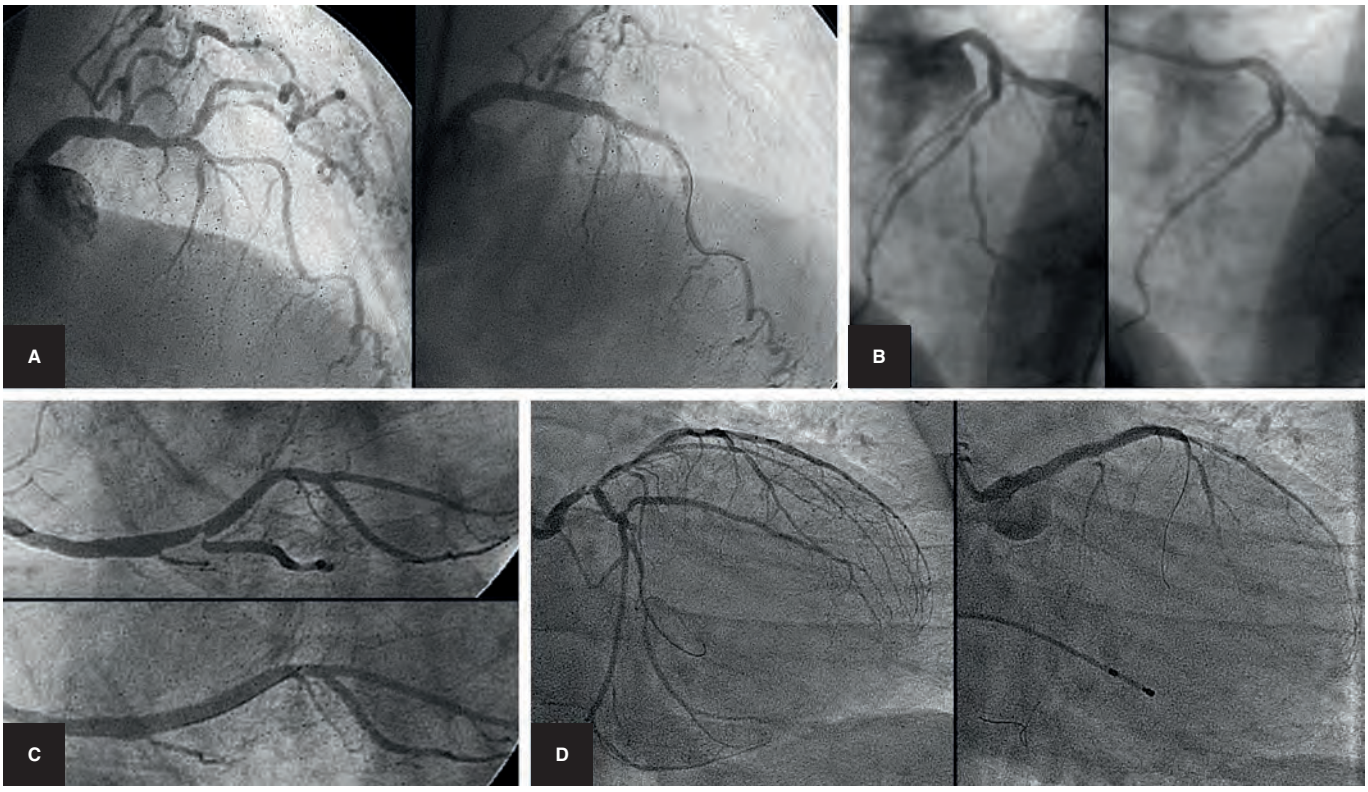

Figure 3. Four examples of side branch sudden occlusion following the implantation of the stent into the main branch. **A** and **B:** anterior descending artery/diagonal branch. **C:** right coronary artery/posterior descending artery. **D:** left main coronary artery with closure of circumflex artery.

European Bifurcation Club has proposed the MADS (Main, Across, Double, Side) classification.[7] According to this classification, there are numerous different modalities of treatment. However, for simplification purposes, an easier classification has been proposed including simple (1 stent in MB) and complex (2 stents in MB and SB) techniques. Both strategies have been compared over and over again both in the era of bare-metal stents and the actual era of drug-eluting stents.

Description of simple techniques. The provisional stenting technique as a treatment philosophy

The provisional stenting approach basically consists of implanting 1 stent in the MB and then see what impact this has on the SB.[2] The stent can be covered, dilated with balloon or it stented based on the actual flow and residual stenosis. To this end, 2 guidewires are introduced, one in the MB and another one in the SB. The size of the stent that will be implanted in the MB is picked based on the length of the diseased section and the reference diameter of the distal vessel. After the implantation, the POT (proximal optimization technique) should be used. The POT consists of the dilation of the stent proximal edge with a short balloon but with a wider diameter compared to the diameter of the release balloon and according to the proximal segment. By doing this, the proximal stent is adapted to a vessel that has a wider diameter compared to the distal component of the bifurcation which, if needed, facilitates the re-crossing of the SB. At this point, the state of the origin of the collateral branch should be assessed. In the absence of significant stenosis or if the vessel is small and with TIMI (Thrombolysis in Myocardial Infarction) flow 3, the procedure is considered finished. If the origin of a major branch has been compromised, a second guidewire should be passed towards the branch in order to treat it, and the jailed guidewire should be extracted. The inflation of the balloon can be performed simultaneously using a second balloon in the MB (the so-called kissing balloon) or in isolation.[8] A second POT is recommended especially if the simultaneous inflation is not attempted. Most bifurcations have good outcomes when implementing these maneuvers. However, in a variable percentage of cases, the origin of the collateral branch maintains a suboptimal outcome and requires the implantation of a second stent followed by final kissing balloon inflation.[2]

The jailed guidewire technique

The provisional stenting technique is often called «simple technique», although there are times when it is not as simple as it seems especially when the SB becomes occluded after implanting the stent in the MB (figure 3). If unsolved, this situation will lead to the occurrence of an acute myocardial infarction. The jailed guidewire technique was described to help solve this situation. It consists of leaving a guidewire in the SB while a stent is implanted in the MB. By doing this, the guidewire is somehow jailed between the vessel wall and the metallic structure of the stent.

Its advantages are:

- The jailed guidewire helps keep the SB open and, in case of SB occlusion, the guidewire becomes the only marker of its position, which facilitates bailout maneuvers in the occluded vessel.
- It facilitates access to the SB since it successfully modifies the bifurcation angle.
- It produces a mechanism that anchors the guidewire which, in turn, facilitates the intubation of the guiding catheter by

providing more solid support to attempt the crossing of the origin of the SB with the balloon.

- Finally, in extreme situations, it can be used to introduce a low-profile balloon, for SB dilation purposes, and eventually to implement the inverted crush technique or re-dilate the stent crushed inside the MB once the occlusion of the branch has been solved.[9]

Risks involved when using the jailed guidewire technique. Since the MB stent is implanted using pressure against the arterial wall, the guidewire jailed between these 2 structures can be damaged and even break when removed.[10] Although rare, cases of guidewire rupture have been reported during the extraction maneuvers; this is a serious complication of this procedure that sometimes requires urgent surgical extraction.[11-13] Several recommendations have been made to prevent the rupture of the guidewire:[14] *a)* avoid placing the distal portion of the guidewire in secondary vessels of small caliber; *b)* avoid high pressures when releasing the stent; *c)* avoid covering a large area of the jailed guidewire with a series of stents; and *d)* use the most traction-resistant guidewire. However, this last recommendation has been controversial over the last few years. Thus, initially, the use of non-polymeric guidewires was recommended following the experts' opinions.[15,16] However, a randomized trial conducted to study the damage sustained by the guidewire after being jailed using stereoscopic microscopy revealed that polymeric guidewires were more resistant and sustained less damaged.[10] However, the new generation of guidewires should be put to the test for this indication.

Pre-dilation or not of the side branch prior to implanting the stent in the main branch

The pre-dilation of the side branch has also been controversial over the last few years. This maneuver has a series of advantages and disadvantages that we will be commenting now:

- Possible advantages: the dilation of the SB would increase the vessel lumen and facilitate re-wiring (re-crossing); it could help maintain flow to the SB and avoid its occlusion after implanting stent into the MB; also, the implantation of the stent into the MB could be the ultimate procedure without having to post-dilate. This is how the procedure could be simplified and the production of deformities inside the MB stent avoided.

- Disadvantages: the presence of one dissection at the origin of the SB could obstruct the passage of the guidewire which would be forced to cross the stent of the MB and the dissected segment of the SB. The luminal increase at the origin of the SB increases the chances of accessing this vessel through the proximal cell of the stent of the MB, which is associated with more deformity of the MB stent and lack of scaffold at the origin of the SB, thereby increasing the changes of a second stent inside the SB.[17,18]

In order to shed some light on the issue of SB pre-dilation when using the provisional stenting technique, our group conducted one randomized trial that compared patients with true bifurcations treated with this strategy plus pre-dilation, or not, of the SB.[19] The primary endpoint of assessment (the presence of TIMI flow 0-1 in the SB right after the implantation of the stent inside the MB) was significantly lower (1% vs 10%; $P < .001$) in the pre-dilation arm. Also, 32% of predilated patients did not require additional treatment on the branch, which simplified the entire procedure. In the remaining patients who did require post-dilation, the pre-dilation was no problem at all for guidewire re-crossing purposes. After this study several registries appeared in favor of this maneuver[20] or opposing it.[21,22] In general, the pre-dilation of the SB is left at operator's discretion and recommended when the SB shows a difficult-to-access, serious, calcified lesion at its origin or compromised coronary flow at baseline level or after the pre-dilation of the MB.[2]

Difficult access to the side branch

This circumstance is still a problem in the management of bifurcations. Excessive angulations, calcifications, and diffuse lesions can obstruct the introduction of the guidewire into the SB (figure 4). And the situation becomes worse after implanting the stent into de MB due to the interposition of a metal layer, more stenosis or even its closure at the origin of the SB. In order to solve this, specific devices and ingenious techniques have been developed for wiring the SB. Deflectable tip catheters or catheters with highly-angulated tips are some of these new devices[23] that can be oriented towards the origin of the SB. Double lumen catheters allow us to use highly-angulated guidewires through the lateral exit with the possibility of moving the entire system back and forth until reaching the origin of the SB.[24] Sometimes this is very hard to do and it is an actual problem we have today in a small number of cases.

Description of complex techniques with 2 stents

The mini-crush, culotte, TAP, and T-stenting techniques starting at the sister branch are widely used techniques when planning 2-stent strategies. All of them were described in detail in a classical review conducted by Louvard et al.[15]. However, most recently, the double kissing crush (DK crush) technique has gained popularity following the results of a series of randomized clinical trials.[25] In the double kissing crush technique, one guidewire is introduced into the MB and SB and then both vessels are predilated. While keeping the guidewire inside the MB, a stent is released into the SB with a 2-4 mm protrusion in the MB. One balloon is advanced into the MB and the stent is implanted into the SB. The balloon is extracted from the SB and the MB balloon is inflated crushing the entire proximal edge of the SB stent. A new re-wiring of the SB is attempted and 2 balloons are introduced for simultaneous inflation (first kissing balloon). The balloons and the SB guidewire are removed and the stent is implanted into the MB covering the SB. The balloon is then removed and a new re-wiring of the SB is attempted. Two balloons are introduced, and the second balloon is simultaneously inflated (second kissing balloon).

Comparison between simple and complex techniques

As mentioned before, this type of comparison has been drawn many times in the medical literature. First, during the era of non-drug-eluting stents,[26] and even though no randomized clinical trials were conducted at the time, all observational comparisons suggested better results when using simple techniques.[26] During the era of drug-eluting stents, the trials were conducted again, randomized trials this time,[27-32] and they confirmed the previous findings on the non-superiority of complex techniques over the simple ones. These results also showed an abundance of meta-analyses that collected the same comparative studies and came to the same conclusions.[33-37] Thus, the European Bifurcation Club and European guidelines both recommend the use of the provisional stenting technique for the management of most coronary bifurcation lesions.[38] However, during the Transcatheter Cardiovascular Therapeutics Congress of 2017 the tables were turned after the presentation of the DKCRUSH-V[25] trial that confirmed better results with the DK crush technique versus the provisional stenting technique for the management of left main coronary artery

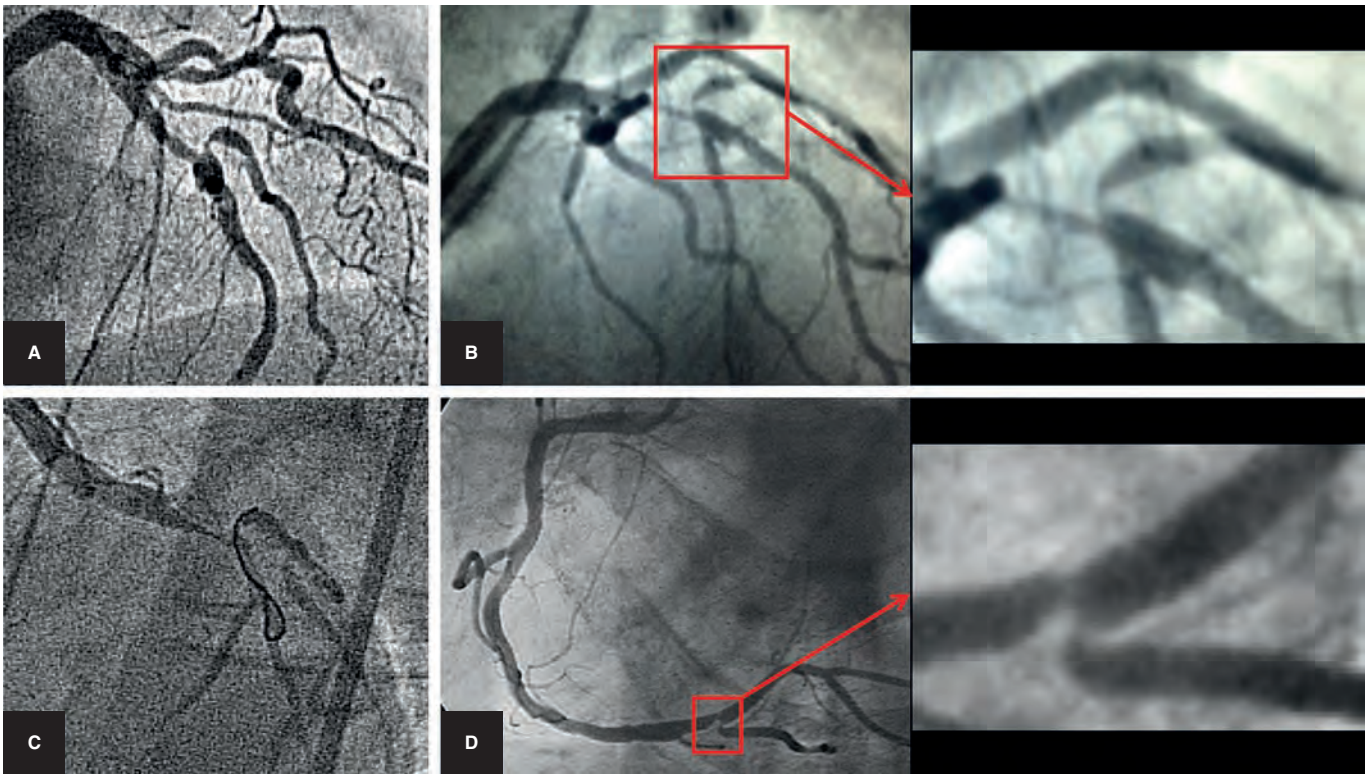

Figure 4. Difficult access to the side branch. **A, B**, and **C:** anterior descending artery/diagonal branch. **D:** right coronary artery/posterior descending artery. To the right: bifurcation angle in detail.

bifurcations. These findings contradicted all comparative studies published to that date. Also, the same group had already disclosed the same results for the management of bifurcations outside the left main coronary artery.[39] If we take these findings into consideration, we would have to change entirely our strategy when it comes to the management of bifurcations. What has been the reaction of the international scientific community to this?

While some have accepted this with no questions asked, others have criticized the paper published by Chen et al.[25]. We believe it has important limitations. Thus, in the arm of the provisional stenting technique no POT was used after the implantation of the stent in the left main coronary artery prior to the re-wiring of the circumflex artery. The percentage of patients randomized to the provisional stenting technique who crossed to 2-stent techniques was high (47%) and the rate of stent thrombosis (3.3%) too; both percentages are much higher that the percentages reported by other recent studies. Finally, most target lesion reinterventions at follow-up happened annually during the systematic angiographic reevaluation period. Thus, the last guidelines published so far on the management of revascularization[38] have issued a type IA recommendation to the provisional stenting technique (stronger recommendation than the one issued by former guidelines), while the DK crush technique has received a IIb recommendation only.

When should we plan a 2-stent technique right from the start?

Although, after all the studies published so far, there is general consensus on the use of the provisional stenting technique in most bifurcation lesions, there are special situations where 2 stent-techniques offer more advantages compared to the use of simple strategies:

- The first obvious situation here is when we have suboptimal outcomes in the SB when using the provisional stenting technique. Although this situation may seem clear to us, there is still controversy on what these suboptimal outcomes actually are. In this sense, coronary flows in the SB below TIMI 3 or the presence of a type A dissection are considered poor outcomes. However, the percentage of crossing to 2 stents is highly variable from one series to the next (from 2% to > 50%),[27-32,40] which may explain the lack of consensus on what poor outcomes in the SB really are.

- Another situation that may be an indication for using the 2-stent technique from the beginning is the presence of a long or diffuse lesion in a major SB. In these cases, it is assumed that the balloon angioplasty will not be successful (figure 5).

- Difficult access to the SB also seems like a good indication for stenting but only if the guidewire has been successfully inserted. Here the implantation of the stent into the MB may complicate things even more, which is why the 2-stent technique starting at the SB is recommended.

- When one bifurcation lesion is associated with a coronary occlusion, we may have important dissections affecting the origin of the SB induced by the process of recanalization.[41,42] Once again, in these case, the elective implantation of a stent into the SB prior to implanting another stent into the MB may be a good strategy.

- Lastly, SB restenosis after performing one simple procedure should also be followed by a second stent implanted in the SB (figure 6).[43]

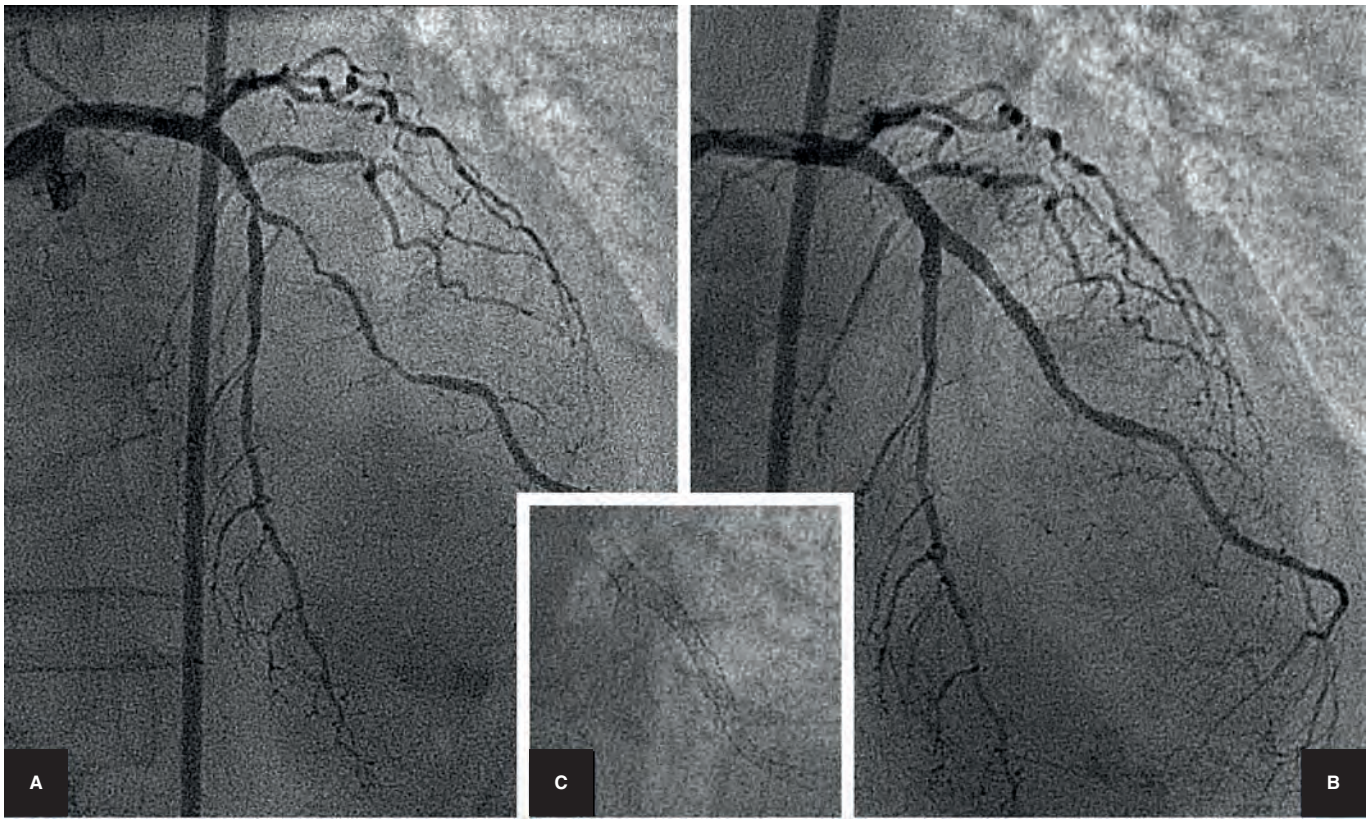

Figure 5. Bifurcation in the anterior descending artery with diffuse lesion in the side branch. Use of 2-stent technique from the beginning (cullotte). **A:** baseline angiography. **B:** final outcome. **C:** image obtained without contrast of the 2 stents.

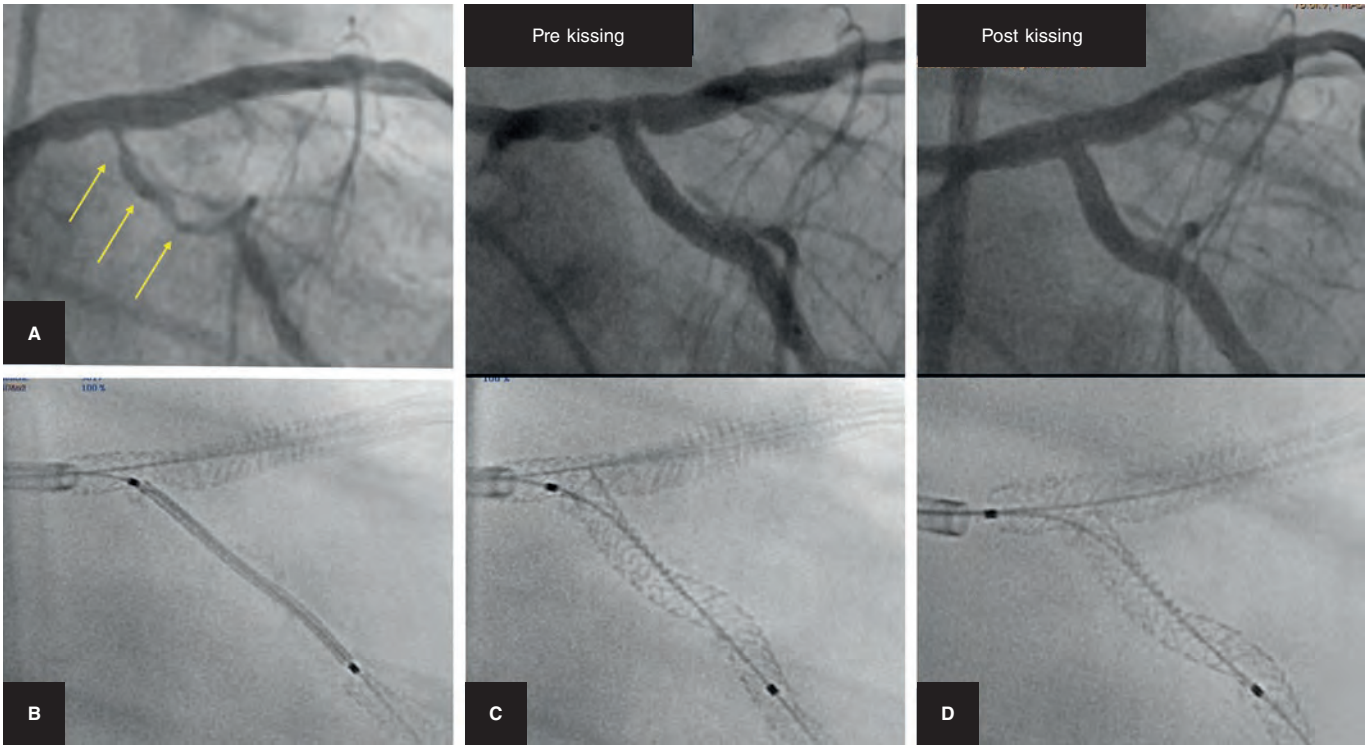

Figure 6. **A:** diffuse restenosis of the origin of the circumflex artery after treatment using the provisional stenting technique of left main coronary artery. Treatment using a second stent (T with protrusion in 2 stages). **B, C,** and **D:** stent boost of left main coronary artery during the different steps of the technique.

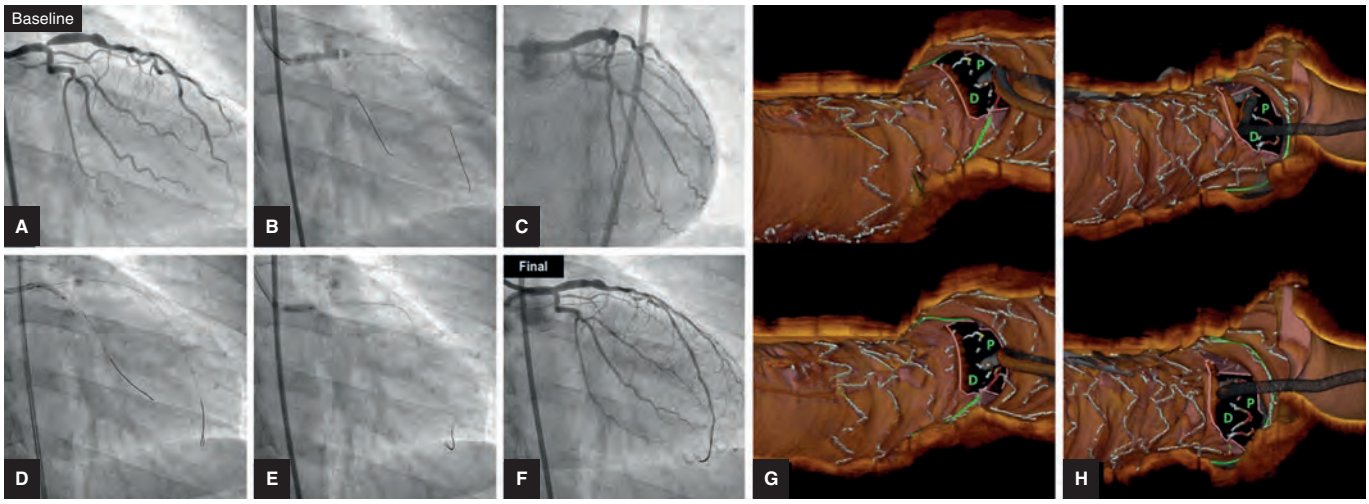

Figure 7. Treatment of an ostial lesion of the anterior descending artery using the provisional stenting technique. **A:** baseline angiography. **B:** stent in left main coronary artery/anterior descending artery. **C:** Compromise to the origin of the circumflex artery. **D:** dilation of the circumflex artery. **E:** proximal re-dilation (Re-POT). **F:** angiographic findings. **G:** optical coherence tomography, incorrect wiring of the circumflex artery through the proximal (P) cell. **H:** after a second attempt, the optical coherence tomography shows the guidewire through the distal cell (D) where dilation will finally occur.

ALTERNATIVES TO THE CORONARY ANGIOGRAPHY IN THE ASSESSMENT OF BIFURCATION LESIONS: IMAGING MODALITIES AND CORONARY PHYSIOLOGY

Intravascular ultrasound

The intravascular ultrasound (IVUS) is a useful tool to assess the lesion prior to treatment and the outcomes after the implantation of the stent. It provides information on the baseline anatomy of the lesion and the distribution of the plaque. This information allows us to make specific selections of the diameter and length of the stent we'll use, and is of paramount importance in the bifurcation of the left main coronary artery.[44] Additionally, the longitudinal withdrawal of IVUS allows us to look into the shape of the carina.[45,46] One sharp carina (the so-called eyebrow sign described by Medina) predicts a high risk of compromise of the SB after the implantation of the stent into the MB.[45,46]

Once the stent has been implanted, the IVUS is useful for the identification of deformities, under expansions and dissection of the stent edges.[47,48] All of these anomalies can be corrected and lead to immediate better outcomes, which has a positive impact on the follow-up of these patients.

Optical coherence tomography

The optical coherence tomography is another recent imaging modality that is actually newer than the IVUS. It has more resolution compared to the IVUS but not so much power of penetration. Another setback is that to be able to actually see the artery, the blood from the lumen needs to be cleaned using contrast or dextran.

During pre-treatment assessment, the optical coherence tomography provides similar information to the IVUS with the aforementioned advantages and drawbacks. Helping in the visualization of stent struts has really been revolutionary. Its resolution added to a new software allow the reconstruction of the stent almost as if we were looking at an in vitro study. It is a highly sensitive imaging modality for the identification of deformations, malappositions, and no expansions of the stent. At the same time, it gives us accurate information on the vessel-stent correlation, especially among the different cells and the origin of the SB. Also, it is the only imaging modality capable of establishing this correlation. Therefore, it allows us to diagnose the access to the SB through the proximal or distal cell. The recommendation here based on in vitro studies is to access through the distal cell, which provides better scaffolding of the branch and less deformity of the stent implanted in the MB. Monitoring the procedure through optical coherence tomography allows us to identify a proximal access and correct it for a more distal one (figure 7). The utility of this imaging modality for the management of bifurcations has been established in a consensus document approved by the European Bifurcation Club.[49]

Study of coronary physiology in bifurcation lesions

The indices of coronary physiology have proven useful in the assessment of angiographically intermediate lesions. They have specifically been used in bifurcated lesions to assess the outcomes of the SB when using the provisional stenting technique. In this situation, the angiography is very much limited to assess the outcomes in a dissected segment after balloon dilation. Proof of this is the great variability of crossing to a second stent in the aforementioned different series published by the medical literature. Fractional flow reserve is used here as an interesting source of information versus the angiography. Therefore, apparently poor angiographic findings show fractional reserve flow values above the cut-off value for treatment.[50] The arrival of new indices for the physiological assessment of coronary lesions opens a new field for the study of bifurcation lesions. The diastolic instantaneous wave-free ratio (iFR), an easy to obtain index that does not require the injection of adenosine, is promising for assessing the outcomes of the SB while using the provisional stenting technique[51] (figure 8).

CONCLUSIONS

The percutaneous management of coronary bifurcation lesions has changed dramatically over the last 20 years and the same thing has happened with the percutaneous management of non-bifurcated lesions. Significant advances have been made and strategies have been systematized for the management of most of these lesions. However, there are still some issued that we will have to solve in the years to come.

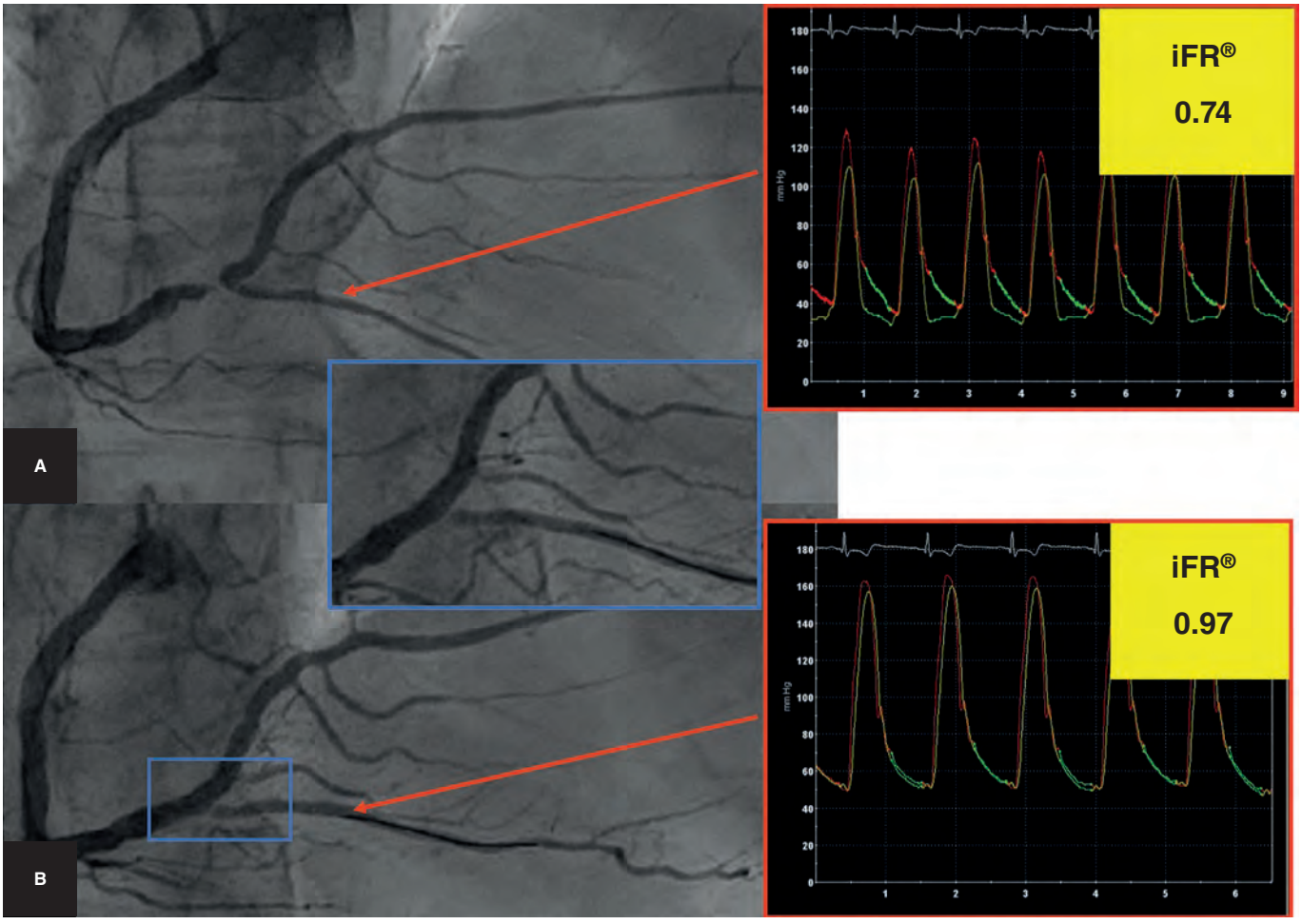

Figure 8. Monitoring of the outcome on the side branch (posterior descending artery) using the diastolic instantaneous wave-free ratio (iFR) diagnostic tool. **A:** baseline angiography. **B:** after the implantation of the stent into the main branch (right coronary artery). Angiographic compromise of the origin of the posterior descending artery with iFR values > 0.90, which is why further dilation will not be necessary.

CONFLICTS OF INTEREST

M. Pan received minor payments for his contributions or consulting jobs for Abbott, Terumo, and Philips. S. Ojeda has received minor payments for her presentations for Terumo, and Philips. A. Lostalo declared no conflicts of interest whatsoever.

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Debate: Closure of patent foramen ovale. A neurologist's perspective

A debate: Cierre del foramen oval permeable. Perspectiva del neurólogo

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Question: What would you say is the current state of the evidence on the closure of the patent foramen ovale (PFO)?

Answer: Recent randomized clinical trials show greater benefits with the closure of the PFO compared to the medical therapy in patients with PFO-related cryptogenic stroke (CS).[1-4] Despite a 64% risk reduction this benefit is only applicable to "high-risk patients" and requires a high number needed to treat (130 patients).[5] Also, there are several gaps that prevent the generalization of its therapeutic indication and required individual indications for every patient.

In spite of everything, to this day there is enough body of knowledge for the reasoned indication of medical therapy or the percutaneous closure of the PFO in patients with PFO-related CS. In this context, the European take on this issue may help. A document signed by 8 scientific societies including the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Heart Rhythm Association (EHRA), the European Association for Cardiovascular Imaging (EACVI), and the European Stroke Organisation (ESO).[6]

The arrival of a new technology or therapy is often like a roller-coaster and the closure of the PFO is not an exception. New discoveries and therapies are followed by unjustified euphoria based on intuition, which eventually leads to overuse. Also, there is no real evidence of its effectiveness followed by a significant risk for iatrogenic disease and, at best, a considerable futile investment. This is precisely what happened during the years when observational and cohort studies were conducted (from 1995 to 2011 approximately). Years of "disbelieve and denial" followed the appearance of the first results of clinical trials, all of which were negative.[7-9] The generalized refusal of the percutaneous closure of the PFO that followed these studies (from 2012 through 2018) was not justified either as the positive results of 4 clinical trials recently published show.[1-4]

Q.: Why do you think it has taken so many years since the first trial was conducted to show the benefits of the closure of the PFO? What is the difference between the first studies that were not positive and the latest ones that are?

A.: The problem with PFO-related CS is that it is not a very aggressive type of stroke with 2 key aspects that make it difficult to obtain solid results in the studies conducted:

- The PFO is very prevalent in healthy populations where it is not a relevant risk factor, which is a significant confounding factor.
- In patients with PFO-related CS, the risk of recurrence is low (annual 0.20% to 1.27%),[5,6] and both the traditional antiplatelet therapy and the percutaneous closure are effective.

The mere fact of showing traditional vascular risk factors like smoking, hypertension, diabetes or old age involves a higher risk of an early stroke and a higher risk of recurrence compared to the presence of PFO. This adds extra difficulty to the routine clinical practice since traditional vascular risk factors coexist with the presence of PFO.

The main problem here is to identify the subgroup of patients in whom the PFO is the direct cause for the stroke. Also, if the study design is assessing the effectiveness of a therapy regarding the risk of recurrence—since it is low—it requires, at best, a large sample and long follow-up. As an added difficulty, preemptive therapy with antiplatelet drugs is effective for the prevention of stroke recurrences in this context. Also, all clinical studies should be compared to this control group since it is already receiving effective treatment.

These aspects can be easily seen in 1 of the 3 negative studies published in 2012 (RESPECT),[8] which becomes 1 of the 4 positive studies after the 9-year follow-up of the original population who participated in the clinical trial was published back in 2017.[3]

Q.: From the clinical perspective and imaging modality standpoint, what patients are good candidates to benefit from the closure of the PFO?

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A: The presence of septal aneurysm or the detection of moderate-acute shunt have been strongly associated with the PFO as the cause for the CS both in clinical and observational studies[6,7] and with the benefits of closure compared to medical therapy.

The therapeutic decision and, in particular, the option to perform the closure of the PFO in patients who have suffered from a CS should be based on how we answer to these 2 questions:

- What are the chances that the PFO identified in the patient is the cause for the stroke and not just an innocent witness?
- If the PFO is the probable cause for the stroke, what is the risk of recurrence?

The most relevant utility factors to confirm the probability that the PFO is the direct cause for the CS are:

- Septal aneurysm.
- Moderate-acute right-to-left shunt (corresponding to the shower and curtain patterns on the transcranial Doppler ultrasound).
- Presence of deep vein thrombosis.

Other less relevant factors identified given the lack of prospective studies are:

- The presence of Eustachian valve, Chiari network or PFO extensive channel.
- Clinical aspects indicative of paradoxical embolism: consistent with the Valsalva maneuver, prolonged immobilization, tourist class syndrome, thrombophilic status, etc.
- Age < 55 years old.
- Score obtained in the RoPE grading system[10] as an additional tool in this evaluation and in association with previous parameters.
- Lack of traditional cardiovascular risk factors.

No neuroimaging patterns have been identified consistently associated with the causal role played by the PFO in the development of CS.

Regarding the assessment of the risk of recurrence, no variable *per se* facilitates any quantitative predictions.

The high-risk patients of clinical trials should be candidates for the closure of the PFO because they are the subgroup in which the analysis of results shows clinical and statistically significant differences (relative risk, 0.27; 95% confidence interval [95%CI], 0.11-0.70).[5]

Old age does not exclude a causal PFO-related CS. As a matter of fact, a similar risk has been reported in young patients. However, to this day we should not consider the percutaneous closure of the PFO given the relatively low risk of recurrence, the profile of patients in the clinical trials (18-60 years old), and the long-term benefit shown with an unfavorable cost-effectiveness ratio for the percutaneous closure in this age group.

To indicate the closure of the PFO these factors are especially important:

- Interatrial septal aneurysm (odds ratio [OR], 3.0; 95%CI, 1.8-4.8).
- PFO of a large size or right-to-left shunt (OR, 3.0; 95%CI, 1.9-4.6).
- In particular, the association between interatrial septal aneurysm and acute shunt.

Other factors identified that should be taken into account are:

- Thrombophilic status (OR, 2.75; 95%CI: 1.17-6.49).
- Previous treatment with acetylsalicylic acid vs oral anticoagulants (OR, 2.5; 95%CI, 1.1-6.1).
- Infarction vs transient ischemic attack as clinical presentation including infarction seen on neuroimages (OR, 3.0; 95%CI, 1.4-6.5).

Q.: What is the best medical therapy after the closure of the PFO?

A.: There is significant controversy among the different guidelines and there are no solid pieces of evidence. Considering that the endothelization process can extend for up to 5 years after the implantation,[6] that clinical trials kept antiplatelet therapy for, at least, 2 years (5 years in 2 of them), and the overall behavior of ischemic stroke and, in particular, CS the pattern should be: keep dual antiplatelet therapy for a month and continue with single antiplatelet therapy (acetylsalicylic acid, 100 mg/day) for, at least, 2 years (5 years if we follow the European recommendation).

At 5 years, before withdrawing antiplatelet therapy, the patient should be assessed by a stroke expert to decide on the withdrawal of the treatment based on the patient's clinical profile (age, coexisting factors of vascular risk, PFO total occlusion or residual shunt, life habits, tolerance to treatment, etc.).

Q.: Which should be the next trial in this setting?

A.: These are some of the aspects that are still under discussion and should be taken into consideration in future trials:

- Better identification of the profile of high-risk patients including the analysis of additional or current risk factors (older age, severity of shunt in baseline conditions, size of interatrial septal aneurysm, presence of Chiari network or Eustachian valve, etc.).
- Conduct adequately designed clinical trials to see the potential benefits of direct-acting oral anticoagulants compared to the percutaneous closure of the PFO.
- Obtain long-term follow-up information since the potential benefit of the closure of the PFO is cumulative over time and the long-term risk of medical therapy is not very well known.
- Assess not only the risk of recurrence, but also quality of life including the degree of disability in basic activities of daily living after recurrence (eg, routine use of the Rankin modified scale in acute stroke studies).

Additionally, observational prospective registries should be conducted in the clinical practice.

In conclusion, to this day we have enough scientific evidence to conclude that the closure of the PFO is superior to antithrombotic therapy regarding the risk of recurrence in patients with PFO-related CS. Patients with interatrial septal aneurysm or massive shunt could benefit the most from this intervention. Future studies should analyze the closure of the PFO in patients not included in the trials like patients > 60 years and patients with other associated cardiovascular risk factors.

CONFLICTS OF INTEREST

None reported.

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Debate: Closure of patent foramen ovale. The interventional cardiologist perspective

A debate: Cierre del foramen oval permeable. Perspectiva del cardiólogo intervencionista

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Question: What would you say is the current state of the evidence available on the closure of patent foramen ovale (PFO)?

Answer: The closure of PFO to prevent embolic events has been a matter of discussion for cardiologists and neurologists in the therapeutic decision-making process for years. The main reason was the lack of randomized clinical trials showing the efficacy (or inefficacy) of performing this percutaneous procedure in certain patients diagnosed with cryptogenic stroke. After the publication of 3 randomized clinical trials in 2017 in one of the highest-impact medical journals and posterior meta-analysis, the results suggest long-term clinical benefits in patients with certain anatomical, echocardiographic, and clinical characteristics who have suffered a stroke (or neurological event of embolic profile) without apparent reason.[1]

Thus, today, heart teams led by neurologists specialized in cerebrovascular disease and interventional cardiologists should assess together the eligibility of these patients. According to studies recently published, certain criteria that can be established individually are predictors of benefits from the percutaneous closure of PFO: age < 60 years old; presence of interatrial septal aneurysm; acute right-to-left shunt; presence of redundant Eustachian valve or Chiari network in the right atrium; and even a length of the PFO tunnel > 10 mm.

Unlike the favorable evidence available on the reduction of long-term embolic events, there is concern on the growing number of atrial fibrillation (AF) events consistently observed in populations treated with devices for the closure of PFO. There may be 2 reasons for this: the existence of a misdiagnosed arrhythmogenic substrate in the form of paroxysmal AF that may be causing the embolic event or the direct correlation between AF and the intracardiac device implantation since many FAs are detected postoperatively within the first few weeks. The need to detect more effectively the presence of FA events in patients with cryptogenic stroke has increased the use of prolonged electrocardiogram tests in the form of prolonged Holter monitoring or subcutaneous Holter to register heart rhythm.

Q.: Why do you think it has taken so many years since the first trial was conducted to show the benefits of the closure of PFO? What is the difference between the first studies that were not positive and the latest ones that are?

A.: In my opinion, there are a number of reasons that can justify the lack of scientific evidence until recently. First, the development of safer and more effective devices, since the first trials were conducted with less optimal devices that are no longer in use. Second, the experience of interventional cardiologists in the management of structural heart disease has grown exponentially over the last 10 years with the development of units specialized in non-coronary procedures. Third, rigor in the study design and conduction and in the selection of patients eligible from the clinical and imaging modality standpoints (bubble echocardiogram; transesophageal echocardiograph; transcranial Doppler ultrasound; magnetic resonance imaging) has improved diagnosis and contributed to plan proper therapeutic strategies. Finally, the recruitment rate of the first clinical trials was very slow, indicative of reluctance from patients and doctors to participate in these trials.

Q.: From the clinical perspective and imaging modality standpoint, what patients are good candidates to benefit from the closure of PFO?

A.: Clinical trials have been recruiting patients < 60 in a similar way thinking that, at that age, the appearance of embolic events may be justified for other reasons (arterial hypertension, diabetes mellitus, hypercholesterolemia, subclinical atheromatous disease, active smoking).

The importance of imaging modalities, in particular echocardiography, has consolidated steadily. On the one hand, transthoracic

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bubble echocardiogram with bubble study (agitated saline solution) can identify the presence of an interatrial septal shunt and determine the severity of right-to-left shunt. Also, the transcranial Doppler ultrasound can quantify the right-to-left shunt considered serious in the presence of shower and curtain pattern. An acute, at least moderate, shunt has been identified as a predictor of greater benefit following the closure of PFO.

The transesophageal echocardiogram prior to the procedure is highly recommended. It discards abnormalities not found on the transthoracic echocardiogram like the presence of other septal defects (multiperforated septa) or even interatrial communication and identifies the presence of interatrial septal aneurysm, Chiari network or redundant Eustachian valve. Several studies identify the aneurysm as a predictor of embolic recurrences[2]; also, it can complicate the procedure when deciding the size and shape of the device that will be used.

Recently, the importance of a large Chiari network and a redundant Eustachian valve has been reported. The implication here is trying to divert blood flow from the inferior cava vein towards the septum in order to favor the passing of thrombi through the PFO.

The length of the PFO tunnel and its degree of separation—clearly visible on the transesophageal echocardiography and important to plan the procedure—has not been studied very much. However, it may be associated with greater benefits from the closure of PFO when the separation is wide (> 4 mm) and the tunnel is long (> 10 mm).[2]

Q.: Are there relevant differences among different devices?

A.: There are several specific devices available for the closure of PFO. To make things easier we can distinguish between 2 different types: double-disc devices (most of them) and devices with different designs. Design is important for several reasons: in the first place because it must seal the shunt completely; secondly, it must be safe enough to not cause any associated problems like the formation of thrombi on the device or the erosion or perforation of interatrial septum or adjacent structures (atria, aorta) that would lead to potentially serious complications. On the other hand, the impact that the implantation of an intracardiac foreign body has on the appearance of atrial tachyarrhythmias (in particular, AF) should be minimal because it can condition antithrombotic therapy after the implant or promote the appearance of embolic events. And lastly, the highly rare (but still worthy of being taken into consideration) possibility that the patient is allergic to some of the metals these devices are made out of, especially nickle.

Double-disc devices are very similar to one another, they have been around for quite a while (they are the most widely used devices of all), there is a wide range of measures, and they are highly effective for the complete closure of PFO. Regarding other designs, maybe the most original of all is the one that allows direct suture of PFO and anchoring of minimal residual material to interatrial septum. Its pitfall is the greater complexity of the procedure and little experience of the results especially in the long-run.

Actually, the objective is to achieve the complete closure of the shunt through the septum without side effects or immediate or long-term complications associated with the device or the most widely used technique, either one of the two.

Q.: Which should be the next trial in this setting?

A.: We have learned from previous trials how difficult it is to randomize patients with this condition due to the reluctancy of patients and doctors.

Now, after seeing all the evidence available in the medical literature, it does not seem logical to repeat similar trials to compare drugs and devices. It is not easy to come up with an original design in this setting because the low rate of events requires longer follow-ups. In my opinion, comparing devices to one another does not make too much clinical sense here. An option would be to reconsider the possible efficacy of the closure of PFO in patients with migraines and right-to-left shunt. Using specific and selected criteria; proper neurologist-cardiologist coordination; follow-up images; biomarkers; and quality of life surveys, patients eligible to undergo the percutaneous closure of PFO vs targeted medical therapy could be randomized. Also, the efficacy and safety endpoints could be assessed in both groups.

CONFLICTS OF INTEREST

F. Hernández Hernández is a proctor of percutaneous closure of patent foramen ovale for Abbott, Izasa, Cathmedical Cardiovascular and SMT.

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Clinical case

Simultaneous transfemoral TAVI and angioplasty of unprotected trifurcated left main coronary artery

Procedimientos simultáneos de TAVI transfemoral y angioplastia de tronco común trifurcado no protegido

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CASE PRESENTATION

Eighty-two year-old-woman with a past medical history of high blood pressure, dyslipidemia, primary hypothyroidism, iron deficiency anemia, chronic renal disease, a glomerular filtration rate of 52 mL/min, an episode of ischemic colitis resolved using conservative therapy 2 years ago and documented peripheral arterial disease with carotid artery atheromatous plaque without significant stenosis.

The patient showed long-term degenerative aortic valve disease with double aortic lesion with severe stenosis (mean flow velocity, 4.1 m/s; mean gradient, 42 mmHg; valve area, 0.98 cm^2) and mild-to-moderate regurgitation, with preserved left ventricular ejection fraction, and symptomatic in class II of the New York Heart Association for dyspnea. The patient complained of episodes of non-exertional angina for which she required several hospital admissions over the last few months.

The coronary angiography revealed coronary artery disease of the left main coronary artery and 2 vessels: calcified and elongated left main coronary artery with a borderline significant distal lesion affecting the bifurcation with the anterior descending coronary artery, 2 ramus medianus and the circumflex coronary artery; the anterior descending coronary artery with a severely calcified ostial lesion, first and second ramus medianus with significant calcified ostial lesions, and circumflex coronary artery with a moderate ostial lesion (figure 1,

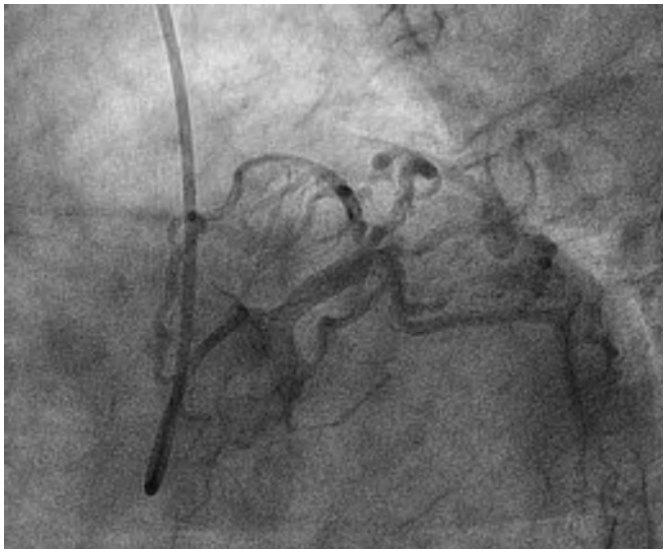

Figure 1. Coronary angiography in caudal left-anterior-oblique view showing significant distal left main coronary artery disease with damage to the anterior descending coronary artery and two intermediate branches.

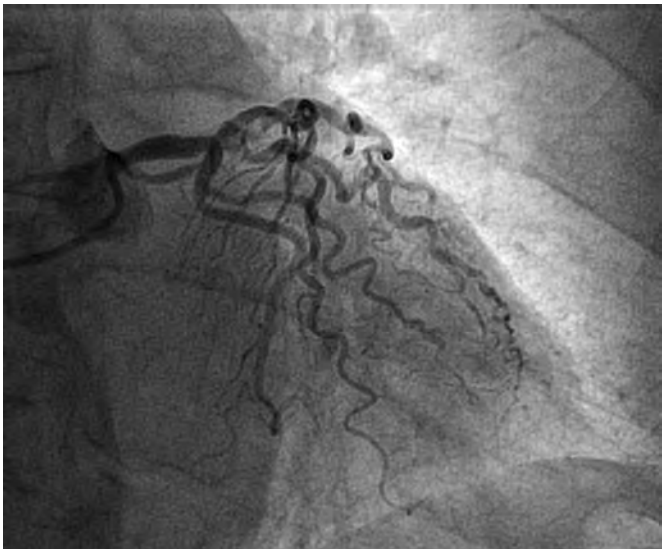

Figure 2. Coronary angiography in caudal right-anterior-oblique view.

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figure 2 and video 1 of the supplementary data) with a narrow-caliber and short distal vessel. The aortogram showed a calcified tricuspid aortic valve with limited opening of the leaflets and mild aortic regurgitation and nondilated aortic regurgitation root and ascending aorta without significant atheromatosis (figure 3 and video 2 of the supplementary data). The arteriography of the lower limbs showed a non-calcified, non-tortuous iliac-femoral axis with a minimum diameter of 7.3 mm in the right common femoral artery and a minimum diameter of 7.7 mm in the left common femoral artery. The short-term risk according to the Society of Thoracic Surgeons was 10.79%.

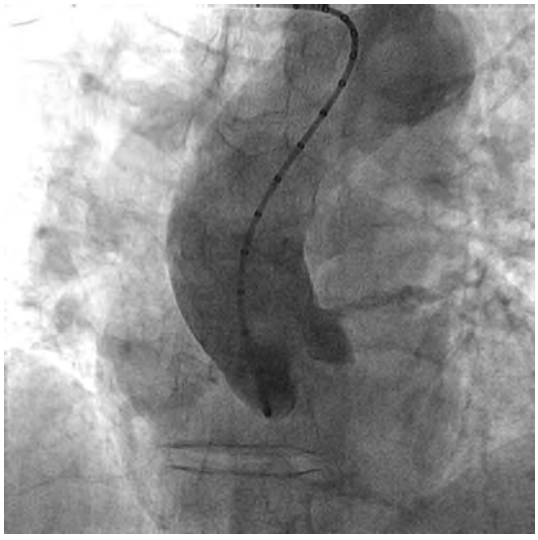

Figure 3. Aortogram showing one tricuspid aortic valve with moderate calcification of the leaflets, nondilated aortic root and ascending aorta without significant atheromatosis.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000047.

Simultaneous transfemoral TAVI and angioplasty of unprotected trifurcated left main coronary artery. How would I approach it?

Procedimientos simultáneos de TAVI transfemoral y angioplastia de tronco común trifurcado no protegido. ¿Cómo lo haría?

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https://doi.org/10.24875/RECICE.M19000047
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HOW WOULD I APPROACH IT?

This is a a challenging case that combines severe coronary artery disease of trifurcated left main coronary artery and severe aortic stenosis in an elderly female patient with chronic kidney disease.

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According to the current clinical guidelines, this patient whose score in the Society of Thoracic Surgeons score is > 10% and with good femoral accesses has an I-B indication for a transcatheter aortic valve implantation (TAVI). No other factor supports performing surgery except for the existence of coronary artery disease, which could be considered eligible for coronary artery bypass graft given the complexity of the left main lesion and the presence of good distal beds. However, what makes this patient's surgical risk nearly unacceptable is the combination of a valve replacement procedure plus coronary bypasses, so if a better percutaneous option is available, and we believe there is, such an option should be pursued. After establishing the indication for TAVI, there is a II-A indication for percutaneous revascularization since the percent diameter stenosis is > 70% in proximal segments, the Syntax I score estimated using the data available is 27 points (29 if intense calcification is considered) and after adding clinical data tinto consideration, the Syntax II score shows a 4-year mortality rate after percutaneous coronary intervention (PCI) of 44.2% vs 33.6% after surgery. All this leaves the decision making process open since the risk involved in both strategies is high. In this case we might choose PCI plus TAVI.

Another controversial aspect is whether PCI and TAVI should be performed simultaneously or as a 2-staged procedure.

The arguments in favor of performing both procedures separately are:

- One of the most important factors to consider when choosing which procedure should come first is the amount of contrast that will be used since the glomerular filtration rate (52 mL/min) and the patient's age elevate the risk of contrast-induced nephropathy. If we follow to the current recommendations that establish a ratio < 3.7 between the amount of contrast administered and the glomerular filtration rate to reduce the risk of contrast-induced nephropathy, the maximum amount of contrast for this patient should be 192.4 cc, which may seem somehow shorthanded for the concomitant management of a trifurcated left main coronary artery and a TAVI procedure. Also, it is necessary to perform a computed tomography scan to plan the TAVI which, in turn, increases the amount of contrast that will eventually be needed. This is why a two-staged procedure seems to be the safest approach.

- The time elapsed between the PCI and the TAVI (we would suggest 4-6 weeks) would allow to assess the response to the PCI after stent endothelization.

- Possibility to perform an aortic valvuloplasty as bridge therapy to TAVI as long as the baseline aortic regurgitation is not significant (in this case it was described as mild in the aortography).

The arguments in favor of performing both procedures simultaneously are:

- Using the secondary femoral access for the PCI with a 8-Fr catheter.

- Using the guiding catheter system and the coronary guidewire for the TAVI with protected left main stem (LMS) during valve implantation.

- Shorter hospital stay.

- The use of contrast may be limited by using additional imaging modalities such as intravascular ultrasound (IVUS) for the management of the left main coronary artery, transesophageal ultrasound for the TAVI, fusion imaging technology such as the Heart/EchoNavigator system or ultrasound-guided femoral access. Also, pigtail catheters can be placed in every aortic sinus to find the coplanar view and guide the implant without the need for contrast.

Taking all this into consideration, and only if the patient's clinical situation allows it, the first step would be to plan the PCI with aortic valvuloplasty and 4-6 weeks later, the TAVI procedure.

Therefore, this is how the management of the LMS should be:

- Secondary femoral access (left) of 8-Fr or 9-Fr based on the type of balloon that will be used for the valvuloplasty.

- 3.5 or 4.0 8-Fr EBU guiding catheter.

- Guidewires to the anterior descending artery (DA) and to both intermediate branches.

- IVUS from the LMS to the DA, intermediate and circumflex branches to assess the distal LMS and the degree of calcification in the ostium.

- In case of circumferential calcification, use rotational atherectomy: if not, predilatation with scoring or cutting balloon.

- Use the DA as the main branch and based on the IVUS findings:

  - If the IVUS on the intermediate branches shows limited damage: use the provisional stenting technique, predilatation of both secondary branches, and stent implantation from the LMS to the DA using the proximal optimization technique to adapt to the disproportionate caliber. If necessary due to poor outcomes in 1 or 2 branches, we would use the T-stenting technique and protrusion or inverted T-stenting with recrossing plus final triple kissing balloon. The use of a drug-eluting balloon may be considered for accessory branches.

  - If the IVUS conducted on both intermediate branches and LMS shows disease with poor predictors of good outcomes without stent implantation: use the triple-stenting technique, the double kissing crush stent technique (stent to both intermediate branches as secondary branches covering the ostium and slightly protruding into the LMS), one final stent from the LMS to the DA, recrossing towards both branches with sequential kissing-balloon plus final triple kissing balloon.

- In both options the circumflex branch is considered a secondary branch with the strategy of keeping it open but not treating it right away.

- Percutaneous closure using the Perclose ProGlide Suture Mediated Closure (Abbott Vascular, Redwood, CA, United States).

Regarding the type of valve, in this decision it is of paramount importance to take into consideration the possible need to access the LMS after the TAVI especially if we think that the rate of restenosis in trifurcations treated with 2 or more stents is usually high. The height of the LMS ostium the length and calcification of the leaflets and the width of the sinuses should all be studied by computed tomography scan prior to planning the implantation and choosing the device. The advantage of the expandable balloon device is that it is shorter preventing in many cases the jailing of the LMS; the setback is that overpacing is required for implantation purposes. Self-expandable and fully recapturable devices can be implanted without overpacing and with little contrast if using fusion imaging technology or transesophageal ultrasound; the setback is that, although these devices have wider cells, the LMS is jailed, which could make access difficult after implantation. Nevertheless, the interventional team should use the model they are most experienced with.

Simultaneous transfemoral TAVI and angioplasty of unprotected trifurcated left main coronary artery. Case resolution

Procedimientos simultáneos de TAVI transfemoral y angioplastia de tronco común trifurcado no protegido. Resolución

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CASE RESOLUTION

After assessment by the Heart Team and taking the patient's age and high surgical risk into consideration, surgical treatment was discarded. The study was completed with a computed tomography angiography that confirmed that the patient was eligible for transcatheter aortic valve implantation (TAVI) through transfemoral access (figure 1A,B).

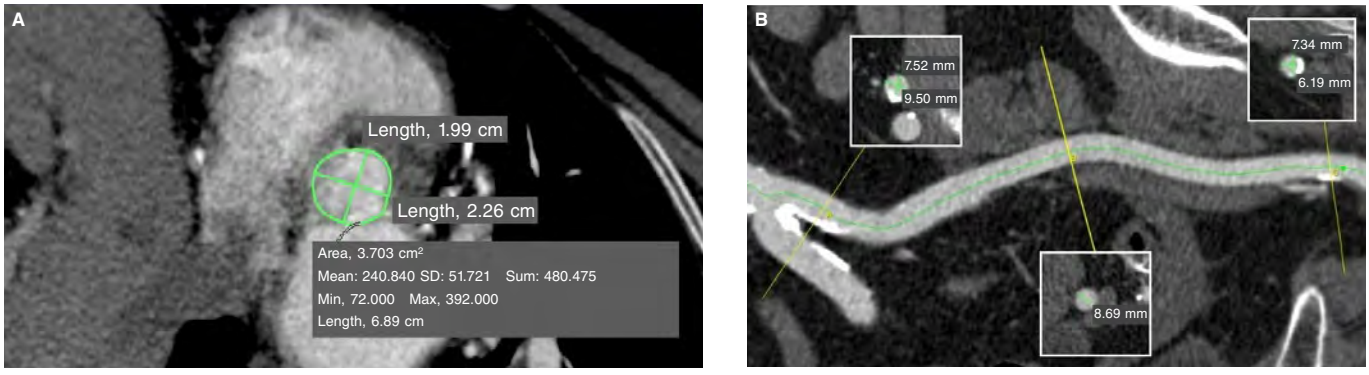

Figure 1. Computed tomography angiography prior to the procedure. **A:** measurements of the aortic valve ring: minimum diameter, 1.99 cm; maximum diameter, 2.26 cm; perimeter, 6.89 cm; area-derived perimeter, 3.70 cm^2. **B:** measurements of the left iliac-femoral axis: minimum diameter of the common femoral artery, 6.19 mm; minimum diameter of the external iliac artery, 8.69 mm; minimum diameter of the primitive iliac artery, 7.52 mm. M, mean; max, maximum; min, minimum; s, sum; SD, standard deviation.

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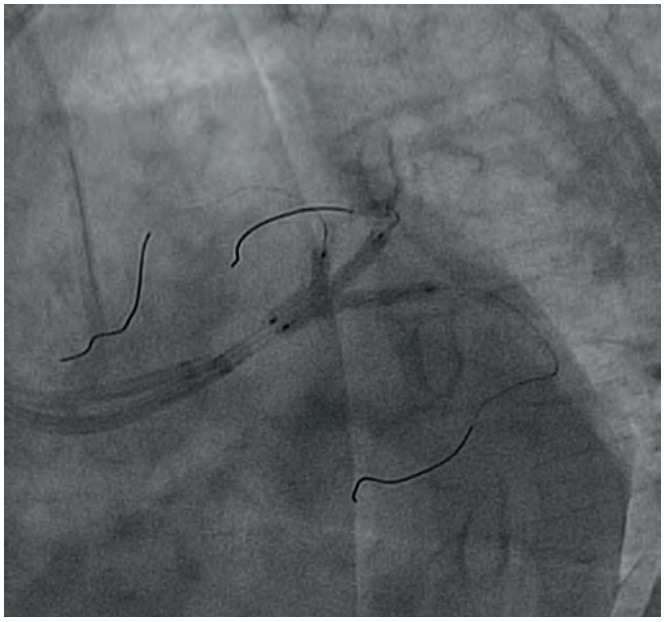

Figure 2. Simultaneous implantation of 3 drug-eluting stents in the anterior descending artery and intermediate branches.

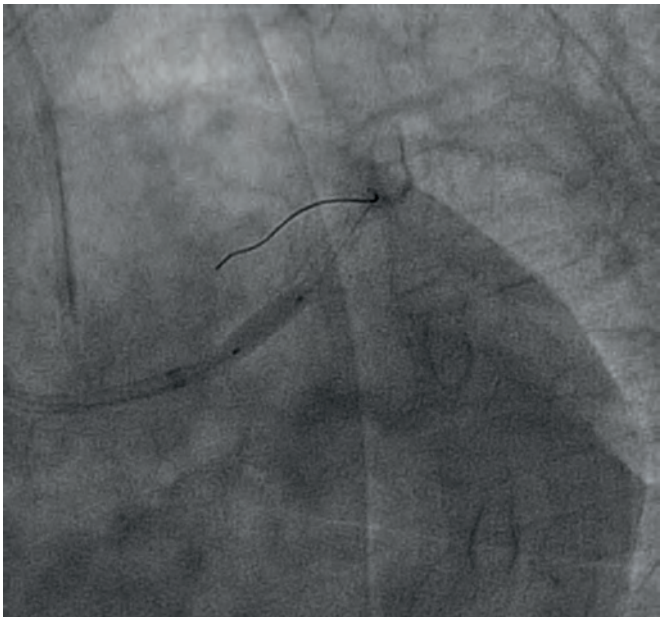

Figure 3. Implantation of a drug-eluting stent in the left main coronary artery.

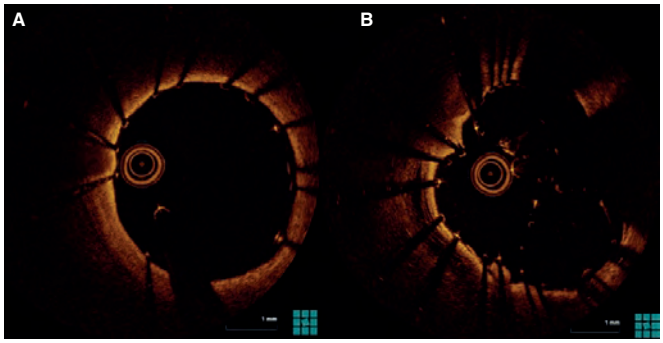

Figure 4. Optical coherence tomography after percutaneous coronary intervention. Good expansion and apposition of the drug-eluting stent in the left main coronary artery **(A),** and of the stents deployed in the trifurcation with adequate lumen **(B).**

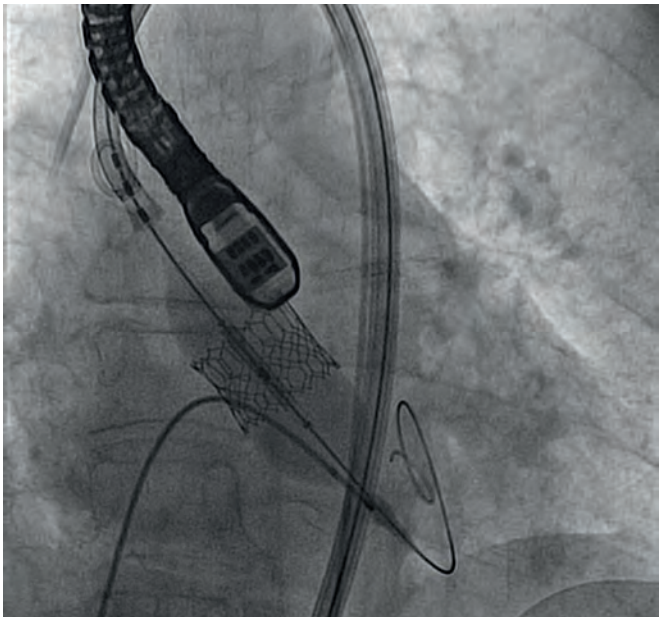

Figure 5. Implantation of an expandable aortic valve with a 23 mm balloon.

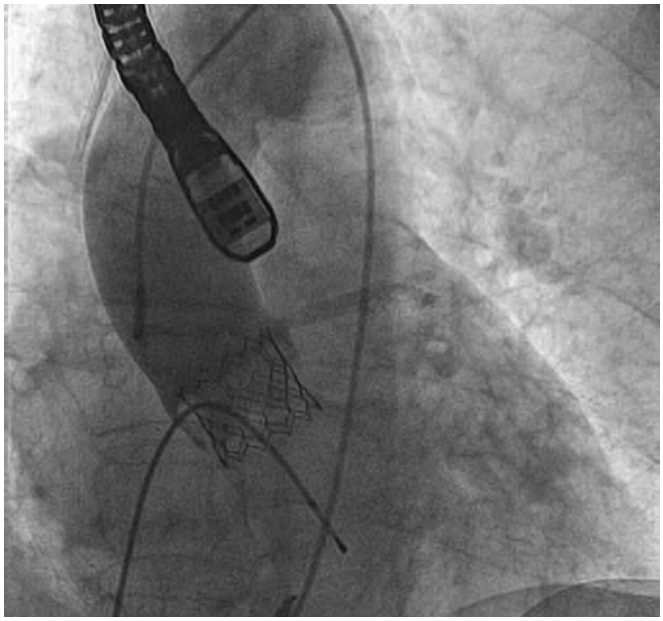

Figure 6. Final aortogram. Correct alignment of aortic valve leaflets and stents patency.

The procedure was performed under general anesthesia using the bilateral femoral access. Two 6-Fr, and 7-Fr Extra Back Up (EBU) guiding catheters were inserted into the left main coronary artery (using the "ping-pong" guiding catheter technique). Both the coronary ostia of the anterior descending coronary artery and the intermediate branches were sequentially predilated using one 2.0 mm cutting balloon (video 1 of the supplementary data) and 3 drug-eluting stents were simultaneously implanted in the anterior descending coronary artery (2.25 x 15 mm sirolimus-eluting stent), the first intermediate branch (2.25 x 18 mm zotarolimus-eluting stent), and in the second intermediate branch (2.25 x 18 mm sirolimus-eluting stent) and in this order; then we proceeded with the simultaneous inflation of the balloons (figure 2). Finally, a fourth drug-eluting stent was implanted (a 4 x 8 mm zotarolimus-eluting stent) in the left main coronary artery (figure 3 and video 2 of the supplementary data) with good results according to the optical coherence tomography (figure 4A,B). Immediately after the percutaneous coronary intervention (PCI), an expandable aortic valve with a 23 mm balloon was implanted (figure 5 and video 3 of the supplementary data) also with good results (figure 6 and video 4 of the supplementary data).

At the 28-month follow-up, the patient remained asymptomatic and with a normal functioning aortic valve.

In patients with severe aortic stenosis and left main coronary artery disease deemed to be at high surgical risk, using combined procedures (TAVI and PCI) is safe, feasible and with similar results compared to an isolated TAVI procedure.[1] The combination of PCI plus TAVI on the left main coronary artery trifurcation lesion is rare.[2] This case shows a safe non-surgical management of a left main coronary artery trifurcation lesion and severe aortic stenosis with good long-term results.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000049.

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REC Interv Cardiol. 2020;2(1):55-58

Clinical trial review

Onyx ONE trial: a new option in patients at high risk of bleeding

Estudio Onyx ONE: una nueva opción en pacientes con alto riesgo de sangrado

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INTRODUCTION

Due to the commotion caused by the growing number of late thrombosis after drug-eluting stents implantation back in 2005,[1] 1 year courses of dual antiplatelet therapy (DAPT) were recommended after the implants. The lower rate of this complication thanks to improved designs of the device has made it possible to shorten these courses. The shortest courses of DAPT are still under discussion[2-4] (figure 1), yet 1-month courses of DAPT with further withdrawal of 1 of the 2 drugs has been agreed on. However, most 1-month DAPT studies have been conducted with low-risk patients[5,6] or have focused on patients with stable coronary artery disease.[7]

With the progressive aging of the population, comorbidity, and the higher rate of atrial fibrillation, it has become more and more common to find patients at high risk of bleeding and rates of 15%.[8] In the LEADERS FREE clinical trial[9], the BioFreedom biolimus A9-eluting stent (Biosensors, Switzerland) without polymer and a stainless steel stent platform proved superior to conventional stents in patients at high risk of bleeding and on a 1-month course of DAPT with clopidogrel. Ever since, it has become the reference device in this type of patients.

To this day, the Resolute Onyx chromium-cobalt stent with zotarolimus and permanent polymer (Medtronic, United States) showed safety data with the 1 month course of DAPT,[10] but no specific randomized clinical trials had been conducted on this issue. However, there were data available on a previous model with zotarolimus in this context, the Endeavor Sprint stent (Medtronic, United States), but with a different drug-release kinetics and off the market for quite a few years now.[11] In the Onyx ONE clinical trial (NCT03344653), the Resolute Onyx stent was compared to the BioFreedom stent in patients at high risk of bleeding. The objective of this review was to analyze such study and put it into context with recent studies published on 1-month courses of DAPT.

DESIGN

The Onyx ONE is a prospective, randomized, multicenter study that compared the safety and efficacy profiles of the chromium-cobalt Resolute Onyx stent with permanent polymer and zotarolimus to the BioFredom biolimus A9-eluting bare-metal stent without polymer in patients at high risk of bleeding and on a 1-month course of DAPT.

The primary endpoint was a composite of cardiac death, infarction, and definitive or probable stent thrombosis at 1 year. The secondary endpoint for which the statistical power of the study was designed, was target lesion failure defined as the factors already mentioned plus ischemia-related lesion revascularization.

Other secondary endpoints were the success of the target vessel, device, procedure, BARC (Bleeding Academic Research Consortium Definition of Bleeding) bleeding score, and each particular component of the primary endpoint. Inclusion criteria are shown on table 1, they are exactly the same ones as those used in the LEADERS FREE study,[9] and focus on patients at high risk of bleeding.

A crucial aspect of this study is antithrombotic regimens. During the first month, all patients should receive 75-100 mg/day of acetylsalicylic acid (ASA) plus a $P2Y_{12}$ receptor inhibitor, preferably clopidogrel. In patients on oral anticoagulation, during this first month, single antiplatelet therapy or DAPT were allowed. After the first month, 1 of the 2 antiplatelet drugs was withdrawn, one or the other.

Its non-inferiority design included 2000 patients randomized on a 1:1 basis with an estimated event rate in each arm of 9.4 for the primary endpoint and a non-inferiority margin of 4.1%. In record time, the study was completed with 1996 patients and a final follow-up period of 98% in both study groups between November 2017 and September 2018.

RESULTS

The mean age of both groups was > 74 years-old and the percentage of diabetics was > 38%. A third of these patients showed atrial fibrillation and the indication was distributed equally between the group of stable patients and those with acute coronary syndrome (ACS), yet only 5% showed ST-segment elevation. The 4 most common inclusion criteria were age ≥ 75 years-old (61% of the patients); oral anticoagulation (38%); anemia or transfusion during the last year (15%) and creatinine clearance < 40 mL/min (15%).

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	2017	2018	2019	2020	2021	2022
1 month on DAPT	**SENIOR** NCT02099617 Synergy	**GLOBAL-LEADERS** NCT01813435 BioMatrix **LEADERS-FREE II** NCT02843633 BioFreedom	**POEM** NCT03112707 Synergy **COBRA-REDUCE** NCT02594501 Cobra, EES, ZES **YONSEI DAPT** NCT02513810 BioFreedom **XIENCE 28 GLOBAL** NCT03355742 Xience **MASTER DAPT** NCT03023020 Ultimaster **Onyx ONE** NCT03344653 ZES-BioFreedom			**STOPDAPT-2** NCT02619760 Xience
3 months on DAPT	**REDUCE** NCT02118870 Combo	**SMART-CHOICE** NCT02079194 Without restriction regarding the type of drug-eluting stent	**MODEL U-SES** NCT02837003 Ultimaster **EVOLVE Short DAPT** NCT02605447 Synergy **TWLIGHT** NCT02270242 Without restriction regarding the type of drug-eluting stent	**XIENCE 90** NCT03218787 Xience		**HOST-IDEA** NCT02601157 Orsiro, Coroflex ISAR
6 months on DAPT	**DAPT-STEMI** NCT01459627 RI-ZES	**ISAR-DAPT** NCT02609698 Coroflex **SMART-DATE** NCT01701453 RI-ZES, EES, BioMatrix Flex				

Figure 1. Studies with short courses of dual antiplatelet therapy. DAPT, dual antiplatelet therapy.

Lesions were type B2 or C in 80% of the cases, and the length of the vessel covered by the stent was 37 mm. No differences were seen in the target lesion and procedural success, yet the Resolute Onyx stent group had better results in success with the device. Crossing from this group to the BioFreedom group occurred in 2 cases, and from this group to the Resolute Onyx group in 40 cases. On the other hand, the zotarolimus-eluting stent also showed significant differences with less residual stenosis and more initial angiographic gain.

Two months after the procedure, 92% of the patients remained on single antiplatelet therapy, 56% on ASA and 44% on clopidogrel. These same percentages remained for a whole year, when 88% of the patients were still on single antiplatelet therapy.

The primary endpoint of non-inferiority was met with an event rate of 17.1% in the Resolute Onyx group and 16.9% in the BioFreedom group (difference, 0.2%; upper limit of the confidence interval, 3.0%; *P* value for non-inferiority = .011). No significant differences were found on the event rate for each particular component of the primary endpoint or on the secondary endpoint of target lesion failure. No differences were reported either in the rates of BARC bleeding (table 2).

DISCUSSION

Who is the winner in this study?

In conclusion, it can be said that the results obtained have been similar with both *stents,* except for the greater success achieved with the Resolute Onyx stent due to a lower crossover rate. This is not unexpected given the different platform designs. The Resolute Onyx is a single sinusoidal strut with an external cobalt alloy frame and an internal core of 90% platinum and 10% iridium alloy with an 81 µm-thick mesh. The BioFreedom has an older 316-L and 120 µm stainless steel design. However, to this day, both stents are the only devices we have evidence of in patients at high risk of bleeding, and both with positives results. On the one hand, the Onyx ONE study confirms the good results obtained by the BioFreedom stent in the LEADERS FREE trial and comes as a response to the criticism on the quality of the conventional stent used whose strut thickness was far beyond that of other available stents. On the other hand, the Resolute Onyx study showed promising data when if DAPT should be withdrawn after the first month,[10] but these data came from studies that we not designed for this analysis and, therefore, with limited reliability. This study confirms the safety profile of this device in patients at high risk of bleeding.

Table 1. Inclusion criteria of the Onyx ONE clinical trial

Indication for percutaneous coronary intervention and, at least, one of the following criteria:
Age ≥ 75 years-old
Oral anticoagulation after stent implantation
Hemoglobin 11 g/L or transfusion during the previous 4 weeks
Platelets < 100 000/mm^3
Hospital admission due to bleeding during the previous 12 months
Stroke during the previous 12 months
Past medical history of intracranial bleeding
Acute liver failure
Creatinine clearance < 40 mL/min
Cancer within the previous 3 years
Scheduled surgery during the 12 following months
Corticosteroids or non-steroidal anti-inflammatory drugs during the first month following stent implantation
Suspicious compliance to dual antiplatelet therapy from the first month

Table 2. 12-month results of the Onyx ONE clinical trial

	Resolute Onyx	BioFreedom	*P*
Cardiac death, infarction, stent thrombosis	17.1	16.9	.84
Cardiac death	4.6	3.9	.40
Infarction	13.5	15	.50
Periprocedural	9.4	7.9	.26
Spontaneous at follow-up	4.6	7.1	.02
Probable or definitive stent thrombosis	1.3	2.1	.22
Early (first month)	0.6	1.3	
Late (between the first month and 1 year)	0.7	0.7	
Target lesion failure	18	17.9	.84
Cardiac death	4.5	3.7	.43
Target lesion-related infarction	12.8	14.0	.43
Ischemia-guided revascularization	2.8	4.0	.17
Successful device	92.8	89.7	.007
BARC bleeding			
1-5	17.7	16.3	.43
2-5	15.1	13.7	.40
3-5	4.5	4.9	.67

BARC, Bleeding Academic Research Consortium Definition of Bleeding.

How should we interpret the study results?

Added to the strut thickness of the conventional stent used in the LEADERS FREE, the rate of events was controversial too. The Onyx ONE study used similar inclusion criteria and, as a consequence, patients were very similar. In this case there is a cardiovascular mortality rate of 4% and an overall stent thrombosis rate slightly < 2%. However, the myocardial infarction rate doubles that of the LEADERS FREE study, which is certainly surprising since the criterion used was similar in both studies: the third universal definition of myocardial infarction.[12] It seems obvious that we have to wait for the publication of the study to know if this is due to differences in the patients' baseline risk or to other reasons. In any case, there is no doubt that the higher event rate seen at the primary endpoint and in its particular components compared to most studies on new generations of stents is explained by the higher risk of the patients included; it is clearly a higher risk profile because of age; percentage of diabetes; prior history of bleeding; and oral anticoagulation.

Is there a class effect for all the drug-eluting stents in these patients?

There are several stents available with CE marking for short DAPT regimens, 1 month included. It should be reminded that CE marking is not an indication but an on-label use under certain circumstance and that this recommendation is always accompanied by the message that the courses recommended by the guidelines should be followed. Also, that early interruptions are the responsibility of the treating physician and that the individual condition of every patient needs to be taken into consideration.

This study shows the results of these 2 stents in patients at high risk of bleeding. Another 3 studies with 1-month DAPT regimens focused on only one model of stent have been conducted: the SENIOR[7], theSTOPDAPT-2,[6] and the GLOBAL LEADERS.[5] Other studies like the SMART-CHOICE[13] and the recently published TWILIGHT[4] assessed 3-month courses of DAPT and included patients with different stents, which is why they design is different from the Onyx ONE.

The SENIOR study[7] randomized 1200 patients ≥ 75 year old to receive a conventional stent or the SYNERGY stent (Boston Scientific, United States) plus a 1-month course of DAPT in stable patients, and a 6-month course in patients with ACS. In 88% of the cases, clopidogrel was used during DAPT. The results were favorable to the drug-eluting stent with a 12% vs 16% event rate in the primary endpoint of all-cause mortality, infarction, stroke or target lesion revascularization, and a similar rate of bleeding (5%), and stent thrombosis (1%). This study provided data on the safety and efficacy profiles of the SYNERGY stent in old patients and followed a 6-month course for the management of ACS, which corresponds to 45% of the patients included. On the other hand, and although they were older patients compared to the Onyx ONE, the percentage of diabetics and patients with atrial fibrillation was significantly lower. For all this, although this study shows favorable data on how the SYNERGY behaved in old patients, we should bear in mind that they were different patients on a different course.

The STOPDAPT-2 study[6] analyzed 3045 patients treated with the chromium-cobalt Xience stent (Abbott Vascular, United States) and compared a standard 12-month course of DAPT plus ASA and clopidogrel (with clopidogrel withdrawal after this time) to a 1-month course of DAPT (with ASA withdrawal after this time and continuation with clopidogrel for another 5 years). During the first month, prasugrel was allowed, but from that moment on the $P2Y_{12}$ receptor inhibitor was always clopidogrel. The primary endpoint of non-inferiority was reached, but again the population risk was lower compared to the Onyx ONE. Mean age was 68.6 years-old, only 38% showed ACS, less than 1% received oral anticoagulation and, above

all, 90% had low or intermediate thrombotic and bleeding risk according to the CREDO-Kyoto and PARIS risk scores. Once again, although it is a very important study with favorable data for the Xience stent, they were different patients on a different course.

Finally, the GLOBAL LEADERS study[5] analyzed 15 968 patients and compared a 1-month course of DAPT plus ticagrelor and ASA followed by a 24-month course of ticagrelor to a 12-month standard therapy of DAPT plus ASA an clopidogrel in patients with stable angina or ticagrelor in patients with ACS followed by another 12 months with ASA only. All patients received the biolimus A9 stent. In this study, the course of the intervention was not superior to the standard one since, although results were favorable during the first year, the heavy bleeding seen during the second year led to a negative study primary endpoint at 2 years. On the other hand, once again the risk profile of patients was lower compared to the Onyx ONE: age was much younger; there were fewer diabetic patients; bleeding rate was < 1%; no patients on oral anticoagulation were included.

FINAL CONSIDERATIONS

Although we still have to wait for its publication, we can say that the Onyx ONE is a landmark study for 2 reasons. First, because it shows that, to this day, the Resolute Onyx stent has the same clinical results, even superior in terms of device success, compared to the reference BioFreedom stent in patients at high risk of bleeding. This means that now we have 2 highly valid options in this context. Second, because of the high prevalence of ACS patients in the trial. Half of the patients included had stable coronary artery disease and the guidelines recommend the administration of 1-month course of DAPT.[14] It is precisely in patients with ACS that the study is more important because it changes completely the course recommended by clinical practice guidelines that indicate DAPT between 6 and 12 months according to the PRECISE-DAPT score.[14] The study is important because it includes patients at high risk of bleeding in whom this complication can be more important than ischemic risk. We should mention that the 12-month recommendation in patients with ACS comes from the CURE study[15] that, although included 12 562 patients, did not show statistically significant differences regarding death and stroke (2 of the 3 major adverse events that were part of the primary endpoint). The study was positive after confirmation of a reduced non-fatal infarction rate. We should also mention that the information provided by the Onyx ONE study on patients with ACS is still limited. This is so because we only have data of the overall study and, although in the LEADERS FREE this subgroup benefited from the use of drug-eluting stents vs conventional stent,[16] we still don't have comparative data of both stents in patients with ACS.

Lastly, in this study, the short course of DAPT includes 2 strategies. One strategy recommends shortening the therapy compared to the guidelines recommendations, 6 to 12 months for the management of ACS. The other strategy is withdrawing ASA in half of the patients as the only antiplatelet agent from the second to the twelfth month. Although the strategy of withdrawing ASA from the first or third months has become a matter of study,[4-6,13] we will still have to wait for the publication of the study to know if there is a really significant interaction here.

CONFLICTS OF INTEREST

None declared.

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Stent implantation in a left ventricular assist device

Implante de stent en un dispositivo de asistencia ventricular izquierda

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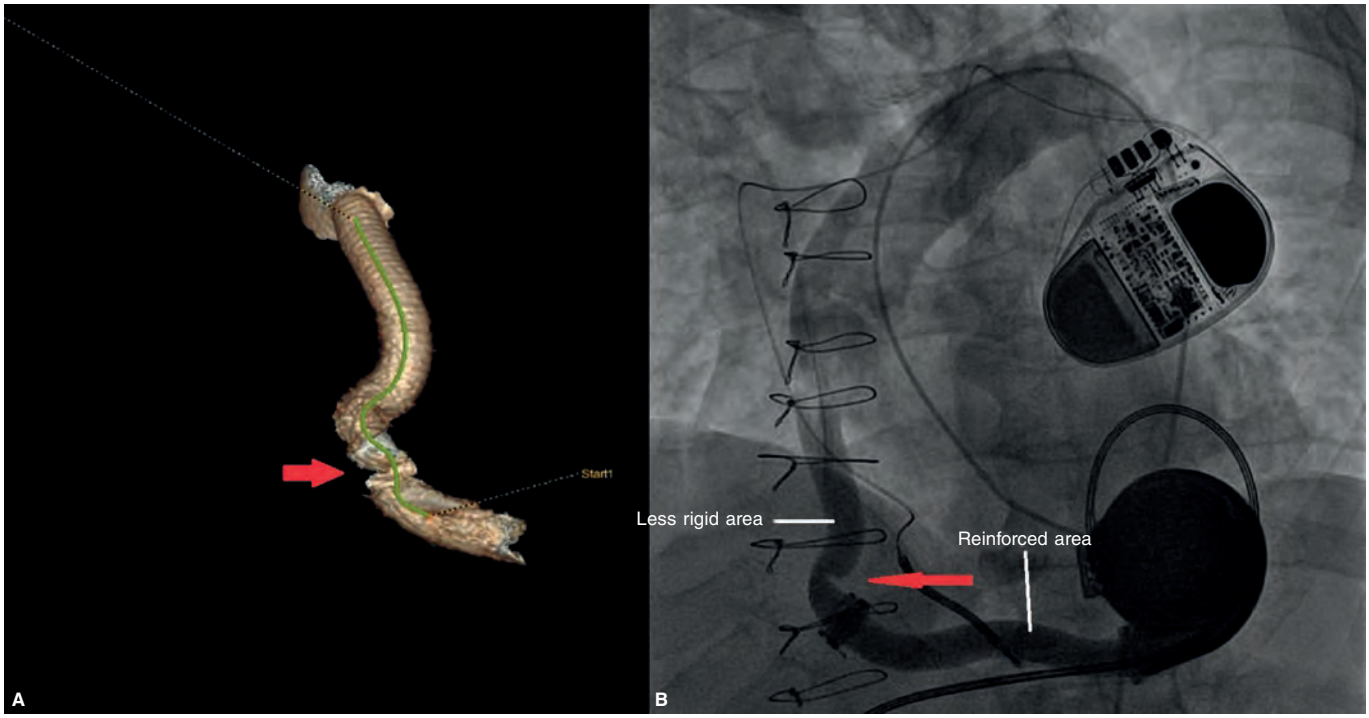

Figure 1.

Sixty-eight-year-old male patient carrier of one HeartWare left ventricular assist device as destination therapy due to ischemic dilated cardiomyopathy. Two years after the implantation, the patient experienced episodes of orthostatic hypotension consistent with low flow alerts of a few seconds duration. He also showed an impaired renal function. On suspicion of device thrombosis one computed tomography angiography was performed that revealed the shortening of the outflow cannula of the pump (figure 1A, arrow).

The interventional cardiology unit was contacted and they performed a ventriculography. The suction of contrast by the pump revealed the existence of kinking of the outflow cannula that was causing a severe stenosis in its mid-section (figure 1B [arrow] and figure 2).

Since the diameter of the cannula was known thanks the specifications established by the manufacturer (10 mm) a 10 x 57 mm BeGraft chrome-cobalt-coated stent was advanced (figure 3A) and deployed in the area of the kinking. Predilatation was performed using a 10 x 30 mm noncompliant balloon with good angiographic results (figure 3B, video 1 of the supplementary data) and normalization of the functioning parameters of the device. The patient had a favorable evolution.

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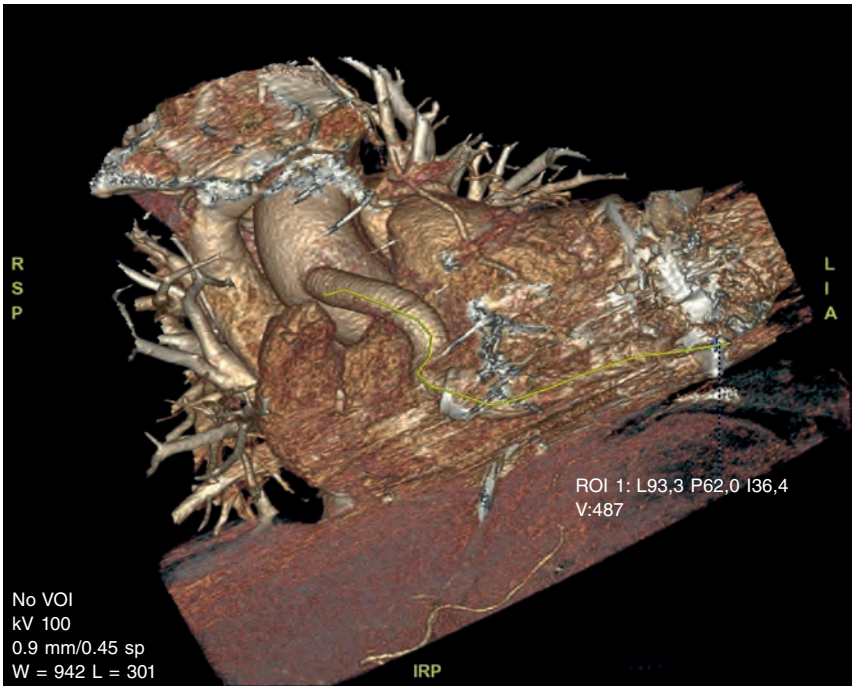

Figure 2.

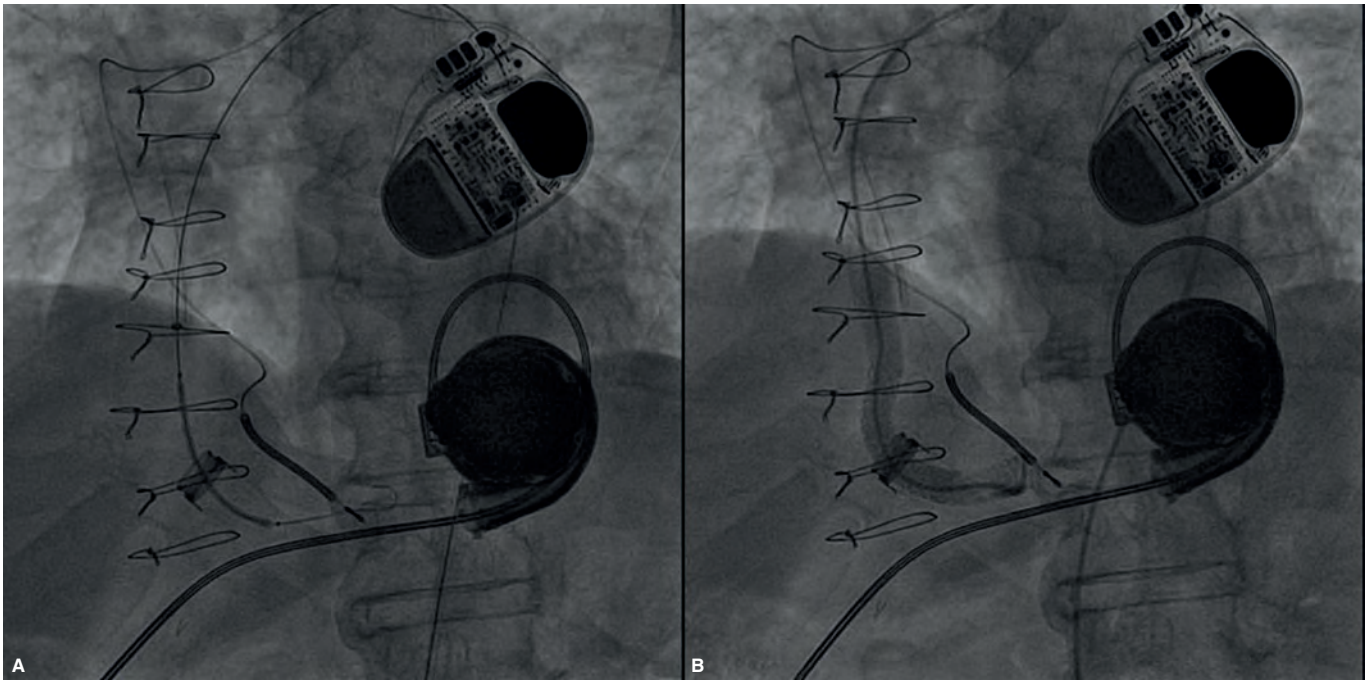

Figure 3.

Two years later the patient experienced thrombosis on the cannula proximal edge, and the cannula had to be replaced. It was confirmed that the stent was still patent.

The shortening of the outflow cannula of the left ventricular assist device is a rare complication and has poor prognosis. In this case we showed the possibility of using percutaneous therapy as an alternative to solve this complication with excellent long-term results.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000057.

Paravalvular leak closure in a Perceval-after-Mitroflow procedure

Cierre de fuga paravalvular en Perceval-tras-Mitroflow

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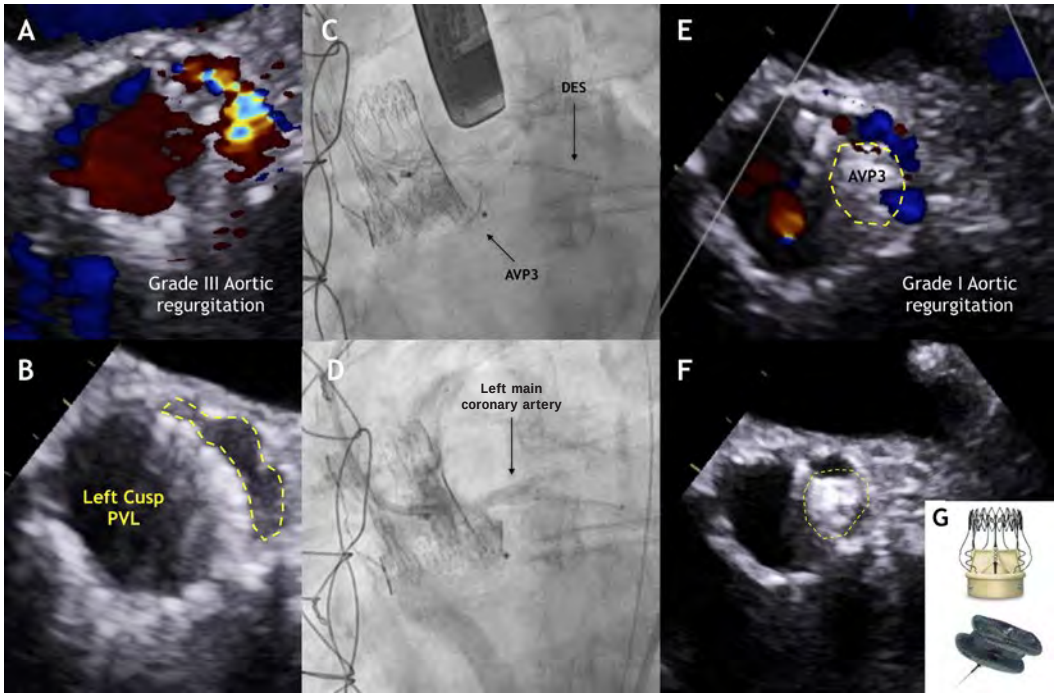

Figure 1.

A 75-year-old female underwent aortic valve replacement with a sutureless Perceval valve due to degeneration of the Mitroflow aortic bioprosthesis. She was admitted 2 years later for heart failure. The transesophageal echocardiography (TEE) performed showed a class III-paravalvular leak (PVL) of the left coronary cusp probably due to calcification (figure 1A,B, video 1 and, video 2 of the supplementary data). Our heart team decided to perform percutaneous closure of the PVL.

The procedure was performed using a 10x5 mm Amplatzer Vascular Plug III (AVP3) (St. Jude Medical, Plymouth, Minessota, United States) (figure 1C,G, video 3 and video 4 of the supplementary data). An undeployed drug-eluting stent (DES) was positioned in the left main coronary artery (LMCA) to prevent any potential occlusions. After the release, the LMCA remained patent therefore the stent was retrieved (figure 1D, video 5 of the supplementary data). The postprocedural TEE showed significant reduction of the PVL (figure 1E,F). The multislice computed tomography (MSCT) was performed at 6 months confirmed the anatomical relationship among the AVP3 device, the Perceval leaflets and the LMCA. Based on the MSCT a 3D model was created that clarified the absence of interference with the valve leaflets or LMCA. The TEE confirmed the presence of a patent LMCA and mild PVL (figure 2, videos 6-8 of the supplementary data).

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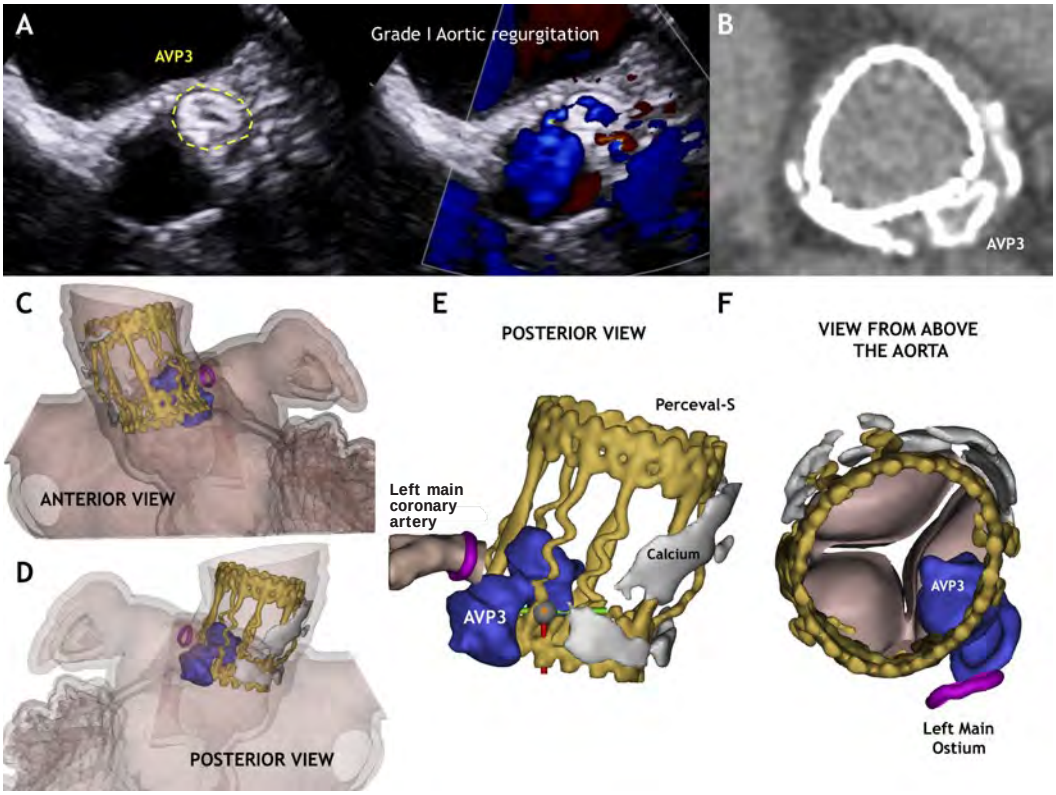

Figure 2.

This is the first case of percutaneous closure of PVL involving a Perceval valve. If the PVL is adjacent to a coronary ostium, protection with an undeployed stent should be considered to prevent an abrupt vessel closure. Three-dimensional models are useful when dealing with complex anatomies for a better understanding of the interaction between the device and surrounding structures.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000069.

Retrograde approach with single radial vascular access

Abordaje retrógrado con un solo acceso radial

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To the Editor,

Up until 2005, the percutaneous management of chronic total coronary occlusions was rare basically due to a low rate of success.[1] This tendency started to change with the arrival of new materials and retrograde access techniques that improved the results of this procedure.[2]

The retrograde access technique is still being perfected and there is a growing number of promising strategies for the management of chronic total coronary occlusions.[3] Retrograde access is often used with septal collaterals. Only in exceptional cases the epicardial collaterals are navigated due to a greater risk of perforation.[4] However, in certain chronic total coronary occlusions of the left anterior descending artery (LAD), the homocoronary collateral vessels of the left circumflex artery (LCx) are often epicardial and require special care and use of a single vascular access.

We present the case of a 68-year old woman with a past medical history of high blood pressure, dyslipidemia, smoking, and hiatal hernia. She had functional class II/IV stable angina[5] of 6-month duration. The myocardial perfusion scintigraphy confirmed the presence of anterior ischemia. The cine coronary arteriography showed a nondominant right coronary artery, a left main coronary artery without lesions, a LCx without lesions, and the total obstruction of the LAD in its proximal segment (figure 1). Our department/service was consulted because the recanalization attempt performed in another center was unsuccessful. While evaluating the case, a total occlusion was found in the proximal segment of the LAD without a stump and with a blunt edge. Other findings were the origin of the major diagonal branch at obstruction level—lesion apparently > 20 mm—and retrograde filling through the collateral circulation of the LCx. The J-CTO (Japanese Multicenter Chronic Total Occlusion Registry)[6] calculated score was 3 (very difficult).

Left radial puncture was performed (due to the absence of right radial pulse) using a 6-Fr radial sheath introducer. Selective catheterization was used in the left coronary artery with an XB 4 6-Fr guide catheter. Using the antegrade access a new recanalization attempt turned out unsuccessful. Since the patient showed no collateral circulation from the right coronary artery to the LAD, retrograde recanalization was decided through the collaterals of the LCx towards the LAD. The septal collateral branches of the LCx and LAD arteries were identified and a 0.014 in Sion Blue guidewire (Asahi Intec, Nagoya, Japan) was advanced mounted on a Corsair microcatheter (Asahi Intec, Nagoya, Japan). Collaterals were navigated and the LAD was recanalized using the retrograde access (figure 2). Also, using the retrograde access, the flexible part of the guidewire was reintroduced into the XB 4 catheter followed by the advancement of the Corsair microcatheter (tip-in technique[7]). The guidewire was removed leaving the Corsair catheter. The guide catheter was reintroduced and using a 0.014 in Cross-IT 200XT guidewire (Abbott, Abbott Park, Illinois, United States) through antegrade access the guidewire flexible tip was threaded with the Corsair distal edge inside the guide catheter. Then the guidewire was advanced. The Corsair device was removed, the LAD proximal lesion was predilated with a 1.5 x 20 mm-balloon and the angioplasty was completed using a 2.75 x 20 mm-XIENCE stent (Abbott, Abbott Park, Illinois, United States). The patient was referred to the outpatient surgery unit and discharged from hospital 6 hours later.

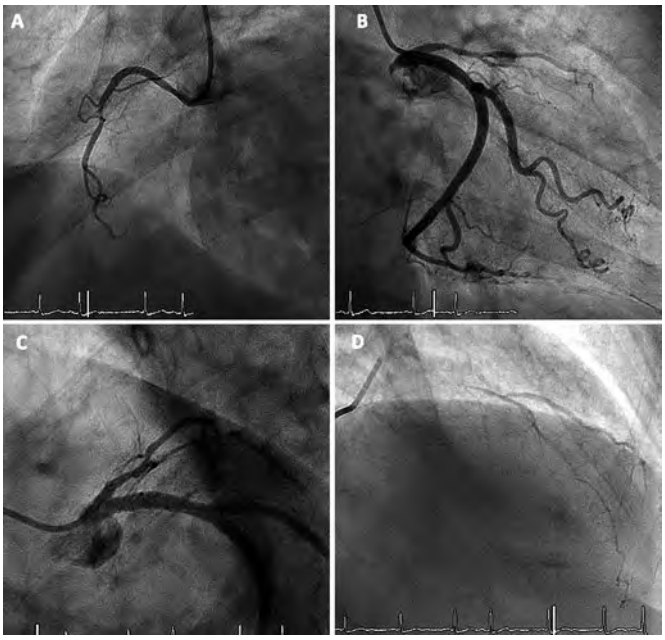

Figure 1. A: nondominant right coronary artery. **B:** circumflex artery without lesions. **C:** total occlusion in the anterior descending artery proximal segment without a stump and with a blunt edge. Origin of a major diagonal branch at obstruction level. **D:** anterior descending artery with retrograde filling through homocoronary collateral circulation.

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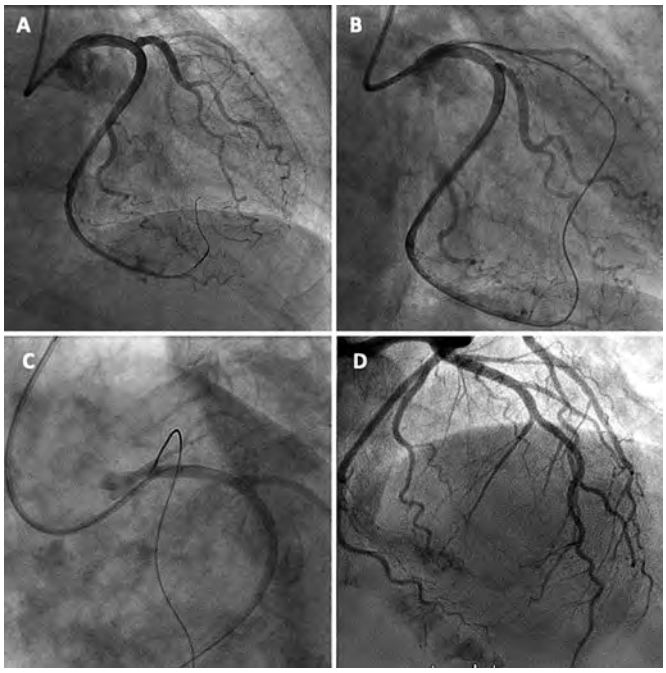

Figure 2. A: advancement of a 0.014 in Sion Blue guidewire through collaterals towards the anterior descending artery. **B:** retrograde recanalization of the anterior descending artery. **C:** reintroduction of guidewire and Corsair microcatheter inside the XB 4 guide catheter (tip-in technique). **D:** final angiography after stent implantation.

Although the homocoronary retrograde access can be performed using the double catheter technique—the so-called "ping-pong technique"[8]—facilitating the manipulation of materials through antegrade access, we chose a single arterial access since it is the less invasive option. However, it may interfere with the movement of materials in the antegrade direction (this limitation could improve with the use of 7-Fr catheters). In this case and even though we used a 6-FR guidewire we did not find any trouble moving the materials in the antegrade direction (using fewer materials also helped). Although feasible, this should be a last resource technique because of the greater risk involved in cases of perforations. In cases of very long total chronic coronary occlusions that require other techniques[9] such as the controlled antegrade and retrograde subintimal tracking (CART), double vascular access is preferred because it requires materials of a lower profile. Coronary angioplasty through retrograde access has improved the rate of success of total chronic coronary occlusions.[9] Although this technique is conceptually simple, it requires the appropriate tools and experienced heart teams to achieve optimal outcomes.

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In-stent restenosis after primary percutaneous coronary intervention: focal versus diffuse pattern. Influence of clinical profile and type of stent

Reestenosis del stent tras una intervención coronaria percutánea primaria: patrón focal frente a difuso. Influencia del perfil clínico y del tipo de stent

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To the Editor,

Although the use of new stents has improved the results after coronary angioplasty, the development of in-stent restenosis (ISR) is still one of the leading problems following these interventions. ISR is defined as a stenosis > 50% developing in a segment or border of the stent (up to 5 mm). It is often due to progressive neointimal proliferation and has been reported in up to 30% of the patients with conventional stents and 10% of drug-eluting stent carriers.[1-3]

ISR can be due to several factors associated with the patient (diabetes, renal failure, acute coronary syndromes), the lesion (type B2-C complexity, length > 20 mm, diameter < 3 mm, chronic occlusions, ostial lesions, bifurcations, and coronary bridges), and the procedure (malapposition, insufficient expansion, luminal areas < 3 mm, multiple stents, stent fractures, border dissections, and type of drug, polymer or stent structure).[1,4,5]

The most widely used system to describe ISRs is the Mehran angiographic classification. Although it was developed for bare metal stents it is used in all stent types. Restenosis are classified into 4 angiographic patterns: I: focal, II: diffuse, III: proliferative, and IV: occlusive; and these patterns have a prognostic value.[1] However, although there are studies on ISR following the implantation of multiple stents, its physiological mechanism after an angioplasty in the setting of ST-segment elevation acute myocardial infarction (STEMI) is not fully understood. Also, it is a situation prone to the appearance of conditions that may favor the occurrence of ISR (insufficient stent expansion or malapposition, small stents for vessels constricted due to circulating catecholamines, thrombophilia, etc.).[2,3]

We conducted a study in our unit whose endpoint was the type of ISR (focal vs diffuse) and analyzed its correlation with the patient profile-procedure and type of stent in patients treated with any type of stent in a primary angioplasty.

All patients diagnosed with angiographically significant ISR (> 50% visual stenosis) in a lesion previously treated with a stent angioplasty during a STEMI were retrospectively included between 2004 and 2014. A total of 76 consecutive patients were included. According to the Mehran angiographic classification, the type of ISR was divided into focal (type I, n = 42) or diffuse (II = 5, III = 17, and IV = 12 which were analyzed together; n = 34). Regarding their position with respect to the stent, focal ISRs were located on the borders in 19 cases (45.2%). Most patients were male (82%) with a mean age of 61.5 years old. The cardiovascular risk factors were common; table 1 shows these stratified according to the type of restenosis. The right coronary artery (53%) was the most commonly compromised vessel followed by the anterior descending artery (32%). The mean follow-up was 88 months (interquartile range, 37.2-111.0) and the mean time until the diagnosis of ISR was 8.7 months (interquartile range: 6.2-24.2). The comparisons between diffuse and focal patterns, and clinical profiles and procedures were similar (table 1). Focal ISRs were diagnosed earlier than diffuse ISRs after the STEMI (figure 1). Also, late ISRs were more common for the diffuse pattern (47.1% vs 21.4%. P = .018) and with higher degrees of angiographic stenosis (mean, 80.56% vs 70.86%. P = .02). Although overall there were no statistically significant differences on the type of restenosis based on the stent generation (P = .41), the focal patter was present in a higher percentage of bare-metal stents and first-generation drug-eluting stents. Also, the state-of-the-art second-generation drug-eluting stents showed a tendency towards a higher percentage of diffuse restenosis (figure 2). Being cautious about the sample size, it is suggested that this may be related to lower doses of antiproliferative drugs, more homogeneous releases, and different polymers (some of them bioresorbable).

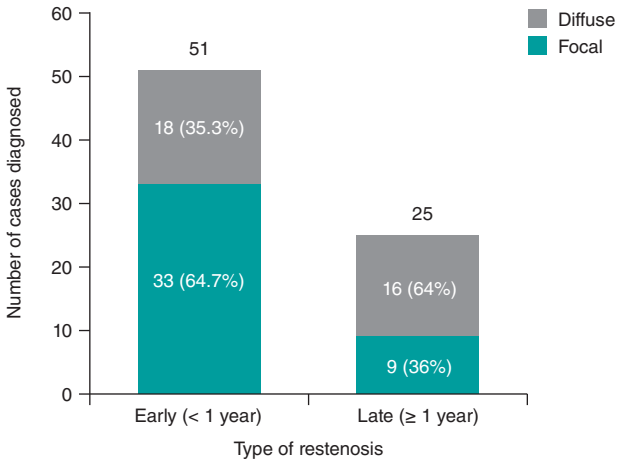

Figure 1. Number of diagnoses based on the time elapsed from primary angioplasty and stratified according to the type of stent restenosis (mean time to diagnosis in diffuse ISR, 29.5 months; in focal ISR, 14.0 months; P = .015). ISR, in-stent restenosis.

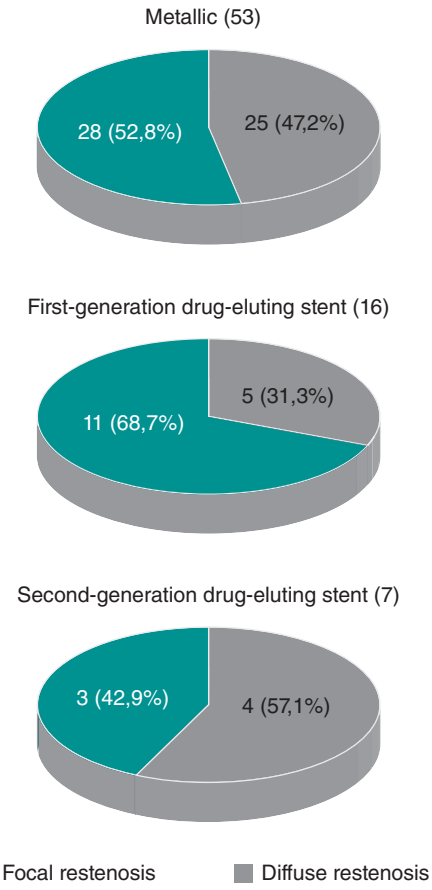

Figure 2. Type of de restenosis according to the Mehran angiographic classification based on the type of stent.

Small stents (≤ 2.5 mm) showed a non-significant tendency towards more diffuse disease (64% vs 37%, P = .17). No significant differences were found on the time elapsed until the diagnosis of ISR stratified according to the type of stent (conventional, first- or second-generation drug-eluting stents).

Table 1. Epidemiological and procedural data of patients analyzed based on their pattern of restenosis

Characteristic	Diffuse pattern (Mehran II-IV)	Focal pattern (Mehran I)	*P*
Sex (male)	26 (76.5%)	36 (85.7%)	.30
Age (years)	62.6 ± 13.2	60.6 ± 11.9	.50
Size (cm)	168.2 ± 6.3	167.5 ± 7.9	.68
Weight (kg)	76.1 ± 10.5	78.8 ± 11.3	.27
Arterial hypertension	21 (61.8%)	24 (57.1%)	.68
Diabetes mellitus	9 (26.5%)	14 (33.3%)	.51
Dyslipidemia	13 (38.2%)	19 (45.2%)	.54
Smoking	20 (58.8%)	31 (73.8%)	.16
Alcohol	1 (2.9%)	1 (2.4%)	.87
Family history of coronary artery disease	2 (5.9%)	0	.11
Peripheral vasculopathy	1 (2.9%)	2 (4.8%)	.68
Chronic nephropathy	0	1 (2.4%)	.36
Prior angioplasty	5 (14.7%)	5 (11.9%)	.71
Index procedure (primary angioplasty)			
Type of stent:			.41
Conventional stent	25 (47.2%)	28 (52.8%)	
First-generation drug-eluting stent	5 (31.3%)	11 (68.7%)	
Second-generation drug-eluting stent	4 (57.1%)	3 (42.9%)	
Maximum inflation pressure (atmospheres), mean (interquartile range)	16 (14-18)	14 (14-18)	.17
Size:			.17
Big (> 2.5 mm)	27 (79.4%)	38 (90.5%)	
Small (≤ 2.5 mm)	7 (20.6%)	4 (9.5%)	
Number of stents	1.0 ± 0.4	1.1 ± 0.4	.73
Time to primary angioplasty, min mean (interquartile range)	170 (120-375)	180 (120-360)	.58
Thromboaspiration	13 (38.2%)	12 (28.6%)	.37
No-reflow	2 (5.9%)	2 (4.8%)	.92
Culprit vessel:			.19
Left main coronary artery	1 (2.9%)	0	
Left anterior descending coronary artery	9 (26.5%)	15 (35.7%)	
Left circumflex artery	7 (20.6%)	2 (4.8%)	
Right coronary artery	16 (47.1%)	24 (57.1%)	
Saphenous vein bridge	1 (2.9%)	1 (2.4%)	
LVEF	53.0 ± 16.1	56.0 ± 11.5	.38
Peak creatine kinase levels, mean (interquartile range)	988 (484-2715)	1446 (480-3808)	.62
Diagnosis of restenosis			
Diagnosis for new catheterization:			.35
Silent ischemia	1 (2.9%)	2 (4.8%)	
Asymptomatic*	12 (35.3%)	21 (50%)	
STEMI	7 (20.6%)	3 (7.1%)	
NSTEMI	6 (17.6%)	8 (19%)	
Unstable angina pectoris	2 (5.9%)	4 (9.5%)	
Stable angina pectoris	3 (8.8%)	0	
Heart failure	2 (5.9%)	3 (7.1%)	
Ventricular tachycardia	1 (2.9%)	1 (2.4%)	
Time correlation:			.01
Early ISR (< 1 year)	18 (52.9%)	33 (78.6%)	
Late ISR (≥ 1 year)	16 (47.1%)	9 (21.4%)	

ISR, in-stent restenosis; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation acute myocardial infarction; STEMI, ST-segment elevation acute myocardial infarction.
*Control catheterization is indicated by the treating physician (for academic purposes, clinical studies, preoperative or other reasons).

Given the characteristics of a study with a small number of cases among other limitations, it was difficult to estimate the exact rate of ISR since no follow-up coronary angiography was performed in all the STEMIs treated in our center during the study period. No timeline of the exact moment when the ISRs developed was given either since they are often oligosymptomatic. However, the patients' clinical characteristics and the behavior of several stents are consistent with data previously published on ISRs in patients in other clinical contexts.[1]

In conclusion, regarding ISR, both pattern and time may be influenced by the type of stent implanted after a STEMI.

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