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Diversity of expertise in a united cardiology specialty

Diversidad de formación e integración asistencial en los servicios de cardiología

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Academic journals devoted to the field of interventional cardiology have become an unmatched source of information over the last decade or so, keeping us up-to-date with the latest developments and broadening our horizons as interventional cardiologists. As we celebrate the arrival of a new peer-reviewed journal in interventional cardiology, *REC: Interventional Cardiology*,¹ we take the opportunity to reflect on recent developments in cardiology and contemplate the future direction of this dynamic and diverse specialty.

The development of coronary catheterisation by Sones in 1958, followed by the introduction of dedicated coronary catheters by Judkins and Amplatz in 1967, and ultimately, the introduction of percutaneous coronary intervention (PCI) by Grüntzig in 1977 established interventional cardiology as a subspecialty of general cardiology.² The first coronary stenting procedures conducted by Sigwart and Paul in 1986 and the subsequent development of drug-eluting stents with succeeding iterations, along with other advances in device technologies, transcatheter techniques, and adjunctive pharmacotherapies, have facilitated treatment of more and more complex patients- and lesion-subsets with PCI. Coincidentally, the development of percutaneous interventions for the management of structural heart disease resulted in the emergence of a new subspecialty of cardiac transcatheter interventions: structural intervention. The inception of transcatheter aortic valve implantation (TAVI) by Cribier in 2002 revolutionised the treatment of aortic stenosis.³ More recently, transcatheter edge-to-edge mitral valve repair has been shown to be beneficial for moderate-to-severe or severe structural or secondary mitral valve regurgitation.^{4,5} Such advances have arguably resulted in structural intervention becoming the fastest growing subspecialty within the field of cardiology. The introduction of the electrophysiology study into clinical practice in the late 1960s, followed by the development of catheter ablation (initially through the delivery of high energy shocks to interrupt conduction, and later using radiofrequency current, the latter pioneered by Budde, Breithardt and Borggrefe) resulted in the widespread adoption of transcatheter therapies for the management of cardiac arrhythmias.⁶ In summary, the field of cardiac transcatheter interventions now includes three distinct subspecialties: coronary intervention, structural intervention, and catheter ablation.

The setting-up of subspecialties of transcatheter intervention is certainly beneficial to patients. It increases the availability of state-of-the-art cardiac care provided by highly-skilled physicians and allows the treatment of high-risk patients who would have previously been managed conservatively. Indeed, it has been

shown that the management of patients by the relevant cardiology subspecialist reduces the length of hospital stay, cardiac readmissions, and mortality.⁷

However, the division of cardiology into niche subspecialties also has potential negative implications for patients and cardiologists alike. With respect to patients, highly subspecialised cardiologists may tend to be more focused on the condition or intervention at hand than on the patient as a whole. However, in our increasingly elderly cardiac patients, such conditions rarely occur in isolation: coronary artery disease, valvular heart disease, and cardiac arrhythmias frequently coexist. In addition, a cardiologist performing an intervention may not see the patient again before discharge and the success of the catheterization may be a distraction from the need to optimize other issues related to medical management, such as intensifying preventive therapies or optimizing heart failure or antianginal medication. For both referring physicians and patients, the division of cardiology adds a degree of complexity to the referral process. It may be difficult for the referring physician to decide at the time of the referral what cardiology subspecialist will most appropriately manage the patient's ailment.

Finally, for cardiologists, subspecialisation has resulted in more difficult training. Is it appropriate for trainees to start to perform catheter ablations before completing their basic cardiology training? Is it advisable that trainees start their training in structural intervention before being competent in performing coronary interventions? Either situation would seem ill-advised but the trade-off is longer training that adds to an already onerous training path in general cardiology.

There is also a risk of isolation from cardiology colleagues in other subspecialties. Ironically, at a time when both European and American guidelines for clinical practice recommend a multidisciplinary or "heart team" approach to the management of patients with valvular heart disease^{8,9} bringing together interventional cardiologists, cardiac surgeons, cardiac imaging specialists, and anesthesiologists, the specialty of cardiology has never been so divided. Structural interventional cardiologists now frequently work more closely with cardiac surgeons than with other cardiologists. Whereas, in the past, ward rounds on the cardiology ward often included cardiologists from numerous subspecialties covering all aspects of cardiac care, nowadays, in many centres, interventional cardiac subspecialties work independently from general cardiology or other subspecialties. We are beginning to reach a point where it can be difficult to set up a heart team with our own cardiology colleagues.

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Whom does such a structure serve? Subspecialisation is defined by the operator and his expertise. Arguably such a structure is more physician- than patient-oriented, with each subspecialty managing one condition rather than the patient as a whole. However, we should not lose sight of the big picture. Our management goals should be patient-centred rather than diagnosis- or procedure-centred. In patients requiring multiple interventions from different subspecialties, decisions on the appropriate order of such interventions should be made collectively with our colleagues and not in isolation. As we continue to treat older, more complex patients with a heavier co-morbidity burden, co-operation between cardiology (and non-cardiology) subspecialties will become more important than ever.

In summary, while the arrival of highly-specialised cardiologists should be welcome, the side-effect of the division of cardiology should be avoided. United as cardiologists, we are in a stronger position to provide better care for our patients, exchange ideas, learn from one another, and collaborate on projects. We need to learn to have the courage to call ourselves cardiologists rather than let our subspecialties define us. Otherwise, if the current trend continues, future clinical practice guidelines in cardiology will need to advocate for a multidisciplinary approach between cardiology subspecialties in patient-care, while the current recommendations for a heart team approach between medical and surgical disciplines will take lower priority.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. REC: Interventional Cardiology. Available at: www.recintervcardiol.org/en.
2. Colleran R, Kastrati A. Percutaneous coronary intervention: balloons, stents and scaffolds. *Clin Res Cardiol.* 2018;107:55-63.
3. Cribier A. Commemorating the 15-year anniversary of TAVI: insights into the early stages of development, from concept to human application, and perspectives. *EuroIntervention.* 2017;13:29-37.
4. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *New Engl J Med.* 2011;364:1395-1406.
5. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *New Engl J Med.* 2018;379:2307-2318.
6. Wellens HJ. Cardiac arrhythmias: the quest for a cure: a historical perspective. *J Am Coll Cardiol.* 2004;44:1155-1163.
7. Pathik B, De Pasquale CG, McGavigan AD, et al. Subspecialisation in cardiology care and outcome: should clinical services be redesigned, again? *Intern Med J.* 2016;46:158-166.
8. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739-2791.
9. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135:e1159-e1195.

Social media as an educational tool in interventional cardiology



Redes sociales como medio educativo en la cardiología intervencionista

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Social media and the internet have changed the way we communicate with each other. We have never had so much information on this or that topic and never in such a direct, fast and global way. However, this new era does not come without risks and because everybody can be a potential creator of content, information itself has never been so susceptible to bias and demagoguery.

The capacity of social media to expose information quickly and generate discussion among users has given rise to its application in the world of policy, business, radio broadcasts and academia world.¹ Medicine is no stranger to this technological renewal and today we have doctors who are media-savvy. As it happens in many other aspects, cardiology is at the frontline of this trend.

As well as practical training and technical skills, essential for interventional cardiologists, theoretical training and constant update are also indispensable. The subjects covered in our core curriculum are increasingly difficult to apprehend since they include topics not only from general cardiology but also from interventional cardiology: physiology and coronary imaging, hemodynamics, techniques for the percutaneous treatment of coronary lesions (more and more complex) and structural cardiomyopathies, knowledge of devices and technical development, etc.

An ideal educational environment for interventional cardiologists should provide interesting and quality information that should be available to the largest possible number of users. Also, it should anticipate the participation of these users and update the contents in an ongoing basis.

Theoretical training that until recently was based on textbooks and printed articles has evolved into digital documents we can read in our computers or smartphones anywhere and at any time. In this context, social media provide a different teaching experience that is complementary and, at times, even better than the teaching experience provided through the traditional mechanisms by which academic information used to be broadcast, used and integrated in the routine clinical practice of interventional cardiologists.²

Today it is common that scientific meetings are announced in advanced, broadcast live and commented later on social media. At every meeting we see influencers competing to turn their contents into trending topics. This is how a series of results and comments

end up in social media creating a virtual link between the attendees to these conferences and those who follow them digitally through viral terms such as #CardioTwitter.²

Aside from the immediacy and speed of broadcasting, the most significant difference between the on-site discussions that are held at meetings and those that take place on the social media is the number of active participants. Probably in no other forum, interventional cardiologists on training can start peer-to-peer debates with the leading researchers of landmark studies.²

So, anybody with a real interest can be instantaneously briefed on the latest studies presented at the most important international meetings without having to actually attend the meetings. And even when it is not possible to watch live from social media, scientific online platforms such as PCRONline.com, tctmd.com, and hemodinamica.com give access to these contents after the meetings. We should emphasize here that we also enjoy these 100% virtual conferences through platforms such as eCardio, organized by the Spanish Society of Cardiology, with an increasing number of followers.

Over the last few years, an increase in the number of users and Twitter activity has been documented during the main scientific cardiological meetings. This not only has not had a negative impact on on-site attendance¹ but has brought the attendees closer to the conferences, improved networking and spurred the wish to attend future events.³ These findings are indicative that the use of social media during scientific meetings improves communication and promotes educational and research efforts. Despite the early resistance from certain medical societies, the use of Twitter during these meetings has become an important and almost essential element for scientific broadcast and medical educational purposes.^{1,2}

Aside from the training that actually takes place in these meetings, scientific journals on interventional cardiology are second to none and they usually include, as part of their editorial team, community managers who run their social media. The number of followers on Twitter is more and more important to them and it has actually grown exponentially over the last few years. Today it is not unusual to see that the leading author's Twitter account user name is one of the requisites established by these journals during the manuscript submission process.

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Another development brought to this context by social media is the possibility to open up debates and create scientific review-like content trends about a specific subject on real time. Traditionally, the publication of this or that research was based on contributions from its authors and comments from selected reviewers and editors. Today, however, the critical analysis that follows the publication of landmark studies on social media has given rise to reviews coming from the CardioTwitter community. We have witnessed the almost surgical dissection of studies such as the #ORBITA (from pre-randomization medication to the design and details of its statistical analysis).²

This new way of broadcasting research studies has put into question what indicators should be used to measure the true impact factor of academic papers since now they are shared not only through traditional means but also through various alternative means including social media.⁴

Beyond meetings and journals, social media facilitate communication with other colleagues which is an essential tool of the learning process. This nearness among colleagues and the creation of scientific communities have become something common among cardiologists who are active on social media. The support expressed through comments, experiences and researches from others or simply by clicking *like* and *retweet* has built social bridges across the world in a way that facilitates and improves academic collaborations.² In the past, technical or technological advances would take years after being discovered before being publicly implemented; today this process has been reduced to a matter of days. The percutaneous access through the distal left radial artery is an example. It was on social media before it was even made public through the traditional means of communication.⁵

Beyond all the potential advantages of social media as an educational tool, we cannot omit aspects that may be negative in this context. We should bear in mind that it is not always possible to confirm the validity of the content being broadcast and the accuracy of data provided. Also, fake news may travel faster on the social media as opposed to actual news.⁶ In cardiology, as it happens in other fields, the speed at which news travel on social media may be governed by factors unrelated to their validity.²

Also, the concision required by this type of platforms favors simplicity as opposed to accuracy and novelty as opposed to detailed information. The democratization brought by participating in these scientific debates where anybody can give their opinion can perversely lead to demagoguery triggered by the popularity of the somehow most sarcastic or impacting comments.²

In sum, social media in general and Twitter in particular have given voice to interventional cardiologists from all across the field, created an open platform for the discussion and instantaneous review of academic and teaching materials on real time, and eventually improved the connection among the different communities that create and receive studies.² However, the practical lack of filters and monitoring in the generation and transmission of these contents comes at a price. Even through the benefits of social media as an educational tool are evident, we should profit from it without losing sight of the complex training process that we, interventional cardiologists, have to go through where conferences, treaties, articles, mentors, teachers, colleagues, and patients are the sources of knowledge we learn from on a daily basis.

CONFLICTS OF INTEREST

The author declared no conflicts of interest whatsoever.

REFERENCES

1. Tanoue MT, Chatterjee D, Nguyen HL, et al. Tweeting the Meeting. *Circ Cardiovasc Qual Outcomes*. 2018;11:e005018.
2. Yeh RW. Academic Cardiology and Social Media: Navigating the Wisdom and Madness of the Crowd. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004736.
3. Mishori R, Levy B, Donovan B. Twitter use at a family medicine conference: analyzing #STFM13. *Fam Med*. 2014;46:608-614.
4. Trueger NS, Thoma B, Hsu CH, Sullivan D, Peters L, Lin M. The Altmetric Score: A New Measure for Article-Level Dissemination and Impact. *Ann Emerg Med*. 2015;66:549-553.
5. Kiemeneij F. Left distal transradial coronary access. Available online: <https://www.youtube.com/embed/-If5oAF0KJo>. Accessed 8 Mar 2019.
6. Lazer DJM, Baum MA, Benkler Y, et al. The science of fake news. *Science*. 2018;359:1094-1096.

Do we have enough radiation protection in cardiology?

¿Tenemos suficiente protección radiológica en cardiología?

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The procedures of interventional cardiology provide an unquestionable benefit for patients who suffer from heart disease but require the intensive use of ionizing radiations that are somehow risky for the patients and the healthcare providers who participate in these interventional procedures. The radiological protection programs should be an important part of the quality systems used in this medical practice.

Should we be worried about the reported cases of radiation-induced skin lesions in patients, or about the radiation-induced cataracts or brain tumors suffered by some interventional surgeons? The answer is "no" but only as long as we are aware of the risks involved when using ionizing radiations, the radiological protection measures available, and know how to use them appropriately. The radiation dose levels that patients and healthcare providers receive should be measured, recorded and audited periodically and the necessary correcting measures implemented when these levels are high.

A question that any interventional cardiologist should be able to answer is whether he knows what doses of radiation are his patients receiving and what occupational doses of radiation is his personal dosage-meter recording. If the answer is negative, then maybe he should be worried because if these levels were high, he would not know what correcting measures he should implement to reduce them.

INTERNATIONAL RECOMMENDATIONS ON RADIOLOGY PROTECTION IN RADIOLOGY

The International Commission on Radiological Protection (ICRP) and other international organizations and interventional cardiology and radiology societies have designed good clinical practice recommendations for the management of ionizing radiations.¹⁻³

The Spanish and European⁴ legislation require quality control programs for all x-ray machines and that the healthcare providers involved have proper radiological protection knowledge and are certified by the corresponding authority. Also, that the doses of radiation received by patients and professionals alike are measured and shared on a regular basis with the so-called reference levels for diagnostic purposes (when it comes to patients)⁵ and with radiation dose limits (when it comes to healthcare providers).

EFFECTS OF IONIZING RADIATION

Exposure to ionizing radiation can produce stochastic effects (probabilistic) and deterministic effects (also called tissue effects).⁶

The ICRP has recently proposed⁷ new dose thresholds of 0.5 Gy for the opacities of the crystalline lens (cataracts) and cardiovascular and cerebrovascular effects and has suggested a new dose threshold for occupational doses of 20 mSv/year for the crystalline lens, much lower than the previous levels of 150 mSv/year. This new threshold has already been included in the European legislation⁴, which translates into a stricter control of occupational doses for interventional healthcare providers.

RISKS OF RADIATION-INDUCED CATARACTS IN HEALTHCARE PROFESSIONALS AND SOME CASES OF BRAIN TUMORS

Over the last few years and long before the ICRP decided to propose a new dose threshold for radiation-induced lesions in the crystalline lens and bring the occupational dose limits down to 20 mSv/year, the International Atomic Energy Agency had already conducted several studies to evaluate radiation-induced opacities in cardiologists of Latin America, Asia, and Europe as part of their RELID (Retrospective Evaluation of Lens Injuries and Dose) program. The overall results showed a significant number of healthcare providers and nurse specialists with opacities that may have been caused by ionizing radiations after years working and not using the adequate radiological protection measures. In the dose estimates, healthcare professionals were found who may have received doses > 1 Gy in the crystalline lens through the years due to inadequate protection. The scarce use of personal dosage meters among professionals was studied too.⁸

If the overhead radiation shields present in almost all cath labs are not used correctly, the disperse radiation exposure of eyes (and head) can be substantial, especially if maintained over several years.

Several cases of brain tumors in interventional surgeons have also been published, although with scarce analyses on the occupational doses that these healthcare providers may have received.⁹

However, no epidemiological studies have been conducted so far that confirm the possible cause-effect relation and further

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research on this issue has been suggested.¹⁰ Recently, several studies have been published that rule out the connection between low doses of radiation and brain tumors.¹¹

NEW EUROPEAN REGULATIONS ON BASIC SAFETY STANDARDS

The recent Council Directive 2013/59/EURATOM on basic safety standards,⁴ that is actually in the process of transposition and implementation in countries of the European Union, stresses several aspects of radiological protection in interventional procedures. X-ray machines should show the dose that is being emitted to the patients while the procedure is being conducted and once it is over. Also, these doses should be shown in the procedural reports, at least in the new x-ray machines, and they should be compared to the reference levels for diagnostic purposes. Also, correcting measures should be implemented without delay if these levels are exceeded.

If the doses of radiation received by the patients turn out to be high with the corresponding risk of causing radiation-induced lesions to the skin, then quality assurance programs with the appropriate clinical follow-up should be taken into consideration. Also, patients should be informed.

RADIATION DOSES IN INTERVENTIONAL CARDIOLOGY IN SPAIN

The European and Spanish legislations establish that the dose of radiation received by populations medically exposed to ionizing radiations should be measured. Based on the results from the activity registries found by the Working Group on Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology (SEC) and the DOCCACI (Dosimetry and quality criteria in interventional cardiology) program¹² the contribution of interventional cardiology to the overall radiation dose in Spain¹³ has been estimated and quantified in 4% of the total use of x-ray machines in medicine. The overall dose per inhabitant derived from interventional cardiology procedures stands at around 0.03 mSv per inhabitant/year. This value is the same as the value found in the United Kingdom, it is half the value found in Switzerland (0.06 mSv), and six times higher than the value found in Germany and the United States (0.2 mSv).¹³

WHAT SHOULD WE DO TO WORK SAFELY WITH IONIZING RADIATIONS?

Since we cannot improve what we are not measuring or what we do not know, we need to stress here how important it is to always use personal dosage meters and elements for personal protection, while paying special attention to the occupational dose levels we are receiving.

All interventional teams have devices available that inform them on the dose of radiation received by the patients. We should be

paying attention to these dose levels and compare them periodically with the reference levels regularly updated by the Working Group on Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology (SEC) through the DOCCACI program.¹²

Also, we should take advantage of the collaboration from specialists on medical physics (or hospital radiophysicists) that the new European Council directive has included as necessary for interventional procedures.

CONFLICTS OF INTEREST

The author declared no conflicts of interest whatsoever with respect to this study.

REFERENCES

1. ICRP Publication 120. Radiological protection in cardiology. *Ann ICRP.* 2013;42:1-125.
2. Sarkozy A, De Potter T, Heidbuchel H, et al. ESC Occupational radiation exposure in the electrophysiology laboratory with a focus on personnel with reproductive potential and during pregnancy: A European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS). *Europace.* 2017;19:1909-1922.
3. Picano E, Vano E, Rehani MM, et al. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J.* 2014;35:665-672.
4. Council Directive 2013/59/EURATOM of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation. EU Official Journal 17 January 2014. Available online: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32013L0059>. Accessed 22 Feb 2019.
5. ICRP Publication 135: Diagnostic Reference Levels in Medical Imaging. *Ann ICRP.* 2017;46:1-144.
6. ICRP Publication 103: The 2007 Recommendations of the International Commission on Radiological Protection. *Ann ICRP.* 2007;37:1-332.
7. ICRP publication 118. ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs - Threshold doses for tissue reactions in a radiation protection context. *Ann ICRP.* 2012;41:1-322.
8. Vano E, Kleiman NJ, Duran A, Romano-Miller M, Rehani MM. Radiation-associated lens opacities in catheterization personnel: results of a survey and direct assessments. *J Vasc Interv Radiol.* 2013;24:197-204.
9. Roguin A. Brain tumours among interventional cardiologists: a call for alarm? *Eur Heart J.* 2012;33:1850-1.
10. Picano E, Vano E, Domenici L, Bottai M, Thierry-Chef I. Cancer and non-cancer brain and eye effects of chronic low-dose ionizing radiation exposure. *BMC Cancer.* 2012;12:157.
11. Linet MS, Kitahara CM, Ntowe E, et al. Multi-Specialty Occupational Health Group. Mortality in U.S. Physicians Likely to Perform Fluoroscopy-guided Interventional Procedures Compared with Psychiatrists, 1979 to 2008. *Radiology.* 2017;284:482-494.
12. Sánchez RM, Vano E, Fernández JM, Escaned J, Goicolea J, Pifarré X. DOCCACI Group. Initial results from a national follow-up program to monitor radiation doses for patients in interventional cardiology. *Rev Esp Cardiol.* 2014;67:63-65.
13. Sánchez Casanueva RM, Vano Carruana E, Fernández Soto JM, Fernández-Ortiz A, Alfonso Manterola F, Goicolea Ruigómez J. Contribution of interventional cardiology to the collective dose in Spain. *J Radiol Prot.* 2018; 38:N1-N7.



Intravenous regadenoson versus intracoronary adenosine for fractional flow reserve measurement

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ABSTRACT

Introduction and objectives: Regadenoson, a selective agonist of the A2a receptors of adenosine, has been proposed as an alternative for the measurement of fractional flow reserve (FFR). The goal of our study was to assess the utility of regadenoson compared to the use of intracoronary adenosine.

Methods: Forty-one intermediate coronary lesions (30%-70%), in which functional assessment with pressure wire was indicated, were included both prospective and consecutively. Each patient was sequentially administered intracoronary adenosine and intravenous regadenoson and hemodynamic data while the adverse effects were recorded with hyperemia induced by both drugs. The differences seen in the final FFR were analyzed using the linear regression model and the clinically relevant discrepancies were identified assuming 0.80 as the cut-off point.

Results: The mean of the FFR was significantly lower with regadenoson compared to adenosine (0.838 ± 0.072 vs 0.852 ± 0.073 , $P = .002$) and in 4 cases (9.8%) clinically relevant differences were found. The regression analysis showed a strong linear correlation between the individual values ($r = 0.925$, $P < .001$). Both adenosine and regadenoson significantly reduced mean arterial blood pressure and only regadenoson significantly increased baseline heart rate. In 2 cases (4.9%) asystole was recorded > 3 seconds after the administration of adenosine and no complications were observed with regadenoson.

Conclusions: The administration of regadenoson through an intravenous single bolus has shown a significant reduction in the value of FFR compared to the administration of intracoronary adenosine boluses and the observed differences may be relevant in the clinical decision-making process.

Keywords: Adenosine. Regadenoson. Fractional flow reserve.

Regadenosón intravenoso frente a adenosina intracoronaria para la medida de la reserva fraccional de flujo

RESUMEN

Introducción y objetivos: El regadenosón, un agonista selectivo de los receptores A2a de la adenosina, se ha propuesto como una alternativa para el cálculo de la reserva fraccional de flujo (FFR). El objetivo de este estudio fue evaluar la utilidad del regadenosón en comparación con el uso de adenosina intracoronaria.

Métodos: Se incluyeron de forma prospectiva y consecutiva 41 lesiones coronarias intermedias (30-70%) en las que se indicó valoración funcional con guía de presión. A cada paciente se le administró de forma secuencial adenosina intracoronaria y regadenosón intravenoso, y se registraron los datos hemodinámicos y los efectos adversos con la hiperemia inducida mediante ambos fármacos. Las diferencias en la FFR final se analizaron mediante regresión lineal y se identificaron las discrepancias clínicamente relevantes asumiendo como punto de corte el valor de 0,80.

Resultados: La media de la FFR fue significativamente menor con regadenosón que con adenosina ($0,838 \pm 0,072$ frente a $0,852 \pm 0,073$; $p = 0,002$), y en 4 casos (9,8%) se encontraron diferencias clínicamente relevantes. El análisis de regresión mostró una fuerte correlación lineal entre los valores individuales ($r = 0,925$; $p < 0,001$). Tanto la adenosina como el regadenosón redujeron de forma significativa la presión arterial media, y solo el regadenosón incrementó significativamente la frecuencia cardíaca basal. En 2 casos (4,9%) se registró asistolia > 3 s tras recibir adenosina y no se observó ninguna complicación con regadenosón.

Conclusiones: La administración de regadenosón en bolo único intravenoso mostró una significativa reducción en el valor de FFR en comparación con la administración de bolos de adenosina intracoronaria, y las diferencias observadas podrían resultar relevantes en la toma de decisiones clínicas.

Palabras clave: Adenosina. Regadenosón. Reserva fraccional de flujo.

Abbreviations

FFR: fractional flow reserve.

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INTRODUCTION

The fractional flow reserve (FFR) measurement has become established as a valuable tool for the functional assessment of intermediate coronary stenoses.¹ Maximum hyperemia is needed to be able to assess the FFR. The most widely used pharmacological agent to induce vasodilation is adenosine through an intravenous infusion or intracoronary injection.²

Regadenoson, a selective agonist of adenosine A2a receptors has been proposed as an alternative given how easy it is to use since only a single peripheral intravenous bolus at a fixed dose is needed regardless of the patient's weight and renal function.³⁻⁷

Several studies have compared regadenoson to intravenous adenosine,⁸ but to our knowledge there are no studies comparing regadenoson to intracoronary adenosine for the assessment of the FFR.

The main objective of this study was to establish individual variability in the measurement of FFR using intracoronary adenosine and intravenous regadenoson administered sequentially so each patient is case and control at the same time.

Secondary objectives included analysis of the hemodynamic response, measurement of hyperemia times and assessment of adverse events.

METHODS

Forty-one intermediate coronary lesions were studied both prospective and consecutively in 39 patients referred to undergo a coronary angiography and who had been prescribed functional assessment with pressure guidewire. Stenoses of 30% to 70% estimated visually or through automatic quantification during the angiography procedure were categorized as intermediate lesions. FFR cut-off values ≤ 0.80 were established to indicate revascularization. An informed written consent was obtained from all patients included in this study.

Procedure

Coronary angiography was conducted following routine clinical practice. The FFR was measured using the PressureWire guidewire (St Jude Medical, St Paul, Minnesota, United States) after administering of unfractionated heparin (50 IU/kg) and placing the sensor distal to the lesion, following the standards recommended for acquisition purposes, registry and interpretation of pressure tracings.⁹

Pharmacological protocol

Based on former dose-response studies, an initial dose of intracoronary adenosine of 100 μg for the right coronary artery and 200 μg for the left coronary artery was established.¹⁰

In an attempt to achieve a degree of optimal hyperemia, patients with values close to the cut-off value (FFR < 0.85) were eligible to receive, at the discretion of the operator, repeated doses of 60 μg in each bolus. The minimum value obtained was selected as the true FFR.

After the administration of adenosine, the registry was started, and the phase of hyperemia was considered over when the FFR returned to baseline values. Then, a peripheral intravenous bolus of 400 μg of regadenoson was injected and the measurements re-taken.

The FFR was obtained using an analysis performed on a beat-to-beat basis and when in doubt or in the presence of artifacts, the tracings stored in the console were reviewed.

Additionally, values such as heart rate and arterial blood pressure, both at baseline level and during the phase of hyperemia, were recorded and the possible side effects monitored.

Lastly, data such as the time required by each drug to achieve hyperemia and the duration of hyperemia were recorded for further analysis.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation and categorical variables as absolute value or percentage. The Student *t* test for paired data was used to compare the different FFR values, hemodynamic values (arterial blood pressure and heart rate) and times of hyperemia observed after the administration of adenosine and regadenoson. Symptoms were studied using the chi-square test. Using the linear regression analysis, Pearson's correlation coefficient and the Bland-Altman plot, the correlation between the different FFR values and both drugs was studied. The statistical analysis was conducted using the SPSS v20 statistical software package (IBM, Armonk, New York, United States) and results were considered significant with *P* values $< .05$.

RESULTS

Study patients

Table 1 shows patients baseline characteristics. Overall, 41 intermediate lesions (average stenosis: $52 \pm 9\%$) were studied, 29 of them located in the anterior descending artery, 7 in the right coronary artery, and 5 in the circumflex artery. The average dose of intracoronary adenosine administered was $236 \pm 60 \mu\text{g}$. No postprocedural complications were observed.

Measurement of FFR with intracoronary adenosine vs intravenous regadenoson

With 1 or both drugs, 13 lesions (33%) showed FFR values ≤ 0.80 , indicating a significant functional stenosis. Also, a strong linear correlation with both hyperemic stimuli was seen ($r = 0.925$; $P < .001$) (**figure 1** and **figure 2**). However, the FFR measured after the administration of regadenoson was lower compared to the one obtained after the administration of intracoronary adenosine (0.838 ± 0.072 vs 0.852 ± 0.073 ; $P = .002$) (**table 2**). Also, in four different cases (9.8%) there were relevant discrepancies when FFR values > 0.80 with adenosine and ≤ 0.80 with regadenoson were obtained, which led to reclassifying the lesion (**table 3**).

Hemodynamic parameters

With both drugs we observed a significant drop in baseline average arterial blood pressure levels, which was even more pronounced with regadenoson. However, only regadenoson significantly increased baseline heart rate (**table 2**).

The average time elapsed until reaching maximum hyperemia was significantly lower with adenosine (15 ± 6 vs 61 ± 49 s; $P < .001$), and this effect was even more prolonged with regadenoson (44 ± 29 vs 174 ± 72 s; $P < .001$) (**figure 3**).

Table 1. Characteristics of the study population

Sample (n = 41)	
Age (years)	65 ± 14
Women	27%
Body mass index (kg/m ²)	30 ± 3
Prior medical history	
Hypertension	73%
Dyslipidemia	58%
Diabetes mellitus	24%
Smoking	36%
Prior infarction	33%
Prior revascularization	49%
Heart failure	3%
Diseased vessels	
1	59%
2	25%
3	16%
Artery studied	
Anterior descending artery	67%
Circumflex artery	15%
Right coronary artery	18%
Degree of stenosis	
30%-50%	42%
50%-70%	58%
70%-90%	0%
Diameter of the vessel (mm)	
	3.3 ± 0.5
Dose of intracoronary adenosine (µg)	
Left coronary artery	243 ± 55
Right coronary artery	206 ± 76

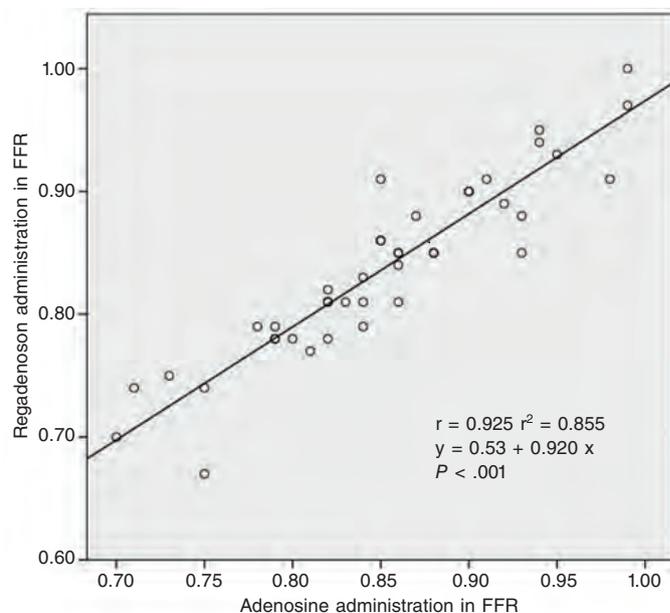


Figure 1. Linear regression analysis. Correlation of fractional flow reserve values measured with intracoronary adenosine and IV regadenoson in each patient. FFR: fractional flow reserve.

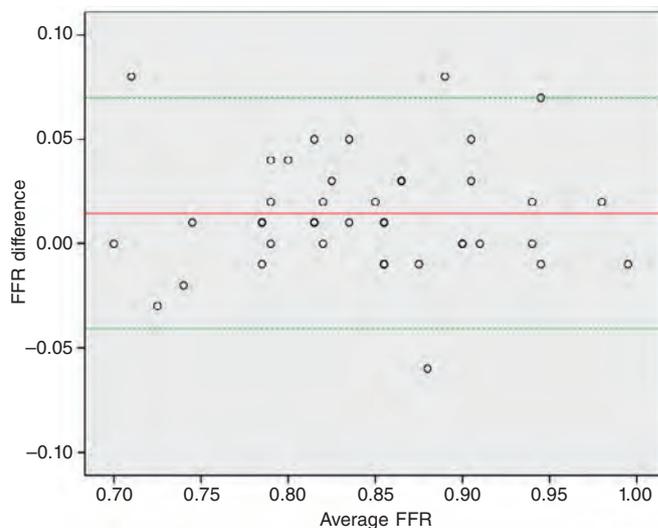


Figure 2. Bland-Altman plot. Graphic representation of the differences seen in the fractional flow reserve measured using intracoronary adenosine and intravenous regadenoson. FFR: fractional flow reserve.

Table 2. Hemodynamic effects of adenosine and regadenoson

	Fractional flow reserve	Average arterial blood pressure (mmHg)	Heart rate (beats/min)
Baseline	0.94 ± 0.05	114 ± 22	69 ± 12
Adenosine	0.85 ± 0.07	92 ± 21	70 ± 14
Regadenoson	0.84 ± 0.07*	85 ± 18*	89 ± 18*

Data are expressed as mean ± standard deviation.

*P < .05 with respect to baseline values and adenosine.

Table 3. Individual values of fractional flow reserve with intracoronary adenosine and intravenous regadenoson

Case	Age (years)	Sex	Coronary artery	Dose of adenosine (µg)	Adenosine administration in FFR	Regadenoson administration in FFR
1	49	Male	ADA	240	0.88	0.85
2	82	Male	Cx	160	0.73	0.75
3	60	Male	ADA	300	0.84	0.81
4	79	Male	ADA	240	0.79	0.78
5	54	Male	ADA	120	0.70	0.70
6	54	Male	RCA	120	0.98	0.91
7	53	Male	RCA	180	0.85	0.86
8	67	Male	ADA	180	0.84	0.83
9	56	Male	ADA	180	0.86	0.84
10	81	Male	ADA	180	0.85	0.91
11	60	Female	Cx	240	0.94	0.95
12	46	Male	RCA	120	0.84	0.79*
13	62	Male	ADA	240	0.92	0.89
14	80	Female	ADA	180	0.93	0.88
15	89	Female	ADA	240	0.86	0.85
16	79	Male	RCA	300	0.95	0.93
17	71	Female	ADA	240	0.85	0.86
18	76	Female	ADA	300	0.78	0.80
19	52	Male	Cx	180	0.86	0.85
20	52	Male	ADA	300	0.81	0.75*
21	67	Male	Cx	300	0.99	0.97
22	63	Male	ADA	240	0.87	0.88
23	49	Female	ADA	300	0.71	0.74
24	45	Female	ADA	180	0.83	0.81
25	58	Male	ADA	240	0.94	0.94
26	62	Male	ADA	300	0.93	0.85
27	64	Male	ADA	240	0.82	0.82
28	64	Male	RCA	240	0.88	0.85
29	57	Female	Cx	180	0.99	1.00
30	54	Male	ADA	300	0.82	0.81
31	81	Male	ADA	300	0.79	0.79
32	81	Male	ADA	300	0.88	0.89
33	77	Female	ADA	240	0.75	0.74
34	75	Male	ADA	240	0.82	0.81
35	62	Female	ADA	300	0.90	0.90
36	58	Male	ADA	120	0.75	0.67
37	65	Male	ADA	240	0.90	0.90
38	67	Male	ADA	300	0.79	0.78
39	61	Female	ADA	300	0.81	0.77*
40	83	Female	ADA	300	0.82	0.78*
41	69	Male	RCA	240	0.91	0.91

ADA, anterior descending artery; Cx, circumflex artery; FFR, fractional flow reserve; RCA, right coronary artery.

*Cases with clinically relevant discrepancies.

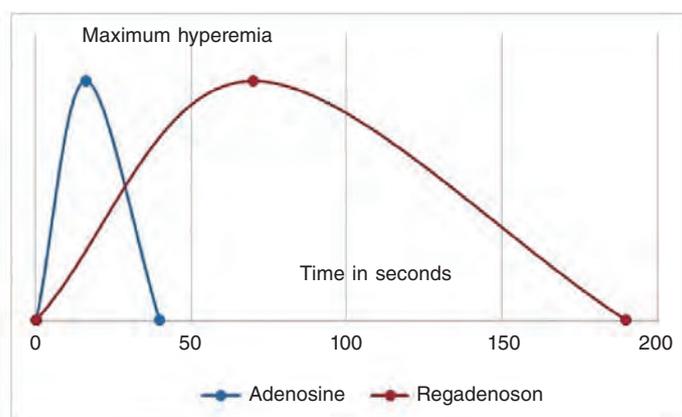


Figure 3. Times of hyperemia. Differences seen in the time elapsed until reaching hyperemia and its average duration (in seconds) between intracoronary adenosine and intravenous regadenoson.

Side-effects profile

Side effects were mild with both drugs (table 4). After the administration of regadenoson, most patients experienced some kind of discomfort that they tolerated well and was not an obstacle to continue with the study.

Two cases of blockade with pauses longer than 3 seconds after the administration of adenosine were observed in the right coronary artery that resolved spontaneously. No conduction disorders or any other kind of complications were reported with regadenoson.

DISCUSSION

The reliability of FFR measurements depends on the capacity to induce maximum coronary hyperemia.¹¹ The pharmacological agent most widely used is adenosine in intravenous infusions, although intracoronary adenosine is also used by many laboratories because it is faster and achieves similar results. The doses recommended are 100 μ g and 200 μ g for the right and left coronary arteries, respectively. However, we know that the response to these different doses varies depending on the patient. Some authors recommend doses of 300 μ g or even higher, but these high doses have adverse effects, particularly unwanted conduction disorders in diagnostic testing.¹²

This study shows that the use of regadenoson in a single peripheral intravenous bolus at a fixed dose regardless of the patient's weight and renal function could be an alternative to adenosine. A good linear correlation has been described between the FFR measured using intracoronary adenosine or intravenous regadenoson ($r = 0.925$; $P < .001$).

Also, the comparative analysis conducted showed that the bolus of intravenous regadenoson achieved FFR values that were significantly lower compared to the FFR values obtained using bolus of intracoronary adenosine (difference of 0.014 ± 0.028 ; 95% confidence interval, 0.005-0.023; $P = .002$).

Maybe the higher hyperemia achieved with regadenoson was the reason why, in four cases with FFR values > 0.80 after the administration of adenosine, FFR values ≤ 0.80 were obtained after the administration of regadenoson, which led to reclassifying the lesion as hemodynamically significant.

Table 4. Symptoms and adverse events while measuring fractional flow reserve

Event	Adenosine	Regadenoson	P
Symptoms*	11 (27)	30 (73)	.29
Asystole > 3 seconds	2 (5)	0	< .001
Other complications	0	0	-

Data express n (%).

*Dyspnea, chest pain, headache, myocardial blush or nausea.

On the other hand, the exact administration of intracoronary adenosine dose required the positioning of the guide catheter inside the coronary ostium, which was not always possible, and was the reason why the dose administered was not always the established one.

Thus, due to the administration of an insufficient dose or the use of an inaccurate technique, the fact of the matter is that in 9.8% of the cases maximum hyperemia was not achieved with adenosine. Our data are consistent with former studies that show that up to 10% of the cases may show suboptimal hyperemia with intracoronary adenosine.¹³⁻¹⁴ In this sense, one recent meta-analysis revealed differences in the FFR similar to those observed in our study when comparing intracoronary adenosine administration and the intravenous infusion of adenosine.¹⁵ This may be relevant to indicate revascularization.

Another interesting aspect of regadenoson is that maximum hyperemia was maintained for longer periods of time. Even though our study only analyzed vessels with focal lesions, the longer average time of hyperemia observed with regadenoson (174 ± 72 s) may be useful to perform multiple FFR measurements in vessels with serial lesions or diffuse disease.

One potential limitation of regadenoson is its higher cost compared to adenosine. In this sense, and with no cost-effectiveness studies, a more efficient use of resources has been reported when regadenoson was administered compared to adenosine and dipyridamol in stress tests with isotopes.¹⁶

Finally, in our study adverse events were mild with both drugs. However, the negative arrhythmogenic and dromotropic effects of adenosine are well-known. The administration of regadenoson in a single bolus at a fixed dose through peripheral intravenous route showed a good safety profile and complications such as broncho-

spasm and high-grade atrioventricular block were rare. On rare occasions, the more prolonged vasodilation effect of regadenoson may be unwanted. A 50 mg bolus of intravenous aminophylline may be administered to reverse its effect.¹⁷

Limitations

The data presented should be interpreted taking into consideration a series of limitations. This was an observational, open, multi-center study with a small sample, meaning that results may be affected by confounding factors common to this type of studies.

Even though the half-life of intracoronary adenosine is short, we cannot rule out that its prior administration may alter the posterior effect of regadenoson due to preconditioning phenomena.

The maximum dose of adenosine was used at the discretion of the operator, which may have turned out insufficient to induce maximum hyperemia.

Finally, we should not forget that new non-hyperemic indices have stormed into the coronary physiology setting as an alternative to the functional assessment of stenosis without requiring vasodilating agents.

CONCLUSIONS

The administration of regadenoson in a single intravenous bolus has shown greater effectiveness in the measurement of FFR compared to the administration of bolus of intracoronary adenosine, and the differences seen may be relevant for the clinical decision-making process. Because of how easy it is to use and because of its safety profile, regadenoson seems like a useful alternative for the hemodynamic assessment of intermediate coronary stenoses.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Measuring the FFR is a useful tool in the functional assessment of intermediate coronary stenoses.
- In order to measure the FFR we need maximum hyperemia and as the vasodilating agent we need regadenoson, one selective agonist of adenosine A2a receptors that seems like a good option since it requires one single intravenous bolus at a fixed dose regardless of the patient's weight and renal function.

WHAT DOES THIS STUDY ADD?

- Several studies have drawn comparisons between regadenoson and intravenous adenosine but, to our knowledge, no study has ever compared regadenoson and intracoronary adenosine.

- Our study showed that the bolus of intravenous regadenoson achieves significantly lower FFR values compared to the ones obtained using bolus of intracoronary adenosine.
- This greater effectiveness in the measurement of FFR, which is essential to indicate revascularization, its ease of use, and good tolerability turn regadenoson into a good option for FFR functional assessments.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.
2. De Bruyne B, Pijls NH, Barbato E, et al. Intracoronary and intravenous adenosine 5'triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation.* 2003;107:1877-1883.
3. Nair PK, Marroquin OC, Mulukutla SR, et al. Clinical utility of regadenoson for assessing fractional flow reserve. *J Am Coll Cardiol Interv.* 2011;4:1085-1092.
4. Arumugham P, Figueredo VM, Patel PB, et al. Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve. *EuroIntervention.* 2013;8:1166-1171.
5. Prasad A, Zareh M, Doherty R, et al. Use of regadenoson for measurement of fractional flow reserve. *Catheter Cardiovasc Interv.* 2014;83:369-374.
6. VanNunen LX, Lenders GD, Schampaert S, et al. Single bolus intravenous regadenoson injection versus central venous infusion of adenosine for maximum coronary hyperaemia in fractional flow reserve measurement. *EuroIntervention.* 2015;11:905-913.
7. Stolker JM, Lim MJ, Shavelle DM, et al. Pooled comparison of regadenoson versus adenosine for measuring fractional flow reserve and coronary flow in the catheterization laboratory. *Cardiovasc Revasc Med.* 2015;16:266-271.
8. Lee JZ, Singh N, Nyotowidjojo I, et al. Comparison of regadenoson and nitroprusside to adenosine for measurement of fractional flow reserve: A systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2018;2:168-174.
9. Toth GG, Johnson NP, Jeremias A, et al. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol.* 2016;7:742-753.
10. Adedj J, Toth GG, Johnson NP, et al. Intracoronary adenosine: dose-response relationship with hyperemia. *J Am Coll Cardiol Interv.* 2015;8:1422-1430.
11. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *N Engl J Med.* 1996;334:1703-1708.
12. Lopez-Palop R, Carrillo P, Frutos A, et al. Comparison of effectiveness of high-dose intracoronary adenosine versus intravenous administration on the assessment of fractional flow reserve in patients with coronary heart disease. *Am J Cardiol.* 2013;111:1277-1283.
13. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximum coronary hyperemia for fractional flow reserve measurements. *Am Heart J.* 2000;140:651-657.
14. Casella G, Leibig M, Schiele TM, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for the assessment of fractional flow reserve? *Am Heart J.* 2004;148:590-595.
15. Rigattieri S, BiondiZoccai G, Sciahbasi A, et al. Meta-Analysis of Head-to-Head Comparison of Intracoronary Versus Intravenous Adenosine for the Assessment of Fractional Flow Reserve. *Am J Cardiol.* 2017;120:563-568.
16. Friedman M, Spalding J, Kothari S, et al. Myocardial perfusion imaging laboratory efficiency with the use of regadenoson compared to adenosine and dipyridamole. *J Med Econ.* 2013;16:449-460.
17. Al Jaroudi W, Iskandrian AE. Regadenoson: A New Myocardial Stress Agent. *J Am Coll Cardiol.* 2009;54:1123-1130.



Effect of implantation technique on outcomes in patients receiving bioresorbable scaffolds in various clinical scenarios

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ABSTRACT

Introduction and objectives: The PSP (pre-dilation, sizing and post-dilation) score, derived from the GHOST-EU registry, has evaluated the relationship between the implantation technique of bioresorbable scaffolds and the clinical outcomes. The objective was to perform an external validation of the PSP technique and to determine its effect on adverse cardiac events in various clinical and anatomical scenarios.

Methods: Data from the REPARA registry (2230 patients) were used for external validation, whereas a common database combining REPARA and GHOST-EU (3250 patients) data was used to evaluate the effect of PSP technique in various clinical and anatomical scenarios. PSP-1 and PSP-3 were used to score the appropriateness of pre-dilation, scaffold sizing, and post-dilation. The primary endpoint was 1-year device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, and target-lesion revascularization. The definite/probable scaffold thrombosis according to the Academic Research Consortium criteria was also evaluated.

Results: A total of 303 (18.2%) patients were treated with an optimal PSP-1, and 182 (8.2%) with an optimal PSP-3. The external validation showed that PSP has a very high negative predictive value for device-oriented composite endpoint and scaffold thrombosis (91.8% and 89.1% for PSP-1; 98.4% and 97.3% for PSP-3, respectively). Patients with an optimal PSP-3 had a numerically lower rate of device-oriented composite endpoint and scaffold thrombosis compared to those without it (0.5% vs 2.9%; $P = .085$ and 0.5% vs 1.8%; $P = .248$, respectively). In the merged database, PSP benefits were seen on many scenarios, except in the

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ST-segment elevation myocardial infarction where a trend towards no benefit of an optimal PSP technique was present ($P_{\text{interaction}} = .100$).

Conclusions: In the REPARA registry, at 1-year follow-up, an optimal PSP technique was not associated with a lower rate of device-oriented composite endpoint. Further research is necessary to assess the impact of the PSP technique in longer follow-ups.

Keywords: Coronary artery disease. Percutaneous coronary intervention. Bioresorbable scaffolds. Bioresorbable vascular scaffolds.

Efecto de la técnica de implantación en los resultados en pacientes tratados con armazón bioabsorbible en diferentes escenarios clínicos

RESUMEN

Introducción y objetivos: La escala de puntuación PSP (*pre-dilation, sizing and post-dilation*), derivada del registro GHOST-EU, evalúa la relación entre la técnica de implante de los armazones bioabsorbibles y los resultados clínicos. El objetivo fue realizar una validación externa de la escala PSP y determinar su efecto en eventos cardíacos adversos en diversos escenarios clínicos y anatómicos.

Métodos: Para la validación externa se emplearon los datos del registro REPARA (2.230 pacientes), mientras que se utilizó una base de datos común que combina datos de REPARA y GHOST-EU (3.250 pacientes) para evaluar el efecto de la técnica PSP en varios escenarios clínicos y anatómicos. Se usó PSP-1 y PSP-3 para calificar la calidad de la predilatación, el dimensionamiento de los armazones y la posdilatación. El objetivo primario fue la variable compuesta orientada al dispositivo (muerte cardíaca, infarto de miocardio del vaso diana y revascularización de la lesión diana) a 1 año. También se evaluó la trombosis definitiva o probable del armazón según los criterios del *Academic Research Consortium*.

Resultados: Se trató a 303 (18,2%) pacientes con una PSP-1 óptima y a 182 (8,2%) con una PSP-3 óptima. La validación externa mostró que la escala PSP tiene un valor predictivo negativo muy alto para el objetivo primario compuesto orientado al dispositivo y la trombosis del armazón (91,8 y 89,1% para PSP-1; 98,4 y 97,3% para PSP-3, respectivamente). En pacientes con PSP-3 óptimo, el objetivo primario compuesto orientado al dispositivo y la trombosis del armazón fueron numéricamente inferiores en comparación con los pacientes sin PSP-3 óptimo (0,5 frente a 2,9%; $p = 0,085$; y 0,5 frente a 1,8%; $p = 0,248$, respectivamente). En la base de datos combinada, los beneficios de la escala PSP se observaron en diversos escenarios, excepto en el de infarto de miocardio con elevación del segmento ST, en el que se observó una tendencia hacia la ausencia de beneficios de una técnica de PSP óptima ($p_{\text{interacción}} = 0,100$).

Conclusiones: Una técnica de PSP óptima no se asoció con una tasa más baja del objetivo primario compuesto orientado al dispositivo. Se necesitan nuevos estudios para evaluar el impacto de la técnica de PSP con un seguimiento más prolongado.

Palabras clave: Enfermedad coronaria. Intervención coronaria percutánea. Armazón bioabsorbible. Armazón vascular bioabsorbible.

Abbreviations

BVS: bioresorbable vascular scaffolds. **DOCE:** device-oriented composite endpoint. **PSP:** pre-dilation, sizing and post-dilation. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Recent meta-analyses of randomized clinical trials have raised concerns about the safety of first-generation bioresorbable vascular scaffolds (BVS).¹ Specifically, a higher than expected scaffold thrombosis rate compared to drug-eluting stents was found.¹⁻⁴

Optimization of the implantation technique was proposed to improve clinical outcomes of patients treated with BVS.^{5,6} The PSP (pre-dilation, sizing and post-dilation) score is a simple model designed to assess the quality of the BVS implantation technique, evaluate the preparation of the lesion, the size of the scaffold, and post-dilation. This score has been developed and internally validated in the GHOST-EU registry and is associated with the occurrence of adverse cardiac events at 1-year follow-up.⁷ However, this score has not been externally validated, and no data are available on whether the effect of the PSP implantation technique is different in various clinical and anatomical scenarios.

Therefore, we tried to perform an external validation of the PSP technique and evaluate its effect on the adverse cardiac events of

patients treated with BRS in various clinical and anatomical scenarios.

METHODS

Population

The REPARA registry is an investigator-initiated, prospective, multicenter registry conducted at 58 Spanish and Portuguese centers. The registry included consecutive patients who underwent single or multivessel percutaneous cardiac intervention with at least one everolimus-eluting BVS device (Absorb BVS; Abbott Vascular, Santa Clara, CA, United States). Patients who underwent percutaneous cardiac intervention for one or two new native coronary artery lesions –up to four lesions– in separate epicardial coronary vessels were eligible for enrollment. Patients with acute myocardial infarction and specific complex lesion features were also included. Data from the REPARA registry were used for external validation of the PSP score. This is a retrospective not pre-specified analysis.

Data from REPARA and GHOST-EU registries were pooled in a single database by one investigator (L. Ortega-Paz) and used to evaluate the effect of the PSP technique in various clinical and anatomical scenarios. Details of the GHOST-EU registry have been described above.⁷

Procedures and follow-up

All interventions were performed according to the actual guidelines on the management of percutaneous cardiac intervention. Briefly, balloon pre-dilation was not mandatory but highly recommended. Scaffold implantation at pressures not exceeding the burst pressure rate was mandatory. Use of post-dilation was left at operator discretion and, if performed, one non-compliant balloon was recommended according to the protocol. Quantitative coronary angiography analysis pre-BVS implantation was analyzed in a centralized CORE Lab, and only patients with complete quantitative coronary angiography data were included in this analysis.

The PSP evaluation of the BVS implantation technique was applied according to the models previously detailed.⁷ Overall, 3 steps of scaffold implantation were evaluated in the PSP models shown on table 1. The PSP-2 model was not assessed because the quantitative coronary angiography after pre-dilation was not available.

Clinical follow-up was obtained through clinical visits or phone calls at 12-month in both registries. In the REPARA registry, the process of data mining was externally monitored, and events were adjudicated by an independent committee. The occurrence of periprocedural myocardial infarction was not systematically assessed.

Outcomes and definitions

The primary endpoint was device-oriented composite endpoint (DOCE) of cardiac death, target-vessel myocardial infarction, and clinically driven target lesion revascularization (CD-TLR). Secondary outcomes were the individual components of the primary

endpoint and definite/probable scaffold thrombosis, defined according to the Academic Research Consortium (ARC) criteria.⁸ REPARA and GHOST-EU registries used the same endpoints definitions according to the ARC criteria.⁸ Optimal PSP technique was defined as the highest PSP score value.⁷ In patient with more than one lesion treated, all the lesions should fulfill the optimal PSP criteria; otherwise the patient was classified as non-optimal. All endpoints were analyzed at 1-year follow-up.

Statistical analysis

Continuous variables are presented as the mean \pm standard deviation or median and interquartile range, as appropriate. Categorical variables are reported as absolute number and percentage. Differences in proportions were tested with chi-square or Fisher exact test and differences in continuous variables were tested with Student *t*-test.

External validation of the PSP score was performed according to TRIPOD type 4 validation.⁹ The PSP scores were evaluated in terms of overall performance, calibration, and discrimination, as previously shown.¹⁰ The overall performance of the models was assessed by Nagelkerke's R^2 .¹⁰ Calibration was measured by the Hosmer-Lemeshow test.¹⁰ Discrimination was measured with the area under the receiver-operator characteristic curves (AUCs).¹⁰ Predictive values and likelihood ratios were also calculated.¹⁰ In the external validation population of the REPARA registry, weight of PSP technique and each component was evaluated by a Cox regression, adjusting for those variables predictors of DOCE at univariate analysis: diabetes, prior myocardial infarction or revascularization, multivessel disease, severely calcified lesion, bifurcations, and scaffold overlapping.

In the pooled database (REPARA and GHOST-EU data), the effect of the PSP technique on the DOCE was evaluated with formal interaction testing in various clinical and anatomical scenarios. These analyses were performed only for the model that performed the best.

Table 1. PSP models for the evaluation of BVS implantation

Implantation steps	PSP-1	PSP-2	PSP-3
Pre-dilation	- Not performed - Performed	- Either not performed or performed with a QCA residual stenosis \geq 30% - Performed with a QCA residual stenosis < 30%	- Not performed - Performed
Scaffold sizing	Correct sizing, defined as the following: - implantation of a 2.5 mm diameter scaffold in a vessel with a proximal/distal RVD \geq 2.5 mm and < 2.75 mm - implantation of a 3.0 mm diameter scaffold in a vessel with a proximal/distal RVD \geq 2.75 mm and < 3.25 mm; or - implantation of a 3.5 mm diameter scaffold in a vessel with a proximal/distal RVD \geq 3.25 mm and \leq 3.75 mm - if proximal and distal RVD differed, the mean value was used Incorrect sizing		
Post-dilation	- Either not performed or performed with a compliant or non-compliant balloon with diameter 0.5 mm greater than the scaffold diameter or performed with a NC balloon with a diameter less than or equal to the scaffold diameter - Performed with an NC balloon of larger diameter than the scaffold, up to a maximum of 0.5 mm		- Either not performed or performed with a compliant or non-compliant balloon with diameter 0.5 mm greater than the scaffold diameter or performed with a NC balloon with a diameter less than or equal to the scaffold diameter at a pressure < 16 atmospheres. - Performed with a NC balloon of larger diameter than the scaffold, up to a maximum of 0.5 mm and at a pressure \geq 16 atmospheres.

BVS, bioresorbable vascular scaffolds; NC, non-compliant; PSP, pre-dilation, sizing and post-dilation; QCA, quantitative coronary angiography; RVD, reference vessel diameter.

A Kaplan-Meier method was used to derive the event rates at follow-up and to plot time-to-event curves, dividing the population according to the optimal PSP technique or each implantation step score. The Kaplan-Meier curves were compared using the log-rank test.

A 2-tailed P -value $< .05$ was considered significant. All data were processed using the Statistical Package for Social Sciences, version 22 (SPSS Inc., Chicago, IL, United States).

RESULTS

External validation population

A total of 2448 patients (3370 lesions) were included in the REPARA registry. Due to missing data for the evaluation of the PSP-1 and PSP-3 scores, only 2230 patients (2553 lesions) were included in this analysis (figure 1 of the supplementary data). The PSP-2 score was not evaluable due to missing residual percentage stenosis after pre-dilation in all patients, and therefore not considered for this analysis. There were no differences between patients included and those excluded in terms of clinical outcomes (data not shown).

Patients treated with an optimal PSP-1 and PSP-3 techniques were 303 (13.6%), and 182 (8.2%), respectively (table 2; figure 2 of the supplementary data). The clinical and procedural data according

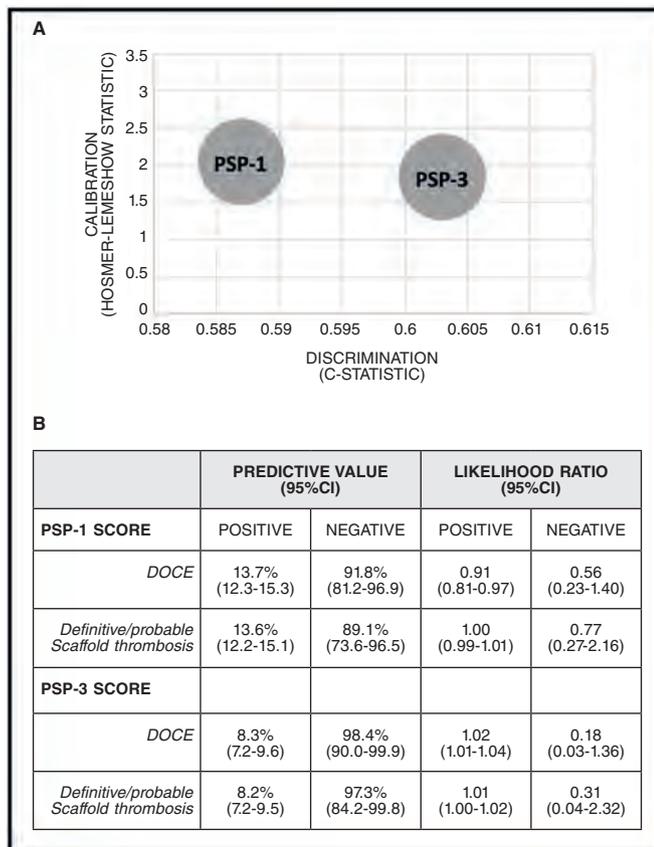


Figure 1. PSP score models performance. A: Rule-in performance: PSP-1: $R^2 = 0.02$, HL: $X^2 = 2.04$ (0.727), and AUCs: 0.587 (0.511-0.664); $P = .020$. PSP-3: $R^2 = 0.03$, HL: $X^2 = 1.84$ (0.606), and AUCs: 0.603 (0.528-0.677); $P = .006$. B: Rule-out performance. 95%CI, 95% confidence interval; AUCs, area under the receiver-operator characteristic curve (95%CI); DOCE, device-oriented composite endpoint; HL, Hosmer-Lemeshow (P -value); R^2 , Nagelkerke's R^2 .

Table 2. Distribution of PSP models

	PSP-1 (n = 2553) ^a	PSP-3 (n = 2553) ^a
Optimal PSP technique (%)	357 (14.0)	219 (8.6)
1:1 pre-dilation, n (%)		
No	497 (19.5)	497 (19.5)
Yes	2056 (80.5)	2056 (80.5)
Scaffold sizing, n (%)		
Incorrect	507 (19.9)	507 (19.9)
2.50 mm	135 (26.6)	135 (26.6)
3.00 mm	193 (38.1)	193 (38.1)
3.5 mm	179 (35.3)	179 (35.3)
Correct ^b	2046 (80.1)	2046 (80.1)
Post-dilation, n (%)		
No	1313 (51.4)	1313 (51.4)
Over-expanded ^b	39 (1.5)	39 (1.5)
NC balloon > 1:1 ^b	623 (24.4)	NA
NC balloon > 1:1 and pressure ≥ 16 atm	NA	393 (15.4)
QCA analysis pre-BVS implantation		
RVD proximal (mm)	3.10 \pm 0.42	3.10 \pm 0.42
RVD distal (mm)	2.92 \pm 0.55	2.92 \pm 0.55
Mean RVD (mm)	3.02 \pm 0.51	3.02 \pm 0.51
Lesion length (mm)	18.15 \pm 9.32	18.15 \pm 9.32
Stenosis (%)	84.10 \pm 13.1	84.10 \pm 13.1
MLD (mm)	0.98 \pm 1.15	0.98 \pm 1.15

^a Lesion-level analysis.

^b Defined as in the development and internal validation.⁷

ATM, atmospheres; BVS, bioresorbable vascular scaffold; MLD, minimal lumen diameter; NA, not applicable; NC, non-compliant; PSP, pre-dilation, sizing and post-dilation; QCA, quantitative coronary angiography; RVD, reference vessel diameter.

to the optimal PSP score are shown on table 1 of the supplementary data, table 2 of the supplementary data, table 3 of the supplementary data, and table 4 of the supplementary data.

External validation

The PSP-3 score displayed the best calibration ($X^2 = 1.84$, $P = .006$ using the Hosmer-Lemeshow statistic test) and the best discrimination (AUC, 0.603; 95% confidence interval [95%CI], 0.528-0.677; $P = .006$) (figure 1A). Both PSP-1 and PSP-3 scores displayed a high negative predictive value with a low negative likelihood ratio either for DOCE or scaffold thrombosis (figure 1B).

At 1-year follow-up, there was no difference in the rate of DOCE between patients with an optimal PSP-1 technique and those

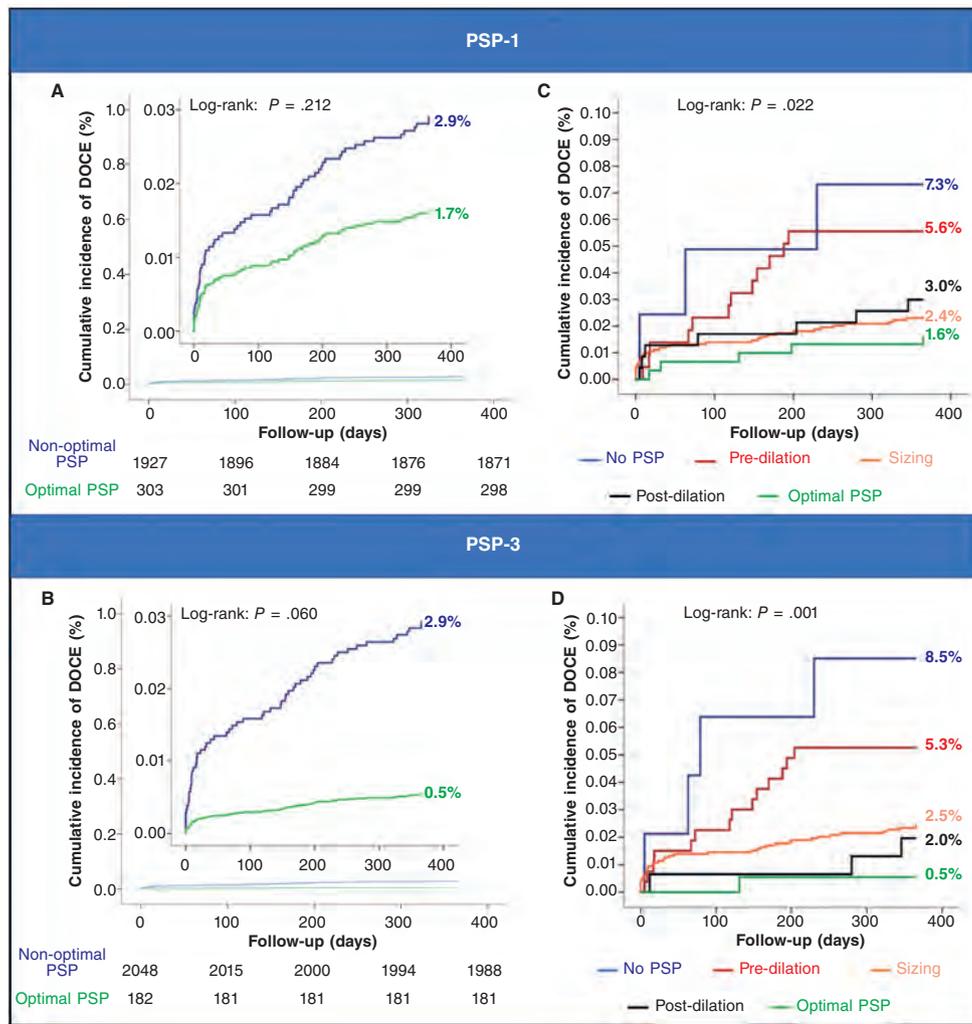


Figure 2. PSP technique: Kaplan-Meier analysis. Panel A: PSP-1: acute events (< 24h): 0% (0/303) vs 0.3% (6/1927), log-rank $P = .331$. Sub-acute events (1-30 d) 0.3% (1/303) vs 0.9% (18/1921), log-rank $P = .286$. Late events (30-235 d) 1.3% (4/302) vs 1.7% (32/1903), log-rank $P = .650$. B: pre-dilation: HR, 1.07; 95%CI, 0.58-2.00; $P = .824$. Scaffold sizing: HR, 0.43; 95%CI, 0.25-0.75; $P = .003$. Post-dilation: HR, 0.66; 95%CI, 0.34-1.26; $P = .208$. Panel B: PSP-3: Acute events (<24h): 0% (0/182) vs 0.3% (6/2048), log-rank $P = .465$. Sub-acute events (1-30 days) 0% (0/182) vs 0.9% (19/2042), log-rank $P = .192$. Late events (30-365 days) 0.5% (1/182) vs 1.8% (36/2023), log-rank $P = .230$. Panel C: pre-dilation: HR, 1.07; 95%CI, 0.58-2.00; $P = .824$. Scaffold sizing: HR, 0.43; 95%CI, 0.25-0.75; $P = .003$. Post-dilation: HR, 0.66; 95%CI, 0.34-1.26; $P = .208$. Panel D: pre-dilation: HR, 1.10; 95%CI, 0.59-2.05; $P = .766$. Scaffold sizing: HR, 0.42; 95%CI, 0.24-0.72; $P = .002$. Post-dilation: HR, 0.33; 95%CI, 0.12-0.92, $P = .035$. Patient-level analysis. DOCE includes TV-MI, and target lesion revascularization. 95%CI, 95% confidence interval; DOCE, device-oriented composite endpoint; HR, hazard ratio; PSP, pre-dilation, sizing and post-dilation; TV-MI, target vessel myocardial infarction.

without it (1.6% vs 2.9%; hazard ratio [HR], 1.75; 95%CI, 0.69-4.45]; $P = .239$, adjusted analysis) (table 3). A trend towards a lower rate of DOCE was found in patients with an optimal PSP-3 technique compared to those without it (0.5% vs 2.9%; HR, 5.73; 95%CI, 0.78-41.88; $P = .085$, adjusted analysis) (table 3). Figure 2A and figure 2B show the Kaplan-Meier curves for DOCE of the PSP scores.

Within the PSP-1 score, correct scaffold sizing was associated with a reduction in DOCE (HR, 0.43; 95%CI, 0.25-0.75; $P = .003$). Within the PSP-3 score, either the correct scaffold sizing (HR, 0.42; 95%CI, 0.24-0.72; $P = .002$) or the correct post-dilation (HR, 0.33; 95%CI, 0.12-0.92; $P = .035$) were associated with fewer DOCE (figure 2C,D).

At 1-year follow-up, simplified strategies considering only the pre-dilation and post-dilation as defined according to the models PSP-1 (HR, 1.50; 95%CI, 0.70-3.19; $P = .294$) and PSP-3 (HR, 1.80;

95%CI, 0.65-5.02; $P = .260$) were not associated with a lower DOCE either.

Effect of an optimal PSP technique on various clinical and anatomical scenarios

In the combined REPARA and GHOST-EU database, patients with the optimal PSP technique have lower rates of DOCE compared to those without it in almost all clinical and angiographic scenarios analyzed. In STEMI patients, there was a trend towards no benefit of an optimal PSP technique ($P_{interaction} = .100$) (figure 3).

DISCUSSION

The main findings of our study are: a) an optimal PSP technique was not associated with a lower rate of DOCE; b) a correct scaffold

Table 3. Clinical outcomes at 1-year follow-up stratified according to the optimal PSP technique

PSP-1 model				
	Optimal PSP (n = 303) ^a	Non-optimal PSP (n = 1927) ^a	HR (95%CI)	P
DOCE ^b	5 (1.7)	56 (2.9)	1.75 (0.69-4.45)	.219
Cardiac death	1 (0.3)	14 (0.7)	2.21 (0.30-16.87)	.444
TV-MI	3 (1.0)	31 (1.6)	1.64 (0.50-5.38)	.419
TLR	3 (1.0)	42 (2.2)	2.23 (0.69-7.23)	.182
Definite/probable scaffold thrombosis	4 (1.3)	33 (1.7)	1.30 (0.46-3.70)	.620
PSP-3 model				
	Optimal PSP (n = 182) ^a	Non-optimal PSP (n = 2048) ^a	HR (95%CI)	P
DOCE ^b	1 (0.5)	60 (2.9)	5.73 (0.78-41.88)	.085
Cardiac death	0	15 (0.7)	NA	.627
TV-MI	1 (0.5)	33 (1.6)	2.96 (0.40-21.80)	.286
TLR	1 (0.5)	44 (2.1)	3.97 (0.54-29.01)	.174
Definite/probable scaffold thrombosis	1 (0.5)	36 (1.8)	3.24 (0.44-23.76)	.248

^a Patient-level analysis.

^b Multivariate adjusted Cox model. DOCE includes cardiac death, TV-MI, and TLR.

95%CI, 95% confidence interval; DOCE, device-oriented composite endpoint; HR, hazard ratio; NA, not applicable; PSP, pre-dilation, sizing and post-dilation; TLR, target lesion revascularization; TV-MI, target vessel myocardial infarction.

sizing and post-dilation were associated with fewer DOCE; *c*) the effect of an optimal PSP technique seems to be less important in the ST-segment elevation myocardial infarction (STEMI) compared to other clinical and anatomical scenarios (figure 4).

Clinical value of the PSP technique in the validation cohort

The PSP technique has been proposed to analyze the quality of the BVS implantation technique with clinical outcomes.⁷ The present analysis applied the PSP score to the population of the REPORA registry in external validation. An optimal PSP technique was not associated with a lower rate of DOCE. Specifically, an optimal PSP-1 technique was not associated with a lower rate of DOCE, meanwhile there was a trend to a lower rate of DOCE in patients treated with an optimal PSP-3 technique. The low rate of DOCE and the improvement of the technique may be related with this finding. Even though we did not confirm the effect of the PSP score on clinical outcomes, we believe that most of the medical literature suggests that an optimal implantation technique may improve the outcomes. In the analysis of the ABSORB trials, the sizing of the vessel and operator technique were strongly associated with the outcomes at a 3-year follow-up.¹¹ Nevertheless, other authors had found no relationship between the PSP technique and the outcomes when the analysis was done at lesion-level.¹²

Also, in the derivation cohort or this validation cohort, the rate of patients treated with optimal PSP technique was very low (13.3% and 8.2%, respectively).⁷ Patients herein treated with an optimal PSP technique exhibited a trend towards a lower rate of DOCE compared to those without it. We should mention here that the PSP technique exhibited a high rule-out performance, with a very high negative predictive value and a low likelihood ratio: this shows that a patient with an optimal PSP technique has a

probability of being DOCE-free at 1-year that is close to 100%.¹⁰ Likelihood ratios are used for assessing the value of performing a diagnostic test or score model, with a lower value associated with a lower probability of an endpoint. Therefore, the very low negative likelihood ratios found in this analysis means that an optimal PSP technique was associated with a large to moderate reduction in DOCE occurrences (-30% to -45%).¹³

Within the individual steps of the PSP technique, the correct scaffold sizing was performed in a higher percentage of patients in this validation cohort compared to the derivation cohort (80% versus 50%, respectively). This improvement could be related to the publication of the ABSORB III trial in between the GHOST-EU and REPORA registries, which showed a higher incidence of events in small vessels.¹⁴ The importance of the correct sizing of the vessels for BVS implantation was further highlighted in our analysis, together with correct post-dilation (figure 2).

Effect of an optimal PSP technique in various clinical and anatomical scenarios

Current data support the use of the pre-specified implantation technique for BVS implantation, but it is unknown if this should be applied to all patients or lesions or if some subgroup may benefit most from it.^{5,7} Whereas calcified lesions may, for example, require a perfect PSP technique for BVS outcome optimization, soft lesions may not. For this reason, in the pooled database, we explored the effect of an optimal PSP technique on DOCE in different clinical and anatomical scenarios. Interestingly, we found that in all situations, the analyzed patients treated with an optimal PSP technique have a lower rate of DOCE compared with patients without it. However, in STEMI patients, there was a trend towards no benefit of an optimal PSP technique. This could be related to

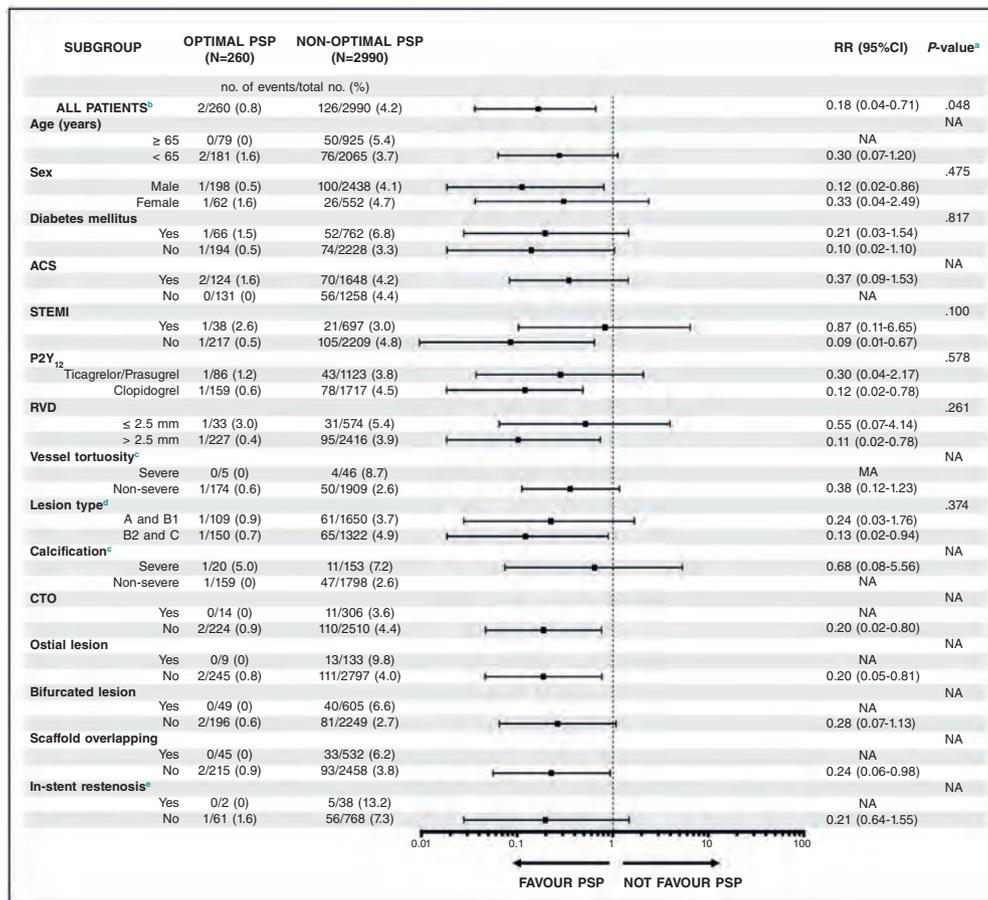


Figure 3. Effect of an optimal PSP technique on DOCE in various clinical and anatomical scenarios at 1-year follow-up. Pooled analysis of the GHOST-EU and REPARA registries.

^a The P-value for interaction represents the likelihood of interaction between the variable and a maximum PSP score.

^b Multivariate adjusted model.

^c Data were only available from the REPARA registry.

^d According to the criteria of the American College of Cardiology-American Heart Association.

^e Data were only available from the GHOST-EU registry.

Patient-level analysis.

95%CI, 95% confidence interval; ACS, acute coronary syndrome; CTO, chronic total occlusion; NA, not applicable; PSP, pre-dilation, sizing and post-dilation; RR, risk ratio; RVD, reference vessel diameter; STEMI, ST-segment elevation myocardial infarction.

the specific characteristic of the STEMI lesions, which are usually soft and thrombotic with less need for lesion preparation or post-dilation in order to reduce distal embolization.¹⁵ In patients with abundant thrombotic material or coronary vasoconstriction, the vessel diameter can be underestimated; use of manual thrombus aspiration and intracoronary nitroglycerin could be useful in these situations, thus allowing the implantation of bigger and shorter stents.¹⁶ A former study suggested, for example, that in STEMI patients a slight scaffold oversizing could help achieve better acute outcomes.¹⁷ It should also be noted here that the percentage of STEMI patients was lower in the derivation than in the validation cohort (15% vs 26%, respectively); this difference could have affected the performance of the score in this specific situation. This finding is supported by the results of the BVS STEMI STRATEGY-IT Study, in which a pre-specified Absorb BVS implantation strategy in STEMI was evaluated. In this study, a low rate of DOCE was observed during the short and mid-term follow-up.¹⁸ Furthermore, in a sub study of the STRATEGY-IT, we found that an optimal PSP technique was not associated with improved outcomes. Interestingly, thrombectomy before optimal BVS implantation showed a trend towards higher post minimal lumen diameter and lower scaffold footprint.¹⁹

Even though the Absorb BVS is no longer available in the clinical practice, there are several BVS ongoing clinical and preclinical evaluation. In these new devices the effect of the implantation technique is unknown, but due to the similarities of these technologies, it seems probable that the implantation technique should also have an effect on the clinical outcomes.

Limitations

This study has limitations that should be acknowledged. First, due to the low rate of events and optimal PSP technique, the clinical relevance of the predictive values may be limited. Secondly, the subgroup analyses are statistically underpowered and should be considered hypothesis-generating only. Thirdly, longer-term follow-up is needed to validate the PSP score models beyond 1-year of follow-up. Despite these limitations, this analysis also has important strengths such as being a large multicenter registry with broad inclusion criteria and few exclusion criteria. The REPARA registry, in particular, facilitated a complete temporal and geographical validation of the score, which reinforces the methodology of this analysis.

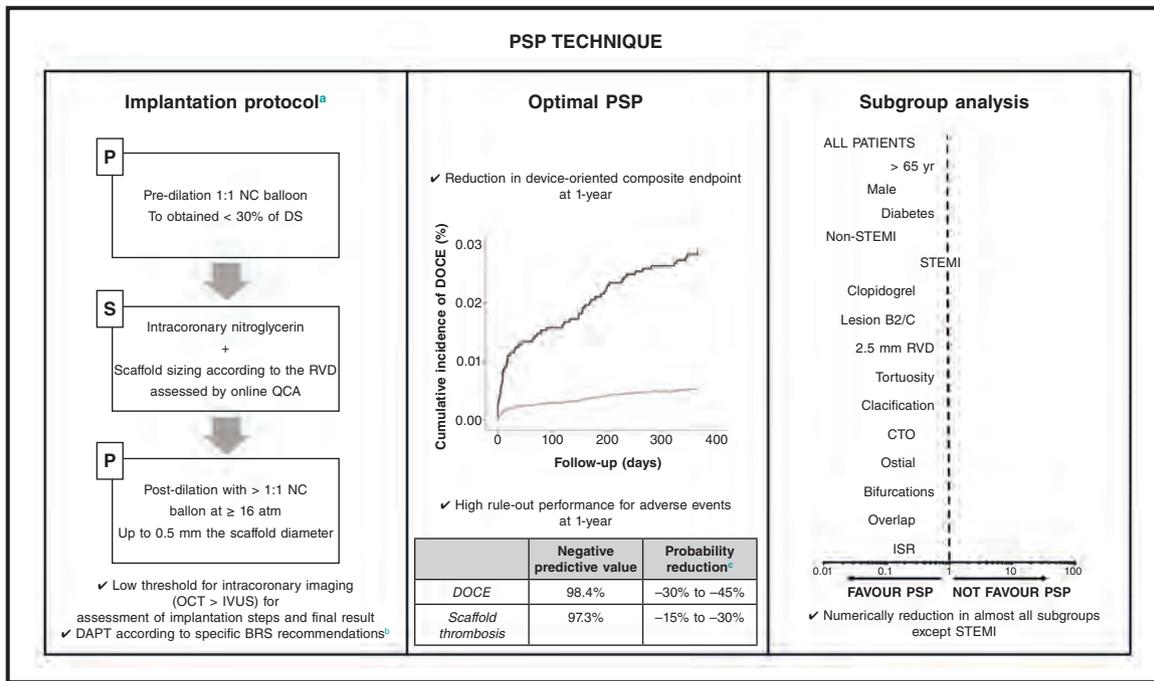


Figure 4. Effect of the PSP technique in various clinical and anatomical scenarios. In the routine clinical practice, the PSP score is a simple score model designed to assess the quality of BVS implantation technique by assessing the 3 fundamental steps of the PSP technique. At 1-year follow-up, an optimal PSP technique is related to fewer DOCE and a very high negative predictive value for DOCE and definite/probable scaffold thrombosis. The effect of an optimal PSP technique on STEMI patients seems to be less significant.

^a Detailed procedural considerations were reported during the development and internal validation.⁷

^b Expert recommendations on DAPT in patients treated with BVS.⁴

^c The probability reduction was estimated by means of negative likelihood ratios.¹³

ATM, atmospheres; BVS, bioresorbable vascular scaffolds; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; DOCE, device-oriented composite endpoint; DS, diameter stenosis; ISR, in-stent restenosis; IVUS, intravascular ultrasound; NC, non-compliant balloon; OCT, optical coherence tomography; PSP, pre-dilation, sizing and post-dilation; QCA, quantitative coronary angiography; RVD, reference vessel diameter; STEMI, ST-segment elevation myocardial infarction.

CONCLUSIONS

In the REPARA, at 1-year follow-up, an optimal PSP technique was not associated with a lower rate of device-oriented composite endpoint. An optimal PSP technique has a very high negative predictive value for BVS DOCE and scaffold thrombosis. It should be noted that, in STEMI patients, there was a trend towards no benefit from using the optimal PSP technique. Studies with longer follow-up are needed to assess the effect of the optimal PSP technique on very-late events and in specific STEMI settings.

WHAT IS KNOWN ABOUT THE TOPIC?

- The PSP score has been proposed to assess the quality of bioresorbable scaffolds implantation technique.
- The optimization of BVS implantation can be related to a reduction in adverse events.

WHAT DOES THIS STUDY ADD?

- In patients treated with an optimal PSP technique, there was a reduction of adverse cardiac events. A maximum PSP score was related to a very high negative predictive value of DOCE and scaffold thrombosis.

- The effect of PSP in STEMI seems less important compared to other clinical and anatomical scenarios.
- Future trials with longer follow-up are needed to assess the effect of an optimal PSP technique beyond 1-year follow-up.
- The effect of an optimal PSP technique among different clinical and anatomical scenarios should be confirmed.
- In STEMI patients, further research is necessary to develop and validate a specific implantation protocol.

FUNDING

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CONFLICTS OF INTEREST

R. Moreno and J. Sanchis are Associate Editors of REC: *Interventional Cardiology*.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000030>.

REFERENCES

1. Ali ZA, Serruys PW, Kimura T, et al. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet*. 2017; 2017;390:760-772.
2. Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016; 388:2479-2491.
3. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. *N Engl J Med*. 2017;376:2319-2328.
4. Capodanno D, Angiolillo DJ. Antiplatelet Therapy After Implantation of Bioresorbable Vascular Scaffolds: A Review of the Published Data, Practical Recommendations, and Future Directions. *JACC Cardiovasc Interv*. 2017; 10:425-437.
5. Puricel S, Cuculi F, Weissner M, et al. Bioresorbable Coronary Scaffold Thrombosis: Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors. *J Am Coll Cardiol*. 2016;67:921-931.
6. Tamburino C, Latib A, van Geuns RJ, et al. Contemporary practice and technical aspects in coronary intervention with bioresorbable scaffolds: a European perspective. *EuroIntervention*. 2015;11:45-52.
7. Ortega-Paz L, Capodanno D, Gori T, et al. Predilation, sizing and postdilatation scoring in patients undergoing everolimus-eluting bioresorbable scaffold implantation for prediction of cardiac adverse events: development and internal validation of the PSP score. *EuroIntervention*. 2017;12:2110-2117.
8. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-2351.
9. Collins GS, Reitsma JB, Altman DG, and Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015;162:55-63.
10. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21:128-138.
11. Stone GW, Abizaid A, Onuma Y, et al. Effect of Technique on Outcomes Following Bioresorbable Vascular Scaffold Implantation: Analysis From the ABSORB Trials. *J Am Coll Cardiol*. 2017;70:2863-2874.
12. Tijssen RYG, Kraak RP, Elias J, et al. Implantation techniques (predilatation, sizing, and post-dilatation) and the incidence of scaffold thrombosis and revascularisation in lesions treated with an everolimus-eluting bioresorbable vascular scaffold: insights from the AIDA trial. *EuroIntervention*. 2018;14:e434-e442.
13. McGee S. Simplifying likelihood ratios. *J Gen Intern Med*. 2002;17:646-649.
14. Steinvil A, Rogers T, Torguson R, and Waksman R. Overview of the 2016 U.S. Food and Drug Administration Circulatory System Devices Advisory Panel Meeting on the Absorb Bioresorbable Vascular Scaffold System. *JACC Cardiovasc Interv*. 2016;9:1757-1764.
15. Zhang ZJ, Marroquin OC, Stone RA, et al. Differential effects of post-dilatation after stent deployment in patients presenting with and without acute myocardial infarction. *Am Heart J*. 2010;160:979-986 e1.
16. Fernandez-Rodriguez D, Regueiro A, Brugaletta S, et al. Optimization in stent implantation by manual thrombus aspiration in ST-segment-elevation myocardial infarction: findings from the EXAMINATION trial. *Circ Cardiovasc Interv*. 2014;7:294-300.
17. Kocka V, Maly M, Tousek P, et al. Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'. *Eur Heart J*. 2014;35:787-794.
18. Ielasi A, Campo G, Rapetto C, et al. A Prospective Evaluation of a Pre-Specified Absorb BVS Implantation Strategy in ST-Segment Elevation Myocardial Infarction: The BVS STEMI STRATEGY-IT Study. *JACC Cardiovasc Interv*. 2017;10:1855-1864.
19. Hioki H, Brugaletta S, Ishida K, et al. Impact of Absorb bioresorbable scaffold implantation technique on post-procedural quantitative coronary angiographic endpoints in ST-elevation myocardial infarction: a sub-analysis of the BVS STEMI STRATEGY-IT study. *EuroIntervention*. 2018. <http://dx.doi.org/10.4244/EIJ-D-18-00504>.

5 year-effectiveness of paclitaxel drug-eluting balloon for coronary in-stent restenosis in a real-world registry

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ABSTRACT

Introduction and objectives: Coronary in-stent restenosis (ISR) is associated with a high target lesion revascularization rate, while the drug-eluting balloon (DEB) presents IA class level of evidence for its treatment. Nevertheless, very long-term outcomes of DEB for ISR in non-selected populations of patients are unknown. Our goal is to evaluate the very long-term (5 year) effectiveness of DEBs in a real-world registry.

Methods: Retrospective registry from an ISR cohort treated with DEB. The primary outcome was the rate of target lesion revascularization (TLR) at 5 years. Secondary outcomes were evaluated according to the ARC-2 criteria.

Results: From January 2010 through December 2013, 53 ISRs were treated using DEBs in 48 patients. Patients were old (69.3 ± 11.8 years-old) and 55.8% had diabetes. The rate of TLR at 1 year was 9.4%, and 20.8% at 3 and 5 years, respectively. The rate of late TLR (after the first year) was 11.4%, only after DEB for bare metal ISR. The 5-year TLR was not associated with diabetes (22.7% vs 19.2%; $P = .76$) and was not significantly lower after cutting-balloon (12.5% vs 24.3%; $P = .47$) or in bare-metal stent ISR (20.6% vs 21.1%; $P = .96$). There was no definite/probable stent thrombosis of the lesions treated with DEB at follow-up.

Conclusions: In a real-world cohort, the 5-year TLR rate after DEB for ISR was 20.8%. Late TLR accounted for half of the TLR at follow-up (after DEB for bare metal ISR), while the rate of TLR seemed to stabilize at 3 years. There was no stent thrombosis of the lesions treated with DEB.

Keywords: Drug-eluting balloon. In-stent restenosis. Target lesion revascularization.

Efectividad a 5 años de balón farmacoactivo con paclitaxel en reestenosis de *stent* coronario en la práctica clínica

RESUMEN

Introducción y objetivos: La reestenosis de *stents* coronarios (RS) presentan altas tasas de necesidad de revascularización, y el balón farmacoactivo (BFA) presenta clase I (nivel de evidencia A) en su tratamiento. La eficacia de esta estrategia a muy largo plazo en pacientes no seleccionados es desconocida. Se pretende evaluar la eficacia del BFA en un registro de pacientes de la práctica clínica a muy largo plazo de seguimiento (5 años).

Métodos: Registro retrospectivo de una cohorte formada por pacientes con ISR tratados con BFA. El evento primario fue la tasa de revascularización de la lesión tratada (RLT) con BFA a 5 años. Se valoraron eventos secundarios según los criterios *Academic Research Consortium-2*.

Resultados: Entre enero de 2010 y diciembre de 2013 se usó BFA de forma eficaz en 53 RS de 48 pacientes. Los pacientes presentaban edad avanzada ($69,3 \pm 11,8$ años) y alta prevalencia de diabetes (55,8%). La tasa de RLT a 1 año fue del 9,4%, y del 20,8% a los 3 y 5 años. La tasa de RLT tardía (más allá del año de seguimiento) fue del 11,4%, tan solo en reestenosis de *stent* convencional. La RLT a 5 años no se asoció a diabetes (22,7 frente a 19,2%; $p = 0,76$) ni fue significativamente menor con el uso de balón de corte (12,5 frente a 24,3%; $p = 0,47$) o en reestenosis de *stent* convencional (20,6 frente a 21,1%; $p = 0,96$). No hubo casos de trombosis de *stent* definitiva/probable de la lesión tratada con BFA.

Conclusiones: En una cohorte de la práctica clínica, el BFA para RS presenta una RLT a 5 años del 20,8%. La RLT tardía supone la mitad de los casos a lo largo del seguimiento, y se produce en RS convencional. La tasa de TLR parece estabilizarse a partir del tercer año de seguimiento. No se evidenció trombosis de *stent* de la lesión tratada con BFA.

Palabras clave: Balón farmacoactivo. Reestenosis de *stent*. Revascularización de lesión tratada.

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Abbreviations

BMS: bare-metal stent. **DAPT:** dual antiplatelet therapy. **DEB:** drug-eluting balloon. **DES:** drug-eluting stent. **ISR:** in-stent restenosis. **TLR:** target lesion revascularization.

INTRODUCTION

In-stent restenosis (ISR) is still a common problem and a therapeutic challenge due to the high rates of culprit lesion revascularization. The treatment of choice for the management of ISR is still to be established.¹ According to several randomized trials, drug-eluting balloon (DEB) angioplasty has better results for the management of ISR compared to conventional angioplasty and similar results compared to in-stent implantation of first-generation drug-eluting stents (DES),²⁻¹³ although it is inferior to second-generation DESs (especially in the ISR of DESs).^{14,15} This strategy has a class I indication (level of evidence A) for the management of ISR both in bare-metal stents (BMS) and DES.¹⁶

The effectiveness of this long-term strategy (over one year of follow-up) has already been established by the medical literature,¹⁷⁻²² yet it is largely unknown in the very long run (over 3 years of follow-up).²³ Similarly, the studies conducted so far claim that high comorbidity is an exclusion criterion because the effect it has on real-world unselected patients is still unknown.

Our aim was to assess the effectiveness of DEBs in a registry of real world patients in a long-term follow-up period (5 years).

METHODS

Retrospective registry of a cohort of patients with ISR treated with DEBs at a high-volume center experienced in performing these procedures (> 1500/year) and percutaneous coronary interventions (> 800/year). The ISR was defined as > 50% angiographic stenosis as seen in 2 radiographic in-stent orthogonal projections or less than 5 mm away from its edges accompanied by symptoms of angina or objective ischemia. All lesions were treated with the same DEB (SeQuent Please, B. Braun Surgical, Melsungen, Germany). No clinical exclusion or angiographic criteria were established in the registry.

Both the clinical and the procedural characteristics were gathered from the center and cath. lab databases. Quantitative coronary angiography of the lesions was carried out using the Philips Xcelera system. Mehran's classification for coronary restenosis was used to characterize the lesions.²⁴ The procedural strategy and predilation with cutting-balloon or non-compliant high-pressure balloon was left at the discretion of the operator. Dilation with DEB was attempted for at least, 60 seconds at nominal pressure.

A 5-year follow-up period was established. The study was approved by the Clinical Trials Committee. All follow-up periods occurred were done in accordance to clinical criteria consulting the regional healthcare system electronic database, which keeps a comprehensive record of all patient-system communications.

All events were defined in a standard way following the Academic Research Consortium-2 (ARC-2) consensus.²⁵ The primary endpoint was the need for target lesion revascularization (TLR) with the DEB and the total number of lesions treated. Secondary endpoints were

any revascularization of acute coronary syndromes/acute myocardial infarctions according to the universal definition established by the European Society of Cardiology (the same or any location),²⁶ all-cause mortality and cardiovascular mortality, and hemorrhage according to the Bleeding Academic Research Consortium (BARC) ≥ 3 .²⁷ Also, the following device-oriented composite endpoints (DOCE): TLR + acute coronary syndrome/acute myocardial infarction of the culprit vessel + cardiovascular mortality or patient-oriented composite endpoints (POCE): any revascularization + acute coronary syndrome/acute myocardial infarction + stroke + overall mortality were estimated on the total number of patients. Stent thrombosis was also defined following ARC-2 criteria and was also estimated on the total number of lesions.

For data analysis, the IBM SPSS 19.0 statistics software package was used. Quantitative variables were expressed as mean \pm standard deviation, and qualitative variables as relative percentage. The cumulative incidence of events at follow-up was measured too. A bivariate analysis was conducted using the chi-square test or Fisher's exact test, and the multinomial logistics regression analysis was used to estimate primary endpoint predictors (statistically significant value: $P < .05$). The Kaplan-Meier method was used to build the cumulative incidence curve during the follow-up of the primary endpoint.

RESULTS

A total of 53 ISRs in 48 patients were efficiently treated with DEBs from January 2010 through December 2013. In one patient, the DEB did not cross the lesion, so the patient was not included in the study (98.2% success rate of the procedure using the DEB). The baseline characteristics of the lesions and the coronary interventions are shown on [table 1](#) and [table 2](#); 49.1% ($n = 26$) of the lesions showed a Mehran I pattern of ISR and 24.5% ($n = 13$) of the lesions were located at the edges of the stent. Good angiographic results were obtained in all the patients (residual stenosis < 30%) and Thrombolysis in Myocardial Infarction grade 3 flow. The mean follow-up was 5.6 years (range: 0.2-8.2 years). There were no losses during follow-up.

Most patients (95.8%, $n = 46$) received clopidogrel as a P2Y₁₂ receptor inhibitor as part of their dual anti-platelet therapy (DAPT) and 22.4% ($n = 11$) oral anticoagulants and short courses of DAPT (3 months).

The rate of TLR at 1 year was 9.4%, and 20.8% at 3 and 5 years. The rate of late TLR (after the follow-up year) was 11.4%. The Kaplan-Meier analysis conducted ([figure 1](#)) shows that events accumulated during the first 3 years. The rate of TLR at 1 year was significantly slower in the ISR of BMSs (2.9% vs 21.1%; $P = .05$), and no late TLR was seen in the ISR of DESs. The rate of 5-year TLR was not associated with diabetes (22.7% vs 19.2%; $P = .76$) and it was not significantly lower with the use of the cutting balloon (12.5% vs 24.3%; $P = .47$) in ≥ 3 mm stents (25.7% vs 11.1%; $P = .29$) or in the ISR of BMSs (20.6% vs 21.1%; $P = .96$). Neither the bivariate analysis nor the logistics regression

Table 1. Baseline characteristic of patients

Characteristics of patients	n = 48
Age (years)	69.3 ± 11.8 (44-93)
Male	77.1% (37)
AHT	75% (36)
Dyslipidemia	56,3% (27)
Smoking	35,4% (17)
Diabetes	
DM + OAD	33.3% (16)
IDDM	12.5% (6)
Atrial fibrillation (OAC)	22.4% (11)
Prior AMI	43.8% (21)
Prior indication for PCI	
Stable IHD	37.5% (18)
ACS	62.5% (30)
Prior CABG	6.3% (3)
CRF (GFR < 60 mL/min)	41.3% (19)
LVEF (%)	55 ± 10.2 (65-29)
Multivessel disease	77.1% (37)
Incomplete revascularization	18.9% (9)
P2Y ₁₂ inhibitors	
Clopidogrel	95.8% (46)
Ticagrelor/prasugrel	4.2% (2)
Duration of DAPT	
3 months	22.4% (11)
6 months	33.3% (16)
12 months	43.8% (21)
ACEI/ARA-II	87.5% (42)
Beta-blockers	91.7% (44)
Statins	100% (48)

ACEI, angiotensin converting enzyme inhibitors; ACS, acute coronary syndrome; AHT, arterial hypertension; AMI, acute myocardial infarction; ARA-II, angiotensin II receptor antagonists; CABG, coronary artery bypass grafting; CRF, chronic renal failure; DAPT, dual anti-platelet therapy; DM, diabetes mellitus; GFR, glomerular filtration rate; IDDM, insulin dependent diabetes mellitus; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; OAC, oral anticoagulants; OAD, oral antidiabetics; PCI, percutaneous coronary intervention.

analysis identified any variables that would act as independent predictors of TLR.

There were no cases of stent thrombosis in the target lesion. Two cases of acute coronary syndrome/acute myocardial infarction on the target vessel were reported: 1 case due to another lesion proximal to the lesion treated with DEB (with good results), and another case of acute coronary syndrome/non-ST-segment elevation acute

Table 2. Characteristics of the lesions and the procedure

Characteristics of the lesion/PCI	n = 53
Location	
Anterior descending artery	50.9% (27)
Circumflex artery	15.1% (8)
Right coronary artery	26.4% (14)
Left main stem	5.7% (3)
Aortocoronary vein graft	1.9% (1)
Bifurcation	26.4% (14)
Diffuse ISR (Mehran II, III, IV)	50.9% (27)
ISR in the edges of the stent	24.5% (13)
Type of stent with ISR	
BMS	64.2% (34)
DES	22.6% (12)
DES over previous BMS	7.5% (4)
DES over previous DES	5.7% (3)
Second generation DES/total DES	84.2% (16)
Stent ≥ 3 mm	66% (35)
Diameter of the stent (mm)	2.9 ± 0.4 (2-4)
Length of the stent (mm)	22.8 ± 7.1 (8-38)
Diameter of the DEB (mm)	3.1 ± 0.3 (2-3.5)
Length of the DEB (mm)	20 ± 5.3 (15-30)
QCA prior to the PCI	
Reference diameter (mm)	3.08 ± 0.39
Minimal lumen diameter (mm)	0.9 ± 0.43
Stenosis (% diameter)	62 ± 15
Length	13 ± 5.3
QCA post-PCI	
Reference diameter (mm)	3.1 ± 0.36
Minimal lumen diameter (mm)	2.27 ± 0.35
Stenosis (% diameter)	15 ± 6
Cutting balloon	30.2% (16)
Non-compliant balloon	62.3% (33)
Radial access	55.1% (27)
Successful PCI (residual stenosis < 30%)	100% (53)

BMS, bare-metal stent; DEB, drug-eluting balloon; DES, drug-eluting stent; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

myocardial infarction due to new onset ISR of the lesion treated with DEB.

At follow-up, a new coronary angiography was performed in 50% of the patients (n = 24). In 29.2% of the patients (n = 14) there was angiographic confirmation of lack of recurrent ISR in the stent treated with DEB. One patient underwent 2 TLRs in 2 different lesions at follow-up.

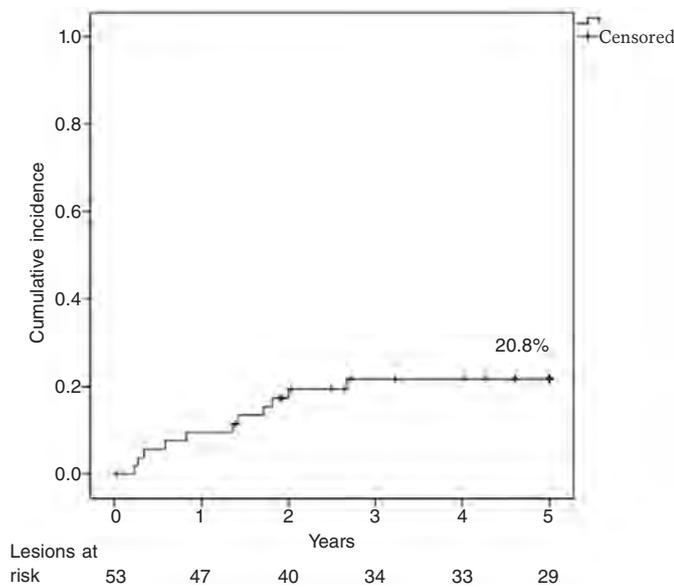


Figure 1. Kaplan-Meier analysis of the cumulative incidence of target lesion revascularization (TLR) at 5-year follow-up.

The remaining secondary and combined endpoints are shown on [table 3](#). The overall mortality rate at 5 years was 33.3% (n = 16), and neoplasms were the most common cause (n = 5). According to the ARC-2 criteria, the cardiovascular mortality rate was up to 10.4% (n = 5): 2 sudden deaths at the 3-year follow-up (both with previous coronary angiography and good results of the lesions treated with DEB) and 3 strokes at the 2-year follow-up (one hemorrhagic stroke on oral anticoagulants).

A total of 13 (27.1%) patients suffered hemorrhages at follow-up, although only 6.3% (n = 3) were on DAPT (one of them on oral anticoagulant medication). Three patients had BARC ≥ 3 hemorrhages: one patient, a BARC 3a GI hemorrhage, and 2 patients had BARC 5b hemorrhages (one due to a GI hemorrhage on DAPT and the other one due to an intracranial hemorrhage on oral anticoagulant medication).

Table 3. Secondary and composite outcomes at the 5-year follow-up

Secondary outcomes at 5 years	n = 48
Any revascularization	29.2% (14)
ACS-AMI in the target vessel	4.2% (2)
ACS-AMI in a different location	10.4% (5)
Overall mortality	33.3% (16)
Cardiovascular mortality	10.4% (5)
Stroke	12.5% (6)
DOCE	31.3% (15)
POCE	54.2% (26)
BARC ≥ 3 hemorrhages	6.3% (3)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; DOCE, device-oriented composite endpoints; POCE, patient-oriented composite endpoints.

DISCUSSION

As far as we know, this study is the first of its kind to describe the long-term progression of ISR lesions treated with DEBs in unselected (outside clinical trials) real-world patients (old and with high cardiovascular risk). The conclusions we can draw from our series are: a) although the per-year rate of TLR is similar to that of other studies already published, in the long run, it seems to be higher than the one reported in selected patients; b) late TLR (after 1 year of follow-up) represents half of the cases that require new revascularizations at follow-up; c) in the long term, TLR is similar in the ISR of both BMSs and DESs, yet late TLR occurs only in the ISR of BMSs; d) the rate of TLR seems to stabilize after 3 years; and e) the use of DEBs for the management of ISRs is a safe strategy from the standpoint of stent thrombosis, even in patients who receive short courses of DAPT.

The mid-term results (6-12 months) of the use of DEBs for the management of ISR have been widely described in randomized studies comparing this strategy with simple angioplasty or DES implantation in populations with clinical and angiographic exclusion criteria. Scheller et al.³ initially reported angiographic 6-month TLR rates of 0% and clinical 12-month-TLR rates of 4% in the PACCOCATH - ISR study (Treatment of in-Stent Restenosis by Paclitaxel Coated PTCA Balloons). Further studies show data more adjusted to actual results, with mid-term TLR rates of 6.6% to 8.8%,^{2,7,8,10,13-15} with differences based on whether we were dealing with the ISR of BMSs (6% to 8.7%)^{2,5,14} or DESs (4.3% to 22.1%).^{4,6-8,13,15,28} In the RIBS studies (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs Everolimus-eluting Stent) V and IV (populations with a geographic location similar to that of the sample), Alfonso et al.^{14,15} reported a 1-year TLR rate of 6% and 13% in the ISR of BMSs and DESs, respectively. Also, these two studies showed 26 TLRs in 249 patients (95 with BMSs and 154 with DESs), that is, a 10.4% rate very similar to the 9.4% rate from our series.

Several studies have published their 3-year follow-up results: PEP-CAD²¹ and RIBS V¹⁹ in BMSs, and RIBS IV,²⁰ PEP-CAD-DES,²² and ISAR-DESIRE³¹⁸ in DESs, with TLR rates of 6.2%, 8%, 15.6%, 19.4%, and 33.3%, respectively. These studies reported a total of 94 TLRs in 524 lesions amounting to a 3-year TLR rate of 17.9% lower than the 20.8% rate from our series. Although in our sample diabetes was not associated with TLR, it is a powerful predictor of ISR.²⁹ This finding may be explained by a much greater prevalence of diabetes in our sample (55.5%) compared to the aforementioned studies (32% to 40%).

Late TLR is defined as a TLR occurring after one year of follow-up. The studies published indicate that TLR usually occurs over the first year of follow-up, not being very relevant thereafter, with rates between 0% and 4.1% (0%-25% of total cases). In our series, late TLR rate was 11.4% in over half of the cases (54% of all TLRs). Only the ISAR-DESIRE¹⁸ study and the study conducted by Habara et al.³⁰ reported rates of late TLR close to the rates shown by our study (14.5% and 7.2%, respectively; 43% and 39% of all TLRs). The differences seen between those randomized studies and our series where TLR is clinical may be explained by the fact that most patients were angiographically followed during the first year, which in turn may have shown prematurely, in asymptomatic patients, a new angiographically significant ISR (> 50%), but not significant enough to cause any symptoms.

In our series there were only cases of late TLR in BMSs, since all TLRs in DESs occurred within the first year of follow-up. Initially, the effectiveness of DEBs was greater in the ISR of BMSs, yet the incidence of TLR went up at follow-up to the point of matching the incidence of TLR in the DES group ([figure 2](#)). These findings may

be explained by the greater initial effect of the DEB over the characteristic pattern of ISR in BMSs (smooth muscle cells) vs the pattern of neoatherosclerosis, more common in the ISR of DESs.²⁸ Thus, this neoatherosclerosis may be causing the late events reported in BMSs as described by Nakazawa et al.³¹ Our findings are different from those published by Habara et al.³⁰ in a long series (550 lesions in 468 patients), where late TLR occurs predominantly in the ISR of DESs (odds ratio = 6; $P = .002$). Although the authors say that there were no differences in the rates of TLR reported between first- and second-generation DESs, 70% of these devices were first-generation DESs (14% were paclitaxel-eluting stents), vs 15% in our series (3 sirolimus-eluting stents and 0 paclitaxel-eluting stents). This study follow-up ends after 2 years, so the question of whether these findings stand in the long run still remains.

Scheller et al.²³ published the 5-year follow-up of the PACCOATH-ISR study, with a 5-year TLR rate of 9.3% and a prevalence of diabetes of 17%. Miura et al.³² reported 5-year TLR rates of 34% in 216 ISRs of DESs, a much higher rate compared to the rate from our sample, with a similar prevalence of diabetes. Both studies suggest that TLR rate increases in the long term. Curiously, in our series, TLR rate stabilized after the third year. In these studies, cases of 2-to-5-year TLR rates have been described, but the exact moment when the TLR occurred was never reported. It is possible that clinical TLR post-DEB occurs after one year follow-up (1-3 years) and then stabilizes over time.

In the ISAR-DESIRE 4 study, the use of cutting-balloon for the management of ISR with DEBs obtained better angiographic results (binary restenosis) and a significant reduction of the 1-year TLR (16.2% vs 21.8%; $P = .26$).³³ In our series, patients treated with cutting-balloon showed a numerically lower rate of TLR (12.5% vs 24.3%), but with no statistical significance due to the size of the sample. Only 30% of the lesions were treated using this technique since when the study was conducted, the benefits of such technique had not yet been established.³³

Our sample had 2 characteristics of which there is scarce information in the medical literature: old age and use of oral anticoagulants. The average age was almost 70 years with data from patients who were extremely old (up to 93 years of age) and over 20% were on oral anticoagulants. Even though this is not an exclusion criterion *per se*, the studies published so far do not provide information on the percentage of patients on oral anticoagulants or the rate of hemorrhages at follow-up.¹⁸⁻²² In these studies, DAPT was extended between 3 and 6 months. In our series, over 50% of the patients received DAPT over a course of 3-6 months and those patients on oral anticoagulants (22.4%) followed a 3-month strategy. The use of DEB with these courses was safe. The overall rate of hemorrhages was moderate, which is consistent with patients' age, and only one patient had a BARC ≥ 3 hemorrhage while on DAPT. Yet despite the high percentage of patients on short courses of DAPT, no cases of definitive/probable target lesion thrombosis were reported. Except for the PEPCAD study, that did not provide information either on stent thrombosis of the lesion treated with DEB, the remaining studies reported long-term rates of stent thrombosis between 0.8% (ISAR-DESIRE study) and 2.6% (RIBS IV study).¹⁸⁻²²

ARC-2 criteria are consensus criteria to make results uniform, although in elderly populations with high ischemic risk they can diminish the effectiveness of the procedure. The high 3-year rate of DOCE reported (31.3%) was this big due to cardiovascular mortality (10.4%), that according to the ARC-2 criteria should also include stroke-induced mortality. As we have already mentioned, based on chronology and causality only, it is unlikely that the cardiovascular mortality rate seen in our sample can be attributed

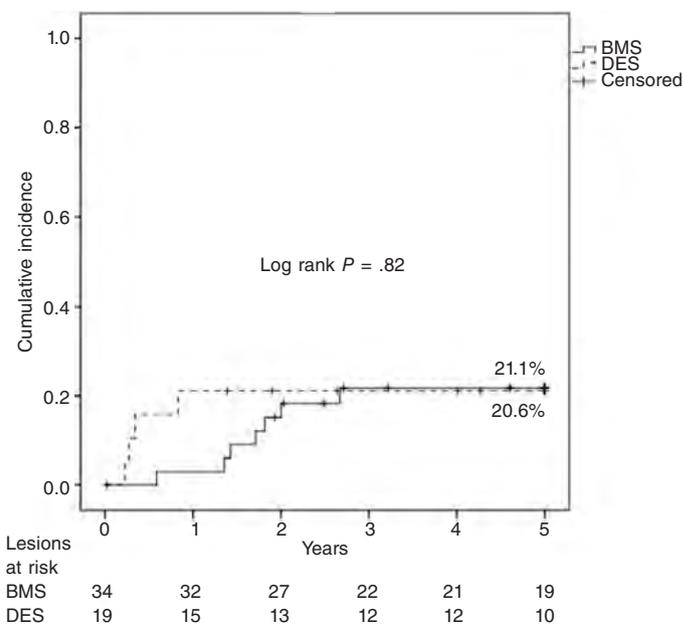


Figure 2. Kaplan-Meier analysis of target lesion revascularization (TLR) at 5 years after the use of drug-eluting balloon for the management of in-stent restenosis of bare-metal stents (BMS) vs drug-eluting stents (DES).

to DEBs. Even though they are combined outcomes with different definitions, DOCEs may look like traditional MACE (major adverse cardiac events), with a similar incidence to the one reported by the studies published, somewhere around 20%-38% at 3 years.¹⁸⁻²² Our patients' high ischemic risk is evident on the high rates of acute coronary syndrome/acute myocardial infarction of the non-target lesions reported (10.2%) and the rates of stroke (12.5%) at follow-up. Both events together with age-related non-cardiovascular mortality (neoplasms) penalized the POCEs by doubling the DOCEs from our series (54.2%). Thus, approximately half of the composite outcomes according to the ARC-2 criteria at 5-year follow-up would not be attributable to the use of DEBs.

Limitations

Our study has some limitations. This was a retrospective, single-center study with limited cases that did not allow to obtain solid scientific evidence. In line with the results published by former studies and reported in the medical literature, our results support the use of DEBs for the management of ISR. Consequently, in the long run, around 80% of patients from unselected populations could avoid having to undergo the implantation of an additional layer of BMS, thus saving this strategy for DEB failure.

CONCLUSIONS

In a clinical practice cohort, DEBs for the management of ISR have a 5-year TLR rate of 20.8%. Late TLR accounts for half the cases at follow-up and occurs in the ISR of BMSs. TLR rate seems to stabilize after three years. No stent thrombosis was reported in lesions treated with DEBs.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- The use of DEBs for the management of ISR is a strategy validated by randomized studies with 1-3-year follow-up in selected populations and TLR rates around 8%-10%.
- Late TLR (after 1-year follow-up) is not very relevant in those studies. The 5-year effectiveness of this strategy has been reported in the literature in a merely formal way.

WHAT DOES THIS STUDY ADD?

- The effectiveness and very long-term follow-up (5 years) of DEBs for the management of ISR in an unselected high cardiovascular risk population. Although the 1-year TLR is similar to that of randomized studies, in a real-world cohort late TLR may be more significant compared to the one described by the studies (above all in conventional stents), and even though it seems to stabilize after three years, it is higher in the very long-term follow-up (5 years).
- In patients with high risk of bleeding, short courses of DAPT were not associated with stent thrombosis of the lesions treated with DEBs.

REFERENCES

1. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol*. 2014;63:2659-2673.
2. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the Efficacy of Paclitaxel-Eluting Balloon Catheters and Everolimus-Eluting Stents in the Treatment of Coronary In-Stent Restenosis: The Treatment of In-Stent Restenosis Study. *Circ Cardiovasc Interv*. 2016;9:e003316.
3. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355:2113-2124.
4. Habara S, Iwabuchi M, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. *Am Heart J*. 2013;166:527-533.
5. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986-2994.
6. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol*. 2012;59:1377-1382.
7. Habara S, Mitsudo K, Kadota K, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv*. 2011;4:149-154.
8. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381:461-467.
9. Indermuehle A, Bahl R, Lansky AJ, et al. Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials. *Heart*. 2013;99:327-333.
10. Baan J, Jr., Claessen BE, Dijk KB, et al. A Randomized Comparison of Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent for the Treatment of Any In-Stent Restenosis: The DARE Trial. *JACC Cardiovasc Interv*. 2018;11:275-283.
11. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. 2015;386:655-664.
12. Giacoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. *BMJ*. 2015;351:h5392.
13. Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv*. 2014;7:204-211.
14. Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol*. 2014;63:1378-1386.
15. Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al. A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol*. 2015;66:23-33.
16. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2018;40:87-165.
17. Xu B, Qian J, Ge J, et al. Two-year results and subgroup analyses of the PEPCAD China in-stent restenosis trial: A prospective, multicenter, randomized trial for the treatment of drug-eluting stent in-stent restenosis. *Catheter Cardiovasc Interv*. 2016;87(Suppl 1):624-629.
18. Kufner S, Cassese S, Valeskini M, et al. Long-Term Efficacy and Safety of Paclitaxel-Eluting Balloon for the Treatment of Drug-Eluting Stent Restenosis: 3-Year Results of a Randomized Controlled Trial. *JACC Cardiovasc Interv*. 2015;8:877-884.
19. Alfonso F, Perez-Vizcayno MJ, Garcia Del Blanco B, et al. Long-Term Results of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With Bare-Metal In-Stent Restenosis: 3-Year Follow-Up of the RIBS V Clinical Trial. *JACC Cardiovasc Interv*. 2016;9:1246-1255.
20. Alfonso F, Perez-Vizcayno MJ, Cuesta J, et al. 3-Year Clinical Follow-Up of the RIBS IV Clinical Trial: A Prospective Randomized Study of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis in Coronary Arteries Previously Treated With Drug-Eluting Stents. *JACC Cardiovasc Interv*. 2018;11:981-991.
21. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. *EuroIntervention*. 2015;11:926-934.
22. Rittger H, Waliszewski M, Brachmann J, et al. Long-Term Outcomes After Treatment With a Paclitaxel-Coated Balloon Versus Balloon Angioplasty: Insights From the PEPCAD-DES Study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter). *JACC Cardiovasc Interv*. 2015;8:1695-1700.
23. Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *JACC Cardiovasc Interv*. 2012;5:323-330.
24. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872-1878.
25. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation*. 2018;137:2635-2650.
26. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-269.
27. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-2747.

28. Alfonso F, Perez-Vizcayno MJ, Garcia Del Blanco B, et al. Usefulness of Drug-Eluting Balloons for Bare-Metal and Drug-Eluting In-Stent Restenosis (from the RIBS IV and V Randomized Trials). *Am J Cardiol.* 2017;119:983-990.
29. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart.* 2014;100:153-159.
30. Habara S, Kadota K, Shimada T, et al. Late Restenosis After Paclitaxel-Coated Balloon Angioplasty Occurs in Patients With Drug-Eluting Stent Restenosis. *J Am Coll Cardiol.* 2015;66:14-22.
31. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol.* 2011;57:1314-1322.
32. Miura K, Kadota K, Habara S, et al. Five-Year Outcomes After Paclitaxel-Coated Balloon Angioplasty for Drug-Eluting Stent Restenosis. *Am J Cardiol.* 2017;119:365-371.
33. Kufner S, Joner M, Schneider S, et al. Neointimal Modification With Scoring Balloon and Efficacy of Drug-Coated Balloon Therapy in Patients With Restenosis in Drug-Eluting Coronary Stents: A Randomized Controlled Trial. *JACC Cardiovasc Interv.* 2017;10:1332-1340.



Diagnostic yield and safety profile of endomyocardial biopsy in the non-transplant setting at a Spanish referral center

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ABSTRACT

Introduction and objectives: Endomyocardial biopsy (EMB) is an established diagnostic tool in myocardial disease. However, this technique may carry major complications. We present the diagnostic and safety results of our experience in EMB in the non-transplant setting. We also present the results after the implementation of a technical and safety protocol developed at our center.

Methods: We retrospectively analyzed the data of all EMBs conducted in non-transplant patients from September 2004 through July 2018. We compared the diagnostic yield and rate of major complications of EMB in two different periods: before and after implementing the protocol.

Results: We included 204 EMBs performed in 190 patients. The most frequent indications were the evaluation of ventricular dysfunction or suspected myocarditis (51.5%) and the evaluation of restrictive cardiomyopathy or suspected infiltrative disease (44.6%). One hundred and seventy-two EMBs were performed in the right cardiac chambers (84.3%) and 30 EMBs in the left cardiac chambers (14.7%). The specimens were taken from both ventricles on 2 cases only. Definite diagnosis was reached in 52% of the cases. After the implementation of the protocol, the diagnostic yield significantly improved (42.5% vs 58.1%; $P = .030$) and the rate of major complications decreased (from 7.5% to 3.2%; $P = .167$), with a statistically significant lower rate of cardiac perforation (6.3% vs 0.8%; $P = .025$).

Conclusions: The EMB is a diagnostic tool with a great potential in patients with suspected cardiomyopathy. Our experience shows that a technical and safety protocol can help decrease the rate of complications and improve the diagnostic yield of EMB.

Keywords: Endomyocardial biopsy. EMB. Cardiomyopathy. Myocarditis. Amyloidosis. Electroanatomical map.

Rentabilidad diagnóstica y seguridad de la biopsia endomiocárdica en corazón nativo en un centro español de referencia

RESUMEN

Introducción y objetivos: La biopsia endomiocárdica (BEM) es una técnica diagnóstica fundamental en el diagnóstico de distintas miocardiopatías, pero no está exenta de posibles complicaciones. Se presentan los resultados en términos de rentabilidad diagnóstica y seguridad de la serie de BEM realizadas en corazón no trasplantado en nuestro hospital, así como las consecuencias de la implementación de un protocolo de actuación y seguridad en BEM desarrollado en nuestro centro.

Métodos: Se revisaron de forma retrospectiva todas las BEM en corazón no trasplantado realizadas desde septiembre de 2004 hasta julio de 2018. Se comparó la rentabilidad diagnóstica y seguridad en dos etapas: antes y después de la puesta en marcha del protocolo.

Resultados: Se incluyeron 204 BEM realizadas en 190 pacientes. La indicación más frecuente fue el estudio de disfunción ventricular o sospecha de miocarditis (51,5%), seguida de estudio de miocardiopatía restrictiva o infiltrativa (44,6%). Se realizaron 172 BEM en cavidades derechas (84,3%) y 30 en cavidades izquierdas (14,7%); solo en 2 de los procedimientos se tomaron muestras de ambos ventrículos. La BEM permitió el diagnóstico definitivo en el 52% de los casos. Tras la implementación del protocolo se observó una mejoría en la rentabilidad diagnóstica (42,5 frente a 58,1%; $p = 0,030$) y una disminución en la tasa de complicaciones mayores (del 7,5% al 3,2%; $p = 0,167$), con una reducción estadísticamente significativa en la tasa de perforaciones cardíacas (6,3 frente a 0,8%; $p = 0,025$).

Conclusiones: La BEM es una técnica con un gran potencial diagnóstico en pacientes con sospecha de miocardiopatía. Aunque puede presentar complicaciones potencialmente graves, la puesta en marcha de un protocolo de actuación y seguridad se asocia a una reducción en la tasa de complicaciones y a una mejoría en la rentabilidad diagnóstica.

Palabras clave: Biopsia endomiocárdica. BEM. Miocardiopatías. Miocarditis. Amiloidosis. Mapa electroanatómico.

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Abbreviations

EMB: endomyocardial biopsy.

INTRODUCTION

Endomyocardial biopsy (EMB) is a key diagnostic tool to monitor rejection in individuals with a heart transplant¹ and also for the diagnosis of different cardiomyopathies.²⁻⁴ Since this technique was born over a century ago,^{5,6} several important advances have been made to improve its diagnostic yield and minimize the risk of complications for the patient. However, EMB-induced major complications, though rare, can be serious.⁷

Our goal was to present the results in terms of diagnostic yield and safety of an EMB series in non-transplanted hearts conducted at our hospital, a national reference center in the diagnosis and management of cardiomyopathies with a huge experience in heart transplants and, consequently, in the monitoring of rejection through EMB in cardiac transplants. Also, we aimed to describe the consequences that implementing a plan of action and safety has on the rate of complications and diagnostic yield of this technique.

METHODS

All EMB procedures conducted in non-transplanted hearts were retrospectively included from September 2004 through July 2018. The demographical and physiological data, relevant echocardiographic parameters (left ventricular ejection fraction and interventricular septum maximum thickness) and times associated with the procedure were all studied.

The main indications for conducting an EMB in a non-transplanted heart were taken into consideration according to the recommendations published by the American Heart Association/European Society of Cardiology back in 2007.^{2,3} In an attempt to facilitate the analysis of data, the indication for the procedure was coded into 4 categories: 1) study of unexplained ventricular dysfunction or suspicion of myocarditis; 2) suspicion of infiltrating disease or restrictive cardiomyopathy; 3) study of ventricular arrhythmias and 4) cardiac tumors. All the histopathological studies extracted from all specimens were reviewed in all the cases (both before and after the protocol) by the same highly-experienced anatomical pathologist in the study of EMBs. The specimens were not reviewed retrospectively in this study again. Instead, the initial 2-stage diagnosis was maintained.

Also, the rate of major complications such as the ones shown in formerly published studies was taken into consideration: mortality, perforation with cardiac tamponade, sustained ventricular arrhythmias with hemodynamic instability, complete atrioventricular block requiring pacemaker, stroke, acute myocardial infarction and appearance of severe valve regurgitation.⁸⁻¹⁰ The main characteristics of the procedures conducted before and after implementing a plan of action and safety were compared including the rate of major complications and diagnostic yield of the EMB in both periods of time.

Plan of action and safety

Back in February 2013, a plan for action and safety was implemented at our center in an attempt to improve the safety of EMBs

and diagnose early whatever complications that may arise. These are the landmarks of this plan:

- Designation of a coordination group for the EMB program in the non-transplant setting including hemodynamic cardiologists, specialists in cardiomyopathies and advanced heart failure, and pathologists.
- Planning the procedure together with the cardiologist who prescribed the test taking the indication and characteristics of the patient into consideration to be able to determine the location of the EMB and the access route. The location of the EMB (right ventricle, left ventricle or both) is basically determined by the gadolinium enhancement pattern on the cardiac magnetic resonance imaging. In highly selected cases with patchy uptake pattern or a prior negative EMB, the electroanatomic mapping-guided EMB is preferred.
- Delivery of the informed consent document by the prescribing cardiologist and explanation to the patient of all potential benefits and risks involved in this procedure.
- Management of perioperative antiaggregant and antiplatelet drugs by the prescribing cardiologist.
 - Antiaggregant action: most EMBs can be conducted without the need to withdraw antiaggregant drugs with acetylsalicylic acid. However, if withdrawal is required, it should occur 7 days in advance. For patients treated with clopidogrel and ticagrelor, it should occur 5 days in advance and for those treated with prasugrel, withdrawal should occur 7 days in advance.
 - Antiplatelet action: each patient's thromboembolic risk is taken into consideration. In patients on dicumarinic treatment, bridge therapy is implemented only in those with high thromboembolic risk, being the drug withdrawn 5 days prior to the procedure and treatment with low molecular weight heparin prescribed 3 days prior to the procedure. In patients on direct-acting anticoagulants, the drug is withdrawn between 24 and 72 hours in advance depending on renal clearance. Bridge therapy is not required.
 - The moment when antiaggregant or antiplatelet drugs are reintroduced is always determined taking into consideration each patient's individual hemorrhagic and thromboembolic risk.
- Conducting or otherwise supervising the procedure should always be the sole responsibility of the interventional cardiologist with the most experience in performing EMBs in non-transplant settings.
- Conducting a transthoracic echocardiography prior to the procedure in order to confirm the lack of pericardial effusion, define cardiac anatomy (size of the interventricular septum and cavities, location of papillary muscles, etc.), and determine the presence and degree of possible valve regurgitation.

- The pericardiocentesis working team should be prepared before starting the procedure.
- Monitorization of vital signs and electrocardiogram during the entire procedure.
- Acquisition of at least 3 good quality specimens from every previously projected location, and confirmation of the position of the bioptome using x-ray imaging and contrast injection before every take.
- Transportation of the specimens preserved in formaldehyde at 4% or a specific preservation medium as per the pathologist instructions.
- Conducting the transthoracic echocardiography immediately after performing the last biopsy or on suspicion of complications during the procedure and monitoring the presence or increase of pericardial effusion or other mechanical complications such as valvular regurgitation. At times (ie, on suspicion of inflammatory or infiltrative cardiomyopathy with segmental damage based on prior imaging modalities), it may be useful to perform an electrocardiogram during the procedure in order to be more precise on the location of the specific segment to be biopsied.
- Hemodynamic and electrocardiogram monitoring for at least 6-8 hours at the diagnostics hemodynamics unit in day-hospital care or, in the case of patients already hospitalized, at the intensive care unit, paying special attention to the appearance of any possible complications of vascular access.
- In the presence of pericardial effusion following the EMB and clinical or echocardiographic data of cardiac tamponade, a

pericardiocentesis for drainage purposes should be attempted at the cath. lab. In most cases, a drainage catheter is inserted and then removed when the amount of drainage fluid is nearly nonexistent and the pericardial effusion has been resolved. In the presence of progressive effusion or hemodynamic instability despite the pericardiocentesis procedure, urgent surgery is indicated to drain the pericardial effusion and repair cardiac perforation.

Description of the procedure

The description of the procedure is shown at in the [supplementary data](#) and in the [figure 1](#).

Statistical analysis

Qualitative variables are expressed as percentages and continuous variables as mean \pm standard deviation as the measure of dispersion. The chi-square test was used to compare qualitative variables and the Student *t*-test was used for independent sample comparison purposes.

The statistical software package SPSS 21 (SPSS, Inc.; Chicago, Illinois, United States) was used for statistical analysis purposes. *P* values < .05 were considered statistically significant.

RESULTS

From September 2004 through July 2018, 204 EMBs were performed in the non-transplant setting in 190 patients (12 with 2 EMBs and 1 with 3 EMBs). After implementing the aforementioned plan,

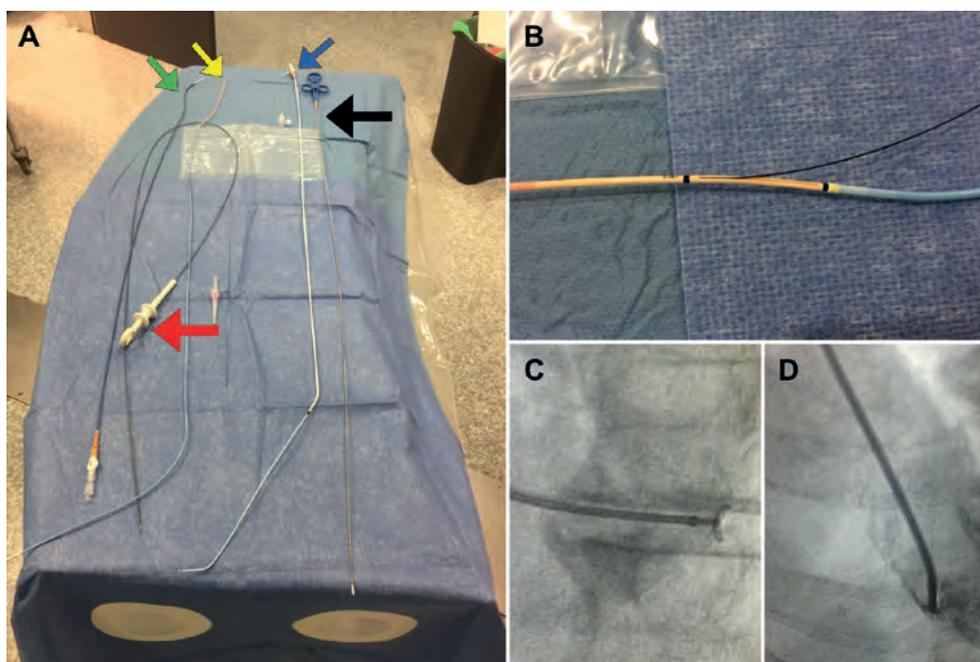


Figure 1. A: Material used to perform EMBs at our center. On the right side, the bioptome (black arrow) and the sheath and the 7-Fr multipurpose catheter (blue arrow) used in right-side EMBs. On the left side, the Endojaw biopsy forceps (red arrow) and 2 of the sheathless systems used for radial access in left-side EMBs: the JR4 7.5-Fr 100-cm-long guidewire catheter (green arrow) and the 7-Fr Railway access system (yellow arrow). B: the latter system described is shown while mounted on a multipurpose catheter at exchange port level. C: open EMB forceps directed towards the left ventricular posterolateral wall for specimen acquisition purposes (left anterior oblique 30° and cranial 15°). D: clockwise rotation in the same projection to direct the guidewire catheter towards the septum using an IV contrast to verify its position.

all EMBs were performed under the direct supervision of an experienced interventional cardiologist or by the cardiologist himself. A total of 172 EMBs were performed in right cavities (84.3%) and 30 in left cavities (14.7%), whereas in only 2 procedures specimens were taken from both ventricles. When it comes to right-side EMBs, the most widely used vascular access was the femoral vein (88.4%) followed by the cephalic or the basilic vein (9.9%) and the right internal jugular vein (1.7%). In the case of left-side EMBs, over half of them were performed through the radial artery (56.7%) and the rest (43.3%) through the femoral artery. One of the cases of biventricular EMB required femoral vein puncture and transseptal access, and another one, arterial and femoral vein puncture separately. In 47.5% of the cases, the EMB was performed in isolation and in the remaining cases in association with another procedure (right catheterization, coronary angiography, and even intra-aortic balloon pump counterpulsation implantation in one patient). Also, it should be mentioned that three of the procedures were electroanatomic mapping-guided EMBs.

Procedural characteristics and diagnostic yield

Table 1 shows the main procedural characteristics by comparing both stages: before and after the implementation of the plan of action and safety. Overall, a definitive anatomopathological diagnosis was achieved in 52.0% of the cases. It is important to stress out that even though the indications were not significantly different in one stage

compared to the other, the diagnostic yield improved significantly after the implementation of the plan (42.5% vs 58.1%; $P = .030$), basically to the detriment of a greater diagnostic yield in cases of ventricular dysfunction or suspicion of myocarditis (28.2% vs 53.0%; $P = .013$). Also, there was a significant increase in the number of specimens obtained and the number of left-side EMBs. There was a significant reduction in procedural time with no differences in the x-ray imaging time, although it is true that this difference may have been related with the fact that the isolated EMB (without an associated procedure) was less common before than after the implementation of the plan (33.8% vs 56.5%; $P = .004$).

Although it never reached statistical significance ($P = .083$), diagnostic yield was different for each and every indication. It was greater in cases of suspicion of restrictive or infiltrative cardiomyopathy and cardiac tumors. Table 2 shows the anatomical pathology diagnosis in each and every indication.

The left-side and biventricular EMB diagnostic yield was similar compared to the right-side EMB diagnostic yield (56.3% vs 51.2%; $P = .384$). It should be mentioned that, in left-side EMBs, the most common indication was the study of ventricular dysfunction or suspicion of myocarditis (70% of the cases). However, this indication was less common in right-side EMBs (48.9% of the cases).

All electroanatomic mapping-guided EMBs were performed after the implementation of the plan. The definitive anatomopathological

Table 1. Baseline characteristics and EMB procedural characteristics. Overall and comparisons before and after the implementation of the plan of action and safety

	Total (n = 204)	Before the implementation (n = 80)	After the implementation (n = 124)	P
<i>Main characteristics</i>				
Age (years)	52.1 ± 17.1	50.4 ± 16.5	53.2 ± 17.4	.252
Males (%)	60.3	55.0	63.7	.214
LVEF (%)	44.2 ± 17.2	48.1 ± 18.9	42.5 ± 16.2	.060
IVS (mm)	12.8 ± 4.5	12.7 ± 4.5	12.8 ± 4.5	.927
BSA (m ²)	1.83 ± 0.21	1.81 ± 0.23	1.84 ± 0.20	.632
Number of valid specimens	3.6 ± 1.4	3.0 ± 1.2	4.0 ± 1.4	< .001
Duration of the procedure (min)	43.3 ± 19.9	47.8 ± 22.5	41.1 ± 18.2	.038
X-ray imaging time (min)	12.1 ± 7.1	12.6 ± 6.3	11.9 ± 7.6	.516
<i>Indications</i>				
Study of unexplained ventricular dysfunction or myocarditis	105 (51.5%)	39 (48.8%)	66 (53.2%)	.698
RCM or suspicion of infiltrative cardiomyopathy	91 (44.6%)	36 (45.0%)	55 (44.4%)	
Ventricular arrhythmias	5 (2.5%)	3 (3.7%)	2 (1.6%)	
Tumors	3 (1.4%)	2 (2.5%)	1 (0.8%)	
<i>Location of the EMB</i>				
Right ventricle only	172 (84.3%)	76 (95.0%)	96 (77.4%)	.003
Left ventricle only	30 (14.7%)	4 (5.0%)	26 (21.0%)	
Biventricular	2 (1.0%)	0	2 (1.6%)	
	52.0	42.5	58.1	.030

BSA, body surface area; EMB, endomyocardial biopsy; IVS, interventricular septum; LVEF, left ventricular ejection fraction; RCM, restrictive cardiomyopathy.

diagnosis was achieved in 2 of the 3 EMBs (one case of myocarditis and one case of enteroviral cardiomyopathy). Also, specific therapy was prescribed in both cases.

Safety and major complications

In our series, there were 10 major complications that amounted to a 4.9% overall rate. No patient died. All complications occurred while performing the EMB in the right cavities, except for two cases of transient ischemic attack that occurred while performing two left-side EMBs. Table 3 shows all major complications and their progression.

Figure 2 shows the main major complications that took place in our series before and after the implementation of the plan of action and safety. It is important to say that after the implementation of this plan the major complications were cut in half (from 7.5% to 3.2%), although this difference was not statistically significant ($P = .167$). This decrease was due to less cases of cardiac perforation with only one case being reported after the implementation of the plan (6.3% before vs 0.8% after the implementation of the plan; $P = .025$).

DISCUSSION

Even though over the last few years we have not had any significant advances in the non-invasive diagnosis of acute rejection in heart transplant recipients^{11,12} or in the non-invasive diagnosis of different cardiomyopathies,¹³⁻¹⁶ the EMB is still the gold standard procedure to achieve a definitive diagnosis in these situations. The findings of the EMB can also have relevant prognostic implications. However, the diagnostic yield of this technique is not absolute and varies from one series published to the next (table 4).^{8,9,17-24} In our series it was impossible to achieve a definitive anatomopathological diagnosis in little over half the cases. It is interesting to see how the diagnostic yield of our series improved significantly after the implementation of the plan basically to the detriment of

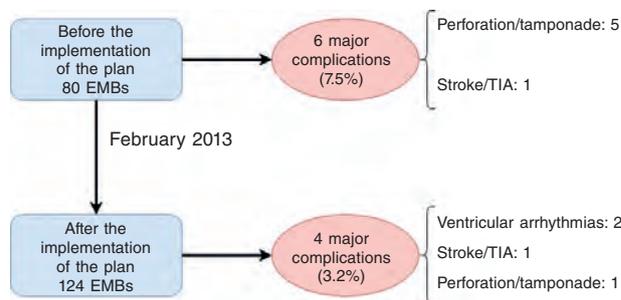


Figure 2. Major complications associated with the EMB before and after the implementation of the plan of action and safety. EMB, endomyocardial biopsy. TIA, transient ischemic attack.

an improved diagnostic yield in cases of ventricular dysfunction or on suspicion of myocarditis. The advances made in immuno-histochemical techniques and genomic detection methods, the planning of all cases by choosing the most suitable approach for each patient (based on the type of cardiomyopathy suspected), the experience accumulated, and the acquisition of a larger amount of specimens in every procedure are some of the reasons that would justify such a change.

The EMB rates from series published by high-volume centers indicate rates of major complications below 1% (table 4). In our series, the rate of complications is higher. The fact that the most common indication in our center was for the study of ventricular dysfunction could explain this, since this group of patients has a higher risk of complications.²⁵ It is important to emphasize here that the implementation of the plan, added to the role played by the learning curve in this technique^{23,24} have cut the occurrence of major complications at our center in half revealing a rate of perforations below 1%. We believe that our results show a more realistic situation of EMBs currently performed in our setting. Therefore, we believe that this type of procedure should not be trivialized and should be performed at centers with enough experience and under the supervision and rules from a clear-cut plan of action of safety.

Table 2. Diagnostic yield in each and every EMB indication

Indication for EMB	Diagnostic yield	Definitive anatomopathological diagnosis
Study of unexplained ventricular dysfunction or suspicion of myocarditis (n = 105)	Total: 43.8% Before the implementation: 28.2% After the implementation: 53.0% ($P = .013$)	Myocarditis: 37 (35.2%) HCM: 4 (3.8%) Amyloidosis: 2 (1.9%) Cobalt toxicity: 2 (1.9%) Mitochondrial cardiomyopathy: 1 (1.0%) Undiagnosed: 61 (58.1%)
Suspicion of RCM or infiltration (n = 91)	Total: 61.5% Before the implementation: 58.3% After the implementation: 63.6% ($P = .611$)	Amyloidosis: 44 (48.4%) HCM: 7 (7.7%) EMF: 2 (2.2%) Sarcoidosis: 1 (1.1%) Myocarditis: 1 (1.1%) Fabry: 1 (1.1%) Undiagnosed: 35 (38.5%)
Ventricular arrhythmias (n = 5)	Total: 40.0%	MCH: 1 (20.0%) Myocarditis: 1 (20.0%) Undiagnosed: 3 (60.0%)
Cardiac tumors (n = 3)	Total: 66.7%	Angiosarcoma: 2 (66.7%) Undiagnosed: 1 (33.3%)

EMB, endomyocardial biopsy; EMF, endomyocardial fibrosis; HCM, hypertrophic cardiomyopathy. The overall diagnostic yield of the entire series is shown here as well as the comparison between the 2 stages (before and after the implementation of the plan of action and safety) in the 2 main indications. The definitive anatomopathological diagnosis of each indication is expressed as absolute numbers and percentages using brackets.

Table 3. Summary of major complications in chronological order of appearance

Patient	Date of the procedure	Age (years)	Sex	Indication for the EMB	Location	Final diagnosis	Complication	Treatment
1	June 2017	66	Female	Study of ventricular dysfunction or suspicion of myocarditis	RV	Undiagnosed	Perforation with cardiac tamponade	Pericardiocentesis
2	November 2016	40	Male	Study of ventricular dysfunction or suspicion of myocarditis	LV	Lymphocytic myocarditis	TIA	Did not need
3	June 2016	35	Male	Suspicion of RCM or infiltrative cardiomyopathy	Biventricular (RV)	Sarcoidosis	SMVT during right-side EMB with hemodynamic instability	Electrical cardioversion
4	May 2015	71	Male	Suspicion of RCM or infiltrative cardiomyopathy	RV	Amyloidosis	Ventricular arrhythmia leading to asystole	Transcutaneous cardiac pacing and IV atropine
5	January 2013	49	Female	Study of ventricular dysfunction or suspicion of myocarditis	RV	Undiagnosed	Perforation with cardiac tamponade	Pericardiocentesis
6	October 2012	55	Female	Study of ventricular dysfunction or suspicion of myocarditis	RV	Undiagnosed	Perforation with cardiac tamponade	Surgery
7	October 2011	82	Male	Suspicion of RCM or infiltrative cardiomyopathy	RV	Amyloidosis	Severe pericardial effusion with no signs of hemodynamic compromise	Delayed surgery (due to persistent pericardial effusion at follow-up)
8	July 2011	67	Male	Suspicion of RCM or infiltrative cardiomyopathy	LV	Amyloidosis	TIA	Did not need
9	June 2008	51	Male	Study of ventricular dysfunction or suspicion of myocarditis	RV	Undiagnosed	Perforation with cardiac tamponade	Pericardiocentesis
10	May 2007	37	Male	Study of ventricular dysfunction or suspicion of myocarditis	RV	Lymphocytic myocarditis	Perforation with cardiac tamponade and cardiorespiratory arrest	Surgery

EMB, endomyocardial biopsy; IV, intravenous; LV, left ventricle; RCM, restrictive cardiomyopathy; RV, right ventricle; SMVT, sustained monomorphic ventricular tachycardia; TIA, transient ischemic attack.

Table 4. Diagnostic yield and major complications in the main EMB series in the non-transplant setting published to date

Author (year)	Number of EMBs	Location/vascular access	Average number of specimens/EMBs	Diagnostic yield	Major complications
Deckers et al. ¹⁷ (1992)	546	RV/jugular (96.2%); femoral (1.3%); subclavian (0.5%).	6 ± 2	Not indicated	0.5% perforations 0.4% mortality
Felker et al. ¹⁸ (1999) ^a	1278	RV/jugular	Not published	16%	0.9%
Bennet et al. ¹⁹ (2013)	851	RV/not indicated	5.6	25.5%	0.9%
Hiramitsu et al. ²⁰ (1998) ^b	19 964	RV (84.3%); LV (56.7%); RA (6.0%)	2.6 in RV 2.8 in LV 2.2 in RA	Not indicated	0.7% perforations 0.05% mortality
Holzmann et al. ⁸ (2008) ^c	3048	RV/femoral	8.2 ± 0.8 (retrospective); 10.1 ± 0.6 (prospective)	Not indicated	0.12% in retrospective series 0% in prospective series
Yilmaz et al. ⁹ (2010)	755	RV (17.1%); LV (35.1%); BiV (47.3%)/femoral	5.6 ± 1.5 in RV; 5.8 ± 1.5 in LV; 8.4 ± 3.5 BiV	BiV 79.3% vs UniV 67.3%	1.1% (BiV 0.56% vs UniV 1.51%)
Fiorelli et al. ²¹ (2012)	1783	RV/jugular + 5 cases LV	Not indicated	Not indicated	0.8% 0.2% mortality
Jang et al. ²² (2013)	228	RV/femoral	5.6 ± 2.3	Not indicated	1.3%
Chimenti et al. ²³ (2013)	4221	RV (15.9%); LV (27.3%); BiV (56.8%)/femoral	4.2 ± 1.6 in RV; 4.5 ± 1.2 in LV; 8.7 ± 1.6 BiV	LV 96.3% vs RV 71.4% in BiV EMBs	0.39% (LV 0.33% vs RV 0.5%)
Isogai et al. ²⁴ (2015) ^d	9167	Not indicated	Not indicated	Not indicated	0.9%

BiV, biventricular; EMB, endomyocardial biopsy; LV, left ventricle; RA, right atrium; RV, right ventricle; UniV, univentricular.

^a Complications studied in 323 patients only.

^b Data published from one multicenter survey including 134 Japanese hospitals. The percentages of the EMB locations are the ones provided by each center. The vascular access used by the different centers varied, mostly venous access and through the femoral artery.

^c Series of 3048 EMBs in 2415 patients (2505 EMBs analyzed retrospectively and 543 prospectively with systematic data mining) for the study of ventricular dysfunction.

^d Multicenter study including data from 491 Japanese hospitals. The table disregards the EMBs performed in the transplant setting. The rate of major complications includes one composite variable of pericardicentesis, surgery or temporary pacing.

In some series, the acquisition of specimens from both ventricles has improved the procedural diagnostic yield without increasing the rate of complications reported.^{9,23} Our experience on this regard is still limited, but still we could confirm that left-side EMBs were more widely accepted after the implementation of the plan. In Spain this approach has been used until recently for the diagnosis of cardiomyopathies. The difference in the diagnostic criteria used in other left ventricle and biventricular EMB series makes it difficult to draw any comparisons with our own results. We would like to highlight that, in our experience, the left-side EMB is a safe technique (with only one complication reported since the implementation of the protocol) with a diagnostic yield similar to the one of right-side EMBs. This statement is even more valuable if we think that main the indication for left-side EMBs was the suspicion of myocarditis where traditionally the EMB has a limited diagnostic yield.²⁶ In sum, we strongly believe that this is a useful approach that can provide with valuable information in these cases.

Over the last few years, the use of radial access to acquire left-side EMBs has been gradually replaced by the femoral access in our series. There is evidence on the medical literature of its feasibility and safety²⁷⁻³¹ with a growing interest in its implementation in the clinical practice since this technique has been perfected with thinner catheters and biotomes, and sheathless catheters specially designed for this access. The risk of complications is potentially lower. Also, same as it happens with coronary interventions through radial access,³² this technique allows to reduce hospital stays and discharge patients just after a few hours under hospital observation.

Performing electroanatomic mapping-guided EMBs is a promising strategy to improve the diagnostic yield of this procedure. Ever since Corrado et al.³³ described for the first time the correlation between areas of low voltage and fibrofatty replacement in patients with arrhythmogenic right ventricular dysplasia, several studies have validated and confirmed the safety of this combined approach for the diagnosis of several cardiomyopathies.³⁴ Our own experience with these cases is still limited. Nevertheless, we believe this is a promising technique for the diagnosis of cardiomyopathies with patchy distribution such as myocarditis or cardiac sarcoidosis. Also, it allows us to optimize the acquisition of specimens, reduce its number, and direct the biotome towards transition areas instead of areas of greater necrosis where the risk of perforation is higher.

Limitations

Our study has several limitations. In the first place, this was a retrospective study with all the biases associated with a study of this nature when it comes to obtaining relevant data. Secondly, this study included the experience of a single center, which is why results are not easy to generalize. On the other hand, and since this is a reference center on the management of cardiomyopathies in advanced functional class and amyloidosis, it is possible that patients were overrepresented in our series.

CONCLUSIONS

In our own experience, the EMB is a technique with an attractive diagnostic potential in patients with suspected cardiomyopathy. However, we should not forget that this procedure can also lead to potentially serious complications. This study shows that the implementation of a plan of action and safety allows to minimize the appearance of complications and improve the diagnostic yield of EMBs.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- The EMB is a key tool for the diagnosis of several cardiomyopathies.
- Yet despite its huge diagnostic potential, this procedure can lead to serious complications.
- The large series of EMBs published so far show rates of complications that are usually low (< 1%) and variable data of diagnostic yield.

WHAT DOES THIS STUDY ADD?

- The results of safety and diagnostic yield of an EMB series in the non-transplant setting performed at our center in a great variety of clinical contexts were presented here. This is the largest Spanish series ever published to this date.
- We describe the technical characteristics of the EMB technique, and the details of the plan of action and safety approved by our center to perform EMBs.
- We proved, for the very first time, that the implementation of a plan of action and safety generates lower rates of major complications and improves the diagnostic yield of EMBs.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000040>.

REFERENCES

1. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant.* 2010;29:914-956.
2. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol.* 2007;50:1914-1931.
3. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34:2636-2648.
4. Caforio ALP, Adler Y, Agostini C, et al. Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. *Eur Heart J.* 2017;38:2649-2662.
5. Kent G, Sutton DC, Sutton GC. Needle biopsy of the human ventricular myocardium. *Q Bull Northwest Univ Evanst Ill Med Sch.* 1956;30:213-214.

6. Sakakibara S, Konno S. Endomyocardial biopsy. *Jpn Heart J.* 1962;3:537-543.
7. Francis R, Lewis C. Myocardial biopsy: techniques and indications. *Heart.* 2018;104:950-958.
8. Holzmann M, Nicko A, Kühl U, et al. Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. *Circulation.* 2008;118:1722-1728.
9. Yilmaz A, Kindermann I, Kindermann M, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. *Circulation.* 2010;122:900-909.
10. Stawek S, Araszkievicz A, Gaczkowska A, et al. Endomyocardial biopsy via the femoral access — still safe and valuable diagnostic tool. *BMC Cardiovasc Disord.* 2016;16:222.
11. Miller CA, Fildes JE, Ray SG, et al. Non-invasive approaches for the diagnosis of acute cardiac allograft rejection. *Heart Br Card Soc.* 2013;99:445-453.
12. Mingo-Santos S, Moñivas-Palmero V, Garcia-Lunar I, et al. Usefulness of Two-Dimensional Strain Parameters to Diagnose Acute Rejection after Heart Transplantation. *J Am Soc Echocardiogr.* 2015;28:1149-1156.
13. Yoshida A, Ishibashi-Ueda H, Yamada N, et al. Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. *Eur J Heart Fail.* 2013;15:166-175.
14. Zhao L, Fang Q. Recent advances in the noninvasive strategies of cardiac amyloidosis. *Heart Fail Rev.* 2016;21:703-721.
15. Bami K, Haddad T, Dick A, Dennie C, Dwivedi G. Noninvasive imaging in acute myocarditis. *Curr Opin Cardiol.* 2016;31:217.
16. Spieker M, Katsianos E, Gastl M, et al. T2 mapping cardiovascular magnetic resonance identifies the presence of myocardial inflammation in patients with dilated cardiomyopathy as compared to endomyocardial biopsy. *Eur Heart J Cardiovasc Imaging.* 2018;19:574-582.
17. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol.* 1992;19:43-47.
18. Felker GM, Hu W, Hare JM, Hruban RH, Baughman KL, Kasper EK. The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients. *Medicine [Baltimore].* 1999;78:270-283.
19. Bennett MK, Gilotra NA, Harrington C, et al. Evaluation of the role of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. *Circ Heart Fail.* 2013;6:676-684.
20. Hiramitsu S, Hiroe M, Uemura A, Kimura K, Hishida H, Morimoto S. National survey of the use of endomyocardial biopsy in Japan. *Jpn Circ J.* 1998;62:909-912.
21. Fiorelli AI, Benvenuti L, Aiello V, et al. Comparative analysis of the complications of 5347 endomyocardial biopsies applied to patients after heart transplantation and with cardiomyopathies: a single-center study. *Transplant Proc.* 2012;44:2473-2478.
22. Jang SY, Cho Y, Song JH, et al. Complication Rate of Transfemoral Endomyocardial Biopsy with Fluoroscopic and Two-dimensional Echocardiographic Guidance: A 10-Year Experience of 228 Consecutive Procedures. *J Korean Med Sci.* 2013;28:1323-1328.
23. Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation.* 2013;128:1531-1541.
24. Isogai T, Yasunaga H, Matsui H, et al. Hospital volume and cardiac complications of endomyocardial biopsy: a retrospective cohort study of 9508 adult patients using a nationwide inpatient database in Japan. *Clin Cardiol.* 2015;38:164-170.
25. Elbadawi A, Elgendy IY, Ha LD, et al. National Trends and Outcomes of Endomyocardial Biopsy for Patients With Myocarditis: From the National Inpatient Sample Database. *J Card Fail.* 2018;24:337-341.
26. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation.* 2008;118:639-648.
27. Schulz E, Jabs A, Gori T, et al. Feasibility and safety of left ventricular endomyocardial biopsy via transradial access: Technique and initial experience. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* 2015;86:761-765.
28. Bagur R, Bertrand OF, Bêliveau P, et al. Feasibility of using a sheathless guiding catheter for left ventricular endomyocardial biopsy performed by transradial approach. *J Invasive Cardiol.* 2014;26:E161-163.
29. Schäufole TG, Spittler R, Karagianni A, et al. Transradial left ventricular endomyocardial biopsy: assessment of safety and efficacy. *Clin Res Cardiol Off J Ger Card Soc.* 2015;104:773-781.
30. Bagur R, Gilchrist IC. Transradial approach to take a little piece of heart. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* 2015;86:766-767.
31. Choudhury T, Schäufole TG, Lavi S, et al. Transradial Approach for Left Ventricular Endomyocardial Biopsy. *Can J Cardiol.* 2018;34:1283-1288.
32. Córdoba-Soriano JG, Jiménez-Mazuecos J, Rivera Juárez A, et al. Safety and Feasibility of Outpatient Percutaneous Coronary Intervention in Selected Patients: A Spanish Multicenter Registry. *Rev Esp Cardiol.* 2017;70:535-542.
33. Corrado D, Basso C, Leoni L, et al. Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation.* 2005;111:3042-3050.
34. Vaidya VR, Abudan AA, Vasudevan K, et al. The efficacy and safety of electroanatomic mapping-guided endomyocardial biopsy: a systematic review. *J Interv Card Electrophysiol.* 2018;53:63-71.

Requirements and sustainability of primary PCI programs in Spain for the management of patients with STEMI. SEC, AEEC, and SEMES consensus document



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ABSTRACT

Primary percutaneous coronary intervention (pPCI) is the best modality of reperfusion in ST segment elevation in acute myocardial infarction (STEMI). Its application requires networked assistance systems whose implementation requires significant organizational and logistical changes. In comparison with other scenarios of urgent action, a series of aspects are specific to the pPCI programs. They require immediate, clearly pre-established strategies, carried out by highly skilled professionals who attend to a high volume of highly complex patients. The lack of homogeneity in the creation and development of reperfusion programs in Spain has led to great differences in their implementation. If the pPCI programs are not carried out under adequate conditions, their sustainability can be complex. The present document, agreed between different scientific societies, aims to analyze the current situation in Spain of the network care programs for STEMI, identify their limitations and deficiencies, assess their vulnerability and establish a series of recommendations to ensure their sustainability.

Keywords: ST-segment elevation acute myocardial infarction. Primary percutaneous coronary intervention. Requirements. Medical emergency systems. Program sustainability.

Requisitos y sostenibilidad de los programas de ICP primaria en España en el IAMCEST. Documento de consenso de SEC, AEEC y SEMES

RESUMEN

El intervencionismo coronario percutáneo primario (ICPp) es la mejor forma de reperfusión en el infarto agudo de miocardio con elevación del segmento ST (IAMCEST). Su aplicación requiere sistemas asistenciales en red cuya implementación exige cambios organizativos y logísticos importantes. En comparación con otros escenarios de actuación urgente, una serie de aspectos son específicos de los programas de ICPp. Requieren de estrategias inmediatas claramente preestablecidas, realizadas por profesionales muy expertos y que atienden a un elevado volumen de pacientes de alta complejidad. La falta de homogeneidad en la creación y desa-

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rollo de los programas de reperfusión en España ha llevado a grandes diferencias en su implantación. Si los programas de ICPp no se efectúan en condiciones adecuadas su sostenibilidad puede ser compleja. El presente documento, consensado entre diferentes sociedades científicas, tiene por objetivos analizar la situación actual en España de los programas de atención en red al IAMCEST, identificar sus limitaciones y deficiencias, evaluar su vulnerabilidad y establecer una serie de recomendaciones para asegurar su sostenibilidad.

Palabras clave: Infarto agudo de miocardio con elevación del segmento ST. Intervencionismo coronario percutáneo primario. Requisitos. Sistemas de emergencias médicas. Sostenibilidad de los programas.

Abbreviations

AACC: autonomous communities. **STEMI:** ST-segment elevation acute myocardial infarction. **PPCI:** primary percutaneous coronary intervention. **SEC:** Spanish Society of Cardiology. **MES:** medical emergency system. **CICU:** cardiac intensive care unit.

INTRODUCTION

Ischemic heart disease is still the leading cause of mortality worldwide and it amounts to up to 20% of the overall deaths in Europe.¹ The ST-segment elevation acute myocardial infarction (STEMI) is one of the most relevant forms of presentation. Early reperfusion is the most effective way to reduce morbimortality in STEMI. It was soon confirmed that fibrinolysis could not reestablish the patency of the coronary artery found in up to 20%-45% of patients² with a 5%-10% acute coronary re-occlusion after successful fibrinolysis and a rate of late occlusion close to 30%.³ Primary angioplasty or more precisely, primary percutaneous coronary intervention (pPCI) did obtain significantly higher success rates in reperfusion above 90%,⁴ which is associated with a 30% relative reduction in mortality rate at 30 days and a lower risk of reinfarction and stroke.⁵ For this reason, pPCI became the gold standard treatment for the management of STEMI. However, the benefit of pPCI over fibrinolysis is only evident when performed at adequate centers by experienced teams (infarction centers) and within the first 120 minutes after the first medical contact.⁶

The pPCI not only is more effective and safer compared to fibrinolysis but recent studies show that it is cost-effective from the socioeconomic point of view, regardless of the initial high cost of its logistical and technological implementation.^{7,8} In a study conducted in the United States,⁹ reperfusion through pPCI was associated with lower hospital costs initially compensated with the higher personnel costs (on call 24/7); however, when used in large volumes of patients, the pPCI was much more cost-effective. This higher cost-effectiveness is the product of eliminating the cost of fibrinolysis, the lower incidence of ischemic and hemorrhagic complications, the lower need for coronary angiographies and ischemia detection imaging modalities, the shorter initial hospital stay due to readmissions, and patients' early return to professional life.

In an attempt to offer the best reperfusion strategy to the highest number of patients and within the recommended timeframes, several scientific societies recommended the creation of STEMI care network systems in the community and regional settings to provide the fastest possible healthcare to these patients.⁶ However, the implementation of these reperfusion networks requires important organizational and logistical changes. And this is a complex situation in Spain since the allocation of resources from the different healthcare administrations of the 17 autonomous communities (AACC) is decentralized and, therefore, budgets are managed independently. The organization and implementation of the

healthcare system is also decentralized in this system. This leads to the heterogeneous provision of services. The way pPCI networks work and the results obtained from these networks are highly influenced by several factors such as geography, the number of pPCI-capable centers, referral times, the availability of adequate resources, infrastructure, and the characteristics of healthcare systems *per se*.¹⁰ Similarly, the heterogeneity of the financial situation and the structures of the different healthcare systems have led to great inequalities in the ways these networks have been organized; differences noticeable not only among different countries, but also among different geographical areas within the same country.¹⁰⁻¹³ All these aspects translate into challenges and threats when it comes to the optimal implementation of STEMI care systems in Spain and they should be studied and analyzed in search of proposals and solutions that meet their needs.

This document has been agreed by different scientific societies (table 1) with the following goals in mind:

- Analyze the actual situation of reperfusion-based STEMI care programs in Spain.
- Identify the limitations and deficiencies of such programs.
- Assess their vulnerabilities and sustainability. Establish a series of recommendations on the needs for personnel, infrastructures and incentives required for their optimization.
- Achieve agreed consensus from the different scientific societies involved in the management and treatment of patients with STEMI.
- Establish a combined national registry of all the actual pPCI programs.

ORGANIZATION OF HEALTHCARE NETWORKS FOR THE MANAGEMENT OF REPERFUSION IN SPAIN

Initial experiences and progress made by healthcare networks

The first experiences with structured programs of reperfusion with pPCI for the management of patients with STEMI in Spain date back to 2000 to 2001 in the Community of Navarre and the Region of Murcia, respectively where all patients were referred to a single reference center.¹⁴ The first multicenter program started in Galicia back in 2005. A series of centralized pPCI programs

were defined then where geographical location-based isochrones were categorized, the healthcare centers where patients should be referred to were identified, and the healthcare and transfer resources needed were described. From early on, it was evident that these networks determined an increase in the number of STEMI patients treated with the best reperfusion therapy available at the time.¹⁵

Back in the year 2008, the AACC of Murcia, Navarre, Galicia, and the Balearic Islands had already implemented network structures that, at that time, meant that 12.8% of the Spanish national territory was covered. That same year, the Stent for Life initiative was born, a European project implemented by the European Association of Percutaneous Cardiovascular Interventions, and designed by interventional cardiologists, health Administration officials, patients, and healthcare industry providers. The goal of this initiative was to stimulate and facilitate the implementation of healthcare networks that would allow any STEMI patient to have access, in the least amount of time possible, to reperfusion therapy through pPCI. Spain started collaborating in this program back in 2009 in an attempt to identify regions with implementation deficiencies and to promote the elimination of barriers responsible for delays in the healthcare process. The project was based on prior experiences in the development of new projects. Also, it was decided to create and maintain reliable activity registries with campaigns aimed at training the population and making health authorities more sensitive to this issue.¹⁶ Nowadays, this initiative is called Stent, Save a Life and it has been brought to other continents to promote the development of healthcare networks in developing counties.

In 2009, Catalonia established its own pPCI and 3 years later, in 2012 Asturias, Cantabria, and Castile-La Mancha followed. Then, it would be the turn for Madrid, Valencia, Aragon, La Rioja, and the Basque Country. All these AACC have active regional programs generically known as *Infarction Code*. These changes in the reperfusion strategies reduced significantly the rates of thrombolysis, while the percentage of patients treated with pPCI increased gradually with an increase of territory coverage and number of interventions performed across the country^{10,17} which is consistent with what was already happening in other European countries.¹⁸

Numerous experiences have been reported that exemplify the benefits of implementing STEMI care networks, both in the European¹⁹ and domestic settings.²⁰ One study¹⁰ analyzed the connection between the implementation of reperfusion networks for the management of STEMI in AACC, the regional rate of pPCI and hospital mortality. Throughout the entire period studied, there was a higher rate of pPCIs in all AACC (54.5% in 2012 vs 21.6% in 2003) (figure 1). It was confirmed that crude mortality rate was higher in non-reperused patients (17.3%) compared to patients who had undergone pPCIs (4.8%) or fibrinolysis (8.6%; $P < .001$), with a lower risk-adjusted standardized mortality ratio (of 10.2% in 2003 and 6.8% in 2012; $P < .001$). In sum, the implementation of reperfusion networks was associated with a 50% increase in the rate of pPCIs and a 14% reduction in mortality rate (figure 2).

Reperfusion networks in Spain: current situation

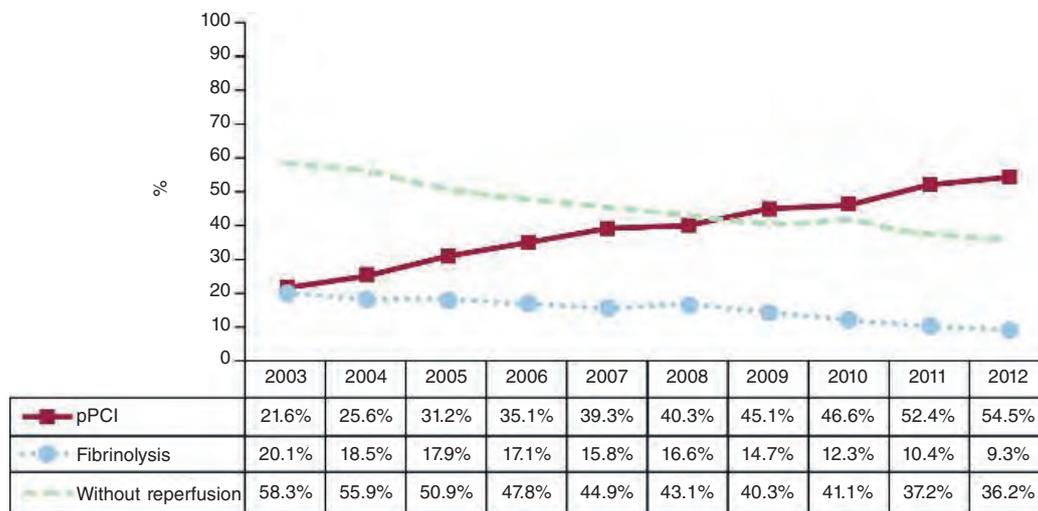
Situation of the pPCI networks

Over the last few months, we have been able to provide coverage to the entire Spanish territory through regional healthcare networks for the management of STEMI patients. In some cases, these pPCI programs do not have fully structured regional networks and depend on local circuits limited to a certain number of hospitals.

Table 1. Scientific societies, working groups, and representatives that have participated and signed the consensus document

Representative	Society
Ángel Cequier	Spanish Society of Cardiology (SEC)
Armando Pérez de Prado	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Ana Belén Cid	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Javier Martín-Moreiras	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Oriol Rodríguez-Leor	Working Group on Hemodynamics and Interventional Cardiology of the SEC
José Ramón Rumoroso	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Ana Serrador	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Raúl Moreno	Working Group on Hemodynamics and Interventional Cardiology of the SEC
Sergio Raposeiras	Working Group on Ischemic Heart Disease and Acute Cardiac Care of the SEC
Albert Ariza	Working Group on Ischemic Heart Disease and Acute Cardiac Care of the SEC
Esteban López de Sá	Working Group on Ischemic Heart Disease and Acute Cardiac Care of the SEC
Andrés Íñiguez	SEC
José Luis López Sendón	SEC
Francisco Javier Delgado	Spanish Association of Nursing in Cardiology
Rocío Gil Pérez	Spanish Association of Nursing in Cardiology
José Julio Jiménez-Alegre	Spanish Society of Emergency Medicine
Manuel José Vázquez	Spanish Society of Emergency Medicine
José Manuel Flores	Spanish Society of Emergency Medicine
Héctor Bueno	SEC
Manuel Anguita	SEC

Taking all these aspects into consideration, the number of per population-pPCIs has changed dramatically in our country, with a reduced number of patients treated with pPCI in AACC that did not have complete and structured programs before¹⁷ (figure 3). Consequently, the lack of homogeneity in the creation and development of the different reperfusion programs in the different AACC has brought many differences to these programs, some of them created exclusively by healthcare providers themselves with almost no institutional support. Also, other programs have seen the involvement of the Administration with detailed analyses of subdivisions, logistics, and infrastructure, and the provision of all necessary resources. This has originated a significant heterogeneity in the structure and organization of the different programs and in the assessment of different quality indicators and results. The information available shows that establishing a systematic and organized pPCI program makes a very favorable impact on prognosis compared to having unstructured pPCI programs



P < .001 for the (increase/reduction) percentage for all treatment groups.

Figure 1. Changes in reperfusion strategies for the management of ST-segment elevation acute myocardial infarction in the Spanish health public system between 2003 and 2012. The evolution of reperfusion strategies can be seen over the entire study period. The percentage of patients treated with primary percutaneous coronary interventions (pPCI) increased gradually and simultaneously with moderate drops in the rate of thrombolysis. (Reproduced with permission from Cequier et al.¹⁰)

without a preestablished transfer logistics²⁰ (figure 4). Since there is not such a thing as a national pPCI registry, we do not know what the real volume of activity is in these programs or under what quality standards they have been implemented. Recent initiatives started by the Spanish Society of Cardiology (SEC) aim at promoting healthcare and evaluating the results of STEMI care (SEC-CALIDAD).²¹

Situation of healthcare providers conducting pPCIs

In an effort to obtain information on how the actual pPCI programs work in Spain, in May 2018 the Working Group on Hemodynamics and Interventional Cardiology of the SEC conducted a survey among all its members called *Needs and requirements of primary angioplasty program: a professional survey* (O. Rodríguez-Leor, personal information). The questionnaire collected information on the activity of the programs already running in all the centers and on the degree of satisfaction of the personnel involved. Out of the 390 interventional cardiologists surveyed, 172 (44%) filled in the questionnaire. The mean age of respondents was 45 ± 8 years old (interquartile range: 39-50 years) and they all had over 9 ± 6 years of experienced managing primary angioplasty programs. The centers performed an average 292 procedures per year (200-410). All AACC were represented in this survey.

A very important aspect was that 45% of the respondents were not getting any breaks after night code activations. In almost half of the cases of those who actually got a break, they did not have access to their resting hours the next day because these hours had to be adjusted to the actual logistics needs or volume of activity of their department (figure 5). Another remarkable aspect is that over 50% of the respondents said their intention was to stop doing night calls whenever they were eligible due to their age (figure 6A). On the other hand, a high percentage of respondents (85%) said that the management of patients had room for improvement within their actual programs (figure 6B).

Back in 2012-2013, another survey was conducted among the nurses of 52 centers that showed that in 64% of the cases, those

who had been on call did not have any time to rest, and only 7% had access to some sort of rest over the next 12 hours (V. Rodríguez, personal information). Eighty-four percent of respondents did not get any time in lieu.

The results from these surveys should make us think of the future threats and risks of the actual models of human resources in certain pPCI programs.

SPECIFICITIES OF pPCI PROGRAMS

The particular characteristics and specific requirements of pPCI programs can put them in a scenario of vulnerability that will gradually make it very difficult to keep their sustainability if these programs are not implemented under the right conditions from the point of view of structure, organization, human resources, and equipment.

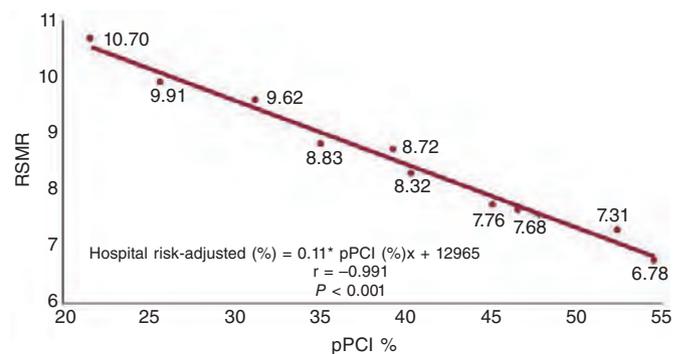


Figure 2. Correlation between the rates of primary percutaneous coronary interventions (pPCI) and mortality in the management of patients with ST-segment elevation acute myocardial infarction in the Spanish health public system between 2003 and 2012. There was a significant correlation between the rates of pPCI and mortality over the entire study period. RSMR, risk-standardized mortality rate. (Reproduced with permission from Cequier et al.¹⁰)

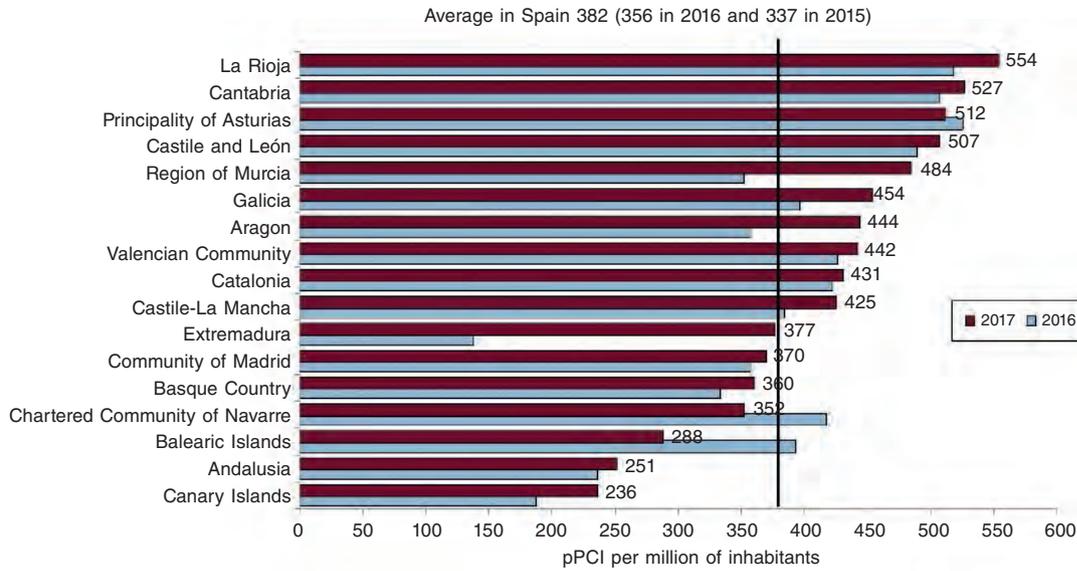


Figure 3. Primary percutaneous coronary interventions (pPCI) per million of inhabitants over the years 2016 and 2017 in all Spanish autonomous communities. Those communities without fully structured network programs (Andalusia, Canary Islands, and Extremadura back in 2016) show the lowest number of patients with ST-segment elevation acute myocardial infarction treated with pPCI (Reproduced with permission from Cid Álvarez et al.¹⁷)

One of the key aspects of pPCI is the immediacy of the healthcare provided. In STEMI patients there is a direct correlation between the time the artery has remained occluded and early and long-term morbimortality. The occluded artery should be opened as soon as possible, which is why the time elapsed since the patient is first assisted until the artery is opened is a critical factor to determine the effectiveness of the procedure and results.^{22,23} Although time limit when it comes to selecting the optimal reperfusion strategy (pPCI vs fibrinolysis) is 120 minutes, the recommendations of the clinical practice guidelines established by the European Society of Cardiology have become more and more demanding. They indicate that the maximum amount of time that should elapse since the diagnosis of STEMI is established until angioplasty guidewire crossing should not exceed 60 minutes in patients admitted to pPCI-capable centers, and should not exceed 90 minutes in patients transferred from other centers.⁶ A pPCI program should guarantee achieving diagnoses immediately, conducting urgent transfers and interventional procedures in a short span of time. The implementation of a pPCI program requires close collaboration of all teams involved in the healthcare system (primary care, regional hospitals, emergency rooms, emergency systems and transfers, and infarction centers).

Compared to other urgent care settings, even high-risk settings, there is a series of aspects exclusive and specific to pPCI programs:

- They require immediate healthcare that should be perfectly coordinated among the different levels of healthcare with clearly preestablished strategies and logistics and conducted by experienced teams. The teams involved should be on call 24/7, and ready to act as swiftly as possible when required, without a preestablished schedule, and in less than a 60-90-minute timeframe after activation.
- The transfer of patients to the corresponding infarction centers should have top priority over all other types of emergencies or procedures.
- Patients have a high mortality risk and they usually need complex healthcare actions, so an adequate infrastructure is required.

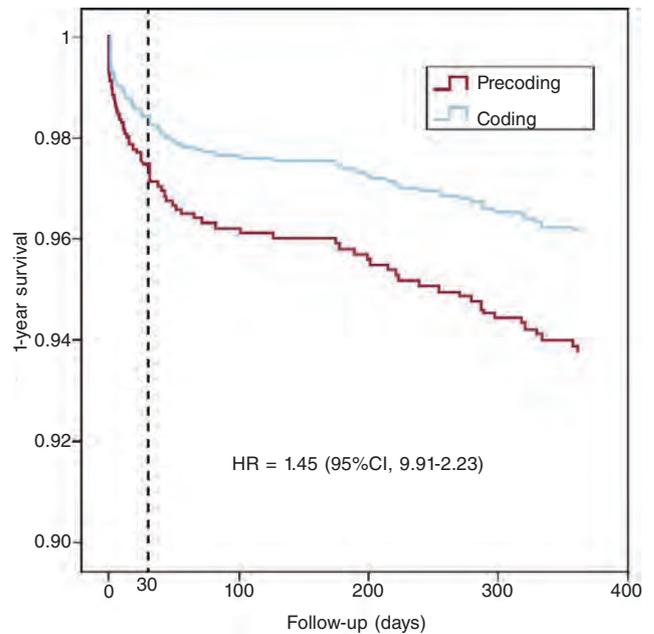


Figure 4. Prognostic impact of patients from a primary percutaneous coronary intervention (pPCI) program in a subdivided region before (precoding) and after (coding) the implementation of pre-established intervention and transfer logistics measures with regional hospitals and emergency medical services. There is a significant improvement of survival rate over the first year after implementation. (Reproduced with permission from Gómez-Hospital et al.²⁰)

- The volume of STEMI patients with an indication for pPCI is very high.

The following features define the landmarks for a healthcare network system to be successful in the management of STEMI patients:

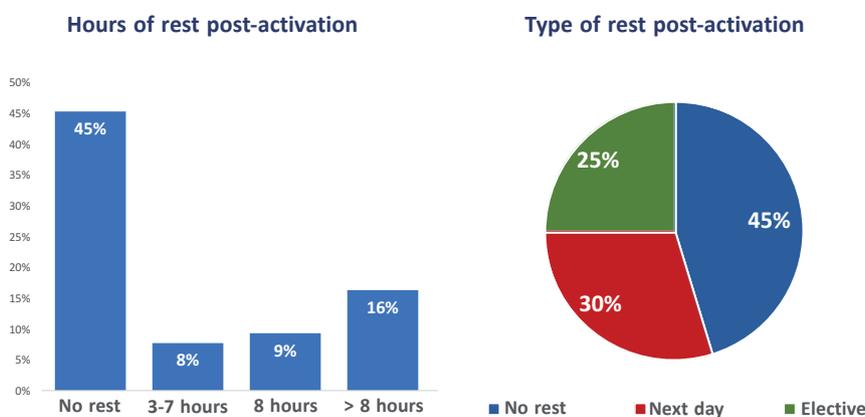


Figure 5. Hourly schedules and types of rest after being activated to perform primary percutaneous coronary interventions during night shift. Only 25% take a break of at least 8 hours after performing this procedure. Forty-five percent immediately move on to their routine clinical practice the next day with no downtime. (Data gathered from a survey conducted among members of the Working Group on Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology.)

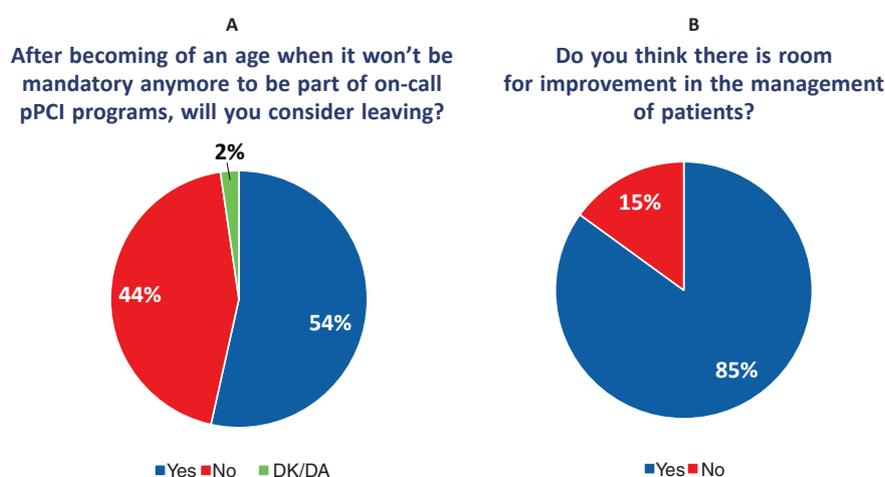


Figure 6. A: Willingness to remain available or leave the on-call primary percutaneous coronary intervention (pPCI) programs after no longer being mandatory due to age. Fifty-four percent of respondents will leave these programs. B: Answers to the question of whether respondents thought that there was room for improvement in the management of patients with ST-segment elevation acute myocardial infarctions within pPCI programs. Eighty-five percent said that there was room for improvement. (Data gathered from a survey conducted among members of the Working Group on Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology.) DK/DA, did not know/did not answer.

- Establish a clear-cut definition of the corresponding geographical regions.
- Have a written, agreed, and common protocol available for all healthcare providers involved.
- Make sure that the transfer of patients is conducted by accredited professionals with a well-established level of competence and on adequately equipped-means of transportation (ambulances or helicopters), that is, through the appropriate systems of medical emergencies.
- Facilitate immediate transfers to pPCI-capable centers. In cases where diagnosis is achieved out of the infarction center setting, the transfer to the hospital should be direct, without stops or re-evaluations in non-pPCI capable hospitals.
- Upon arrival at the infarction center, the patient should be immediately transferred to the cath. lab and without any prior stops at the ER.
- If a patient is initially assisted at a non-pPCI capable center, he should be evaluated in a monitored area by experienced personnel. If the patient is to be transferred to an infarction center to undergo the pPCI, then the time elapsed from diagnosis until the patient leaves the center should not exceed 30 minutes.

REQUIREMENTS AND NEEDS FOR THE RIGHT DEVELOPMENT OF pPCI HEALTHCARE NETWORKS

Subdivisions. Geographical regions

Spain is the fourth largest country in Europe, yet its population density is lower than most Western European countries, with a very irregular territorial distribution. This circumstance, especially in healthcare network systems makes it difficult to provide similar health coverage in the entire territory. In order to solve this problem, it is important to subdivide healthcare into geographical regions where healthcare to patients can be provided effective and homogeneously. Although certain recommendations have

already been established by the European Society of Cardiology on what the reference population should be per cath. lab, its implementation in the pPCI setting is much more complex. Initially, a subdivision based on time isochrones is required so access to pPCI is guaranteed from the different healthcare providers to the largest amount of patients possible with transfer times within the timeframes recommended by the clinical practice guidelines, but only towards adequately equipped infarction centers capable of performing a minimal number of pPCIs each year.²⁴ The geographical barriers among different AACC should not be an obstacle for transfer logistics, since patients with an indication for pPCI should be transferred to the closest infarction center. Prior administrative agreements signed by the AACC involved should be taken into consideration. Patients who live in remote areas or who due to logistics or climate issues cannot undergo pPCI within the timeframe recommended should be treated as soon as possible with fibrinolysis and then transferred to infarction centers so that the pharmaco-invasive strategy can be initiated.^{25,26}

Logistics-related aspects. Communications systems

To achieve these goals, logistics requires a 100% commitment from all healthcare providers involved, particularly from the transfer systems. It is important to have agile communication systems from a centralized structure (emergency coordination centers) capable of promptly notifying the infarction centers on the arrival of a patient, the transfer estimate time, and the patient's clinical state so that the receiving center can adapt its daily activity to the arrival of an unexpected urgent procedure.²⁴ Some programs include patients' clinical description and electrocardiogram results before activation, thereby reducing the amount of diagnostic mistakes. On rare occasions, when several patients need to be transferred to the same center at the same time, or when the receiving center is busy with uncancelable activities, patients should be transferred to other close-by infarction center capable of providing the healthcare required.

Medical emergency systems

Medical emergency systems (MES) with doctors aboard the ambulance are a reality in Spain; however, the decentralization and transfer of health competences to the different AACC has generated different healthcare models. In the pPCI programs, MESs should be easily accessed over the phone through emergency coordination centers capable of triaging the urgent care requested. This request for help can come from private households, the street, or primary hospital or care centers. Afterwards, MESs activate the units that provide initial care and, if required, the transfer of the patient to the infarction center. Emergency coordination centers should have STEMI categorized as a time-dependent condition that requires priority care to achieve better results.²⁴ Within the pPCI program setting, emergency coordination centers should meet a series of prerequisites and have:

- A system capable of taking calls that will not collapse.
- A computer system capable of recording the time of call, preliminary medical examination, type of resources allocated, the time these resources were allocated, activation time of the healthcare unit, arrival time to the place help was requested from, and timeframes of initial transfer and final arrival at destination.
- A multidisciplinary team including phone dispatchers, nurses, doctors, and technicians trained in the management of telephone calls.

- A periodic quality re-assessment protocol of the different components of the care provided.

The care provided to STEMI patients should be initiated by the first medical team available with the aim to examine the patient and interpret the electrocardiogram in less than 10 minutes. If diagnosis is confirmed, the corresponding healthcare protocol should be activated, and the patient transferred to a pPCI-capable center. A complete transfer of information on the patient's clinical situation among the healthcare unit, the emergency coordination center, and the destination hospital is crucial. This approach should also be used with patients initially assisted in non-pPCI capable centers.^{6,24}

The initial transfer of these patients should happen in MES mobile units with teams including physician, nurse and paramedics trained and accredited according the level of competence established. The receiving hospital should know what the estimated time of arrival should be able to organize the care to be provided (on business hours) or to activate the treating hemodynamics team (off business hours). The patient should be transferred directly to the cath lab without stopping at the ER.^{6,24}

It is essential that the MES team writes down a complete medical report including the aforementioned timeframes, the initial assessment, the interpretation of electrocardiograms, the medication administered, the patient's progression, and any other complications that may arise. These teams should conduct periodic quality assessments of the healthcare provided to detect possible ways to improve this process. A system for the periodic exchange of information between the MESs and the hospitals treating the patients transferred should be established to analyze the quality and observance of the plans of action previously agreed on. There should always be MES resources available based on the established population ratios.

Infrastructure and equipment

The pPCI-capable interventional cardiology units and the cardiology services and centers where these units are headquartered should meet structural, functional, and organizational requisites to guarantee safety, quality, and efficiency conditions to perform such procedures. The following quality standards and accreditation criteria for reference units on the performance of pPCIs procedures²⁷ and the standards and criteria that regulate the entire STEMI process have been recently agreed upon and published by the SEC (*SEC-EXCELENTE*):²¹

- The receiving pPCI unit should have a protocol agreed by the hospital board of directors.
- This unit should design and implement a training program including continuous practical training for its staff.
- The pPCI reference units should guarantee non-stop 24/7 all year round full medical coverage. Units with 12-hour-day programs are acceptable but not recommended and only if the MES coordination system incorporates clear-cut criteria on the transfer of STEMI patients based on hourly availability.
- As well as the standard equipment including ventilators, the cath lab should also have circulatory support systems, intra-aortic balloon counter-pulsation systems, electro-catheters, external pulse generator units, and a fully equipped crash cart to be able to perform advanced resuscitation maneuvers in the context of a patient with STEMI and its possible complications.
- The hospital where the pPCI unit is headquartered should have the following services available:

- It is advisable to have a cardiac intensive care unit (CICU) or general intensive care unit (ICU) available capable of providing level-2 and level-3-care according to the standards established by the Acute Cardiovascular Care Association²⁸ and meeting the standards recommended for this type of units.²⁹
- Cardiac surgical services. In units that do not offer this service within the same hospital, a formal agreement signed with a nearby cardiac surgical service should be available for the quick transfer (< 60 minutes) of patients who may require urgent heart surgery.³⁰
- Hematology and blood bank service or unit.
- Diagnostic imaging service including computed tomography scan capabilities.
- Cardiologist on call on location.

Regarding CICUs, the care of patients after undergoing pPCI should be consistent with the structure and functioning of each hospital. It is advisable that the centers of pPCI receiving units have a cardiology unit-dependant CICU. The decision to hospitalize a patient should be based on the level of care required by each patient (table 2).

CICUs with level-2 and level-3 care should:

- Have a medical and nursing responsible.
- Keep a physician in charge of the unit on call and on location 24 hours/day.
- Maintain the ratio of 1-2 nurses per patients requiring level-3-care and 1-3 nurses per patients requiring level-2-care.
- Be fully equipped with material that meet the standards established by the clinical guidelines designed by the SEC.
- Have at least two beds for every 100 000 inhabitants within the area of influence the pPCI program specifies for receiving units, and no less than six beds.

Units with level-1-care should have a nurse/patient ratio > 1:6, have the necessary equipment and material available, and meet the standards designed by the European clinical practice guidelines.⁶ The amount of beds recommended is nine beds for every 100 000 inhabitants within the scope of influence of the pPCI program, but it can be smaller if there is a referral program to send the patients back to their reference hospital. The amount of beds required for level-1-care is and conventional hospitalization (level-0-care) is reduced accordingly.

Human resources

The interventional cardiology units included in the pPCI network should have a 24/7, all year round service on call.⁶ The team on call should include:

- Interventional cardiologists: during the procedure, together with the interventional cardiologist, the presence of a second physician responsible for the patient's clinical stability is required. It is advisable that the team of a pPCI program includes at least four cardiologists accredited by the Working Group on Hemodynamics and Interventional Cardiology of the SEC.⁶ To achieve and maintain the training required for the

Table 2. Levels of care

Level	Description of the need for healthcare
0	Patients whose needs can be met through normal ward care in an acute hospital
1	Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team
2	Patients requiring closer observation or intervention including support for a single failing organ system or post-operative care and those 'stepping down' from higher levels of care
3	Patients requiring advanced respiratory support alone or monitoring and support for two or more organ systems. This level includes all complex patients requiring support for multi-organ failure

management of STEMI, 30 pPCIs need to be performed per year and per operator.³¹ Small-volume centers should be included into wider infarction care networks.^{32,33}

- Graduate nurses: two graduate nurses trained in direct procedural care with sufficient knowledge of the equipment and material at hand are required. It is advisable that nursing staff be part of the unit and accredited in the field of hemodynamics based on defined criteria. Although the presence of an additional specialist is advisable, he should not replace the nurses in any of their fields of expertise. The participation of an assistant nurse trained in pPCI procedures is also advisable.

After activation, the time of arrival of the hemodynamics team should not exceed 30 minutes. The necessary measures to work within this timeframe should be implemented.

Post-procedural transfers. Early discharge

The transfer of patients once the pPCI has been performed is not uniform and is influenced by several aspects. Depending on the infrastructures, the personnel available, the availability of beds, the initial location of the patient after the pPCI, his clinical stability, and the level of complexity of the receiving hospital, the strategies for the management of patients post-pPCI can vary significantly. There are centers that accept and hospitalize all patients after the pPCI; others, however, keep them under observation for 12-24 hours prior to transferring them, and there are centers that transfer all patients as long as they remain stable after the pPCI.

Taking into consideration the pPCI setting and its possible complications, it is advisable that patients remain under strict observation the 12-24 hours following the procedure, preferably at the infarction center. Depending on the degree of clinical stability and the characteristics of the receiving center, patients can be transferred to their reference hospitals or remain hospitalized under observation or complete the necessary additional treatments that may be required. The models established for the transfer of patients to other centers are determined by the patient's clinical characteristic, the applicable regional protocols, and the resources available. Patients whose procedure has had optimal results, who have undergone an adequate clinical evaluation, have no signs or symptoms compatible with persistent ischemia, do not show any traces of arrhythmia, remain hemodynamically stable, do not require vasoactive or mechanical support, and without a new

revascularization scheduled are eligible for early transfers. Although some MESs already implement them, the widespread use of risk stratification indices and scores to allocate the most adequate resource for the transfer of these patients, and the systematic assessment of these indices and scores is strongly advisable.

Several studies have shown that after a successful pPCI in low-risk patients who were completely revascularized, a significant percentage of patients can be discharged from hospital to their home two or three days after the procedure. Patients eligible for early discharge after STEMI can be identified using risk scores such as the PAMI-II criteria (Second Primary Angioplasty in Myocardial Infarction), the Zwolle risk score, etc.⁶

Additional prerequisites of pPCI programs

The units that are part of a pPCI network should meet a series of additional requisites:

- Be able to perform over 400 conventional pPCIs per year and over 75 conventional pPCIs per interventional cardiologist per year.³⁴
- Have an organizational and functions manual available that includes the actual clinical practice guidelines for the management of acute myocardial infarctions approved by SEC and procedural guidelines adapted to the unit setting.
- Make available specific informed consent forms to patients and their families, explaining the characteristics of the diagnostic and therapeutic process to be performed.
- Implement a specific mechanism to assess the pPCI program with indicators of process (especially timeframes) and results including complications.
- Carry out a formalized process to improve the safety and quality provided to patients and also keep a record of adverse events.
- Together with the cardiology service, these units should be incorporated into a system that compares quality optimal practices (benchmarking), process indicators (especially timeframes), severity scores, complexity, and results to eventually to make comparisons with the other pPCI units.
- pPCI units and the cardiology services should hold periodic meetings to systematically analyse any safety incidents that may have occurred in the unit and, especially, to establish the corresponding prevention measures.
- Both should provide detailed information of all patients in order to constitute the STEMI National Registry of the Working Group on Hemodynamics and Interventional Cardiology of the SEC, quantify the activity that goes on in the Registry and for code insertion purposes, in the Basic Minimum Data and the RECALCAR Registry.

VULNERABILITIES OF THE ACTUAL pPCI PROGRAMS

Some pPCI programs were initially developed with partial or incomplete prior analyses, limited official support, and poor resources. The progressive expansion of pPCI programs and their widespread use in most STEMI patients have allowed to identify a series of deficiencies and shortfalls that may make them vulnerable and eventually jeopardize their own sustainability.

Impact on daily activity and volume-based care

According to the 2017 registry run by the Working Group on Hemodynamics and Interventional Cardiology, pPCIs amount to almost 30% of all interventional procedures performed in the cath lab.¹⁷ Data from different studies^{35,37} show that between 55% and 70% of all pPCI procedures are performed during off business hours (nights and weekends); however, the remaining 30%-45% procedures on STEMI patients are performed during business hours. The arrival of this large and unexpected volume of urgent and non-scheduled patients to the cath lab disturbs the scheduled daily activity of the unit since the patients require the fastest possible care these cath lab can provide. Depending on the level of adequacy that each center can establish to anticipate this, the routine activity of these cath labs may change, and cases may be suspended (ie, in-patients, cath lab scheduled patients or patients from other centers) and the usual working hours extended to avoid cancellations. Thus, optimizing the STEMI treatment may deteriorate the care that should be provided to other patients with serious heart conditions.

Psychological, legal, and economic implications in healthcare providers

The lack of appropriate sizing of the personnel involved in pPCI programs may be the reason behind two important issues: the development of psychosocial issues and the emergence of situations with legal implications. Dealing with large volumes of pPCIs during night shift requires an adequate number of healthcare providers to take on the unit activity scheduled for the next day. Both the design and makeup of the personnel of infarction centers should take this matter into serious consideration. Without an appropriate sizing of the personnel involved, staff will often have to perform elective procedures deprived of sleep and without the adequate resting time. These procedures have been associated with a higher number of suboptimal results,³⁸ which may have legal consequences for the healthcare providers due to civil liability insurance limitations. If the pPCI procedures are performed during the night shift, an 8-hour resting period after the procedure seems like a reasonable amount of time before the staff goes back to their daily routine.

Also due to the fast action required the peculiarities of pPCI for the management of STEMI often puts a lot of stress on the healthcare providers, because of the complexity of the procedure, and the risk of complications for the patients, all of it due to the procedure *per se* or due to morbimortality. The variability of schedules, the required urgent action, and the immediate availability of the personnel involved determine a very particular type of "availability". This may contribute to the higher incidence of the so-called burnout syndrome, depression and anxiety among the staff under high healthcare and emotional pressure as experienced in the cath lab.³⁹ Added to this, there is the high incidence of trauma problems interventional cardiologists suffer³⁹ and, in the long run and with a stochastic component, the possibility of developing certain types of neoplasms.⁴⁰

In this context it should be mentioned that many pPCI programs in Spain are not categorized as individual specialty programs. Therefore, the financial retributions to these healthcare providers are no different from the retributions of other providers dealing with urgent interventions of lower complexity less frequently, in low or no risk patients and that can often be scheduled several hours in advance. All these aspects are perceived by interventional cardiologists as a mismatch that goes against their best interest. In Spain this is specifically seen in transplant programs and is probably one of the reasons that explains the level of excellence that these programs have achieved in this country.

Ignoring all these aspects can be detrimental to the teams and could in fact lead to situations of discouragement among the staff working in some of these programs. This may have negative repercussions in the level of excellence required by pPCI programs, especially taking into consideration the special profile of the patients involved. Recent data indicate that because of this many highly-experienced healthcare providers (who also happen to be those who do better) will leave these programs as soon as they are entitled due to their age. Also, in order to legally request leaving these mandatory programs, they may claim physical or psychological issues, which would be totally justified and easy to accomplish. All of this puts pPCI programs in a situation of great vulnerability.

PROPOSALS TO ENSURE THE SUSTAINABILITY OF pPCI PROGRAMS

Perfectly established subdivisions to reduce any possible delays

The national territory should be subdivided based on the nearness of hospital centers in order to make sure that the management of STEMI patients happens with the lowest possible delays. This subdivision should entertain concepts such as distance and transfer times to infarction centers. Isochrones should identify distance-related delays to these centers and delays affecting the state of communications. Patients who live in distant neighborhoods or with logistics issues should not undergo pPCI procedures within the intervals recommended; instead, they should be treated immediately with fibrinolysis, and then transferred to the corresponding cardiac center.⁶

Consensus strategies to reduce transfer times

Regardless of the initial level of care when the diagnosis of STEMI is achieved and when the system is activated (whether from private households, the street, primary care center or regional hospital), protocols for the transfer of patients to pPCI centers should be established. Each pPCI center should agree with the MESs and their corresponding reference hospitals on the best possible strategy to reduce the intervals of treatment. The adequate sizing of these may also be necessary to guarantee the level of care required. Agile communication systems with a centralized structure (emergency coordination center), are key if we want to establish the logistics of the entire process.

The MES emergency coordination center should prioritize the transfer of STEMI patients. Communication with the tertiary hospital through internal phone lines should be established to inform on the estimated transfer timeframe and the patient's clinical state so that the receiving center can adapt its scheduled daily activity to the arrival of this unexpected emergent procedure. All these timeframes should be recorded prospectively to make the corresponding analysis of any delays that may have occurred during the transfer and be able to identify potential room for improvement. These protocols should be reviewed periodically on a result assessment basis.

Adequacy of pPCI-capable infarction centers

The degree of adequacy will depend on the number of pPCIs performed. The scope and benefit of the pPCI to a significant number of STEMI patients requires specific measures that should take into consideration a series of aspects that make it a particularly complex procedure. pPCI centers should be structured,

organized, and properly sized to be able to handle significant increases in the number of urgent procedures. These programs should also include the transfer of patients through the entire intrahospital pathway. Several additional resources are necessary with different factors in each and every one of them:

- Ensure the presence of a second physician while the pPCI is being performed.
- The nursing staff should have the experience required while the pPCI is being performed. Depending on the patient's clinical situation, additional nurses trained in cardiology care may be needed so that the interventional cardiology team can be solely committed to achieving reperfusion.
- Prepare specific areas with personnel trained on the initial care of STEMI patients while they are waiting for the procedure to be performed and once it has been performed, and also additional beds in the cardiac intensive care unit depending on the volume of pPCIs to be performed.
- Have large enough teams available to take on additional unscheduled urgent tasks depending on the volume of tasks to be performed.
- Establish strategies to return pPCI patients to their reference hospitals in the hours following the procedure. This scenario should be protocolized based on the procedural results obtained, the patient's clinical situation, and the characteristics of the receiving center. This approach is mandatory in centers with high pPCI volumes.

Priority phone availability versus physical presence

Physical presence of hemodynamics teams to perform pPCIs at the very hospital is an option that has always been entertained, but it is an actual reality in very few hospitals worldwide. The timeframe between activation and the opening of the artery using the appropriate strategy of phone location should not exceed 60 minutes and different studies have found no differences at all when it comes to delays in the provision of adequate care and results regardless of whether the team that performs the intervention is physically stationed at the center or is available through the phone. Additionally, considering an adequate number of interventional cardiologists per center, accredited nurses, and the remaining personnel involved in the program, the activities scheduled for the next day could be compromised if the team on call is physically stationed at the hospital, not if it is available through the phone.

Recognition and the right incentives

It is advisable to give pPCI programs a special status by taking into consideration that we are dealing with professionals with a high level of training who need to be available at all time, have an immediate capacity of reaction, and be available on different schedules and all at stressful settings due to the complexity of the procedures performed and the risk involved when managing this type of patients. A similar example of this is the special consideration given today to heart transplant programs.

Mandatory audited registry with periodic comparative analyses

It is essential to keep a mandatory prospective registry that includes patients' baseline characteristics, those of the infarct, the

time elapsed between symptom onset and revascularization, the procedural characteristics and the results obtained, and the patient's clinical progression until he is discharged from the hospital (including reference centers when transferring patients during the acute phase). Both intervention times and results should be monitored periodically in every center and compared to other centers in order to guarantee the quality of the services provided and, if necessary, make the necessary adjustments. Keeping track of all this through a nationwide, verifiable, and independent registry with public data available of all the existing pPCI programs with results by sectors and centers should be mandatory in our country.

There is this pressing need to know the results of the programs implemented in different AACC. Mortality in STEMI is highly dependent on the quality of care received and comparing results among different countries, AACC and hospitals is not only a need but also an obligation that the Administration and the scientific societies should observe to keep healthcare providers and the population duly informed.

CONFLICTS OF INTEREST

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

REFERENCES

- Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* 2016;37:3232-3245.
- Grines CL. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? Primary angioplasty — the strategy of choice. *N Engl J Med.* 1996;335:1313-1316.
- GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med.* 1993;329:1615-1622.
- GUSTO Angiographic Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682.
- Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet.* 2006;367:579-588.
- Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-177.
- Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction — Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. *Am Heart J.* 2010;160:322-328.
- Wailoo A, Goodacre S, Sampson F, et al. Primary angioplasty versus thrombolysis for acute ST-elevation myocardial infarction: an economic analysis of the National Infarct Angioplasty project. *Heart.* 2010;96:668-672.
- Stone GW, Grines CL, Rothbaum D, et al. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. The PAMI Trial Investigators. *J Am Coll Cardiol.* 1997;29:901-907.
- Cequier A, Ariza-Sole A, Elola FJ, et al. Impact on Mortality of Different Network Systems in the Treatment of ST-segment Elevation Acute Myocardial Infarction. The Spanish Experience. *Rev Esp Cardiol.* 2017;70:155-161.
- Alter DA, Austin PC, Tu JV, Canadian Cardiovascular Outcomes Research T. Community factors, hospital characteristics and inter-regional outcome variations following acute myocardial infarction in Canada. *Can J Cardiol.* 2005;21:247-255.
- Bertomeu V, Cequier A, Bernal JL, et al. In-hospital mortality due to acute myocardial infarction. Relevance of type of hospital and care provided. RECALCAR study. *Rev Esp Cardiol.* 2013;66:935-942.
- Laskey W, Spence N, Zhao X, et al. Regional differences in quality of care and outcomes for the treatment of acute coronary syndromes: an analysis from the get with the guidelines coronary artery disease program. *Crit Pathw Cardiol.* 2010;9:1-7.
- Carrillo P, Lopez-Palop R, Pinar E, et al. Program of Coronary Angioplasty in Acute Myocardial Infarction in the Region of Murcia (Spain): APRIMUR Registry. *Rev Esp Cardiol.* 2002;55: 587-596.
- Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J.* 2010;31:943-957.
- Feldman MF, Goicolea J, Macaya C. The Aims of the Stent-for-Life Initiative in Spain in 2010-2013. *Rev Esp Cardiol.* 2011;11(Supl):6-8.
- Cid Álvarez AB, Rodríguez Leor O, Moreno R, Pérez de Prado A. Spanish Cardiac Catheterization and Coronary Intervention Registry. 27th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2017). *Rev Esp Cardiol.* 2018;71: 1036-1046.
- Kristensen SD, Laut KG, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J.* 2014;35:1957-1970.
- Schiele F, Hochadel M, Tubaro M, et al. Reperfusion strategy in Europe: temporal trends in performance measures for reperfusion therapy in ST-elevation myocardial infarction. *Eur Heart J.* 2010;31:2614-2624.
- Gómez-Hospital JA, Dallaglio PD, Sanchez-Salado JC, et al. Impact on delay times and characteristics of patients undergoing primary percutaneous coronary intervention in the southern metropolitan area of Barcelona after implementation of the infarction code program. *Rev Esp Cardiol.* 2012;65: 911-918.
- Rodríguez-Padial L, Bertomeu V, Elola FJ, et al. Quality Improvement Strategy of the Spanish Society of Cardiology: The RECALCAR Registry. *J Am Coll Cardiol.* 2016;68:1140-1142.
- Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA.* 2010;303:2148-2155.
- Tarantini G, Razzolini R, Napodano M, Bilato C, Ramondo A, Iliceto S. Acceptable reperfusion delay to prefer primary angioplasty over fibrin-specific thrombolytic therapy is affected (mainly) by the patient's mortality risk: 1 h does not fit all. *Eur Heart J.* 2010;31:676-683.
- Cequier A, Maristany J. Angioplastia primària. Estratègies per a la seva aplicació a diferents àmbits sanitaris. *Rev Soc Catalana Cardiol.* 2005;5:290-297.
- Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med.* 2009;360: 2705-2718.
- Sinnaeve PR, Armstrong PW, Gershlick AH, et al. ST-segment-elevation myocardial infarction patients randomized to a pharmaco-invasive strategy or primary percutaneous coronary intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-year mortality follow-up. *Circulation.* 2014;130:1139-1145.
- López-Sendón J, González-Juanatey JR, Pinto F, et al. Quality Markers in Cardiology. Main Markers to Measure Quality of Results (Outcomes) and Quality Measures Related to Better Results in Clinical Practice (Performance Metrics). INCARDIO (Indicadores de Calidad en Unidades Asistenciales del Área del Corazón): A SEC/SECTCV Consensus Position Paper. *Rev Esp Cardiol.* 2015;68:976-995.
- Bonnefoy-Cudraz E, Bueno H, Casella G, et al. Editor's Choice — Acute Cardiovascular Care Association Position Paper on Intensive Cardiovascular Care Units: An update on their definition, structure, organisation and function. *Eur Heart J Acute Cardiovasc Care.* 2018;7:80-95.
- Palanca I, Elola FJ, Bernal JL, Paniagua JL. Unidad de cuidados intensivos. Estándares y recomendaciones. Agencia de Calidad del SNS. Madrid: Ministerio de Sanidad y Política Social; 2009.
- Dehmer GJ, Blankenship JC, Cilingiroglu M, et al. SCAI/ACC/AHA Expert Consensus Document: 2014 update on percutaneous coronary intervention without on-site surgical backup. *J Am Coll Cardiol.* 2014;63:2624-2641.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation.* 2011;124:e574-651.
- Tubaro M, Danchin N, Goldstein P, et al. Pre-hospital treatment of STEMI patients. A scientific statement of the Working Group Acute Cardiac Care of the European Society of Cardiology. *Rev Esp Cardiol.* 2012;65:60-70.
- Núñez Gil IJ, Fernández-Ortiz A, Escaned J, et al. Long term experience with a novel interventional cardiology network model: Learned lessons. *J Hos Administ.* 2016;5:87-94.

34. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.
35. Dharma S, Dakota I, Sukmawan R, Andriantoro H, Siswanto BB, Rao SV. Two-year mortality of primary angioplasty for acute myocardial infarction during regular working hours versus off-hours. *Cardiovasc Revasc Med.* 2018;19:826-830.
36. Graham MM, Ghali WA, Southern DA, Traboulsi M, Knudtson ML; APPROACH Investigators. Outcomes of after-hours versus regular working hours primary percutaneous coronary intervention for acute myocardial infarction. *BMJ Qual Saf.* 2011;20:60-67.
37. Siudak Z, Rakowski T, Dziewierz A, et al. Primary percutaneous coronary intervention during on- vs off-hours in patients with ST-elevation myocardial infarction. Results from EUROTRANSFER Registry. *Kardiol Pol.* 2011;69:1017-1022.
38. Sandoval Y, Lobo AS, Somers VK, et al. Sleep deprivation in interventional cardiology: Implications for patient care and physician-health. *Catheter Cardiovasc Interv.* 2018;91:905-910.
39. Klein LW, Miller DL, Balter S, et al. Occupational health hazards in the interventional laboratory: Time for a safer environment. *Catheter Cardiovasc Interv.* 2009;73:432-438.
40. Roguin A, Goldstein J, Bar O, Goldstein JA. Brain and neck tumors among physicians performing interventional procedures. *Am J Cardiol.* 2013;111:1368-1372.



Debate: Renal denervation. The interventional cardiologist perspective

A debate: Denervación renal. Perspectiva del intervencionista

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QUESTION: After the negative results of the SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) study, what new studies are dealing with renal denervation (RD) as a possible therapeutic option?

ANSWER: The results of the SYMPLICITY HTN-3 study¹ were totally unexpected, particularly because those of us who had some sort of experience with this technique had lived a completely different reality. The limitations of the study have to do with the arguable selection of patients (with non-optimized pharmacological treatment that was adjusted during follow-up and generated an unexpectedly positive response in the control group), the operators' lack of experience (most of them conducted their first procedures within the study), and the lack of knowledge on how to conduct this procedure in order to optimize the results.

After the detailed analysis of the SYMPLICITY HTN-3 study,¹ two different studies were designed with an improved device to conduct the procedure and their results have recently been made public.

The first study, the SPYRAL HTN-OFF MED² was a randomized sham-controlled clinical trial (with a sham control group) as the proof-of-concept on the efficacy of RD to reduce arterial blood pressure (BP) in patients without concomitant pharmacological treatment. Patients with mild-to-moderate arterial hypertension (HT) (office systolic BP 150 mmHg to 180 mmHg and diastolic BP > 90 mmHg, and 24-hour ambulatory systolic BP 140 mmHg to 170 mmHg) were included in the study. Patients did not receive any prior treatment or had been without any pharmacological treatment for 3 to 4 weeks. The protocol included a drug screening of serum and plasma to confirm the absence of drugs. Patients were randomized on a 1:1 basis to RD using the multi-electrode radiofrequency catheter designed by Symplicity Spyral

(Medtronic Inc., Minneapolis, United States) (n = 38) or to sham control (n = 42). The primary endpoint included changes in the 24-hour ambulatory BP, much more sensitive and specific to detect changes in the BP that measuring BP at the doctor's office. The analysis of the first 80 patients showed a significant reduction of the 24-hour ambulatory systolic BP and office systolic BP at 3 months in favor of RD. We should mention here that during follow-up no relevant adverse events were reported in any of the two treatment arms and, as former studies had already shown, the procedure turned out to be safe and had an extremely low rate of complications.¹

The endpoint of the second study, the SPYRAL HTN-ON MED,³ was to assess the efficacy of RD in a different context. The study population were not patients with resistant HT or HT naïve to drug therapy but non-severe hypertensive patients on drug therapy. Same as it happened with the SPYRAL HTN-OFF MED² study, the primary endpoint included changes in the 24-hour BP instead of office-recorded BP changes. The patients included in the study had mild-to-moderate HT (office systolic BP between ≥ 150 mmHg and < 180 mmHg, office diastolic BP ≥ 90 mmHg, and 24-hour ambulatory systolic BP between 140 mmHg and 170 mmHg). RD reduced the 24-hour ambulatory systolic BP and the office systolic BP at 6-month follow up compared to the control arm.²

Also, a third study with a totally different device based on ultrasounds and not radiofrequency, the RADIANCE-HTN SOLO,⁴ confirmed the good results shown by the SPYRAL HTN-OFF MED² in patients with moderate untreated HT with similar results in the monitoring of BP figures at follow-up, which reinforces the idea of RD for the management of HT.

Q.: What kind of technical advances have led to these positive results and what are the limitations of this kind of therapy?

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A.: The critical analysis of the results shown by the SYMPLICITY HTN-3¹ taught us how to improve the results obtained with this procedure. It confirmed that the patients' response was significantly better when the four quadrants of the renal artery were treated. Also, further studies showed that RD was more effective not only when the main stem of the renal artery was treated but also when the secondary branches were treated as well. A look at the anatomy of the sympathetic innervation revealed that although there were more nervous fibers at a proximal level (where treatment was formerly recommended), these fibers were at a distance from the vascular lumen that made it difficult for the radiofrequency energy released inside the blood vessel to actually reach them. On the contrary, at the most distal portion, nervous fibers are closer to the lumen and they are affected by the radiofrequency lesion. Finally, the number of radiofrequency applications somehow had something to do with efficacy in such a way that today it is advisable to perform the maximum number of applications.

In order to simplify the procedure and taking all these premises into consideration, a new RD catheter was developed, the Symplixity Spyrax, whose main characteristics with respect to the Symplixity Flex catheter (Medtronic Inc., Minneapolis, United States) with which the SYMPLICITY HTN-3¹ study was conducted were that it was a tetrapolar catheter (compared to the former one that was monopolar) meaning that up to 4 simultaneous radiofrequency applications could be performed; also, it cut down the duration of the application from 120 to 60 seconds. Also, the spiral-shaped catheter allowed the radiofrequency application to cover the 4 quadrants of the renal artery. Finally, the optimized caliber of the new device facilitated treating arteries of up to 3 mm in diameter vs 4 mm with the former device.

Q.: What would the actual indications of this technique be, if any?

A.: The clinical practice guidelines established by the European Society of Cardiology and the European Society of Hypertension that have been published recently⁵ are older compared to the knowledge acquired from the last studies we mentioned before. In these clinical guidelines, recommendations were based on the SYMPLICITY HTN-3¹ and its use was recommended in the setting of clinical trials only and outside the routine clinical practice.

The results of the new studies consistently show that RD is effective when it comes to improving the monitoring of the BP. Similarly, different observational registries have shown significant improvements in a large number of patients with resistant HT. In Spain we conducted a registry⁶ that included 125 of these patients and saw a good response in over 80% of these patients, not only when it comes to the office BP but also, and most important, when it comes to monitoring ambulatory BP. Also, RD significantly reduced pharmacological treatment, a finding that opens the door to future studies. With the evidence available today, in my opinion, patients with maintained non-monitored HT on multi-drug therapy, including aldosterone antagonists, can benefit from this procedure. We know that a reduction of 20 mmHg in systolic BP or 10 mmHg in diastolic BP cuts in half mortality risk due to cardiovascular causes. This improvement is not difficult to achieve in many of these patients after RD.

On the other hand, there are many gaps of knowledge still to be filled in in the field of RD. It is essential to identify those patients who may respond better to this procedure since the pathophysiology of HT is complex and is not always due to alterations in the regulation of the sympathetic nervous system. With regard to the procedure itself, the lack of markers to determine whether RD has been successful or not puts us on a holding pattern to see how the BP figures have evolved before determining its efficacy.

The development of a non-invasive test to obtain this information should be the goal of future research. Also, the arrival of new technologies to perform RD procedures requires assessing its safety and efficacy profile in the long run.

Q.: What studies do we need so that clinical practice guidelines can recommend RD as a therapeutic alternative for the management of HT?

A.: Yet despite the raising awareness on the risks of HT and the development of new and better drugs over the last 70 years, data from 2010 in developed countries showed that one third of those who had the disease did not know about it, a little over half of them received pharmacological treatment, and less than a third had an adequate blood pressure monitoring. In this sense, the road ahead of us is a long one.

With the new Symplixity Spyrax catheter the long-term safety profile is an issue we should take into consideration to give more robust guarantees that the treatment algorithm—substantially more aggressive than the algorithm used in the SIMPLICITY studies—does not cause complications.

The number of patients included in the studies is not large enough to give us evidence that the reduced BP levels observed after RD actually reduce the rate of cardiovascular events at follow-up. Improving BP is but a surrogate primary endpoint, although it is accepted that there is a correlation between lower BP levels and less cardiovascular events. Also, similar BP reductions to the ones obtained in these studies led to less events in pharmacological studies. A study that showed clinical benefits beyond the monitoring of BP would actually be conclusive in this context. Unfortunately, the high number of patients who should be included in this study probably makes such a study unfeasible. However, we should not forget that damage caused by sympathetic hyperactivity goes beyond hypertension itself and is cause for the worse glucose metabolism seen in diabetic patients, the arterial stiffness of atherosclerosis, the poor prognosis of heart failure and the impaired renal function seen in renal failure, to mention but a few.

The SPYRAL HTN-OFF MED² and RADIANCE SOLO⁴ clinical trials have given us the first evidence, in a consistent way, on the possible clinical utility of RD for the management of hypertensive patients who may wish, or not, to use antihypertensive drugs. These preliminary results should be confirmed by the ongoing fundamental studies that intend to include a much larger number of patients. The pharmacological treatment of HT is a long-term option and, in most cases, for life. Even though drugs are usually well-tolerated, the noncompliance to pharmacological treatment is a common problem to the extent that almost one third of all hypertensive patients do not start a new prescription of antihypertensive medication and 50% of them become noncompliant during the first year after starting their antihypertensive medication.

In my opinion, should these results be confirmed, there will be a change of paradigm in the management of hypertension. Also, we will have to take every patient's individual preference (shared decision-making process) into consideration on whether to follow pharmacological treatment for life or undergo a more individualized therapeutic approach through a catheter-based invasive procedure that has proven safe and with an active effect at all time.

Finally, in light of the preliminary results seen in other conditions, it will be essential to see if there is an added benefit to regulating the activity of the sympathetic nervous system beyond reducing the BP in other diseases where there is an increased sympathetic nervous system activation such as within cardiology, atrial fibrillation, and heart failure.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Bhatt DL, Kandzari DE, O'Neill WW, et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. *N Engl J Med.* 2014;370:1393-1401.
2. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of anti-hypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet.* 2017;390:2160-2170.
3. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet.* 2018;391:2346-2355.
4. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet.* 2018;391:2335-2345.
5. Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens.* 2018;36:2284-2309.
6. Rodríguez-Leor O, Segura J, García Donaire JA, et al. Renal denervation for resistant hypertension treatment in Spain. Flex-Spyral registry. *Rev Esp Cardiol.* 2019. <https://doi.org/10.1016/j.recesp.2019.05.013>.



Debate: Renal denervation. The clinician perspective

A debate: Denervación renal. Perspectiva del clínico

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QUESTION: After the negative results of the SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) study, what new studies support renal denervation (RD) as a possible therapeutic option?

ANSWER: The introduction of RD as a therapeutic approach in patients with resistant arterial hypertension (RAHT) was very well received due to the difficulties in adequately reducing arterial blood pressure (BP) levels and, consequently, the cardiovascular and renal risk associated with the persistence of high BP. Also, this technique was backed by the extensive knowledge of the role renal sympathetic nerves play regulating BP. Some non-randomized studies revealed the virtues of this technique with significant reductions of BP levels. However, the first double-blind comparative study conducted, the SYMPLICITY HTN-3,¹ did not confirm the superiority of RD over the pharmacological treatment of RAHT. This study showed that the response to RD had been lower in African-Americans and patients who had received anti-aldosterone drugs as antihypertensive therapy. The study was then heavily criticized because of the procedures used, the reduced number of ablations performed, the scarce experience of participant centers, etc.

After this first failure, several studies were designed, both in patients with and without RAHT to determine the capacity of RD to reduce the BP levels. The reason for this change can be found in the very nature of RAHT itself, the huge heterogeneity of patients, and the variability of BP values themselves. Among the studies in patients with RAHT, the DENER-HTN study (Renal Denervation in Patients With Resistant Hypertension)² showed that RD was better compared to step-care treatment with antihypertensive drugs, although the degree of BP reduction may be biased because baseline values were much higher in the intervention group versus the control group. Among the studies in patients with no RAHT, the SPYRAL HTN-OFF MED (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications)³ focused on patients without prior antihypertensive therapy and naïve to treatment during the study. The SPYRAL HTN-ON MED study (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy)⁴ included patients on antihypertensive treatment with 1 to

3 drugs and the RADIANCE-HTN SOLO⁵ study included controlled or non-controlled patients with low cardiovascular risk and on medication with 0 or up to 2 antihypertensive drugs. Whereas in the former, the antihypertensive treatment was kept, in the latter it was withdrawn. These studies confirmed reductions between 5 mm Hg and 7.4 mmHg in ambulatory systolic BP.⁶

Q.: What kind of technical advances have led to these positive results and what are the limitations of this kind of therapy?

A.: Together with the type of patients who are deemed eligible to receive RD, research has been made to develop devices capable of improving the ablation capabilities of the sympathetic nervous system and additional anatomical regions have been considered eligible for these ablations. Nonetheless, the number of ablations required has been controversial and there is no clear consensus on the different protocols used.

The new systems available today offer the possibility to act upon larger territories with every ablation by placing the electrodes around the spiral catheter and other changes in the design.

Other controversial aspects relate to what anatomical sections of the renal arteries should these ablations be performed on or what is the necessary number of ablations to be performed to achieve significant reductions in the renal sympathetic activity. Sympathetic fibers penetrate the kidney through the walls of the main renal arteries, and it is precisely on this location where these ablations were initially performed. The introduction of protocols to perform ablations in the distal branches of the renal arteries seems to achieve a greater sympathetic block and, consequently, higher effectiveness. Currently, studies should include the segments of renal arteries on which the ablations should be performed, and indicate how many of them are required, although there is not such a thing as a standard recommendation yet.

Q.: What would the current indications for this technique be, if any?

A.: The current indications for RD use are also controversial. The first possible indication would be for patients with true RAHT in whom the right pharmacological treatment cannot keep BP under control and below 140/90 mmHg.

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Drug-resistance is due to several causes, many of which can be detected and fixed. An easy protocol on this regard should include: a) checking high BP levels using outpatient measures, such as home or 24-hour ambulatory monitoring; b) anamnesis aimed at detecting compliance and adherence to pharmacological treatment; c) evaluating excessive salt and alcohol intake, weight gain in cases of obesity, and use of medication or drugs that may elevate BP levels; d) excluding the presence of sleep apnea; e) assessing the need to rule out secondary arterial hypertension requiring specific treatment; and f) administering a combination of the right drugs at the right doses, especially in the case of diuretic treatment.

When this protocol is implemented, the percentage of patients diagnosed with uncontrollable RAHT does not exceed 10% and it is precisely those patients who may be eligible for RD. However, the various aspects that are still controversial today led the European Society of Cardiology and the European Society of Hypertension to avoid recommending RD outside research protocols in their latest clinical practice guidelines.⁷

The off-label use of RD for the management of RAHT is still far from being recommended. There is no objective reason to perform RD in situations where the right medication achieves the therapeutic goals suggested by the clinical practice guidelines.

Q.: What studies do we need so that clinical practice guidelines can recommend RD as a therapeutic alternative for the management of AHT?

A.: The development of RD technique still has a long way to go in the near future since we are still unaware of key aspects regarding its effectiveness, safety profile or who are the best candidates for this procedure.

First of all, when performing an ablation it is not possible to know when the denervation is effective enough. Until now we have tried to identify markers capable of determining whether the ablations performed were effective in suppressing adrenergic activity, because the changes in the BP levels that take place during the procedure are not associated with the degree of denervation. Therefore, the procedure is performed in the blind, with no control, and without being able to predict whether it will be successful or not. Also, it is impossible to bring procedural time down to the minimum possible with guaranteed success.

In part connected to this limitation, there is also the number of radiofrequency applications required for this procedure. Since the repetition of these may have long-term repercussions, the ideal number would be the minimum necessary to achieve the denervation we are aiming at, but, as before, it is not possible to ascertain its effectiveness during the procedure.

Similarly, to this day we still do not know the duration of the antihypertensive effect. It is well-known that after cutting the sympathetic nerves, they have the capability of reinnervation as it has been confirmed in post-transplant patients. The duration of the response, if any, is not well-known, and there are no records on its effectiveness beyond 2 or 3 years of follow-up. Although the persistence of the effect can be anticipated, it is difficult to verify because of the very nature of RAHT, as we have already seen and because this persistence is influenced by several factors related to the hypertensive state.

Also, it is important to mention the great variability in patient's individual response to ablation. The clinical characteristics of

patients who may respond better to RD are still to be established; we only have evidence that patients with isolated systolic hypertension or patients with high pulse wave velocity fare worse with RD, maybe because they have an important component of impaired vascular elasticity. Similarly, patients with a good response to anti-aldosterone drugs would also have attenuated responses since the high BP levels seen in these patients are volume-dependant. Apart from these exceptions, there are no validated markers available of a better antihypertensive response to RD.

A key element of which there is still no evidence is whether RD is better than pharmacological treatment in reducing the incidence of cardiovascular and renal events. Several studies have analyzed the reduction of organ damage, especially in left ventricular hypertrophy, and the improvement of vascular elasticity following RD, but there is no evidence that the impact RD has on morbidity is higher compared to the one achieved with drug-induced control of the BP levels.

Last but not least, it is important to know what the possible long-term consequences of ablation may be on the renal arteries and, consequently, on renal function. The data available today tells us that in the short term there is no high risk of damage to the renal arteries, but there is no long-term data on the possible side effects.

All these questions will need to be answered in the future if renal denervation hopes to have a prominent place in the management of RAHT.⁸

CONFLICTS OF INTEREST

None declared.

REFERENCES

- Bhatt DL, Kandzari DE, O'Neill WW, et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. *N Engl J Med*. 2014;370:1393-1401.
- Azizi M, Sapoval, M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet*. 2015;385:1957-1965.
- Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of anti-hypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet*. 2017;390:2160-2170.
- Kandzari DE, Böhm M, Mahfoud F, et al.; SPYRAL HTN-ON MED Trial investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391:2346-2355.
- Azizi M, Schmieder RE, Mahfoud F, et al. Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control Following Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial. *Circulation*. 2019. <https://doi.org/10.1161/CIRCULATIONAHA.119.040451>.
- Mahfoud F, Schlaich M, Böhm M, Esler M, Lüscher TF. Catheter-based renal denervation: the next chapter begins. *Eur Heart J*. 2018;39:4144-4149.
- Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens*. 2018;36:2284-2309.
- Moss JG, Belli AM, Coca A, et al. Executive summary of the joint position paper on renal denervation of the Cardiovascular and Interventional Radiological Society of Europe and the European Society of Hypertension. *J Hypertens*. 2016;34:2303-2304.

Neointimal healing pattern of a drug-eluting stent in a coronary hematoma

Patrón de cicatrización neointimal de un stent farmacoadactivo en el hematoma coronario

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CASE PRESENTATION

Fifty-three-year-old woman, smoker and with dyslipidemia who was admitted due to effort angina of 1-week duration and an episode of angina at rest the night before. The electrocardiogram did not show any repolarization alterations. Troponin T levels were measured with a 4-h interval and they duplicated the normal reference levels (28 ng/L, 31 ng/L; normal reference value: 0-14 ng/L). Initially, acetylsalicylic acid was administered (300 mg). That same morning an exercise testing was conducted that turned out clinically inconclusive and electrically non-assessable to rule out ischemia because it did not reach 85% of the theoretical maximum frequency.

The coronary angiography showed non-significant angiographic lesions in the anterior descending and circumflex arteries. The right coronary artery (RCA) showed a severe lesion in its middle segment. Taking into consideration that therapy with only acetylsalicylic acid was used, the patient's clinical manifestations at rest, and the markers on borderline significance it was decided that the patient was suffering from unstable angina and a loading dose of ticagrelor (180 mg), a bolus of tirofiban (25 µg/kg, without infusion), and heparin (70 U/kg) were administered. A 3.5 x 24 mm drug-eluting stent was deployed in the middle RCA with optimal results (figure 1).

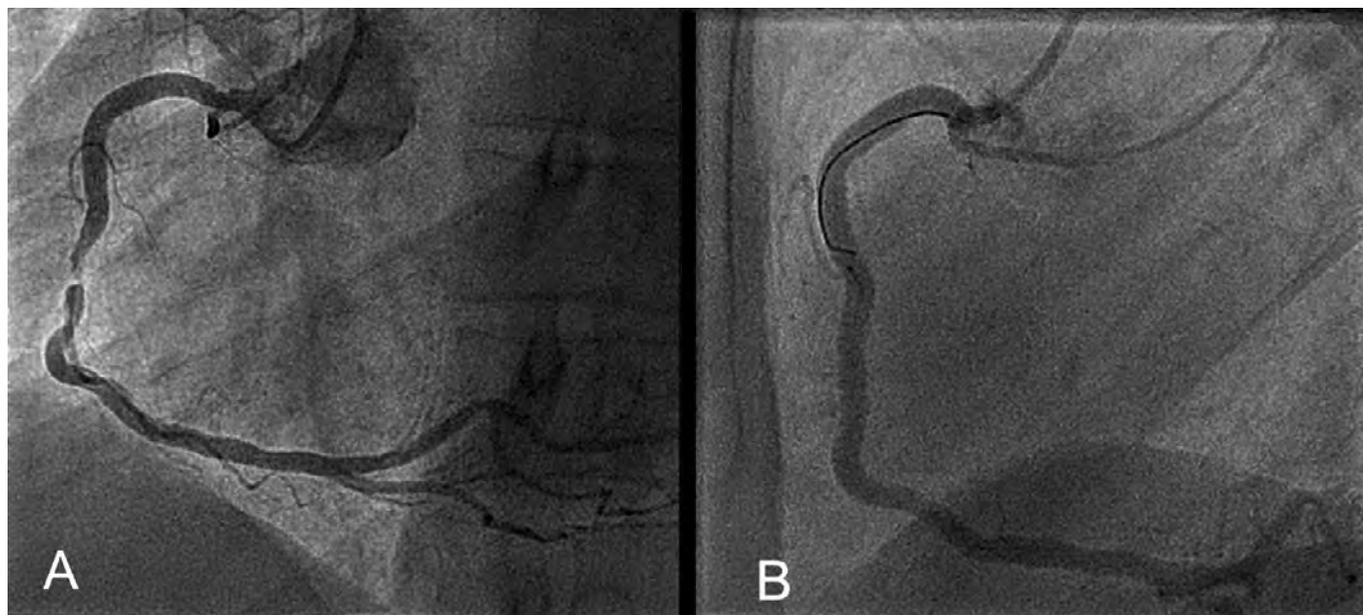


Figure 1. Right coronary artery before (A) and after deploying the 3.5 x 24 mm stent (B).

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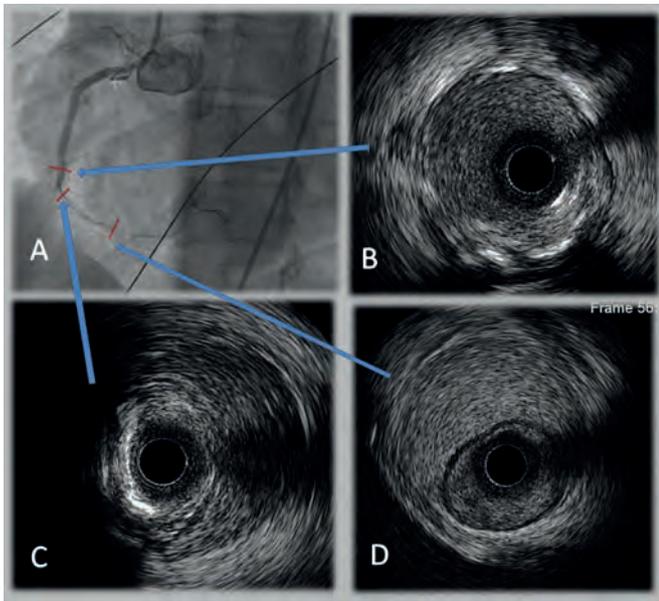


Figure 2. Angiography (A) and intravascular ultrasound imaging, in-stent (B), distal stent margin (C) and in distal right coronary artery (D).

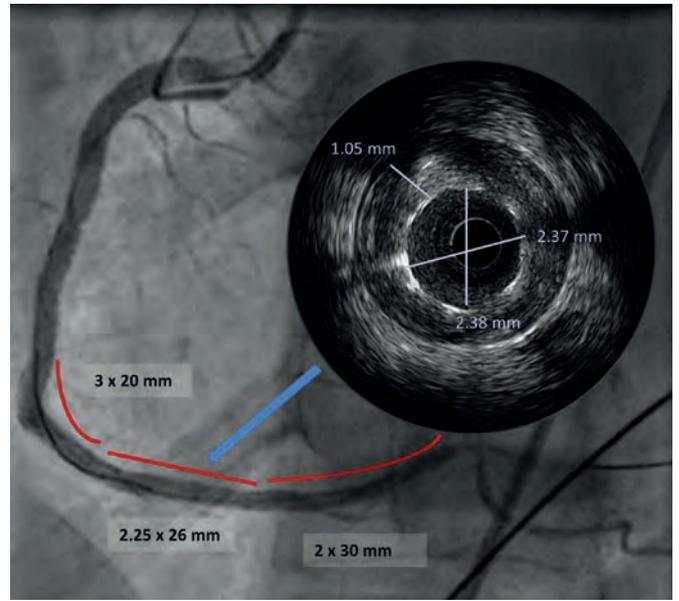


Figure 3. Final result after implanting three drug-eluting stents (lines) in the posterolateral right coronary artery.

Forty minutes after the procedure, the patient started experiencing chest pain and ST-segment elevation in the inferior leads, which is so a new cardiac catheterization procedure was conducted that confirmed the presence of an occlusion distal to the stent. On suspicion of dissection/hematoma, an intravascular ultrasound study was conducted that confirmed the presence of a wall hematoma from the stent towards the posterior-posterolateral (PL) descending bifurcation (figure 2).

Initially, a 3 x 20 mm drug-eluting stent was implanted overlapping the stent deployed in the middle RCA, but since the RCA distal occlusion was persistent, another 2.25 x 26 mm overlapping stent had to be implanted distally with which the hematoma progressed towards the PL and occluded the posterior descending artery. Then we proceeded with the overlapping deployment of another 2 x 30 mm drug-eluting stent from the distal RCA towards the PL resulting in recovered TIMI (Thrombolysis in Myocardial Infarction) flow 3 in the PL with still a persistent occlusion of the posterior descending artery. The stents of the distal CRA and PL have a smaller caliber compared to the initial vessel lumen in order to avoid the distal progression of the hematoma (figure 3). Although the stents are apposed to the endothelium, the intravascular ultrasound imaging shows that the distance from the stent to the blood vessel middle layer is 1 mm.

Although both the symptoms and the ST-segment elevation persisted, the procedure was completed due to the risk of the hematoma progressing even more distally towards the PL and the impossibility to re-cross the guidewire towards the posterior descending artery.

The electrocardiogram that followed the procedure showed the persistence of the ST-segment elevation in the inferior leads; 3 h after the procedure the patient's pain improved and the ST-segment became normal. Considering that an excess of antiplatelet therapy could have favored the appearance of hematoma, it was decided to switch from ticagrelor to clopidogrel.

Afterwards, the patient remained asymptomatic and with an enzyme reaction progress curve with peak troponin T levels at 24 h (4490 ng/L, 4a-type myocardial infarction). The echocardiogram showed a non-dilated left ventricle at discharge with preserved global systolic function, and inferior segments and basal posterior segment hypokinesia.

Neointimal healing pattern of a drug-eluting stent in a coronary hematoma. How would I approach it?



Patrón de cicatrización neointimal de un stent farmacológico en el hematoma coronario. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

The case presented here is very representative of a certain complication that luckily, we rarely find nowadays: vessel acute occlusion following a coronary intervention. In this context, the use of intracoronary imaging modalities is essential to determine the mechanisms underlying this occlusion and to guide the treatment. Probably the most widely known mechanisms have to do with stent thrombosis such as the infra-expansion or dissection of stent edges, but in this case, there is a less common cause: the distal progression of a coronary intramural hematoma.

It could be argued if this iatrogenic intramural hematoma is related to the damage caused by the stent to the coronary wall, the powerful antiplatelet therapy used, etc., or whether a spontaneous hematoma is underlying the culprit lesion of the right coronary artery. Although the angiographic imaging is not typical of a dissection/spontaneous intramural hematoma, there are indistinguishable cases of type III atherosclerotic coronary lesions (figure 1) according to the classification established by Saw et al.¹ that require the use of intracoronary imaging modalities to achieve diagnosis. The use of imaging modalities in culprit lesions of an acute coronary syndrome prior to the coronary intervention provides important information to guide the procedure and even change our therapeutic approach. For example, in this case and even though it can be controversial if it is confirmed that the cause is a spontaneous hematoma and taking into consideration the patient's clinical stability, the absence of pain or ST-segment elevation and the presence of normal coronary flow, conservative therapy without stent implantation could be prescribed in an attempt to promote the vessel spontaneous healing.

Regarding the strategy of this case, I agree with the authors on the use of intravascular ultrasound (IVUS) as the imaging modality to use here since distal to the stent the vessel has a total occlusion that makes it difficult to perform an optical coherence tomography (OCT). As well as confirming the diagnosis of intramural hematoma, the IVUS would also allow us to evaluate its distal spreading, damage to lateral branches and, if coronary intervention is required, confirm the position of the guidewire inside the true lumen.

In this case it was decided to use a direct stent, which is probably the safest option to recover distal flow and prevent the re-occlusion of the vessel. However, some authors recommend the implantation of a stent only when flow cannot be restored using balloon dilatation. There are several reasons for this: in the first place, it is common that the stent causes the distal or proximal progression of the hematoma or dissection that may require multiple stents, occlude the lateral branches and, at times, lead to high-risk situations such as progression towards the left main coronary artery. Also, if an appropriate distal flow is finally recovered using balloon dilatation and myocardial ischemia is prevented, the healing of the vessel has been reported in numerous cases, with complete resolution of the hematoma and no long-term possible complications associated with the implantation of the stents (restenosis, thrombosis, etc.) Another option that has been suggested for the recovery of distal flow is the fenestration of the hematoma using a cutting or a scoring balloon.² Fenestration allows the decompression of the hematoma, which improves flow in the compressed true lumen, thereby reducing the risk of hematoma progression.

In response to the question "how would I approach it?", here follows my strategy for this case: in the first procedure I would not have used a IIb/IIIa inhibitor; I would have only used it in case of complex catheterization or increasing thrombus load. There is little experience on its safety profile in combination with ticagrelor or prasugrel, and the clinical practice guidelines only give a class IIb level of evidence C in patients with acute coronary syndrome treated with percutaneous coronary intervention who did not receive a P2Y₁₂ inhibitor as a second antiplatelet agent. In the second procedure, I would perform an IVUS to assess the mechanism underlying vessel occlusion and when diagnosing the intramural hematoma I would also determine its distal spreading. If one healthy region were

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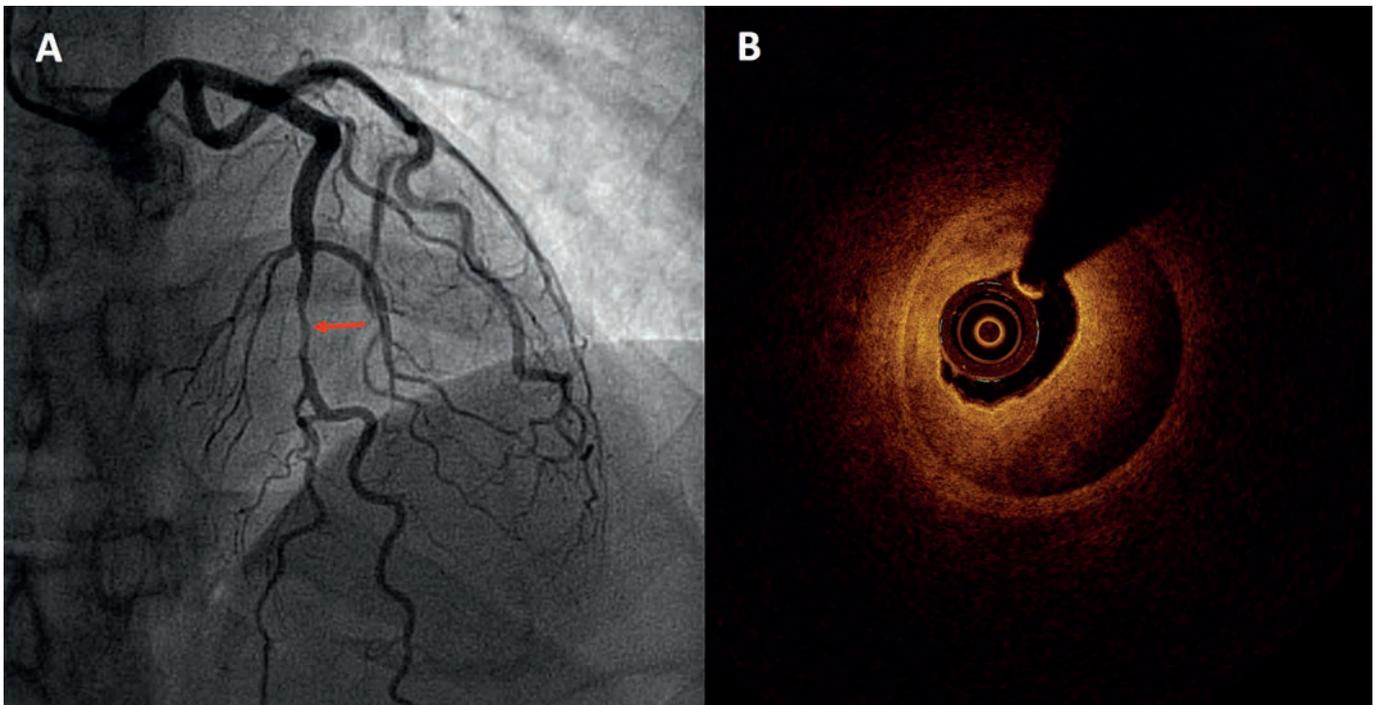


Figure 1. A: coronary angiography in a patient with acute coronary syndrome without ST-segment elevation showing one serious lesion in the mid anterior descending artery (arrow). B: the optical coherence tomography showed evidence of an intramural hematoma as the cause for such lesion.

identified distally using the IVUS, I would implant one stent whose diameter would be adjusted to the size of the distal vessel in the healthy region and I would deploy it at nominal pressure until it overlaps with the former stent in an attempt to somehow contain the hematoma and avoid distal progression. If more than just one stent is needed, then I would first deploy the most distal stent making sure it lands on a healthy region. If, on the contrary, the IVUS shows diffuse damage towards the small caliber distal branches, in my attempt to recover the distal flow, I would first try balloon dilatation. In this case, damage to the posterior/posterolateral descending bifurcation is reported, which is why I would try to advance the guidewire towards both branches and also balloon dilatation. If flow is not recovered, then I would try fenestration with a slightly undersized cutting balloon. If normal coronary flow still fails to recover with all these measures, I would never implant the stent. If I couldn't recover the distal flow, I would implant the stents following the strategy used by the authors in the case at stake, with long undersized stents while trying not to cause greater damage to the vascular wall.

Then I would schedule a new coronary angiography between 1 and 3 months later and I would assess, through one OCT, the presence of hematoma and the apposition of the stents. Since undersized stents have been used intentionally, we can anticipate finding no apposition, but even after achieving complete apposition following the implantation, the reabsorption of the hematoma can lead to stent malapposition. Also, the OCT would provide information on the early neointimal coverage that, on many occasions, can even cover the nonapposed stent struts and spontaneously solve the lack of apposition. In case of severe stent malapposition, especially if it had to do with a lack of strut coverage, I would consider stent post-dilatation³ to facilitate neointimal coverage and potentially reduce the risk of thrombosis.

REFERENCES

1. Saw J, Mancini GBJ, Humphries KH. Contemporary Review on Spontaneous Coronary Artery Dissection. *J Am Coll Cardiol.* 2016;68:297-312.
2. Motreff P, Ronchard T, Sanguinetti F, et al. Coronary Artery Fenestration: A Promising Technique for Rescue Management of Spontaneous Intramural Hematoma With Luminal Compression. *JACC Cardiovasc Interv.* 2018;11:1905-1907.
3. Sanchez-Recalde A, Moreno R, Jimenez-Valero S. Stenting of spontaneous intramural coronary haematoma: long-term consequences. *Eur Heart J.* 2008;29:1593.

Neointimal healing pattern of a drug-eluting stent in a coronary hematoma. Case resolution



Patrón de cicatrización neointimal de un stent farmacoadactivo en el hematoma coronario. Resolución

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CASE RESOLUTION

Six weeks later a coronary angiography was performed to assess any possible stent malapposition after the reabsorption of the hematoma. From the angiographical point of view, the patency of the stents was evident with Thrombolysis in Myocardial Infarction flow 3 in the posterior-posterolateral descending bifurcation. The optical coherence tomography (OCT) revealed the stent malapposition with respect to the vessel wall but with tissue proliferation from the wall towards the struts (figure 1), indicative that strut coverage happened earlier compared to the reabsorption of the hematoma.

The pattern of tissue proliferation with battlement-like morphology in the most proximal stent and tissue bridges from the strut vascular wall in the most distal stents may be indicative of late acquired stent malapposition during the reabsorption of the wall vessel

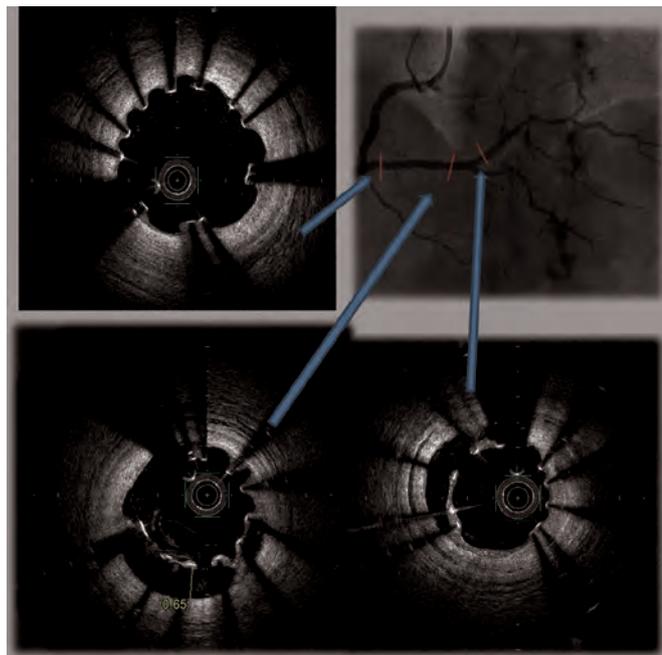


Figure 1. Angiography and optical coherence tomography at 6 weeks.

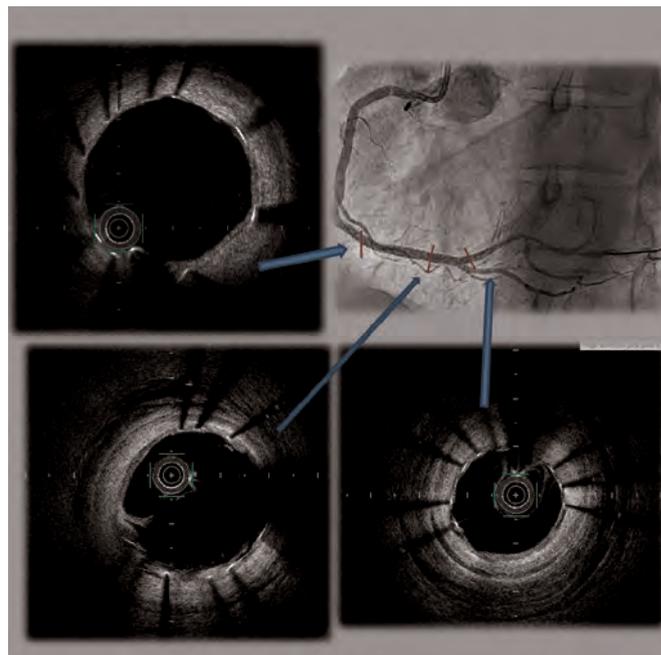


Figure 2. Angiography and optical coherence tomography after post-dilation at 6 weeks.

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hematoma. Initially, the struts were apposed to the endothelium and as the hematoma was being reabsorbed, the lumen recovered its caliber extending from the stent cover towards the arterial wall.

Considering the ample double-lumen segments (that from the covered stent and that from the arterial wall) with distances from the stent to the wall of up to 650 μ it was decided to post-dilate the stent achieving the optimal result seen both in the angiography and the OCT (figure 2).

Intramural hematomas are blood accumulations located in the middle layer that move the internal elastic membrane towards the vessel lumen, and the external elastic layer towards the outside with or without identifiable entry or exit sites.¹

Intravascular ultrasound identifies the presence of intramural hematomas in up to 3.2% of all cases after the implantation of drug-eluting stents.²

Although the management of hematomas is still controversial, some of the approaches currently used are deploying stents, with the progression of the hematoma as a possible setback; or dilating using cutting balloons in order to fenestrate the endothelium or reducing intramural pressure and, therefore, the compression of the vessel. In this case, we implanted stents and the OCT performed at 6 weeks to identify strut malapposition following the resolution of the hematoma and, in the presence of malappositioning, we proceeded to post-dilate the stents.

The OCT showed that, even though the struts were covered, this coverage prolapsed from the vessel wall (after the hematoma had been resolved) thus creating double-lumen (one in-stent and the other between the stent and the vessel wall), which is the reason why we decided to post-dilate the stents in order to reduce the risk of late thrombosis.

In cases of hematomas following the implantation of a drug-eluting stent, if new stents are deployed, a control angiography procedure may be indicated after 4-8 weeks to identify strut malapposition and, if any, proceed to post-dilate the stents.

REFERENCES

1. Maehara A, Mintz GS, Bui AB, et al. Incidence, morphology, angiographic findings, and outcomes of intramural hematomas after percutaneous coronary interventions: an intravascular ultrasound study. *Circulation.* 2002;105:2037-2042.
2. Liu X, Tsujita K, Maehara A, et al. Intravascular Ultrasound Assessment of the Incidence and Predictors of Edge Dissections After Drug-Eluting Stent Implantation. *JACC Cardiovascular Interv.* 2009;2:997-1004.

DinoSAVR struck by the TAVR asteroids

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ABSTRACT

Over the last decade, transcatheter aortic valve replacement (TAVR) has become the preferred treatment for patients with severe aortic stenosis at increased risk for surgery. Consequently, this new technology has been recently tested in low-risk subjects. The PARTNER 3 trial randomized 1000 patients (mean Society of Thoracic Surgeons score, 1.9%; mean age, 73 years) to undergo TAVR with a balloon-expandable valve or surgical aortic valve replacement showing that TAVR was superior in terms of the composite endpoint of death, stroke and re-hospitalization at 1 year. In the Evolut Low Risk trial that randomized 1468 patients with the use of a self-expandable prosthesis, TAVR was non-inferior to surgery for the primary composite endpoint of death or disabling stroke at 24 months. While the available 1-year follow up does not answer the question of transcatheter valves durability, these results will definitely change our everyday clinical practice.

Keywords: Transcatheter aortic valve replacement. Low surgical risk. Randomized trial.

DinoSAVR noqueado por los asteroides TAVI

RESUMEN

En la última década, el reemplazo valvular aórtico transcáteter (TAVR, por sus siglas en inglés) se ha convertido en el tratamiento preferente para los pacientes con estenosis aórtica grave y con alto o incluso moderado riesgo quirúrgico. En consecuencia, esta nueva tecnología ha sido evaluada en sujetos de bajo riesgo quirúrgico. En el estudio PARTNER 3 se aleatorizó a 1.000 pacientes (puntuación media de la *Society of Thoracic Surgeons*, 1,9%; edad media, 73 años) para ser sometidos a TAVR con una válvula balón expandible o a reemplazo quirúrgico de válvula aórtica, y se halló que la TAVR fue superior en términos del objetivo final compuesto de muerte, ictus y reingreso a 1 año. En el ensayo Evolut Low Risk, en el que 1.468 pacientes fueron aleatorizados a TAVR con una prótesis autoexpandible o cirugía, la TAVR no fue inferior a esta última en términos del criterio de valoración principal compuesto de muerte o accidente cerebrovascular discapacitante a los 24 meses. Si bien el seguimiento a 1-2 años disponible no responde a la pregunta sobre la durabilidad de las válvulas transcáteter, estos resultados cambiarán nuestra práctica clínica diaria.

Palabras clave: Reemplazo de válvula aórtica transcáteter. Riesgo quirúrgico bajo. Ensayo aleatorizado.

Abbreviations

AS: aortic stenosis. **CAD:** coronary artery disease. **TAVR:** transcatheter aortic valve replacement. **THV:** transcatheter heart valve. **PVL:** paravalvular leak. **SAVR:** surgical aortic valve replacement.

Percutaneous coronary angioplasty took approximately 30 years, from the first pioneering experience of Andreas Gruentzig back in 1977, to reach class I indication in the international clinical practice guidelines on myocardial revascularization of left main/3-vessel coronary artery disease (CAD) and replace coronary artery bypass grafting for the management of most patients with CAD. Similarly, 17 years have passed since the very first transcatheter aortic valve replacement (TAVR) was performed in a prohibitive-risk patient with severe aortic valve stenosis (AS) until the arrival

of the contemporary randomized trial of TAVR vs surgical aortic valve replacement (SAVR) in a low-surgical risk population. This road has been paved with substantial technical improvements in transcatheter heart valves (THV), increased operators' experience and rigorously-designed randomized trials. As a matter of fact, TAVR first proved to be superior to medical therapy in patients considered inoperable,^{1,2} and confirmed it was non-inferior to SAVR in high^{3,4} and intermediate risk^{5,6} patients. Actually, when performed using the transfemoral access, TAVR proved to be

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superior to SAVR.⁷ So, time was ripe to test this disruptive technology in low-risk patients who amount to 80% of the patients who, to this day, undergo SAVR procedures.^{8,9}

The PARTNER 3 trial¹⁰ was a multicenter randomized study that compared TAVR and SAVR procedures for the management of severe symptomatic AS in low-surgical risk patients (Society of Thoracic Surgeons [STS] score < 4%). This trial randomized 1000 low-risk subjects (mean STS score 1.9%) from 71 centers (98% of the patients were recruited in the United States) to transfemoral TAVR with the balloon-expandable SAPIEN 3 (Edwards Lifesciences, Irvine, California, United States) THV or SAVR. The primary endpoint was a composite of all-cause mortality, stroke and rehospitalization due to heart failure at 1 year. The trial was designed to test both the non-inferiority (with a prespecified margin of 6 percentage points) and superiority of the TAVR procedure, in the as-treated population. There was a 46% reduction in the rate of the primary composite endpoint at 1 year for TAVR compared to SAVR that met the criteria of both non-inferiority (8.5% vs 15.1%; absolute difference, -6.6%; 95% confidence interval [95%CI], -10.8 to -2.5; $P < .001$) and superiority (hazard ratio [HR], 0.54; 95%CI, 0.37-0.79; $P = .001$). Even excluding rehospitalization due to heart failure, arguably the weaker endpoint of the composite, TAVR had better results than surgery (death or stroke 1.8% vs 4.9%, treatment effect 0.36; 95%CI, 0.17-0.79). Several hierarchical pre-specified secondary endpoints were also tested, resulting in significantly lower 30-day rates of stroke (0.6% vs 2.4%; $P = .02$), death or stroke (1.0% vs 3.3%; $P = .01$), life-threatening or major bleeding (3.6% vs 24.5%; $P < .001$) and new-onset atrial fibrillation (5.0% vs 39.5%; $P < .001$) in the TAVR group. No statistically significant differences were seen in moderate or severe paravalvular leak (PVL) (0.8% vs 0%), need for a new permanent pacemaker (6.5% vs 4.0%) or major vascular complications (2.2% vs 1.5%) between the 2 populations.

Another randomized study on low-risk patients with AS, the Evolut Low Risk trial,¹¹ confirmed the non-inferiority of TAVR with a self-expandable THV (Evolut R and Pro, Evolut Medtronic Inc., Minneapolis, Minnesota, United States) compared to surgery in the primary composite endpoint of all-cause mortality or disabling stroke at 24 months.¹¹ The 24-month estimated incidence rate of the primary endpoint was 5.3% in the TAVR group vs 6.7% in the surgery group (difference, -1.4 percentage points; 95% Bayesian credible interval for difference, -4.9 to 2.1; posterior probability of noninferiority > 0.999). In this study, TAVR was not superior to SAVR, but had numerically lower rates of hard endpoints (main results of both trials are shown on Table 1). In short, patients who underwent TAVR procedures had lower incidence rates of disabling stroke, bleeding complications, acute kidney injury, and atrial fibrillation, but a higher incidence rate of moderate/severe PVL and pacemaker implantation. Although comparing the 2 trials is difficult because of differences of statistical design and endpoints (and beyond the scope of this manuscript), it is important to notice that both studies pointed in the same direction, suggesting a class effect of TAVR in this low-risk population.

These trials represent a landmark in interventional cardiology and, broadly speaking, in modern medicine for two reasons. Firstly because it is the last step down the surgical risk ladder for TAVR, finally proving that the transcatheter management of severe AS has similar (if not superior) results compared to SAVR regardless of the surgical risk. Secondly, and more importantly, these are the first randomized trials to put the transcatheter management of AS to the test in a younger population with a longer life expectancy. As a matter of fact, the mean age of the study population was 73-74 years, with roughly 10% of the subjects < 65 years of age in the PARTNER 3 trial. Prior to these studies, despite a reduction in the surgical risk score, the mean age of

patients treated with TAVR had been largely over 80 years of age (Figure 1).⁸ Focusing on the PARTNER 3 trial, in this younger and "healthier" population the surgical control arm had very good outcomes, with 30-day mortality rates as low as 1.1% and 30-day disabling stroke rates of 0.4% (non-disabling stroke 2.0%). Nevertheless, the TAVR group had even lower 30-day mortality rates (0.4%) and no disabling stroke rates (non-disabling stroke 0.6%). To this regard, the extremely low rate of strokes seen in the TAVR group questions the need for the routine use of cerebral embolic protection devices. Also, 1-year all-cause mortality was extremely low in both groups compared to previous PARTNER trials. If we examine the data carefully, it is clear that almost all of the very few deaths reported had to do with cardiac causes (with a 0.8% cardiac mortality seen in the TAVR group vs 2.0% in the SAVR group). This finding is new compared to previous TAVR trials in which cardiac mortality accounted for less than 60% of deaths at 1-year, which is likely due to the younger age and low prevalence of comorbidities in the PARTNER 3 population.

Another striking finding of this trial was that previous TAVR setbacks such as vascular complications, need for new pacemaker implantations, and moderate/severe PVL rates were as low as those of SAVR. This is likely due to the major technical advances made in new-generation THVs¹² (with the arrival of external sealing skirts and lower sheath profile compatibility), careful pre-procedural CT assessments (thus reducing prosthesis oversizing), and greater operators' experience (resulting in more precise THV implantations). The reduction in the number of periprocedural complications together with the adoption of a minimally invasive approach (only one third of the TAVRs were performed under general anesthesia, for the most part not even requiring intensive care unit admission) resulted in significantly shorter hospital stays of TAVR patients (3.0 vs 7.0 days) and higher discharge or self-care rates (95.8% vs 73.1%) compared to SAVR. Thus, 30-day functional status and quality of life were better among TAVR patients.

With regard to the echocardiographic findings, although moderate/severe PVL was similar in the 2 groups, TAVR had significantly higher rates of mild PVL compared to surgery (28.7% vs 2.9%). It should be noted that the impact of mild PVL on long-term outcome of younger patients is still unknown. Moreover, TAVR patients had lower mean aortic valve areas and higher transvalvular gradients at 30-day compared to SAVR (1.7 cm² vs 1.8 cm² and 12.8 mmHg vs 11.2 mmHg, respectively). This finding, which was not described in any of the previous PARTNER trials, is probably explained by the greater use of larger bioprostheses in the surgical arm (80% of the prosthesis were ≥ 23 mm). If the larger valve area of the surgical group will translate into hemodynamic or clinical benefits at a longer follow up remains to be seen. We should mention here that in the Evolut Low Risk trial, patients undergoing TAVR with a supra-annular self-expandable THV had lower aortic-valve gradients (8.6 mmHg vs 11.2 mmHg) and larger effective orifice areas (2.3 cm² vs 2.0 cm²) compared to the patients in the surgical group at 12 months.

The major limitation of these trials is that the short term follow-up does not answer the question of THV durability, which becomes of course of paramount importance when treating younger, low-risk subjects. It is remarkable that the long-term data available (up to 8-year follow up)^{13,14} do not seem to show any signs of early deterioration of the THVs. Although this still represents a major concern for many clinicians, we should mention that many surgical bioprostheses that are currently used worldwide have even fewer long-term data compared those available for THVs. To address this issue, the trial protocol includes an annual evaluation of up to 10 years, at least, after the index procedure, which will finally shed light on the long-term hemodynamic performance (in

Table 1. Summary of baseline characteristics and outcomes of low-risk aortic valve stenosis patients enrolled in the PARTNER 3 and Evolut Low Risk randomized trials

	PARTNER 3			Evolut Low Risk		
	TAVR (n = 496)	SAVR (n = 454)	Treatment effect [95%CI]	TAVR (n = 725)	SAVR (n = 678)	Difference [95%CI]
<i>Baseline characteristics</i>						
Age (years)	73.3±5.8	73.6±6.1	-	74.1±5.8	74.1±5.8	-
STS score (%)	1.9±0.7	1.9±0.6	-	1.9±0.7	1.9±0.7	-
Male sex (%)	67.5	71.1	-	64.0	66.2	-
Mean LVEF (%)	65.7±9.0	66.2±8.6	-	61.7±7.9	61.9±7.7	-
NYHA class III-IV (%)	31.2	23.8	-	25.1	28.4	-
<i>Primary endpoint</i>						
All-cause mortality, stroke, or rehospitalization due to heart failure at 1 year (%)	8.5	15.1	0.54 [0.37-0.79]	-	-	-
All-cause mortality or disabling stroke at 2 years (%)	-	-	-	5.3	6.7	-1.4 [-4.9- 2.1]
<i>30-day outcomes</i>						
All-cause mortality (%)	0.4	1.1	0.37 [0.07-1.88]	0.5	1.3	-0.8 [-1.9- 0.2]
Cardiac mortality (%)	0.4	0.9	0.46 [0.08-2.49]	0.5	1.3	-0.8 [-1.9- 0.2]
Disabling stroke (%)	0	0.4	N/A	0.5	1.7	-1.2 [-2.4- -0.2]
Life threatening/disabling bleeding (%)	1.2	11.9	0.09 [0.04-0.22]	2.4	7.5	-5.1 [-7.5- -2.9]
Major vascular complications (%)	2.2	1.5	1.44 [0.56-3.73]	3.8	3.2	0.6 [-1.4- 2.5]
Stage II-III acute kidney injury (%)	0.4	1.8	N/A	0.9	2.8	-1.8 [-3.4- -0.5]
New-onset atrial fibrillation (%)	5.0	39.5	0.10 [0.06-0.16]	7.7	35.4	-27.7 [-31.8- -23.6]
New pacemaker implantation (%)	6.5	4.0	1.66 [0.93-2.96]	17.4	6.1	11.3 [8.0-14.7]
Moderate-severe paravalvular leakage (%)	0.8	0	N/A	3.4	0.4	-
Mean aortic valve area (cm ²)	1.7±0.02	1.8±0.02	-0.1 [-0.1- 0]	2.2±0.06	2.0±0.06	-
Mean aortic valve gradient (mmHg)	12.8	11.2	1.5 [0.9-2.0]	3.4	0.4	-
<i>1-year outcomes</i>						
All-cause mortality (%)	1.0	2.5	0.41 [0.14-1.17]	2.4	3.0	-0.6 [-2.6-1.3]
Cardiac mortality (%)	0.8	2.0	0.40 [0.12-1.30]	1.7	2.6	-0.9 [-2.7- 0.7]
Disabling stroke (%)	0.2	0.9	0.22 [0.03-2.00]	0.8	2.4	-1.6 [-3.1- -0.3]
Rehospitalizations due to heart failure (%)	7.3	11.0	0.65 [0.42-1.00]	3.2	6.5	-3.4 [-5.9- -1.0]

95%CI, 95% confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

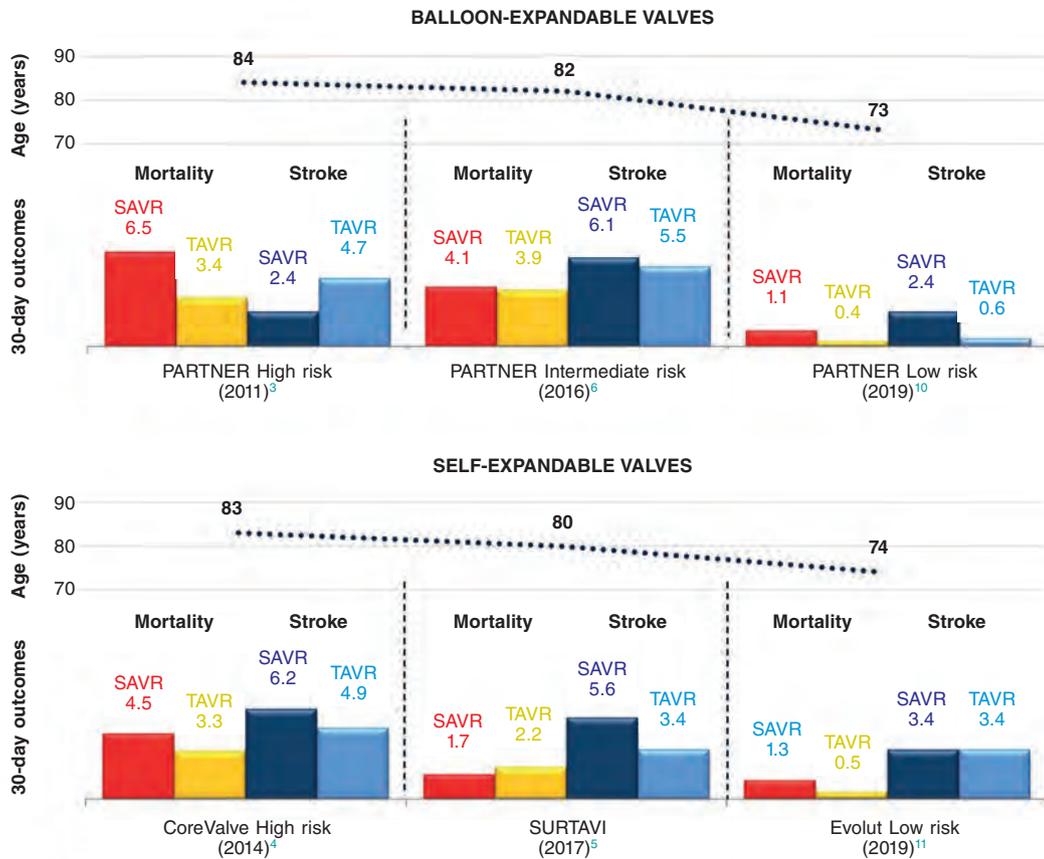


Figure 1. Thirty-day mortality and stroke rates in major transcatheter aortic valve replacement (TAVR) vs surgical aortic valve replacement (SAVR) trials across the surgical risk spectrum. Notably, mean age of the study population decreased significantly in the PARTNER 3 (PARTNER Low Risk) and Evolut Low Risk trials.

terms of bioprosthetic valve dysfunction and failure rates) of both transcatheter and surgical heart valves. Moreover, a prespecified computed tomography angiography sub-analysis of the PARTNER 3 trial will look at valve-leaflet dysfunction and asymptomatic valve thrombosis. On this issue, at 1-year, five patients in the TAVR arm vs one patient in the surgical arm had evidence suggestive of valve thrombosis.

Importantly, the findings of these trials should not be generalized to all AS patients at low surgical risk. For example, patients with bicuspid aortic valve -who are representative of a relevant portion of younger subjects with AS- were excluded from the analysis, mainly because of concerns related to the presence of an elliptic annulus and asymmetric leaflet calcifications possibly leading to eccentric prosthesis expansion and higher rates of PVL and risk of annular rupture.^{15,16} In a recent propensity-matched analysis of the STS/TVT registry, TAVR in bicuspid vs tricuspid valve was associated with a higher risk of aortic injury and conversion to open heart surgery (although the overall rate was < 1.0%) but similar survival at 30 days and 1 year. A dedicated randomized trial in patients with bicuspid AS is needed at this point. Also, these studies excluded patients with an unsuitable transfemoral access, low-flow low-gradient AS, severe coronary artery disease (SYNTAX score > 32), absence of symptoms.¹⁷ Finally, the patients recruited were treated by experienced operators at high volume centers. In this sense, such low rates of events might not be reproducible in smaller centers with less experienced physicians.

The PARTNER 3 and the Evolut Low Risk trials will have profound implications in clinical practice, and will likely lead to class I

indication of TAVR also in low-risk subjects in the upcoming international clinical practice guidelines. Treatment choices in patients with severe symptomatic AS should not rely on surgical risk anymore, but rather be influenced by clinical and anatomical considerations and patient preference. Unless there is a clear anatomic characteristic driving the choice towards SAVR (e.g. bicuspid aortic valve, high SYNTAX score, no feasible transfemoral approach), from now on every patient considered for SAVR with a bioprosthetic valve should be informed about the possibility to undergo TAVR. Transcatheter aortic valve replacement may soon become the preferred therapy for most of AS patients, thus leading to a long-awaited change of paradigm: Rather than asking ourselves if a patient is candidate for TAVR, we will have to justify if a patient is eligible for surgery. We will have to wait for the long-term durability data, but it looks like SAVR is on the brink of becoming an endangered species.

CONFLICTS OF INTEREST

G. Tarantini has received lecture fees from Edwards Lifesciences, Medtronic, Boston Scientifics, Abbott. L. Nai Fovino has declared no conflicts of interest whatsoever.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-1607.

2. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol.* 2014;63:1972-1981.
3. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-2198.
4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370:1790-1798.
5. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med.* 2017;376:1321-1331.
6. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med.* 2016;374:1609-1620.
7. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet.* 2016;387:2218-2225.
8. Tarantini G, Nai Fovino L, Gersh BJ. Transcatheter aortic valve implantation in lower-risk patients: what is the perspective? *Eur Heart J.* 2018;39:658-666.
9. Tarantini G, Lefèvre T, Terkelsen CJ, et al. One-Year Outcomes of a European Transcatheter Aortic Valve Implantation Cohort According to Surgical Risk. *Circ Cardiovasc Interv.* 2019;12:e006724.
10. Mack MJ, Leon MB, Thourani VH, et al.; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1695-1705.
11. Popma JJ, Deeb GM, Yakubov SJ, et al.; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1706-1715.
12. Nai Fovino L, Badawy MRA, Fraccaro C, et al. Transfemoral aortic valve implantation with new-generation devices: the repositionable Lotus versus the balloon-expandable Edwards Sapien 3 valve. *J Cardiovasc Med (Hagerstown).* 2018;19:655-663.
13. Barbanti M, Costa G, Zappulla P, et al. Incidence of Long-Term Structural Valve Dysfunction and Bioprosthetic Valve Failure After Transcatheter Aortic Valve Replacement. *J Am Heart Assoc.* 2018;7:e008440.
14. Tarantini G, Purita PAM, D'Onofrio A, et al. Long-term outcomes and prosthesis performance after transcatheter aortic valve replacement: results of self-expandable and balloon-expandable transcatheter heart valves. *Ann Cardiothorac Surg.* 2017;6:473-483.
15. Tarantini G, Basso C, Fovino LN, Fraccaro C, Thiene G, Rizzo S. Left ventricular outflow tract rupture during transcatheter aortic valve implantation: anatomic evidence of the vulnerable area. *Cardiovasc Pathol.* 2017;29:7-10.
16. Tarantini G, Fabris T, Cardaioli F, Nai Fovino L. Coronary access after transcatheter aortic valve replacement in bicuspid aortic valve: lights and shades. *JACC Cardiovasc Interv.* 2019. <http://doi.org/10.1016/j.jcin.2019.03.031>.
17. Tarantini G, Nai Fovino L, Tellaroli P, Fabris T, Iliceto S. Asymptomatic Severe Aortic Stenosis and Noncardiac Surgery. *Am J Cardiol.* 2016;117:486-488.

Optical coherence tomography assessment of intracoronary guidewire fractures

Rotura de guía intracoronaria evaluada por tomografía de coherencia óptica

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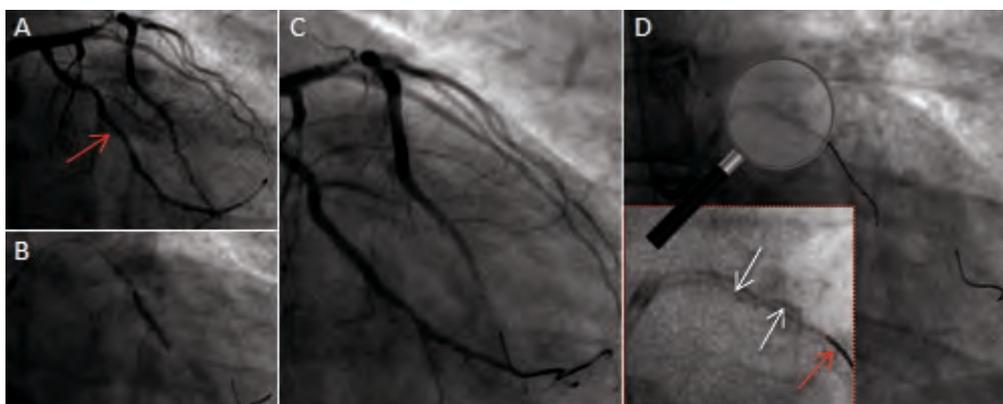


Figure 1.

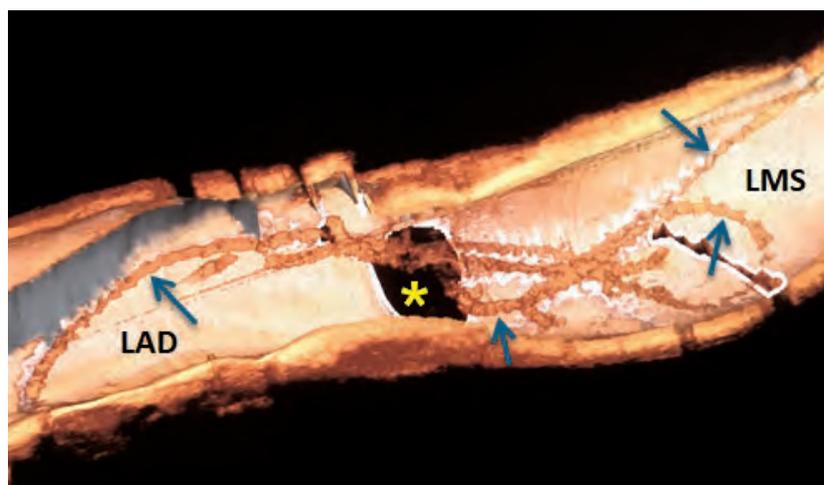


Figure 2.

One 72-year-old male who recently suffered from a non-ST-segment elevation myocardial infarction (NSTEMI) underwent a staged percutaneous coronary intervention (PCI) due to significant stenosis of his mid left anterior descending (LAD) and mid left circumflex (LCX) arteries (figure 1A; red arrow). After placing one hydrophilic Hi-Torque intracoronary guidewire into the LCX, one drug-eluting stent (DES) was deployed uneventfully (figure 1B and figure 1C). However, we were unable to extract the guidewire afterwards probably due to entrapment with a calcified plaque. The stronger traction resulted in the partial fracture of the guidewire followed by the disruption of the coils (figure 1D, white arrows; the red arrow points to a second inserted guidewire). Retrieval was unsuccessfully attempted using different techniques like the snare loop technique and the twisting wire technique (video 1 of the supplementary data). After the uncomplicated stenting of the mid LAD, we conducted an optical coherence tomography (OCT). A three-dimensional reconstruction showed remains of the broken wire (figure 2; blue arrows) coming out of the LCX (figure 2; yellow asterisk) and into the left

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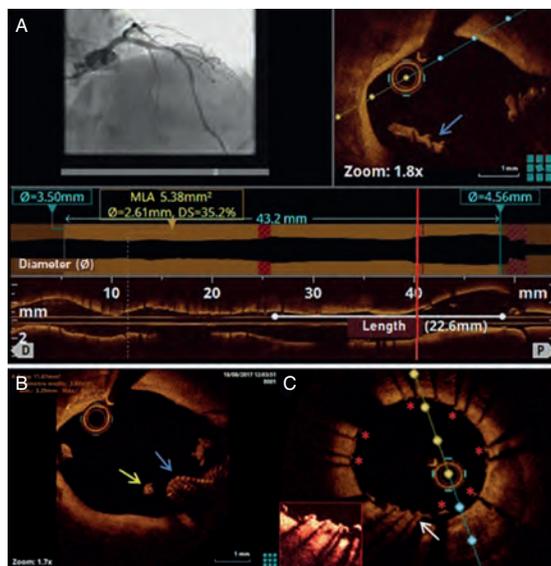


Figure 3.

main stem (LMS) and proximal LAD with presence of adhered and free-floating thrombotic material as shown in the cross-sectional views (figure 3A and figure 3B; blue arrows point to the wire remains; the yellow arrow points to the thrombotic material; MLA, minimal lumen area; video 2 of the supplementary data). We immediately proceeded to eliminate the uncoiled filaments from the circulation by deploying one DES into the distal LMS and the proximal LAD. The control OCT conducted showed the wire remains trapped by the struts of the stent against the vessel wall (figure 3C; white arrow: wire remains, highlighted in red-framed box; red asterisks: stent struts).

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at (<https://doi.org/10.24875/RECICE.M19000020>).

Parallel stenting for the recanalization of an in-stent coronary occlusion

Stent paralelo en la recanalización de una obstrucción coronaria intra-stent

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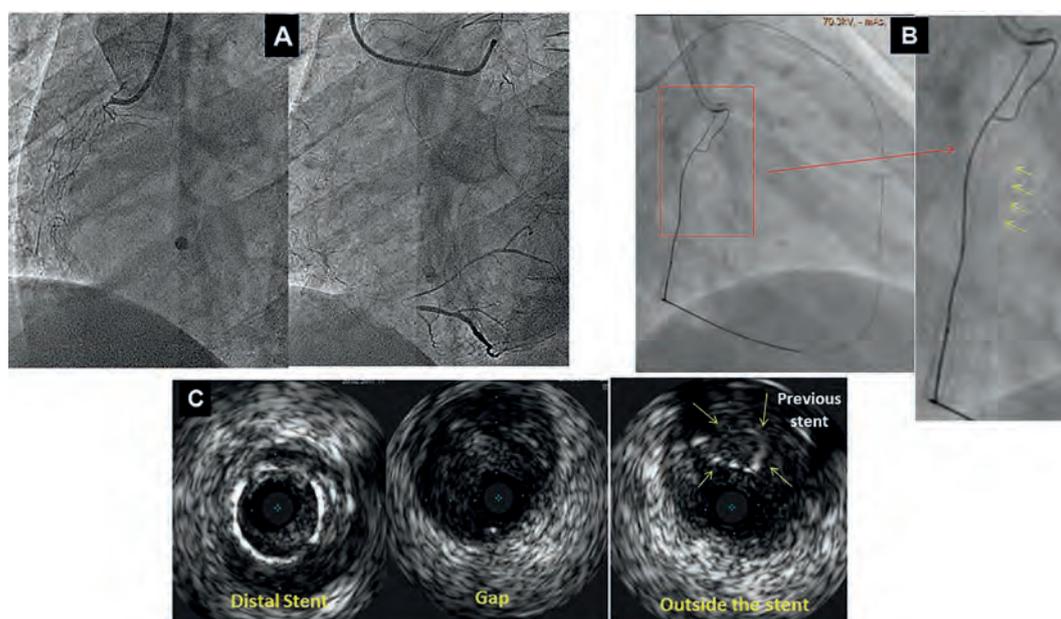


Figure 1.

A 48-year-old male was admitted to the hospital due to stable angina. The coronary angiography showed a very long in-stent coronary chronic total occlusion in his right coronary artery (RCA) (figure 1A). We attempted the retrograde access following failed antegrade access. At mid-RCA level, the guidewire was advanced outside the stent (arrows) (figure 1B). The intravascular ultrasound (IVUS) conducted confirmed the correct position of the guidewire at the stent distal edge. However, in the gap between both stents, the guidewire was advanced to the subadventitial space and maintained this position along the full length of the proximal stent (arrows) (figure 1C). After predilation, 3 drug-eluting stents were successfully implanted (figure 2A). A double stent can be seen in the angiographic and IVUS images obtained (figure 2B and figure 2C): the previous (arrows) and the newly implanted stent. The computed tomography scan conducted 3 months later confirmed the exclusion of the old stent (arrows) from the coronary flow and the patency of the stents implanted

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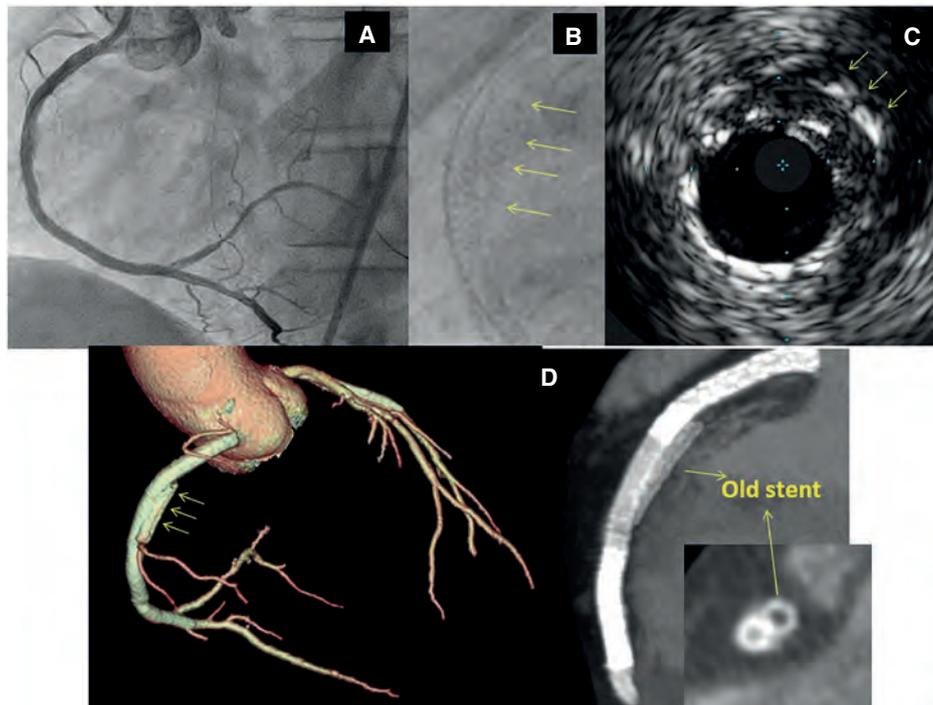


Figure 2.

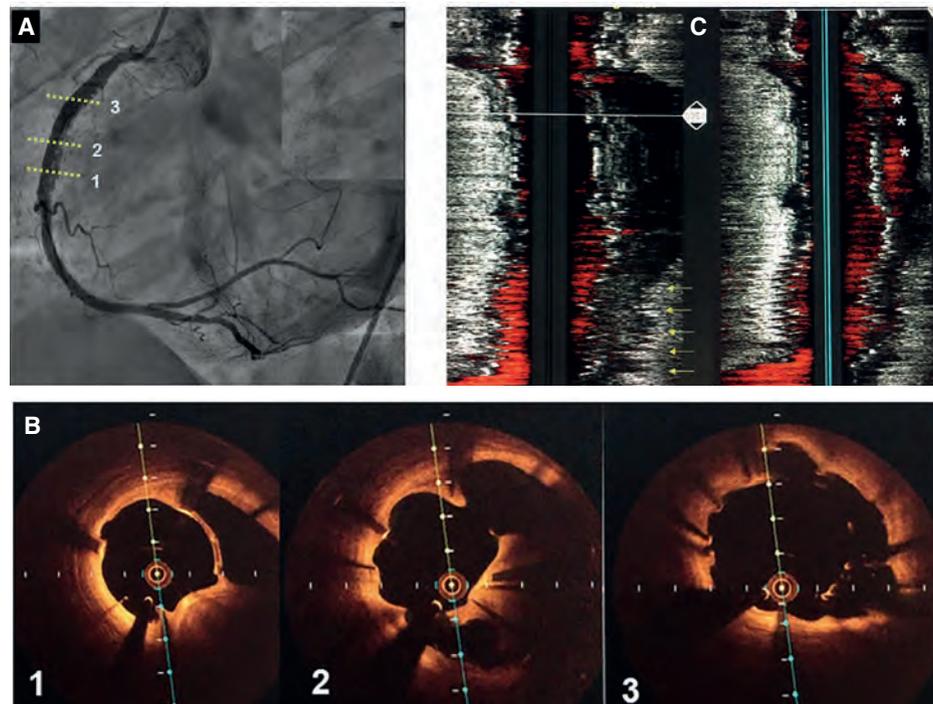


Figure 3.

in the subadventitial space (figure 2D). Six months after the index procedure, a new angiographic assessment confirmed the long-lasting good results (figure 3A). However, the optical coherence tomography showed significant late-acquired stent malapposition (figure 3B). The IVUS longitudinal views showed the old occluded stent (arrows) and, on the other plane, the stent malapposition (asterisks) (figure 3C), probably due to the hematoma reabsorption induced during the recanalization process. The patients remained asymptomatic. It was decided to maintain aspirin and ticagrelor until the next reassessment scheduled after an 18-month follow-up.

Pericardial calcification: Don't rush! The importance of invasive hemodynamic assessment



Calcificación pericárdica: ¡no se precipite! La importancia de la valoración hemodinámica invasiva

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To the Editor,

Constrictive pericarditis (CP) is cause for diastolic heart failure due to the presence of a non-distensible pericardium. Diagnostic suspicion is key here because, even though it is a potentially curable condition, if untreated, its morbimortality rate is high.¹ Its differential diagnosis with restrictive cardiomyopathy can be a real challenge.² We present a case where the invasive hemodynamic assessment performed through cardiac catheterization showed its validity and diagnostic importance in the therapeutic decision-making process.

We present the case of a 59-year old hypertensive woman, former smoker and with a prior medical history of Hodgkin lymphoma at 18 years old—for which she was treated with tele-cobalt therapy and chemotherapy—and carcinoma located in her left breast that was mastectomized when she was 52 years of age. She was re-admitted twice in 2 months due to right heart failure with presence of the Kussmaul sign ([video 1 of the supplementary data](#)). Due to the poor acoustic window, the transthoracic echocardiography conducted only showed pericardial thickening and preserved

biventricular systolic function without significant valvular heart disease. In the presence of severe pericardial calcification ([figure 1](#)) and due to the patient's clinical manifestations and prior medical history of chest radiation, cardiac catheterization was decided to confirm the suspicion of post-radiotherapy CP and indicate surgical pericardiectomy.

The hemodynamic assessment confirmed a reduced cardiac index (1.82 L/min/m^2) and a significant increase of pressure in the right cardiac cavities and other classical signs of constrictive pericarditis,¹⁻³ such as very deep x and y descent in the right atrium ([figure 2A](#)) and dip-plateau morphology in the right ventricular pressure curve ([figure 2B](#)). The simultaneous registry of pressures from both ventricles also showed the equalization of their end-diastolic pressures ([figure 2C](#)) and ruled out the expected increase of ventricular interdependence with the existence of parallel changes in both pressures with breathing movements ([figure 2D](#)). Also, the patient showed moderate postcapillary pulmonary hypertension ([figure 2E,F](#)). No significant coronary lesions were found, although the most distal branches of the right coronary artery were somehow fixed at the level of the inferior pericardial calcification

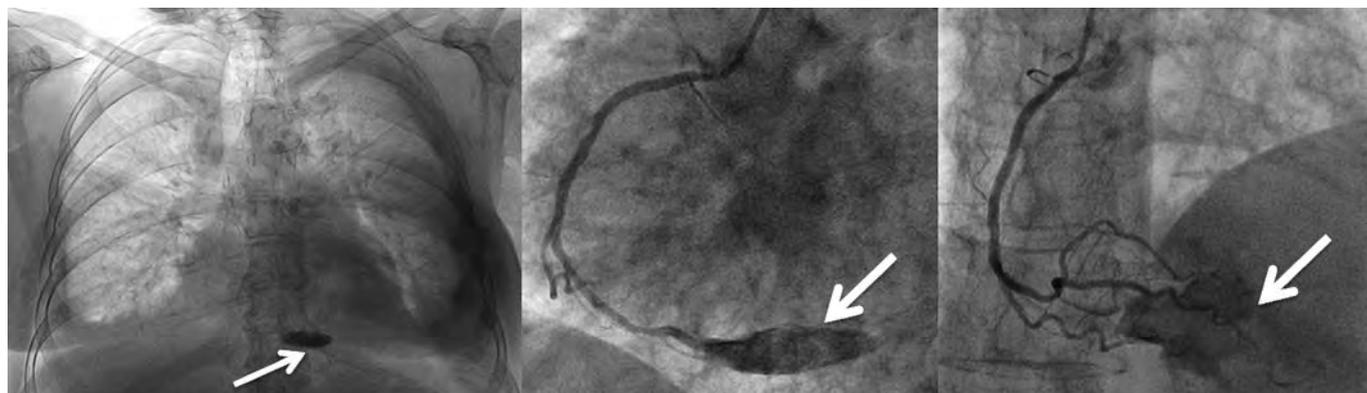


Figure 1. Inferior pericardial calcification (arrows).

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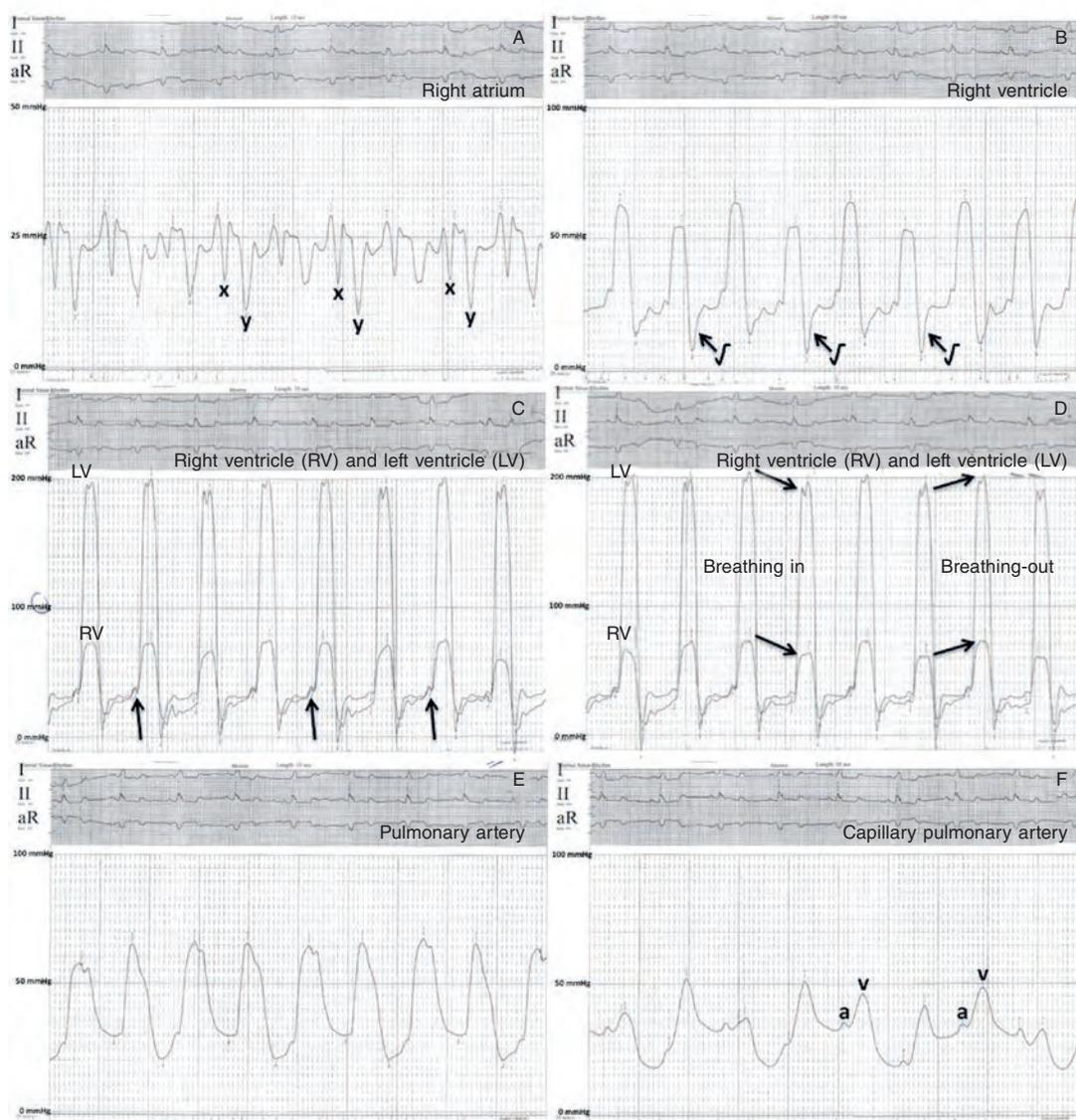


Figure 2. Registry of pressures. A: right atrium (average 22 mmHg) with deep sinus x and y; B: right ventricle (61/10-27 mmHg) with square root symbol (arrow); C and D: right and left ventricles with equalization of both end-diastolic pressures (arrows), parallel decrease (ventricular match) of pressure curves while breathing in parallel increase while breathing-out; E: pulmonary artery (65/25/42) mmHg; and F: capillary pulmonary artery (31 mmHg) with a prominent v wave.

(figure 1 and video 2 of the supplementary data), a finding considered specific of CP.¹

We should consider the diagnosis of CP in the presence of mainly right heart failure-like symptoms. Clinical findings and non-invasive diagnostic modalities allow to diagnose it in 70% of all cases.¹ However, the remaining patients may need cardiac catheterization for a correct differentiation between CP and restrictive cardiomyopathy, especially those with a prior medical history of radiotherapy or heart surgery in whom pericardial and myocardial damages are usually coexistent.^{2,3}

The classical criteria of CP (eg, early fast ventricular filling or end-diastolic pressure equalization of the 4 cardiac chambers, lack of pulmonary hypertension, etc.) have low sensitivity and specificity for differential diagnosis purposes when it comes to restrictive cardiomyopathy.^{1,3} To this day, it is widely accepted that the dynamic breathing variations of intracardiac pressures are very

accurate^{1,2} and have a 97% sensitivity rate and a 100% positive predictive value for the identification of patients with CP.³ In CP there is a dissociation between intrathoracic and intracardiac pressures with reduced intrathoracic pressure not transferred to the cardiac cavities during breathing, which leads to reduced left ventricular filling. In the presence of a non-distensible pericardium with a relatively fixed intrapericardial volume, this reduced left ventricular filling simultaneously increases to the right ventricular filling. The opposite happens when breathing out. This increased ventricular interdependence automatically translates into impaired ventricular systolic pressures. In other clinical scenarios there is an increase and decrease of both pressures consistent with the breathing cycle (ventricular match), but in the case of CP, these variations simply do not match,^{1,2} which is a highly sensitive and specific marker³ not found in our patient.

Even though the Doppler echocardiogram can assess these changes during the respiration phase using the analysis of transmitral

flow pattern and septal movements,¹ patients who have undergone heart surgery or received radiotherapy in the past usually show acoustic windows that complicate this assessment. As it has already been confirmed, the detection of thickening or pericardial calcification in the different imaging modalities available today does not necessarily reflect a purely constrictive pathophysiology.³

Our hemodynamic assessment shows a probable mixed condition of myocardial constriction and restriction due to chest radiation sustained by the patient in her youth. With the data presented here, we believe that the case reinforces the need to perform very precise hemodynamical assessments of these patients before indicating any surgical interventions² especially when the perioperative mortality rate of pericardiectomy of these patients can exceed 20%.¹ That is why we initially took a conservative approach and waited on the patient's clinical progression after a slow and adequate optimization of the medical therapy.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000027>.

REFERENCES

1. Miranda WR, Oh JK. Constrictive Pericarditis: A Practical Clinical Approach. *Prog Cardiovasc Dis*. 2017;59:369-379.
2. Geske JB, Anavekar NS, Nishimura RA, Oh JK, Gersh BJ. Differentiation of Constriction and Restriction: Complex Cardiovascular Hemodynamics. *J Am Coll Cardiol*. 2016;68:2329-2347.
3. Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol*. 2008;51:315-319.



Pulmonary artery pseudoaneurysm as a Swan-Ganz catheter complication

Seudoaneurisma de arteria pulmonar como complicación de catéter de Swan-Ganz

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To the Editor,

We present the case of a 65-year-old woman without any known drug allergies and with a previous cardiac history of atrial fibrillation treated with warfarin and rheumatic poly-valve disease with double mitral valve lesion (severe mitral stenosis and moderate-to-severe mitral regurgitation) and severe tricuspid regurgitation with indirect data of pulmonary hypertension admitted due to progressive worsening of her usual dyspnea until becoming dyspnea of minimal exertion and with important limitations in activities of daily living.

She was examined at the cardiovascular surgery unit and on April 17, 2018 she was intervened to replace her mitral valve for a mechanical prosthesis and tricuspid annuloplasty back on April 17, 2018 without intraoperative incidents or complications in the immediate postoperative period neither at the intensive care unit nor at the hospital ward from where she was discharged in due course.

Back in May 31, 2018, the patient was admitted to the emergency room due to exacerbated dyspnea that became dyspnea on moderate exertion accompanied by an increased abdominal perimeter and swelling in both her lower limbs. The blood test confirmed the presence of elevated levels of natriuretic propeptides. The chest x-ray conducted showed congestive signs and the image of a right lung base pulmonary nodule suggestive of phantom tumor not detected in previous x-ray studies. After depletion therapy another follow-up x-ray was performed showing a round well-established image. A chest CT scan was requested that confirmed the presence of a partially thrombosed pseudoaneurysm of the pulmonary artery.

The case was discussed with the cath lab and the embolization of the pseudoaneurysm was decided in June 20, 2018. Using the right femoral access, a 5-Fr JR 4 diagnostic catheter was advanced towards the right pulmonary artery. Then, the catheter was changed over a 0035" guidewire with a MP 4-Fr catheter to perform

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Figure 1. Pulmonary artery pseudoaneurysm as seen on the arteriography.

the selective arteriography of the medial basal segmental branch of the right pulmonary artery. After confirming the diagnosis of ruptured pseudoaneurysm we managed to keep the selective catheterization of the nourishing branch in order to embolize it through the same catheter using two AZUR 0035 4.0/7 mm metallic detachable coils. The patient did not experience any complications during the intervention, and she remained cardiologically asymptomatic until she was discharged from hospital on June 29, 2018 (figure 1 and figure 2).

This patient, after mitral valve replacement and tricuspid annuloplasty, incidentally showed a right basal nodular image and was diagnosed with a iatrogenic pseudoaneurysm in her pulmonary artery as the first possibility and probably in relation to the Swan-Ganz catheter. The catheter insertion was difficult during the entire perioperative period. We did not include chest x-rays because of the poor quality of those performed during surgery and the Swan-Ganz catheter positioning was not clearly shown.

The use of Swan-Ganz catheters is a common practice for hemodynamic monitorization purposes in patients undergoing surgery. The pulmonary artery laceration with hemorrhage and the formation of pseudoaneurysms are among the complications associated with the use of these catheters. It is a rare complication with an incidence rate between 0.001% and 0.5% but it is one of the most life-threatening situations with a mortality rate of up to 50%.¹ In some cases, the initial tear is asymptomatic to later be found incidentally on a chest x-ray. However, a pseudoaneurysm can appear after a few days causing another tear. The rate of pseudoaneurysm-induced recurrent hemorrhage is around 30%-40% and mortality rate is high between 40% and 70%.² In a review of

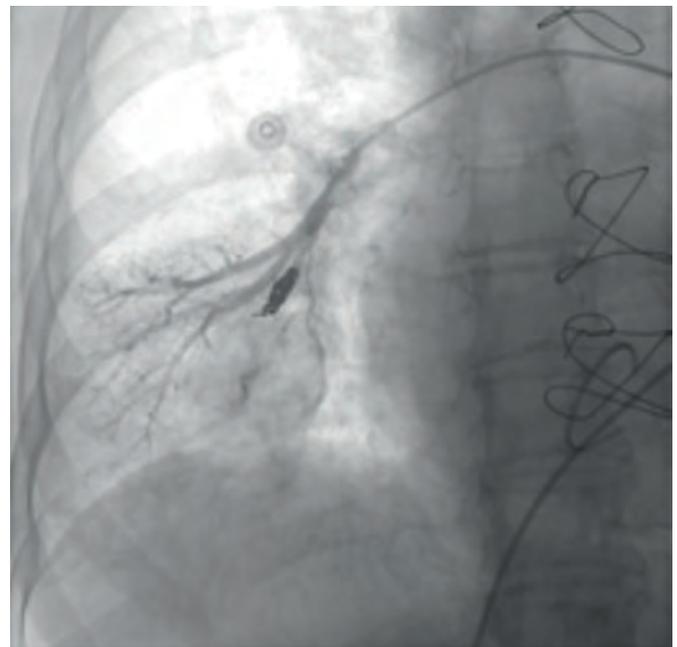


Figure 2. Arteriography after implantation of metallic coil.

28 patients with iatrogenic pulmonary artery pseudoaneurysms, all patients who underwent endovascular procedures prior to the tear of the pseudoaneurysm survived, whereas mortality rate was 100% in those whose pseudoaneurysms ruptured before treatment.³

Our patient showed many risk factors for the development of pseudoaneurysms such as pulmonary hypertension, systemic anticoagulation, age > 60-year-old, female, and cardiac manipulation during surgery. Our patient's elevated risk added to the high mortality risk involved following a tear as reported in the literature made us decide to perform an endovascular procedure (elective since it is a less invasive procedure). The surgical alternative of resecting the diseased pulmonary lobe is only indicated in cases of persistent pseudoaneurysms refractory to endovascular therapy.⁴

REFERENCES

1. Burrell M, Real MI, Barrufet M, et al. Pulmonary Artery Pseudoaneurysm after Swan-Ganz Catheter Placement: Embolization with Vascular Plugs. *J Vasc Interv Radiol.* 2010;21:577-581.
2. Ferretti GR, Thony F, Link KM, et al. False aneurysm of the pulmonary artery induced by a Swan-Ganz catheter: clinical presentation and radiologic management. *AJR Am J Roentgenol.* 1996;167:941-945.
3. DeLima LG, Wynands JE, Bourke ME, Walley VM. Catheter-induced pulmonary artery false aneurysm and rupture: case report and review. *J Cardiothorac Vasc Anesth.* 1994;8:70-75.
4. Nellaiyappan M, Omar HR, Justiz R, Sprenger C, Camporesi EM, Mangar D. Pulmonary artery pseudoaneurysm after Swan-Ganz catheterization: a case presentation and review of literature. *Eur Heart J Acute Cardiovasc Care.* 2014;3:281-288.