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REC: Interventional Cardiology. Fulfilling an unmet need

REC: Interventional Cardiology, un proyecto necesario

Armando Pérez de Prado,* Belén Cid, Oriol Rodríguez Leor, and Raúl Moreno

Junta Directiva, Sección de Hemodinámica y Cardiología Intervencionista, Sociedad Española de Cardiología



Dear colleagues,

This is one of those assignments that one willingly accepts with joy. Have the opportunity to present the birth of our most exciting project so far is an honor and a pleasure. When we joined the board of directors of the «working group» —the most commonly used term to refer to our Working Group on Hemodynamics and Interventional Cardiology (SHCI) at the Spanish Society of Cardiology— we committed ourselves to the development and implementation of this project. Yet we did not know whether we would be able to deliver the first issue before our term was over. Well, here it is. On time. And all the credit in the world should go to our unbelievable editorial team: the enthusiasm from Dr. de la Torre Hernández, MD as editor-in-chief; the determination from Dr. Alfonso, MD and Dr. Sanchis, MD, and the coordination from Iria del Río as head of the editorial team. From the very first meeting where we felt the warmth and support from both Dr. Ferreira, MD -the actual editor-in-chief of *Revista Española de Cardiología*- and the Spanish Society of Cardiology executive committee, our board of directors started working giving full back up to this project.

But why jump into the creation of an interventional cardiology journal? Although we had always discussed it in our meetings, the spark that lit the fuse was an e-mail sent by Dr. Romaguera, to several colleagues interested in research studies back in 2017. The success of *Revista Española de Cardiología* had already achieved in the first quartile in the impact factor scale among cardiology journals made it very hard for authors to actually publish. As a matter of fact, barely 10% to 20% of the original papers received are finally published meaning that over 300 original papers are rejected every year. The unanimous believe is that Spanish research is excellent: both Spanish researchers and our Latin American colleagues have a great production of excellent papers. Why then go to other journals where our language is not even a thing? After analyzing the journal feasibility, we made the decision that this would be our most important project.

The very first decisions that we made would come easy. Spanish, English, or bilingual? Bilingual. Paper or digital edition? Digital. And even though this first issue is also printed on paper, we believe that the spread of knowledge is basically digital in this day and age. Picking the editorial team, the calendar of events, the editorial committee and council, the relation we would keep with

Revista Española de Cardiología, our innovation goals, etc., were decisions we made along the way until we faced the most complex part of the project: its economic feasibility. What would the best publishing model be for our new journal? Soon we decided that it was the open access model the one we were looking for. Cost zero for both authors and readers. This would facilitate the spread of knowledge. It seemed easy at the beginning, but then we had to find the funding. And here is where we want to show our gratitude for the support we have had from all our collaborator at SHCI who, year after year, have been supporting all our training and research initiatives. In the back cover of this issue we actually thank ALL those who have contributed to make this dream a reality when we asked for help. We decided that this project would be so universal that all sponsors would need to provide specific back up to its development. And we hope they stay with us for years to come because it certainly has been a team work. Thank you very much indeed.

Well, here is your new journal: *REC: Interventional Cardiology*. The fight to become what we envisioned (a good, innovative scientific interventional cardiology journal that will be indexed in the main bibliometric indexes and have a high impact factor in the years to come) depends on one thing and one thing only: your enthusiasm. We need your help to turn what we dreamed about into a reality. The first original papers, cases, images, etc., have already been sent. It will be the editorial committee that will be requiring continuity in this scientific flow from you, meaning that this continuity actually depends on you.

From our standpoint -the SHCI board of directors- we also wish that this journal will be the communication vehicle of our working group, meeting point, communications body, and expression of opinion for our members. In these changing times when we are seeing that the model is changing in many of our activities with frequent debates and conflicts, this journal raises as the go-to tool. Time has come for interventional cardiologists to show what we are really made out of. And although others may be hesitant about what we do, we believe we can provide excellent healthcare and state-of-the-art science.

We have probably left out many names and organizations that have played and will play a key role in the birth and growth of *REC: Interventional Cardiology*. To all of you who believed in this project from day one, thank you and congratulations.

* Corresponding author:

E-mail address: aperez@secardiologia.es (A. Pérez de Prado).

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REC: Interventional Cardiology: A new journal, but not just one more journal

REC: Interventional Cardiology: una nueva revista, pero no una revista más

José M. de la Torre-Hernández,^{a,*} Fernando Alfonso,^b Juan Sanchis,^b and Raúl Moreno^b

^a Editor Jefe, REC: Interventional Cardiology

^b Editor Asociado, REC: Interventional Cardiology

Back in 1947 the first issue of *Revista Española de Cardiología* (REC) was published. And this journal has been leading the Spanish-speaking biomedical publishing field for over 70 years.^{1,2} REC has witnessed and given testimony of numerous changes in the field of cardiology – being one of these changes the tremendous growth of interventional cardiology.

Interventional cardiology revolutionized our specialty with the very first coronary angioplasty performed four decades ago. We just need to make a historical comparison of data on our hemodynamic activity data in Spain:^{3,4} in just 25 years we have gone from 42 000 studies total and 6700 angioplasties to 154 000 studies and 71 000 angioplasties, while implementing techniques not used at the time (some 7000 studies on pressure wires and 7000 studies on intracoronary imaging). But we also need to bring forward an activity that years ago was almost a formality: structural heart intervention with nearly 5000 procedures being conducted including almost 3000 percutaneous implants of the aortic valve prosthesis.

It is obvious that our activity in interventional cardiology on coronary heart disease has grown 10-fold, but we should not forget the progression that our activity in structural heart disease has had becoming more important with the passing of time.

This huge increase of indications and techniques in interventional cardiology has run parallel to the resources used in Spain, both human and material. Such an expansion has elevated the scientific production in our field in our country. This statement is easy to validate. We just need to look at the growing number of abstracts presented in national and international congresses and the numerous papers published in high impact scientific journals by interventional cardiologists. And this has been a global process that has seen the birth of various international publications («sister journals» of other general cardiology journals) specialized in interventional cardiology only. However, the strong international competitiveness and the growing requirements and demands from the most prestigious publications, make publishing hard for our researchers who only get to author a very small number of the original papers that eventually end up being published.

Given it is a monthly publication, our very own REC limits the presence of original papers in interventional cardiology to just 12-14 a year, with a rejection rate up to 75% that leaves out over 50 manuscripts each year.² These manuscripts rarely make it to

quality journals; some of them do though in journals that do not have the accuracy needed in medical publishing,^{5,6} while others, though interesting, will never see the inside of a publishing house with the corresponding frustration for the authors. This situation can move young researchers (especially the youngest ones) away from quality research, not wanting to spend their time trying to get published but providing healthcare instead.

For these reasons, back in 2017, the board of directors of the Working Group on Hemodynamics and Interventional Cardiology (SHCI) at the Spanish Society of Cardiology (SEC), decided to implement an initiative envisioned a long time ago. The creation of a high-quality scientific publication on interventional cardiology that would be born within REC. The dream has come true and it is called *REC: Interventional Cardiology*.

BILINGUAL

We believe it is essential to publish in two languages, Spanish and English. And this is so because we wish to reach not only the Spanish-speaking world -essential for us- but also, like REC, other geographical areas (we just need to look at the growing number of REC contents that come from non-Spanish-speaking countries). And even though this goal could have been achieved in English only, the Spanish language is indispensable as it is part of our DNA. Also, over 500 million speakers speak Spanish in the world, and Spanish ranks #3 as the most widely spoken language in the world today only after Mandarin Chinese and English. This makes Spanish the perfect vehicle for the widespread open exposure of science. In this sense, the commitment of *REC: Interventional Cardiology* to Latin America is unquestionable.

ONLINE

In this day and age, the only way of being published is online which basically puts the last nail on the coffin of paper publishing while reducing costs and environmental impact. Today, science is being read on tablets and smartphones and that is exactly how *REC: Interventional Cardiology* is born – as a century scientific journal of the 21st century. The advantages of online communication such as universality, immediacy, and possibility of wide interaction with the different agents involved will catapult the informative and educational potential of our journal.

* Corresponding author: REC: Interventional Cardiology, Ntra. Sra. de Guadalupe 5, 28028 Madrid, Spain.
E-mail address: rec@intervcardiol.org (J.M. de la Torre-Hernández).

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OPEN ACCESS

REC: Interventional Cardiology is an open access journal totally free of charge for authors and readers alike. Best case scenario, science should spread itself without any boundaries or restrictions. Researchers should be able to have access to all the science that is being published today, and patients, who give their time and data, deserve open access to the research they make possible. However, this publishing activity is not cost free and this open access good intention is actually very hard to achieve. It is with this intention in mind that the SHCI has created this journal and it will be the contributions from the industry that will make open access a reality for all.

A NEW JOURNAL, BUT NOT JUST ONE MORE JOURNAL

We receive e-mails on a daily basis from different publications asking for manuscripts with a pledge to accept them and offering us to join their editorial team, even become editors-in-chief. This outbreak of scientific journals has achieved epidemic proportions, but this should not draw our attention away from the fact that very few of these journals actually have wide circulation. *REC: Interventional Cardiology* is a new journal, but not just one more journal; it is backed by hundreds of members from the SHCI and by the leading journal *REC*, considered one of the best cardiology journals in the world today.

We are aware that we will have to wait when it comes to indexing and obtaining the long-awaited questioned citation metrics,⁷ and that this will limit drawing manuscripts to our journal during the first few years. However, we have the conviction that researchers in our country and other countries will have a positive response to this new and attractive editorial adventure.

Everybody in the editorial committee has been carefully selected for their capacity of commitment and active collaboration, but this committee is also open to periodic renewal; almost everybody has joined this project. Almost everybody, but still not everybody.

We will ensure the best standards in editorial quality following the double-blind peer-review process for the assessment of our papers. We know this kind of review has defects, but it is still the best way to ensure the methodological accuracy and scientific

quality of the manuscripts that will eventually be published. Our commitment is that this review is a fast quality review process, respectful with the authors, rigorous, with a reasonable level of demand, and constructive criticism for the sake of improving the paper to be.

The table of content will include original research papers, editorials, thematic reviews, clinical trials so popular among interventional cardiologists, imaging and interesting videos and, last but not least, debates on controversial issues, discussions on relevant trials and, finally, news on technological achievements. One of our goals is to make the journal a place for open scientific practical discussion among interventional cardiologists.

There is a huge team behind this project, and we wish to give special thanks to the SHCI board of directors and *REC* editorial team alike.

Without further ado, we literally want you to turn this page or rather let your mouse button click again and read and enjoy the contents of this new journal. Your journal.

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The future of interventional cardiology

El futuro de la cardiología intervencionista

Spencer B. King III*

Emory University School of Medicine, Atlanta, Georgia, United States

Before speculating on where interventional cardiology is heading to, it may be helpful to reflect on its true origin. For many of you, early or halfway through your career, interventional cardiology may seem a well-established and mature subspecialty. For you it has always been a major component within the field of cardiology. However, for those of us who were already here before interventional cardiology even existed and have witnessed its birth, childhood, and adolescence, interventional cardiology is just a moment in time. Currently, we feel pretty confident that we are treating coronary artery disease adequately with prompt interventions for the management of acute myocardial infarctions and chronic conditions with sophisticated instruments, excellent results, and satisfied patients. We also felt confident when we had balloons only. Yes, there were many failures back then, but interventional cardiology would have never flourished if it was not for optimism. I keep a video recording of our colleague and father of interventional cardiology, Andreas Gruentzig, MD, just before his untimely death. He said that balloons were the solution for many conditions, but also that we needed much more than that if we wanted to solve the obvious problems of coronary artery obstruction. The next decade would witness innovation attempts, some of them ranging from excellence to eccentricity.¹ All types of lasers to burn, seal, selectively ablate only abnormal tissue; hot-tip catheters; cold freezing instruments; cutters and scrapers; and finally scaffolds that we would call stents. Peripheral artery interventions followed a similar path. Although these came before coronary interventions, these techniques evolved slower. The ability to perform minimally invasive procedures for structural heart disease lagged behind. In the late 1980s, Alain Cribier, MD presented the idea of balloon dilatation of the aortic valve at our Emory courses.² We tried it for some time. Fifteen years later he implanted the first transcatheter aortic valve. It takes a while before ideas come to life. Back in 1990, we predicted that restenosis would be conquered by a device to hold the artery open combined with locally-delivered anti-proliferative agents. At first, we tried radiation, but cell-cycle inhibition stents eventually became the standard of care.

There were many difficulties then. Some were overcome, and some carried their own issues. What are the problems we face today, and how will they be approached in the future? The most successful coronary intervention occurs in the setting of acute myocardial infarctions. Making this technology widely available is still challenging because even though it can be done, myocardial salvage has not been completely solved. Innovations such as left ventricular support combined with reperfusion while paying special attention to microcirculation and its response to reperfusion deserve further research. We still do not know what to do with

non-culprit but narrowed coronary arteries in the setting of myocardial infarctions.

Techniques for opening chronic total occlusions and bifurcation lesions have progressed, but we still don't have dedicated devices for bifurcations, and reopening chronic total occlusions through the true lumen requires innovations that are still to come. Although percutaneous aortic valve implantation has evolved faster than any of us would have anticipated, long-term results are still awaited, and mitral and tricuspid valve replacements are still in their infancy. Peripheral endovascular therapies seem spectacular, but endo-leaks and aneurysm expansion have not been completely solved yet.

Also, the lines between disciplines are blurry. Stroke intervention is the most dramatic advance in the field. Will clot retrieval from cerebral arteries remain the scope of neurologists only? There are not enough of them, and cardiologists are entering their specialty. On the other hand, interventional cardiology will not be the sole domain of cardiologists. A recent approach to the excessive stroke rate from carotid stenting has resulted in the direct surgical exposure of the artery with stent implantation combined with reverse carotid blood flow enabled by a shunt via the femoral vein. This kind of innovations combine surgical skills and training together with catheter skills. An interdisciplinary collaboration that can be perfected in some healthcare systems. A trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) is now underway to assess the validity of a hybrid approach for the management of coronary revascularization, ie left internal mammary artery to the left anterior descending artery through minimally invasive techniques combined with drug-eluting stents for the management of other lesions.³

The problem of cardiovascular disease will not be solved with devices alone. Recognizing the progression of atherosclerosis not only in non-stented segments but also inside the stents will turn interventional cardiologists into preventive cardiologists. The dramatic breakthroughs in the management of lipids and the cardiovascular effects of new drugs for the management of diabetes means that interventional cardiologists must be competent in these fields as well, since these therapies may become the most relevant "devices" in the future. A total paradigm shift may be underway in the management of stable ischemic heart disease. Diagnosis is now moving away from ischemia detection only to non-invasive coronary imaging in the assessment of physiology and anatomy. Right now the U.S. is behind other countries when it comes to the implementation of CT angiography, but I predict

* Corresponding author: Emory St Joseph's Hospital, 5665 Peachtree Dunwoody Rd, NE, Atlanta, GA 30342, United States.
E-mail address: spencer.king@emoryhealthcare.org (S.B. King III).

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it will become the diagnostic catheterization laboratory of the future. Ad hoc percutaneous coronary interventions during invasive catheterizations may have been acceptable so far, but now with the ability to define coronary obstructions and their physiological significance non-invasively, we can better plan medical therapy, percutaneous coronary interventions, or surgery. Unlike ad hoc percutaneous revascularizations during invasive catheterizations, this will allow true informed consents and facilitate proper diagnoses in patients who may not have agreed previously to an invasive diagnostic procedure.⁴

It will not reduce the number of interventions but it will certainly guarantee that only the correct ones are performed. A critical consideration for this subspecialty is what the training should look like in this rapidly changing field. Not everyone will be an expert in every aspect, which is why training and continuing medical education will create the expertise required.

The future is always unpredictable but if the past teaches us anything is that the field of interventional cardiology has a challenging and rewarding future. It is a new field of expertise where there is still much to be done. The launch of this new journal will give you the opportunity to disseminate new knowledge that will shape the future. As my term as editor of *JACC: Cardiovascular Interventions* was coming to an end I wrote an editorial that was published both in our journal and *EuroIntervention*.⁵ I called it "The golden age of publishing in interventional cardiology". Well, that age has not passed yet. I believe that the ability to publish good papers in quality journals has stimulated young investigators to do what needs to be done. This journal will be unique because

it will be published in both English and Spanish. I hope that those who feel more comfortable using Spanish will be stimulated not only to read about the advances made on interventional cardiology, but also to contribute to its progress with more publications of their own research. This journal should be popular not only in Spain but throughout the Spanish-speaking countries in the Americas. Congratulations and best wishes to the editors of *REC: Interventional Cardiology* for this important contribution to our field.

CONFLICTS OF INTEREST

None declared.

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A newborn journal of interventional cardiology. Where are we going? A dialogue between generations



A propósito de la nueva REC: Interventional Cardiology. ¿Hacia dónde vamos? Un diálogo entre generaciones

Rodrigo Modolo^{a,b} and Patrick W. Serruys^{c,*}

^a Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

^b Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

^c Department of Cardiology, Imperial College of London, London, United Kingdom

Instead of writing a conventional editorial I have tried to respond to the question of Dr Fernando Alfonso, Associate Editor of *REC: Interventional Cardiology*: "where are we going?" by letting myself be interviewed by a senior interventional cardiologist from South America, Dr Rodrigo Modolo, who is currently writing his PhD thesis in Rotterdam.

QUESTION: Professor, do we need another interventional cardiology journal?

ANSWER: Rodrigo, in the United States we have, ranked by their impact factors, 3 influential interventional cardiology journals: *JACC: Cardiovascular Interventions*, *Circulation: Cardiovascular Interventions*, and *Catheterization and Cardiovascular Interventions*.

In Europe, *EuroIntervention* is the journal of the EAPCI (European Association of Percutaneous Intervention). But we have a tendency to forget that the language of the South American continent is Spanish (...and Portuguese, as Dr Modolo reminded me), and the Spanish language represents one of the 3 most widely spoken languages in the world.

Revista Española de Cardiología currently has a major impact factor and faces the challenge of creating a new subspecialty journal, *REC: Interventional Cardiology*. It is a challenging decision but also a great opportunity.

Q.: Do you think that interventional cardiology has reached its peak maturity?

A.: Interventional cardiology has reached the peak of its 40 years of existence and it is difficult to predict the future. The advent and adoption of balloon angioplasty with an initial success rate of 80% to 85% and a restenosis rate of 30% will not happen again, nowadays. Bare-metal stents and drug-eluting stents were and are successful stories, but, purely as examples, directional atherectomy and laser for the treatment of coronary artery disease did not survive rigorous randomized controlled trials.^{1,2}

Q.: Prof. following Andreas Grüntzig, has there been in your view another major pioneer in the field?

A.: After Andreas Grüntzig, the second great pioneer was Alain Cribier, who has revolutionized the field of valvular treatment.

Over the last decade, interventional cardiologists have systematically "copied the technical approach, tips and tricks of the surgeons" (eg, the Alfieri edge-to-edge clip technique for mitral repair)—and will keep doing so (figure 1).³ The 20th and the early 21st century have been and will be the centuries of implantable devices (starting with the pacemaker implanted by Åke Senning, a surgeon and pioneer). Today, "drugs and surgeon" seem to be being supplanted by permanently implanted devices, due to their benefits, cost-effectiveness, and other advantages.

However, we have attempted and we keep trying to replace permanent metallic implants by a bioresorbable template to facilitate a vascular or valvular restoration therapy with cellular colonization of the template. So far we have not convinced the interventional community.^{4,5} But a first attempt with a novelty in interventional cardiology is frequently imperfect, facing new enemies and sometimes it is doomed to disappear.

Q.: Fernando Alfonso asked you the question: "where are we going?" Could you provide him with your personal response?

A.: How could I possibly answer the question? I will try, but let me tell you that the history of interventional cardiology has so far been unpredictable and intimately related to the history of medicine, biology, physics, and other disciplines.

Q.: Why does interventional cardiology have to be related and connected to the world of molecular biology, biomechanics, epidemiology, physics, etc?

A.: Let me answer your question by telling you my recent perception of progress in medicine at a meeting in December 2018, at the Cardiovascular Symposium of Valentín Fuster in New York. In the last session I was a speaker, sandwiched between 2 giants in medicine: Eugene Braunwald and Alain Carpentier, the surgeon who revolutionized the treatment of the mitral valve. It gave me the opportunity to dialogue with the generation that preceded my generation and to ask them (it's my turn) the question "where are we going?"

Dr Braunwald gave a very clear and succinct answer. Number 1, the use of genomics for the early detection and prevention of disease will fully emerge in the next decades. Number 2, the predominance of noninvasive imaging (multislice computed

* Corresponding author: Erasmus University Medical Center, P.O. Box 2125, 3000 CC Rotterdam, The Netherlands.

E-mail address: patrick.w.j.c.serruys@gmail.com (P.W. Serruys).

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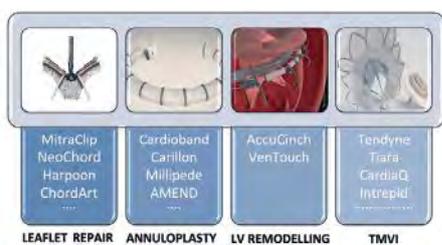


Figure 1. Different approaches for mitral valve interventions. Reprinted from Taramasso et. al.,³ with permission from Europa Digital & Publishing. LV, left ventricular; TMVI, transmitral valve implantation.

tomography scans, positron emission tomography, magnetic resonance imaging, and a combination of these imaging techniques) will be predominant and replace conventional diagnostic cinefluoroscopy as well as many other diagnostic tests. In our weekly research discussion and as a joke, the fellows and myself frequently evoke the “Imagomics” era (a combination of imaging and genomics). Number 3, the discovery of new biomolecules and physiological principles such as PCSK9 blockers (not only monoclonal antibodies against PCSK9 but microRNA inhibitors of PCSK9 production) and others such as iSGLT2, which inhibits sodium-glucose pump reabsorption in the kidney while differently affecting the afferent and efferent vessel of the kidney glomeruli, a drug that might have major effects not only on diabetes, but also on heart failure and proteinuria. With child-like enthusiasm Dr Braunwald described that drug as the “statin of heart failure”.

When he was asked about the relationship with percutaneous intervention his response was swift. The Fourier study on monoclonal antibodies against PCSK9 has already demonstrated a 22% reduction in coronary interventions, warning us, interventional cardiologists, that a drastic change in the treatment of stable angina may be on the horizon in the next decade.⁶

Early detection by genomics of coronary artery disease risk factors, early demonstration by noninvasive imaging of the subclinical phenotype of the disease and early treatment by biannual injection of microRNA to block the production of PCSK may potentially “eradicate” the disease as predicted by the 2 Nobel prize laureates for their discovery of low-density lipoprotein receptors, Michael Stuart Brown and Joseph L. Goldstein in 1985 in their inaugural lecture in Stockholm.⁷ He added that so far there is no real device treatment for heart failure, a complex multifactorial disease, although resynchronization and mechanical bipartition of the dyskinetic aneurysmal left ventricle are partially successful.⁸

Table 1. Primary outcomes of recent stent trials

Trial	Follow-up	Tested device	Number of patients	Target vessel failure	Comparator	Number of patients	Target vessel failure	Primary result
BIONYX	1 year	Ultrathin-BP-SES (Orsiro)	1243	4.5%	Thin-DP-ZES (Resolute Onyx)	1245	4.7%	Noninferiority met
TARGET	1 year	Thin-BP-SES (FIREHAWK)	823	6.1%	Thin-DP-EES (Xience)	830	5.9%	Noninferiority met
TALENT	1 year	Ultrathin-BP-SES (Supraflex)	720	4.9%	Thin-DP-EES (Xience)	715	5.3%	Noninferiority met
ReCre8	1 year	Thin-PolymerFree-SES (Cre8)	747	6.2%*	Thin-DP-ZES (Resolute Integrity)	744	5.6%*	Noninferiority met

* Refers to target lesion failure as the primary outcome.

As far as diabetes is concerned, a late key opinion leader in interventional cardiology did benefit from an implanted insulin micro-pump but beyond that device there is no specific device for the “causal” treatment of diabetes (such as renal denervation) and we still have to depend on pancreas transplantation.⁹

For his part, Alain Carpentier has for many years been focusing on the intrathoracic artificial heart as a final mechanical treatment of heart failure. His artificial heart CARMAT (Carpentier and Matra Company) is a marvel of technology, and has been implanted in 14 patients. These 2 giants, Braunwald and Carpentier, have obviously opposite but complementary views on the topic of heart failure.

Valentín Fuster, our host at this meeting in New York, relies strongly on primordial prevention (prevention in children between 3 and 5 years), primary and secondary prevention in an attempt to alleviate the burden of coronary artery disease in the decade to come.¹⁰ More modestly, at that meeting I reviewed our work on tailor-made decision-making between percutaneous coronary intervention and coronary artery bypass graft based solely on non-invasive imaging.¹¹⁻¹⁴ Clearly one of my predictions is the disappearance of diagnostic cinefluoroscopy from conventional catheterization laboratories, which in future will have to be used exclusively in an interventional suite.¹¹⁻¹⁴

After SYNTAX III, the Revolution CABG trial—on the verge of starting—on the planning and execution of surgery without prior cineangiography, thus guided solely by multislice computed tomography, will be an important first-in-man trial and a proof-of-concept.

Q.: Then, what about the “unpredictability” of the evolution of interventional cardiology?

A.: Dr Modolo, let me illustrate that unpredictability by the following anecdotes. In 1974, in Frankfurt, at a meeting organized by Paul Lichten and as a young catheterization laboratory physician, I went to see the poster of a young radiologist called Andreas Grüntzig. Honestly I could not anticipate that his technique, called percutaneous transluminal balloon angioplasty, applied on a dog’s left anterior descending coronary artery ligated by a piece of catgut, would ever mark the beginning of a new clinical era just 1 year later.¹⁵

In 1986 when I tried to follow and to apply the pioneering endeavor of Jacques Puel and Ulrich Sigwart with the Wallstent, I could not anticipate that I would report in the New England Journal of Medicine in 1991 a rate of acute or chronic occlusion above 20%!¹⁶

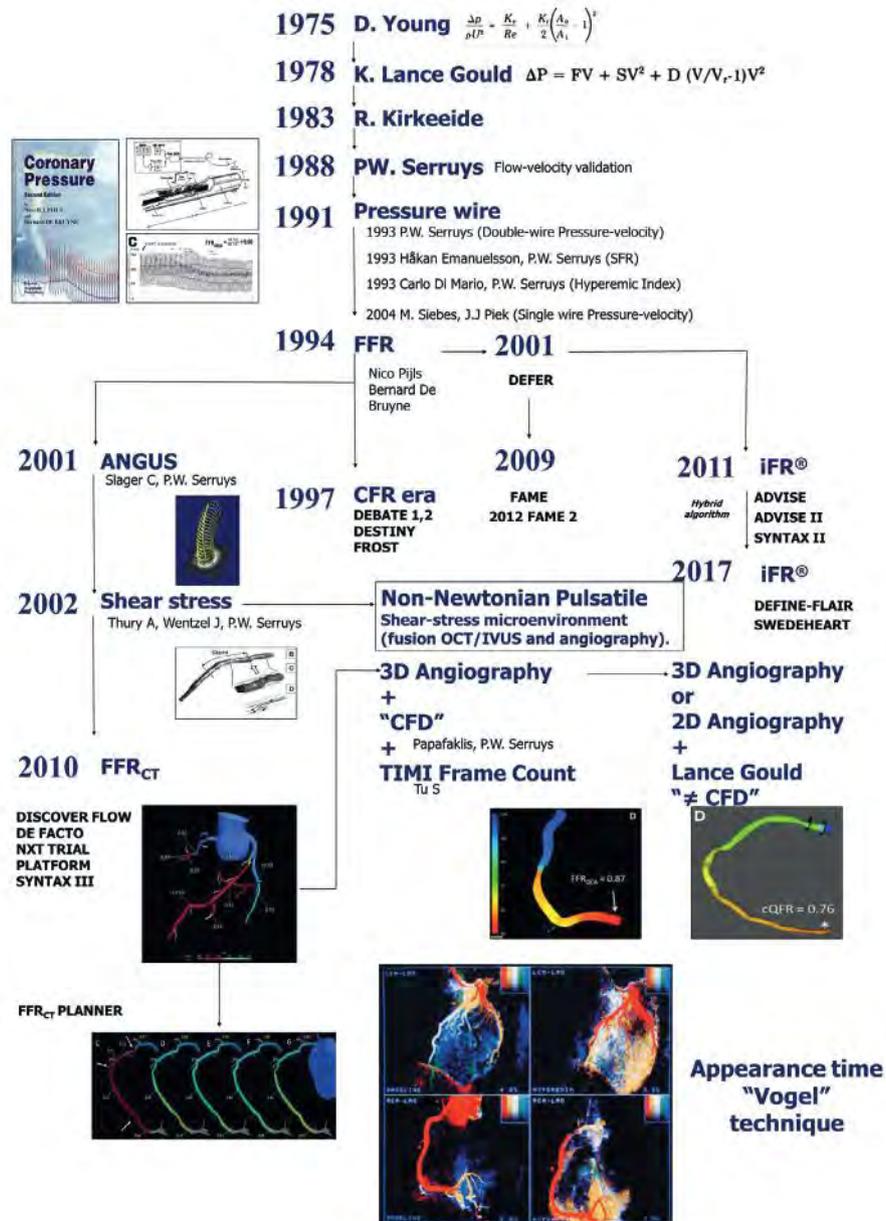


Figure 2. Introduction and evolution of coronary physiology in the clinical laboratory. CFD, computational flow dynamics; FFR_{CT}, fractional flow reserve in cardiac tomography; SFR, stenotic flow reserve.

It took me 3 years to recover from this disastrous publication; in 1994 in the New England Journal of Medicine the results of the Benestent trial¹⁷ with the balloon expandable Palmaz-Schatz were embraced swiftly by the interventional community.

I must admit that in 1999 I immediately saw the tremendous potential of rapamycin (sirolimus drug-eluting stent) when I was exposed to the experimental animal work of Robert Falotico at the headquarters of Cordis in New Jersey.¹⁸

In 2002, I implemented a policy of unrestricted use of drug-eluting stents fiercely criticized at that time, but today fully endorsed by the interventional community.¹⁹

In 2004, Alain Cribier helped me to perform our first antegrade valve replacement at the ThoraxCenter; but it took me another year to start the CoreValve program in collaboration and competition

with Eberhard Grube. In both institutions, initial cases were performed either with extracorporeal membrane oxygenation or TandemHearts. These historical anecdotes show that I was not and am still not a visionary pioneer but just a fast adopter, and that the future of interventional cardiology is quite unpredictable; Rodrigo, as another example, the surge, demise and the rebirth of renal denervation. So, do not ask me to be precise in futuristic prediction.

Q.: Thus you will not answer the question of Dr. Alfonso, where are we going?

A.: I will try to answer this question but the prediction would have to be checked over the next decade.

This decade is ending with a "war on stents". All the clinical outcomes of the novel stents are in the range of 5% for target vessel failure (table 1), but 1 patient in 5 has residual angina.²⁰

That has to be elucidated by sophisticated physiology that has to identify the epicardial stenotic lesion to be treated, for significant physiological reasons, the epicardial angiographic stenosis that should not be treated, and the presence of diseased microcirculation.²¹ We will have to resolve the concordance and discordance between fractional flow reserve and coronary flow reserve and find a biological treatment for the microvascular disease. Noninvasive imaging is also emerging to make the triage between the lesion that needs to be treated and those that have to be left alone (figure 2).

In figure 2 I summarize the introduction and the evolution, which I have witnessed, of physiology in the clinical lab starting with the Young equation in 1975 and ending up with the quantitative flow ratio. I would not be surprised if I see a return of the so called "Vogel technique",²² which combines the appearance time of the contrast medium in the epicardial vessel during conventional angiography and the videodensitometric assessment of the myocardial blush to assess the coronary flow reserve from cineangiography. Combined with the quantitative flow ratio, it may again become an appealing technology not requiring the use of the pressure wire, and providing the clinician with fractional flow reserve and coronary flow reserve simultaneously.

It is superfluous to describe the extraordinary explosion of structural heart treatment. Just to put history and prediction into perspective, in a keynote lecture at EuroPCR in May of 2007, I reviewed the outcomes of 677 patients with aortic stenosis treated worldwide with transcatheter aortic valve implantation. At that time, the ThoraxCenter had treated 61 patients (nearly 10% of the worldwide population with transcatheter aortic valve implantation!). Today, all 4 valves (with stenosis or regurgitation) have been treated and hundreds of thousands of patients have been treated. I have already mentioned in this interview the concept of restorative therapy aiming to replace the animal bioprosthesis fixed in glutaraldehyde. Certainly another decade will be necessary to achieve that goal. Alain Carpentier wants to put an end to the "cannibal activity" of heart transplantation.

Q.: Will interventional cardiology expand in other noncardiologic fields?

A.: In the next decade, the field of ischemic stroke treatment will have to be conquered more aggressively and become a successful story like "stent for life". As pointed out by Petr Widimsky in a recent editorial in *EuroIntervention*,²³ the bar for training in neurointervention for interventional cardiologists has maybe been set too high by neurointerventionists in their attempt to collaborate with interventional cardiologists. Fusion of specialized knowledge -neurointervention- and long battlefield practice of interventional cardiologists in revascularization of myocardial infarction has to be accomplished in the next decade.

Artificial intelligence, learning machines, and big data are today common in our scientific discussions. However my personal experience is that you need a specific target. With Imperial College, we are currently focusing on a fully automatic anatomic SYNTAX score derived from multislice computed tomography (segmentation, tortuosity, length of lesion, identification of long diffuse lesion, metric evaluation of calcium... all can be mastered by the so called artificial intelligence) (figure 3).

Finally, big data has become a reality. Just a few weeks ago on all European TV screens we saw the first results obtained from 8 million data collected on implants, thereby detecting unusual and rare complications otherwise not reported by industries or physicians.

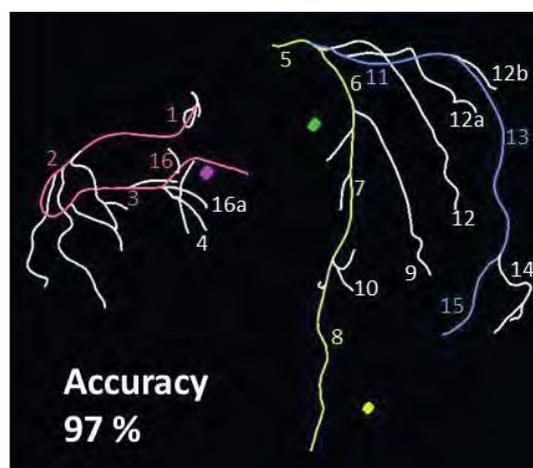


Figure 3. Automatic segmentation of the coronary tree derived from multislice computed tomography showing an accuracy of 97%.

Finally, 2 very important clinical fields, as I mentioned earlier, diabetes and heart failure remain outside and beyond our device approach (so far...). In the previous decade, there was the tremendous hope that myogenesis would be a fast solution to this endemic cardiovascular entity.²⁴ Bipartition of the dyskinetic aneurysmatic ventricle is only a very specific approach, close to a niche, and on the horizon there is at this point of time nothing very promising. Basic science will have to make major discoveries before we, interventional cardiologists, get seriously involved in the field of myocardial repair. But as usual we will be surprised by the ingeniousness of the human mind. To end on an optimistic note, renal denervation almost died a few years ago as a consequence of rigorously controlled trials with sham,^{25,26} but this year there was clearly a rebirth or renaissance of renal denervation with 2 new positive trials using a sham arm as a comparator.^{27,28}

In the next decade, the wealth of knowledge stemming from the use of genomics, big data, and artificial intelligence will deeply affect our lives as human beings, physicians, and interventional cardiologists. More than ever, the new journal will have to guide us through the enormous flow of information.

CONFLICTS OF INTEREST

The authors declare no conflict of interest for the present editorial.

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Present and future of medical journals

Presente y futuro de las publicaciones médicas

Borja Ibáñez^{a,b,c,*} and Josep Rodés-Cabau^d

^a Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

^b Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz, Madrid, Spain

^c CIBER de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

^d Department of Cardiology, Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada



Access to medical literature has seen dramatic changes over the last few years. In less than two decades it has gone from a paper-based system to an online digital sending system. The advances made on computing and, above all, the Internet has revolutionized not only the way manuscripts are sent, but also how fast these get to the public (including reference manager software adaptable to the different format of various journals). This revolution has also touched the way information is being accessed these days. The databases generated at the beginning of the 21st century are «prehistoric» compared to the ones we use today. The digitalization of clinical histories and the creation of software for data mining purposes have accelerated exponentially the preparation and analysis of the data included in the studies. Even researchers have a much more transversal training and it is common to see research teams that are savvy in statistics and that facilitate data analysis. However, all these important changes are nothing compared to the actual access to general medical information. Even though access to medical literature is not actually open (something we will refer to later), access to a great deal of information is just huge. And all this has resulted in an exponential increase in the amount of papers that scientific journals receive on a monthly basis. Also, this is accentuated by the growing productivity of emerging countries or powers, such as China, that has noticeably multiplied the number of scientific papers published over the last few years. As an example, one of the leading journals in the field of cardiovascular disease, the Journal of the American College of Cardiology (JACC), received some 4000 manuscripts every year (3200 original papers/reviews) in a five-year span of time ever since the Spaniard Valentín Fuster took over as editor-in-chief back in 2014. Due to the acceleration in the generation of knowledge and how technical different subspecialties have become, the audience of cardiology journals is particularly interested in certain areas. The large volume and ongoing specialization of the manuscripts being sent to journals, added to the limited number of monthly publications lead to reduced success rates, since quality interesting papers for the cardiological community end up being rejected. Following the JACC example, the acceptance rate of original papers/reviews in the aforementioned span of time was barely 9%. These circumstances have resulted in the creation of sister journals of major journals such as those specialized in interventionism, imaging, heart failure, or arrhythmias, among others. It is expected that this increase in the number of manuscripts submitted to journals will go on and with it, the number of cardiology and subspecialty journals. This growth not only does not dilute the relevance of

these journals, but it also promotes medical science while increasing access to knowledge and how this knowledge is spread. A common practice of high-impact journals for high-quality papers that are considered highly specialized is to offer the authors the re-submission of the manuscript to sister journals. In the aforementioned years, around 4% of the original papers/reviews published by the JACC were re-submitted and ultimately accepted by JACC: Cardiovascular Interventions. This practice accelerates the process of publication and guides authors on the possible interest of the journal at hand.

It is a paradox that, with all the digitalization we have seen so far, the main scientific journals, particularly the cardiology ones, still have the classic format of a paper journal with a limited number of papers being published each year. We believe that the actual global tendency will put this format to rest any time soon. It was with this idea in mind that the digital format open access journals were born. But yet despite its appeal, its impact is nowhere close to that of classical journals, which opens the debate on what readers and authors of journal manuscripts are really looking for. In a general sense, readers want to have access to information to know about the advances being made and be briefed on a particular theme. On many occasions, the reader cannot evaluate whether the studies published have been done correctly, or whether the existing literature on a particular issue has been reviewed appropriately. That is why the reader is in a quest for «leading» journals with a quality seal that will guarantee that the material being published has passed all the filters and has, therefore, been appropriately arranged and exposed for the public. In this sense, the role of editors is just essential since, in a way, they bring their own imprint to the journal. There are several quality seals for the assessment of journals, among them, the impact factor (IF) is the most popular one to assess the impact a journal has made among its audience. The IF is an annual «official» estimate - it is the measure between the citations received during a year to the articles published in a journal over the two previous years and the number of articles published during the same period. The higher the IF the higher the quality of a journal. The IF is estimated annually by a private company (Clarivate Analytics) that establishes the ranking of journals within their field of expertise. There are other metrics for the assessment of the impact journals make (Google Scholar¹ is becoming more and more popular these days) but, as it occurs with the IF, these metrics are imperfect and do not make assessments of all the quality aspects included in a

* **Corresponding author:** Departamento de Investigación Clínica, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro 3, 28029 Madrid, Spain.

E-mail address: bibanez@cnic.es (B. Ibáñez).

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scientific journal. As the JACC editor-in-chief says in an editorial from 2017,² the IF is a curious fanciful metrics, since the presence of a highly cited paper (clinical guidelines would be the most significant example here) plays a very important role in the journal overall IF, even if the remaining papers do not draw much attention. On the other hand, the author of a paper wants to be published in a journal that will give his or her study the highest visibility possible for all the professional implications this brings to the author. Again, the IF plays a very important role when it comes to deciding what journal a paper should be sent to for evaluation purposes. Also, scientists are always looking for national and international funding for their studies, and most assessment agencies measure CVs based on the number and quality of the publications included, which is estimated by the IF and its position relative to other journals in the field. There is, therefore, some sort of vicious circle where readers and authors alike end up looking for the same journals, and it is these journals that will eventually choose, first hand, the most relevant papers, which will, in turn, guarantee good citation levels, high IFs and, eventually, the audience's interest. Although this system has been highly criticized, there are so many factors orbiting around metrics, that it is hard to imagine a future where readers and authors will abandon these parameters.

A very relevant issue for the editorial committee of a scientific journal is to know what the target audience looks like and, especially, what type of information will be transmitted to them. On this regard, journals can be purely scientific (with predominant original papers) or educational (with predominant reviews on issues of high clinical interest). Journals usually go for some sort of mixed format between the two. However, some purely educational journals have ended up having very high IFs in the field of cardiology such as *Nature Reviews Cardiology*, that back in 2017 was positioned among the top spots in its field of expertise.

Over the last few years, the Internet revolution has resulted in the creation and vertical growth of social networks that have become a significant ingredient to spread the papers that are being published in scientific journals.³ Social networks are essential when it comes to spreading research not only among scientists and doctors, but also among the general public, thus contributing to promote health. This aspect of information spread to non-medical audiences is critical and has become more and more relevant through the years. Recently created metrics such as the Almetric scores measure the impact of journals based on the activity they generate in the social media.⁴ A study conducted on the Almetric scores of the four most relevant cardiology journals revealed some interesting data:⁵ a) the Almetric scores from cardiology journals are usually very high; b) over half of the most popular papers were not original papers but editorials, points of view, clinical practice guidelines, and consensus documents; c) the papers with the highest impact based on this metric were those based on nutrition and lifestyles; and d) open access papers did not have a higher impact compared to pay per read papers.⁵

One final relevant controversial issue is the cost associated with the publication of a paper and the access to this paper. Several journals -certainly those with the highest IFs of all- usually sign

exclusivity deals with major publishing houses that will be formatting, publishing, and editing the papers. In order to have access to complete papers, universities, research centers and even individual professionals pay a subscription fee. This pay per read system certainly limits the spread of knowledge. Several authors decide to pay a fee when their paper has been accepted by a journal so that it is open access, and anybody can have access to it without having to pay a subscription. This fee -usually between 2500€ and 4500€- is already included in the public funding received by the authors. The journals send the manuscript to external unpaid reviewers who are only moved by responsibility and altruism. Therefore, we face a complex situation where the creator of the paper -the author-, the evaluator -the external reviewer and, on many occasions, the editorial committee- and the end user -the reader- pay for the journal in such a way that the economic benefits only go to the distributor of the material -the publishing house- that has only participated in the editing and distribution stages. The fact that studies conducted with public funds are not open access and, therefore, cannot be read by the community and the public, is highly questionable. That is why in some European countries like Sweden they have decided to cancel all subscriptions with big publishing houses in an attempt to push forward the open access to science.⁶

In sum, at the present time, medical journals are undergoing major changes, mainly due to the advance of the Internet and the social media. The future of this road is hard to predict but it seems that journals will end up being completely digital and will go open access for the readers, and with quality seals different than the classical IFs. Due to the huge amount of information available, the creation of subspecialty journals is a tendency that will become more and more popular in order to update professionals on their specific fields of expertise. *REC: Interventional Cardiology* already possesses many of these future traits. For this reason, we strongly believe the future looks bright ahead thanks to its excellent editorial team and parenting from *Revista Española de Cardiología*.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest whatsoever.

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Quantitative flow ratio in myocardial infarction for the evaluation of non-infarct-related arteries. The QIMERA pilot study



Carlos Cortés,^{a,b} Tania Rodríguez-Gabella,^a Hipólito Gutiérrez,^{a,c} Roman Arnold,^{a,b,c} Ana María Serrador,^{a,b} Benigno Ramos,^a Pablo Catalá,^a Álvaro Aparisi,^a Williams Hinojosa,^a Itziar Gómez,^a Manuel Carrasco Moraleja,^a Juan Luis Gutiérrez-Chico,^d José A. San Román,^{a,c} and Ignacio J. Amat-Santos^{a,b,c,*}

^a Departamento de Cardiología, Hospital Clínico Universitario, Valladolid, Spain

^b Servicio de Cardiología, Instituto de Ciencias del Corazón, ICICORELAB, Hospital Clínico Universitario, Valladolid, Spain

^c Departamento de Cardiología, Hospital Clínico Universitario, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Valladolid, Spain

^d Departamento de Cardiología, Hospital Punta de Europa, Algeciras, Cádiz, Spain

ABSTRACT

Introduction and objectives: Complete revascularization is recommended for the management of ST-segment elevation myocardial infarctions (STEMI). Although physiological evaluation is recommended for the assessment of nonculprit lesions, in this context, the use of fractional flow reserve (FFR) is limited. The quantitative flow ratio (QFR) is a new angiography-based tool for the assessment of functional severity. We evaluated the functional changes occurring in nonculprit lesions after the acute phase and the QFR/FFR correlation in non-infarct-related arteries.

Methods: We recruited all patients with multivessel disease admitted to our institution due to STEMI from January 2016 through December 2017 who underwent staged interventions for the management of nonculprit lesions. We conducted a retrospective QFR assessment at both the index and the staged procedures and drew a comparison. Also, the QFR/FFR concordance and agreement were prospectively evaluated between January and May 2018 in a cohort of patients with STEMI and multivessel disease.

Results: We analyzed a total of 131 lesions in 88 patients. During the initial procedure, 93.1% of the lesions were considered significant based on the angiography compared to only 56.3% studied through QFR ($P \leq .001$). The QFR reassessment during the staged intervention brought this percentage down to 32.1%. All patients with QFR values ≥ 0.82 during the index procedure remained nonsignificant at the staged assessment. Both the FFR and the QFR were compared in 12 patients showing good agreement and a mean difference of 0.015 ± 0.02 ($P > .1$).

Conclusions: The QFR-based physiological assessment of nonculprit lesions in STEMI patients led us to consider nonsignificant 40% of the lesions classified as significant by the angiography. Also, the QFR significantly increased from the acute phase to the staged procedure, indicative that in patients with QFR ≥ 0.82 in the acute phase a new coronary angiography procedure may be unnecessary.

Keywords: Fractional flow reserve. Quantitative flow ratio. Non-infarct-related artery. STEMI.

Quantitative flow ratio en infarto de miocardio para la evaluación de lesiones en arterias no culpables. Estudio piloto QIMERA

RESUMEN

Introducción y objetivos: En pacientes con infarto agudo de miocardio con elevación del segmento ST y enfermedad multivascular se recomienda la revascularización completa. La evaluación funcional con reserva fraccional de flujo (RFF) de las arterias no culpables del infarto es limitada. El *quantitative flow ratio* (QFR) es una herramienta basada en la angiografía para valorar la gravedad funcional de las lesiones. Se analizaron la evolución funcional de las arterias no culpables del infarto tras la fase aguda y la correlación QFR/RFF en este contexto.

Métodos: Se incluyeron pacientes ingresados con infarto agudo de miocardio con elevación del segmento ST entre enero de 2016 y diciembre de 2017, con enfermedad multivascular y revascularización diferida de lesiones no culpables. Se evaluaron retrospectivamente con QFR durante el procedimiento índice y el diferido, y se evaluó la concordancia QFR/RFF de manera prospectiva entre enero y mayo de 2018.

Resultados: Se incluyeron 131 lesiones de 88 pacientes. Durante el procedimiento índice, el 93,1% de las lesiones se consideraron significativas de acuerdo con la angiografía, pero solo el 56,3% cuando se evaluaron con QFR ($p < 0,001$). El QFR del

* **Corresponding author:** Instituto de Ciencias del Corazón, Hospital Clínico Universitario, Ramón y Cajal 3, 47005 Valladolid, Spain.

E-mail address: ijamat@gmail.com (I.J. Amat-Santos).

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procedimiento diferido demostró una mayor reducción, con solo el 32,1% de las lesiones significativas. Todos los pacientes con $QFR \geq 0,82$ durante el procedimiento índice continuaron con estenosis no significativas en la evaluación diferida. La comparación del QFR y la RFF en este contexto demostró buen acuerdo, con una diferencia media de $0,015 \pm 0,02$ ($p > 0,1$).

Conclusiones: La evaluación fisiológica mediante QFR de las lesiones en arterias no culpables del infarto descartó la significación en el 40% de las consideradas significativas por angiografía. El valor de QFR se incrementó significativamente del procedimiento índice al diferido, lo que sugiere que en pacientes con $QFR \geq 0,82$ en la fase aguda podrían evitarse procedimientos diferidos innecesarios.

Palabras clave: Reserva fraccional de flujo. *Quantitative flow ratio*. Arteria no culpable. IAMCEST.

Abbreviations

FFR: fractional flow reserve. **IRA:** infarct-related artery. **PCI:** percutaneous coronary intervention. **QFR:** quantitative flow ratio. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Up to 50% of the patients admitted with ST-elevated acute myocardial infarction (STEMI) show multivessel disease.¹ Currently, complete revascularization is recommended before hospital discharge but the benefits of non-infarct-related artery (non-IRA) revascularization during primary percutaneous coronary interventions (PCI) or subsequent procedures is still controversial.¹ As a matter of fact, the strategy for the management of non-IRA has widely varied across landmark studies.²⁻⁴

The lack of consensus can be partially explained by the inaccuracy of angiography when assessing the severity of stenosis in non-IRA, with less than 30% to 50% of the lesions initially considered eligible for revascularization finally confirmed when assessed using the fractional flow reserve (FFR).^{3,4} In particular, the severity of non-IRA stenosis is more frequently overestimated during primary PCIs due to the hemodynamic conditions.⁵ However, also in this context, the FFR measurements are usually invalid due to altered micro and macrovascular tone or microvascular flow obstruction.^{3,6} Also, little has been said on the variability of FFR results over time in non-culprit lesions. All these factors probably explain why most interventional cardiologists still use angiography as the only tool when it comes to deciding whether or not to treat nonculprit lesions.⁷ The quantitative flow ratio (QFR) is a new tool to assess the severity of coronary stenosis based on computational fluids dynamics and the three-dimensional reconstruction of coronary angiography without a wire or the need for inducing hyperemia, which favorably correlates with FFR in stable coronary disease.⁸⁻¹⁰ On the other hand, and although good agreement between FFR and QFR has also been suggested in the acute phase of myocardial infarctions,¹¹ it is widely known that the presence of microvascular dysfunction is associated with a worse correlation.¹²

We conducted one pilot study to conduct physiological assessments of the severity of non-IRA lesions based on the QFR during primary PCIs and in staged angiographies. Also, the FFR and QFR correlation was explored in this context.

METHODS

Study design

Single-centre retrospective and observational study conducted in full compliance with the Declaration of Helsinki and after

approval from the local ethics committee. All the patients included in this research provided informed consent for the anonymous use of their clinical and imaging data with scientific purposes only.

Study population

The study included consecutive patients of ≥ 18 years of age admitted to our institution due to STEMI between January 2016 and December 2017 with $> 50\%$ diameter coronary stenosis in non-culprit arteries after angiographic assessment. A two-procedure strategy to achieve complete revascularization was decided in these patients during the index procedure. The staged procedure to treat the nonculprit lesions was conducted before hospital discharge as the standard care in this setting and according to the actual recommendations.¹ Consecutive patients with ≥ 18 years of age admitted to our institution due to STEMI between January 2018 and May 2018 with coronary stenosis after coronary angiographic assessment in non-IRA lesions were prospectively included in our study to evaluate the concordance between the QFR and the FFR. The decision to conduct FFR assessments in these patients was made at operator's discretion based on interventional and clinical criteria. The level of concordance and agreement between the FFR and the QFR were established here.

Exclusion criteria included inability to provide informed consent, lack of adequate coronary angiographic images for valid QFR analysis, presence of normal coronary arteries in the index procedure, surgical revascularization, and death or presence of other conditions precluding revascularization during the index procedure or contraindicating the staged procedure within the same admission.

Angiographic and physiological assessments

Standardized angiographic projections were performed in both procedures following the center acquisition protocol. The computation of the QFR was performed offline using specific software (QAngio XA 3D prototype, Medis Medical Imaging System, Leiden, the Netherlands). Details from the QFR assessment have been previously reported elsewhere.¹³ In short, two projections $> 25^\circ$ apart recorded at 15 frames per second were used for the three-dimensional reconstruction of the target non-IRA. The diameter stenosis, area stenosis, minimal luminal area, maximal, minimal and reference vessel diameters were estimated. The QFR values were obtained by applying computational principles of fluid

dynamics to the aforementioned software. The modeled virtual hyperemic flow velocity derived from contrast flow (contrast QFR, cQFR) without adenosine was implemented. Two independent certified software users blinded to the visual assessment of the severity of stenosis and the QFR value obtained during the first or staged procedure, respectively, conducted the offline assessment in a core laboratory.¹⁴ The inter- and intra-observer variability were examined in 20 lesions through repeated measurements conducted by both certified software users (10 lesions to determine the intra-observer variability and 10 lesions to assess the inter-observer variability).

Finally, the correlation between the FFR and the QFR values was estimated in the prospective group of patients during the index or staged procedures. The FFR measurements were performed using the Aeris device (St. Jude Medical, St. Paul, MN, United States). Maximal hyperemia was induced through the continuous IV infusion of adenosine (140- μ g/kg/min) that was maintained for 2 minutes or until symptom onset. The QFR analysis was conducted in a blind fashion with respect to the FFR values. Values ≤ 0.8 were considered significant stenosis for both the QFR and the FFR.

Statistical analysis

The qualitative variables are expressed as absolute frequencies and percentages. The quantitative ones as mean \pm standard deviation. The normal distribution of the quantitative variables was determined using the Kolmogorov-Smirnov test and Q-Q plots. Data were analyzed on a per-patient basis for the clinical characteristics and on a per-vessel basis for the quantitative coronary angiography and QFR values. The agreement between the FFR and the QFR was determined using the Bland-Altman plot method and the intraclass correlation coefficient. The paired sample t-test was used to determine the evolution of measurements between the index and the staged procedures. The receiver operating characteristic curve was analyzed to assess the capacity of the QFR at the index procedure to predict the QFR at the staged procedure. Finally, both the intra- and inter-observer variability were determined using the intraclass correlation coefficient for these measurements with repeated analysis 1-month apart in 20% of the lesions. All analyses were conducted using the statistical package SPSS, version 24.0 (Armonk, NY: IBM Corp) and R 3.4.3.

RESULTS

Study population

A total of 828 patients were admitted or transferred to our department with suspected STEMI between January 2016 and December 2017. The diagnosis was confirmed in 455 patients of which 196 (43.1%) showed multivessel disease. Among them, 31 patients (15.8%) underwent complete revascularization during the index procedure and in 165 patients (84.2%) the operation on the non-culprit lesions was postponed or never conducted. Finally, 46 patients with multivessel disease and staged procedure were excluded due to suboptimal angiographic images precluding an adequate QFR analysis during the primary (13 patients) or staged (33 patients) procedure. The study population included 88 patients with a total of 131 lesions in nonculprit arteries. The main characteristics of the overall population are shown on table 1. Most patients were males (86.4%) with inferior or anterior STEMI in 57.9% and 37.5%, respectively, and admitted due to primary PCI in 64.8% of the cases. The culprit artery Thrombolysis in Myocardial Infarction flow grade was 0-1 in 51.1%, and 4.5% were in shock. The left anterior descending artery was the most common non-IRA (50%). Following the index procedure, the staged

revascularization of 1 (56.8%), 2 (38.7%), or more arteries (4.5%) was performed during the hospital stay for an average 5 days [interquartile range, 2-6]. Successful revascularization of the IRA and complete revascularization were achieved in 100% and 76% of the patients, respectively.

Validation of QFR assessment in nonculprit lesions

The prospective assessment of the correlation between the QFR and the FFR was conducted in 12 patients (15 lesions) of the study population following the protocol described elsewhere.¹¹ The main characteristics of this validation sample were similar to those of the QFR cohort as shown on table 1. No complications followed the use of pressure wires. The mean FFR value was 0.87 ± 0.06 and the mean difference compared to the QFR was

Table 1. Baseline characteristics of patients admitted due to ST-segment elevation myocardial infarction

Variables	Retrospective sample N = 88	Prospective sample N = 12
<i>Baseline characteristics</i>		
Age (y)	67.8 \pm 11.2	70.1 \pm 9.3
Gender (male) (%)	86.4	75
Hypertension (%)	45.5	66.7
Dyslipidemia (%)	36.4	33.3
Height (cm)	167.8 \pm 8.2	164.9 \pm 7.8
Weight (kg)	79.5 \pm 10.6	78.3 \pm 8.9
Obesity (%)	29.5	33.3
Chronic kidney disease (%)	3.4	0
<i>STEMI main features</i>		
AMI Killip I (%)	85.2	100.0
AMI Killip II (%)	10.4	0
AMI Killip III (%)	0	0
AMI Killip IV (%)	4.5	0
<i>Procedural characteristics</i>		
Radial access (%)	95.3	83.3
Primary PCI (%)	64.8	100.0
Post thrombolysis routine PCI (%)	25	0
Rescue PCI (%)	10.2	0
IRA LAD (%)	40.9	50.0
IRA RCA (%)	47.8	16.7
IRA Cx (%)	11.3	33.3
TIMI grade-0 flow IRA (%)	44.3	41.7
TIMI grade-1 flow IRA (%)	6.8	25.0
TIMI grade-2 flow IRA (%)	3.4	0.0
TIMI grade-3 flow IRA (%)	45.5	33.3
Time to staged procedure (d)	5.8 \pm 3.6	N/A

Data are expressed as no. (%) or mean \pm standard deviation.

AMI, acute myocardial infarction; Cx, circumflex artery; IRA, infarct related artery; LAD, left anterior descending; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

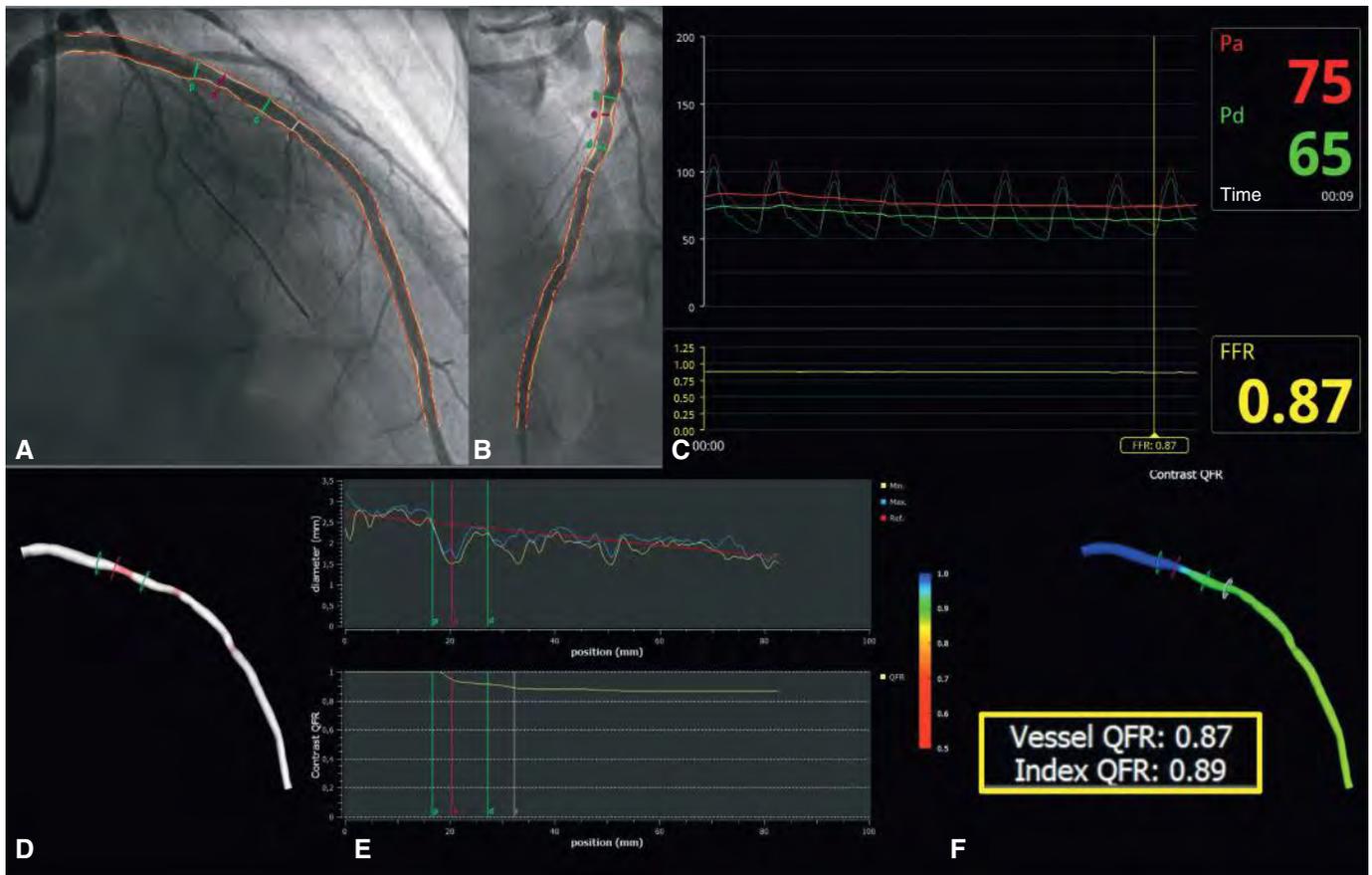


Figure 1. Representative example of agreement between the FFR and the QFR in non-IRA lesion. A: RAO, 30°; CRA, 30°; B: LAO, 40°; CRA, 20°; C: FFR; D: 3D angiographic reconstruction; E: lumen diameter and QFR pullback; F: QFR value. CRA, cranial; FFR, fractional flow reserve; IRA, infarct related artery; LAO, left anterior oblique; QFR, quantitative flow ratio; RAO, right anterior oblique.

0.017 ± 0.02 . One paradigmatic example of a lesion assessed through FFR and QFR is shown on [figure 1](#). The intraclass correlation coefficient was 0.959 [95% confidence interval, 0.882-0.986]. In 4 lesions (26.7%) the FFR was performed during the first procedure after the revascularization of the culprit lesion. No difference was found on the diagnostic accuracy of the QFR between the first and the staged procedures in this sample (relative mean difference 0.0346 ± 0.29 and 0.114 ± 0.10 , $P = .214$); The Bland Altman plot used to see the degree of agreement between these measures and the correlation according to the procedure is shown on [figure 2](#).

QFR changes across index and staged procedures

One hundred and twenty-two (93.1%) of the 131 lesions in non-culprit vessels were considered eligible for scheduled percutaneous revascularizations according to the angiography visual assessment. Among them, only 56.3% showed QFR values ≤ 0.80 in the index procedure when assessed retrospectively ([figure 3](#)). A statistically nonsignificant decrease of the QFR values was confirmed between the index and the staged procedure in patients with initial QFR values > 0.80 ; however, 2 patients with initial nonsignificant QFR values showed a drop < 0.80 in the staged angiography assessment. All patients with initial values > 0.82 showed non-significant stenosis in the second procedure. On the other hand, 45.9% of the lesions with significant QFR values were considered non-significant when assessed during the second procedure, with

larger mean diameters and stenotic areas ($P < .001$ for both) as shown on [table 2](#). The main changes seen between both procedures are shown on [figure 4](#) and one paradigmatic example is shown on [figure 5](#). The sensitivity and specificity of QFRs > 0.82 during the index procedure to predict significant stenosis (QFR < 0.80) during the staged procedure were 84% and 58.7%, respectively, with a positive predictive value of 52.5% and a negative predictive value of 87% ([figure 6](#)). The therapeutic strategy was implemented regardless of the findings from the QFR assessment since it was estimated retrospectively. This allowed us to compare the strategy based on the angiography visual assessment interpretation and posterior QFR findings leading to a total of 46 lesions treated with stents despite showing nonsignificant QFRs.

Intra- and inter-observer variability

Also, the optimal intra- and interobserver variability for measuring the QFR were confirmed by intraclass correlation coefficients of 0.958 [95% confidence interval, 0.877-0.984] and 0.991 [95% confidence interval, 0.960-0.997], respectively.

DISCUSSION

It is well known that the visual assessment of coronary stenosis usually overestimates its severity,⁵ but operators are often reluctant to conduct functional assessments of nonculprit lesions in

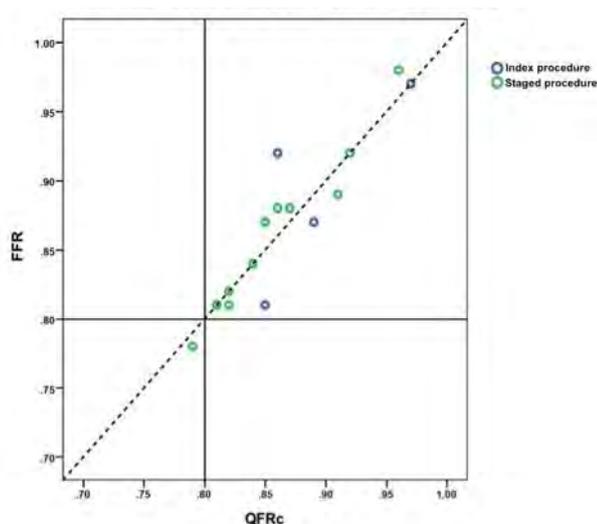
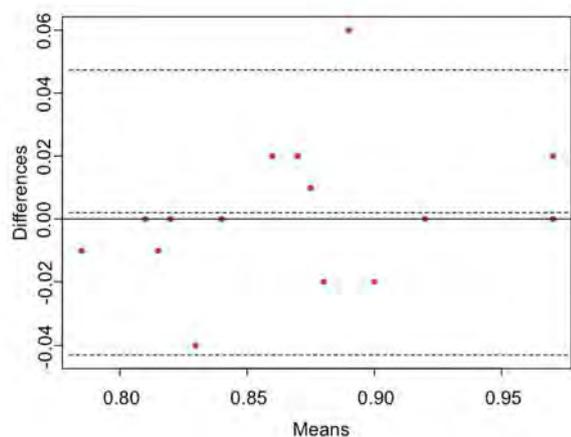


Figure 2. Correlation and agreement between the QFR and the FFR in non-IRA stenosis based on index or staged procedure. FFR, fractional flow reserve; QFR, quantitative flow ratio.

this context due to potential risks associated with the FFR and the altered physiology of this condition. The QFR value for the assessment of nonculprit lesions in STEMI patients was already investigated in a small pilot study⁸ and offers potential advantages mainly based on its quick application and no need for wiring coronary arteries or administering adenosine. The main findings of our study are: a) The QFR has a good correlation with both the FFR and the optimal intra- and inter-observer variability in trained operators in the assessment of functional severity in coronary lesions, suggestive that this may be an excellent tool also in STEMI; b) The severity of stenosis in nonculprit lesions is higher in the acute phase of STEMI, which is mainly confirmed by the angiography but also by the QFR; c) The functional assessment of nonculprit lesions through the QFR may be useful in the acute phase of STEMI. On the one hand, stenoses with QFR values > 0.82 remained nonsignificant in the follow-up in all cases, which may lead to avoiding staged procedures and stenting in up to 1/3 of these patients; on the other hand, significant QFR values during the index procedure should not lead to treating the lesion in the same intervention since, according to the QFR, 45.9% of significant lesions became nonsignificant during the staged assessment.

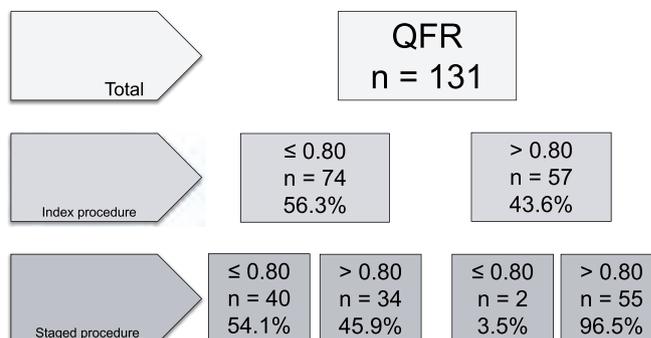


Figure 3. QFR changes across index and staged procedures in patients with angiography-confirmed significant stenosis in nonculprit vessels. QFR, quantitative flow ratio.

Table 2. Quantitative coronary angiography measures and quantitative flow ratio analysis according to procedure

Total: 131 non-IRA	Index procedure	Second procedure	<i>P</i>
Diameter stenosis (%)	58.9 ± 12.0	51.15 ± 10.6	< .001
Area stenosis (%)	70.1 ± 15.1	63.9 ± 15.1	< .001
Maximal proximal vessel diameter (mm)	2.7 ± 0.6	2.8 ± 0.6	.182
Minimal proximal vessel diameter (mm)	2.4 ± 0.5	2.5 ± 0.6	.231
Maximal distal vessel diameter (mm)	2.6 ± 0.7	2.6 ± 0.6	.850
Minimal distal vessel diameter (mm)	2.3 ± 0.6	2.3 ± 0.5	.751
Reference vessel diameter (mm)	2.5 ± 0.7	2.5 ± 0.6	.295
Minimal lumen diameter (mm)	1.0 ± 0.3	1.2 ± 0.4	< .001
Quantitative flow ratio	0.76 ± 0.14	0.82 ± 0.12	< .001

IRA, infarct related artery.

*Significant *P*-values in bold letters.

Differences in anatomical and physiological assessments

The growing evidence that places physiology above anatomy in the field of coronary disease deserves its own research when it comes to STEMI patients in order to reduce the rates of over-treatment. Overestimation when decisions are made based on angiographies⁵ and underestimation when based on FFR have been reported in this context.⁶ In the COMPARE-ACUTE trial, the physiological assessment of non-IRA was conducted during the index procedure and showed that only half of the lesions angiographically considered significant were confirmed through the FFR.³ On the contrary, in the DANAMI-3-PRIMULTI trial, the assessment of nonculprit lesions was conducted during staged procedures rising the percentage of lesions with FFR < 0.80 to almost 70%.⁴ The changes in the macrovascular tone or the obstruction of microvascular flow during the acute phase of myocardial infarctions may partially explain these findings in large trials. This difference when estimating severity between both procedures both through quantitative coronary

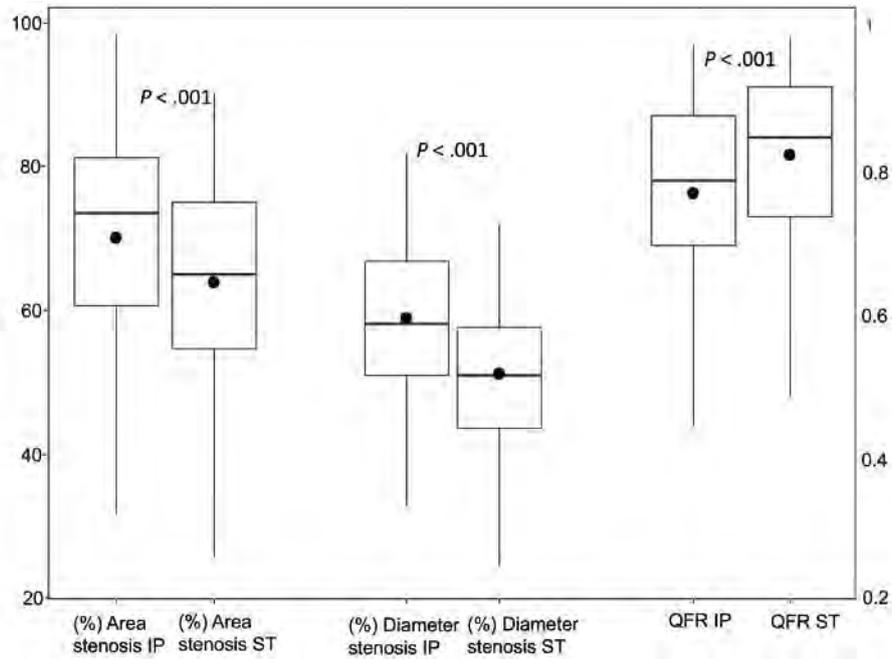


Figure 4. QFR changes in nonculprit lesions across index and staged procedures in patients with angiography-confirmed significant stenosis. IP, index procedure; QFR, quantitative flow ratio; ST, staged procedure.

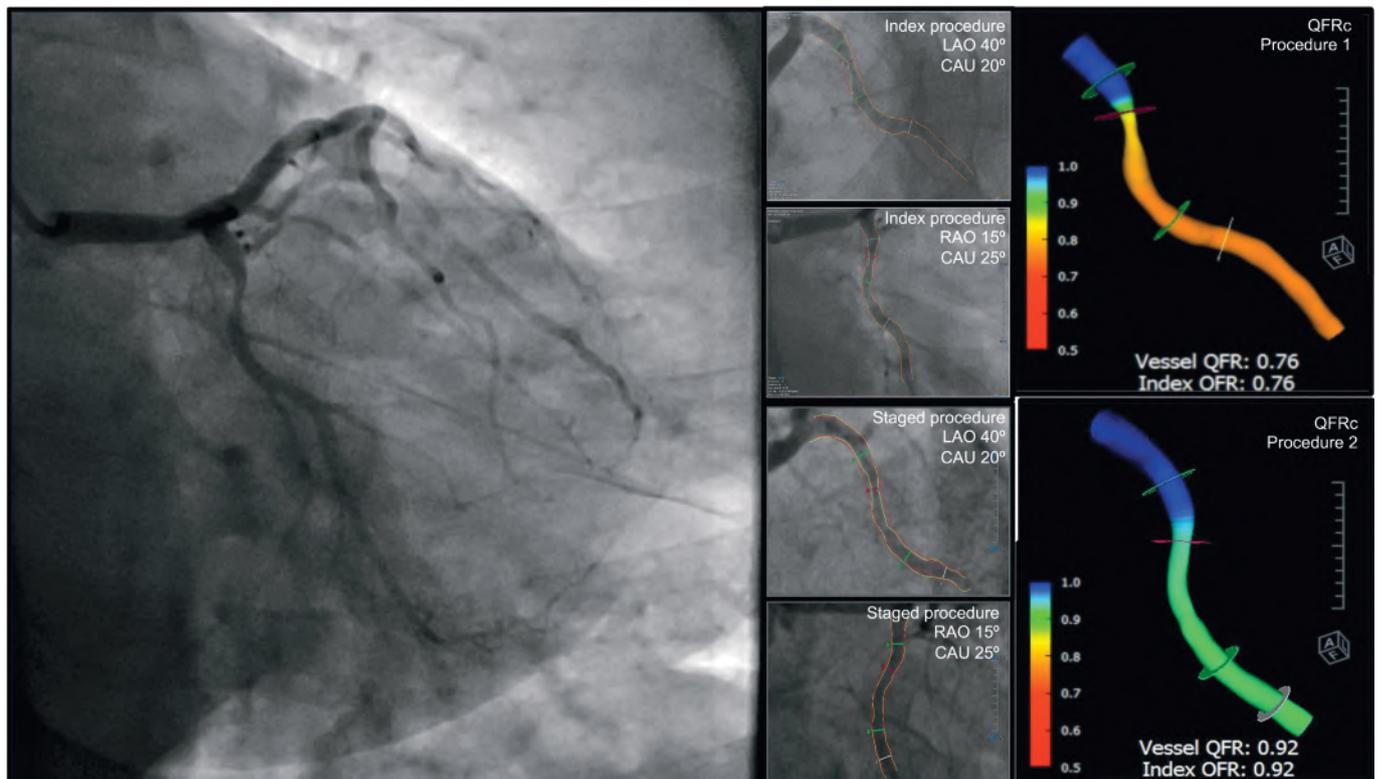


Figure 5. Changes in QFR value for the circumflex artery during index and staged procedures in one patient with inferior STEMI due to right coronary artery occlusion. QFR, quantitative flow ratio; STEMI, ST-segment elevation myocardial infarction.

angiography and QFR should be taken into consideration to avoid treating non-IRA lesions during primary PCIs. This is especially important even when only the angiographic assessment is taken into account since the need for complete revascularization is under discussion and still not recommended by the actual guidelines.

Potential new contributions of QFR in STEMI patients

The QFR can be safely conducted during primary percutaneous coronary interventions. A cut-off value of 0.82 helped to identify the patients who were not eligible for sequential revascularization. The QFR assessment in the staged procedure showed no

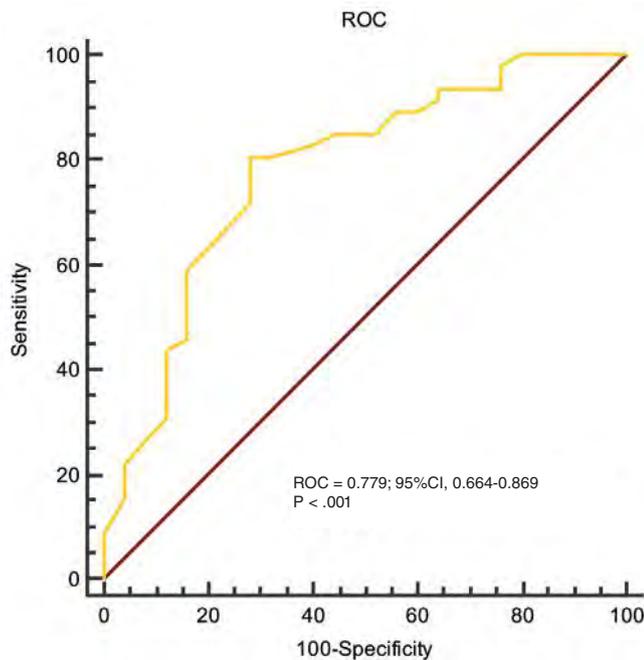


Figure 6. ROC curve analysis showing the sensitivity and specificity of $QFR > 0.82$ during the index procedure to predict significant stenosis during the staged procedure based on repeated QFR measurements. 95%CI, 95% confidence interval; QFR , quantitative flow ratio; ROC, receiver operating characteristic.

significant differences compared to the acute phase probably due to the limited sample size. However, a trend towards higher QFR values in the staged procedure—similar to that of FFR —was observed. This may be explained by the presence of microvascular dysfunction in the acute phase,¹² though the quality of coronary angiography may have had an influence here. Nevertheless, the potential of QFR in non-IRAs to identify lesions that should not be treated and, therefore, avoid unnecessary staged procedures is very interesting. From this perspective, the QFR may be that long-awaited tool to help determine what the best strategy is when making the complex decision of treating multivessel disease in STEMI patients. Ongoing studies that are putting this hypothesis to the test while assessing the need for urgent revascularization during follow-up with this new strategy will determine the clinical relevance of QFR .

Limitations

The main limitations of this study are its retrospective nature and limited sample size. The QFR assessment requires good quality from the angiographic assessment and, although a standard protocol was routinely performed for coronary angiographies, several studies had to be excluded due to their inadequate quality, which may be a bias that should be analyzed by future prospective studies. Also, the limited sample size may have associated limited power in the diagnostic accuracy of the QFR in certain subgroups of patients and in terms of validating the QFR compared to the FFR .

CONCLUSIONS

In sum, coronary functional assessments based on the QFR of non-culprit lesions after an acute myocardial infarction showed a high percentage of angiographic overestimation in the severity of stenoses ($> 40\%$). $QFRs > 0.82$ during the index procedure accurately

identified those nonculprit lesions that are no flow-limiting and nonculprit lesions and QFR values below this threshold triggered re-assessments before recommending the angioplasty procedure. The prospective validation of this hypothesis is totally justified.

FUNDING

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CONFLICTS OF INTEREST

There is no conflict of interest to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

- Over half of the patients admitted due to STEMI show multivessel disease, which is why complete revascularization is recommended.
- The functional assessment of nonculprit lesions after STEMI has proven useful when establishing the revascularization strategy to be followed; however, most interventional cardiologists base their decision on the angiography because of the challenges and limitations of FFR in this context.
- The QFR is a new functional index based on the three-dimensional reconstruction of the coronary anatomy and computational fluid dynamics while keeping a good correlation with the FFR and without having to wire the coronary arteries.

WHAT DOES THIS STUDY ADD?

- Good degree of agreement between the QFR and the FFR confirmed for nonculprit lesions in STEMI patients.
- The QFR values in the acute phase of STEMI suggested greater severity compared to deferred assessments. QFR thresholds = 0.82 in the acute phase better identified patients threshold who may not need deferred procedures for new functional assessments or angioplasties in nonculprit lesions, thus reducing risks and unnecessary costs.

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Access to side branches with a sharply angulated origin: usefulness of a specific wire for chronic occlusions

Iñigo Lozano,* Juan Rondan, José Miguel Vegas, Julio García Rubio, Sergio Santos, and Eduardo Segovia

Servicio de Cardiología, Hospital de Cabueñes, Gijón, Asturias, Spain



ABSTRACT

Introduction and objectives: Accessing sharply angulated side branches using intracoronary guidewires sometimes poses great challenges, and even after using its distal end for accessing purposes, it usually prolapses inside the main vessel. We hereby present an easy way to perform these procedures using a specific guidewire for the management of chronic total occlusions.

Methods: From January 2017 through September 2018, patients with lesions on sharply angulated side or large branches that required protection in bifurcations were approached using straight, angled tip and/or double-lumen microcatheters with regular guidewires. In cases of unsuccessful access, a specific wire designed for chronic total occlusions was used with the straight tip microcatheter after a drastic overhaul of the shape in its distal end.

Results: In 9 patients access to the side branch was not achieved with the initial strategy, in 3 patients due to access inability and in the remaining 6 due to guidewire prolapse when trying to advance the microcatheter. In all 9 cases, the access could be completed using the Gaia First guidewire that combines an excellent torque with enough rigidity to prevent the prolapse of the tip. All procedures were performed without complications.

Conclusions: The percutaneous coronary intervention of sharply angulated side branches can be challenging when advancing the guidewire. However, these procedures can be performed easily and quickly with a specific guidewire for the management of chronic total occlusions.

Keywords: Bifurcation. Coronary guidewire. Angulated lesion. Chronic total occlusion.

Acceso a ramas laterales con origen muy angulado: utilidad de una guía específica de oclusión crónica

RESUMEN

Introducción y objetivos: El acceso con la guía intracoronaria a las ramas laterales con origen muy angulado en ocasiones presenta gran dificultad, e incluso después de acceder con el extremo distal frecuentemente se produce su prolapso en el vaso principal. Presentamos una forma fácil de realizar estos procedimientos con el uso de una guía específica de oclusión crónica.

Métodos: Entre enero de 2017 y septiembre de 2018, los pacientes con lesiones en las ramas laterales o en ramas de gran tamaño que requerían protección en las bifurcaciones cuyo origen era muy angulado se abordaron con microcatéteres recto, angulado o de doble luz con guías regulares; posteriormente, en caso de imposibilidad de acceso, se pasó una guía específica de oclusión crónica con el microcatéter recto tras una modificación muy marcada de la forma del extremo distal de la guía.

Resultados: En nueve pacientes no se consiguió el acceso a la rama lateral con la estrategia inicial, en tres de ellos por imposibilidad de acceso y en los seis restantes por prolapso de la guía al intentar progresar el microcatéter. En todos los casos el acceso pudo completarse con una guía Gaia First, que combina un excelente torque con una rigidez suficiente para evitar el prolapso. Todos los procedimientos se realizaron sin complicaciones.

Conclusiones: El intervencionismo percutáneo en las ramas laterales con una marcada angulación puede conllevar una gran dificultad para el acceso con la guía. Estos procedimientos pueden realizarse de forma fácil y rápida con una guía específica de oclusión crónica.

Palabras clave: Bifurcación. Guía intracoronaria. Lesión angulada. Oclusión crónica.

* **Corresponding author:** Servicio de Cardiología, Hospital de Cabueñes, Avda. Los Prados 395, 33203 Gijón, Asturias, Spain.
E-mail address: inigo.lozano@gmail.com [I. Lozano].

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INTRODUCTION

At times, using intracoronary guides to access sharply angulated lateral branches with a lesion that requires protection when treating bifurcations is extremely difficult. There is not too much information in the medical literature on the number of branches that cannot be accessed, but experienced groups say that the rate is around 3%.¹ Accessing the lateral branch is usually easy when the angle between the main branch and the lateral branch is $< 70^\circ$, more difficult with distal bifurcation angles $> 70^\circ$, and especially difficult with angles $> 90^\circ$.

Different techniques and devices have been designed such as angulated microcatheters, double-lumen catheters² or deflectable catheters,^{3,4} which, combined with the use of hydrophilic guidewires allow us to be able to perform procedures. However, even when access has not occurred, the prolapse of the guidewire towards the main branch is a common thing when advancing the guidewire or the microcatheter, especially when dealing with sharp angles and large caliber main branches.

We hereby present a way to conduct this kind of procedure using a specific chronic occlusion guidewire that combines excellent maneuverability with great support in its distal edge to avoid prolapse. Additionally, we will be reviewing the different techniques and devices available today to perform these procedures.

METHODS

Between January 2017 and October 2018, we analyzed patients with an indication for percutaneous intervention in their lateral branches or branches requiring a second guidewire when treating a bifurcation whose origin had a $\geq 80^\circ$ angle through visual assessment. In all cases, the initial strategy was to use one Caravel microcatheter (Asahi, Japan) with the Sion and Fielder XT guidewires followed by the Stride angulated microcatheter (Teleflex, United States) or the Crusade double-lumen microcatheter (Kaneka, Japan).

In those cases where the guidewire advanced successfully with such devices, the Gaia First guidewire (Asahi, Japan) with the Caravel microcatheter was used. This guidewire was picked because of its excellent maneuverability, capacity to maintain the shape of its distal edge and the support granted by its distal segment. The characteristics of the procedures conducted with the

Gaia First guidewire as well as the properties of this guide are described here because, in our opinion, they can be of great help in these cases.

RESULTS

During the entire period of the study, 1342 percutaneous coronary interventions (PCIs) were conducted at our center, and in 52 (3.8%) of them, the lesion was found in a lateral branch whose origin had a $\geq 80^\circ$ angle or was a bifurcation with an oversized lateral branch and the mentioned exit angle. In nine patients we were not able to access the lateral branch using the Sion or the Fielder XT guidewires and straight, angulated, or double-lumen microcatheters; in three cases it was due to the fact that we could not access using the guidewire distal edge, and in the remaining six because the main vessel prolapsed when trying to advance the guidewire or the microcatheter. All procedures were conducted using 6-Fr catheters, eight of them using the radial approach and the remaining one using the femoral approach. [Table 1](#) shows the characteristics of the different cases.

The last step that was successful in all the patients consisted of using the Caravel straight microcatheter and the Gaia First guidewire after modifying the shape of the tip to make it match the angle of the vessel ([figure 1](#)). Thanks to its excellent maneuverability and the support granted by its distal edge, this guidewire allows easy access to the vessel and facilitates the advance of the microcatheter so that we can change this guide by another guidewire with a softer tip. No coronary dissections, or vessel occlusions were reported, and all procedures were completed with optimal results.

[Video 1 of the supplementary data](#) shows a case with a sharply angulated origin in a dominant circumflex artery of a very high-risk patient with a 25% ejection fraction who suffered from an anterior infarction back in 2002. The left anterior descending artery had a chronic occlusion of 50 mm in length with a scab in its anterior side. The procedure was conducted using the Impella CP ventricular assist device (Abiomed, United States) and the circumflex artery was accessed using the Gaia First guidewire and the aforementioned technique after trying the Sion and Fielder XT guidewires and one angulated microcatheter. Two 2×15 mm Resolute Onix stents (Medtronic, United States) were implanted at the beginning of the circumflex artery with optimal angiographic results ([video 2 of the supplementary data](#)). The patient was discharged three

Table 1. Characteristics of patients and lesions

	Age (years)	Bifurcation	Location	Indication of guidewire in lateral branch	Previous microcatheter	Angle
Case 1	58	LAD-diagonal	Diagonal	Protection	Angulated + double lumen	80°
Case 2	53	CX-OM1	OM1	Percutaneous interventionism	Angulated	80°
Case 3	71	CX-OM1	OM1	Protection	Angulated + double lumen	100°
Case 4	80	LAD-diagonal	Diagonal	Protection	Angulated	100°
Case 5	60	LAD-diagonal	Diagonal	Percutaneous interventionism	Angulated + double lumen	100°
Case 6	53	CX-OM1	OM1	Protection	Double lumen	90°
Case 7	64	LAD-diagonal	Diagonal	Protection	Angulated	100°
Case 8	55	LAD-diagonal	Diagonal	Percutaneous interventionism	Angulated + double lumen	100°
Case 9	76	Trunk-CX	CX	Percutaneous interventionism	Angulated	120°

CX, circumflex artery; LAD, left anterior descending artery; OM1, obtuse marginal.



Figure 1. Modification of the Gaia First guidewire tip.

days after the uneventful implantation of a triple chamber defibrillator.

Figure 2 and figure 3 show two cases with double angulation with unsuccessful access using conventional guidewires; and figure 4 and figure 5, show two cases where the problem was the prolapse of the tip of the guidewire when trying to advance the guidewire or the microcatheter.

DISCUSSION

Accessing sharply angulated lateral branches with intracoronary guidewires can be difficult. To be able to solve this problem, several options⁵ have been described, among these, shaping the curvature of the tip of the guidewire, using guidewires with hydrophilic or more rigid polymeric coating, the double guidewire technique, inflating the balloon inside the main branch to modify the access, and use microcatheters with different designs (angulated, double-lumen, or deflectable).

The tip of the guidewire should have an adequate shape to facilitate access to the lateral branch. The curves typically used to access bifurcations are basically four: one single curve with a short tip (2-3 mm), one single curve with a long tip (4-6 mm), one single curve without rough angulation, and a double curve.⁶ The latter are the most suitable shapes in cases of sharp angulations.

This study details the use of a guidewire designed for chronic occlusions⁷ and facilitate access to sharply angulated branches. The Gaia First guidewire, same as it happens with the Gaia Second and Third guidewires was first introduced into the market back in 2014. Seventeen years after its manufacturer, Asahi, would develop the very first prototype of specific guidewires for the management of chronic occlusions, the Miracle guidewire. Its design includes the 400 mm long SLIP-COAT coating that improves maneuverability inside the microcatheter with a distal coil structure of 150 mm, a 0.010" diameter and a load of 1.7 g on the tip. Such a design enables an excellent 1:1 capacity of manipulation which, in turn, helps maneuver the guidewire under optimal conditions. Although it was designed for the management of chronic occlusions, its perfect maneuverability of the tip added to how rigid the 150 mm distal segment is, and its capacity to maintain the shape of the tip make it an excellent guidewire for the access of sharply angulated branches granting the right support for the advancement of the microcatheter. We think it is important to say

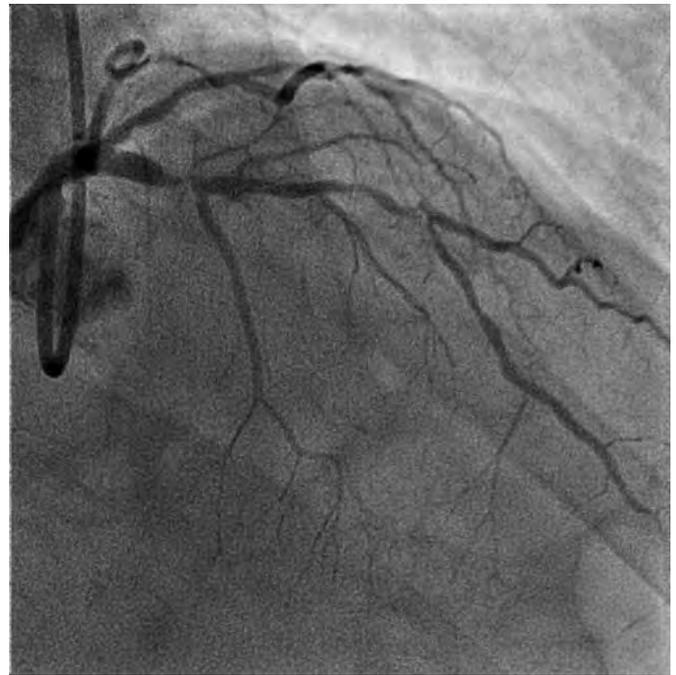


Figure 2. Access to the distal anterior descending artery, with a severe lesion, double angulation and diagonal bifurcation in the middle segment. Filed access with conventional guidewires and microcatheters.

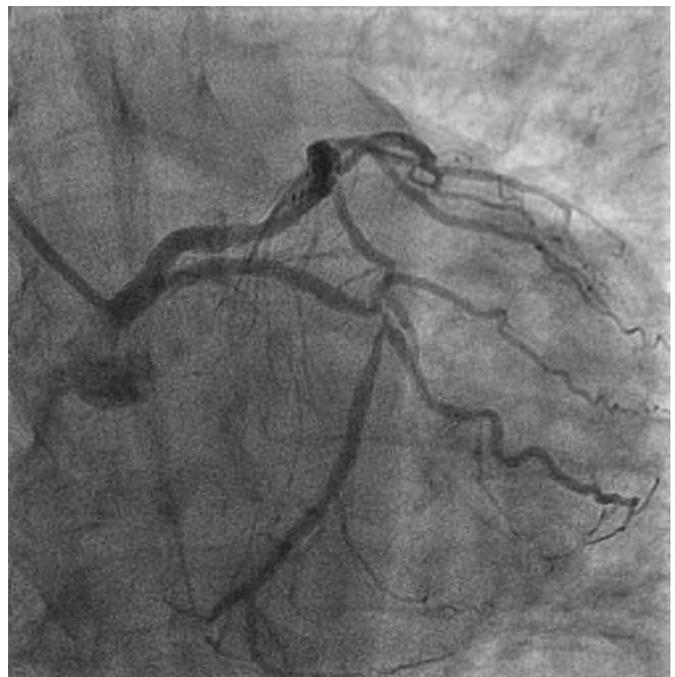


Figure 3. Access to the distal circumflex artery with double bifurcation and double angulation in the middle segment. Failed access with conventional guidewires and microcatheters.

that this strategy used as a first choice strategy after the hydrophilic guidewire has failed added to a straight microcatheter, can be very attractive financially since we do not need to use any additional curved, double-lumen, or deflectable microcatheters. However, we should not forget that although no complications were reported in the series described, the number of cases is limited and we always



Figure 4. Access to the second marginal obtuse artery with double angulation. It was accessed using a conventional guidewire but repeated prolapse occurred when trying to advance the guidewire.



Figure 5. Access to the diagonal with angulated origin. It was accessed using a conventional guidewire but repeated prolapse occurred when trying to advance the guidewire.

have to bear in mind that, even though it is a guidewire of limited lightweight and excellent maneuverability, it was designed for the management of chronic occlusions, so it should be used with care due to the theoretical risk of dissection or occlusion of the blood vessel.

There are other guidewires specifically designed for this type of lesions such as the Sion Black (Asahi, Japan), but, since this guidewire was not used in the lesions presented in this series, we cannot give any information on how it may behave in cases like the one presented here. Also, it is very difficult to have access to all the guidewires available in the market today and the goal of this study was to give an alternative solution when the first intention guidewires fail.

Another technique is the retrograde access to the lateral branch by giving the lateral branch guidewire much more curvature and trying to access the branch when the guidewire has been removed.⁸ This is a sophisticated technique when using double-lumen microcatheters since we insert one hydrophilic guidewire whose very curved distal edge stands out through the lateral orifice of the microcatheter.^{2,9-12} The idea is almost the same, to advance the double-lumen catheter over the guidewire located in the monorail compartment while the guidewire tries to access the lateral branch located in the coaxial compartment and standing out 5 mm to 10 mm through the lateral orifice and with the curve oriented almost 180° with respect to the main vessel. This way, when removing the microcatheter, we should be able to access the lateral branch using the bent guidewire.

We can also use the Venture deflectable catheter (Teleflex, United States) -compatible with e 6-Fr guidewire catheter- available in coaxial and monorail design, that allows us to use any 0.014" coronary guidewires.^{4,13} The 8 mm distal tip is radiopaque and it can bend up to 90° rotated with clockwise torque in the catheter proximal area. In order to avoid any traumas, it is advanced towards the lesion over a guidewire in straight position and, once

the point of interest has been reached, the tip starts to bend until it reaches the target angle. This deflection capability added to the possibility of turning the tip of the catheter in a circumferential plane, allows us to direct the guidewire and, once it has passed, rotate it in the counterclockwise direction to make the catheter return to its straight position and then be able to remove it.³ The rate of success when accessing lateral branches is said to be close to 80%-85%,^{3,4} and the rigidity of the tip requires being extremely careful to limit the possibility of traumatizing the vessel. A few cases of destructured guidewire due to over-manipulation have been reported.

Finally, it has also been suggested that we should inflate a balloon inside the bifurcation in order to change the plaque and allow access to the branch,¹⁴ but this solution should only be used when the other solutions have failed because, although it is easy to do, previous dilatations can cause changes in the plaque and eventually lead to occluding the branch.¹⁵

CONCLUSIONS

Accessing sharply angulated lateral branches is very hard to do with the guidewire, at times, because the access site will not allow it, or due to posterior prolapse towards the main vessel. On top of angulated, double-lumen, or deflectable microcatheters with routine guidewires, these procedures can be performed easily using a specific guidewire for the management of chronic occlusions that combines the excellent maneuverability of the tip and support of the distal edge which facilitates the advancement of the straight microcatheter to later change the guidewire for another guidewire with a softer distal edge.

CONFLICTS OF INTEREST

No conflicts of interest declared whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Accessing sharply angulated lateral branches is usually very difficult. Different techniques and devices have been designed such as angulated microcatheters, double-lumen catheters or deflectable catheters to make these procedures easier, but even when access has been successful, there are times when we witness the prolapse of the guidewire towards the main branch when advancing the guidewire or the microcatheter, especially with sharply angulated origin branches and large caliber main branches.
- Not all interventional suites have a full arsenal of the aforementioned microcatheters available, particularly, in small volume suites, which is why it is interesting to know what the easiest techniques are to be successful when performing these procedures.
- Over the last few years, we have witnessed the arrival of new intracoronary guidewires, especially those for the management of chronic occlusions.

WHAT DOES THIS STUDY ADD?

- The applicability of the Gaia First guidewire was presented here for the first time. Also, its particular characteristics of excellent maneuverability, easy advancement thanks to its high-quality hydrophilic coating, and moderate support of its distal edge. All these features make it an excellent tool to access sharply angulated lateral branches.
- The Gaia First guidewire gives us an easy, highly effective, fast technique to be able to perform complex interventions when we need to access sharply angulated lateral branches.
- The series described is short and from one single center only but, if we could confirm these results in a larger multicenter series and, therefore, extrapolate these results, the Gaia First guidewire could become the first choice guidewire; also, this would save costs since we would be getting rid of all of the aforementioned microcatheters that are usually the second options when the straight microcatheter has failed.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000006>.

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Drug-eluting versus bare-metal stents in primary PCI. Analysis of an 8-year registry

Alfredo Redondo Diéguez,* Ana B. Cid Álvarez, Ramiro Trillo Nouche, Alejandro Ávila Carrillo, Belén Álvarez Álvarez, Fernando Gómez Peña, Xoán Sanmartín Pena, Diego López Otero, and José R. González Juanatey

Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela (CHUS), Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCv), Santiago de Compostela, A Coruña, Spain



ABSTRACT

Introduction and objectives: Evidence of the long-term prognostic benefit of new-generation drug-eluting stents (DES) is limited, especially in the context of primary percutaneous coronary interventions. The goal of this study was to compare the long-term prognostic impact of the implantation of DES versus bare-metal stents (BMS) in real-world patients undergoing primary percutaneous coronary interventions.

Methods: A cohort study was conducted with 1499 consecutive patients diagnosed with ST-segment elevation myocardial infarction who underwent percutaneous coronary interventions between January 2008 and December 2015. A total of 24.9% of the patients received a DES. A matched propensity score analysis yielded 2 groups of 262 matched patients depending on whether they were treated with a DES or a BMS.

Results: During follow-up (median 1015 days), the patients who received DES had a lower all-cause mortality rate (6.5% vs 12.2%; $P = .049$), a lower composite endpoint of major adverse cardiac events (16.4% vs 25.2%; $P = .049$) and a lower patient-oriented composite endpoint of death from any cause, myocardial infarction and revascularization at follow-up (12.6% vs 22.5%; $P = .017$). No differences were seen in the definite stent thrombosis rate.

Conclusions: In our registry, in a real-world population of consecutive patients undergoing primary percutaneous coronary interventions, the use of DES versus BMS associated more survival and less clinically significant major adverse cardiac events and patient-oriented composite endpoints in a long-term follow-up, without any differences in stent thrombosis.

Keywords: Drug-eluting stent. Bare-metal stent. Primary PCI. ST-segment elevation myocardial infarction.

Stents farmacoactivos frente a metálicos en pacientes tratados con angioplastia primaria. Análisis de un registro de 8 años

RESUMEN

Introducción y objetivos: La evidencia del beneficio en el pronóstico a largo plazo de los *stents* farmacoactivos (SFA) de nueva generación es limitada, en especial en los pacientes con angioplastia primaria. El objetivo de este trabajo fue comparar el impacto en el pronóstico a largo plazo de la implantación de SFA frente a *stents* metálicos (SM) en pacientes del mundo real tratados con angioplastia primaria.

Métodos: Estudio de cohortes en el que se incluyeron 1.499 pacientes ingresados de forma consecutiva con diagnóstico de infarto agudo de miocardio con elevación del segmento ST y sometidos a angioplastia primaria entre enero de 2008 y diciembre de 2015. El 24,9% recibió un SFA. Mediante un análisis de emparejamiento por puntuación de propensión se obtuvieron 2 grupos de 262 pacientes emparejados según la implantación de SFA o SM.

Resultados: Durante el seguimiento (mediana de 1.015 días), los pacientes que recibieron SFA tuvieron tasas más bajas de mortalidad por todas las causas (6,5 frente a 12,2%; $p = 0,049$), así como en el objetivo combinado de eventos adversos mayores (16,4 frente a 25,2%; $p = 0,049$) y un objetivo combinado orientado al paciente que incluía muerte por cualquier causa, infarto de miocardio y revascularización en el seguimiento (12,6 frente a 22,5%; $p = 0,017$). No se observaron diferencias en cuanto a trombosis definitiva del *stent*.

Conclusiones: En nuestro registro, en una población del mundo real de pacientes consecutivos tratados con ICP primaria, la utilización de SFA frente a SM se asoció con una mayor supervivencia y una reducción de los eventos clínicos en el seguimiento a largo plazo, sin observar diferencias en la trombosis del *stent*.

Palabras clave: *Stent* farmacoactivo. *Stent* metálico. Angioplastia primaria. Infarto agudo de miocardio con elevación del segmento ST.

* **Corresponding author:** Servicio de Cardiología, Hospital Clínico Universitario de Santiago de Compostela, Cardiología (Planta -2), Travesía da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.

E-mail address: alfredoredondo@gmail.com. [A. Redondo Diéguez].

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Abbreviations

BMS: bare-metal stent. **DES:** drug-eluting stent. **MACE:** major adverse cardiovascular event. **PCI:** percutaneous coronary intervention. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Percutaneous coronary intervention (PCI) is the treatment of choice for the management of ST-segment elevation myocardial infarction (STEMI). First-generation drug-eluting stents (DES) reduced restenosis and the need for reinterventions compared to bare-metal stents (BMS).^{1,2} However, the higher incidence rates of late thrombosis,³ mortality and infarction⁴ fueled controversy over the implementation of these devices in patients with STEMI, a population with an identified increased risk of stent thrombosis.⁵

Second-generation DES with thinner struts, biocompatible polymers, and thromboresistant properties proved to be safe and more effective than first-generation DES and traditional BMS, particularly with significant reductions in angiographic restenosis and unplanned revascularizations of the target injury or culprit artery.⁶ The actual clinical guidelines for the management of STEMI recommend the use of new-generation DES.⁷

In a combined analysis of the EXAMINATION and COMFORTABLE-AMI clinical trials that compared new-generation DES versus BMS, the use of a DES was associated with increased safety and efficacy at 1 year.⁸ In the 2-year follow-up of patients included in the COMFORTABLE-AMI trial, the use of DES was associated with a reduction in a composite of all-cause mortality, follow-up myocardial infarction, and new revascularizations.⁹ The results of the 5-year follow-up of the EXAMINATION¹⁰ that compared an everolimus-eluting stent to a BMS showed that the new-generation DES was associated with more survival and less myocardial infarctions at follow-up.⁶

Our goal was to analyze the long-term prognostic impact of new-generation DES in a real-world population of patients with STEMI.

METHODS

Study population

This is a retrospective observational study that included (n = 1499) all consecutive patients admitted due to STEMI who underwent primary percutaneous interventions (PCI) at our center between January 2008 and December 2015. The patients who were not implanted with a stent during the percutaneous coronary intervention (PCI) (n = 131) and those implanted with a bioabsorbable scaffold (n = 11) were excluded. In 24.9% of patients (n = 374), the PCI was conducted with DES implantation in the infarct-related artery.

The PCI was conducted following the guidelines from the European Society of Cardiology^{7,11} and the decision to implant a DES or a BMS was left to the attending interventional cardiologist clinical criteria. Antiplatelet therapy consisted of acetylsalicylic acid and a P2Y₁₂ inhibitor (clopidogrel during the early years and ticagrelor, and prasugrel more recently).

Demographic, clinical, echocardiographic, coronary angiography and laboratory data were collected by cardiologists in a computerized database. Both the material used during the PCI and the

characteristics of the procedure were included at the time of the PCI by the specialist in hemodynamics and the attending operator. The structured follow-up was conducted using the IANUS electronic health record system (the only one available and mandatory in Galicia, Spain). Events were independently adjudicated by 2 independent cardiologists and when they disagreed, by a third cardiologist.

Definitions

The diagnoses of STEMI and myocardial infarction were established based on the actual clinical guidelines.^{7,12} Ischemia time was defined as the time elapsed between symptom onset and reperfusion (the passage of the guide wire through the culprit artery during PCI). Target vessel revascularization and target lesion revascularization were defined following the ARC (Academic Research Consortium) criteria.¹³

Major adverse cardiovascular events (MACE) included all-cause mortality, acute myocardial infarction, heart failure requiring hospitalization and new, unplanned revascularizations. Following the recommendations from the ARC for the study of stent prognosis, a composite goal of major patient-oriented composite endpoint (POCE) of death from any cause, any myocardial infarctions or new unplanned revascularization was included.¹³ The device-oriented composite endpoint (DOCE) included cardiac death, target vessel myocardial infarction and ischemia-driven target lesion revascularization. Definite stent thrombosis was considered as angiographically proven thrombosis.

Study objectives

The main objective of this study was to compare the long-term prognosis of revascularization with DES vs BMS in consecutive patients admitted due to STEMI who underwent PCI. The clinical outcomes were assessed based on all-cause mortality, a composite of MACE, POCE, and DOCE endpoints, and on each component separately. The median follow-up was 1015 days, and the interquartile range (IQR), 400-1800 days.

Statistical analysis

The differences in the descriptive analysis were assessed using the difference of means Student t test and the chi-square test of comparison of proportions, depending on whether the variable was continuous or categorical. To minimize the bias involved when studying the prognostic effect of the DES versus the BMS implant from an observational point of view, a propensity score matching analysis was performed. The variables included in the model were age, sex, body mass index, arterial hypertension, diabetes, dyslipidemia, smoking, ischemic heart disease, time of ischemia, infarct location, culprit artery involved in the infarction, use of glycoprotein IIb/IIIa inhibitors, number of diseased vessels, the glomerular filtration rate, the creatinine levels at admission, the peak troponin I levels, hemoglobin, glucose, heart rate, systolic blood pressure, Killip class, left ventricular ejection

fraction, GRACE score, CRUSADE score, and year of inclusion in the analysis. An analysis of the variance inflation factor showed no issues of multicollinearity in the variables used (variance inflation factor 1.56 and no variable > 4). The caliper used was 0.25, and the sensitivity-specificity ratio obtained was high (75% area under the curve). No variable had a strong bias, being the average bias, 3.3%. After propensity score matching, no statistically significant differences were seen in any of the variables studied.

The graphs (figure 1 and figure 2) show the Nelson-Aalen estimate of the cumulative hazard function, and the differences were assessed using the log-rank test. The hazard ratio was calculated using the univariate Cox regression analysis.

Statistical analysis was performed using the STATA 14 and SPSS 22.0 statistical packages.

RESULTS

Baseline characteristics

The overall study cohort included 1357 patients; 983 patients received BMS and 374 received DES. The patients in the DES group were younger, more frequently males, with a higher body mass index and CRUSADE scores of higher hemorrhagic risk. The patients revascularized with BMS usually had anterior wall infarctions, lower hemoglobin levels, and poor renal function. The total length of the implanted stents was higher in the DES group, and the diameter of the stents was larger in patients with BMS. There were no significant differences in other cardiovascular risk factors, time of ischemia, peak troponin levels, hemodynamic status, Killip class at admission, left ventricular ejection fraction, GRACE score, number of lesions treated, number of stents used, or pharmacological treatment at discharge, with the exception of antiplatelet therapy (table 1).

The propensity score-matched cohort study consisted of 262 patients of each pair and showed no significant differences in any of the aforementioned variables (table 1).

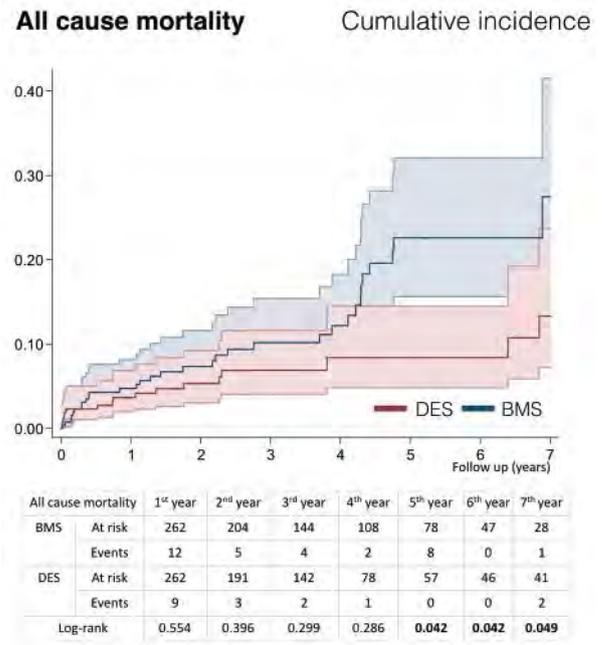


Figure 1. Cumulative incidence curves for survival. BMS, bare-metal stent; DES, drug-eluting stent.

Events at follow-up

The events at follow-up are shown on table 2. The overall mortality rate was 16.9% (n = 205). In the overall study cohort, the DES implant was closely associated with lower risk of death from any cause (6.9% vs 12.2%; log-rank test, P < .001); the combined MACE and POCE were also less common in patients treated with DES. No differences were seen in the DOCE, cardiovascular mortality, myocardial infarction, target vessel myocardial infarction, target vessel revascularization, target lesion revascularization or revascularization by another vessel. No

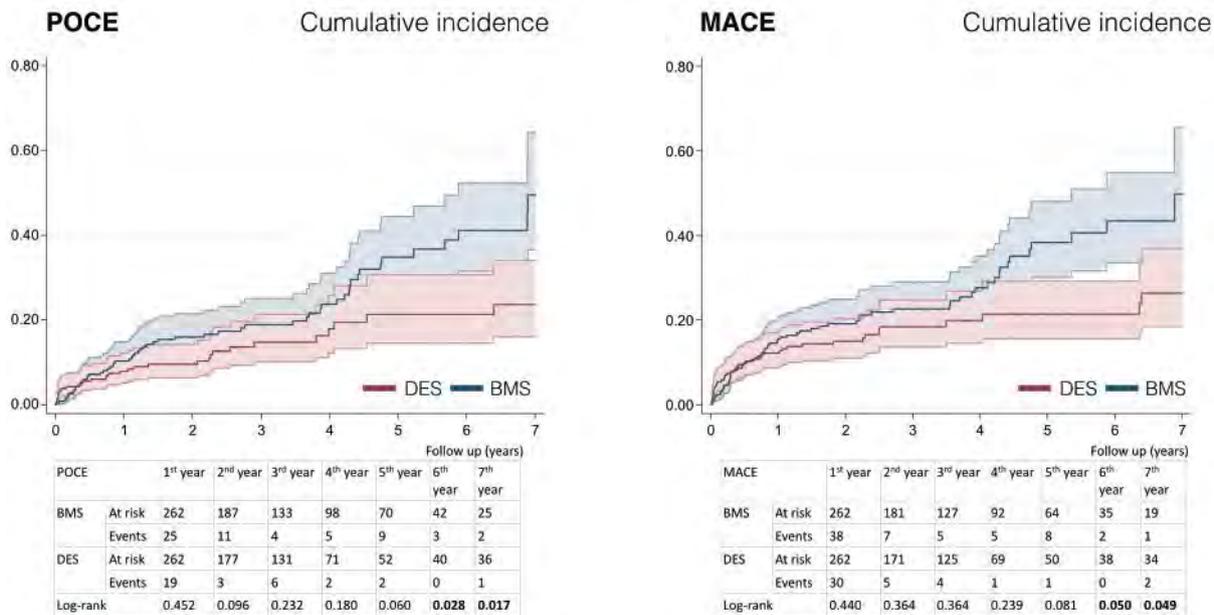


Figure 2. Cumulative incidence curves for POCE and MACE-free survival. BMS, bare-metal stent; DES, drug-eluting stent; MACE, major adverse cardiovascular events; POCE, patient-oriented combined endpoint.

Table 1. Baseline characteristics of the overall cohort and the propensity score matched cohort

	Overall cohort			Propensity score matched cohort		
	BMS	DES	P	BMS	DES	P
	(n = 983)	(n = 374)		(n = 262)	(n = 262)	
Demographics						
Age (years)	65 (14)	62 (12)	< .001	62 (14)	63 (12)	.847
Gender (male)	76.5%	81.6%	.037	80.9%	81.3%	.911
BMI (kg/m ²)	28 (4)	29 (4)	.039	29 (4)	29 (4)	.981
Personal history						
Hypertension	48.3%	49.5%	.707	50.8%	49.6%	.794
Diabetes mellitus	19.9%	28.6%	.001	26.0%	24.8%	.764
Dyslipidemia	46.6%	54.3%	.012	51.1%	51.9%	.862
Tobacco	49.5%	48.1%	.642	49.6%	49.6%	1
Ischemic heart disease	9.6%	11.5%	.309	11.8%	11.5%	.892
PCI data						
Ischemia time (min.)	271 (202)	289 (232)	.227	291 (215)	279 (222)	.549
Anterior wall location	41.6%	25.9%	< .001	32.4%	31.3%	.779
Culprit artery in the infarction			.033			.130
LAD	40.5%	42.8%		40.8%	38.2%	
Cx	15.4%	18.5%		17.2%	20.2%	
RCA	43.2%	36.4%		42.0%	39.3%	
LM	0.7%	1.6%		-	1.2%	
Number of diseased vessels			.626			.696
Two vessels	28.1%	27.0%		28.2%	25.2%	
Three vessels	14.8%	16.8%		13.4%	14.9%	
Number of lesions treated			.387			.537
1	93.9%	92.8%		95.0%	93.5%	
2	5.3%	6.2%		5.0%	5.7%	
3	0.8%	0.8%		-	0.4%	
Pre-PCI TIMI flow			.380			.982
0	80.9%	80.8%		83.6%	83.2%	
1	4.7%	2.9%		3.1%	2.7%	
2	7.5%	9.4%		7.2%	8.0%	
3	6.9%	7.0%		6.1%	6.1%	
Post-PCI TIMI flow			.262			.917
0	0.9%	0.8%		1.2%	1.2%	
1	0.9%	0.5%		0.8%	0.8%	
2	2.8%	1.1%		1.9%	1.2%	
3	98.4%	97.6%		96.2%	97.0%	
Use of glycoprotein IIb/IIIa inhibitors						
Thrombectomy	68.8%	69.0%	.939	73.3%	72.5%	.845

Table 1. (Continued) Baseline characteristics of the overall cohort and the propensity score matched cohort

	Overall cohort			Propensity score matched cohort		
	BMS	DES	<i>P</i>	BMS	DES	<i>P</i>
	(n = 983)	(n = 374)		(n = 262)	(n = 262)	
Number of stents			.619			.192
1	71.4%	67.9%		70.6%	69.1%	
2	22.6%	24.3%		21.8%	24.4%	
3	4.6%	6.4%		5.0%	5.7%	
4	1.0%	0.8%		2.7%	0.4%	
5	0.3%	0.5%		-	0.4%	
6	0.1%	-		-	-	
Laboratory parameters						
GFR (mL/min)	83 (37)	97 (38)	< .001	96 (44)	93 (35)	.378
Creatinine levels (mg/dL)	1.1 (0.6)	0.9 (0.6)	.001	1.0 (0.6)	1.0 (0.6)	.752
Peak troponin I levels (ng/mL)	107 (133)	105 (113)	.747	111 (127)	108 (113)	.769
Hemoglobin (g/dL)	14.3 (1.8)	14.6 (2.9)	.018	12.4 (1.6)	14.4 (1.7)	.860
Glucose (mg/dL)	170 (87)	174 (115)	.552	169 (79)	166 (81)	.662
Clinical data						
Heart rate (bpm)	77 (21)	76 (19)	.339	74 (19)	75 (19)	.639
SBP (mmHg)	128 (29)	130 (29)	.209	132 (25)	129 (29)	.320
Killip class			.379			.731
Class I	82.7%	84.0%		87.4%	88.6%	
Class II	6.3%	7.2%		4.6%	5.7%	
Class III	2.9%	1.3%		2.7%	1.5%	
Class IV	8.1%	7.5%		5.3%	6.1%	
LVEF (%)	51 (12)	52 (11)	.200	52 (11)	52 (10)	.699
GRACE score	162 (46)	158 (78)	.432	152 (40)	153 (41)	.785
CRUSADE score	27 (18)	22 (14)	< .001	21 (14)	22 (13)	.581
Treatment at discharge						
Acetylsalicylic acid	99.0%	99.5%	.401	99.6%	99.2%	.563
P2Y ₁₂ inhibitor			< .001			.126
Clopidogrel	88.2%	59.6%		69.1%	73.3%	
Prasugrel	5.19%	15.1%		11.5%	13.7%	
Ticagrelor	5.74%	24.7%		19.5%	12.6%	
Beta-blockers	87.8%	89.5%	.754	84.4%	88.8%	.132
ACE inhibitor	81.0%	84.3%	.247	80.9%	83.8%	.381
Statins	97.4%	97.8%	.282	98.1%	96.9%	.514

ACE inhibitor, angiotensin-converting enzyme inhibitor; BMI, body mass index; BMS, bare-metal stent; Cx, circumflex artery; DES, drug-eluting stent; GFR, glomerular filtration rate; LAD, left anterior descending artery; LCA, left coronary artery; LM, left main; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

Table 2. Adverse events during follow-up

	Overall cohort			Propensity score matched cohort		
	BMS (n = 983)	DES (n = 374)	log-rank test P value	BMS (n = 262)	DES (n = 262)	log-rank test P value
Death from any cause	18.3% (180)	6.7% (25)	< .001	12.2% (32)	6.5% (17)	.049
MACE	33.2% (326)	16.0% (60)	< .001	25.2% (66)	16.4% (43)	.049
POCE	28.0% (275)	13.1% (49)	.004	22.5% (59)	12.6% (33)	.017
DOCE	10.0% (98)	5.9% (22)	.706	10.6% (28)	7.3% (19)	.764
Cardiovascular mortality	3.76% (37)	1.87% (7)	.860	2.7% (7)	3.8% (10)	.409
MI at follow-up	5.3% (52)	2.1% (8)	.437	5.0% (13)	2.7% (7)	.243
Target MI at follow-up	2.0% (20)	0.8% (3)	.765	2.3% (6)	1.1% (3)	.713
Heart failure	4.0% (39)	3.5% (13)	.97	3.1% (8)	3.4% (9)	.759
TVR	6.7% (66)	4.0% (15)	.435	8.4% (22)	4.6% (12)	.114
TLR	6.2% (61)	4.0% (15)	.664	7.6% (20)	4.6% (12)	.199
Definite thrombosis	3.7% (36)	2.7% (10)	.973	2.7% (7)	1.9% (5)	.686

BMS, bare-metal stent; DES, drug-eluting stent; DOCE, device-oriented composite endpoint; MACE, major adverse cardiovascular events; MI, myocardial infarction; POCE, patient-oriented combined endpoint; TLR, target lesion revascularization; TVR, target vessel revascularization.

differences were seen in definite stent thrombosis at follow-up either.

In the propensity score-matched cohort study, patients who received a DES had a significantly lower all-cause mortality rate (6.7% vs 18.3%; log-rank test, $P < .001$) and lower incidence rates of MACE and POCE at follow-up (16.8% vs 25.6%, log-rank test, $P = .049$; 12.6% vs 22.5%, log-rank test, $P = .017$, respectively). Target vessel revascularization (4.6% vs 8.4%) and target lesion revascularization (4.6% vs 7.6%) tended to drop but were not statistically significant. The DOCE was numerically lower in the DES group. No differences were seen in cardiovascular mortality, myocardial infarction, target myocardial infarction or revascularization by another vessel. Survival curves revealed that both groups diverged over time compared to the beginning of the follow-up, and the differences were significant after five years of follow-up (figure 1). The cumulative incidence curves for MACE and POCE (figure 2) show a similar pattern, although the differences were statistically significant after six years of follow-up in both of them. Finally, no significant differences were observed in the rate of definite stent thrombosis showing both groups low rates of 2.7% in the BMS group and 1.9% in the DES group (log-rank test, $P = .686$).

DISCUSSION

The results of this study show that in a real-world population of consecutive patients with STEMI who underwent PCI, the use of new-generation DES was associated with a lower overall mortality rate and long-term MACE and POCE and no differences in the incidence rate of definite stent thrombosis. The protective effect of DES was maintained in analyses of the cohort grouped by propensity score matching, where both subgroups had similar distributions of covariates.

Our results indicate that the use of new-generation DES in PCI in patients with STEMI is associated with a prognostic benefit compared with BMS, indicative that they may be the first-choice

approach in these patients, which is consistent with the actual recommendations of the clinical practice guidelines.¹¹

In our study, we saw a reduction in all-cause mortality in the group of revascularized patients with DES, with no differences in cardiovascular mortality. When it comes to reducing the overall mortality rate the protective effect of DES cannot be established directly; however, these findings are consistent with the long-term results of former studies.¹⁰ It is known that the luminal loss of BMS is greater than that of DES.¹⁴ An explanation for this difference in the overall mortality rate may have to do with a higher rate of subclinical restenosis in patients with BMS that could be causing silent ischemia, a reduced ejection fraction and/or a lower coronary flow reserve, which in the event of intercurrent events such as infections, bleeding or cancer, among others, could lead to worse prognosis. The NORSTENT study,¹⁵ a large multicenter trial of 9013 patients randomized to receive new-generation DES or BMS, showed no differences in the composite primary endpoint of all-cause mortality or new nonfatal myocardial infarction after 6 years of follow-up. In this study, no differences were found in the overall mortality rate. The population had a lower risk profile compared to our registry: less than one-third of the patients were admitted due to STEMI, and patients with prior percutaneous revascularization, life expectancy below 5 years, on anticoagulant therapy and with bifurcation lesions were excluded. Despite the fact that no differences were found in the primary endpoint, the DES proved their effectiveness which was associated with a reduced need for new revascularizations (16.5% vs 19.8%; $P < .001$) and target lesion revascularizations (5.6% vs 10.2%; $P < .001$). Likely due to the small sample size of our study, we saw a statistically nonsignificant tendency towards less target lesion revascularizations and target vessel revascularizations in patients who received DES.

The reduction of POCE in our registry had a similar pattern to the one observed in the 5-year follow-up of the EXAMINATION trial,¹⁰ where the differences favorable to the DES grew progressively bigger during follow-up, being statistically significant from the third year onwards. In the EXAMINATION trial, DES also lowered the follow-up DOCE, being the differences statistically

significant after the 3-year follow-up.¹⁰ In our registry the rate of DOCE was similar to that of the EXAMINATION trial at 2 years ($\approx 9\%$); in any case, we only found a numerical reduction of the DOCE, probably due to the lack of statistical power.

The long-term evidence available of DES vs BMS is very limited; most clinical trials that compare BMS to first-generation DES conducted <2 year-follow-up studies,¹⁶⁻²² yet usually they showed a greater efficacy of DES at the cost of less new revascularizations of the target lesion, with no differences in other clinical events or survival. Only 2 clinical trials, the EXAMINATION¹⁸ and the COMFORTABLE-AMI, have compared second-generation DESs vs BMS in patients with STEMI, and in both cases a 1-year follow-up was conducted: in the COMFORTABLE-AMI trial, the use of biolimus-eluting stents (BioMatrix; Biosensors Europe SA, Morges, Switzerland) was associated with less new infarctions based on the culprit vessel and ischemia-guided target vessel revascularizations.²³ Similarly, in the EXAMINATION study, the use of an everolimus-eluting stent (Xience V; Abbott Vascular, Santa Clara, CA, United States) was associated with lower target vessel revascularizations and target lesion revascularization rates.¹⁸ In a combined analysis of both studies, the use of DES reduced the POCE which, in turn, led to less target lesion revascularization and a lower risk of infarct-related artery new infarctions.⁸ The late catch-up phenomenon (ie, thrombosis or restenosis 1 year after stent implantation) has been described for first-generation DES, which has raised concerns about their long-term efficacy and safety.^{24,25} Compared to BMS, that show maximum intimal hyperplasia at 6 months,²⁶ first-generation DES show progressive luminal loss after 2 years of angiographic follow-up.²⁷ Some studies suggest that this effect is also present in new-generation DES.²⁸ Our results and those from the long-term EXAMINATION study support the hypothesis that the clinical effectiveness of new-generation DES in terms of increased survival and decreased MACE and POCE is seen during long-term follow-up studies.

Finally, the safety of new-generation DES when it comes to their low rate of definite stent thrombosis, with no differences from BMS being reported, is consistent with what some clinical trials have published on new DES in patients with STEMI.^{8,10,15} On the timing of stent thrombosis, it is remarkable that there was no very late stent thrombosis among patients who received DES.

Limitations

This was a retrospective observational and nonrandomized study with consecutive inclusion of patients conducted in a single center. Thus, it is the limitations inherent to this type of study that need to be taken into consideration.

To avoid bias and to control the effects of possible confounding factors, propensity score adjustment was conducted; however, the effects of the confounding factors that were not analyzed cannot be precluded. Due to the lack of data on treatment modifications during follow-up, we cannot rule out the possibility that the observed differences may be influenced, at least partially, by treatment. Finally, the existence of the effect of heterogeneity among the different types of DES cannot be precluded either.

CONCLUSIONS

According to our registry, in a real-world population of patients, the implementation of new-generation DES compared to BMS was associated with increased survival rates at long-term follow-up, reductions of MACE and POCE and no differences in definite stent thrombosis.

FUNDING

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Despite recommendations from the actual guidelines, the evidence on the long-term outcomes of new drug-eluting stents in the management of STEMI is limited and mostly based on clinical trials.

WHAT DOES THIS STUDY ADD?

- The population of this study reflects the management of a real-world STEMI cohort.
- Our results confirm the long-term efficacy and safety of new-generation drug-eluting stents in an all-comers registry

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Changes in mitral annular morphology following transcatheter mitral valve repair. Clinical repercussion and importance of etiology



Alberto Alperi García, Isaac Pascual,* Víctor León Argüero, Remigio Padrón Encalada, Iria Silva Conde, Daniel Hernández-Vaquero, Félix Fernández, Jacobo Silva, Beatriz Díaz Molina, César Moris de la Tassa, and Pablo Avanzas

Área del Corazón, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

ABSTRACT

Introduction and objectives: Mitral regurgitation is one society's most prevalent valvular diseases. Transcatheter mitral valve repair with the MitraClip system has become more widely used for the management of this condition. The endpoints of the study were the changes in the mitral annular morphology, the recurrent grade III-IV mitral valve regurgitation, and a composite endpoint of heart failure readmission and all-cause mortality.

Methods: Single-centre, prospective and observational study. We included patients admitted due to transcatheter mitral valve repair between October 2015 and October 2018. The three-dimensional analysis of the mitral valve annulus was performed using the MVQ QLAB mitral valve quantification software (Philips; Amsterdam, The Netherlands).

Results: Fifty procedures were performed on 48 patients. A significant decrease of both annular diameters, perimeter and area was observed after the procedure. The antero-posterior diameter reduction was more significant in patients with functional mitral regurgitation compared to patients with organic mitral regurgitation (13.2 ± 8.8 vs 8.6 ± 7.5 ; $P = .05$). The posterior leaflet grasping was the only parameter associated with less chances of significant recurrent mitral regurgitation (OR = 0.89; 95CI%, 0.79-0.98).

Conclusions: Mitral annular morphological changes occur after MitraClip implantation. The magnitude of these changes varies depending on the etiology of mitral regurgitation. Posterior leaflet grasping is the main factor associated with these changes and prevents the recurrence of significant mitral regurgitation.

Keywords: Transcatheter mitral valve repair. MitraClip. Severe mitral regurgitation. Mitral annulus.

Cambios morfológicos anulares tras reparación mitral transcatóter: repercusión clínica y relevancia de la etiología

RESUMEN

Introducción y objetivos: La insuficiencia mitral es una de las enfermedades valvulares más prevalentes en nuestro medio. La reparación mitral transcatóter con el sistema MitraClip es un procedimiento cada vez más utilizado en este contexto. Los objetivos del estudio fueron evaluar los cambios morfológicos anulares, la recurrencia de la insuficiencia mitral significativa y un objetivo combinado de reingreso por insuficiencia cardíaca y mortalidad global.

Métodos: Estudio prospectivo, observacional y unicéntrico. Se incluyeron pacientes tratados con reparación mitral transcatóter entre octubre de 2015 y octubre de 2018. Se realizó un análisis tridimensional del anillo con el software de cuantificación mitral MVQ QLAB 10.0 (Philips; Amsterdam, Países Bajos).

Resultados: Se realizaron 50 procedimientos en 48 pacientes. Tras el procedimiento se observó una disminución significativa de ambos diámetros anulares, así como del perímetro y del área, y una mayor reducción del diámetro anteroposterior en los pacientes con insuficiencia mitral funcional con respecto a aquellos con insuficiencia mitral orgánica ($13,2 \pm 8,8$ frente a $8,6 \pm 7,5$; $p = 0,05$). El porcentaje de *grasping* sobre el velo posterior fue el único parámetro que se asoció estadísticamente a una menor probabilidad de desarrollar insuficiencia mitral significativa (OR = 0,89; IC95%, 0,79-0,98).

Conclusiones: Tras el implante de MitraClip se producen cambios morfológicos en el anillo mitral. La magnitud de estos cambios es diferente según la etiología de la insuficiencia mitral. El *grasping* del velo posterior es el principal factor asociado a dichos cambios y previene la recurrencia de la insuficiencia mitral significativa.

Palabras clave: Anillo mitral. Insuficiencia mitral grave. MitraClip. Reparación mitral transcatóter.

* **Corresponding author:** Área del Corazón, Hospital Universitario Central de Asturias, Avda. de Roma s/n, Oviedo, Asturias, Spain.

E-mail address: ipascua@live.com [I. Pascual Calleja].

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Abbreviations

MR: mitral regurgitation. **TMVR:** transcatheter mitral valve repair.

INTRODUCTION

Mitral regurgitation (MR) is the most prevalent valvular disease in the United States and the second most prevalent in Europe.^{1,2} The transcatheter mitral valve repair (TMVR) treated with the MitraClip system (Abbott Vascular, Menlo Park, California, United States) imitates the edge-to-edge approach surgical technique proposed by Alferi to achieve an effective reduction of the degree of MR.^{3,4} This technique is more widely used, particularly in patients of high or prohibitive surgical risk because it is less invasive and has shown good efficacy and safety results in the mid-term.⁵⁻⁷

This procedure is thought to be able to operate changes in the anatomy of the mitral annulus beyond the edge-to-edge approach of the valvular leaflets, but there is very little information on this regard. Some studies speak about a significant change of antero-posterior diameters in RM of functional etiology⁸ while others describe changes of diameter, in non-constant areas and in etiology-dependent areas.⁹

The goal of this study is to analyze the morphological changes occurring in the mitral valve after the TMVR and its relation to the degree of reduction of MR in the short and mid-terms, and its association with the clinical goals.

METHODS

This is an observational, prospective study conducted at Hospital Universitario Central de Asturias de Oviedo, Spain.

Inclusion of patients

Patients were included between October 2015 and October 2018. These were the inclusion criteria: patients with grade III-IV symptomatic mitral failure despite the optimal medical therapy considered of high surgical risk by the multidisciplinary team and who would adequately meet the anatomical criteria needed for the implant.^{4,7} These patients were excluded: patients with prior mitral surgical annuloplasty due to the impossibility of measuring annular anatomic changes. A prior transesophageal echocardiography was conducted in all patients. The etiology of MR was categorized into organic or degenerative, and functional. Patients with a mixed etiological profile in their MR were recategorized into one of the aforementioned groups based on their predominant component after 2 expert cardiologists studied the transesophageal echocardiography and achieved consensus. All patients received oral written information on the risks and benefits of the procedure, and they all signed a written informed consent according to the Declaration of Helsinki.

Description of the procedure

The TMVR was performed using the MitraClip system, which received the European certificate of conformity (CE mark) in March 2018. The implantation procedure has already been described in prior studies.⁷ In sum, the intervention is conducted under general anesthesia and guided by a 3D transesophageal

echocardiography and under the supervision of a MitraClip technical expert. More than one clip was implanted in cases where the reduction of the degree of MR was not of, at least, one grade, and as far as there was no significant residual mitral stenosis estimated through the average diastolic transmitral valve pressure gradient.¹⁰

Echocardiographic study

All patients underwent transesophageal echocardiographic studies in 2 and 3 dimensions before and right after the completion of the procedure that was conducted by an expert echocardiography expert using a state-of-the-art echocardiography machine model EPIQ 7 (Philips; Amsterdam, The Netherlands). The patient's after-load hemodynamic condition was taken into consideration before and after the procedure.

In order to conduct the 3D study of the mitral annulus, 3D images were acquired (Zoom 3D, Philips; Amsterdam, The Netherlands) during the procedure that were later analyzed using the MVQ QLAB 10.0 mitral quantification software (Philips; Amsterdam, The Netherlands). **Figure 1** shows an example of 3D reconstruction before and after the procedure.

The analysis of the leaflet grasping was estimated using the lengths of both leaflets before and after the procedure in the same plane of the implant of the device. The length before the clip was measured between the anchor site of the leaflet to the annulus and the leaflet free-edge and, the length after the clip was estimated between the anchor site of the leaflet to the annulus and the leaflet site immediately proximal to the part of the leaflet inside the device:

- Total grasping (mm): pre mitral leaflet length – post mitral leaflet length.
- Per cent grasping (%): $\frac{(\text{pre mitral leaflet length} - \text{post mitral leaflet length})}{\text{pre mitral leaflet length}} \times 100$.

Study variables

Echocardiographic variables

The technical success, the device success, and the procedure success were all defined according to the consensus document put together by the Mitral Valve Academic Research Consortium.¹¹ Both the etiology and severity of the MR were classified and assessed according to the clinical practice guidelines designed by the European Society of Cardiology,¹²⁻¹⁴ being severity subdivided into four degrees in a similar way to what the EVEREST clinical trial did.^{4,7}

Clinical variables

The patient's functional capacity was assessed following the New York Heart Association classification. Admission to due heart failure was defined as patients coming back to their hospital floor or being assisted in the ER and having to stay and sleep over. The

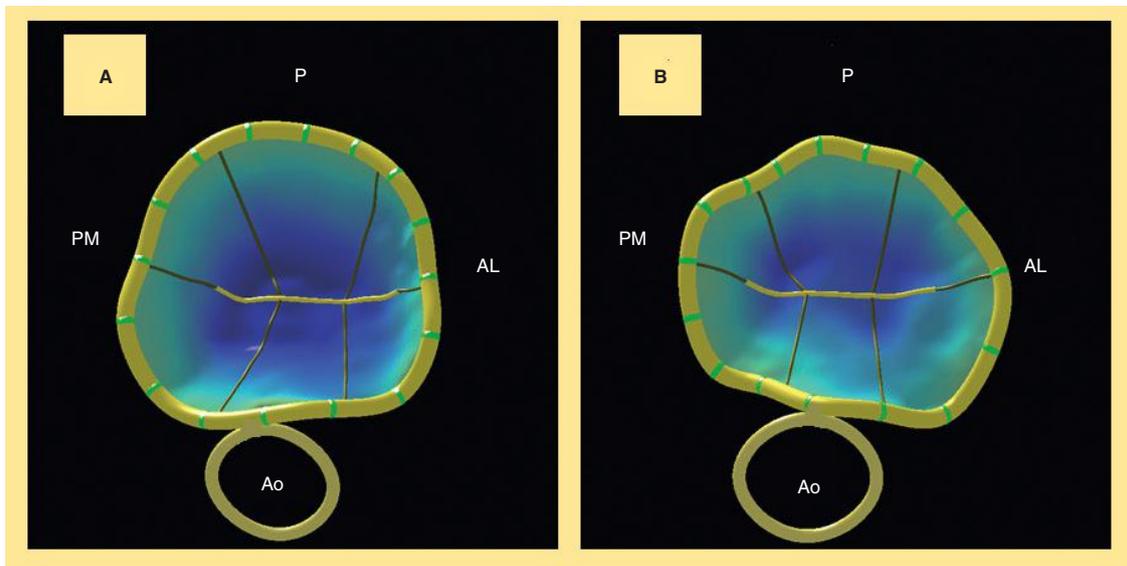


Figure 1. 3D analysis before the clip (A) and after the clip (B) of mitral annulus in frontal view from the left ventricle. A, anterior; AL, anterolateral; Ao, aorta; P, posterior; PM, posteromedial.

EuroSCORE II and the Surgeon Thoracic Score were estimated too. Follow-up event was defined as a hospitalization due to heart failure or all-cause mortality.

Study goals

The study goals were the assessment of the annular morphological changes, the recurrence of MR (at least grade III/IV) and a composite endpoint of rehospitalization due to heart failure and global mortality.

Statistical analysis

Qualitative variables were expressed as absolute number and percentage and quantitative variables as mean \pm standard deviation. The Student *t* test for paired data was used to assess morphological changes before and after the procedure. The chi-square and Student *t* tests were used for different groups as methods to compare categorical and quantitative variables. Linear regression analyses were conducted to assess the predictors of annular quantitative modification, the binary logistics regression analysis was used for the study of MR recurrence, together with the survival analysis using the Kaplan-Meier method. A peak alpha error of 0.05 was assumed. All analyses were conducted using the Stata 14 software (Stata Statistical Software: Release 14. College Station, Texas: Stata- Corp LP).

RESULTS

Fifty TMVR procedures were conducted between October 2015 and October 2018 in 48 patients: 48 MitraClip primary implants and two reinterventions due to the partial detachment of the posterior leaflet. The average age was 74.8 ± 7.2 years and 31.3% of the patients were females. Ten procedures (20.8%) were conducted in patients with organic MR and 38 (79.2%) in patients with functional MR. The baseline characteristics of the population based on the etiology of the MR and the echocardiographic data are shown on [table 1](#) and [table 2](#). An average 1.5 ± 0.5 clips per procedure were implanted. In 43 (86%) cases, the first-generation clip

was used, while in 7 (14%) cases, the XTr clip was used. Technical success was 100% and the procedural success was close to 92% (46/50). The four unsuccessful cases were due to partial detachments, one failed reintervention, and persistent grade III/IV MR after the implant.

After the procedure, in the 3D analysis of the mitral annulus, there was a significant reduction of both annular diameters, the perimeter and both 2D and 3D areas ([table 3](#)). The comparative analysis based on etiology ([table 4](#)) found a greater reduction in the anteroposterior diameter in patients with functional MR compared to those with organic MR (13.2 ± 8.8 versus 8.6 ± 7.5 of per cent reduction, respectively; $P = .05$) and a greater tendency to a reduced area in the same sense (13.3 ± 12.4 versus a 7.2 ± 11.1 of per cent reduction, respectively; $P = .01$).

When it comes to both leaflet-grasping it was observed that in patients with organic MR, a greater percentage of anterior leaflet tissue inside the device is approached ($36.6 \pm 11.5\%$ in the organic MR versus $27.8 \pm 11.4\%$ in the functional MR; $P = .02$), while posterior leaflet grasping is similar in both subtypes ($34 \pm 8.1\%$ in the organic MR versus $34.4 \pm 10.6\%$ in the functional MR; $P = .04$).

In the simple linear regression analysis conducted of predictor factors of reduction of the annular anteroposterior diameter we observed that the percentage of posterior leaflet grasping and the anteroposterior diameter before the implant were the only factors associated with a greater reduction. After adjusting for the etiology of the MR, the indexed ventricular volumes, the annular diameters before the implant, and the anterior leaflet grasping, this association between the posterior leaflet grasping and the reduction of anteroposterior annular diameter was still statistically significant (β coefficient = 0.27; 95%CI, 0.05-0.48; $P = .02$).

After an average 454 days of follow-up (interquartile range, 195-699), 7 out of the 48 patients (14.6%) and 8 out of the 50 procedures conducted (16%) showed grade III/IV MR. In the binary logistics regression analysis conducted for grade III-IV/IV MR predictors at the echocardiographic follow-up ([table 5](#)) it was observed that the

Table 1. Baseline characteristics of the population

	Global N = 48 (100%)	Organic n = 10 (2.8%)	Functional n = 38 (79.2%)	P
Age, years	74.8 ± 7.2	76.6 ± 2.2	74.3 ± 1.2	.70
Women	15 (31.3)	5 (50)	10 (26.3)	.15
Weight, kg	74.8 ± 14.2	75.3 ± 5.2	74.8 ± 2.2	.90
Height, cm	164.1 ± 9.1	158.6 ± 2.4	165.6 ± 2.5	.03
Hypertension	36 (75)	9 (90)	27 (71.1)	.22
Diabetes mellitus	16 (33.3)	5 (50)	11 (29)	.21
Dyslipidemia	22 (45.8)	6 (60)	14 (36.8)	.24
Renal disease	20 (41.6)	3 (30)	17 (44.7)	.19
Prior stroke	10 (20.8)	2 (20)	8 (21)	.94
Ischemic heart disease	23 (47.9)	4 (40)	19 (50)	.48
PCI	16 (33.3)	3 (30)	13 (24.4)	.34
CABG	7 (14.6)	1 (10)	6 (15.8)	.36
Atrial fibrillation	30 (62.5)	6 (60)	24 (63.2)	.84
Degree of MR				
III/IV	8 (16.7)	2 (20)	6 (15.8)	.79
IV/IV	40 (83.3)	8 (80)	32 (84.2)	.80
SPAP, mmHg	43.5 ± 12.4	49.5 ± 4.4	41.8 ± 2.2	.06
COPD	11 (22.9)	3 (30)	8 (21)	.55
Functional class				
NYHA III	35 (72.9)	7 (70)	28 (73.7)	.83
NYHA IV	13 (27.1)	3 (30)	10 (26.3)	.79
EuroSCORE II	5.4 ± 4	4.7 ± 1.6	5.6 ± 2.2	.62
STS mortality	5.2 ± 3.2	7.2 ± 5.4	4.7 ± 2.1	.02

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SPAP, systolic pulmonary artery pressure; STS, Society of Surgeon Thoracic score. Data are expressed as n (%) or mean ± standard deviation.

Table 2. Echocardiographic characteristics

	Global	Organic MR	Functional MR	P
Left ventricular ejection fraction	41.5 ± 12.8	50.46 ± 4.1	39.15 ± 1.9	.01
LVESVi, mL/m ²	85 ± 32.2	61.1 ± 19.9	91.4 ± 32	.01
LVESDi, mm/m ²	60.5 ± 9.5	29.9 ± 4.1	33.9 ± 5	.02
ERO, cm ²	0.38 ± 0.12	0.43 ± 0.12	0.36 ± 0.13	.09
Intercommissural diameter, mm	39.2 ± 4.7	37.8 ± 2.5	39.4 ± 5.1	.17
Anteroposterior diameter, mm	38.1 ± 5.3	35.8 ± 3.2	39.2 ± 5.6	.01
Bidimensional perimeter, mm	124.6 ± 14.6	114.9 ± 10.4	126.7 ± 14.6	.02
3D perimeter, mm	130.6 ± 16	117.7 ± 10	133.8 ± 15.7	.01
2D area, cm ²	12.04 ± 3.1	10.1 ± 2.1	12.5 ± 3.1	.02
3D area, cm ²	12.45 ± 3.2	10.2 ± 1.9	12.9 ± 3.2	.01
Anterior leaflet length, mm	24.7 ± 3.2	25.1 ± 2.8	26.2 ± 3.1	.11
Posterior leaflet length, mm	13.7 ± 2.4	12.6 ± 2.4	13.8 ± 2.4	.12
Anterior annulus-leaflet length, degrees	27.9 ± 6.3	25.8 ± 2.7	28.5 ± 6.5	.12
Posterior annulus-leaflet length, degrees	43.3 ± 10.8	39.7 ± 8.5	44.2 ± 11.2	.13

ERO, effective regurgitant orifice; LVESVd, left ventricular end-diastolic volume diameter; LVESVi, left ventricular end-diastolic volume index; MR, mitral regurgitation. Data are expressed as n (%) or mean ± standard deviation.

Table 3. Global annular changes

	Absolute reduction	Relative reduction (%)	P
Intercommissural diameter, mm	2.4 ± 2.2	5.99 ± 5.6	< .01
Anteroposterior diameter, mm	4.7 ± 3.8	12.1 ± 8.7	< .01
2D annular perimeter, mm	7.6 ± 7.1	6.1 ± 5.6	< .01
3D annular perimeter, mm	8.5 ± 6.2	6.4 ± 6.1	< .01
2D annular area, cm ²	1.43 ± 1.3	11.8 ± 11.4	< .01
3D annular area, cm ²	1.52 ± 1.3	11.9 ± 12.2	< .01

2D, 2 dimensions; 3D, 3 dimensions.

Data are expressed as n (%) or mean ± standard deviation.

percentage of grasping over the posterior leaflet was the only parameter statistically associated with a lower probability to develop significant MR (OR, 0.89; IC95%, 0.79-0.98).

There was a 16% rate of rehospitalizations due to heart failure and a global mortality rate of 12.5% (table 6). The composite endpoint of all-cause mortality or rehospitalization due to heart failure occurred in 10 (20.8%) patients. In the regression analysis for the composite endpoint of mortality or rehospitalization due to heart failure we did not observe an association between the parameters of annular reduction or the leaflet grasping and the endpoint under study. The heart failure-free or all-cause mortality-free survival curve is shown on figure 2.

DISCUSSION

The main finding of our study is that after TMVR with MitraClip there are important anatomical changes when it comes to the reduction of anteroposterior and intercommissural diameters, the annular diameters and areas, measured both in 2D and 3D. It was observed that, except for the intercommissural diameter, the remaining annular measurements (anteroposterior diameter, perimeter, and area) were significantly enlarged in patients with functional MR compared to patients with organic MR.

Similar to other studies published,^{8,9} it has been observed a significant reduction of the anteroposterior diameter after the implant. However, unlike Remy et al.⁹ describe in patients with functional MR, there was a greater relative reduction of the anteroposterior diameter and a non-significant tendency to a greater reduction of these patients' area. Also, in our series, we saw a reduction of the intercommissural diameter, which may have to do with a significant and sudden reduction of the regurgitation volume and with left intra-articular pressure, rather than with a direct mechanical effect coming from the clip.

With respect to the repercussion of these anatomical changes in the significant clinical results during follow-up, we did not observe any statistically significant correlation between these changes and rehospitalizations due to heart failure or global mortality. There was, however, an inversely proportional correlation between the reduced anteroposterior diameter and the possibility of III/IV MR recurrence (OR, 0.95; 95%CI, 0.89-1.05). This data has been published in former statistically significant studies.¹⁵ It is believed that the lack of signification in our study when it comes to these goals, and the non-association between the magnitude of diameters before the implant and MR recurrence may be associated with

Table 4. Annular changes and mitral leaflet grasping based on the etiology of mitral regurgitation

	Organic MR	Functional MR	P
Intercommissural diameter reduction, %	6.1 ± 5.1	5.9 ± 6.3	.48
Anteroposterior diameter reduction, %	8.6 ± 7.5	13.2 ± 8.8	.05
2D annular perimeter reduction, %	5.4 ± 6.1	6.2 ± 5.5	.35
3D annular perimeter reduction, %	5.6 ± 5.5	6.7 ± 6.2	.35
2D annular area reduction, %	6.8 ± 11.3	13.1 ± 12.4	.09
3D annular area reduction, %	7.2 ± 11.1	13.3 ± 12.4	.10
Anterior leaflet grasping, mm	9.1 ± 3.8	7.3 ± 3.2	.07
Anterior leaflet grasping, %	36.6 ± 11.5	27.8 ± 11.4	.02
Posterior leaflet grasping, mm	4.3 ± 1.4	4.8 ± 1.8	.19
Posterior leaflet grasping, %	34 ± 8.1	34.4 ± 10.6	.44

2D, 2 dimensions; 3D, 3 dimensions; MR, mitral regurgitation.

Data are expressed as n (%) or mean ± standard deviation.

the number of patients of the overall cohort and the low number of events during follow-up.

There was a greater per cent anterior leaflet grasping in patients with organic MR compared to those with functional MR. This data may be explained by the greater anteroposterior annular diameters of patients with MR of functional etiology and by their association with the tenting phenomenon or apical displacement from the coaptation site, thus making an angle of greater magnitude between the annulus and the leaflet and, therefore, more difficulties to encompass the anterior leaflet during the procedure. On the other hand, it was observed that the posterior leaflet grasping was similar in both groups, which is a particularly important aspect because larger grasping percentages are associated with a greater

Table 5. Binary logistics regression analysis. Predictors of grade III-IV/IV mitral regurgitation after transcatheter mitral valve repair

	OR (95%CI)	P
Left ventricular ejection fraction	1.03 (0.97-1.1)	.29
LVESVi	1.01 (0.98-1.03)	.31
Intercommissural diameter relative reduction	1.02 (0.9-1.16)	.65
Anteroposterior diameter relative reduction	0.95 (0.86-1.05)	.50
3D annular perimeter reduction	0.94 (0.8-1.1)	.47
3D annular area reduction	0.99 (0.92-1.06)	.41
Anterior leaflet grasping	0.99 (0.93-1.06)	.96
Posterior leaflet grasping	0.89 (0.79-0.98)	.04

95%CI, 95% confidence interval; LVESVi, left ventricular end-diastolic volume index; OR, odds ratio.

Table 6. Mortality causes

Global mortality	n (%)
Cardiovascular mortality	4 (8.33)
Congestive heart failure	2 (4.17)
Sudden death	1 (2.08)
Acute coronary syndrome	1 (2.08)
Non-cardiovascular mortality	2 (4.17)
Sepsis	1 (2.08)
Neoplasm	1 (2.08)
Total	6 (12.5%)

relative reduction of the anteroposterior diameter with coefficients close to 0.3, which implies that by achieving just a 10% more grasping of the posterior leaflet we would be achieving a 3% reduction in the anteroposterior annular diameter. The posterior grasping was also a protective element against the possibility of significant MR recurrence at follow-up. In this sense, it is believed that patients whose mitral annulus will not allow minimum leaflet coaptation at baseline or will cause excessive tension in the leaflets while grasping with the corresponding risk of tear and break are those patients that may benefit the most from an associated annuloplasty system.

The role that the new generation MitraClip XTr may play in the mitral annular changes of our cohort has not been studied due to the low number of implants of this last device. It would be interesting to publish in the future whether this new device causes changes of different magnitude compared to the previous device, and whether these changes have to do with significant clinical changes at follow-up.

Limitations

This is a single-center study with a modest number of patients (48) and procedures (50). The analysis of predictors of mortality and rehospitalizations due to heart failure may be affected by the small size of the sample and small number of events reported. Also, this is a relatively new technique at our center, meaning that the representation of patients who were followed in the long-term is scarce. Also, no long-term 3D analysis of the mitral annulus after the implant was conducted.

CONCLUSIONS

After TMVR with MitraClip there are morphological changes in the mitral annulus. The magnitude of these changes is different based on the MR etiology. The posterior leaflet grasping is the main factor that influences the appearance of changes and is also associated with a lower probability of significant MR recurrence at follow-up.

FUNDING

This study received no funding whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- After a TMVR procedure, there are morphological changes in the mitral annulus.

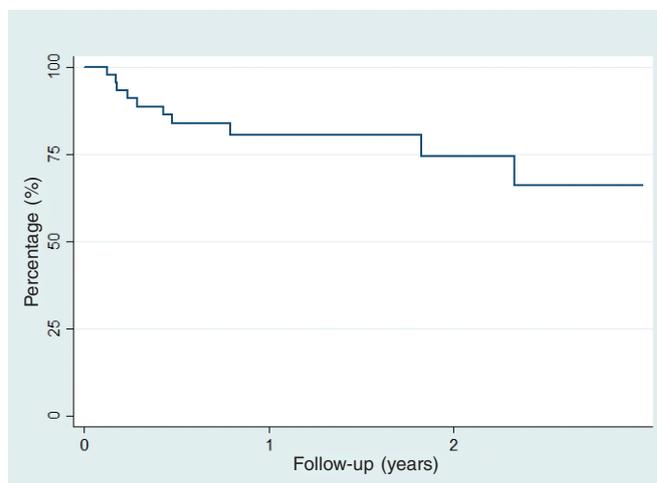


Figure 2. Mortality-free or readmission due to heart failure-free survival estimated using the Kaplan-Meier method.

- Significant reduction of the patients' anteroposterior diameters with functional MR were confirmed, as well as an inverse relation between the reduction of the anteroposterior diameter and the probability of significant MR recurrence.

WHAT DOES THIS STUDY ADD?

- Morphological changes do not happen in isolation in the mitral anteroposterior diameter, but they also affect other diameters, the area, and the perimeter.
- We hereby state that the TMVR with the MitraClip system may induce the reconfiguration of the 3D structure of the mitral valve, due not only to its direct mechanical effect, but also to the modifications of the intracavitary volumes and pressures. How big these changes are is different based on the etiology of MR.
- Posterior leaflet grasping turned out to be a crucial parameter in the morphological changes observed, and a protective factor of significant MR recurrence.

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Antithrombotic therapy after percutaneous revascularization in patients on chronic oral anticoagulation treatment

Juan M. Ruiz-Nodar^{a,*} and José Luis Ferreiro^b

^a Servicio de Cardiología, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

^b Área de Enfermedades del Corazón, Hospital Universitario de Bellvitge - IDIBELL, Universidad de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain



ABSTRACT

The antithrombotic treatment after percutaneous revascularization in patients with chronic indication for oral anticoagulation has always been a matter of great interest and complexity, basically because of the high ischemic and thromboembolic risk of this population and high hemorrhagic risk associated with combination therapy with antiplatelet and anticoagulant drugs. The actual invasive management of ischemic cardiomyopathy has made this population of patients grow and raised concerns on which the optimal drugs and therapeutic strategies really are. Yet despite the scarce scientific evidence available, different antithrombotic regimens have been studied over the last few years in an attempt to reduce hemorrhagic events without affecting the efficacy of the new combination therapies. The strategies studied have been based on shortening the duration of triple anticoagulation therapy, and even on the use of dual anticoagulation therapy (anticoagulation plus one single antiplatelet drug) prioritizing clopidogrel. But it has been the arrival of direct-acting anticoagulants, with important clinical trials conducted on this population, that has provided us with relevant and fundamental information that will undoubtedly contribute to change the actual clinical practice.

Keywords: Atrial fibrillation. Percutaneous coronary intervention. Stent. Oral anticoagulation.

Tratamiento antitrombótico tras revascularización percutánea en pacientes con indicación crónica de anticoagulación oral

RESUMEN

El tratamiento antitrombótico tras una revascularización percutánea en los pacientes con indicación de anticoagulación oral crónica ha sido siempre un tema de máximo interés y de gran complejidad, debido sobre todo al alto riesgo isquémico y tromboembólico intrínseco de esta población, y al elevado riesgo hemorrágico que comporta la combinación de fármacos antiagregantes y anticoagulantes. El manejo invasivo actual de la cardiopatía isquémica hace que esta población esté en crecimiento, aspecto que incrementa el interés por definir cuáles son los mejores fármacos y estrategias terapéuticas. A pesar de la escasa evidencia científica, a lo largo de los últimos años se han estudiado diferentes regímenes antitrombóticos, buscando fundamentalmente una reducción de los eventos hemorrágicos, sin que esto repercutiera en la eficacia de las nuevas combinaciones. Las estrategias estudiadas se han basado en el acortamiento de la duración del tratamiento triple e incluso en el uso del tratamiento doble (anticoagulación más un único antiagregante) priorizando el clopidogrel. Sin embargo, ha sido la llegada de los anticoagulantes de acción directa, con la realización de importantes ensayos clínicos en esta población, lo que está aportando información relevante y trascendente que, sin lugar a dudas, contribuirá a modificar la práctica clínica.

Palabras clave: Anticoagulación oral. Fibrilación auricular. Intervencionismo coronario percutáneo. Stent.

Abbreviations

ACS: acute coronary syndrome. **AF:** atrial fibrillation. **ASA:** acetylsalicylic acid. **DAPT:** dual antiplatelet therapy. **DAT:** dual antithrombotic therapy. **DOAC:** direct oral anticoagulation. **NOAC:** non-vitamin K antagonist oral anticoagulant. **PCI:** percutaneous coronary intervention. **P2Y₁₂:** P2Y₁₂ receptor inhibitor. **TAT:** triple antithrombotic therapy. **VKA:** vitamin K antagonist.

* **Corresponding author:** Unidad de Hemodinámica, Hospital General Universitario de Alicante, Maestro Alonso s/n 2.ª planta, 03010 Alicante, Spain. E-mail address: ruiz_jmi@gva.es (J.M. Ruiz-Nodar).

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INTRODUCTION

The antithrombotic management of patients with atrial fibrillation (AF) who undergo percutaneous coronary interventions (PCI) has been, is, and will always be cause for study discussion, and research. The complexity of this population with high comorbidity leads to a poor prognosis in the mid and long term with a high rate of ischemic events. On the other hand, the use of combined antithrombotic therapies (dual or simple antiplatelet and anticoagulant drugs) aimed at improving the ischemic prognosis of these patients generates a number of hemorrhagic complications we should not overlook that has made us have to look for safer antithrombotic regimens (both in intensity and time) without affecting the efficacy.

The complexity of these patients and the difficulty when trying to include them in clinical trials that are actually representative of the real world has led to us obtain the information on the optimal antithrombotic regime from the information provided by registries, meta-analyses, and expert and work group recommendations.

It is precisely the arrival of direct-acting oral anticoagulants (DOAC), safer drugs and, at least, as efficient as vitamin K antagonists (VKA) for the management of AF, that has brought us new evidence on this regard. The existence of an important number of patients with AF treated with stents has produced four large clinical trials that compare the safety and efficacy of DOAC and VKA with the use of different antithrombotic regimens.

Throughout this article we will be reviewing the evidence available on this fundamental population so important for its elevated prevalence, poor prognosis and amazing advances we have witnessed over the last few years and the new advances that are still to come.

MAGNITUDE OF THE PROBLEM AND PROGNOSIS

The prevalence of patients with AF treated with PCI goes from 6% to 10% depending on the different registries, the populations included, and the syndromes treated. There seems to be a higher prevalence of AF in patients revascularized due to stable angina compared to those due to acute coronary syndrome. Thus, Rohla et al.¹ describe a 10.2% prevalence in stable patients versus 6.5% in patients revascularized due to ACS. This prevalence grows bigger in the Spanish registries with ACS up to 8%-9%.^{2,3} We are, therefore, talking about very well-known patients in the cardiology units and interventional suites.

However, what is really important here is to be able to recognize how the presence of AF in patients who have been percutaneously revascularized is one of the predictors of the worst prognoses possible. In general, and without evaluating what the influence of the treatment is in all this, in the mid-term (20-month follow-up) one out of every three patients (32.3%) will have a major adverse event and almost 1 in out of every 4 (22.6%) will die because of it.⁴ When comparing this population to patients without AF, we can see how long-term mortality (56 months) triples for just having AF (41% versus 13%), being the presence of arrhythmia one of the greatest predictors of mortality.

Another aspect that we should take into consideration is the appearance of de novo AF in patients hospitalized due to ACS. The information from the ARIAM registry (Analysis of delay in acute myocardial infarction)² describes how patients with de novo AF can amount to 55% of all patients with AF who are hospitalized due to ACS.

What is important here is not only the high percentage of this presentation, but also the poor hospital prognosis associated with it, which happens to be an independent predictor of hospital mortality and is associated with a higher presence of reinfarction, malignant arrhythmia, and heart failure.

The worst prognosis of these patients is associated with their advanced age, greater comorbidity and, on many occasions, because they go undertreated both with recommended strategies (fewer catheterizations and percutaneous revascularizations) and drugs.^{2,5}

Another fundamental aspect in this poor prognosis situation is the use of the recommended antithrombotic therapies. The high ischemic risk of these patients requires regimens that are based on a combination of dual or simple antiplatelet and anticoagulant drugs. The quest for reducing ischemic events increases the number of drug-induced severe hemorrhages that have been correctly prescribed. Eventually, these hemorrhagic complications end up being determinant in the patient's prognosis.

So, it is essential to identify this population and its associated risk to be able to come up with the optimal treatment strategies and measures during the hospital stay, discharge, and follow-up, in an attempt to improve the prognosis that is severe per se.

ANTITHROMBOTIC THERAPY WITH VITAMIN K ANTAGONISTS: DUAL OR TRIPLE THERAPY

Chronic oral anticoagulation (OAC) is superior to antiplatelet therapy (whether monotherapy or dual therapy) when it comes to the prevalence of thromboembolic complications (stroke and systemic embolism) of AF,^{6,7} while the dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a P2Y₁₂ receptor inhibitor (P2Y₁₂) is the antithrombotic therapy of choice to prevent atherothrombotic ischemic events (myocardial infarction and stent thrombosis) in patients who undergo PCI (in the context, or not, of an ACS).^{8,9} When both situations occur picking the antithrombotic therapy becomes a clinical issue because it is well-known that the easiest choice, that is, the use of triple antithrombotic therapy (TAT plus OAC and dual antiplatelet therapy) increases the risk of major hemorrhages at least 2 to 3-fold compared to any other antithrombotic regimens, whether dual antiplatelet therapy or dual antithrombotic therapy (DAT plus OAC and one antiplatelet drug).^{10,12} Therefore, controversy arises on whether or not using TAT due to the increase of hemorrhagic complications and the possible increase of ischemic events when using less aggressive therapies like DAT.

The higher hemorrhagic risk associated with the use of TAT has been consistently confirmed by numerous observational studies (including large registries), while findings on the prevention of antithrombotic events are not that clear, although, in general, no significant differences have been found between the TAT and the DAT when it comes to reducing ischemic events.^{12,14} It is important to say here that the higher hemorrhagic risk associated with TAT is kept throughout the entire duration of the TAT regimen¹² which is why, if we decide to give it a go, the evidence available tells us we should keep it the shortest time possible to obtain the benefit of less atherothrombotic events. On the other hand, we should look back at studies conducted in the 1990s that started talking about dual antiplatelet therapies in the context of PCI with coronary stents.^{15,18} In these studies, the dual antiplatelet therapies (ASA plus thienopyridine) was beneficial for reducing ischemic events, particularly the first month after the PCI compared to a DAT strategy (ASA plus VKA) (table 1). Also, we should mention here that the ischemic events (myocardial infarction or stent thrombosis) that happen the first month after the PCI have worse

Table 1. Randomized clinical trials comparing dual antiplatelet therapy (ASA and VKA) and dual antithrombotic therapy after coronary stenting

Clinical trial	Treatment groups	Major cardiac adverse events		Hemorrhagic events	
		Definition	Results	Definition	Results
ISAR ¹⁵ (n = 517)	DAPT (ASA + ticlopidine) versus DAT (ASA + VKA)	Cardiac death, MI, revascularization surgery or reintervention at 30 days	1.6% versus 6.2%; <i>P</i> = .01	Any bleeding at 30 days	0% versus 6.5%; <i>P</i> < .01
STARS ¹⁶ (n = 1.653)	ASA versus DAPT (ASA + ticlopidine) versus DAT (ASA + VKA)*	Death, MI, ST or target lesion revascularization at 30 days	0.5% versus 2.7%; <i>P</i> = .01	Any bleeding at 30 days	5.5% versus 6.2%; <i>P</i> = .99
MATTIS ¹⁷ (n = 350)	DAPT (ASA + ticlopidine) versus DAT (ASA + VKA)	CV death, MI or new revascularization at 30 days	5.6% versus 11.0%; <i>P</i> = .07	Major hemorrhage or major vascular complication at 30 days	1.7% versus 6.9%; <i>P</i> = .02
FANTASTIC ¹⁸ (n = 485)	DAPT (ASA + ticlopidine) versus DAT (ASA + VKA)	Death, MI, or stent occlusion at 6 weeks	5.7% versus 8.3%; <i>P</i> = .37	Any bleeding at 6 weeks	13.5% versus 21.0%; <i>P</i> = .03

ASA, acetylsalicylic acid; CV, cardiovascular; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; MI, myocardial infarction; ST, stent thrombosis; VKA, vitamin K antagonist.

* Only the results from the comparison between dual antiplatelet therapy and dual antithrombotic therapy are reported here.

prognosis when it comes to mortality compared to those that happen later in time.^{19,20}

However, we should be cautious when drawing conclusions or making comments in favor or against TAT based on observational studies since, down the road, they are limited and non-randomized which can produce significant biases (such as, in this case, confusion bias by indication of different antithrombotic regimens based on the characteristics of the patients). For all this, we should emphasize the results from randomized clinical trials although, as we will see below, they also have limitations especially when it comes to the assessment of efficacy (prevention of ischemic events).

Before jumping into what we could call the era of the DOAC, two randomized clinical trials that assessed the safety of different antithrombotic strategies with VKA were conducted: the WOEST and the ISAR-TRIPLE.^{21,22} The WOEST trial included 573 patients with need for OAC (for several indications, 69% with AF or atrial flutter) who were randomized to receive TAT with VKA versus DAT consistent of clopidogrel plus VKA, and confirmed a significant reduction of the risk of bleeding (all bleeding events) at one year-follow-up in patients who received DAT (19.4% versus 44.4%; hazard ratio [HR], 0.36; 95% confidence interval [95%CI], 0.26-0.50; *P* < .001),²¹ although this benefit was mainly due to the occurrence of less minor bleeding events, while no increase of atherothrombotic events was confirmed in the group on DAT (figure 1). The study has been criticized for its numerous limitations among which we find the lack of statistical power to assess the variables of efficacy, the inclusion of patients with relative low risk of ischemic events (little more than 25% with ACS) and the presence of other aspects that may favor an increase of bleeding such as an excessive duration of the course of TAT in the control group (1 year, the most highly recommended), the femoral access in most cases, and the low use of proton pump inhibitors (PPI).²³ Yet despite all this, the relevance of the WOEST trial is evident since it was the very first trial to ever question the need for TAT and hypothesized whether using DAT right after the PCI in this scenario was a real possibility.

The ISAR-TRIPLE trial randomized 614 patients with an indication for OAC (83.9% with AF) who underwent PCIs with drug-eluting stents and 2 different courses of TAT: 6 months (long) versus 6

weeks (short) (both including ASA, clopidogrel plus VKA followed by ASA plus VKA).²² No differences between the 2 courses of TAT were reported when it comes to the main variable (a composite endpoint of death, myocardial infarction, definitive stent thrombosis, and major bleeding according the Thrombolysis in Myocardial Infarction [TIMI]) classification at 9 months (9.8% versus 8.8%; HR, 1.14; 95%CI, 0.68-1.91; *P* = .63). No significant differences were found either when it comes to the ischemic events and the hemorrhagic events separately. However, the analysis of the events that occurred at 6 weeks (once clopidogrel was withdrawn in the arm that received the short TAT course) confirmed a slight increase of all bleeding events according to the classification established by the Bleeding Academic Research Consortium (not the TIMI classification) in the arm that received the long TAT course. Yet despite the limitations of both studies, and the fact that the main absence was the lack of statistical power for an adequate assessment of the efficacy of the different strategies analyzed on the prevention of atherothrombotic events, its results suggest that the duration of the TAT should not be extended for no reason to avoid increasing the hemorrhagic risk beyond necessary.

WHERE DO DIRECT-ACTING ORAL ANTICOAGULANTS STAND?

Among the strategies used to reduce hemorrhagic complications due to the use of antithrombotic drugs and on top of reducing the courses of TAT or withdrawing ASA in certain high-risk groups, the use of DOAC is another strategy to take into consideration here.

The best safety profile of these new anticoagulant drugs, together with the logical interest to make them the leading therapy in large populations and their room for improvement, fostered a clinical trial for each and every DOAC already approved.

With the information available today, the last European guidelines on clinical practice recommend the use of DOAC in this population of patients to the detriment of VKA.^{8,24}

Although the 4 clinical trials conducted compared patients with AF who were revascularized with PCI, the safety of the new

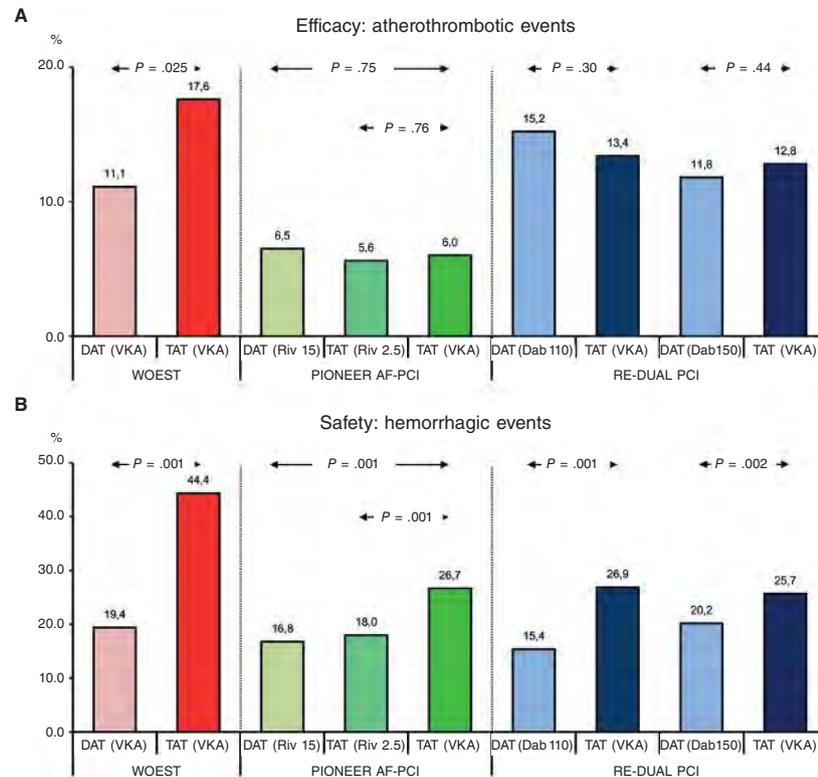


Figure 1. Results from randomized clinical trials of triple therapy versus dual antithrombotic therapy in patients with an indication for chronic oral anticoagulation undergoing percutaneous coronary interventions. Safety: hemorrhagic events (A). Efficacy: major adverse cardiac events (B). The definitions of the main variable of safety vary depending on the study: WOEST, any hemorrhagic event at 12 months; PIONEER AF-PCI, clinically significant hemorrhage (TIMI) at 12 months; RE-DUAL PCI, major bleeding or clinically relevant bleeding (ISTH) at follow-up (average, 14 months). The definitions of major adverse cardiac events vary from one study to the next: WOEST, death, myocardial infarction, stroke, target vessel revascularization, or stent thrombosis at 12 months; PIONEER AF-PCI, cardiovascular mortality, myocardial infarction or stroke at 12 months; RE-DUAL PCI, death, thromboembolic event (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization at follow-up. Dab 110, dabigatran at 110 mg/12 hours; Dab 150, dabigatran at 150 mg/12 hours; DAT, dual antithrombotic therapy; Riv 2.5, rivaroxaban 2.5 mg/12 hours; Riv 15, rivaroxaban at 15 mg/24 hours; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist.

anticoagulant drugs versus TAT (VKA, ASA and clopidogrel) and showed very similar inclusion and exclusion criteria, there are significant differences in the antithrombotic regimens and drug dosage used, which in turn could influence the conclusions of the trials and eventually have practical repercussions. We hereby present, in chronological order, the 4 large clinical trials already published or in follow-up stages today, including the most relevant aspects and most controversial issues. Table 2²⁵ shows the design, goals, and main findings of each and every one of these trials.

The PIONEER AF-PCI trial

The PIONEER AF-PCI trial was the first trial published. It is a multicenter international trial that randomized 2124 patients with AF revascularized with stents into three treatment strategies: rivaroxaban at 15 mg/day and P2Y₁₂; rivaroxaban at 2.5 mg/12 hours and ASA plus P2Y₁₂; or TAT (VKA, ASA plus clopidogrel).²⁶ The primary endpoint was the occurrence of clinically significant bleeding (major or minor bleeding according to the TIMI classification) or hemorrhages requiring medical attention.

The goal of this study was achieved for both groups on rivaroxaban (16.8% and 18% versus 26.7%; $P < .001$). When it comes to

efficacy, ischemic events (cardiovascular death, infarction, or stroke) and global mortality were similar in the 3 groups, yet the study did not have enough statistical power to be able to assess differences when it comes to efficacy. The authors concluded that the treatment with rivaroxaban at 15 mg/day plus clopidogrel with or without rivaroxaban at 2.5 mg/12 hours plus clopidogrel and ASA is safer than TAT with VKA, clopidogrel and ASA.

This was the first study that brought DOAC to this population, but many more things should be said on this regard. We do not know if these two doses of rivaroxaban are enough to prevent strokes from happening in patients with AF compared to VKA or rivaroxaban in doses of 20 mg/day in patients with normal renal function.^{27,28} The dose of rivaroxaban at 15 mg/24 hours has not been studied widely in patients with AF in thromboembolic prevention and can be controversial when it comes to recommending it in all kinds of patients. And the same thing happens with doses at 2.5 mg/12 hour studied for the management of ischemic heart disease but not for the management of atrial fibrillation, but still presumed clearly insufficient.

The use of these doses not approved for the management of AF has placed rivaroxaban as the first studied DOAC in this population of patients with a positive safety profile and has generated an indication with a level IIB evidence only in the European

Table 2. Differential characteristics and fundamental findings of the 4 clinical trials comparing direct-acting oral anticoagulants versus antithrombin K anticoagulants in patients with atrial fibrillation percutaneously revascularized

Study	Population	Patients	Study groups	Control groups	Objetivo primario de seguridad	Principales hallazgos	Eficacia	
PIONEER AF-PCI ²⁶	Patients with AF undergoing PCI	2.124	Rivaroxaban at 15 mg/24 h + P2Y ₁₂	Warfarin + P2Y ₁₂ + ASA	Clinically significant bleeding (TIMI classification)	TIMI major (12%), minor (7%) bleeding requiring medical attention (85%)	The percentage of bleeding was lower in the two rivaroxaban groups (16.8% and 18%) compared to the control group (26.7%); <i>P</i> < .0001	Non inferior. Study not statistically powered to detect efficacy differences
RE-DUAL PCI ²⁹	Patients with AF undergoing PCI	2.725	Dabigatran at 150 mg/12 h + P2Y ₁₂	Warfarin + P2Y ₁₂ + ASA	Major bleeding or clinically relevant bleeding (ISTH classification)	ISTH major bleeding (32%) or non-major clinically relevant bleeding (68%)	The percentage of bleeding was lower in the two dabigatran groups (20.2% and 15.4%) compared to the control group (25.7% and 26.9%, respectively); <i>P</i> < .0001	Non inferior. Study not statistically powered to detect efficacy differences
AUGUSTUS ³¹	Patients with AF or PCI	4.614	Apixaban at 5 or 2.5 mg/12 h + P2Y ₁₂ + ASA	Warfarin + P2Y ₁₂ + ASA	Major bleeding or non-major bleeding (ISTH classification)	Warfarin + IP2Y ₁₂	The percentage of bleeding was lower with apixaban compared to VKA (10.5% and 14.7%; <i>P</i> < .001) and with placebo versus ASA (9% and 16.1%; <i>P</i> < .001)	Less hospital admissions with apixaban, and a similar incidence of ischemic events
ENTRUST-AF PCI ³²		1.500	Edoxaban at 60 mg/24 h + P2Y ₁₂	Warfarin + P2Y ₁₂ + ASA	Major bleeding or non-major bleeding (ISTH classification)		In the follow-up stage	In the follow-up stageswww

ASA, acetylsalicylic acid; ACS, acute coronary syndrome; AF, atrial fibrillation; ISTH, International Society on Thrombosis and Hemostasis; P2Y₁₂, P2Y₁₂ receptor inhibitor; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; VKA, vitamin K antagonist. Modified with permission from Lip et al.²⁵

guidelines on dual antiplatelet drugs (rivaroxaban at 15 mg/day),⁸ strangely enough lower to the one assigned to the use of doses of rivaroxaban at 20 or 15 mg/day (based on the renal function), based on its general study and sub-studies (IIaC).^{8,27}

The RE-DUAL PCI trial

The RE-DUAL PCI clinical trial randomized 2725 patients into 3 groups (TAT plus VKA, dual therapy with dabigatran at 150 at mg/12 hours and dual therapy with dabigatran at 110 mg/12 hours) based on the hypothesis that dual therapy with dabigatran and P2Y₁₂ may be safer than the standard therapy with TAT in patients with AF who undergo PCI.²⁹ The incidence of the primary event (major or clinically relevant bleeding according to the International Society on Thrombosis and Haemostasis [ISTH]) classification was 15.4% for doses of dabigatran at 110 mg and 26.9% for TAT (HR, 0.52; $P < .0001$ for non-inferiority and superiority), and 20.7% for doses of dabigatran at 150 mg versus 25.7% for TAT (HR, 0.72; $P < .0001$ for non-inferiority). The incidence of the composite event of efficacy was similar in all 3 groups. The study concludes that in patients with AF who undergo PCI, the risk of bleeding was lower in both groups of dabigatran compared to TAT, with no significant differences of efficacy.

The most relevant issue is the safety profile dabigatran brings to the table with a reduction of 48% in patients treated with dabigatran at doses of 110 mg and 24% in those treated with dabigatran at doses of 150 mg. In defense of this study, we should mention that the doses used were the same ones than the doses used in the RELY trial,³⁰ that proved its efficacy and safety for the management of non-valvular AF which would later be confirmed in wide real world registries.

The main doubt following this study came with the finding of an incidence of stent thrombosis close to 1.5% in the dabigatran group at 110 mg versus 0.8% in the TAT group ($P = .15$), and a higher infarction rate (4.5% versus 3.0%; $P = .09$). We should mention here that these rates of thrombosis and infarction were not observed with the highest possible dose of 150 mg/12 hour. And even though the differences were not statistically significant, these data should make us think whether we are going from very powerful antithrombotic regimens to too light antithrombotic regimens in an attempt to prioritize safety over efficacy. And the second question here that still remains is that we still need to know whether the best safety profile of dabigatran is so due to the greater safety of the drug or to the non-exposure to the ASA. At the end of the day, these two clinical trials do not compare similar strategies (triple versus dual therapy) which means that they will not be able to solve issues that are absolutely critical.

In spite of everything, the REDUAL-PCI trial should be considered a landmark study that accurately assessed this new therapeutic option in patients with AF treated with stents and even more accurately in patients with high hemorrhagic risk.

The AUGUSTUS trial

The AUGUSTUS³¹ trial is undoubtedly the one that was best structured and answered a lot of questions. This trial was designed with a factorial 2 x 2 design to compare apixaban with VKA plus ASA versus placebo in patients with AF and ACS undergoing PCI or receiving P2Y₁₂. This is the largest study and included 4614 patients.

The primary endpoint is a composite of major bleeding and non-clinically relevant bleeding following the ISTH classification.

The study secondary endpoints are all-cause mortality, all-cause hospitalizations, and ischemic events.

The primary event incidence rate was 10.5% in the apixaban group vs 14.7% in the VKA group (HR = 0.69; $P < .001$ for inferiority and superiority) and 16.1% in patients who received ASA vs 9% in those who received placebo (HR = 1.89; $P < .001$). The patients in the apixaban group had a lower incidence rate of hospitalization compared to those from the KVA group and a similar number of ischemic events

It seems clear that this study confirms the superiority of DOACs in this population of patients thanks to their more evident safety profile. However, it probably does not generate enough evidence to withdraw ASA and make it the standard routine in these patients. We should emphasize here the presence of more thromboembolic events in the placebo group compared to the ASA group with twice as much stent thrombosis. This difference was not statistically significant and can generate doubts due to the lack of statistical power to detect ischemic events. Also, we should remember that patients were randomized days or weeks after the ischemic event happened and that they had ASA until the randomization stage.

The ENTRUST-AF PCI trial

The ENTRUST-AF PCI clinical trial³³ still in the follow-up stage, randomized 1500 patients with AF on anticoagulant therapy and revascularized with PCI, to 2 therapeutic strategies: edoxaban at 60 mg/24 hours (or 30 mg if the necessary criteria are met for this dose) plus one P2Y₁₂ versus TAT with VKA. The primary safety endpoint is the incidence of major bleeding and non-clinically relevant bleeding following the ISTH classification, and the primary efficacy endpoint is a composite of cardiovascular mortality, stroke, embolism, infarction, or definite stent thrombosis.

The small size of the study will only answer to whether a dual therapy with edoxaban is safer than a therapy with TAT and VKA. It is easy to hypothesize that this will be the case since, at the end of the day, identical conditions are not being compared since ASA is being withdrawn from the edoxaban group, same as it happened with the REDUAL-PCI trial. Also, the lack of statistical power should not be able to show any differences in efficacy between both strategies.

CONSIDERATIONS OF CLINICAL PRACTICE GUIDELINES

Over the last few years, different clinical practice guidelines have been designed by different scientific societies and consensus documents have been established by different expert groups that have brought a series of recommendations for the management of anti-thrombotic therapy in patients with a need for chronic OAC who undergo PCI.^{7,8,24,25,33,34} The fact that the recommendations established by these documents are not always coincidental added to the fact that most of them show low levels of evidence only tells us how complex this clinical scenario is.

When it comes to antithrombotic therapy post-PCI, the most recent recommendations (that incorporate results from studies on DOAC) from the European scientific societies can be summed up in the following items:^{8,24,25}

- TAT with ASA, clopidogrel and OAC for a month is the strategy of choice in patients who receive a stent, regardless of the type of stent being implanted.

- TAT at least 1 month in patients with high ischemic risk due to ACS or other anatomical or procedural characteristics that exceeds their hemorrhagic risk.
- Initial DAT with OAC and clopidogrel (the preferred one) or ASA in patients with high hemorrhagic risk that exceeds their ischemic risk.
- In patients with non-valvular AF, the use of DOAC should be recommended.
- DOAC should be administered in their lowest effective dose to avoid strokes as assessed by AF trials.
- The use of a 15 mg dose of rivaroxaban (instead 20 mg) can be considered, although its efficacy in the prevention of stroke has not been appropriately assessed yet.
- When DAT is used the preferred dose of dabigatran is 150 mg/12 hours.
- In case of using VKA, the objective International Normalized Ratio should be in the low range while time in the therapeutic range should be > 65%.
- The use of ticagrelor or prasugrel as part of the TAT is not recommended.
- Withdrawing antiplatelet therapy should be considered and only leave the OAC 12 months after the procedure, although we can still add antiplatelet drugs in particular cases based on ischemic risk.

On this regard, we should mention a consensus document written by US experts that has been controversial because it recommends, among other things, DAT as the strategy of choice in most cases plus withdrawing TAT 1 entire month, at most, in patients with high ischemic risk and low hemorrhagic risk.³⁴ In sum, these differences emphasize how difficult it is to manage these patients, how varied the different interpretations of the studies available are, and how important it is to have more scientific evidence available on this regard.

OPTIMIZE THE BALANCE BETWEEN EFFICACY AND SAFETY. PRACTICAL CONSIDERATIONS

Once the evidence generated by the studies and the clinical practice guidelines have been analyzed, it seems evident that we need to make thorough assessments of the individual risk of each patient to suffer ischemic, thromboembolic, and hemorrhagic events (figure 2). These individual assessments should incorporate the evaluation of factors associated with the patient and the procedure being conducted.

Therefore, there are clinical characteristics (presentation as ACS, prior history of myocardial infarction or stent thrombosis, presence of comorbidity such as diabetes mellitus, renal failure, or peripheral artery disease, etc.), coronary anatomy characteristics (multivessel diffuse disease) and PCI characteristics (complex procedures with treatment of various lesions, implantation of several stents or stents of a significant length, 2-stent techniques in bifurcations, chronic occlusions, etc.) that suggest higher ischemic risk, and that should be taken into consideration when choosing more powerful and longer regimens.^{8,35} The other side of this story would be those factors that may condition higher hemorrhagic risk (prior history of major bleeding or hemorrhagic stroke, short life expectancy, anemia, older age, active neoplasm, severe renal

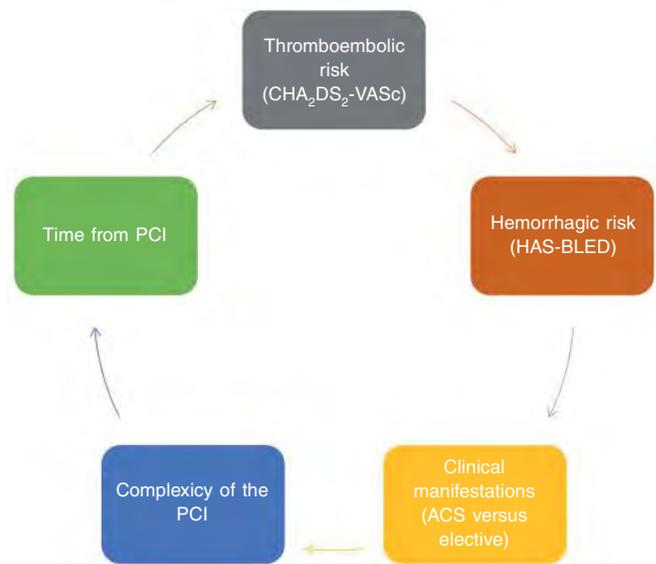


Figure 2. Variables that should be taken into consideration when deciding what the optimal antithrombotic therapy is in patients with atrial fibrillation undergoing percutaneous coronary interventions. AF, atrial fibrillation; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome.

failure, frailty, etc.) that should also be taken into consideration when choosing less powerful shorter antithrombotic strategies. When it comes to the type of stent being implanted, the greater safety profile that last generation drug-eluting stents bring is a reality these days in patients of high hemorrhagic risk,^{24,36} and their use should be generalized. In any case, from the practical point of view, the first step in all patients is to consider and apply a series of measures that contribute to minimize the risk of bleeding, when possible, before, during, and after the PCI (figure 3).

Both the aforementioned clinical trials that compared TAT plus VKA versus strategies of DAT plus VKA or DOAC,^{21,26,29} and some meta-analyses that grouped the data of such trials^{37,38} showed higher hemorrhagic risks with the use of TAT without finding a clear benefit of this regimen when it comes to reducing ischemic events. However, with the actual evidence available, ruling out the TAT does not seem justified in this scenario for several reasons: 1) none of the clinical trials had enough statistical power to assess adequately the variables of efficacy (ischemic and thromboembolic events); 2) another limitation of these clinical trials was the inclusion of patients with relatively low risk of atherothrombotic events, which means that we do not have enough information to ensure the efficacy of DAT regimens in individuals with high risk of ischemic events or strokes; and 3) the ischemic events (myocardial infarction and stent thrombosis) that occur early after the PCI have worse prognosis, which would also suggest ruling out the TAT, at least, in the initial period after the procedure. For all these reasons, the authors' opinion (which is consistent with the European guidelines) is that, with the actual evidence available, after an individualized thorough assessment of the patient's ischemic and hemorrhagic risk, it seems advisable to implement an initial TAT strategy during the shortest time possible (when each patient has the highest probability of suffering from an ischemic adverse event) in order to not increase, unnecessarily, the risk of bleeding, thus leaving DAT as an alternative in those individuals with high hemorrhagic risk -actually higher than their ischemic risk. In sum, patients in whom there is not clear leverage from using TAT for the prevention of atherothrombotic events. As

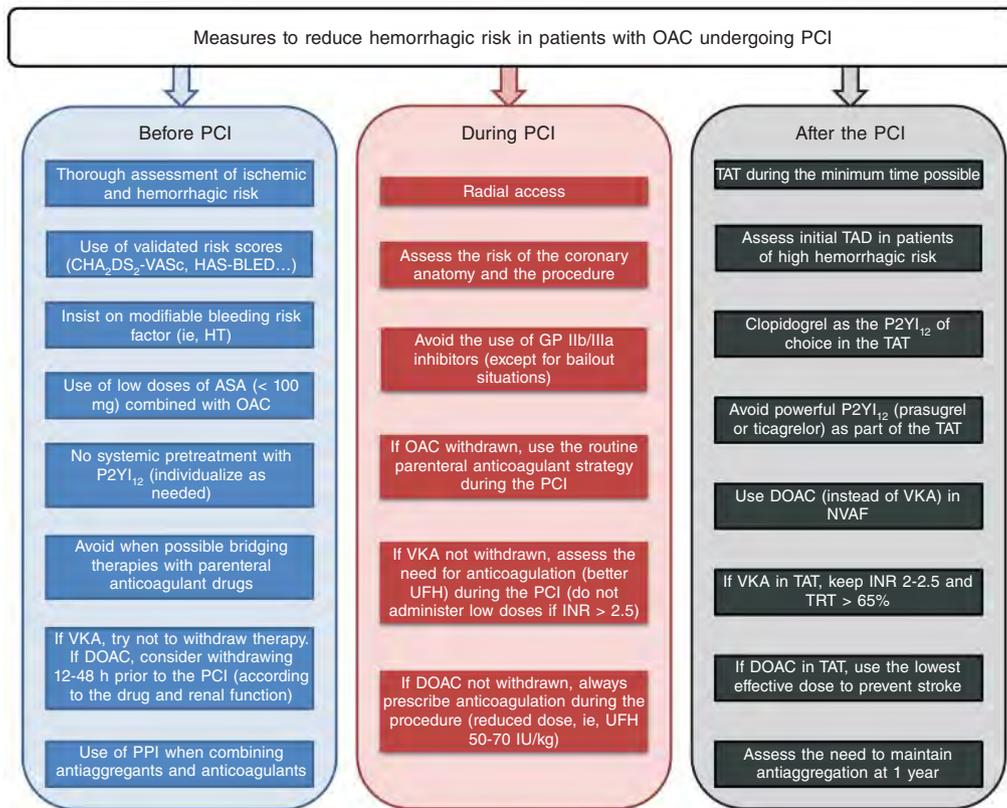


Figure 3. Measures that should be taken into consideration to reduce the hemorrhagic risk of patients with an indication for chronic oral anticoagulation undergoing percutaneous coronary interventions. AAS, acetylsalicylic acid; DAT, dual antithrombotic therapy; DOAC, direct-acting oral anticoagulants; GP, glycoprotein; HT, hypertension; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulation; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; P2Y₁₂, P2Y₁₂ receptor inhibitor; TAT, triple antithrombotic therapy; TTR, time in the therapeutic range; UFH, unfractionated heparin; VKA, vitamin K antagonist.

a practical, though empirical recommendation, one month of TAT seems enough in most patients with PCI and in the context of stable ischemic disease, while in patients with ACS, it is recommended to implement individual courses of TAT (1 through 6 months) and always based on the aforementioned balance of risks. However, the 6-month duration of TAT seems advisable for patients with a very high risk of ischemic events only.

When it comes to choosing the anticoagulant drug, the DOAC, due to their safety profile, seem the optimal drugs in a clinical context where the risk of bleeding is very high due to the necessary combination of antiplatelet drugs.²⁴ When it comes to the dose of DOAC used, in the TAT we should be using the minimum dose possible that has proven effective for the prevention of strokes in landmark trials on AF.^{8,24} And this is a particularly relevant aspect since there are more and more evidences that tell us that using unnecessary reduced doses of DOAC (not meeting the adjustment criteria specified in the label) is associated with more thromboembolic events at follow-up.³⁹ If we choose dabigatran, it is recommended to use doses of 110 mg during the TAT and doses of 150 mg if the patient is on DAT.

And even though data from clinical trials on the combination of OAC plus a powerful P2Y₁₂ are really scarce (< 6% in the PIONEER AF-PCI trial and approximately 12% of ticagrelor in the RE-DUAL PCI trial), several observational studies have shown very high rates of bleeding with the use of prasugrel or ticagrelor as part of the TAT.^{40,41} Choosing ASA or clopidogrel as part of the DAT can be somehow controversial; even though the clinical

guidelines advocate for the use of clopidogrel as the antiplatelet drug of choice in this context, the combination of ASA plus OAC is also valid and can be an option especially if we take into account that a significant number of patients (around 15%-30% in our context) show inadequate answers to clopidogrel.⁴²

CONCLUSIONS

The patient treated with anticoagulant drugs who is percutaneously revascularized has a poor prognosis in the mid and long-term and a high incidence rate of ischemic, thromboembolic, and hemorrhagic events.

As a summary to this paper, we could make the following overall recommendations while taking into consideration that the complexity of these patients will always require individual therapies in each case:

- The intensity and duration of antithrombotic therapy should be determined by the patient's clinical manifestations which established the revascularization and by the patient's ischemic, thromboembolic, and hemorrhagic risks. The type of stent is no longer a variable that will influence the decision-making process on the antithrombotic therapy of this population, and most patients will require drug-eluting stents because they are safer and more effective compared to conventional stents.

- When choosing TAT, its duration should be reduced as much as possible and it should focus on the period of highest ischemic risk and stent thrombosis in order to minimize hemorrhagic risk. With the information available today, the use of TAT seems justified in patients where ischemic risk is prioritized and in whom hemorrhagic risk is somehow acceptable.
- In patients where hemorrhagic risk is prioritized over ischemic risk, DAT may be indicated (anticoagulation plus one single antiaggregant agent, being clopidogrel the one preferred by the clinical practice guidelines) from revascularization.
- The use of new antiaggregant agents (prasugrel or ticagrelor) is clearly not recommended in this population. They should be contraindicated as part of the TAT (except for certain exceptions) and there is little evidence on their use in DAT regimens.
- The use of DOAC in this context seems especially beneficial and is recommended by the most recent clinical practice to the detriment of VKA. Although we do not have enough statistically powerful trials to be able to determine differences of efficacy, the evidence we have so far speaks to us about the superiority of DOAC as safer drugs of a similar efficacy. It is important to emphasize that we should indicate DOAC doses that have proven their efficacy in the prevention of thromboembolic events in general studies of patients with AF.
- Regardless of the antithrombotic recommendations, general measures should always apply associated with the procedure in an attempt to reduce hemorrhagic events (radial access, avoid bridging therapies when possible, or contraindicate the use of glycoprotein IIb/IIIa inhibitors except when in bailout situations).

CONFLICTS OF INTEREST

J.M. Ruiz-Nodar declares to have received fees for lectures given on behalf of AstraZeneca, Biosensor, Boston Scientific, Medtronic, and Terumo. J.L. Ferreiro declares to have received fees for lectures given on behalf of Eli Lilly Co., Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, and Boehringer Ingelheim; and fees received in his capacity of consultant for AstraZeneca, Eli Lilly Co. and Ferrer declares to have received research grants from AstraZeneca.

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Debate: MitraClip. The heart failure expert perspective

A debate: MitraClip. Perspectiva del experto en insuficiencia cardiaca

Julio Núñez^{a,b,*}

^a Servicio de Cardiología, Hospital Clínico Universitario de Valencia, INCLIVA, Universidad de Valencia, Valencia, Spain

^b CIBER de Enfermedades Cardiovasculares (CIBERCIV), Spain



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QUESTION: There is no doubt that the most significant advances made back in 2018 in interventional cardiology were the long-awaited results from clinical trials with MitraClip (Abbott Laboratories, Abbott Park, Illinois, USA): the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) presented at the congress organized by the European Society of Cardiology, and the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) presented at the Transcatheter Cardiovascular Therapeutics (TCT) congress. Both trials have been discussed extensively. Could you please tell us what the basic differences are in the results obtained by these 2 trials?

ANSWER: That's right, both trials have put the spotlight on mitral regurgitation (MR) as the therapeutic target in patients with heart failure and reduced ejection fraction (HF-REF). The COAPT trial randomized 614 patients with HF-REF (left ventricular ejection fraction between 20% and 50%) and moderate-to-severe HF treated with the optimal medical therapy in order to follow 2 therapeutic strategies (1:1): a) optimal medical therapy, or b) optimal medical therapy plus percutaneous implant of MitraClip.¹ After 2 years there was a 47% reduction in the risk of the primary endpoint of efficacy (hospitalizations due to heart failure) in the intervention group. Similarly, there was a significant drop in all-cause mortality (hazard ratio, 0.62; 95% confidence interval, 0.46-0.82; $P < .001$) and other secondary endpoints.¹ When it comes to the primary endpoint of safety, a relatively low number of complications due to the technique 12 months after the intervention was reported. The number of patients needed to treat to avoid hospitalization was 3.1 and 5.7 to avoid mortality. These data of clinical efficacy are far more superior than the ones seen in most drugs with confirmed effectiveness in the management of HF-REF and similar to those from other measures such as the administration of antibiotics for the management of infectious diseases or the percutaneous implant of aortic valve prostheses for the management of severe aortic stenosis.

However, this fairy tale is shadowed by the almost simultaneous publication (nearly a month earlier) of the results from the open randomized clinical trial MITRA-FR that evaluated the efficacy and safety of MitraClip device in 307 individuals with HF-REF and moderately severe secondary MR.² In this trial, compared to the standard treatment, MitraClip did not improve the risk of the composite endpoint of all-cause mortality or admission due to heart failure at 12 months.²

A priori, both trials included patients with HF-REF and moderately severe secondary MR. Also, we should not forget that the baseline characteristics of the individuals included in both studies are similar in significant clinical and risk features. However, we should not take into consideration certain echocardiographic differences, results from the intervention, medical treatment, and follow-up time that may be behind these conflicting results:

- Echocardiographic differences: this is one of the key issues when it comes to interpreting both trials. As a matter of fact, the MR effective regurgitant orifice area was lower in the MITRA-FR compared to the COAPT ($31 \pm 10 \text{ mm}^2$ versus $41 \pm 15 \text{ mm}^2$). Similarly, the left ventricular end-diastolic volumes were higher in the MITRA-FR compared to the COAPT ($135 \pm 35 \text{ mL/m}^2$ versus $101 \pm 34 \text{ mL/m}^2$). This suggests that the patients who may benefit the most from this intervention are those with a higher degree of valvular dysfunction and less left ventricular dilatation; in other words, patients with predominant valvular heart disease over left ventricular disease.
- Differences in the results obtained with the intervention: the COAPT trial says that the frequency of perioperative complications or suboptimal results immediately or 12 months after the intervention was much more inferior compared to the MITRA-FR trial. For instance, in the COAPT trial only 5% of the patients showed grade \geq III MR after 12 months of follow-up,² while this percentage rose to 17% in the MITRA-FR trial.² This suggests that the experience and skills from the

* Corresponding author: Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Avda. Blasco Ibáñez 17, 46010 Valencia, Spain.
E-mail address: yulnunez@gmail.com [J. Núñez].

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interventional team play a crucial role during the implantation stage. In this sense, and even though in both studies the number of participating centers was high, it would have been useful to know the efficacy and safety results based on the number of implants managed by each center.

- Differences in the pharmacological approach: at baseline there was a high percentage of patients treated with drugs with confirmed effectiveness in the management of HF-REF in both trials. However, in the COAPT trial, the number of patients treated at baseline with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor antagonists, or sacubitril/valsartan was slightly superior in the intervention group. It is striking to see that these differences became more significant during follow-up. As a matter of fact, after 12 months, 13.4% more patients from the intervention group were receiving ACE inhibitors, angiotensin II-receptor antagonists, or sacubitril/valsartan. Similarly, after 12 months of follow-up, in the intervention group, the percentage of patients treated with beta-blockers was just 6.6% higher. The fact that it is an open trial may be indicative of performance bias (knowing the group the participants are assigned to in the trial has its echo in the form of systemic differences in care and therapies between both intervention groups) and detection bias (knowing the treatment group may affect important clinical decisions such as whether a patient should be hospitalized or not). Another aspect on medical treatment that we should also mention here is the lack of information on the absolute doses of the drugs used for the management of HF-REF. It is shocking to see that the COAPT trial, that required optimal medical therapy for the inclusion of patients, never mentions the absolute doses of the main groups of drugs used at the beginning or while the trial is being conducted (it only mentions relative changes in doses). Similarly, there is very little information on the intensity of clinical follow-up conducted or the administration of outpatient intravenous diuretic therapy (many hospital admissions can be avoided with close monitoring and intensification of diuretic therapy). Apart from the intervention per se, all these aspects may have tipped the scales towards one of the two groups of treatment, especially when it comes to the risk of hospitalizations.
- Different assessment times: it is important to emphasize that the results relative to the effectiveness of MITRA-FR were reported 12 months after the intervention compared to the results from the COAPT trial that were reported 24 months post-intervention. If we take a closer look into the results from both trials according to their time frames, we will see that the highest benefit from MitraClip in the COAPT study was observed after 12 months of follow-up. Actually, in the COAPT study, all-cause mortality after 1 year did not change in either one of the two therapeutic strategies implemented (hazard ratio, 0.81; 95% confidence interval, 0.57-1.15). We should also mention here that follow-up in the COAPT study was longer in the intervention group, due not only to the higher mortality rate of the control group, but also to the higher number of patients who withdrew from the study medical treatment group (attrition bias).

Q.: The virtues of the COAPT trial have been praised and the limitations from the MITRA-FR brought to everyone's attention but, in your opinion, which would be the most positive aspects of the MITRA-FR and the most negative aspects of the COAPT?

A.: In the first place, both are open randomized clinical trials not compared with placebo. From a general perspective, we should highlight the limitations and biases that may affect studies like these compared to double-blind clinical trials. Also, given the lack of sham procedures in both trials we cannot estimate the importance of the placebo effect in this context. In our interventional

arena, we have the recent examples of the significant and dramatic difference of the results observed for renal denervation between open clinical trials and double-blind studies with a «sham procedure».

The main negative aspects of the COAPT trial have already been mentioned above, but on this regard, we should also focus on the selection criteria used by this study that do not fully explain in detail what kind of rigorous selection of patients has been followed (out of the 1576 preselected patients, only 614 were randomized). As a matter of fact, the most common explanation to not be eligible after preselection (n = 419) was as vague as «incomplete preselection or others».

In general, I would say that the MITRA-FR has been a sort of comeback to reality after showing us that acting on the mitral valve does not seem to work in all patients with HF-REF and grade III-IV secondary MR. Once again, it has been confirmed that new advances in precision medicine need to be made while we look for the tools that will eventually allow us to better understand the heterogeneity of this complex syndrome and make better treatment selections for every particular case.

Q.: How do both studies complement each other to define what the ideal candidate for this technique really looks like?

A.: As we've already said, I think both studies show us that the ideal patient who would benefit the most from this technique is a patient on optimal medical therapy who remains symptomatic and who, in a situation of clinical stability, shows more severe MR (an effective regurgitant orifice area > 30 mm²) and has a not very dilated left ventricle. However, the adequacy of this profile will need to be confirmed in future studies.

Q.: One of the key differences between both trials was the degree of optimization of medical treatment achieved before randomization that influenced the frequency and magnitude of the therapeutic changes conducted during follow-up in both studies. Do you think it is possible to bring the level of adequacy or maximization of the COAPT trial to the routine clinical practice? How would this work from the organizational standpoint?

A.: This is an essential issue. Although in both studies the treatment before randomization could be considered appropriate, the optimization of medical therapy was more liberal in the MITRA-FR. Unfortunately, as we mentioned before, there is a lot of unavailable information on absolute doses, titration over time and intensity of follow-up. Knowing this missing information would shed light on the influence and adequacy of medical therapy in the results obtained by each study. What seems to be clear is that the optimization of medical therapy should be a prior condition before considering MitraClip a therapeutic alternative.

In sum, based on the results from both trials, it seems evident that to obtain satisfactory clinical outcomes a careful selection of patients is required while avoiding generalizing the percutaneous management of secondary MR in most patients with HF-REF. Right now, we run the risk that an inadequate selection of candidates will lead to questionable results. On the one hand, the excessive enthusiasm from some interventional teams that wish to approach MR with percutaneous treatments and, on the other hand, the clinicians' quest for new therapeutic alternatives in very advanced patients with poor clinical progression may threaten the successful implementation of percutaneous interventional programs for the management of MR in patients with HF-REF.

Luckily, we'll soon be getting new results that will tip the scales of this war on either side and, eventually, will allow us to make

precise selections of the patients who are real candidates to undergo interventional procedures with MitraClip. In the meantime, healthcare providers (imaging technicians, heart failure specialists, and interventionists) should come to terms and set the foundations for the implementation of machines and programs that will help make reasonable and quiet assessments of each particular case. As the old Spanish proverb goes «haste makes waste».

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CONFLICTS OF INTEREST

J. Núñez declared receiving fees from Abbott for his lectures.

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Debate: MitraClip. The interventional cardiologist perspective

A debate: MitraClip. Perspectiva del intervencionista

Rodrigo Estévez-Loureiro*

Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Madrid, Spain



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QUESTION: There is no doubt that the most significant advances made back in 2018 in interventional cardiology were the long-awaited results from clinical trials with MitraClip (Abbott Laboratories, Abbott Park, Illinois, USA): the MITRA-FR presented at the congress organized by the European Society of Cardiology and the COAPT presented at the Transcatheter Cardiovascular Therapeutics (TCT) congress. Both trials have been discussed extensively. Could you please tell us what the basic differences are in the results obtained by these two trials?

ANSWER: The clinical studies MITRA-FR¹ and COAPT² share the honor of being the very first two studies in history with a rigorous design that randomized patients with functional mitral regurgitation (FMR) to receive optimal medical therapy or optimal medical therapy plus the FMR correction device MitraClip. There were opposing results. In the MITRA-FR the device did not produce any benefits over the composite event of death or rehospitalizations after one year of follow-up. In the COAPT, the MitraClip group showed a significant reduction of hospitalizations at 2 years, and a reduced composite endpoint of death/rehospitalizations at 2 years. It seems reasonable to try to analyze the differences between both studies in an attempt to understand these opposing findings. These are the most significant differences I have seen:

Magnitude of the FMR. This is probably one of the most important aspects that may explain the differences seen. According to the clinical guidelines established by the ESC, the MITRA-FR included patients with severe FMR defined as an effective regurgitant orifice area (EROA) ≥ 20 mm² or regurgitation volumes > 30 mL. This brought these patients' average EROA to 31 ± 10 mm². On the contrary, according to the American clinical guidelines,³ the COAPT considered significant FMR EROAs ≥ 30 mm² or regurgitation volumes > 45 mL (average EROA 41 ± 15 mm²). Also, in the MITRA-FR over half of the patients (52%) showed EROAs between 20 and 30 and in the COAPT, 87% of the patients showed EROA values > 30 mm². In sum, the COAPT included patients with more severe FMR which would, logically, have a bigger impact on the patients' events when corrected.

- Ventricular volumes. The patients from the MITRA-FR showed higher average ventricular volumes compared to those from patients from the COAPT (end-diastolic volume index: 135 ± 35 mL/m² versus 101 ± 34 mL/m²). This means that the disease was far more advanced in the French study compared to the American study. This can also be one of the keys that may explain the differences seen. Treating some FMR in patients with very dilated ventricular volumes may have no effect at all on major cardiovascular events.
- Optimal medical therapy. This is another essential aspect if we want to understand the differences seen between both trials. In the MITRA-FR, the medical treatment that patients were receiving before randomization was the one the treating physician considered optimal. Also, this treatment could be modified during follow-up without the study committee knowing about it. Thus, even though the drug doses administered to manage heart failure may have been the correct ones at the beginning of the study, they may have been modified later on. And it is well-known that optimizing drug doses has a major impact on patients' events and functional class. This effect can be seen in the functional class improvement experienced by the group that received medical treatment in the MITRA-FR. However, in the COAPT an «eligibility committee» monitored that every patient would receive the right drugs and the maximum tolerated doses before randomization. That's why there were not too many dose modifications in the COAPT follow-up compared to the beginning of the trial.
- MitraClip performance. There are substantial differences when it comes to the level of success and performance achieved by this device. In the MITRA-FR, 9% of the patients never received the device. The number of complications was higher in the MITRA-FR (14.5% versus 8.5%) and the percentage of success at one year was lower in the French trial (17 versus 5% with FMR $> 2+$).
- Selection of candidates. The COAPT trial paid special attention to the selection of candidates. Patients whose baseline cha-

* **Corresponding author:** Unidad de Cardiología Intervencionista, Hospital Universitario Puerta de Hierro, Manuel de Falla 1, 28220 Majadahonda, Madrid, Spain. E-mail address: roiestevez@hotmail.com (R. Estévez-Loureiro).

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characteristics offered poor prognosis in the short-term and in whom the intervention wouldn't probably lead to significant clinical improvements were excluded. Irreversible pulmonary hypertension, moderate or severe right ventricular dysfunction, stage D heart failure, hemodynamic instability, and inotropic therapy were cause for exclusion from the trial. These patients were not in the exclusion list presented by the MITRA-FR. Also, all patients from the MITRA-FR should have been hospitalized, at least, one time before joining the trial, but the COAPT never considered this as a prerequisite which favors the selection of a less evolved population. The possible inclusion of these cases added to the inclusion of patients with ventricles in a far more advanced stage of the disease and not too much mitral regurgitation may have been decisive and explain the results obtained.

- Follow-up time. In the COAPT, survival curves start to separate clearly after one year of follow-up. The MITRA-FR has one year of follow-up only. We may see a different progression of these patients in time, in this study, as follow-up goes on.
- Methodological aspects. The minimum primary endpoint of the MITRA-FR was a composite of rehospitalizations or death at one year. In order to analyze this variable, the Kaplan-Meier survival analysis was used which, even though is correct from the methodological point of view, it presents us with one problem: rehospitalization is an event that may occur in time but this analysis does not take it into consideration. This is especially important here since one of the problems of this type of patients is the number of rehospitalizations. Being hospitalized once or five times a year is certainly not the same. This is something that the MITRA-FR did not pay attention to. On the other hand, the COAPT was actually designed to analyze recurring events. As a matter of fact, the COAPT primary endpoint was the number of rehospitalizations at 2 years (not only if the patient was admitted or not). The COAPT included a composite of death/rehospitalizations as a secondary endpoint, but the way it analyzed this varies from the MITRA-FR. The events death and hospitalization are not exclusionary, but one is more relevant than the other. In the MITRA-FR, both events were considered the same and the only thing that would cancel the survival analysis was suffering from one or the other, whichever would come first. However, the COAPT had a more appropriate way to analyze this type of intercurrent events: the WIN ratio (the win/loss ratio in the treatment group). The WIN ratio analyzes the most important clinical event (death) giving it relevance even though it may have occurred after hospitalization. This way of analyzing the composite event shows differences that the traditional Kaplan-Meier model does not detect or does not detect so sharply.

Finally, we have to say that the COAPT was a more rigorous study than the MITRA-FR. In the French study, 43 patients were excluded from the protocol in the MitraClip group due to several reasons which amounts to 28% of the sample in the intervention group. Also, the numerous losses of secondary variables such as quality of life, analytical values, functional class and, most surprisingly, control echocardiograms, leaves these events unscrutinized in the study since they may be prone to bias. In this sense, the percentage of significant FMR relapses at one year is an approximate estimate and, therefore, inaccurate.

Q.: The virtues of the COAPT trial have been praised and the limitations from the MITRA-FR brought to everyone's attention but, in your opinion, which would be the most positive aspects of the MITRA-FR and the most negative aspects of the COAPT?

A.: The positive aspects of the MITRA-FR are that it is the very first study to conduct a rigorous analysis on this issue by teaching

us that choosing the optimal therapy for the management of heart failure and optimizing the maximum doses significantly improves patients and reduces their FMR (let's not forget that we're dealing with a dynamic process that can change in time). Also, maybe its most positive aspect is that it tells us what patients shouldn't probably be eligible for this therapy: patients in advanced stages with not too much mitral regurgitation and without an optimized medical treatment. This subgroup of patients may have to be overlooked.

The negative aspects of the COAPT are that it was a lab experiment: all the variables were perfectly controlled, all treatments to their maximum doses, and the MitraClip device with an almost absolute success at 2 years. It will probably be difficult to replicate all this in the real world, but there is no doubt that it is the perfect example that FMR kills and that correcting it may lead to a substantial reduction of cardiovascular events. The COAPT trial sets the ideal we should aspire to in real life.

Q.: How do both studies complement each other to define what the ideal candidate for this technique really looks like?

A.: The interesting thing about these studies is that they should be implemented together to set the foundations of how we should choose the candidates. It seems obvious that we have to forget about patients in advanced stages (greater ventricular dilation), non-severe FMR and without optimal treatments. If we want to have more positive results, our candidates need to be in the early stages of the disease, have a significant degree of FMR (that really contributes to the clinical situation), be perfectly treated, and have good results with the device (which means that the anatomical selection and the experience of the interventional team need to be high). However, we always have to be cautious with assumptions like these. These data show the «average» patient, but a COAPT trial subanalysis reveals that as long as the FMR is very relevant (EROA > 30 mm²) there will always be a benefit, regardless of the degree of ventricular dilatation. That's why every case should be treated individually, and in my opinion, we should be very serious about the amount of FMR. On top of reducing major events, MitraClip also improves quality of life and functional class. These are goals that we should take into account when selecting patients because this may be the only therapy that will alleviate very advanced symptoms.

Q.: In the last TCT we also saw the results from a smaller clinical trial, the REDUCE-FMR, that evaluated a system of percutaneous annuloplasty. Given the results of MitraClip, which could be the role of percutaneous annuloplasty systems in patients with heart failure and severe FMR?

A.: In the COAPT study, the results from the clip were excellent because the anatomical selection of the candidates was excellent as well. However, in the real world we won't find cases like this all the time. In my opinion, in patients with great annular dilatation, so big that will prevent leaflet coaptation, the clip may have suboptimal results. It is in these cases where the role played by percutaneous annuloplasty systems may be essential - alone or in combination with the clip. According to the COAPT, the idea is that we should leave as little FMR as possible and that repair should be long-lasting, because this is what will eventually lead to less cardiovascular events. Percutaneous annuloplasty systems will complement our therapeutic arsenal to achieve this goal. However, to be taken into consideration, they need to show the same safety and efficacy profile as MitraClip.

CONFLICTS OF INTEREST

R. Estévez-Loureiro is proctor for MitraClip and declares to have received a research grant from Abbott Vascular.

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Evolute R implantation in Perceval bioprosthesis with periprosthetic leakage



Implante de Evolute R en bioprótesis Perceval con insuficiencia periprotésica

Ramiro Trillo Nouche,* Fernando Gómez Peña, Diego López Otero, Xoan Carlos Sanmartín Pena, Ana Belén Cid Álvarez, and José Ramón González Juanatey

Unidad de Cardiología Intervencionista, Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIVERCV), Santiago de Compostela, A Coruña, Spain

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PRESENTATION OF THE CASE

We hereby present the case of an 83 year old hypertense, diabetic male patient with asymptomatic severe aortic stenosis, preserved ventricular function, mild mitral regurgitation and no coronary artery disease.

He had low-intermediate surgical risk (3.1% in the Society of Thoracic Surgeons scoring system) and, in medical-surgical session, it was decided to proceed with the surgical replacement of his aortic valve.

Perceval Sutureless Aortic Heart Valve, Sorin size L was implanted. The follow-up echocardiogram prior to hospital discharge showed an aortic transvalvular gradient of 22/11 mmHg and 2 periprosthetic regurgitation jets indicative of mild-to-moderate aortic failure with pulmonary artery systolic pressure of 40 mmHg.

Five months after valvular replacement, the patient was hospitalized due to acute heart failure with acute pulmonary edema. During the physical examination, the auscultation showed murmurs indicative of grade III/IV aortic regurgitation and bilateral pulmonary rales. The echocardiogram showed severe aortic failure due to the lack of stent coverage of the aortic bioprosthesis at the level of the aortic annulus and in the area corresponding to the non-coronary sinus and most of the right coronary sinus which conditioned 2 regurgitation jets towards the left ventricle that appeared slightly dilated. The left ventricular ejection fraction was somehow depressed. Both mitral regurgitation and pulmonary hypertension were categorized as severe being the pulmonary artery systolic pressure, 60 mmHg.

CONFLICTS OF INTEREST

R. Trillo Nouche is proctor for Medtronic.

* **Corresponding author:** Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Rúa da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.

E-mail address: ramirottrillo@mac.com (R. Trillo Nouche).

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Evolute R implantation in Perceval bioprosthesis with periprosthetic leakage. How would I approach it?



Implante de Evolute R en bioprótesis Perceval con insuficiencia periprotésica. ¿Cómo lo haría?

Pablo Avanzas^{a,b,c,*}

^a Servicio de Cardiología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

^b Departamento de Medicina, Universidad de Oviedo, Oviedo, Asturias, Spain

^c Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Asturias, Spain

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HOW WOULD I APPROACH IT?

The authors hereby present the clinical case of an 80-year old male with symptomatic severe aortic stenosis, preserved ventricular function, mild mitral regurgitation and no coronary heart disease. He had low surgical risk (3.1% score in the Society of Thoracic Surgeons risk scale) and, in medical-surgical session, it was decided to proceed with a surgical aortic valvular replacement using the Perceval Sutureless Aortic Heart Valve, Sorin – size L. The follow-up echocardiogram prior to the patient's discharge showed lack of significant aortic transvalvular gradient and periprosthetic regurgitation jets indicative of mild-to-moderate aortic regurgitation. Five months after the implantation of the valve, the patient was admitted to the hospital due to acute pulmonary edema. The echocardiogram showed severe aortic regurgitation due to the lack of stent coverage of the aortic bioprosthesis at the level of the aortic annulus and in the area of the non-coronary sinus and most of the right coronary sinus with two regurgitation jets towards the left dilated ventricle. The left ventricular ejection fraction was slightly depressed.

Before considering any therapeutic approaches in a patient with aortic regurgitation following a valvular implantation there are 3 fundamental issues we should all be aware of: 1) the exact degree of regurgitation severity; 2) the location (transvalvular or paravalvular); and 3) the underlying mechanism according to the appropriate imaging modalities.

The information we got told us that the aortic regurgitation was serious. When it comes to the location of this regurgitation, if we take a look at the results obtained following the implantation and the description of the echocardiogram at admission, the location was periprosthetic. The third main aspect to decide the future therapeutic approach is to find out what mechanism is causing the periprosthetic severe aortic regurgitation in a patient carrying a Perceval device. Here we are dealing with a bovine pericardial prosthesis mounted on a nitinol stent frame (nickel and titanium). The frame structure has two cylindrical rings (figura 1): one proximal (outflow ring) and one distal (inflow ring).¹ Once mounted, it is placed inside the valve and deployed in the aortic root. Three different suture sites are used inside the native aortic annulus as a guide to find the exact spot for the implant. It is deployed by turning a release screw

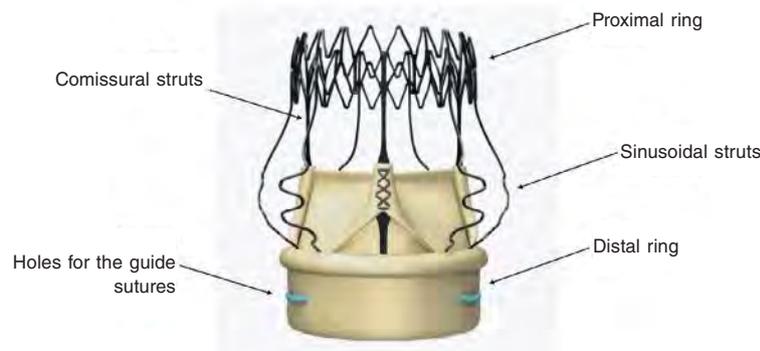


Figure 1. Components of the Perceval Sutureless Aortic Heart Valve, Sorin.

* **Corresponding author:** Servicio de Cardiología, Hospital Universitario Central de Asturias, Avda. Roma s/n, 33011, Oviedo, Asturias, Spain.
E-mail address: avanzas@secardiologia.es [P. Avanzas].

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and is fully expanded with the use of a balloon catheter. Once deployed, the sutures are removed. As far as we know, there are four different sizes available in the market today: size S (19 mm to 21 mm), size M (21 mm to 23 mm), size L (23 mm to 25 mm), and size XL (25 mm to 27 mm). Every size is the right size for different aortic annuli and sinotubular diameters, which is why it is essential to know the patient's exact anatomical measures. Its use is not recommended in patients with a dilated ascending aorta and with a sinotubular junction/aortic annulus diameter ratio ≥ 1.3 , or in patients with bicuspid aortic valve.

As it is the case with transcatheter prostheses, after implanting the Perceval device, it is not rare to find some sort of perivalvular leakage. These are some of the mechanisms we already know:

- Valvular malapposition: the valve is deployed correctly, but the distal ring is placed above or below the aortic annulus causing the leakage.
- Inadequate size of the prosthesis: small (undersizing) and big devices (oversizing) with respect to the ring can lead to perivalvular leakages.

Taking into consideration the description of the echocardiogram and the fact that the most common mistakes are due to oversizing, and assuming the correct placement of the device, I think that the mechanism that made the prosthesis fail was the recoil or collapse of the metallic structure that harbors the bioprosthetic leaflets and that usually affects the area of the non-coronary sinus – a complication that surgeons know so well and that has been described extensive in the medical literature.² We should bear in mind that this deformity of the stent that causes the lack of contact between the device and the aortic root anywhere from the aortic annulus to the sinotubular junction can occur intraoperatively or days after the intervention and it is more common with small rings; that is why various authors recommend using the smallest prosthesis available when the dimension of the aortic annulus is somehow between two different device sizes.

According to the medical literature, when the metallic frame collapses, these are the therapeutic options available:³

- Reintervention or valvular replacement for a smaller device, Perceval M, or a valve with sutures.
- Percutaneous treatment with a 22 mm to 23 mm balloon valvuloplasty, since the true internal diameter of the Perceval device size L goes from 21.5 mm to 23 mm according to the manufacturer.
- Percutaneous treatment through the percutaneous implantation of the aortic valve, the so-called valve-in-valve procedure.

Personally, I would do a valvuloplasty as my first option, but since the underlying problem is still unsolved (too big of a device for the aortic annulus), such a maneuver would probably be ineffective. In that case, I would implant a transcatheter valve with the strongest possible radial strength (valve-in-valve procedure).

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Evolute R implantation in Perceval bioprosthesis with periprosthetic leakage. Case resolution



Implante de Evolute R en bioprótesis Perceval con insuficiencia periprotésica. Resolución

Ramiro Trillo Nouche,* Fernando Gómez Peña, Diego López Otero, Xoan Carlos Sanmartín Pena, Ana Belén Cid Álvarez, and José Ramón González Juanatey

Unidad de Cardiología Intervencionista, Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIVERCV), Santiago de Compostela, A Coruña, Spain

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CASE RESOLUTION

With an 8.5% score in the Society of Thoracic Surgeons risk score for mortality rate, we decided to implant one Evolute PRO transfemoral bioprosthesis on an underexpanded bioprosthesis. The computed tomography confirmed the lack of coverage of the bioprosthetic stent over the aortic annulus at the level of the Valsava, non-coronary and right coronary sinuses (figure 1), indicative of stent recoil of the stent harboring the bioprosthetic leaflets as the possible mechanism of periprosthetic failure and causing malapposition with the aortic annulus. The perimeter of the aortic annulus was 79.3 mm (minimum diameter: 22 mm; maximum diameter: 25 mm).

One self-expandable prosthesis was selected with leaflets at the supra-annular level, since it has already been confirmed that in valve-in-valve procedures, the hemodynamic outcome is better compared to the annular implantation that leaves a more significant trans-prosthetic gradient. Also, the position of the prosthesis inside the prosthesis needs to be optimal, which makes the Evolute R the perfect device for this kind of procedure for its recapture and repositioning capabilities.

The selection of the size of the prosthesis to be implanted was based on the true internal diameter of the 25 mm Perceval L valve, that is, 21.5 mm to 23 mm according to the manufacturer. The size recommended for the Evolute PRO is between 26 mm and 29 mm. Finally, the 29 mm size was picked to ensure a correct annular sealing.

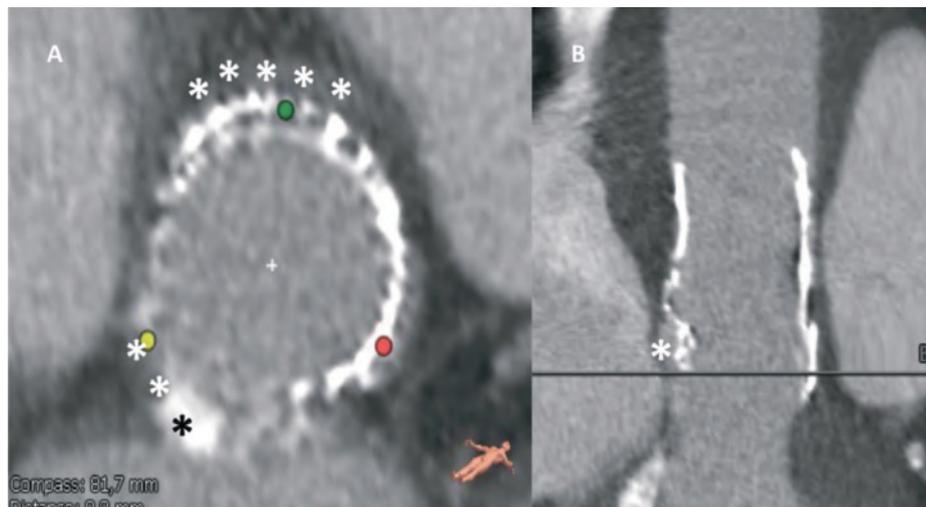


Figure 1. Lack of coverage of the bioprosthetic stent over the aortic annulus at the level of the Valsava, non-coronary and right coronary sinuses (asterisk). The colored dots are indicative of the location of coronary sinuses.

* **Corresponding author:** Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Rúa da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.

E-mail address: ramirottrillo@mac.com (R. Trillo Nouche).

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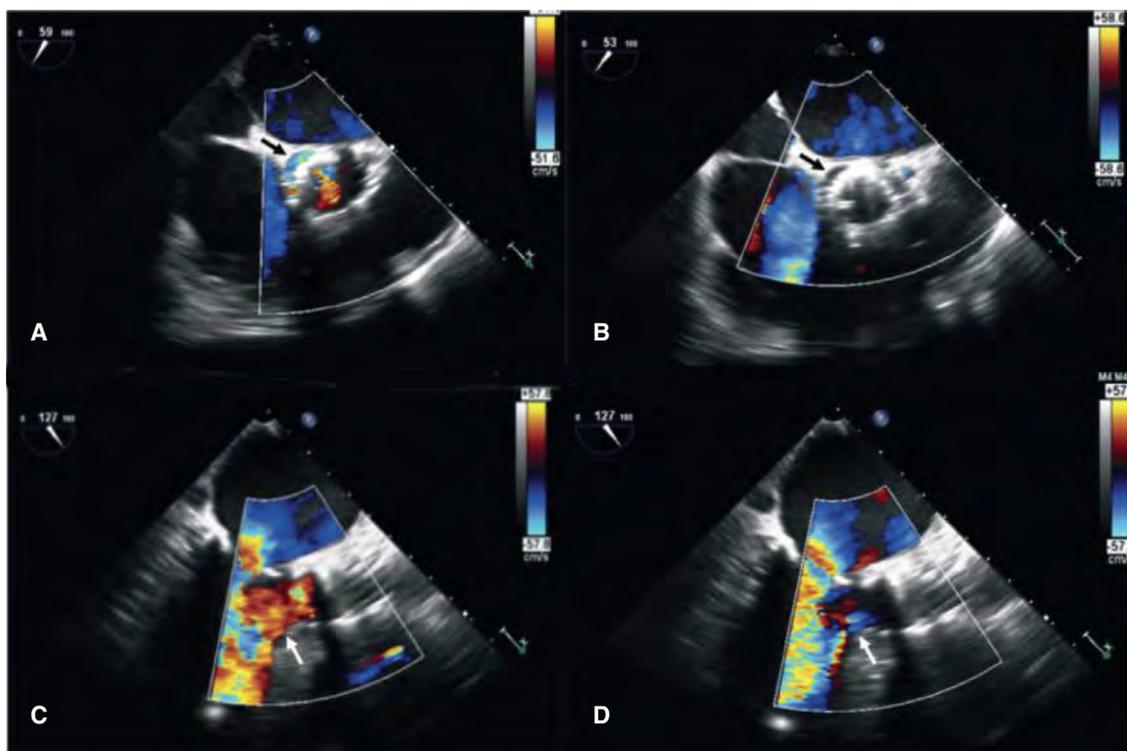


Figure 2. Transesophageal echocardiography: transversal view of the aortic annulus (A, B) and three chambers (C, D). A, C: regurgitation jet towards the left ventricle before the percutaneous implant of the aortic valve (arrows). B, D: no aortic regurgitation jet after the percutaneous implant of the aortic valve (arrows).

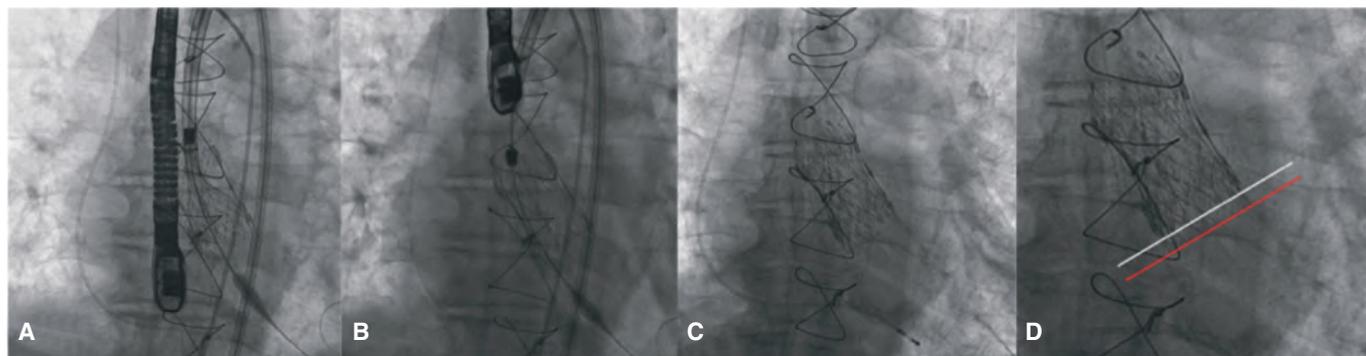


Figure 3. Implant of Evolute PRO 29 over Perceval L. A: deployment of the prosthesis at 80%. B: prosthesis being deployed in its final position. C: removal of the release catheter. D: inferior edge of the Perceval prosthesis (white line) and inferior edge of the Evolute PRO (red line).

The procedure was conducted under general anesthesia, with mechanical ventilation and transesophageal echocardiography (figure 2).

We picked the working projection where the inferior edge of the malfunctioning prosthesis was aligned. The pigtail catheter was placed proximal to the dysfunctional prosthesis to conduct the corresponding maneuvers during the implantation stage. The radio-opacity of the Perceval prosthesis gives us enough information for the correct deployment of the Evolute device.

The procedure was conducted using fluoroscopic monitoring and transesophageal echocardiography. The Perceval prosthetic leaflets were placed intra-annularly and for correct implantation purposes, the location picked for the Evolute device was the inferior edge of the Perceval prosthesis in such a way that the inferior edge of the Evolute 2 mm would match the Perceval device underneath. The deployment of the Evolute device is slightly distal to the dysfunctional bioprosthesis (figure 3). When 80% of the deployment had already been completed, the transesophageal echocardiography (figure 2) confirmed the correct positioning and functioning of the Evolute device, and the aortic failure being sealed. The remaining of the prosthesis was then fully deployed. The procedure was conducted without any conduction alterations and it was completed uneventfully. The progression of the patient was good with no traces of heart failure.

CONFLICTS OF INTEREST

R. Trillo Nouche is proctor for Medtronic.

Aspirin-free antithrombotic management following coronary stenting. Myth or reality?

Davide Capodanno,^a Roxana Mehran,^b and Dominick J. Angiolillo^{c,*}

^a Division of Cardiology, CAST, P.O. "Rodolico", Azienda Ospedaliero-Universitaria "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy

^b Icahn School of Medicine at Mount Sinai, New York, NY, United States

^c Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, United States



ABSTRACT

The use of aspirin in combination with a P2Y₁₂ receptor inhibitor, also known as dual antiplatelet therapy, is at the cornerstone of treatment for patients undergoing coronary stenting. The use of newer generation P2Y₁₂ inhibitors (ie, prasugrel and ticagrelor), characterized by more potent antiplatelet effects and better clinical outcomes compared to clopidogrel, are recommended in high-risk patients, such as those with an acute coronary syndrome. However, this occurs at the expense of increased bleeding that accumulates with the duration of treatment. Given the poor prognostic implication, including an increased mortality rate associated with bleeding, a number of strategies aimed at reducing the risk of this adverse event while preserving efficacy have emerged. Among these, withdrawing aspirin represents an ongoing line of clinical investigation. The pharmacological reason behind such strategy relies on the central role played by the metabolic pathway of P2Y₁₂ receptor inhibitors on platelet activation and its contribution amplifying thrombotic processes. Thus, it has been hypothesized that in the presence of a powerful P2Y₁₂ receptor blockade, aspirin may offer minimal contribution when it comes to reducing thrombotic complications, but rather contribute to increased bleeding complications. A number of ongoing clinical investigations are currently challenging the dogma of aspirin as a mandatory background therapy in patients undergoing coronary stenting.

Keywords: Aspirin. Ticagrelor. Stent. Thrombosis.

Tratamiento antitrombótico sin ácido acetilsalicílico tras implante de *stent*: ¿mito o realidad?

RESUMEN

El uso del ácido acetilsalicílico en combinación con un inhibidor del receptor P2Y₁₂, es decir, la doble terapia antiplaquetaria, representa la piedra angular del tratamiento para los pacientes en los que se implanta un *stent* coronario. El uso de inhibidores P2Y₁₂ de nueva generación (prasugrel y ticagrelor), caracterizados por efectos antiplaquetarios más potentes y mejores resultados clínicos en comparación con clopidogrel, se recomienda en pacientes de alto riesgo, como aquellos con un síndrome coronario agudo. Sin embargo, este beneficio es a expensas de un aumento del riesgo de sangrado que se acumula con la duración del tratamiento. Dada la adversa repercusión pronóstica, incluido el aumento de la mortalidad, asociada al sangrado, han surgido una serie de estrategias destinadas a reducir el riesgo de este evento adverso a la vez que se preserva la eficacia. Entre estos, retirar el ácido acetilsalicílico representa una línea de investigación clínica. La justificación farmacológica de dicha estrategia se basa en el papel central de la vía de inhibición de P2Y₁₂ en la activación de las plaquetas y su contribución a la amplificación de los procesos trombóticos. Por lo tanto, se ha planteado la hipótesis de que, en presencia de un potente bloqueo del receptor P2Y₁₂, el ácido acetilsalicílico puede ofrecer una contribución mínima para la reducción de las complicaciones trombóticas, pero de hecho contribuye al aumento de las complicaciones hemorrágicas. Una serie de ensayos clínicos actualmente en curso cuestionan el dogma del ácido acetilsalicílico como una terapia de base obligatoria en pacientes tratados con *stents* coronarios.

Palabras clave: Ácido acetilsalicílico. Ticagrelor. *Stent*. Trombosis.

Abbreviations

ACS: acute coronary syndrome; **CAD:** coronary artery disease; **DAPT:** dual antiplatelet therapy; **PCI:** percutaneous coronary intervention.

* **Corresponding author:** University of Florida College of Medicine-Jacksonville, 655 West 8th Street, Jacksonville, FL 32009, United States.

E-mail address: dominick.angiolillo@jax.ufl.edu (D.J. Angiolillo).

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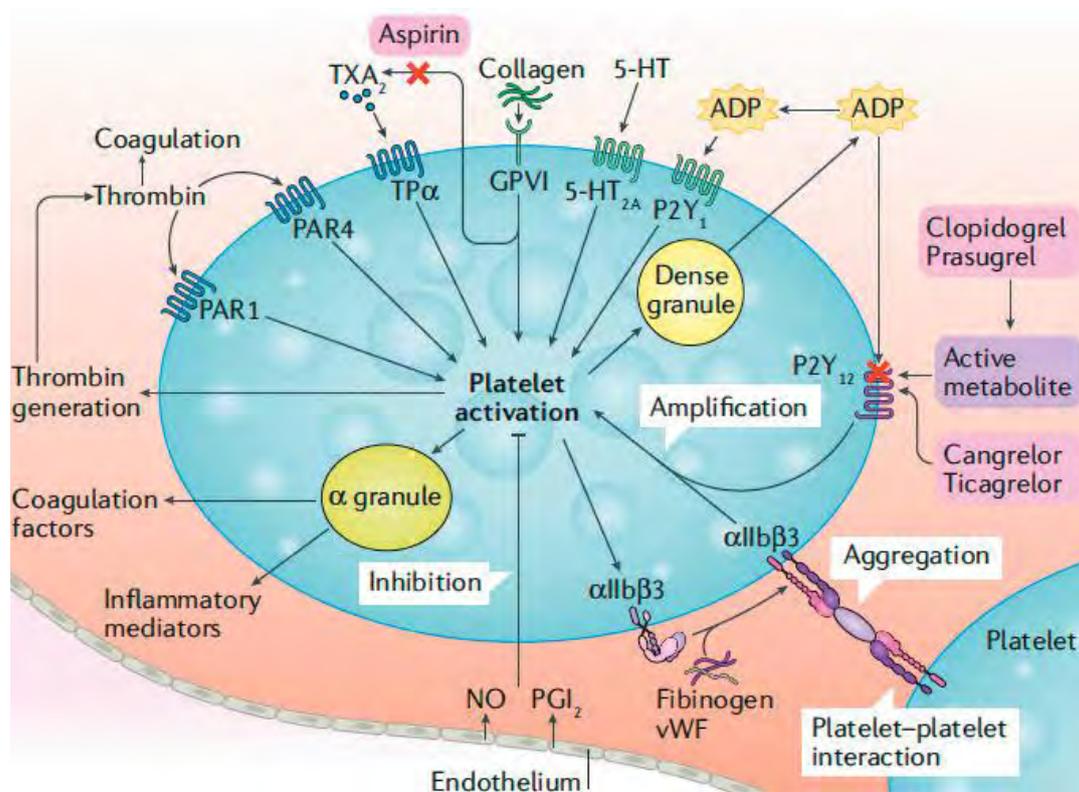


Figure 1. Platelet activation mechanisms. Platelet activation is initiated by soluble agonists, such as thrombin, thromboxane A₂ (TXA₂), 5-hydroxytryptamine (5-HT), adenosine diphosphate (ADP [via P2Y purinoceptor 1, P2Y₁]), and adenosine triphosphate (ATP), and by adhesion ligands, such as collagen and the von Willebrand factor (vWF). Consequently, the dense granule secretion of platelet agonists and the associated responses. The P2Y purinoceptor 12 (P2Y₁₂) receptor plays a major role in the amplification of platelet activation, which is also supported by outside-in signaling via integrin αIIbβ3 (the glycoprotein IIb/IIIa receptor). Thus, the combined blockade of P2Y₁₂ and integrin αIIbβ3 has additive effects on platelet activation and the associated platelet responses. 5-HT_{2A}, 5-HT receptor 2A; GPVI, platelet glycoprotein VI; NO, nitric oxide; PAR, proteinase-activated receptor; PGI₂, prostacyclin receptor; TPα, TXA₂ receptor isoform α. Adapted from Capodanno et al.⁹ with permission of Springer Nature Ltd.

Aspirin is at the cornerstone of treatment for patients with clinical manifestations of coronary artery disease (CAD).¹ However, the high rate of recurrent ischemic events despite aspirin therapy has inevitably led to explore the effects associated with the use of adjunctive antithrombotic therapies, particularly in high-risk settings. Among these, the adjunctive use of oral P2Y₁₂ inhibitors has proven essential in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary interventions (PCI) with stent implantation.² The combination of aspirin and a P2Y₁₂ inhibitor, also known as dual antiplatelet therapy (DAPT), has been the gold standard treatment for ACS/PCI patients and included in the clinical guidelines for now nearly two decades.³ Clopidogrel is the most commonly used P2Y₁₂ inhibitor. Despite its proven efficacy a number of studies have shown wide variability in individual response profiles to clopidogrel with a considerable number of patients having inadequate platelet inhibitory effects.⁴ Notably, a number of studies have shown that these individuals also suffer from an increased risk of ischemic events, especially stent thrombosis.⁵ This has led to the development of P2Y₁₂ inhibitors, such as prasugrel and ticagrelor, characterized by more powerful and reliable antiplatelet effects.² Indeed, compared to clopidogrel, both agents have proven to reduce significantly ischemic recurrences in ACS patients, including stent thrombosis at the expense of an increased risk of bleeding.² In the absence of

contraindications, practice guidelines advocate for the preferred use of prasugrel or ticagrelor over clopidogrel.³

Although large-scale head-to-head comparisons between prasugrel and ticagrelor are scarce, ticagrelor appears to have a somehow more favorable safety profile in terms of bleeding potential compared to prasugrel.² These observations may be attributed to the different pharmacological profiles of these agents, being ticagrelor a reversibly-binding P2Y₁₂ inhibitor and prasugrel an irreversible binding agent.² Moreover, in ACS patients, ticagrelor associates lower cardiovascular mortality compared to clopidogrel, a finding not seen with prasugrel compared to clopidogrel.² These findings have been reported, although a causal relationship has never been attributed to ticagrelor,⁶ as off-target effects (ie, inhibition of ENT-1 transporter leading to increased adenosine levels). Overall, these observations as well as the expanded ACS clinical scenarios in which ticagrelor has proven beneficial, have led ticagrelor being more widely used than prasugrel. Nevertheless, concerns surrounding the risk for bleeding associated with longer DAPT courses of aspirin and ticagrelor persist.⁷ It should be noted here that the occurrence of a bleeding complication even during the DAPT maintenance phase, has importance prognostic implications including increased mortality.⁸ These observations have led to a series of investigations aimed at identifying strategies associated with

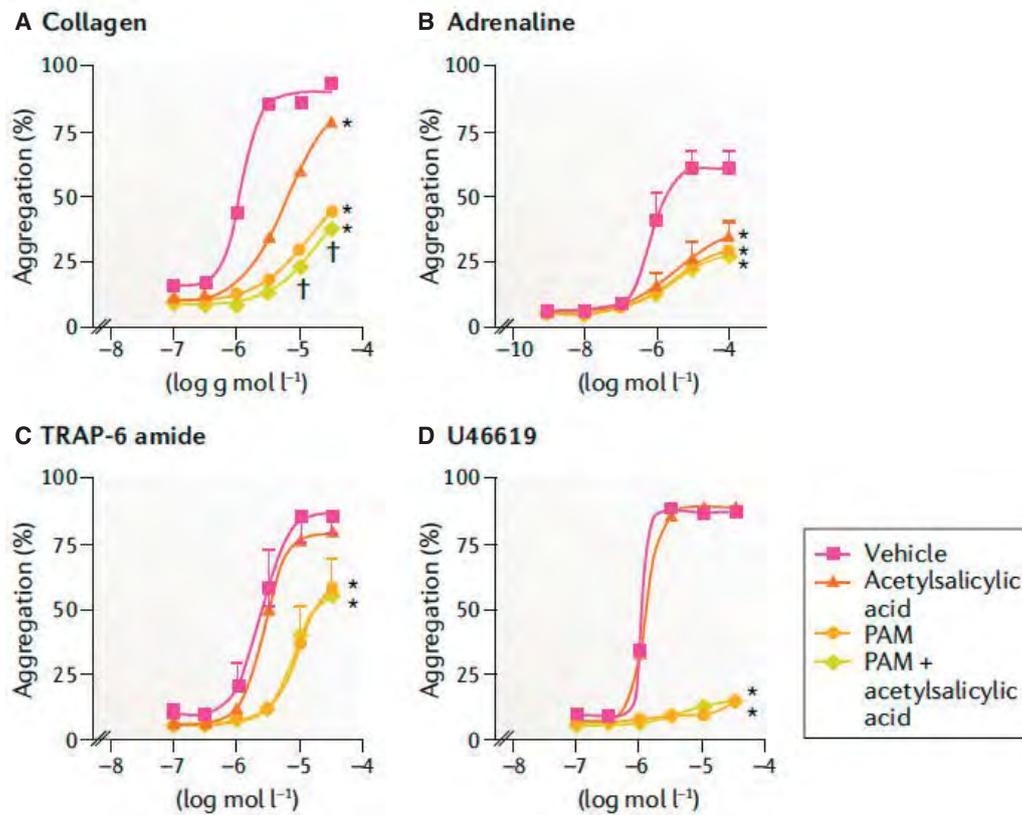


Figure 2. In the presence of strong P2Y₁₂ receptor blockade, acetylsalicylic acid provides little additional inhibition of platelet aggregation. In these studies, platelet aggregation was induced by four different platelet agonists: collagen 0.1–30.0 µg/mL (part a), adrenaline 0.001–100.0 µmol/L (part b), the synthetic protease-activated receptor 1 (PAR1) antagonist TRAP-6 amide (H-Ser-Phe-Leu-Leu-Arg-Asn-NH₂) 0.1–30.0 µmol/L (part c), and the thromboxane A₂ mimetic U46619 0.1–30.0 µmol/L in the presence of acetylsalicylic acid 30.0 µmol/L and/or prasugrel active metabolite (PAM) 3.0 µmol/L (part d). Data are expressed as mean ± standard deviation of the mean responses measured by 96-well plate aggregometry in citrated platelet-rich plasma prepared from four different individuals. **P* < .05 for difference from vehicle by two-way analysis of variance (ANOVA) plus a Bonferroni post hoc test. †*P* < .05 for difference between PAM and PAM plus acetylsalicylic acid. Symbols at the end of lines mean difference in sets; symbols at individual points mean particular differences. Adapted from Capodanno et al.⁹ with permission of Springer Nature Ltd.

reduced bleeding without an efficacy trade-off. These include shortening DAPT duration, de-escalating the antiplatelet therapy, and withdrawing aspirin.^{9–12} Indeed, evolution in stent design has led to safer (ie, less thrombogenic) platforms that have facilitated investigations in this field.¹⁰

The use of aspirin-free strategies following PCI has been prospectively tested in randomized trials of patients with atrial fibrillation undergoing PCI and requiring oral anticoagulant therapy.¹³ These studies have consistently shown that withdrawing aspirin as early as possible and favoring a double antithrombotic therapy approach (mostly clopidogrel combined with an oral anticoagulant) significantly reduced bleeding without an efficacy trade-off. Consequently, a double antithrombotic therapy strategy is now immediately recommended after PCI.^{13,14} The reason behind considering an aspirin-free strategy among PCI patients not requiring oral anticoagulant therapy largely comes from the overall very effective degree of P2Y₁₂ inhibition achieved with ticagrelor.¹⁵ Notably, the P2Y₁₂ signaling pathway plays a key role in platelet activation and amplification of thrombotic processes (figure 1).¹⁶ In vitro investigations have also shown that the use of aspirin offers limited pharmacodynamic effects in the presence of effective P2Y₁₂ receptor blockade (figure 2).¹⁷ In light of the well-established association between aspirin and bleeding, especially GI bleeding, it has been

hypothesized that withdrawing aspirin therapy after the highest thrombotic risk phase (eg, 1–3 months post-PCI) has passed, can reduce the risk of bleeding complications without any efficacy trade-off.⁹ It has also been suggested that in light of the detrimental impact of bleeding on clinical outcomes, an aspirin-free strategy can actually improve efficacy.¹⁸

GLOBAL LEADERS (Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use) was a superiority trial conducted in 15 968 patients undergoing PCI with Biolimus A9-eluting stents, designed to assess whether a 24-month antithrombotic regimen with ticagrelor and one month with aspirin improves the composite of all-cause mortality or new Q-wave myocardial infarction compared to conventional DAPT for 12 months followed by aspirin monotherapy.¹⁹ However, despite a directional trend towards the benefit of P2Y₁₂ monotherapy, the trial failed to meet its primary endpoint (experimental strategy 3.81% vs reference strategy 4.37%; rate ratio, 0.87; 95%CI, 0.75–1.01; *P* = .073). Moreover, there were no differences in the key safety endpoint of class 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria. A series of

Table 1. Ongoing trials of aspirin-free strategies in patients undergoing percutaneous coronary interventions

Study	n	Population	Treatment arms	Primary outcome measure
TWILIGHT (NCT02270242)	9000	High risk PCI on ticagrelor, event-free at 3 months	Placebo for 12 months versus ASA for 12 months	Bleeding at 12 months
TICO (NCT02494895)	3056	ACS-PCI	DAPT for 3 months followed by ticagrelor for 9 months versus DAPT for 12 months	MACCE at 12 months, major bleeding at 12 months
SMART CHOICE (NCT02079194)	3000	PCI	DAPT for 3 months followed by clopidogrel for 9 months versus DAPT for 12 months	Death, MI or stroke at 12 months, major bleeding at 12 months
SHORT-DAPT 2 (NCT02619760)	3045	PCI	DAPT for 1 month followed by clopidogrel for 59 months versus DAPT for 12 months followed by ASA for 48 months	NACE at 12 months
ASET (NCT03469856)	200	PCI	Prasugrel monotherapy	Cardiac death, target-vessel MI (spontaneous > 48 h) or definite stent thrombosis BARC 3 or 5 bleeding
AUGUSTUS (NCT02415400)	4600	Atrial fibrillation on oral anticoagulation with ACS and/ or undergoing PCI	ASA for 6 months versus placebo for 6 months	Major or clinically relevant bleeding at 6 months
ENTRUST-AF PCI (NCT02866175)	1500	Atrial fibrillation on oral anticoagulation undergoing PCI	Edoxaban and clopidogrel or ticagrelor for 12 months versus vitamin K antagonist for 12 months plus DAPT for 1-12 months	Major or clinically relevant bleeding at 12 months

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; n, number of patients; NACE, net adverse cardiac events; PCI, percutaneous coronary intervention.

considerations need to be made when interpreting the GLOBAL LEADERS trial. First, the study is one of the largest PCI studies ever conducted with a new generation drug-eluting stent platform and even though it did not meet its primary endpoint, there were no safety signals associated with early (ie, one-month post-PCI) aspirin withdrawal. These observations provide reassurance for other ongoing studies evaluating aspirin-free strategies post-PCI and support the findings from pharmacodynamic investigations on the maintained efficacy associated with powerful P2Y₁₂ inhibitor monotherapy. It is worth mentioning that, at 12 months, a statistically significant difference between groups was observed, but this was not maintained after a 2-year follow-up. It is also worth taking into consideration that during the first year of the trial a comparison was made between 2 DAPT regimens the first month, followed by a comparison of ticagrelor monotherapy versus DAPT the following 11 months. Conversely, between 12 and 24 months, ticagrelor was compared to aspirin, showing no difference and ultimately diluting the overall treatment effect of the experimental strategy. Reduced adherence to randomized therapy has also been suggested as a contributing factor. Indeed, a study with a larger sample would have likely been statistically significant enough and would have favored P2Y₁₂ inhibitor monotherapy at 2 years. Second, the inclusion of patients with stable CAD (53% of the overall study population) may have diluted the potential benefit of the study. In fact, a significant interaction for BARC 3 or 5 bleeding ($P = .007$) was observed in favor of patients with ACS. Indeed, extending the study up to 24-months and including stable CAD patients with no established benefit of ticagrelor may also be reasons for the lack of differences seen in the primary safety endpoint of bleeding. Third, it may be argued that the primary endpoint (all-cause mortality and Q-wave myocardial infarction) chosen for this study was overly ambitious. While the selection of these endpoints was specifically chosen to facilitate the assessment of events, including other traditional endpoints

would have facilitated even more the detection of differences between the treatment arms. Although in this trial nonfatal ischemic recurrences or bleeding events were not adjudicated, the GLASSY study will assess the superiority of the experimental treatment strategy over standard of care in more than 7000 patients on a composite endpoint of fatal and non-fatal ischemic and bleeding events.²⁰

The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial is a double-blind, superiority study that is analyzing the comparative efficacy and safety of antiplatelet therapy with ticagrelor plus placebo versus continued DAPT with aspirin and ticagrelor in up to 9000 high-risk patients on DAPT who are event-free at 3 months from PCI treated with commercially available drug-eluting stents.²¹ There are key differences between the TWILIGHT and the GLOBAL LEADERS. First, the double-blind design (aspirin vs placebo), which is one of the strengths of the study, aimed at eliminating the chance of reporting bias. Second, the primary endpoint is focused on safety (BARC class 2, 3 or 5 bleeding at 12 months), which is a more plausible endpoint to achieve following withdrawal of aspirin therapy. The non-inferiority of DAPT for ischemic events is also being studied. Third, the study population is enriched with clinical and angiographic risk factors which increases the anticipated event and, in turn, the probability to detect treatment effect. This trial has recently completed recruitment, and the primary results are expected for Q2 2019. Other trials are being conducted to provide new insights on the potential role of P2Y₁₂ monotherapy as an alternative to long-term platelet inhibition in patients undergoing PCI (table 1).

In sum, the advances made in interventional pharmacotherapy with the introduction of antithrombotic agents with more effective pharmacodynamics effects have called into question the standard

approach that consisted on piling up on aspirin as a background therapy. The growing recognition of the importance of reducing bleeding complications has called into question whether in a more modern arsenal of antithrombotic therapies aspirin is still irreplaceable. The long-term use of aspirin is not indispensable as already proven in certain settings such as patients treated with oral anticoagulants and current evidence shows that in the presence of effective blockade of other pivotal platelet signaling pathways withdrawing aspirin is harmless. Thus, what would have been a myth a few years ago, the possibility of doing without long-term aspirin following coronary stenting is not that far from reality anymore. Whether we will be able to overcome the dogma of mandatory long-term use of aspirin will indeed depend on the findings from the ongoing clinical trials that are being conducted in this field.

CONFLICTS OF INTEREST

D. Caponanno declared receiving consulting fees/honoraria from Bayer and AstraZeneca. R. Mehran declares that she has received consulting fees from Abbott Vascular, Abiomed, Boston Scientific, Bristol-Myers Squibb, Cardiovascular Systems, Elixir, Medscape, Shanghai BraccoSine Pharmaceutical, The Medicines Company, and executive committee fees from Janssen Pharmaceuticals, Osprey Medical. She also declares that her institution receives funding from AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb, Cardiokinetix, Claret Medical, CSL Behring, Eli Lilly/DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Spectranetics and Watermark Research Partners. D.J. Angiolillo declared receiving: a) consulting fees/honoraria from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; b) consulting fees/honoraria for his participation in review activities from CeloNova and St Jude Medical. Institutional grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions; Also, D.J. Angiolillo received funding from the Scott R. MacKenzie Foundation and the NIH/NCATS Clinical and Translational Science Award to the University of Florida UL1 TR000064 and NIH/NHGRI U01 HG007269, outside the submitted work.

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Accelerated neoatherosclerosis in a heart transplant recipient

Neoateroesclerosis precoz en un paciente con trasplante cardiaco

Rafael Romaguera,* Josep Gómez-Lara, and Joan A. Gómez-Hospital

Àrea de Enfermedades del Corazón, Hospital de Bellvitge - IDIBELL, Universidad de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

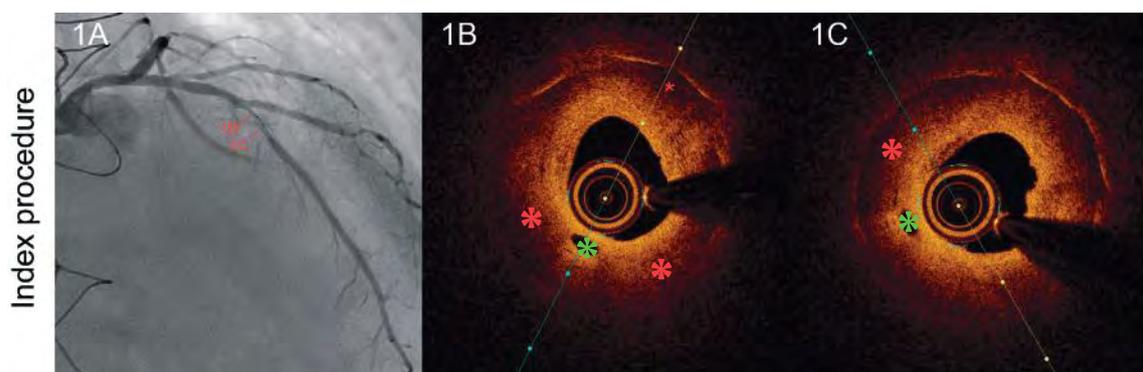


Figure 1.

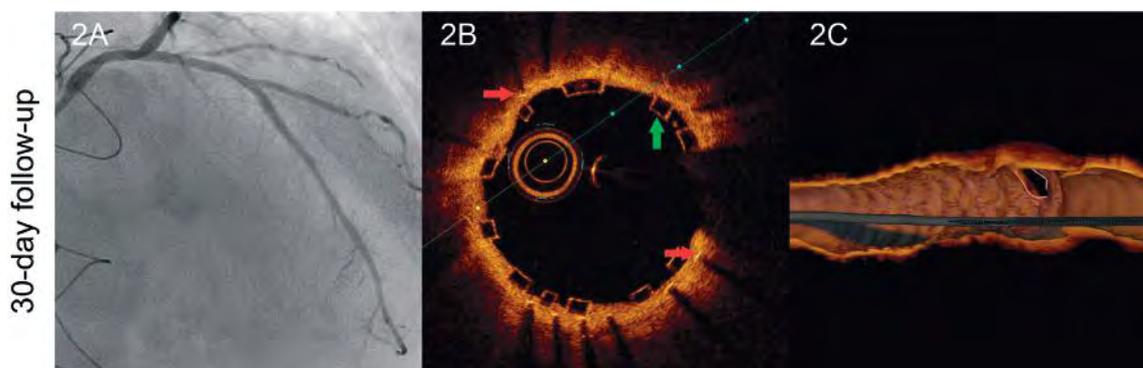


Figure 2.

Cardiac allograft vasculopathy is characterized by the absence of lipid-rich plaques. However, transplant recipients may also develop lesions that resemble traditional atherosclerosis. Tacrolimus and everolimus, which are commonly used in transplant recipients, are associated to proatherogenic side effects such as hyperglycemia, hyperlipidemia and hypertension. Everolimus also triggers the release of several proinflammatory cytokines such as interleukin-6 and tumor necrosis factor α . Thus, inflammation, endothelial failure and hyperlipidemia are shared pathophysiological processes common to native in-stent neoatherosclerosis and transplant atherosclerosis.

We hereby present the case of a 50 year-old-male with a history of heart transplant 18 years ago with a zotarolimus-eluting stent implanted in his left anterior descending artery 16 months ago. The patient was administered immunosuppressive agents including quadruple therapy with corticosteroids, mycophenolate, tacrolimus and everolimus. The patient was admitted to the hospital due to acute heart failure. The coronary angiography conducted showed severe in-stent restenosis (figure 1A). The optical coherence tomography (OCT) showed the presence of early in-stent neoatherosclerosis with lipid-laden plaque similar to the morphological appearance so typical of native neoatherosclerosis (red asterisk) and vasa vasorum (green asterisk) (figure 1B,C). To avoid multiple metallic layers (red arrows), one bioresorbable vascular scaffold (green arrows) was deployed in-stent. The angiographic and OCT follow-up 1-month later confirmed the presence of scaffold patency with most struts uncovered (figure 2A-C). This is the first description of in-stent neoatherosclerosis in a transplant recipient that occurred a few months after deploying the stent. Since the cardiac allograft vasculopathy is often silent and catastrophic, close metabolic control and invasive monitoring through images is advisable in these patients.

* Corresponding author: Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.
E-mail address: rafaromaguera@gmail.com [R. Romaguera].

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Very late thrombosis induced by neoatherosclerosis in bioresorbable stent

Neoateroesclerosis que causa trombosis muy tardía de stent bioabsorbible

Guillem Muntané-Carol, Josep Gómez-Lara,* and Ángel Cequier

Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

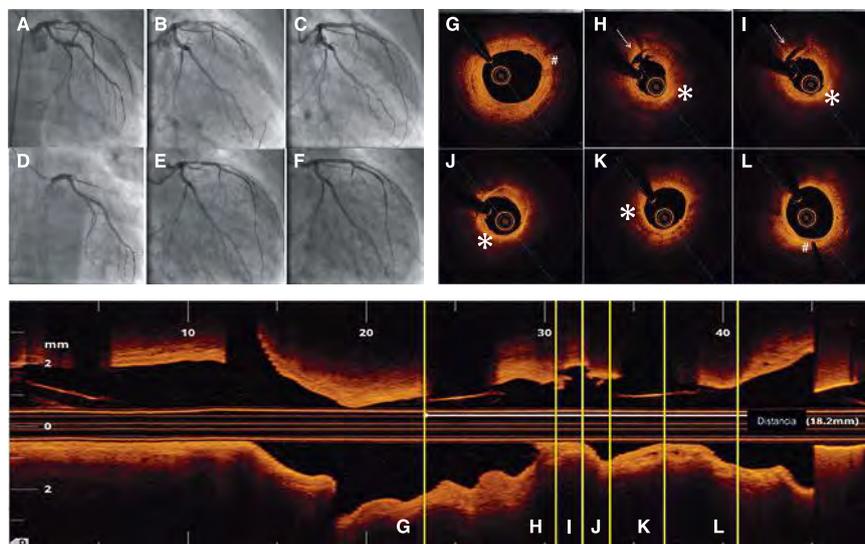


Figure 1.

Sixty-four year-old male patient with ST-segment elevation acute myocardial infarction due to occlusion of his anterior descending artery who received one 3 × 18 mm direct bioresorbable vascular scaffold (BVS) (figures 1A-C). Then he received acetylsalicylic acid and atorvastatin.

Fifty-two months later he experienced an anterior reinfarction due to the occlusion of the same segment of the anterior descending artery. Thrombo-aspiration with flow recovery (figures 1D, E) was conducted and the optical coherence tomography showed strut remnants almost indistinguishable in the BVS segment. Thrombosis was attributed to a tear in the neoatherosclerotic lipid plaque (figures 1H-I, video of the supplementary data). Figures 1G-L show the BVS markers (pound sign) and the presence of the aforementioned torn lipid plaque (asterisk and arrow, respectively). One drug-eluting metallic stent was implanted inside the stent (figure 1F).

The primary goal of BVSs is to eliminate the risk of very late thrombosis once the device is gone. In several series of very late thromboses in drug-eluting metallic stents, one of the main causes seen in the optical coherence tomography is the tear of the neoatherosclerotic lipid-laden plaque (26% to 31%). Therefore, we should expect a significant drop in stent thrombosis when the BVS process of resorption is complete. However, the restoration of geometry and the arterial vessel-motricity may promote neoatherosclerosis in patients with BVS. As far as we know, this is the very first case of ST-segment elevation acute myocardial infarction induced by a neoatherosclerotic plaque tear 4 years after BVS implantation.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000018>.

* Corresponding author: Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.
E-mail address: gomezjosep@hotmail.com [J. Gómez-Lara].

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Part-time interventional cardiology activity as a source of inequity in the reperfusion therapy of patients with STEMI



Hemodinámica a tiempo parcial como causa de inequidad en el tratamiento de reperfusion del IAMCEST

Pablo Ramos-Ruiz,* Luciano Consuegra-Sánchez, Samantha Wasniewski, Francisco Guillermo Clavel-Ruipérez, José Domingo Cascón-Pérez, and Juan Antonio Castillo-Moreno

Servicio de Cardiología, Hospital General Universitario Santa Lucía, Cartagena, Murcia, Spain

Dear editor,

In Spain the implementation of ST-segment elevation acute myocardial infarction (STEMI) networks between 2003 and 2012 was associated to a higher rate (50%) of primary percutaneous coronary interventions (PCI) and a lower mortality rate (that dropped from 10.2% to 6.8%). However, throughout the years we have been able to witness the appearance of inevitable differences in the development and implementation of primary PCI programs among the different regions.¹ And, although these differences are slowly disappearing, some situations can generate inequity while managing reperfusion. One of these differences can be found in those interventional laboratories that only do primary PCIs part-time ignoring the recommendations from the European Society of Cardiology that establishes that primary PCI-capable centers should conduct this procedure on a 24/7 schedule and categorizes other healthcare models as "non-desirable".²

Thus, given the limited availability of our hospital interventional laboratory (from 8 AM through 3 PM only on business days), we decided to explore the in-hospital mortality rate of patients with STEMI who received primary PCIs in our center and compare it to that of patients who received another reperfusion therapy (primary PCI at the regional reference center or fibrinolysis).

Our hemodynamic laboratory provides healthcare to nearly 400 000 inhabitants. Whenever a patient suffers a STEMI on business hours he is transferred to the interventional suite and undergoes a primary PCI. Outside this schedule, the management of the patient is heterogeneous (primary PCI in the reference hospital, which is 50 kilometers away, or fibrinolysis) and it is the interventionist on call at the reference hospital who, based on recommendations from the regional network on the management of STEMI, will pick one modality or the other. This situation is exceptional in our country³ which is why we think it deserves some analysis.

We conducted a retrospective study of all the patients in our unit with a diagnosis of STEMI from January 2014 through September 2016 who had received reperfusion therapy. We categorized them into two groups: those who had received a primary PCI at our hospital (the so-called "in situ PCI" group), and those who had already received a different reperfusion strategy, whether a

primary PCI at the reference hospital or fibrinolysis (the so-called "other reperfusion" group). The main study hypothesis was that in-hospital all-cause mortality can be different based on the possibility to conduct primary angioplasties at our center. We conducted logistic regression analysis adjusted by age, Killip class, shock or out-of-hospital cardiac arrest, diabetes, or chronic renal disease.

Out of the 459 patients included, 174 were categorized into the "in situ PCI" group, and 285 into the "other reperfusion" group (139 of these patients underwent fibrinolysis, and 146 underwent a primary PCI at the reference hospital). Both cohorts were similar when it comes to the main clinical variables (table 1). Thirty-three in-hospital deaths were reported (7.2%; 95% confidence interval [95%CI], 5.2-9.9). The "in situ PCI" group had lower in-hospital mortality rates compared to the "other reperfusion" group (4.0% versus 9.1%; $P = .040$). Mortality was particularly high in the latter group of patients compared to those who underwent

Table 1. Basal characteristics of the sample based on the reperfusion modality

	<i>In situ</i> PCI group (n = 174)	Another reperfusion group (n = 285)	<i>P</i> value
Age, years	63.8 ± 12.8	62.6 ± 13.2	.35
Women, n (%)	33 (19)	63 (22.1)	.42
DM, n (%)	56 (32)	72 (25.3)	.109
CKD, n (%)	26 (14.9)	42 (14.7)	.95
LVEF, %	51.5 ± 11.2	50.8 ± 11.2	.56
Killip class ≥ II, n (%)	38 (22.4)	53 (18.8)	.36
CA, or shock, n (%)	19 (10.9)	26 (9.1)	.53
In-hospital mortality, n (%)	7 (4)	26 (9.1)	.040

DM, diabetes mellitus; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention (primary); CA, cardiac arrest.

* **Corresponding author:** Servicio de Cardiología, Hospital General Universitario Santa Lucía, Mezquita s/n, 30202 Santa Lucía, Cartagena, Spain. E-mail address: pablo.ramos1989@gmail.com (P. Ramos-Ruiz).

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fibrinolysis (12.2%). Receiving the primary PCI at our center was associated with a significant reduction of the risk of in-hospital mortality (adjusted RR, 0.238; 95%CI, 0.055-0.600; $P = .004$; C-statistic = 0.90; Hosmer-Lemeshow test = 0.74) even after re-sampling.

Most interventional laboratories are open for business 24/7; the so-called "business hour" schedule is something exceptional. However, we did not find any studies like the one we conducted that evaluated whether there are in-hospital mortality differences depending on the reperfusion modality used in this context. Maybe the potential benefit seen in the *in situ* primary PCI compared to other reperfusion modality had to do with the advantages of primary PCI versus fibrinolysis,⁴ and the fact that the procedure was conducted in the same hospital rather than the reference hospital after the transfer of the patient.⁵ One of the limitations of our study was the fact that reperfusion times were not available. Our data suggest that in populations whose hospital has one interventional laboratory available by limited time there may be differences in STEMI-induced mortality that may have to do with the

different reperfusion modality used, which would confirm the "non-desirable" category of this healthcare model.

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