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Transcatheter mitral valve replacement: there is no one-size-fits-all solution



Recambio mitral transcatóter: la talla única no existe

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Mitral regurgitation (MR) is the most prevalent form of valve disease in developed countries¹ and its prevalence increases with age affecting ~10% of people > 75 years.² MR is a very heterogeneous disease that damages not only the mitral valve apparatus but also its surrounding structures. In primary MR, mitral valve surgery is the therapy of choice in symptomatic patients or asymptomatic patients with left ventricular dysfunction. Surgical repair is generally preferred over replacement if technically feasible.^{3,4} In secondary MR, the surgical approach is still under discussion⁵ and it is spared for patients with indications for other surgical cardiac procedures (ie, coronary artery bypass graft).^{3,4}

Several studies suggest that a large proportion of MR patients are never treated due their high surgical risk⁶ and that such a conservative approach results in high re-hospitalization (~90%) and mortality rates (50%) within 5 years following the initial diagnosis.⁷ This population has become a clear unmet need and a target for the development of less invasive therapeutic approaches. Several transcatheter mitral valve repair (TMVR) technologies inspired by well-established surgical techniques have been developed and have already been approved for clinical use. The most commonly used, the MitraClip device (Abbott Vascular, United States) has reached more than 100 000 implants and demonstrated safety and efficacy in several MR subsets.⁸⁻¹⁰ Although clinical adoption continues to increase, edge-to-edge repair does not fully resolve MR and has some anatomical limitations too (ie, calcified leaflets) that prevent a wider use. Transcatheter mitral valve replacement (TMVR) offers a more universal concept for the management of mitral valve disease with a more predictable abolition of MR severity in a procedure that could be less invasive compared to current surgical techniques.¹¹

Important lessons have been learned from ongoing TMVR clinical studies. First, the patients screened for these trials, considered of high or prohibitive surgical risk display more complex anatomical substrates than originally thought that lead to very high rejection rates. Imaging sizing algorithms used to confirm patient eligibility are patient- and valve-design specific, but have not been standardized in all valve programs. The availability of different device sizes has also limited the wider adoption of this technology.

One of the biggest earliest technical concerns was the ability to achieve valve stability in the absence of sutures. To tackle this issue, several anchoring mechanisms have been developed resulting in high periprocedural success and low early

dislodgment rates.¹² The potential for left ventricular outflow tract obstruction is still the biggest Achilles' heel of this technology. Several factors including¹³ aorto-mitral-annular angle, degree of septal hypertrophy, the left ventricle size, and device protrusion into the cavity may contribute to left ventricular outflow tract obstruction. The short and mid-term valve leaflet performance has not been an issue to this day. Mean transvalvular gradients and paravalvular leaks have been similar to those obtained after surgical mitral valve replacement.

The rate of periprocedural complications varies based on the valve program we are dealing with. The mean 30-day all-cause mortality reported is ~13.6%.¹⁴ Approximately 4.6% of periprocedural death rate mainly due to unsuccessful TMVR deployment that ends up leading to conversion to open heart surgery. Also, issues with the management of access site are responsible for some deaths mainly associated with myocardial tears. The remaining deaths occur following the TMVR procedure. Transapical access has been associated with a higher rate of periprocedural complications (particularly bleeding) and mortality in TMVR procedures.¹⁴ The negative effects of thoracotomy in frail populations and the higher degree of myocardial injury associated with the transapical approach may be particularly deleterious in patients with reduced left ventricular ejection fraction.¹⁴ Finally, acute hemodynamic changes due to valve implantation in patients with severely depressed left ventricular ejection fraction (< 30%) is a very well-known phenomenon in the surgical field that worsens the prognosis of these patients.

Long-term data in a large cohort of patients is still lacking. In the largest series reported so far, no cases of structural valve degeneration, new occurrence of paravalvular leaks or valve dislocation requiring reintervention have been reported.¹⁴ However, a more systematic clinical and echocardiography follow-up of patients undergoing TMVR is crucial to provide consistent data on valve durability and structural valve failure in the future. Data on the risk of long-term thrombosis is scarce too. No episodes of clinically relevant valve thrombosis have been reported with other TMVR devices. Three-month anticoagulation therapy is currently recommended although no long-term data on the real thrombogenic profile of these devices has been reported yet.^{3,4,15}

TMVR is evolving to become a new alternative for treating patients with severe MR of very high or prohibitive surgical risk. The complexity of the mitral valve apparatus and the heterogeneity of

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Online: 18-05-2020.

<https://doi.org/10.24875/RECICE.M20000122>

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the disease have limited the wide adoption of these technologies. Several devices are under clinical evaluation and the early experience gained with some of them proves the feasibility of their implantation. Larger studies including a larger number of patients are still needed to test the clinical performance of these technologies. Emerging transseptal TMVR systems have the potential to overcome some of the limitations of current transapical devices. However, technical and anatomical challenges will remain the same. The TMVR field is rapidly evolving, what is somehow clear now is that it will benefit a specific population subset and that there is no such thing as a one-size-fits-all solution.

CONFLICTS OF INTEREST

The CRF Skirball Center for Innovation has received research grant support from Edwards Lifesciences, Neovasc, Abbott Vascular, Sinomed and Cephea. J.F. Granada is one of the co-founders of Cephea.

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Drug-coated balloon catheters. Discussing mortality from the coronary perspective



Balones liberadores de fármaco. Discusión sobre la mortalidad desde la perspectiva coronaria

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INTRODUCTION

The history of coronary balloon angioplasty began in 1997 with the first percutaneous transluminal coronary angioplasty (PTCA) ever performed by Andreas Grüntzig.¹ Some of the limitations of this technology were solved with the introduction of stents.² Added to an improved pharmacological concomitant therapy in the form of dual platelet inhibition,³ the local drug delivery initially through stents (drug-eluting stents, DES)⁴ and then balloons (drug-coated balloons, DCB)⁵ improved long-term outcomes significantly. The history of coronary angioplasty was summarized in detail in various articles on the 40th anniversary of this technology.^{6,7}

The local application of paclitaxel through DCB had begun to revolutionize the treatment of peripheral arterial disease (PAD).⁸ This advance was very helpful for patients regarding primary patency and quality of life, but received a severe setback in a meta-analysis that claimed that the use of paclitaxel DES and DCB was associated with a higher mortality rate at the 2- and 5-year follow-up.⁹

The objective of this editorial is to discuss the safety profile of drug-coated devices in the historical context of the 2006 "European Society of Cardiology (ESC) firestorm" on coronary DES, data available on the coronary use of paclitaxel coated devices, and the potential role of limus-based agents in DCB.

FIRST-GENERATION DES AND THE 2006 "ESC FIRESTORM"

After the publication of the RAVEL clinical trial on the Cypher sirolimus-eluting stent⁴ and the TAXUS trials on the Taxus paclitaxel-eluting stent,¹⁰ the DES rapidly gained momentum thanks to their significantly lower rate of restenosis compared to uncoated bare metal stents (BMS). In a direct comparison with the Cypher stent, the Taxus showed a higher rate of recurrence at the 9- to 12-month follow-up.¹¹ The common view that sirolimus is more effective than paclitaxel is essentially based on these data. However, it should be emphasized that the Taxus stent was almost as effective as the Cypher stent beyond the 12-month follow-up and up to 10 years.¹² The progress made by these first-generation DESs compared to modern DESs was based on the nowadays better controlled coating processes especially after improving stent platforms with thinner stent struts.¹³

However, there were also critical remarks to be made on the safety profile of coronary DESs. It has been reported that the delayed drug delivery from the stent struts prevents the implant endothelialization and increases the risk of thrombotic occlusion of the stent.¹⁴ The BASKET-LATE trial reported between 3 and 4 times more late deaths or myocardial infarctions¹⁵ with first-generation DESs. A hotline session held in Barcelona at the ESC congress of 2006 reported on 2 meta-analyses on a safety risk after sirolimus DES implantation.^{16,17} In both meta-analyses the events published at study level were divided by the total number of patients with intention-to-treat without observation of cross-over treatments and lost to follow-up numbers. This is similar to the recently controversial meta-analysis on paclitaxel coated devices for the management of PAD.⁹ The first DES meta-analysis showed significant differences in the mortality and Q-wave myocardial infarction rate at the late follow-up when the Cypher and bare metal stents were compared.¹⁶ This finding may be explained by a possibly higher rate of late stent thrombosis. However, the second meta-analysis showed that the higher mortality rate associated with the Cypher stent was due to a higher non-cardiac mortality rate, thus contradicting the mechanism of stent thrombosis.¹⁷ Despite these conflicting results, the government regulatory agencies worldwide were alarmed. The Food and Drug Administration (FDA) published several warning letters that eventually limited the indications for DESs.¹⁸ However, further analyses did not confirm such an increased risk.¹⁹ Also, the clinical trials that compared the Taxus stent to the BMS or the Cypher did not show higher rates of myocardial infarction or death.^{10,12} Thus, DES became the standard treatment for the management of coronary heart disease.²⁰ Similarly, large contemporary registry studies and randomized studies have not confirmed any mortality signals for paclitaxel devices for the management of PAD.²¹⁻²⁴ It remains to be seen whether a similar comeback as with coronary DES will eventually happen.

PACLITAXEL-COATED BALLOONS

Currently, the clinical practice guidelines recommend DCBs for the management of in-stent restenosis (ISR) only.²⁰ However, there is an increasing number of positive data on the treatment of de novo stenoses, particularly in small coronary vessels^{25,26} and risk indications.^{27,28} A patient-based meta-analysis of the trials that compared DCBs and DESs in DES-treated ISRs showed a similar 3-year safety

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Online: 02-04-2020.

<https://doi.org/10.24875/RECICE.M20000098>

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profile for DCBs and DESs with numerically lower rates of events with DCB.²⁹ Even individual studies that compared DCB with first-generation DES,³⁰ BMS,²⁷ or plain old balloon angioplasty^{31,32} reported significantly lower mortality rates after DCB implantation in the long term. However, these studies did not have enough statistical power to analyze this question. A recent meta-analysis of all randomized data on DCBs showed no differences in the mortality rate of DCBs and alternative treatments at the 1- and 2-year follow-up, but a significant survival benefit for DCBs regarding all-cause mortality and cardiac mortality at the 3-year follow-up.³³

SIROLIMUS VS PACLITAXEL FOR LOCAL DRUG DELIVERY

When comparing paclitaxel and sirolimus regarding local drug delivery it is often said that sirolimus has a wider therapeutic window and paclitaxel is cytotoxic. However, these statements are not correct.

Cell culture experiments tell us that the exposure of smooth muscle cells or endothelial cells to paclitaxel leads to more pronounced dose-dependent growth inhibition compared to sirolimus.^{34,35} There is an increasing release of cytosolic lactate dehydrogenase—a marker for cell death—when incubating the cells with paclitaxel from a concentration of ≥ 100 ng/mL.³⁴ It should be mentioned that the paclitaxel DES only released 10% of the total amount of drug just as the comparable sirolimus DES because of this stronger antiproliferative effect. Regarding DCB, there are typically acute tissue levels of less than 100 ng/mg in the vessel wall.³⁶ Also, only about 10 ng/mg of paclitaxel are biologically active. Otherwise, the solubility product in the tissue is exceeded. While toxic concentrations may well be reached in the DES in the area of the stent struts, distribution in the vessel wall is very homogeneous with local drug delivery through DCB.³⁷ Also, tissue concentration decreases very rapidly after DCB treatment.³⁶ Therefore, the theoretically possible cytotoxicity of paclitaxel is not a factor in the clinical use of DCB.

The second myth is the therapeutic window. A typical total dose of a paclitaxel DCB equals 0.4 mg (3 $\mu\text{g}/\text{mm}^2$, 20 mm length, 3 mm diameter). The single dose per cancer treatment cycle is 100-175 mg/m² of body surface area through intravenous administration,³⁸ usually 300 mg per infusion. This results in a factor of 750 for paclitaxel as therapeutic window compared to systemic therapy. The typical daily oral dose of sirolimus for restenosis prevention is 2 mg.³⁹ Depending on the specific sirolimus DCB used, the balloon dose is somewhere between 0.2 and 0.6 mg (1-4 $\mu\text{g}/\text{mm}^2$, 20 mm length, 3 mm diameter). So far, clinical efficacy could only be proved for the high dose of sirolimus,⁴⁰ which means a factor of 3 only compared to systemic therapy, a clearly smaller therapeutic window. If a sirolimus DCB is implanted on the superficial femoral artery, the dose delivered through the balloon is already above the systemic dose and should be contraindicated (table 1).

DISCUSSION AND FINAL REMARKS

The 2006 "ESC Firestorm" can be seen as a blueprint for the current paclitaxel controversy on the management of PAD. Interestingly enough, discussion at that time focused on sirolimus and not on paclitaxel. The current meta-analysis on the management of PAD with paclitaxel devices has several methodical flaws and has already been refuted. In any case, it has caused great damage to the entire field of local drug delivery for restenosis prevention. Too many patients are currently not receiving the therapy that works best for them and have to receive unnecessary revascularizations.

Regarding coronary paclitaxel DCB no associated mortality signals were seen. Just the opposite, there are indications that the therapy

Table 1. Systemic vs local treatment. Therapeutic window of paclitaxel and sirolimus

	Paclitaxel	Sirolimus
Systemic treatment	300 mg Single IV dose of 100-175 mg/m ² per cancer treatment cycle ³⁸	2 mg Daily oral dose for restenosis prevention ³⁹
Local treatment (DCB)	0.4 mg CAD 3.0/20 mm at 3 $\mu\text{g}/\text{mm}^2$ 5.5 mg PAD 5.0/80 mm at 3.5 $\mu\text{g}/\text{mm}^2$	0.2-0.6 mg CAD 3.0/20 mm at 1-4 $\mu\text{g}/\text{mm}^2$ 1.6-6.4 mg PAD 5.0/80 mm at 1-4 $\mu\text{g}/\text{mm}^2$
Therapeutic window	CAD \times 750 PAD \times 55	CAD \times 3-10 PAD none

CAD, coronary artery disease; DCB, drug-coated balloons; IV, intravenous; PAD, peripheral arterial disease.

could even offer survival advantages in the longer term by avoiding permanent implants. The alternative of a sirolimus-coated balloon endorsed by many interventional cardiologists still has to prove its clinical efficacy. However, considering the necessary local doses compared to systemic therapy, the use of a sirolimus DCB for the management of PAD is questionable.

CONFLICTS OF INTEREST

B. Scheller is a shareholder of InnoRa GmbH, Berlin, and co-inventor on patent applications filed by Charité university hospital, Berlin, Germany.

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Scientific debates among professionals in social media: a fantastic, but not risk-free scenario



Debates científicos entre profesionales en las redes sociales: un fantástico escenario no exento de riesgos

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"Don't say anything online that you wouldn't want plastered on a billboard with your face on it."

Erin Bury, Sprouter community manager

Scientific dissemination has always been at the forefront of medicine. It consists of bringing the advances made in research to all professionals and the general population. The traditional way to do this was through books. However, the growing accumulation of knowledge and the need to communicate it in a timely manner prompted the appearance of periodic publications: the scientific journals.

Currently, the enormous speed at which knowledge is generated and the lust for knowledge have found an ally in the Internet and the inevitable social media. The possibilities are just amazing, and they allow the spread of ideas and opinions with greater impact in education, networking, and public health.^{1,2}

In our journal, Jurado-Román reviewed the role of social media in the educational setting and highlighted its importance without obviating its potential risks and limitations.^{3,4} Some have already coined the term "twitterology" to refer to the medical use of this social network.⁵

Over the last year an example of this have been the ISCHEMIA and PARTNER-3 landmark clinical trials that have prompted ongoing discussion and debate on social media.^{6,7} But new studies do not have the monopoly on this. We have also witnessed fierce debates about a not so recent trial that gave rise to methodological considerations; I am referring to the EXCEL trial and the update of its 5-year results.^{8,11}

The recent pandemic of COVID-19 has been the largest dissemination of medical-scientific information on social media ever. We have learned so much from this world-shocking experience in this regard.

I would like to share my views on scientific dissemination or discussion in social media with the readers of our journal.

CHARACTERISTICS AND PREVALENT VALUES OF COMMENTS POSTED ON SOCIAL MEDIA

Here is a brief description of the characteristics of communication in social media based on what is being posted on a daily basis.

Totally open access

Anybody can post their opinion or comment on social media. This means that the capacity to spread knowledge has been democratized with the corresponding benefits and risks involved. There is no peer review nor filters on authors or content. Rigor and truth are not guaranteed either, only if imposed by the author himself.

Communication on real time and immediacy

The comments are published and available online immediately. There are no delays anymore. Communication needs to happen as quickly as possible after public exposure or after the publication of the study or even better during its presentation at the congress. Being the "first to shoot" is the only thing that matters.

Concision

These comments are limited in size and thoughts on a particular study have to be summarized in a few words. Regarding Twitter, complexity has to be summarized in just 280 characters. Simplicity over concision is the rule to follow.

Impact

Communication needs to generate sensations and induce reactions whether of agreement or of rejection; anything goes but indifference.

The group: tribalism

The study results perceived as favorable are cheered by the group and those considered negative are ignored, questioned or even rejected in a sort of medical tribalism already identified and questioned by some.¹² This mimics the fierce style of political or football discussions.

The influencer

The communicator becomes the "man of the hour"; it is not about the actual value of the message anymore but about the messengers

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Online: 12-05-2020.

<https://doi.org/10.24875/RECICE.M20000103>

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themselves. The author feels compelled to comment on all studies. These comments are awaited by those who receive them with sympathy or rejection. These influencers have followers who can't wait to give their feedback as well; this division is related to the author's profession and the group represented by the author.

The reactions

Reactions are subject to similar conditions. However, in this case, they may not be preceded by the acquisition of information and reflection on the opinion given; feedback is posted in a rather direct way often guided by feelings and emotions rather than reason. There are times that the comment is posted simply because a certain opinion is expected to be given by the author's professional group.

"Twitter is a great place to tell the world what you're thinking before you've had a chance to think about it."
Christopher J. Pirillo, blogger

THE REAL VALUES OF SCIENTIFIC DISCUSSION

Having said all this, we should not forget about the real values of scientific communication. The interpretation of a study requires a detailed analysis of methods and results, confirmation through previous studies, and the assessment of the different interpretations given. All of it requires elaborating and presenting one's personal opinion in the most basic way possible. This process takes time, space, and moderation. That is the only way to achieve precise and balanced results.

The rule of the 3 Rs to have a scientific debate on social media: rigor, responsibility, and respect

The contrast between the characteristics and values of success on social media and the real values that should inspire scientific discussion is obvious. The only way to bring together the true virtues of both is through the commitment to communicate with rigor, responsibility, and respect:

- **Rigor.** Scientific rigor, that is, sticking to the actual content of a study and what it is actually implied regardless of the prejudices or preferences of the group we belong to.
- **Responsibility.** Responsibility with the professional group that will be following the comments posted —not always experts— and many times not even health professionals but patients, families, and the general population. The effect on the latter —who don't have the same critical capacity as experts— can be misleading, alarming or doubtful.
- **Respect.** Respect to professionals from other groups and subspecialties, especially those capable of interpreting things differently. Topics often admit different readings in such a complex setting as ours. Respect to the population who can have access to this information, such as patients and families.

RECOMMENDATIONS FOR SCIENTIFIC COMMUNICATORS ON SOCIAL MEDIA

Before posting anything on social media you should inform yourself, delve into the studies, think about your interpretation, and reflect on the reactions your post might generate. Take your time

and don't be obsessed with the topic under discussion right away. Don't try to amaze everyone at all times, but shake consciences to a certain point, appeal to reason rather than feeling, and respect other people's opinions.

To mitigate the effects of tribalism it is essential to recognize the natural tendency to create an us-vs-them-based state of opinion and to move away from such a state towards a more problem-focused approach. Group-based approaches should be left aside to favor a more positive collaboration and interaction with others.¹²

Finally, take your time to fight back, but do not do it right away. The true value should be in the message, not the messenger. If you respect privacy, listen more than you talk, see things from the other people's perspective, and focus only on doing good to others, then you cannot go wrong.¹³

I would like to conclude with a quote by social media expert Erik Qualman that perfectly summarizes this editorial: «We don't have a choice on whether we do social media, the question is how well we do it».

CONFLICTS OF INTEREST

J. M. de la Torre Hernández has received funding to conduct his study from Abbott Medical, Biosensors, Bristol Myers Squibb, and Amgen; he has also received funding for his work as a consultant for Boston Scientific, Medtronic, Biotronik, and Daiichi-Sankyo.

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Bioresorbable vascular scaffolds in the routine clinical practice: long-term results



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ABSTRACT

Introduction and objectives: Recent publications suggest that bioresorbable vascular scaffolds (BVS) are associated with an excess of thrombotic complications. We present the real-world, long-term results of a series of patients who received the Absorb BVS (Abbott Vascular, United States).

Methods: A total of 213 consecutive patients who received at least 1 BVS between May 2012 and December 2016 were analyzed. The main objective of the study was the rate of target vessel failure, a composite endpoint of infarction or target vessel revascularization and cardiac death.

Results: Seventy-five per cent of the patients were men (mean age, 61.4 years). The most common cause for admission was non-ST-elevation myocardial infarction (53.52%). The median follow-up was 44 months [28 months], the rate of the primary endpoint was 6.57% for the first 24 months and 7.98% at the end of the follow-up. Regarding the device, there were 6 cases (2.81%) of thrombosis (definitive, probable or possible) and 10 cases (4.69%) of restenosis. Patients with a past medical history of diabetes mellitus (HR, 1.72; 95%CI, 1.01-2.95; $P = .05$) and/or chronic oral anticoagulation (HR, 5.71; 95%CI, 1.12-28.94; $P = .04$) had a higher risk of target vessel failure.

Conclusions: In this series of patients, the rate of target vessel failure was similar to the one previously described by randomized clinical trials. Events were more common during the first 2 years of follow-up and in the presence of greater cardiovascular comorbidity.

Keywords: Absorb. Bioresorbable scaffolds. Coronary angioplasty.

Armazones vasculares bioabsorbibles en la práctica habitual: resultados a largo plazo

RESUMEN

Introducción y objetivos: Las publicaciones sugieren que los armazones vasculares bioabsorbibles (AVB) conllevan un exceso de complicaciones trombóticas. Se describen los resultados en la vida real y a largo plazo de una serie de pacientes a los que se implantó un AVB Absorb (Abbott Vascular, EE.UU.).

Métodos: Se analizaron 213 pacientes consecutivos que recibieron al menos un AVB entre mayo de 2012 y diciembre de 2016. El objetivo principal del estudio fue la incidencia de fracaso del vaso diana, un evento compuesto que incluye infarto de miocardio, revascularización del vaso diana y muerte cardíaca.

Resultados: El 75% de los pacientes eran varones (edad media, 61,4 años). La causa más común de ingreso fue el infarto sin elevación del ST (53,52%). La mediana de seguimiento fue de 44 meses [28 meses]. La incidencia del evento primario fue del 6,57% durante los primeros 24 meses y del 7,98% al final del seguimiento. Respecto al dispositivo, hubo 6 casos (2,81%) de trombosis (definitiva, probable o posible) y 10 casos (4,69%) de reestenosis. Los pacientes con antecedentes de diabetes mellitus (HR = 1,72; IC95%, 1,01-2,95; $p = 0,05$) o con anticoagulación oral crónica (HR = 5,71; IC95%, 1,12-28,94; $p = 0,04$) tuvieron mayor riesgo de fracaso del vaso diana.

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Received 2 November 2019. Accepted 23 January 2020. Online: 31-03-2020.

<https://doi.org/10.24875/RECICE.M20000099>

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Conclusiones: En esta serie de pacientes, la incidencia de fracaso del vaso diana fue comparable a la descrita previamente en ensayos clínicos aleatorizados. Los eventos adversos fueron más frecuentes en los primeros 2 años de seguimiento y en presencia de mayor comorbilidad cardiovascular.

Palabras clave: Absorb. Armazón vascular bioabsorbible. Angioplastia coronaria.

Abbreviations

BVS: bioresorbable vascular scaffold. **AMI:** acute myocardial infarction. **DES:** drug-eluting stent.

INTRODUCTION

Drug-eluting bioresorbable vascular scaffolds (BVS) were initially presented as a technological breakthrough to overcome the limitations and adverse events associated with permanent bare-metal stents, especially the development of neoatherosclerosis that is associated with a risk of thrombosis (0.2% per year) and secondary revascularization (2% to 3% per year).¹⁻³

At the time, the implantation of a BVS was an innovative approach to treat coronary atherosclerosis by releasing the artery from a permanent metal jail and restoring the flow architecture. Also, it preserved parietal motility and its response to stimuli generated by coronary flow (shear stress). The Absorb (Abbott Vascular, United States)—a polymer everolimus-eluting scaffold with 157 μm -thick struts—was one of the first ones to be available in Spain and several clinical trials were conducted.⁴⁻⁸ The excellent initial results led to the widespread use of this device for several clinical indications.⁹⁻¹⁰ The Absorb BVS was approved by the U.S. Food and Drug Administration and obtained the CE marking certification in January 2011.¹¹

However, the mid- and long-term data of the AIDA research group^{12,13} on the Absorb were disappointing. They showed a higher rate of late scaffold thrombosis compared to the XIENCE (Abbott Vascular, United States) (3.5% vs 0.9%; hazard ratio [HR], 3.87; 95% confidence interval [95%CI], 1.78-8.42; $P < .001$), an everolimus-eluting stent (EES).^{14,15} Therefore, the manufacturer stopped making the Absorb BVS and removed it from the market according to the European regulatory agency; however, some of these devices remain approved and are still available in Europe.¹⁶

Since the Absorb BVS was widely used in different clinical settings during market launch more than 7 years ago, the long-term follow-up results are available today. The objective of this study is to describe the incidence of long-term adverse events in a series of patients implanted with the Absorb BVS in different clinical settings of our multicenter registry.¹⁷

METHODS

Population, design, and definitions

The cases treated with percutaneous transluminal coronary angioplasty with at least 1 Absorb BVS in 3 hospitals between May 2012 and December 2016 were studied.¹⁷ Implantation was performed to the discretion of the operator in charge.

The study primary composite endpoint was the target vessel failure rate, a composite event of target vessel revascularization, target vessel related acute myocardial infarction (AMI), and cardiac death.

The study secondary endpoint was the rate of the overall clinical endpoint including these adverse events: all-cause mortality, myocardial infarction, and all the new coronary revascularizations (including those of the non-target vessel).

The registry of the interventional cardiology unit of our hospital network was periodically reviewed every 6 to 12 months at the follow-up consultation at the interventional cardiology unit by a cardiologist. Also, it was completed through follow-up phone calls.

Statistical analysis

Data regarding quantitative variables are expressed as mean \pm standard deviation and qualitative variables are expressed as percentages. Patients were grouped according to whether they had target vessel failure or not; inter-group averages were compared using the Student *t* test. Percentages were compared using the chi-square test. Kaplan-Meier analysis was conducted to estimate the likelihood of target vessel failure-free survival and BVS thrombosis and restenosis. Finally, the multivariate Cox regression analysis was conducted to study the survival function adjusted by different predefined variables: sex, age, cardiovascular risk factors, past medical history, clinical signs, size and length of the BVS implanted, overlapping of, at least, 2 BVSs, and use of intracoronary imaging modalities (optical coherence tomography [OCT] or intravascular ultrasound [IVUS]). Two-tailed $P \leq .05$ were considered statistically significant in all tests. Data were analyzed using the statistical software package Stata IC 14 (StataCorp, United States).

RESULTS

Study population

Two hundred and thirteen consecutive patients implanted with, at least, 1 Absorb BVS between May 2012 and December 2016 were included. **Table 1** shows the baseline clinical characteristics of these patients. Most of the participants were males (75.12%) with a mean age of 61.40 ± 12.74 years, and a high prevalence of dyslipidemia (62.44%) and smoking (65.26%). Diabetes mellitus was present in 23.94% and 21.60% had been previously treated with a percutaneous coronary intervention. The most common clinical presentation during recruitment was non-ST-segment elevation acute coronary syndrome (53.52%).

Index procedure of the bioresorbable vascular scaffold implantation

Table 2 shows the characteristics of the patients' index procedure. Two hundred and thirty-three coronary lesions were treated with

Table 1. Baseline clinical characteristics of patients and differences based on the primary endpoint

Characteristics	Patients who received BVS (n = 213)	Patients with BVS and target vessel failure (n = 17)	Patients with BVS without target vessel failure (n = 196)	P
Age (years)	61.40 ± 12.74	66.71 ± 9.62	61.14 ± 12.98	.07
Sex (male)	160 (75.12)	12 (70.59)	148 (75.51)	.65
<i>Risk factors</i>				
Diabetes mellitus	51 (23.94)	7 (41.18)	44 (22.45)	.06
Hypertension	118 (55.40)	11 (64.71)	107 (54.59)	.42
Dyslipidemia	133 (62.44)	13 (76.47)	120 (61.22)	.21
Active smoking	139 (65.26)	10 (58.82)	129 (65.82)	.56
<i>Past medical history</i>				
Chronic kidney disease	8 (3.76)	1 (5.88)	7 (3.57)	.63
LVEF < 30%	5 (4.5)	1 (5.88)	4 (2.04)	.55
Previous stroke or TIA	9 (4.2)	3 (17.65)	6 (3.06)	.01
Chronic oral anticoagulation	10 (4.69)	3 (17.65)	7 (3.57)	.01
Peripheral vascular disease	13 (6.10)	1 (5.88)	12 (6.12)	.96
Previous myocardial infarction	31 (14.55)	1 (5.88)	30 (15.31)	.29
Previous PCI	46 (21.60)	4 (23.53)	42 (21.43)	.84
Previous coronary artery bypass surgery	7 (3.29)	2 (11.76)	5 (2.55)	.04
<i>Clinical presentation</i>				
STEACS	31 (14.55)	4 (23.53)	27 (13.78)	.25
Non-Q-wave AMI type of NSTEMI	77 (36.15)	6 (35.29)	71 (36.22)	.66
Unstable angina type of SCASEST	37 (17.37)	3 (17.65)	34 (17.35)	.88
Stable angina or documented ischemia	68 (31.4)	4 (23.53)	64 (32.65)	.52

AMI, acute myocardial infarction; BVS, bioresorbable vascular scaffold; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEACS, ST-segment elevation acute coronary syndrome; TIA, transient ischemic attack. Data are expressed as no. (%) or mean ± standard deviation.

an average 1.3 ± 0.3 lesions per patient. Implantation was successful in 99.5% of the cases but failed in 1 patient due to the difficulty advancing the device across the lesions. The patient required the implantation of a DES, which is why he was excluded from the analysis. Predilatation occurred in 89.3% of the cases and postdilatation in 33.5% of the cases. Intracoronary imaging modalities (OCT or IVUS) were used to optimize the BVS implantation in 86 patients (40.38%).

Clinical follow-up

The median follow-up was 44 months [28 months] with minimum times < 1 month. The primary composite endpoint of target vessel failure rate was 6.57% at the 24-month follow-up (table 3) and 7.98% at the end of the follow-up. Figure 1 shows the target vessel failure-free survival curve; at the 48-month follow-up it was 0.92 (95%CI, 0.87-0.95; $P = .02$). Regarding the secondary endpoint, the overall rate was 11.74% at the 24-month follow-up (table 3) and 17.84% at the end of the follow-up.

Figure 2 shows the rate of all adverse events depending on the time of clinical presentation. Regarding the primary endpoint, there were 3 (1.41%) cases of cardiac death, 4 (1.87%) cases of target vessel

related AMI, and 14 (6.57%) cases of target vessel revascularization. Regarding the secondary endpoint, there were 7 (3.29%) cases of all-cause mortality, 7 (3.29%) cases of AMI, and 31 (14.56%) cases of any coronary revascularizations. Finally, regarding the device, there were 6 (2.81%) cases of thrombosis (definite, probable, and possible) all reported within the first 12 months. Dual antiplatelet therapy was kept, at least, for 12 months in 157 (73.7%) patients and 1 patient with late definite thrombosis received dual antithrombotic therapy (acenocoumarol and clopidogrel). Similarly, there were 10 (4.69%) cases of BVS restenosis within the first 48 months of follow-up (figure 3).

Patients with target vessel failure had a higher prevalence of cerebrovascular disease (17.65% vs 3.06%; $P = 0.01$), chronic oral anticoagulation (17.65% vs 3.57%; $P = .01$), and previous coronary artery bypass graft surgery (11.76% vs 2.55%; $P = .04$). Similarly, there was a tendency towards a higher prevalence of diabetes mellitus in this group (41.18 vs 22.45%; $P = .06$) (table 1).

In the multivariate Cox regression analysis, a prior history of diabetes mellitus (HR, 1.72; 95%CI, 1.01-2.95; $P = .05$) and chronic oral anticoagulation (HR, 5.71; 95%CI, 1.12-28.94; $P = .04$) were identified as risk factors to develop target vessel failure at the follow-up. On the other hand, the use of intracoronary imaging

Table 2. Characteristics of the index procedure and treatment

Characteristics	Patients who received BVS (n = 213)
Lesions treated per patient	1.3 ± 0.3
Number of devices per patient	1.2 ± 0.4
Total length of the device per patient (mm)	21.5 ± 13.5
Minimum device diameter per patient (mm)	2.75 ± 0.25
Device implantation	
At least 1 BVS	212 (99.5)
BVS only	204 (95.8)
Overlapping with at least 2 AVBs	20 (9.39)
Any DES	8 (3.8)
After BVS implantation failure	1 (0.5)
Procedural time (min.)	44 ± 23
Iodinated contrast used per procedure (mL)	161 ± 72
Predilatation of the first lesion treated	189 (88.7)
Procedural success	212 (99.5)
Lesions treated	
Total number	233
Predilatation	208 (89.3)
Postdilatation	78 (33.5)
0.5 mm postdilatation balloon plus BVS	21 (9.86)
Overall number of devices implanted	261
Overall number of devices per lesion	1.12 ± 0.4
Intracoronary imaging modality during implantation	
OCT or IVUS	86 (40.38)

BVS, bioresorbable vascular scaffold; DES, drug-eluting stent; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

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

modalities (OCT or IVUS) during BVS implantation showed a clear tendency towards significance as a protective factor (HR, 0.33; 95%CI, 0.10-1.07; $P = .06$) (table 4).

DISCUSSION

This study analyzed a consecutive series of patients who were implanted with, at least, 1 BVS in a high-volume setting and in real-life conditions. The primary composite endpoint of target vessel failure and the overall secondary composite clinical endpoint were similar to what had been reported by other previous randomized clinical trials on percutaneous coronary interventions.¹⁸⁻²²

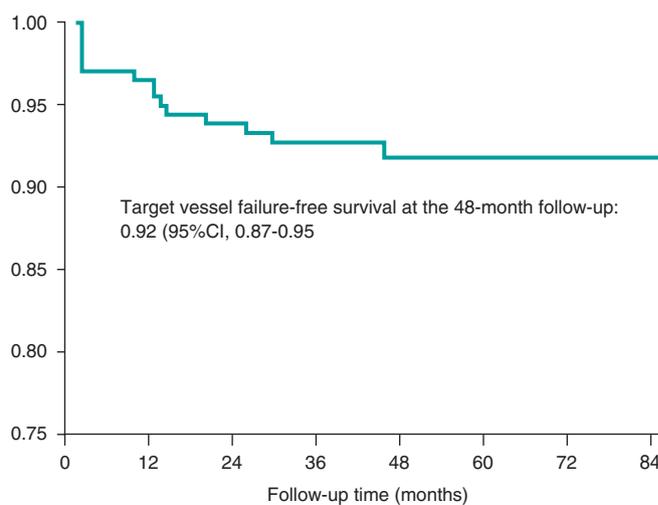
The AIDA clinical trial²⁰ confirmed the lower rate of target vessel failure related AMI from our series. In our study, the patients' baseline clinical characteristics and clinical presentation were similar to those of the population of the AIDA clinical trial. However, regarding the index procedure, the use of postdilatation was lower in our series. It has been reported that postdilatation

Table 3. Adverse events at the 2-year follow-up

Adverse event	Patients who received BVS 2-year follow-up (n = 213)
Clinical events	
All-cause mortality	5 (2.34)
Cardiac	3 (1.41)
Non-cardiac	2 (0.94)
All myocardial infarctions	6 (2.82)
During index procedure	2 (0.94)
Not during index procedure	4 (1.88)
Target vessel	3 (1.41)
Non-target vessel	1 (0.47)
Death or myocardial infarction	11 (5.16)
Any revascularization	18 (8.46)
Target vessel	11 (5.16)
Target lesion	11 (5.16)
Device thrombosis	3 (1.41)
Device restenosis	8 (3.76)
Any other vessel	7 (3.29)
Composite endpoint	
Target vessel failure	14 (6.57)
Overall clinical endpoint	25 (11.74)
Device thrombosis	
Definite	3 (1.41)
Probable	2 (0.94)
Possible	1 (0.47)

BVS, bioresorbable vascular scaffold.

Data are expressed as no. (%).

**Figure 1.** Kaplan-Meier survival curve for target vessel failure.

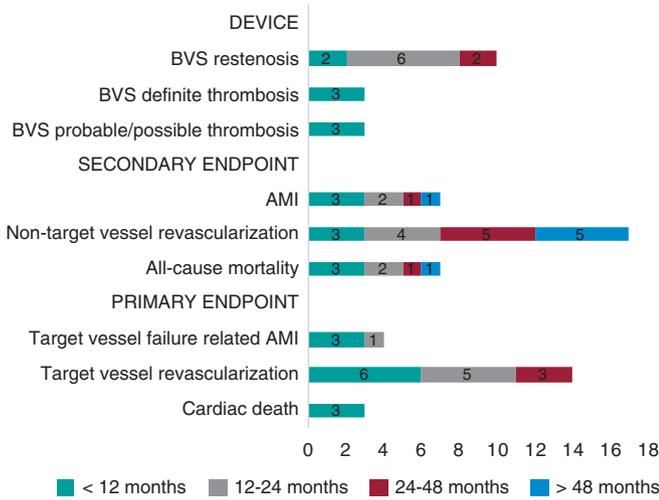


Figure 2. Chart of adverse events based on the time of presentation after the index procedure. AMI, acute myocardial infarction; BVS, bioresorbable vascular scaffold.

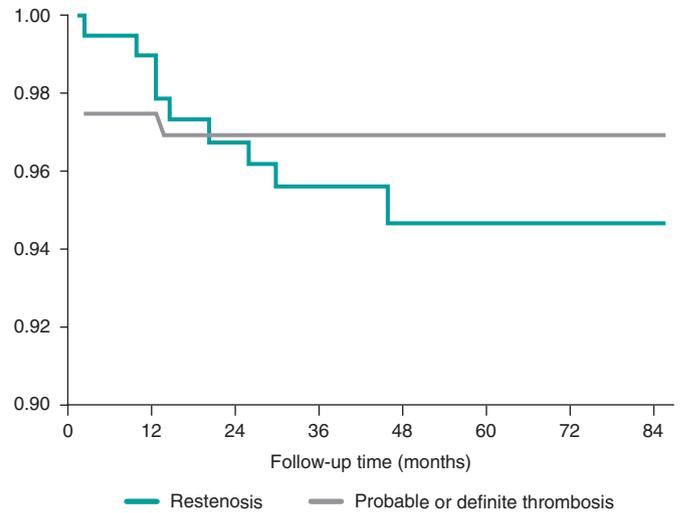


Figure 3. Kaplan-Meier survival curves for bioresorbable vascular scaffold restenosis and thrombosis.

Table 4. Factors associated with target vessel failure: Cox regression analysis

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
<i>Past medical history</i>						
Diabetes mellitus	1.72	1.04-2.86	.04	1.72	1.01-2.95	.05
Previous stroke or TIA	6.28	1.76-22.31	.01	1.94	0.40-9.23	.40
Chronic oral anticoagulation	5.34	1.51-18.97	.01	5.71	1.12-28.95	.04
<i>Use of intracoronary imaging modalities during implantation</i>						
OCT or IVUS	0.32	0.11-1.03	.06	0.33	0.10-1.06	.06

95%CI, 95% confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; TIA, transient ischemic attack.

does not bring any additional benefits to the implantation of a BVS in the ST-segment elevation acute coronary syndrome clinical setting. If elevation is excessive it could even have deleterious effects when destructuring or tearing the nonmetallic structure of the scaffold.²³ The GHOST-EU registry²⁴ proved that the PSP strategy (predilatation, scaffold sizing, and postdilatation) was a predictor of cardiovascular events.

The right selection of the lesion plays a crucial role in the clinical performance of BVS. Most of the patients of this series showed acute coronary syndrome. It is feasible that patients with AMI may benefit the most from BVS treatments.¹⁸ First, patients with acute coronary syndrome (with or without ST-segment elevation) often show a visible thrombus in the proximal segments and a less complex morphology with thin-cap fibroatheroma plaques and fewer calcified lesions. Secondly, aggressive antithrombotic therapy after an acute coronary syndrome may mitigate the rate of thrombotic complications.

Bioresorbable vascular scaffold thrombosis

A few studies have reported on a higher rate of BVS thrombosis associated with next-generation DESs,^{25,26} especially all in off-label uses.²⁷ In our series, the definite or probable device thrombosis

occurred in a similar percentage of the patients to that previously reported.¹² Several mechanisms that may explain BVS thrombosis have been suggested including edge dissection, strut fracture, malapposition, and inadequate BVS sizing.²⁸ In our series there were 2 cases of subacute definite thrombosis. In the coronary angiography, the OCT performed confirmed the presence of some structural mechanism (underexpansion or malapposition) that favored it. Early presentation at the follow-up is consistent with what has already been reported.²⁹

Similarly, we identified that the use of intracoronary imaging modalities (OCT or IVUS) during BVS implantation showed a clear tendency towards significance as a protective factor of target vessel failure as Caixeta et al.³⁰ had already confirmed in an international registry of 1933 patients. The recommendation here is to use intracoronary imaging modalities to optimize implantation and secure the correct apposition of the BVS, lack of underexpansion, and proper cover of the lesion.³¹

The main setback of the Absorb BVS is probably strut thickness and width (157 x 190.5 µm in 2.5 mm and 3.0 mm BVSs, and 157 µm x 216 µm in 3.5 mm BVSs), which can make the device more thrombogenic, especially when apposition is not the right one or expansion is incomplete. Today, ultra-thin drug-eluting stents (strut thickness < 70 µm) have lowered the risk of target lesion failure

to just 1 year compared to modern second-generation DESs thanks to fewer AMIs and stent thrombosis.³² On this issue, the sirolimus-eluting MeRes100 BVS (Meril Life Sciences Pvt. Ltd., India) with thinner strut thickness (100 μm) confirmed the sustained efficacy and safety profile at the 2- and 3-year follow-up.³³

Resistance to antiplatelet therapy can also be an important cause for BVS thrombosis.³⁴ Both acetylsalicylic acid and clopidogrel are effective antiplatelet drugs for the secondary prevention of cardiovascular events. Still their clinical efficacy varies from one individual to the next.³⁵ In our series, most of the patients remained on dual antiplatelet therapy for, at least, 12 months and there was 1 case of late thrombosis with dual antithrombotic therapy (acenocoumarol and clopidogrel). Due to his high bleeding risk, this last patient received dual antiplatelet therapy for the first 3 months; we do not know the international normalized ratio when the complication occurred, which is why the possibility of antiplatelet drug resistance cannot be discarded. However, the potential association between the BVS thrombosis and oral antiplatelet therapy had already been described.³⁶ We know that the selection of duration of antiplatelet therapy following the implantation of the Absorb BVS was difficult,³⁷ especially in anticoagulated patients because they are a population with comorbidities and high cardiovascular risk. Our data show that the implantation of the Absorb BVS in patients at high bleeding risk (including anticoagulated patients) shouldn't probably be recommended according to the consensus document reached by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. This document does not recommend the use of the Absorb BVS in patients intolerant to prolonged dual antiplatelet therapy or who require oral anticoagulation.¹⁶

Bioresorbable vascular scaffold restenosis

The most common cause for target lesion revascularization was stent restenosis within the first 48 months of follow-up. The mechanisms involved in bioresorbable vascular scaffold restenosis that may occur in the same patient are varied.^{38,39} The less intrinsic radial strength and its possible destructuring with an aggressive implantation may explain some of the early recurrences. In this study, aggressive implantation was less common since postdilatation with an up to 0.5 mm balloon combined with BVS implantation occurred in 9.86% of the cases. Also, postdilatation was not associated with restenosis at the follow-up. Also, it has been suggested that the slow resorption of the study device may have been associated with a significant spatial abnormality with loss of alignment of its structural elements, which favors restenosis.^{40,41} The complete disappearance of the BVS from the vascular wall won't happen for another 3 years⁶ and most cases of scaffold restenosis occurred within the first 2 years of follow-up.

Our study results show that there is a correlation between the history of diabetes mellitus and chronic oral anticoagulation and the development of target vessel failure. It is well-known that this past medical history elevates cardiovascular morbimortality and that the CHADS₂ and CHA₂DS₂-VASc scores can be used to estimate the risk of adverse clinical events in patients with acute coronary syndrome.⁴² In this sense, patients with a past medical history of diabetes mellitus, chronic oral anticoagulation, and coronary artery disease start with CHA₂DS₂-VASc scores of 4, that is, high risk of adverse clinical events.

Limitations

Selection bias was inevitable because, according to the operator's criterion, the clinical assessment that may have influenced the

decision to implant a BVS maybe did not come from the database, which is a common problem with observational studies like this one. However, the study shows a pragmatic approach to the use of this device in the real world.

CONCLUSIONS

In this series of patients implanted with the Absorb BVS, the composite endpoint of target vessel failure and the overall clinical composite endpoint were similar to what had already been reported by randomized clinical trials. Adverse events were more common within the first 2 years of follow-up in case of greater cardiovascular comorbidity and without intracoronary imaging modalities (OCT or IVUS) during implantation. Although the BVS studied is not available anymore there other bioresorbable devices are in the pipeline.¹⁶

FUNDING

R. Mori-Junco received the 2018 training grant from the European Society of Cardiology (APP000019660). L. Furuya-Kanamori received funding from the Australian National Health and Medical Research Council Early Career Fellowships (APP1158469).

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- The implantation of a BVS is an innovative approach for the management of coronary atherosclerosis because it releases the coronary artery from a permanent metallic jail and restores the vessel architecture.
- However, the Absorb BVS has a higher rate of thrombotic complications compared to modern DESs, which is why it was removed.

WHAT DOES THIS STUDY ADD?

- In our interventional cardiology network, the implantation of the Absorb BVS showed rates of target vessel failure that were similar to those previously described by randomized clinical trials.
- Target vessel failure occurred basically within the first 24 months in patients with diabetes mellitus or chronic oral anticoagulation. The use of intracoronary imaging modalities during implantation showed a tendency towards becoming a protective factor.
- Our results will contribute to the proper selection of patients eligible for BVS implantation and to the implantation technique as well.

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Pharmacoinvasive strategy as reperfusion treatment in non-capable primary percutaneous coronary intervention areas

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ABSTRACT

Introduction and objectives: Reperfusion therapy during an ST-segment elevation acute coronary syndrome (STEACS) can be performed using fibrinolytic agents or primary percutaneous coronary intervention (pPCI). The pPCI is the reperfusion strategy of choice, but many patients with STEACS initially come to non-PCI capable hospitals. Regional networks have been launched with both reperfusion therapies using thrombolysis in indicated cases followed by routine angiographic studies (pharmacoinvasive strategy). Our objective was to analyze the results of treatment in patients with STEACS in the Region of Murcia, Spain based on the patient's place of origin.

Methods: Retrospective study of a cohort of patients admitted due to STEACS to 3 health areas: pPCI-capable Area I (Hospital Clínico Universitario Virgen de la Arrixaca), and non-pPCI capable Areas IV and V (Hospital Comarcal del Noroeste, Caravaca de la Cruz, and Virgen del Castillo, Yecla).

Results: Six hundred and seventy-nine patients from health areas I, IV, and V of the Region of Murcia were treated of STEACS from 2006 through 2010. Out of the 494 patients from Area I, 97.6% (482 patients) were treated with pPCI while 2.4% (12 cases) received thrombolysis. In Areas IV and V, 73% (135) of patients were treated with pPCI and 27% (50) with thrombolysis. After thrombolysis, 46 patients (34%) required rescue angioplasty and 79 (58.5%) underwent a scheduled coronary angiography (pharmacoinvasive strategy). No statistically significant differences were reported in the overall mortality rate at 30-day (8.3% in Area I vs 6% in Areas IV and V; $P = .31$) or 1 year follow-up (11.3% vs 8.2%; $P = .23$) in Area I compared to Areas IV and V, nor for cardiac mortality.

Conclusions: Although immediate pPCIs are less accessible in remote health areas, the healthcare network from the Region of Murcia can achieve similar mortality results compared to populations with pPCI availability.

Keywords: ST-segment elevation acute coronary syndrome. Reperfusion therapy. Fibrinolysis. Primary percutaneous coronary intervention.

Estrategia farmacoinvasiva como tratamiento de perfusión en áreas sin disponibilidad de angioplastia primaria

RESUMEN

Introducción y objetivos: El tratamiento de perfusión en un síndrome coronario agudo con elevación del segmento ST (SCACEST) se puede realizar con agentes fibrinolíticos o con angioplastia primaria (ICPp). La ICPp es la estrategia de elección, pero muchos de los pacientes con SCACEST acuden inicialmente a hospitales sin ICPp. Se han desarrollado programas de asistencia al SCACEST

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Received 2 December 2019. Accepted 12 March 2020. Online: 27-05-2020.

<https://doi.org/10.24875/RECICE.M20000113>

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en los que se integran ambos tratamientos, utilizando la trombolisis en casos indicados, seguida de un estudio angiográfico (estrategia farmacoinvasiva). El objetivo del estudio es analizar los resultados del tratamiento del SCACEST según sea diagnosticado en áreas de salud con o sin disponibilidad de ICPp inmediata.

Métodos: Estudio retrospectivo de una cohorte de pacientes diagnosticados de SCACEST en 3 áreas de salud de Murcia: área I con ICPp (Hospital Clínico Universitario Virgen de la Arrixaca) y áreas IV y V sin ICPp (Hospital Comarcal del Noroeste, Caravaca de la Cruz y Virgen del Castillo, Yecla).

Resultados: Entre 2006 y 2010 se atendió por SCACEST a 679 pacientes de las áreas I, IV y V de Murcia. De los 494 pacientes del área I, recibieron tratamiento con ICPp el 97,6% (482) y trombolisis el 2,4% (12). En los pacientes de las áreas sanitarias IV y V se realizó trombolisis al 73% (135) e ICPp al resto 27% (50). De los pacientes sometidos a trombolisis, el 34% (46) precisaron angioplastia de rescate y al 58,5% (79) se les realizó coronariografía programada (estrategia farmacoinvasiva). No hubo diferencias en la mortalidad total a 30 días (8,3% en el área I y 6% en las áreas IV y V; $p = 0,31$) ni al año (11,3 frente a 8,2%; $p = 0,23$); tampoco en la mortalidad por causa cardíaca.

Conclusiones: A pesar de la menor accesibilidad a la ICPp en las áreas sanitarias más alejadas, la red asistencial regional de Murcia permite unos resultados comparables a los de las áreas sanitarias con disponibilidad de ICPp.

Palabras clave: Síndrome coronario agudo con elevación del segmento ST. Reperusión. Fibrinólisis. Angioplastia primaria.

Abbreviations

pPCI: primary percutaneous coronary intervention. **STEACS:** ST-segment elevation acute coronary syndrome.

INTRODUCTION

The management of ST-segment elevation acute coronary syndrome (STEACS) is based on the quick opening of the culprit artery through the use of fibrinolytic drugs or a percutaneous coronary intervention (PCI) that limits the size of the infarction and improves prognosis.¹ Fibrinolytic drugs have proven capable of increasing survival,² but they are more effective when administered within the first 3 hours after symptom onset. The primary percutaneous coronary intervention (pPCI) improves survival and reduces recurrent infarctions and strokes, which is why it is seen as the optimal therapy as long as it can be performed in a timely manner.^{3,4}

The pPCI main limitation is the impossibility to use it in the entire population due to its limited geographic availability and the delays involved in the transfer of patients from non-pPCI centers to reference hospitals. Clinical practice guidelines recommend performing pPCI < 120 min. after the diagnosis of STEACS.¹ Regional networks have been created to speed up these times and increase access to pPCI for patients with STEACS in non-pPCI hospitals. Yet despite this effort, many patients with STEACS are transferred late to pPCI centers which increases mortality and morbidity rates.

In order to improve results and administer reperfusion therapy as early as possible the so-called pharmacoinvasive strategy was implemented. It consists of the administration of fibrinolytic drugs in the pre-hospital or non-pPCI setting followed by the immediate transfer of the patient to a pPCI center capable of performing a bailout angioplasty if drug therapy fails or an early systematic angiography if it is successful.^{5,6}

The experience gained over the years performing pPCIs at the *Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA)* has been used for the optimal management of patients with STEACS. The recommendations established by the clinical guidelines have been followed and adapted to the geographic characteristics of the region, structure, and healthcare resources available. A protocol for

the management of reperfusion in the acute phase that distinguished 2 groups has been established: the first group with patients treated in pPCI centers; the second one, with patients from regional hospitals who live in remote areas far from reference hospitals where the treatment recommended is fibrinolysis in the absence of contraindications.

METHODS

Retrospective study of a cohort of 679 patients diagnosed with STEACS from 2006 through 2010 in 2 groups of healthcare regions: region I, with pPCI capabilities at the HCUVA (El Palmar, Murcia), and non-pPCI regions assigned to the HCUVA intensive care unit. This second group includes region IV with the *Hospital Comarcal del Noroeste (Caravaca de la Cruz)* and region V with the *Hospital Virgen del Castillo (Yecla)*.

Patients diagnosed with STEACS based on traditional criteria¹ and symptoms of less than 24-hour duration were included. Selection was done by reviewing the HCUVA catheterization laboratory database on all ICU admissions, hospital urgent care provided, and 061 ambulance emergency transfer reports during the study period. The most adequate reperfusion therapy was administered following recommendations and the regional protocol.

Follow-up was conducted by reviewing the patients' medical records by phone or through physical consultations.

The variables analyzed were past medical history, time elapsed since symptom onset until reperfusion therapy, electrocardiogram, echocardiographic and angiographic characteristics of angioplasty, patient progression, and treatment after hospital discharge. Major hemorrhages were defined as lethal or symptomatic in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular) causing compartmental syndrome or bleeding with reduced hemoglobin levels > 20 g/L (1.24 mmol/L) or need for 2 concentrate transfusions.

The short and long-term cardiovascular events were recorded at the 30-day and 1-year follow-up, respectively including the rates of overall mortality and cardiac mortality, acute myocardial reinfarction (re-AMI), stroke, and need for a new revascularization.

The study primary endpoint was to compare mortality and major cardiovascular events in patients treated of STEACS from the Region of Murcia based on the healthcare region they received care at. The study secondary endpoints were the analysis and comparison of the clinical characteristics of these populations and the identification of angiographic or PCI differences.

Statistical analysis

The results of continuous variables were expressed as mean ± standard deviation, and those of categorical variables as frequency or percentage. Categorical variables were compared using the chi-square test with Yates correction when necessary. Quantitative variables were compared using the Student *t* test based on the variables normal distribution. Event-free survival rates (overall and cardiac mortality, stroke, re-AMI, and restenosis) were calculated using the Kaplan-Meier method and their results were represented through survival curves. The log rank test was used to compare the event-free survival rate. The level of statistical significance used for hypothesis testing was *P* < .05. The Mac OS version of the SPSS statistical software (version 20) was used.

The study was conducted in full compliance with the Declaration of Helsinki and the good clinical practice guidelines approved by HCUVA Research Ethics Committee.

RESULTS

From January 2006 through December 2010, 679 patients from regions I, IV, and V of the Region of Murcia Healthcare System were treated of STEACS of less than 24-hour duration and received reperfusion therapy (figure 1). Ninety-seven-point-six per cent of the 494 patients from region I (HCUVA) underwent pPCI (482) while 2.4% received thrombolysis (12). Seventy-three percent (135) and 27% (50) of patients from regions IV and V (127 and 58, respectively) underwent thrombolysis and pPCI, respectively. Thirty-four percent (46) of those who received thrombolysis required a bailout angioplasty and 58.5% (79) a scheduled coronary angiography (pharmacoinvasive strategy) during their hospital stay. Only 10 patients (7.4%) did not undergo a coronary angiography.

Baseline characteristics of the populations

Baseline characteristics are shown on table 1. The HCUVA population was older and had more diabetic patients compared to the population from regional hospitals. On the contrary, the rate of atrial fibrillation was higher in the latter. No significant differences were seen based on sex or the remaining risk factors.

No differences were seen in the time to reperfusion between both groups with a mean of 180 min. (interquartile range: [120-240]) in HCUVA vs 150 min. in regional hospitals (interquartile range: [90-240]; *P* = .4). Ischemia times < 3 hours were achieved in 59.6% of the HCUVA patients compared to 68.9% of patients from regional hospitals (table 2). Forty-nine patients (9.9%) from the first group had cardiogenic shock vs 17 patients (9.2%) from the second one (not statistically significant differences).

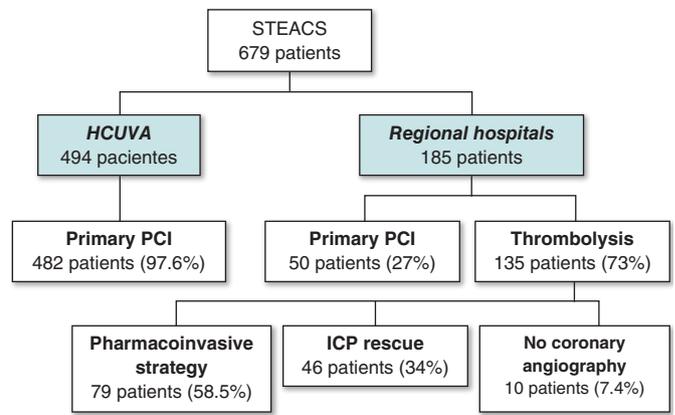


Figure 1. Summary of the study patients and the reperfusion strategies used based on the patients' healthcare regions. HCUVA, Hospital Clínico Universitario Virgen de la Arrixaca; PCI, percutaneous coronary intervention or angioplasty; STEACS, ST-segment elevation acute coronary syndrome.

Table 1. Baseline characteristics of the population

	HCUVA (n = 494)	Regional hospitals (n = 185)	<i>P</i>
Age (years)	65.3 ± 13.7	62.9 ± 13	.044
Sex (women)	111 (22.5)	41 (22.2)	.93
High blood pressure	290 (58.7)	111 (60)	.76
Diabetes	180 (36.4)	52 (28.1)	.042
Dyslipidemia	200 (40.5)	64 (34.6)	.16
Smoking	304 (61.5)	112 (60.5)	.81
Previous ischemic heart disease	53 (10.7)	21 (11.4)	.810
Previous revascularization	53 (10.7)	18 (9.7)	.88
Peripheral arterial disease	25 (5.1)	4 (2.2)	.096
Previous stroke	43 (8.7)	12 (6.5)	.35
Atrial fibrillation	21 (4.3)	16 (8.6)	.025
Heart failure	12 (2.4)	2 (1.1)	.271
Kidney disease	39 (7.9)	19 (10.3)	.324
COPD	43 (8.7)	18 (9.7)	.677
Valve disease	9 (1.8)	1 (0.5)	.217
Previous angina	122 (24.7)	39 (21.1)	.324

COPD, chronic obstructive pulmonary disease; HCUVA, Hospital Clínico Universitario Virgen de la Arrixaca.

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

Regarding the coronary angiography, the percentage of radial access was similar: 45% and 48%, respectively. No significant differences were found either in the location of the STEACS (table 2). However, significant differences were seen in the culprit artery since it was a common thing to not be able to identify the vessel in patients from regional hospitals because the coronary arteries were patent. Differences were seen too in the initial TIMI flow (Thrombolysis in Myocardial Infarction) between both groups

Table 2. Progression time (from symptom onset to reperfusion) and angiographic and electrocardiographic characteristics

	HCUVA (n = 494)	Regional hospitals (n = 185)	P
<i>Progression time (median, min.)</i>	180	150	.4
< 3 h	295 (59.7)	128 (69.1)	
3-6 h	141 (28.5)	33 (17.7)	
6-9 h	32 (6.4)	10 (5.6)	
9h -12 h	15 (3.1)	7 (4)	
> 12 h	11 (2.2)	7 (4)	
<i>STEACS location</i>			.298
Anterior	205 (41.6)	89 (48.1)	
Inferior	236 (47.7)	75 (40.5)	
Lateral	49 (9.9)	18 (9.7)	
Indeterminate	4 (0.8)	3 (1.6)	
<i>Culprit vessel</i>			.022
Left anterior descending coronary artery	205 (41.5)	83 (44.9)	.429
Circumflex artery	62 (12.6)	25 (13.5)	.738
Right coronary artery	204 (41.3)	64 (34.6)	.111
Left main coronary artery/graft	9 (1.8)	0	.065
Unidentified	14 (2.8)	13 (7)	.013
<i>Previous stent thrombosis</i>	24 (4.8)	3 (1.6)	.075
<i>Number of injured vessels</i>			.001
0	5 (1)	15 (8)	.001
1	274 (55.4)	109 (58.9)	.416
2	133 (27)	38 (20.6)	.093
3	82 (16.6)	23 (12.6)	.227
<i>Initial TIMI flow</i>			.001
0	351 (71.1)	65 (34.9)	.001
1	21 (4.2)	4 (2.4)	.281
2	13 (2.7)	9 (4.7)	.206
3	109 (22)	107 (58)	.001
<i>Final TIMI flow grade 3</i>	464 (93.9)	171 (92.3)	.845
<i>Second revascularization</i>	95 (19.2)	30 (16.2)	.322
<i>Complete revascularization</i>	347 (70.2)	138 (74.6)	

HCUVA, Hospital Clínico Universitario Virgen de la Arrixaca; STEACS, ST-segment elevation acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction. Data are expressed as no. (%)

($P = .001$) at the expense of a worse initial flow in HCUVA patients. After reperfusion therapy, TIMI flow grade-3 was achieved in the culprit artery in 93.9% of HCUVA patients and 92.3% of patients from regional hospitals. Revascularization was complete in 70.2% of the patients from region I and 74.6% of the patients from regions IV and V.

Table 3. Analytic, echocardiographic and disease progression characteristics at the hospital floor

	HCUVA (n = 494)	Regional hospitals (n = 185)	P
<i>Peak creatine kinase levels (µg/dL)</i>	1864.4 ± 1917.3	1938.3 ± 1834.4	.671
<i>Peak creatine kinase-MB levels</i>	175.39 ± 132.34	182.26 ± 159.86	.668
<i>Peak troponin T levels</i>	5.79 ± 9.4	9.38 ± 27.5	.118
<i>Ejection fraction (%)</i>	52.15 ± 10.93	52.29 ± 11.46	.886
Normal	255 (50.6)	95 (51.5)	
Mild dysfunction	152 (30.7)	52 (28.1)	
Moderate dysfunction	63 (12.8)	32 (17.3)	
Severe dysfunction	29 (5.9)	6 (3.5)	
<i>Diastolic pattern</i>			.056
Restrictive pattern	19 (3.9)	10 (5.3)	
Pseudo-normal pattern	125 (25.3)	33 (18)	
Prolonged relaxation	307 (62.2)	113 (61.3)	
Normal	37 (7.6)	23 (12.4)	
Atrial fibrillation	5 (1.1)	6 (3.3)	
<i>Hospital stay (days)</i>	9.04 ± 5.72	9.81 ± 7.94	.259
<i>Major hemorrhage</i>	11 (2.2)	7 (3.8)	.261
<i>STEACS related complications</i>	6 (1.2)	3 (1.6)	.71
<i>Killip Class I</i>	357 (72.3)	154 (83.3)	.012

HCUVA, Hospital Clínico Universitario Virgen de la Arrixaca; STEACS, ST-segment elevation acute coronary syndrome; Data are expressed as no. (%) or median ± standard deviation.

Analytic and echocardiographic characteristics and clinical progression

No differences were seen in the highest levels of cardiac necrosis markers between the different regions (table 3). On average the left ventricular ejection fraction was 52.15% in HCUVA patients and 52.29% in patients from regional hospitals without any significant differences in the systolic or diastolic function (table 3).

No differences were seen in the rates of major bleeding and complications (cardiac ruptures: 2 and 2; intraventricular communication: 1 in regional hospitals, 2 in the HCUVA; papillary muscle rupture: 1 and 1). Patients from region I had more heart failure during their hospital stay (28.7% in the HCUVA vs 16.7% in regional hospitals).

30-day and 1-year follow-up results

Mean follow-up was 962 days in HCUVA patients and 1062 days in patients from regional hospitals. No differences were seen in the overall mortality or cardiac mortality rates at the 30-day or 1-year follow-up. No differences were seen either in the rates of AMI,

Table 4. Mortality and major cardiovascular events

Results (%)	HCUVA (n = 494)	Regional hospitals (n = 185)	P
<i>Mortality</i>			
30 days	41 (8.3)	11 (6)	.312
1 year	56 (11.3)	15 (8.2)	.229
<i>Cardiac death</i>			
30 days	35 (7.1)	8 (4.3)	.19
1 year	43 (8.7)	9 (4.9)	.095
<i>Reinfarction</i>			
30 days	7 (1.4)	2 (1.1)	.735
1 year	20 (4)	5 (2.7)	.409
<i>Stroke</i>			
30 days	8 (1.6)	3 (1.6)	.996
1 year	15 (3)	3 (1.6)	.309
<i>Revascularization</i>			
30 days	7 (1.4)	4 (2.2)	.494
1 year	35 (7.1)	9 (4.9)	.294

HCUVA: Hospital Clínico Universitario Virgen de la Arrixaca.
Data are expressed as no. (%).

stroke, and revascularization at the follow-up (table 4). Kaplan-Meier survival curves (figure 2) did not show any significant differences regarding mortality, cardiac death, AMI, and stroke.

DISCUSSION

This study assessed the results of the management of STEACS from a population perspective and analyzed the consequences of the different care provided in each patient's healthcare region. This was an observational and retrospective study conducted in 3 population areas from the Region of Murcia that share the same interventional cardiology unit and the same intensive care unit. A 5-year period was analyzed with an mean annual rate of 140 patients with STEACS who were admitted to the ER with symptoms of < 24-hour duration. To make the analysis more consistent and thorough, the past medical histories of patients admitted to their respective hospitals and the out-of-hospital ER system and 061 emergency service reports were reviewed to detect prehospital deaths.

The regional plan for the management of STEACS⁷ is part of the recommendation of designing regional networks beyond the idea of isolated hospital healthcare towards more comprehensive community healthcare systems including scientific recommendations, geographical peculiarities, resources and infrastructures available, and the characteristics of healthcare organization. This plan suggests initiating reperfusion therapy as early as possible whether mechanical with pPCI or pharmacological with fibrinolysis.

The pPCI is considered the treatment of choice for patients admitted to the ER within 60 min. since symptom onset.^{1,8,9} This is how patients diagnosed with STEACS in the metropolitan area of Murcia and nearby municipalities are treated.⁷ For remote areas such as healthcare regions IV and V, fibrinolytic therapy is recommended

in the absence of contraindications followed by transfer to the HCUVA ICU plus urgent coronary angiography in the absence of reperfusion signs (bailout PCI) or elective coronary angiography within the first 24 hours to 48 hours (pharmacoinvasive strategy).⁷ The hospitals from such areas are 75 km and 110 km away (figure 3) respectively from the pPCI reference hospital.

Populations from pPCI-capable regions (494 patients) and those from remote regions (185 patients) are rather similar: 78% males, many diabetic patients (> 28%), and over 60% smokers. The only differences between both groups are that patients from region I are older and have a higher prevalence of diabetes (36.4% vs 28.1%). The percentage of diabetics in this series is higher compared to that of international studies like the STREAM trial (12.1% to 13.1%) and other national studies like those conducted by Rodríguez-Leor et al.¹⁰ (24.8%), and Hernández-Pérez et al.¹¹ (19.1%), and similar to the EUROASPIRE-IV registry (27%).¹²

The studies conducted until 2006 in patients with STEACS admitted to the ER in a timely manner showed that up to 25% to 30% did not receive reperfusion therapy.^{13,14} This has improved with the implementation of STEACS care networks. Proof of this are the results from several networks in Europe and the United States with percentages from 100% (the Mayo Clinic network)¹⁵ to 84% (the Alberta network, Canada).¹⁶ Our data are indicative of a high percentage of reperfusion therapy in the studied regions.

In region I the pPCI was performed in almost all of the cases (97.6%) while in the remaining 2 regions 27% of the 185 patients were referred to other centers for mechanical reperfusion. The existence of contraindications for thrombolysis, the long progression time or the possibility of agile hospital transfers to the interventional cardiology unit facilitated the performance of pPCI in 1 out of every 4 patients with STEACS from these regions; the rest (73%) received fibrinolysis. These data are indicative of a greater use of fibrinolytic therapy compared to the one reported by other studies. Thus, a Belgium registry¹⁷ reported that fibrinolytic therapy was prescribed to 28.7% of the population from regional hospitals over the first few years (2007-2008). However, this percentage dropped to 12.6% over the last few years (2009-2010). The higher percentage of thrombolytic therapy seen in our study is associated with a longer distance between regional hospitals and the reference pPCI hospital. Even so, over the last few years, a higher percentage of patients with STEACS referred to pPCI centers has been reported in our region. At the program early stages,¹⁸ in healthcare regions IV and V, the percentage of pPCIs performed was between 1% and 2% of all reperfusion therapies. In our study, this percentage grew to 27% after reducing patient transfer times between hospitals.

Coronary angiography was performed in 95% of the patients who received fibrinolytic therapy, a similar percentage compared to that reported by other registries (96% in the FAST-MI,¹⁹ and 97% in the Mayo Clinic Care Network registry¹⁵) and higher to the one reported by the Belgium registry (69%).¹⁷

Reperfusion mean times are also similar to those reported by the registries mentioned above. Time delay until reperfusion therapy was < 3 hours in 59.6% of the patients from region I and 68.9% of the patients from regions IV and V. These are similar rates to those from the Belgium trial¹⁷ in which the time elapsed since symptom onset until reperfusion therapy was < 4 hours in 67% of the patients from pPCI hospitals and 63% of the patients from regional hospitals and to those from the Mayo Clinic Care Network AMI protocol.¹⁵ This protocol establishes a pharmacoinvasive strategy where total ischemia times were 103 min. in patients who received thrombolysis and 278 min. in those referred to undergo pPCI (with a mean time until reperfusion in regional hospitals of 181 min.).

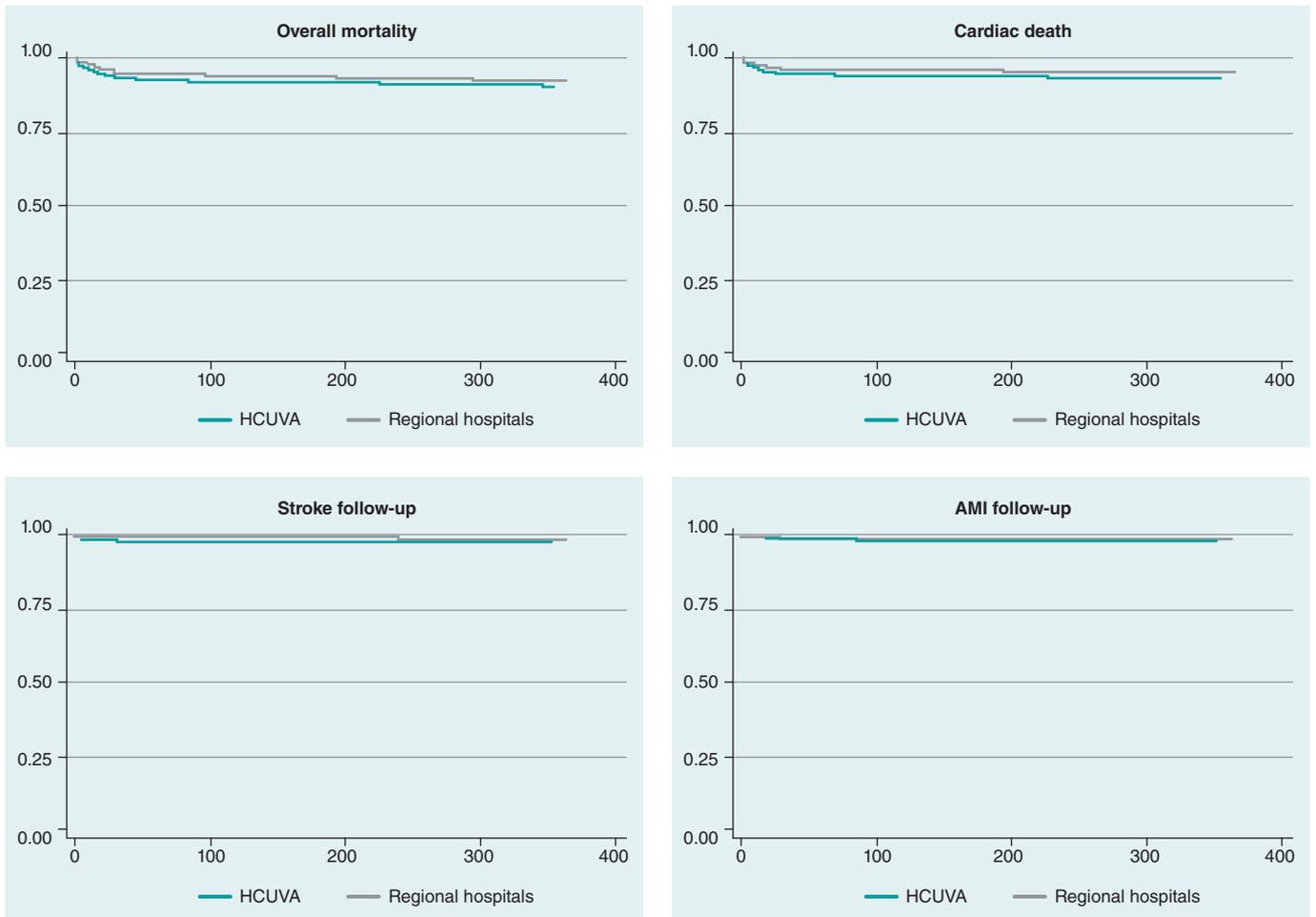


Figure 2. Survival curves. Mortality, cardiac death, stroke, and AMI at the follow-up. AMI, acute myocardial infarction; HCUVA, Hospital Clínico Universitario Virgen de la Arrixaca.

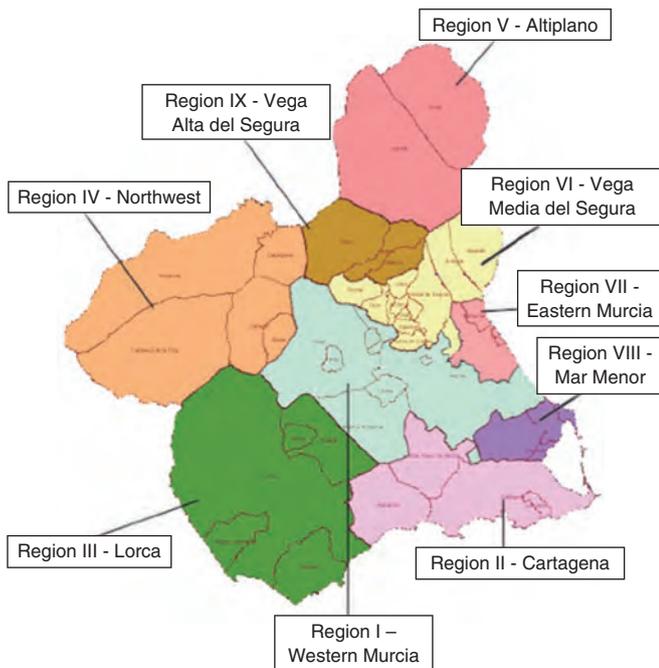


Figure 3. Healthcare regions within the Region of Murcia, Spain.

No differences were seen in the location of the infarction between both groups. Patients referred from regional hospitals had more coronary arteries without lesions and a higher preprocedural rate of TIMI flow grade-3 compared to a higher rate of occluded infarct related culprit arteries in those referred for pPCI. Upon arrival to the catheterization laboratory, the initial TIMI flow grade was 0-1 in 75.6% of the patients referred for pPCI and 37.3% in those who received thrombolysis. Different studies show that when the coronary angiography is performed there is a higher percentage of patients with TIMI flow grade-3 among patients who received thrombolysis.²⁰

Clinical progression was similar with no differences regarding major bleeding complications (2.2% vs 3.8%), stroke (1.6% vs 1.6% at 30 days), re-AMI (1.4% vs 1.1% at 30 days), and need for revascularization (1.4% vs 2.2% at 30 days, 7.1% vs 4.9% at 1 year). However, the rate of heart failure during the hospital stay was higher in HCUVA patients (27.3% vs 16.7%). This result may be explained by a tendency towards a greater grade of advanced diastolic dysfunction in these patients (25.3% vs 18%). However, despite the longer ischemia time there were no significant differences in the AMI size due to systolic dysfunction or peak creatinine kinase-MB levels with peak values of 175 vs 182 µg/dL.

The mortality of patients looked after in regions assigned to non-pPCI regional hospitals is similar to that of patients looked after in the reference pPCI hospital. At 1-month, the overall mortality

rate was 8.3% in region I with pPCI capabilities and 6% in the most remote areas assigned to regional hospitals; cardiovascular mortality rate was 7.1% and 4.3%, respectively. These rates are similar to those reported by other studies conducted in our setting like the 7.5% from the RESCATE II,²¹ 7.26% from the RECALCAR trial,²² 11% from the PRIAMHO-II trial,²³ and 7.6% from the MASCARA trial.²⁴ They are also similar to those from the Belgium infarction care network¹⁷ where the mortality rates of regional and pPCI hospitals were 7% and 6.7%, respectively or the Mayo Clinic AMI Care Network where the mortality rates of patients from regional hospitals and pPCI hospitals were 5.2% and 7.2%, respectively.¹⁵

Based on these findings a reflection is to be made on some of the things that worry healthcare providers, Administration, and patients such as accessibility and equity in the healthcare system. In the STEACS setting there is an ongoing debate on how to make pPCI available for the entire population. Data from this and other studies,^{19,25} show that even if pPCI is the preferred reperfusion strategy, it is not the only one. In patients looked after in remote areas far from hospitals with experienced heart teams a pharmacoinvasive strategy with fibrinolytic treatment in the absence of complications is a good alternative.

Limitations

The scarce population from regions IV and V brings down the annual number of patients with STEACS, which is why the time-frame studied had to be a large one in order to study a representative sample. This was a retrospective analysis with the limitations of this type of studies. Basically, this shows how difficult it was to obtain certain data like those regarding different timeframes. The findings from this study where patients were always transferred to the reference hospital intensive care unit may vary from those of other regions where delays could occur if fibrinolysis was not successful. Another possible limitation would be that only patients treated with reperfusion therapy were studied. As already discussed, patients who may have died during the transfer or at the ER were searched for to discard differences in the results obtained from patients assigned to a reperfusion strategy and those finally treated. However, patients with STEACS who did not receive reperfusion therapy were not studied (cases with long symptom duration, etc.). The study compared the results based on the patients' healthcare region, which may be decisive when assessing the management of STEACS in different healthcare regions, and the different ways of administering various types of reperfusion therapy. This does not seem to be a problem at the moment since reperfusion therapy is administered to over 80% of the cases without significant regional differences.

CONCLUSIONS

Patients diagnosed with STEACS from the most remote healthcare regions of the Region of Murcia (regions IV and V) show similar clinical characteristics compared to patients from region I. However, they are younger patients with not so much diabetes. Yet despite the lower accessibility to immediate pPCI for populations from these healthcare regions, the regional network gives results that are similar to those of populations from pPCI-capable healthcare regions. Pharmacoinvasive strategy is a valid reperfusion therapy for populations from non-pPCI healthcare regions within the times recommended, with similar survival rates to those of pPCI regions, without a higher rate of complications, and with similar short and long-term results.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Fibrinolysis and pPCI are reperfusion therapies for the management of STEACS. The latter is superior to the former if performed in a timely manner and under the right conditions.
- The pPCI main limitation is that it is impossible to offer it to the entire population due to time delays and availability issues.
- Regional networks have been created to reduce time to reperfusion and increase the availability of pPCI.
- Yet despite this effort, some patients with STEACS do not make it on time to the ER to be treated with pPCI. This delay is associated with higher mortality and morbidity rates.

WHAT DOES THIS STUDY ADD?

- Accessibility to pPCI for patients diagnosed with STEACS from remote areas is much lower.
- Being part of a healthcare regional network gives results that are similar to those of populations from pPCI-capable regions.
- This study shows that in an infarction care regional network system, reperfusion therapy can be performed by combining pharmacoinvasive strategy and pPCI.
- That is the way to achieve survival rates similar to those of patients who live close to pPCI-capable hospitals without a higher rate of complications.

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Fifteen years of percutaneous coronary interventions for chronic total coronary occlusions. Experience, results, and clinical outcomes

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ABSTRACT

Introduction and objectives: Chronic total coronary occlusion (CTO) is often a complex entity to deal with through a percutaneous coronary intervention, and the clinical benefits of successful recanalization still remain uncertain. Most registries feature data in limited time periods and do not reflect the impact that specific dedicated programs have on recanalization. Our study evaluates the results of a CTO program on a long-term period of time.

Methods: All patients' CTOs treated with percutaneous coronary interventions at our center from 2002 through 2017 were prospectively included in the registry. The clinical, angiographic and procedural data were collected, and clinical follow-up was conducted. Three consecutive periods of time were considered for the analysis of temporal trends.

Results: A total of 424 CTOs (408 patients) were included. In 339 patients (80%) the procedure was successful. The rate of success increased over time, from 57% in 2002-2006 to 87% in 2012-2017 ($P = .001$). The most important independent predictor of procedural failure was lesion tortuosity. After a median follow-up of 39.7 months, the rates of major adverse cardiovascular events and cardiovascular mortality in success vs failed groups were 13.9% vs 24.7% ($P = .015$) and 3.6% vs 14.1% ($P = .001$), respectively. These were the independent predictors of cardiovascular mortality: chronic kidney disease, left anterior descending artery occlusion, and procedural failure.

Conclusions: Our series shows a high rate of success in CTO recanalization, which has increased over the last few years due to greater expertise and improved program-specific technical advances. Several angiographic and procedural variables have been identified as predictors of failure. Successful procedures, especially on the left anterior descending coronary artery, were associated with lower rates of cardiovascular mortality.

Keywords: Chronic total coronary occlusion. Percutaneous coronary intervention. Ischemic heart disease.

Quince años de intervencionismo percutáneo de la oclusión total coronaria crónica. Experiencia, resultados y pronóstico clínico

RESUMEN

Introducción y objetivos: La oclusión total coronaria crónica (OTC) es generalmente compleja de abordar con intervencionismo percutáneo y el beneficio clínico de su recanalización sigue siendo incierto. La mayoría de los registros aportan datos limitados en el tiempo y no reflejan el impacto de un programa específico para su tratamiento. Nuestro estudio evalúa los resultados de un programa de OTC a largo plazo.

Métodos: Se incluyeron de forma prospectiva todos los pacientes tratados con un intento de revascularización percutánea de una OTC entre los años 2002 y 2017. Se obtuvieron datos clínicos, angiográficos, intraprocedimiento y del seguimiento. Se consideraron 3 periodos temporales consecutivos para el análisis.

Resultados: Se incluyeron 408 pacientes (424 OTC). La desobstrucción fue exitosa en 339 lesiones (80%). El éxito se incrementó con el tiempo, de un 57% en 2002-2006 a un 87% en 2012-2017 ($p = 0,001$). El predictor independiente más potente de procedimiento fallido fue la tortuosidad intralesional. Tras una mediana de seguimiento de 39,7 meses, las tasas de eventos adversos cardíacos mayores y de muerte cardíaca en los grupos de éxito y fracaso fueron del 13,9 frente al 24,7% ($p = 0,015$) y del 3,6 frente al 14,1% ($p = 0,001$), respectivamente. Los predictores independientes de mortalidad cardíaca fueron la insuficiencia renal crónica, la oclusión de la arteria descendente anterior y el fallo del procedimiento.

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Received 12 November 2019. Accepted 20 December 2019. Online: 19-02-2020.

<https://doi.org/10.24875/RECICE.M19000090>

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Conclusiones: Nuestra serie muestra unas tasas elevadas de éxito en la recanalización de una OTC, incrementada en los últimos años debido a la experiencia y al desarrollo técnico del programa. Se han identificado numerosas variables clínicas y angiográficas como predictoras de fallo del procedimiento. El éxito en el procedimiento, en especial en la arteria descendente anterior, se asoció con una menor mortalidad cardíaca.

Palabras clave: Oclusión total crónica. Intervención coronaria percutánea. Cardiopatía isquémica.

Abbreviations

ACS: acute coronary syndrome. **CABG:** coronary artery bypass graft. **CTO:** chronic total coronary occlusion. **LAD:** left anterior descending coronary artery. **MACE:** major adverse cardiovascular events. **PCI:** percutaneous coronary intervention.

INTRODUCTION

Percutaneous coronary interventions (PCI) of chronic total coronary occlusions (CTO) represent up to 12% of all PCIs performed.¹ The reason to perform the percutaneous recanalization of a CTO is to improve clinical symptoms which, ultimately, has potential survival benefits as suggested by some observational studies.²⁻⁴ However, the clinical benefits of successful recanalization remain undefined and to this day accepting that opening CTOs saves lives, despite the favorable consistent results from several contemporary registries, is still not supported by randomized clinical trials.⁵

Given the complexity of these procedures, a specific program with dedicated CTO-trained operators is encouraged. Also, most of the published registries and randomized clinical trials are performed in highly skilled centers and feature results in limited periods of time usually on specific devices, but not long-term results.²⁻⁵

We present the results of a specific PCI program for CTO lesions, starting with the introduction of drug-eluting stents from 2002 through 2017. The profile of patients and lesions, procedural data, results, and long-term clinical outcomes have been analyzed during the time frame of the program.

METHODS

This prospective registry conducted in a single center with an active PCI program for CTOs started back in 2002. It included 1 single operator who would progressively develop proper skills.

All consecutive patients treated of their CTOs, at least once, through percutaneous recanalization during the period 2002-2017 were included. Clinical data, angiographic characteristics, and procedural features were collected. The patients gave their informed consent and the study was approved by the local review board.

The indication for the recanalization of the CTO was the presence of angina, confirmation of ischemia through provocation tests or viable myocardium assessed through magnetic resonance imaging since 2004 when this diagnostic imaging modality became available at our center. No angiographic exclusion criteria were applied. Therefore, long occlusions, severely calcified lesions, and ostial locations were included if clinically indicated. Patients with an indication for coronary artery bypass graft (CABG) were excluded.

CTOs diagnosed in the setting of an ST-segment elevation acute coronary syndrome were scheduled for intervention that was

performed at least 4 weeks after the index procedure. In cases of non-ST-segment elevation, CTOs were approached during the initial catheterization or in a subsequent staged procedure at the operator's discretion. Also, in 28 out of the 101 cases of CTOs diagnosed in the context of an ACS, the ad-hoc desobstruction of the CTO was attempted.

Most CTOs were performed by the lead operator who focused their experience on trying to improve the rate of success for the benefit of the patient.

For the analysis of temporal trends regarding techniques and results, patients were classified into 3 consecutive periods of time: 2002-2006, 2007-2011, and 2012-2017. Also, the entire cohort was divided into 2 groups regarding success or failure in the recanalization of the CTO. Follow-up data were obtained from hospital records and the contact kept with the patients and the information provided were prospectively included in a database. No routine angiographic follow-up assessment was conducted.

Procedures were performed according to standard practices through the femoral or radial approach. Antithrombotic therapy consisted of unfractionated heparin (100 U/Kg) with additional administration when appropriate, to achieve activated clotting times of 250 seconds or 300 seconds using the antegrade and retrograde approaches, respectively. Aspirin 100 mg was administered orally prior to the PCI. Before stent implantation patients received perioperatively 300 mg to 600 mg of clopidogrel followed by a daily administration of 75 mg for the prescribed period of dual antiplatelet therapy.

CTOs were defined as coronary obstructions with TIMI flow grade 0 of at least 3 months duration.

Procedural success was defined as achieving residual post-PCI stenosis < 30% associated with TIMI flow 2-3.

Mortality was considered cardiovascular unless an evident non-cardiac cause was identified. Myocardial infarction was defined according to the Third Universal Definition established by the European Society of Cardiology and the American College of Cardiology Foundation. Target lesion revascularization was defined as a repeated PCI on the target lesion or CABG on the target vessel following ischemia-driven restenosis. Target vessel revascularization was defined as repeated PCI or CABG on any segments of the target vessel. Major adverse cardiovascular events (MACE) were defined as cardiovascular death, myocardial infarction or need for surgical or percutaneous target vessel revascularization. Stent

thrombosis was defined according to the Academic Research Consortium criteria.

The angiographic characteristics expected to be predictive of procedural success were classified according to the recommendations proposed by the Euro-CTO club consensus document.⁶ The J-score was calculated for each lesion based on the length of the occlusion, morphology of the stump, calcification, tortuosity, and prior attempt to open the CTO.⁷

Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), when appropriate. Categorical variables were expressed as percentages. The chi square test or Fisher's exact test were used to compare the categorical variables. The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous data. Continuous variables were compared according to their distributions using the Student *t* test or Mann-Whitney *U* test (success vs failed subgroups), and the ANOVA or Kruskal-Wallis test (comparison of 3 time periods). The estimates of cardiovascular death-and-MACE-free survival were shown by the Kaplan-Meier curves. Inter-group differences were assessed using the log-rank test. The logistic regression and Cox proportional hazard models were used to assess the independent contribution of variables to procedural success and mortality, respectively. Multivariate models included variables with *P* values < .2 in the univariate analysis. All statistical analyses were 2-tailed, and *P* values < .05 were considered statistically significant. The statistical analysis was performed using the statistical software package SPSS 15.0 (SPSS Inc., United States).

RESULTS

A total of 424 CTOs (408 patients) were included. In 339 patients (80%) procedural success was achieved. The number of procedures and the corresponding rate of success per period is shown on figure 1.

The baseline characteristics regarding the success or failure of the CTO procedure are featured on table 1 and table 2. Previous CABG and the ACS setting were more common among failed cases.

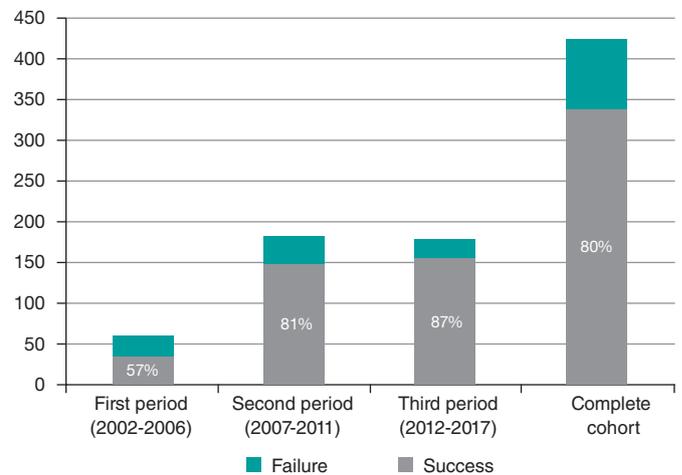


Figure 1. Number of procedures and corresponding rate of success per period.

Patients with successful procedures were more prone to left anterior descending coronary artery (LAD) involvement, microchannels, and Rentrop grade 3 collateral blood flow. Procedural success was higher in the LAD compared to other target vessels (87% vs 77%; *P* = .02). Procedural success in the circumflex artery was the lowest of all (76%). The complexity of the CTO according to the J-score was higher in failed cases.

Procedural details are shown on table 3. The use of 8-Fr catheters and dual injections was significantly higher among successful cases with a strong trend towards retrograde approach and intravascular ultrasound guidance. Drug-eluting stents were deployed in most of cases and limus-eluting stents were the most widely used by far (79%). PCIs were performed on at least 1 additional vessel in about two-thirds of the patients from the 2 groups. Independent predictors of failure were previous CABG, moderate-to-severe lesion tortuosity, tandem occlusions, lack of dual injection, and CTOs diagnosed in the ACS setting (table 4).

Table 1. Baseline characteristics

	All (n = 424)	Success (n = 339)	Failure (n = 85)	<i>P</i>
Age	63 ± 12	63 ± 12	64 ± 13	.48
Male sex	350 (83%)	277 (82%)	73 (86%)	.37
Hypertension	279 (66%)	217 (64%)	62 (73%)	.15
Diabetes Mellitus	120 (28%)	95 (28%)	25 (29%)	.91
Dyslipidemia	275 (65%)	222 (65%)	53 (62%)	.45
Past/current smoker	292 (69%)	236 (70%)	56 (66%)	.48
Previous infarction	147 (35%)	111 (33%)	36 (42%)	.72
Previous CABG	31 (7%)	18 (5%)	13 (15%)	.002
Multivessel disease	297 (70%)	234 (69%)	63 (74%)	.38
Left ventricular ejection fraction	55 ± 13	55 ± 13	57 ± 13	.17
Serum creatinine (mg/dL)	1.03 ± 0.53	1.02 ± 0.49	1.04 ± 0.64	.76
Acute coronary syndrome	103 (24%)	74 (22%)	29 (34%)	.021

CABG, coronary artery bypass graft. Data are expressed as no. (%) or mean ± standard deviation.

Table 2. Angiographic characteristics of occlusive lesions

	All (n = 424)	Success (n = 339)	Failure (n = 85)	P
Left anterior descending coronary artery	129 (30%)	112 (33%)	17 (20%)	.02
Right coronary artery	211 (50%)	163 (48%)	48 (56%)	.17
Left circumflex artery	81 (19%)	62 (18%)	19 (22%)	.39
Diameter (mm)	3.15 ± 0.45	3.15 ± 0.46	3.16 ± 0.58	.97
Length (mm)	23 ± 16	21 ± 13	29 ± 21	.001
Moderate-to-severe calcification	303 (74%)	232 (72%)	71 (84%)	.028
Moderate-to-severe tortuosity	150 (35%)	95 (28%)	55 (65%)	.001
Severe distal disease	122 (29%)	91 (27%)	31 (36%)	.14
Tandem occlusions	53 (13%)	31 (9%)	22 (26%)	.001
Microchannels	86 (20%)	75 (22%)	11 (13%)	.04
Ostial/side branch location	163 (38%)	120 (35%)	43 (51%)	.033
Tapered stump	208 (49%)	171 (50%)	37 (44%)	.12
Retrograde grade 3 collateral flow	206 (48%)	171 (50%)	35 (41%)	.09
J score > 3	192 (45%)	129 (38%)	63 (74%)	.001

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

Table 3. Procedural characteristics

	All (n = 424)	Success (n = 339)	Failure (n = 85)	P
<i>Femoral access</i>	265 (63%)	215 (63%)	50 (59%)	.39
<i>8-Fr catheter</i>	207 (49%)	175 (52%)	32 (38%)	.03
<i>Dual injection</i>	367 (87%)	302 (89%)	65 (76%)	.02
<i>Intervention</i>				
Drug-eluting stent		294 (87%)	NA	
Bare metal stent		20 (6%)	NA	
Drug-eluting and bare-metal stent		15 (4%)	NA	
Balloon		10 (3%)	1 (1.2%)	
<i>Retrograde approach</i>	94 (22%)	69 (20%)	25 (29%)	.07
<i>IVUS</i>	61 (14%)	56 (17%)	5 (6%)	.06
<i>Duration (min)</i>	105 ± 41	106 ± 42	102 ± 39	.43
<i>Fluoroscopy dose (cGy/m²)</i>	26 037 ± 2066	26 403 ± 2222	24 867 ± 13 019	.57
<i>Contrast volume (mL)</i>	367 ± 175	377 ± 177	327 ± 158	.002

IVUS, intravascular ultrasound.

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

Twenty-six coronary dissections (6.2%) and 21 femoral hematomas (5%) were the most common procedural complications of all. In the course of the attempts, perforations occurred in 5 successful cases (1.5%) and in 9 failed cases (10.8%). However, emergent pericardiocentesis due to cardiac tamponade was required in 1 patient only. Contrast-induced nephropathy occurred in 8 successful cases (2.5%) and in 1 failed case (3.1%). One patient died during hospitalization due to cardiogenic shock that occurred 24 hours after a failed CTO attempt.

The differences seen among the 3 time periods led us to think that procedural technical advances, the operator's increasing skills, and the improvements made in the assessment of the patients' profile and selection of the lesions, contributed to the 87% rate of success reported at the final time frame. The temporal trends shown on table 5 describe the techniques developed in each corresponding period, not that all procedures were performed with that technique. Since June 2013 numerous cases have been successfully completed using the dissection/re-entry technique. The median follow-up was 39.7 months

Table 4. Multivariate predictors

Failed procedure	HR	95%CI	P
Previous CABG	7.51	2.83-19.90	.0001
Moderate-to-severe tortuosity	3.78	2.02-7.08	.0001
ACS setting	2.42	1.26-4.61	.008
Tandem occlusion	2.32	1.11-4.87	.027
Lack of dual injection	2.43	1.14-5.55	.027
Cardiovascular mortality	HR	95%CI	P
Renal failure (< 60 mL/min)	5.67	1.95-16.48	.002
LAD occlusion	3.30	1.12-9.74	.032
Failed procedure	7.14	2.44-20.0	.0001

95%CI, 95% confidence interval; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; LAD, left anterior descending coronary artery.

[22–102]. Follow-up information was available in 407 patients (99.8%). Clinical outcomes during follow-up are shown on [table 6](#).

In the success group, 33 restenosis (9.7%) were angiographically diagnosed, 42% of which ended up being occlusive. Target lesion revascularization was achieved in 31 of these restenotic lesions (9.2%). Four of the 5 cases of definite thrombosis corresponded to a successfully opened right coronary artery.

One case of severe radiodermatitis was identified and it was successfully treated with local surgery 6 years after the intervention.

A remarkable difference in MACE was observed in favor of the success group, mainly driven by a lower rate of cardiovascular mortality. The cumulative cardiac survival and MACE survival curves associated with the success or failure of the PCI are shown on [figure 2](#) and [figure 3](#).

The multivariate analysis confirmed that a past medical history of chronic kidney disease with creatinine clearance < 60 mL/min,

Table 5. Temporal trends in baseline angiographic characteristics, procedural data, and results

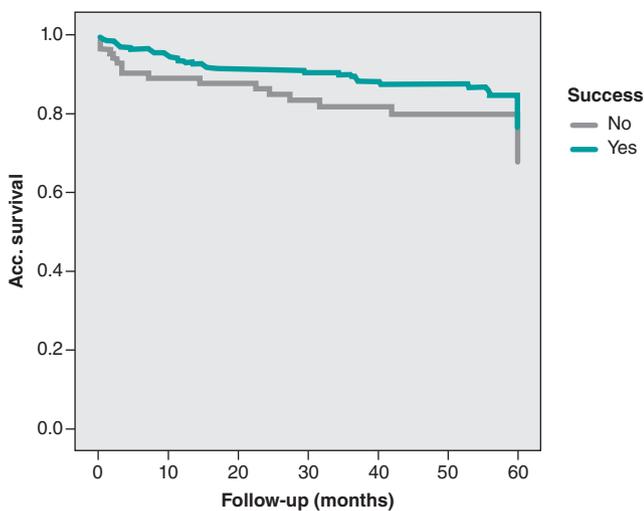
	1st period (2002-2007)	2nd period (2007-2011)	3rd period (2011-2017)	Total	P
Age	62 ± 16	63 ± 11	64 ± 11	63 ± 12	NS
Multivessel disease	61.7%	60.1%	82%	70%	.0001
ACS setting	36.1%	21.8%	23.6%	24.3%	.025
Previous CABG	9.8%	10.0%	3.9%	7.3%	.020
LAD	27.9%	33.3%	28.5%	30.4%	NS
Length (mm)	23 ± 14	22 ± 13	21 ± 18	23 ± 16	NS
J score > 3	45.0%	44.8%	45.8%	45.2%	NS
Rentrop grade 3 cc.	44.8%	62.8%	39.4%	48.6%	.0001
Femoral access	49.2%	68.0%	62.6%	62.5%	.016
8-Fr catheter	11.7%	58.3%	54.3%	48.8%	.0001
Dual injection	65.0%	90.1%	92.1%	86.5%	.0001
Retrograde approach	1.6%	23.3%	28.8%	22.1%	.0001
IVUS	21.2%	18.3%	11.1%	14.4%	.033
Fluoroscopy time (cGy/m ²)	33245	30310	19830	26037	.0001
Contrast volume (mL)	453 ± 208	434 ± 178	281 ± 127	367 ± 175	.0001
Success rate	57%	81%	87%	80%	.001
More widely used wires	Polymer coated wires (Whisper ES or MS, Pilot 50, 150 or 200, Abbott Vascular, United States) and tapered, stiff wires (Confianza Pro 12, Asahi Intecc., Japan). Used in 58%.	Runthrough wire (Terumo, Japan) and nontapered, stiff wires (Miracle 3 or 6 and Ultimate Bross 3, Asahi Intecc., Japan). Used in 62%.	Runthrough and nontapered, stiff wires widely used (59%). Sion and Gaia wires (Asahi Intecc., Japan) were used in 21%.		
Specific devices and techniques	Antegrade approach only. Parallel and seesaw wiring techniques.	Retrograde approach, Corsair specific catheter (Asahi Intecc., Japan) and Guideliner (Vascular Solutions, United States). Kissing and reverse CART techniques.	Double lumen Nhancer catheter (Interventional Medical Device Solutions, The Netherlands). Hybrid techniques with the CrossBoss and Styngrey catheters (Boston Scientific, United States).		

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; ES, extra support; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; MS, medium support.

Table 6. Clinical outcomes at follow-up

	All (n = 424)	Success (n = 339)	Failure (n = 85)	P
Overall mortality	64 (15.1%)	40 (11.8%)	24 (28.2%)	.001
Cardiovascular mortality	24 (5.7%)	12 (3.6%)	12 (14.1%)	.001
Myocardial infarction	10 (2.4%)	8 (2.4%)	2 (2.4%)	.99
Target vessel revascularization	45 (10.6%)	34 (10.1%)	11 (12.9%)	.44
Target lesion revascularization	40 (9.5%)	31 (9.2%)	9 (10.6%)	.69
CTO stent thrombosis				
Definite		5 (1.5%)	NA	
Probable		1 (0.3%)	NA	
MACE	68 (16.1%)	47 (13.9%)	21 (24.7%)	.0015

CTO, chronic total coronary occlusion; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction or need for surgical or percutaneous target vessel revascularization).
Data are expressed as no. (%).



Number at risk		12	24	36	48	60
Months						
Success	339	273	215	151	126	105
Failure	85	65	60	45	42	38

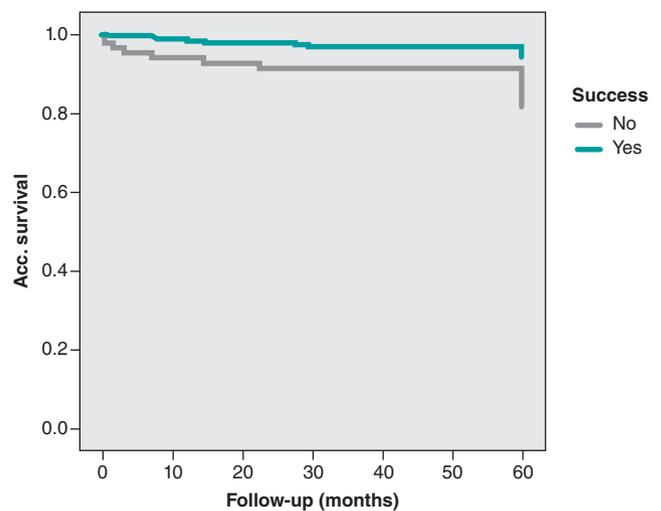
Figure 2. MACE-free at the 5-year follow-up. The rate of MACE (cardiovascular death, infarction, and surgical or percutaneous TVR) was lower in successful cases ($P = .03$).

MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction or need for surgical or percutaneous TVR); TVR, target vessel revascularization.

LAD occlusions, and procedural failure were independent predictors of cardiovascular mortality (table 4). Actually, increased mortality-related success rates were only seen in cases of failed LAD-CTO recanalization attempts compared to failed non-LAD CTO attempts (35% vs 9% $P = .012$).

DISCUSSION

These are the main results of this registry: a) the higher rates of success seen over the last 15 years confirm the improvements made



Number at risk		12	24	36	48	60
Months						
Success	339	292	239	175	151	132
Failure	85	71	66	52	50	46

Figure 3. Cardiovascular mortality-free at the 5-year follow-up. Significant lower cardiovascular mortality in the success group ($P = .005$).

in CTO recanalization devices and in the operator's skills; b) the recanalization of CTOs shows high rates of success (80.0%) and low rates of complications; c) the rates of success were significantly lower in patients with previous CABG, moderate-to-severe lesion tortuosity, tandem occlusions, lack of dual injection, and patients with CTO treated in the ACS setting; d) successful procedures, especially in LAD occlusions, were associated with lower rates of cardiovascular mortality and MACE at the long-term follow-up.

The recanalization of the CTO is still uncertain and is not yet supported by randomized clinical trials. Several retrospective observational studies⁸⁻¹⁰ provide evidence that support this strategy. The results found in this analysis are consistent with previously published data, but disagree with others.^{11,12} In this sense, the more recent registries show better results regarding cardiovascular and overall mortality.^{13,14}

Regarding randomized clinical trials, the EUROCTO trial revealed that the PCI of a CTO improves health status with improvements in angina frequency in patients with stable angina.¹⁵ However, the EXPLORE trial did not reveal any differences in the left ventricular function of patients with ST-segment elevation myocardial infarction. The DECISION-CTO showed similar inter-group rates of death, MI, stroke or TLR in patients with ACS or stable angina at the 3-year follow-up.^{16,17} The most recent clinical trial (REVASC) did not show an improved regional myocardial function. Although it was underpowered to measure clinical outcomes, it showed the advantage of performing the PCI of a CTO for clinically-driven repeat revascularization.¹⁸

Several characteristics of the current study should be emphasized to put the results into perspective. We believe this series of CTOs to be the big picture of interventional cardiology regarding CTOs since the start of the drug-eluting stent era until the arrival of contemporary new technologies. The study is based on a large cohort of consecutive patients from a single center. Most of them had multivessel disease and were treated in different time frames according to a specific dedicated CTO program.

Among the procedural characteristics that could explain the lower rates of success obtained with CTOs in the ACS setting we found the lowest use of retrograde approach and 8-Fr catheters in non-adequately staged procedures.

Regarding procedural features, the use of IVUS was limited to cases that required assessment of the distal vessel diameter and to optimize procedures with severe calcifications. It is very likely that more IVUS-guided procedures should have been performed.

Regarding variables related to procedural outcomes in the multivariable analysis, previous CABGs and more complicated CTOs were associated with failure as shown by other registries.¹³ However, intralésional tortuosity seems to us like the most consistent multivariable predictor with greater contribution to the model due to its narrow confidence interval. It might be possible that the inclusion of several angiographic variables in the regression model is responsible for the J-score not becoming an independent predictor. The high rate of retrograde procedures reveals the complexity of the CTOs in our series with J score > 3 in 45% of cases.

After dividing the series into 3 different periods of time, significant improvements in the rates of success were emphasized. As a result, we saw some interesting changes over time, such as the contribution of the retrograde approach to success. Considering that 73% of retrograde procedures were successful, it can be said that this technique led to a 19% increase in the rates of success in absolute terms. The rate of complications was quite similar to that from other studies.^{2-4,8-14}

Our data provide additional evidence on the lower rate of cardiovascular mortality reported in patients with successful CTO recanalization in the long-term follow-up. As a matter of fact, the success of the PCI was a strong independent predictor of survival as several observational studies and 1 meta-analysis have consistently suggested.^{13,14,19}

Possible explanations of the survival benefit from revascularizing a CTO may include a better left ventricular function and more tolerance for future acute coronary occlusive events.²⁰ However, this cannot be confirmed as we didn't measure the left ventricular ejection fraction systematically during follow-up. However, the trend showing a worst clinical profile in failed CTOs would validate this statement.

The role of LAD occlusions is decisive, as it seems an independent predictor of mortality. It should be mentioned that this effect of

LAD occlusions on cardiovascular mortality was basically due to the higher mortality rate of failed cases compared to LAD recanalization attempts. The fact that LAD CTOs are much easier to open than CTOs located in other vessels makes LAD attempts not only feasible but also mandatory.

In conclusion, we think that this study —performed in a contemporary single cardiac catheterization laboratory for a long period of time practice in the drug eluting stent era— features new information on procedural results and long-term outcomes on CTO recanalizations.

This study was a prospective analysis and is subject to the limitations inherent to this type of research. The study does not allow us to draw any comparisons with other therapeutic strategies like medical therapy or CABG. Patients with failed procedures had different clinical and angiographic characteristics, which may have impacted prognosis.

Angiographic characteristics were not analyzed in a core lab but provided by a local investigator. There was no adjudication of clinical outcomes by a clinical events committee.

CONCLUSIONS

The implementation of a specific PCI program for CTOs has been associated with higher rates of success over time thanks to growing expertise and new technical advances. The rate of procedural success was lower when there was a history of previous CABG, moderate-to-severe lesion tortuosity, tandem occlusions, lack of dual injection, and in CTOs diagnosed in the ACS setting. Preserved renal function and successful recanalization —especially of the LAD— were associated with a lower rate of cardiovascular mortality in the long-term follow-up.

CONFLICTS OF INTEREST

J.M. de la Torre Hernández is the Editor-in-chief of *REC: Interventional Cardiology*; the editorial procedure established by REC Publications was followed to guarantee the fair and unbiased handling of the manuscript.

WHAT IS KNOWN ABOUT THE TOPIC?

- CTOs are the most complex lesions to treat, and the prognostic benefit associated with their recanalization has not been properly established and if so, it could be selective.
- Most registries are limited in size and feature results in restricted time frames, often focused on specific devices, and not on long-term outcomes.
- The results of specific CTO programs in the long run have not been reported.

WHAT DOES THIS STUDY ADD?

- Our study describes the very long-term evolution of a PCI program for CTOs including the management and outcomes of PCI attempts on CTOs from 2002-2017.

- Our data, collected since the start of the drug-eluting stent era, confirm that implementing a program leads to higher rates of success over time. Independent predictors of PCI failure were identified in this large cohort.
- Lower rates of cardiovascular mortality were found in patients with successful recanalizations in the long-term follow-up.
- Also, the study provided new insights on the role played by LAD-CTO recanalizations on better outcomes.

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Single low-dose of apixaban in patients with atrial fibrillation after transcatheter aortic valve implantation



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ABSTRACT

Introduction and objectives: A significant amount of patients undergoing transcatheter aortic valve implantation (TAVI) have an indication for oral anticoagulation due to atrial fibrillation. In these patients the bleeding risk is often high. The purpose of this study was to compare the clinical outcomes of patients treated with low doses of apixaban or the vitamin K antagonist (VKA) acenocumarol in this setting.

Methods: Multicenter observational registry including patients treated after TAVI with low doses of apixaban (2.5 mg/12 hours) or VKA both without associated antiplatelet therapy. Propensity score matching was conducted to select 2 comparable cohorts. Data were gathered for 12 months following the procedure. Coprimary endpoints of efficacy (death, myocardial infarction, and stroke) and safety (bleeding BARC ≥ 2) were considered.

Results: A total of 236 patients were included. They were divided into 2 comparable groups of 64 patients each. Only 19 patients (30%) strictly met the dose adjustment criteria for apixaban. The rate of death, myocardial infarction, and stroke was similar at the 12-month follow-up (12.5% with VKA vs 9.3% with apixaban, $P = .5$), but the rate of bleeding BARC ≥ 2 was significantly higher in the VKA group (7.8% vs 0%; $P = .02$). Most of the events seen in the apixaban group occurred in patients with incorrect dose titration.

Conclusions: In this registry of patients treated with TAVI and atrial fibrillation the use of low-dose apixaban compared to VKA—both without antiplatelet agents—was associated to a lower rate of actionable bleeding and a similar rate of thrombotic events.

Keywords: TAVI. Anticoagulation. Apixaban. Vitamin K antagonist.

Dosis baja de apixabán en pacientes con implante transcatóter de prótesis valvular aórtica y fibrilación auricular

RESUMEN

Introducción y objetivos: Una proporción significativa de pacientes sometidos a implante percutáneo de válvula aórtica (TAVI) presenta indicación de anticoagulación oral por fibrilación auricular. En estos pacientes, con frecuencia el riesgo hemorrágico es alto. El objetivo del estudio fue comparar los resultados clínicos en pacientes tratados con dosis baja de apixabán o con acenocumarol, un antagonista de la vitamina K (AVK).

Métodos: Registro observacional multicéntrico que incluyó pacientes sometidos a TAVI tratados con dosis baja de apixabán (2,5 mg/12 h) o AVK, en ambos casos sin tratamiento antiplaquetario asociado. Se llevó a cabo un emparejamiento por puntuación de propensión

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Received 18 Feb 2020. Accepted 12 March 2020. Online: 27-05-2020.

<https://doi.org/10.24875/RECICE.M20000114>

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para seleccionar dos cohortes comparables. Se recabó la información de los 12 meses posteriores al procedimiento. Se consideraron objetivos coprimarios de eficacia (muerte, infarto de miocardio e ictus) y de seguridad (hemorragias BARC \geq 2).

Resultados: Se incluyeron 236 pacientes y se obtuvieron 2 grupos de 64 pacientes comparables en cuanto a características basales. Solo 19 (30%) cumplieron estrictamente los criterios de ajuste a la baja de la dosis de apixabán. A los 12 meses, la incidencia de muerte, infarto de miocardio e ictus fue comparable (12,5% con AVK frente a 9,3% con apixabán; $p = 0,5$), pero la incidencia de hemorragia BARC \geq 2 fue significativamente mayor en el grupo de AVK (7,8 frente a 0%; $p = 0,02$). La mayoría de los eventos trombóticos en el grupo de apixabán se observaron en pacientes con reducción de dosis no ajustada a criterios.

Conclusiones: En este registro de pacientes con TAVI y fibrilación auricular, el uso de la dosis baja de apixabán en comparación con el uso de AVK, sin antiagregantes concomitantes, se asoció a una menor incidencia de hemorragias mayores con una incidencia similar de eventos tromboembólicos.

Palabras clave: TAVI. Anticoagulación. Apixabán. Antagonistas vitamina K.

Abbreviations

AF: atrial fibrillation. **BARC:** Bleeding Academic Research Consortium. **DOAC:** direct oral anticoagulants. **MACE:** major adverse cardiovascular events. **TAVI:** transaortic valve implantation. **VKA:** vitamin K antagonist.

INTRODUCTION

The growing number of transaortic valve implantation (TAVI) procedures over the last few years is the consequence of the large and solid scientific evidence available that has broadened its indications.¹⁻³

Atrial fibrillation (AF) is a common finding in these patients.⁴ Its presence prior to the implant and its new appearance at the follow-up are associated with a higher mortality rate and a higher incidence of stroke,⁵ but also with more hemorrhages mainly due to the need for anticoagulation.^{6,7} The risk of hemorrhage is particularly high in patients who undergo TAVI since they are often old patients.

Direct oral anticoagulants (DOAC) have proven a better safety and efficacy profile compared to vitamin K antagonists (VKA) in the nonvalvular AF setting. However, few studies have analyzed their role in patients with valvular AF and, today, only the guidelines on the management of valvular heart disease established by the European Society of Cardiology de 2017 recommend them with a class IIa level of evidence C 3 months after the implant of a surgical bioprosthesis.⁸ No obstante, to this day dabigatran is the only DOAC that has proven non-inferior to VKA in patients with surgical bioprosthesis.⁹

Regarding patients with AF treated with TAVI there is not much evidence available for DOAC. In one of the very few cases published, the use of apixaban was associated with a significantly lower rate of adverse events at 30 days compared to the use of VKA.¹⁰ However, there were significant differences between the groups, no statistical matching was conducted, and patients with associated antiplatelet therapy were included.

The population treated with TAVI is often old (> 80 years), shows different stages of chronic kidney disease, and at times low body weight. These conditions may justify the relatively high prevalence of low-dose apixaban (2.5 mg/12 h).

This study assessed the use of low-dose apixaban in patients with TAVI and compared its long-term clinical outcomes to patients treated with VKA. A multicenter registry was designed including patients with an indication for oral anticoagulation (without

associated antiplatelet therapy) post-TAVI on VKA or apixaban at doses of 2.5 mg/12 h. The registry included propensity score matching of these patients to estimate the effect of treatment.

METHODS

Study population

A multicenter, retrospective and observational registry was designed from a review of individual TAVI registries from 4 hospitals nationwide.

The study population included all consecutive patients treated with TAVI from 2008 with a diagnosis of AF at hospital discharge and an indication for chronic oral anticoagulation only whether VKA or apixaban at a dose of 2.5 mg/12 h, and with a 1-year follow-up. Patients dead at admission were, therefore, excluded and there were no additional exclusion criteria.

The decision on the dose of apixaban was the responsibility of the patient's treating physician. European Medicines Agency recommends low-dose apixaban in patients with non-valvular AF and glomerular filtration rate of 15-29 mL/min and in patients with, at least, 2 of the following characteristics: age \geq 80 years, body weight \leq 60 kg or serum creatinine levels \geq 1.5 mg/dL (133 μ mol/L).¹¹

Study endpoints and definition of events

All clinical variables, demographic data, and cardiovascular risk factors were recorded from each case. Also, previous TAVI procedures, the presence of cardiovascular disease or previous heart surgeries, chronic lung or kidney disease, liver cirrhosis or neoplasms was also recorded in all of the patients. Variables associated with cardiovascular status such as ventricular function, aortic stenosis and coronary artery disease were included as well. Surgical risks were assessed using the following risk scores: EuroSCORE log, EuroSCORE II, and the Society of Thoracic Surgery (STS) score. Given the presence of AF at hospital discharge (whether known or de novo), the annual risks of thromboembolic

events were assessed using the CHA2DS2-VASc score while bleeding risk was assessed using the HAS-BLED score in all of the patients. Other data on the procedure and complications derived from it were also recorded as defined by the updated criteria established by the Valve Academic Research Consortium-2 (VARC-2).¹²

The rate of major adverse cardiovascular events (MACE) at the 1-year follow-up was studied in all of the patients after TAVI implantation in each center. MACE was defined as all-cause mortality, stroke (whether ischemic or hemorrhagic), and acute myocardial infarction, all of them defined according to the criteria established by VARC-2.¹¹ Also, the rate of hemorrhages categorized according to the classification established by the Bleeding Academic Research Consortium (BARC)¹² and considered relevant if BARC ≥ 2 was also studied. The net composite endpoint of efficacy-safety including all MACE and BARC type ≥ 2 bleeding was studied as well.

Two coprimary endpoints were studied: efficacy (through MACE) and safety (BARC type ≥ 2 bleeding). Secondary endpoints were a net composite endpoint of efficacy-safety, overall mortality, cardiac death, myocardial infarction, stroke, and hemorrhagic stroke.

The adjudication of events was left at the discretion of the researchers from each center according to the definitions previously indicated. The database did not include any events that allowed the identification of patients and anonymity was guaranteed at all time. The study was approved by the coordinating center ethics committee.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range according to their distribution. Categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. If so both groups were compared using the independent-samples t-test was used. In cases of non-normal distribution Wilcoxon test was used. Qualitative or categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. Cox proportional hazards regression model was used in the entire sample before the matching to identify predictor variables of net composite event. Variables with P values $< .1$ in the univariate analysis were included.

Given the limitations and interpretation biases of the possible associations in the comparison of unadjusted variables of an observational study like this propensity score adjustment was made using the logistics regression model. The type of high anticoagulation was established (apixaban 2.5 mg vs VKA) as a dependent variable and the baseline characteristics shown on [table 1](#) were included in the analysis as independent variables. Since the number of patients was clearly lower in the apixaban group, the goal of the propensity score matching to estimate the effect of treatment was to match each patient from the apixaban group with a patient from the VKA group. This procedure included 2 stages: 1) Propensity scores were estimated using the logistics regression model and treatment with apixaban was used as the outcome variable. All the covariables analyzed were used as predictors; and 2) patients were matched on a 1:1 ratio using the nearest neighbor matching based on a correlation algorithm that categorizes observations in the apixaban group based on the estimated propensity score. Then each unit was sequentially combined with a unit from the VKA group with the nearest propensity score. All the

differences seen in the standardized means after matching were $< 10\%$. Calibration was estimated using the Hosmer-Lemeshow test while precision was assessed using the area under the ROC (Receiver Operating Characteristic) curve. The PS Matching software and SPSS statistical package version 22.0 (IBM, United States) were used. The PS Matching software performs all R analyses using the SPSS R-Plugin. Event-free survival was studied using the Kaplan-Meier method. The log-rank test was used for group comparison. All analyses were 2-tailed and P values $< .05$ were considered statistically significant. Statistical analyses were conducted using the SPSS statistical package version 22.0.

RESULTS

Of a total of 1791 patients a final cohort of 236 patients who met the inclusion criteria was obtained. Of these 64 (27%) were treated with low-dose apixaban at discharge after TAVI, and 172 (73%) were treated with VKA. Using propensity score matching to estimate the effect of treatment 2 groups of 64 patients each were made. The flow chart of patients is shown on [figure 1](#). The center-based distribution of cases with apixaban was 60%, 20%, 14%, and 3%.

Regarding the adequacy of low-dose apixaban with respect to the degree of compliance of the characteristics recommended by the European Medicines Agency,¹¹ it was confirmed that only 19 patients (30%) strictly met the criteria ([figure 2](#)). Sixty-eight per cent of the patients ≥ 80 years had chronic kidney disease stage IIIA (glomerular filtration rate 30-59 mL/min) and that factor was considered enough to indicate a dose of 2.5 mg.

[Table 1](#) shows the baseline characteristics of the overall cohort and those adjusted by propensity score. In the overall cohort the group on apixaban included more males, more patients with previous coronary and valve interventions and less patients with a past medical history of strokes. The values of EuroSCORE were lower compared to the VKA group, but bleeding risk scores were similar. No significant differences were seen between the matched groups.

The procedural characteristics and complications seen in the groups already matched are shown on [table 2](#). No significant differences were found for any of the aspects studied. It should be mentioned here that patients from the apixaban group showed higher hemoglobin levels at hospital discharge. Also, in this group, 10 patients had made it to TAVI on anticoagulant and antiplatelet therapy (suspended after TAVI) compared to only 1 patient from the VKA group. Regarding the timeline of AF, all the patients from the VKA group already showed it before TAVI, while only 5 patients from the apixaban group developed it after TAVI.

No patients were lost to the follow-up. [Table 3](#) shows the cardiovascular events seen from hospital discharge until 1 year later without significant differences between both groups regarding MACE. Four deaths occurred in the VKA group (6%) of which 2 were cardiac deaths (heart failure and sudden death) and the remaining 2 were due to major hemorrhages (hemorrhagic stroke and hypovolemic shock after a fall with hip fracture). The 3 deaths from the apixaban group were caused by pulmonary disease. It is interesting to see the events that occurred in the apixaban group based on the use of adjusted low doses and not on criteria since MACE occurred in the group with unadjusted doses.

Only relevant hemorrhages were reported (BARC ≥ 2) in the VKA group with a significant difference compared to the apixaban group. Events occurred during months 1, 3, 5, 6, 11 after TAVI. Three of these major hemorrhages were due to digestive problems,

Table 1. Baseline characteristics before and after propensity score adjustment

	Overall cohort			Matched cohort		
	Apixaban (n = 64)	VKA (n = 172)	P	Apixaban (n = 64)	VKA (n = 64)	P
Male sex	41 (64)	60 (35)	< .001	41 (64)	38 (59)	.6
Age (years)	82 ± 6	83 ± 6	.3	82 ± 6	81 ± 7.5	.7
Weight (kg)	72 ± 12	71 ± 17	.6	72 ± 12	74 ± 14	.5
Height (cm)	161 ± 10	158 ± 14	.1	161 ± 10	160 ± 9	.32
HBP	55 (86)	140 (81)	.4	55 (86)	48 (75)	.11
Diabetes mellitus	27 (42)	51 (30)	.07	27 (42)	19 (30)	.14
Baseline glomerular filtration rate (mL/min)	58 ± 20	61 ± 23	.3	58 ± 20	60 ± 25	.6
Previous ACS	4 (6)	10 (6)	.9	4 (6)	4 (6)	1
Previous PTA	9 (14)	10 (6)	.04	9 (14)	8 (13)	.8
Previous CABG	3 (5)	12 (7)	.52	3 (5)	4 (6)	.7
Previous AVR	7 (11)	6 (4)	.03	7 (11)	4 (6)	.3
Previous stroke	3 (5)	26 (15)	.03	3 (5)	3 (5)	1
COPD	19 (30)	39 (23)	.27	19 (30)	15 (23)	.4
Cirrhosis	0	4 (2)	.6	0	1 (1.6)	1
Neoplasm	11 (17)	16 (9)	.09	11 (17)	6 (9)	.2
Peripheral vascular disease	7 (11)	4 (5)	.15	7 (11)	2 (6)	.4
NYHA III-IV	30 (51)	111 (65)	.06	30 (51)	37 (58)	.4
Baseline LVEF (%)	53 ± 12	56 ± 13	.1	53 ± 12	56 ± 12	.3
EuroSCORE log	13.3 ± 9	18.5 ± 13	.002	13.3 ± 9	14 ± 8	.7
EuroSCORE II	4.2 ± 5	6.4 ± 6	.013	4.2 ± 5	4.7 ± 4	.55
STS mortality	6 [2-10]	7 [5-15]	.4	6 [2-10]	11 [3-11]	.5
CHA ₂ DS ₂ -VASc	4.5 ± 1.1	4.6 ± 1.4	.55	4.5 ± 1.1	4 ± 1.3	.07
HAS-BLED	2.8 ± 1	2.74 ± 1	.8	2.8 ± 1	2.5 ± 1.1	.3

ACS, acute coronary syndrome; AVR, aortic valve replacement; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HBP, high blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PTA, percutaneous transluminal angioplasty; STS, Surgeon Thoracic Score; VKA, vitamin K antagonists. Data are expressed as no. (%) or mean ± (standard deviation) or median [interquartile range].

1 due to subarachnoid hemorrhage, and the other due to a spontaneous hematoma in the anterior rectus abdominis muscle. All of these patients required admission, surgery, and received 4 blood transfusions. In the apixaban group the rate of BARC type ≥ 2 bleeding seen (0%) was lower than anticipated by the HAS-BLED score (3.4%), but in the VKA group it was exactly the other way around: the rate seen (7.8%) was higher than expected (2.8%).

The cumulative MACE-free survival at 1 year showed no significant differences between the groups as shown on figure 3. Figure 4 shows the hemorrhage-free survival curves (BARC ≥ 2) with significant differences that favor the apixaban group. Mortality-free survival, infarction, stroke, and BARC type ≥ 2 bleeding curves did not show significant differences, but they did favor apixaban (figure 5). The Cox multivariate analysis conducted on the overall sample prior to case matching identified the use of apixaban as an independent predictor for the net composite endpoint of efficacy and safety (hazard ratio, 0.56; 95% confidence interval, 0.23-0.98; *P* = .04).

DISCUSSION

The main study findings are: *a/* the use of apixaban is still not widespread compared to VKA in the population with TAVI and AF; *b/* the use of low-dose apixaban is very common in this context, but on many occasions it does not strictly adjust to the instructions for use and underdosing is a common thing; *c/* compared to VKA treatment with low-dose apixaban was associated with very similar rates of thrombotic-ischemic events and a significantly lower risk of major bleeding.

These findings together with the reservations derived from the study limitations would be consistent with the results of the ARISTOTLE trial subanalysis¹³ in patients with bioprosthesis. These results would confirm the safety and efficacy profile of apixaban in valvular patients, although only 31% of these were > 75 years old. A substudy of the ENGAGE AF-TIMI 48 trial¹⁴ of 191 patients with previous implant of a surgical or transcatheter bioprosthesis and AF showed a significant reduction of major

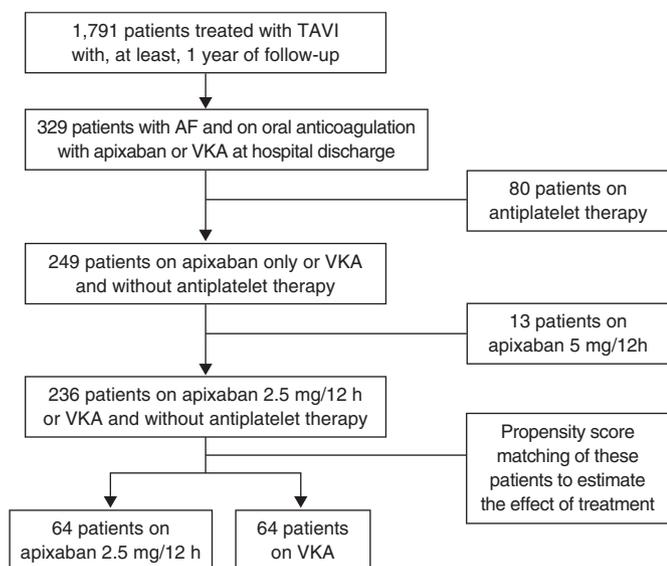


Figure 1. Study flow chart. AF, atrial fibrillation; TAVI, transaortic valve implantation; VKA, vitamin K antagonist.

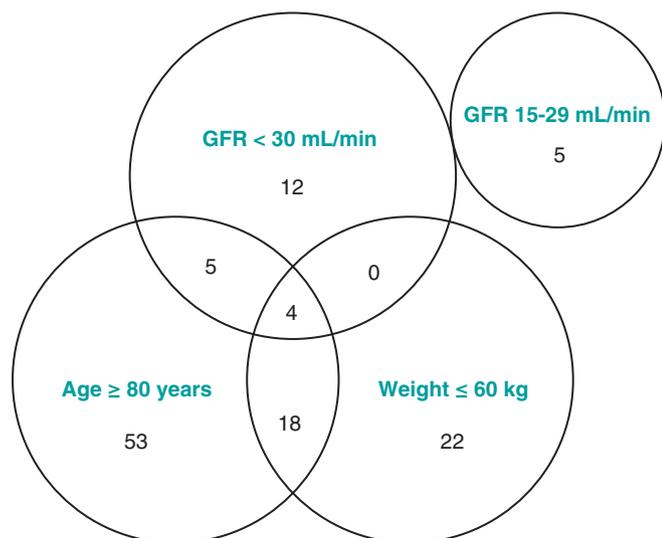


Figure 2. Group of patients treated with low-dose apixaban according to the variables contemplated for the reduction of doses. The number of patients who met each and every criterion and the possible combination of these is shown too. The European Medicines Agency recommends low-dose apixaban in patients with non-valvular atrial fibrillation and glomerular filtration rates (GFR) of 15-29 mL/min, as well as in patients with, at least, 2 of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg or serum creatinine levels ≥ 1.5 mg/dL (133 μmol/L).¹¹

bleeding with low-dose edoxaban (30 mg) compared to warfarin. The low and high doses (60 mg) of edoxaban were associated with a reduced composite of stroke, systemic embolism, major bleeding or death.

The population treated with TAVI includes elderly patients with multiple comorbidities who are not very well represented in the clinical studies of other contexts such as non-valvular AF.

The presence of previous or de novo AF after TAVI is not an uncommon finding in this population, and embolic and

Table 2. Procedural characteristics, complications, and characteristics at hospital discharge of the matched cohort

	Apixaban (n = 64)	VKA (n = 64)	P
Balloon-expandable aortic valve	51 (80)	50 (78)	.8
Femoral access	64 (100)	62 (97)	.5
Successful implant	64 (100)	64 (100)	1
Transfusions	7 (11)	5 (8)	.5
Coronary occlusion	0	0	
Valve embolization	0	0	
Annular rupture	0	0	
Periprocedural stroke	1 (1.6)	1 (1.6)	1
Vascular complication	7 (11)	10 (16)	.4
BARC type ≥ 2 bleeding	4 (6.3)	4 (6.3)	1
Periprocedural ACS	0	0	
Need for pacemaker	8 (13)	10 (16)	.6
De novo atrial fibrillation	5 (8)	0	.06
Hemoglobin levels (g/dL) at hospital discharge	12 ± 1.6	11 ± 1.4	.05
Platelet levels at hospital discharge (10 ⁹ /L)	133 ± 92	160 ± 60	.2
Glomerular filtration rate (mL/min) at hospital discharge	68 [53-82]	66 [40-82]	.5

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; VKA, vitamin K antagonists. Data are expressed as no. (%) or mean ± (standard deviation) or median [interquartile range].

Table 3. Major cardiovascular adverse events and hemorrhages at the 12-month follow-up

	Apixaban			VKA (n = 64)	P*
	LD (n = 64)	ALD (n = 19)	NALD (n = 45)		
MACE	6 (9.3)	1 (5.3)	5 (11)	8 (12.5)	.5
Death	3 (4.7)	0	3 (4.7)	4 (6.2)	.7
Cardiac death	0	0	0	2 (3.1)	.3
Myocardial infarction	1 (1.6)	0	1 (2.2)	1 (1.6)	1
Stroke	2 (3.1)	1 (5.3)	1 (2.2)	3 (4.7)	.9
Hemorrhagic stroke	0	0	0	2 (3.1)	.5
BARC type ≥ 2 bleeding	0	0	0	5 (7.8)	.02
Safety-efficacy target**	4 (6.2)	0	4 (8.8)	8 (12.5)	.23

ALD, adjusted low dose; LD, low dose; MACE, major cardiovascular adverse events; NALD, non-adjusted low dose; VKA, vitamin K antagonists. Data are expressed as no. (%).

* P values for the comparison between apixaban LD vs VKA.

** Composite of death, myocardial infarction, stroke, and BARC ≥ type 2 bleeding.

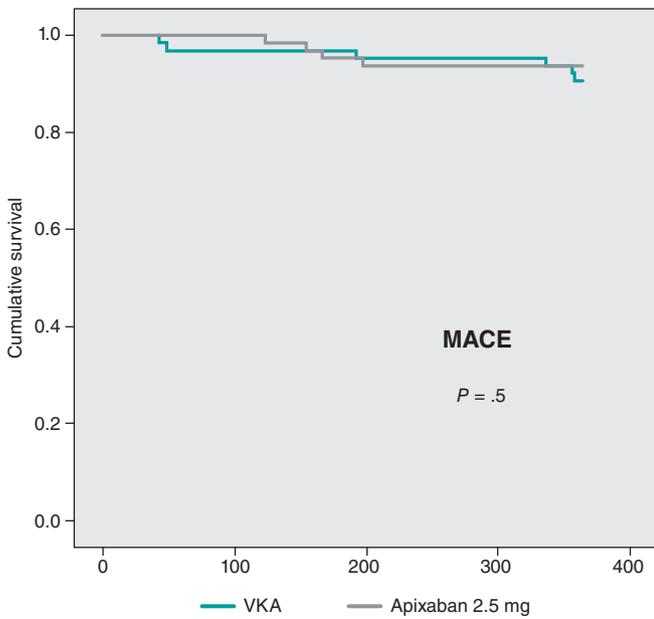


Figure 3. Major cardiovascular events (MACE)-free Kaplan-Meier survival curves at the 1-year follow-up. VKA, vitamin K antagonist.

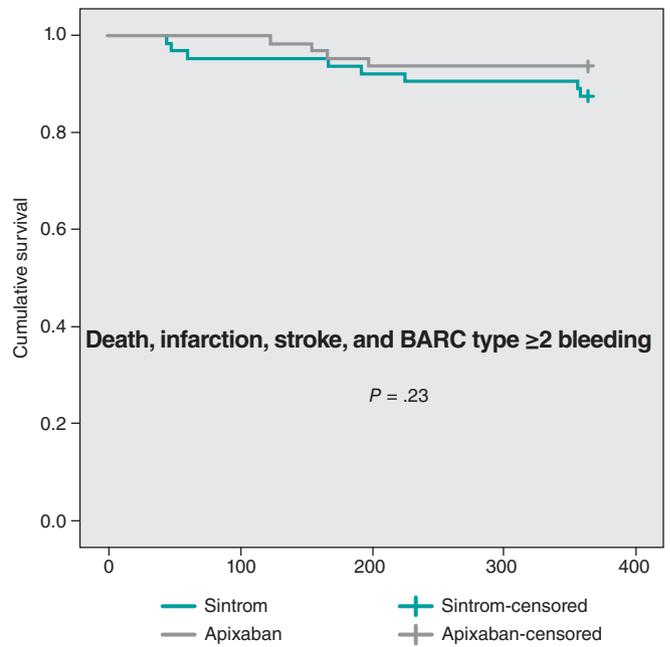


Figure 5. Mortality-free Kaplan-Meier survival curves, infarction, stroke, and BARC type ≥ 2 bleeding.

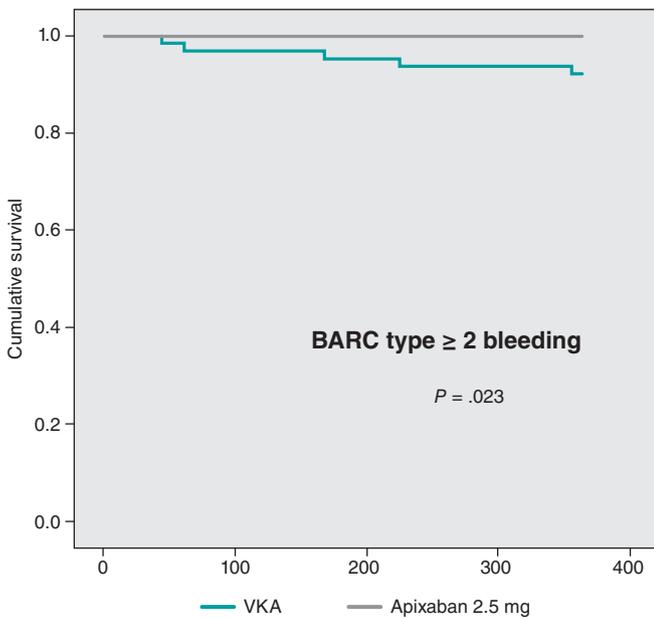


Figure 4. BARC type ≥ 2 bleeding-free Kaplan-Meier survival curves. VKA, vitamin K antagonist.

hemorrhagic risk is higher compared to other populations, which poses a significant challenge when having to decide what the best antithrombotic treatment should be.

There are still few studies that compare DOAC to VKA in the TAVI setting, and they are often registries. In the aforementioned Seeger et al.,¹⁰ 141 patients treated with apixaban (most of them with doses of 5 mg) and 131 with VKA, the safety profile was better with apixaban and efficacy was similar. However, in this registry the low-dose apixaban and statistical matching were not studied and cases with concomitant antiplatelet therapy were included. In our study we thought it was very important to exclude

patients with associated antiplatelet therapy and perform propensity score matching to estimate the effect of treatment. That is so because both aspects reduce significantly the load of biases associated with registry-based comparative studies. On the other hand, the low-dose study was very pertinent given its frequency of use in this population.

A different study compared the clinical progression of 154 patients treated with several DOAC and 172 treated with VKA always without antiplatelet therapy¹⁵ without statistical matching but with significant differences between the groups. The authors found very similar efficacy and safety profiles, although the DOAC group had a more adverse hemorrhagic and thrombotic baseline risk profile.

Finally, in the RESOLVE (The assessment of transcatheter and surgical aortic bioprosthetic valve thrombosis and its treatment with anticoagulation) and SAVORY (Subclinical aortic valve bioprosthesis thrombosis assessed with four-dimensional computed tomography) registries no significant differences were found regarding the move of the valve leaflets between DOAC and warfarin (3% vs 4%, respectively; $P = .72$), although both seemed better than non-anticoagulation.¹⁶

The high prevalence of underdosing of apixaban in this population is worth mentioning. We believe that it can be conditioned by the perception of a very high bleeding risk in these patients (most of them 80-year-old patients with a high prevalence of chronic kidney disease and other conditions) and a variable degree of frailty. Although it is not an established criterion per se to change the type and dose of anticoagulation it can certainly influence the decision-making process.

The fact that we found differences that favored apixaban at doses of 2.5 mg compared to VKA may lead us to think that underdosing does not penalize as much as in the general context of patients with non-valvular AF,¹³ as a matter of fact, it is associated with a better safety profile without affecting efficacy. However, the use of low doses cannot be recommended openly and we believe in

the rigor of dose adjustment. Although the size of subgroups based on correct dose adjustment was not small and we cannot draw conclusive results, more thrombotic-ischemic events were seen within the apixaban group in the incorrect adjustment group. However, we should mention that dosing needs to be dynamic since dose adjustment conditions vary across follow-up and that is how the treatment of these patients is optimized at all time.

Having said this, the indications for treatment with these drugs are changing due to recent real-world data available. Until a year ago, apixaban was contraindicated in patients with acute kidney injury in whom VKA were still the treatment of choice. The studies most recently published show a clear benefit regarding hemorrhages with doses of apixaban of 2.5 mg, and thromboembolic events and mortality with doses of 5 mg in patients with acute kidney injury and dialysis.¹⁷

The difficulty of this was seen in the results reported by the GALILEO trial¹⁸ (Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes). This study showed that in patients without indication for oral anticoagulation after TAVI, a treatment strategy including rivaroxaban at doses of 10 mg/day plus antiplatelet therapy within the first 90 days was associated with a higher risk of death or thromboembolic complications and hemorrhages compared to a 90-day course of dual antiplatelet therapy and then single antiplatelet therapy.

The ongoing studies that are being conducted now will provide more solid evidence on what the best antithrombotic strategies are in patients after TAVI with and without AF.¹⁹

Limitations

The main limitation of this study is that it was not randomized. As any other observational registry, it is subject to more and less evident confounding factors. Although the use of propensity score matching to estimate the effect of treatment produced 2 groups with very similar baseline characteristics, the chances of bias were still present.

The size of the sample is the second most important limitation. The volume of patients with TAVI plus an indication for oral anticoagulation only is not high in any centers in our setting, especially if we wish to include those specifically treated with low-dose apixaban. Therefore, a multicenter study with high-volume centers was designed (compared to the average of the country), but still the size of the sample could not be higher. This creates an underpowered study that should be considered exploratory and hypothesis-generating only. This limitation is even more evident for subgroup comparisons based on dose adjustment. However, until statistically powered studies become available, the results from registries like this contribute to expand our knowledge base. Event adjudication was not centralized although the previously established standardized definitions were adjusted.¹¹

CONCLUSIONS

The use of low-dose apixaban (2.5 mg/12 h) in patients treated with TAVI often did not strictly match the official recommendations. In this registry, the use of low-dose apixaban was associated with very similar figures of thrombotic-ischemic events compared to the use of acenocoumarol, but a significantly lower risk of major hemorrhages. This study suggests that, in patients treated with TAVI who have AF, the use of low-dose apixaban (if

adequately prescribed) is safer and equally efficient compared to acenocoumarol.

CONFLICTS OF INTEREST

J.M. de la Torre Hernández has received unconditional institutional research grants and fees for as a counselor for Bristol-Myers Squibb. Also, he is the editor-in-chief of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

WHAT IS KNOWN ABOUT THE TOPIC?

- The performance of TAVI has experienced significant growth. The prevalence of AF among patients with TAVI is high. DOAC have proven better safety and efficacy profile compared to VKA in the non-valvular AF setting. There are few studies analyzing the role of patients with TAVI and AF, and in particular none assessing low-dose apixaban.

WHAT DOES THIS STUDY ADD?

- This multicenter registry shows that the use of apixaban is not widespread compared to the use of VKA in the population with TAVI and AF. In patients treated with apixaban the use of low doses is very common, but many times, it does not strictly follow the instructions for use. In this sense compared to VKA, treatment with low-dose apixaban was associated with very similar rates of thrombotic-ischemic events and a significant lower risk of major hemorrhages.

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Management of ischemic heart disease in catheterization laboratories during the health contingency generated by the COVID-19 pandemic. Recommendations of the Mexican Interventional Cardiology Society (SOCIME)



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ABSTRACT

In Mexico, the number of confirmed and estimated cases of COVID-19 has been going up gradually from the second week of March 2020. This directly and indirectly altered the normal care of patients with ischemic heart disease. This is a consensus document achieved by different societies (the Mexican Society of Interventional Cardiology [SOCIME], the Mexican Society of Cardiology [SMC], the Mexican National Association of Cardiologists [ANCAM], the National Association of Cardiologists at the Service of State Workers [ANCISSSTE]), and the Coordinating Commission of National Institutes of Health and High Specialty Hospitals [CCINSHAE]). Its main objective is to guide the decision-making process on coronary revascularization procedures for the management of patients with acute coronary syndrome in catheterization laboratories during the current health emergency generated by the SARS-CoV-2 pandemic.

Keywords: Myocardial infarction. Acute coronary syndrome. Percutaneous coronary intervention. COVID-19. SARS-CoV-2. Pandemic.

Atención de la cardiopatía isquémica en salas de cateterismo durante la contingencia sanitaria por pandemia de COVID-19. Recomendaciones de la Sociedad de Cardiología Intervencionista de México (SOCIME)

RESUMEN

En México, el número de casos confirmados y estimados de COVID-19 inició su ascenso progresivo a partir de la segunda semana de marzo de 2020, lo que alteró de forma directa e indirecta la atención habitual de los pacientes con cardiopatía isquémica. Este documento es un consenso de la Sociedad de Cardiología Intervencionista de México (SOCIME), la Sociedad Mexicana de Cardiología (SMC), la Asociación Nacional de Cardiólogos de México (ANCAM), la Asociación Nacional de Cardiólogos al Servicio de los

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Online: 25-05-2020.

<https://doi.org/10.24875/RECICE.M20000126>

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Trabajadores del Estado (ANCISSTE) y la Comisión Coordinadora de Institutos Nacionales de Salud y Hospitales de Alta Especialidad (CCINSHAE) que tiene como objetivo prioritario orientar las decisiones de revascularización coronaria, en particular en los pacientes con síndrome coronario agudo, en las salas de cateterismo, durante el tiempo que dure la urgencia sanitaria por la pandemia de SARS-CoV-2.

Palabras clave: Infarto de miocardio. Síndrome coronario agudo. Intervención coronaria percutánea. COVID-19. SARS-CoV-2. Pandemia.

INTRODUCTION

Ischemic heart disease is the leading cause of death in Mexico. Consequently, the number of patients with acute coronary syndrome (ACS) or stable chronic coronary syndrome who will require medical services is not expected to go down during the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The ongoing need to manage this disease during the COVID-19 pandemic compels us to recognise the exceptional situation and to search for an adequate response.

Several places across the world have suspended the management of ischemic patients or decided to use less invasive—also less effective—treatments. The idea behind this is to reduce the risk of contagion for patients, relatives, and healthcare workers. However, this decision has created huge controversy in the medical establishment: is it safe? Is it ethical? Is the safety of the medical team more important than the patients' health? For how long should this measure be effective?

The Mexican Interventional Cardiology Society (SOCIME) backed by the Mexican Society of Cardiology (SMC), the National Association of Cardiologists of Mexico (ANCAM), and the National Association of Cardiologists at the Service of State Workers (ANCISSTE) have published this document to guide the medical personnel in the decision-making process during the current COVID-19 pandemic.

PATIENT CLASSIFICATION

Healthcare workers looking after patients with ischemic heart disease should classify them into 2 groups based on the information available during the healthcare process: 1) patients with suspected SARS-CoV-2 infection or patients with symptoms of concurrent myocardial ischemia or other heart-related complications; 2) other patients, without a diagnosis or suspicion of SARS-CoV-2 infection, who require medical attention due to symptoms of myocardial ischemia. The reason for making this subdivision is to minimise the contagion of other patients, relatives, medical and hospital personnel by avoiding contact between uninfected patients and patients with SARS-CoV-2. Before being transferred to the cath lab all patients will be actively screened for the presence of fever, cough, and respiratory distress. The patients' temperature and arterial oxygen saturation will need to be checked as well.

STABLE CHRONIC CORONARY SYNDROMES

There is general consensus that invasive procedures—whether percutaneous or surgical—should be differentiated in patients with stable chronic coronary syndrome during the current health emergency.^{1,2} The undersigned working group that participated in the

writing of this document agrees on the adoption of this measure. However, it also admits that the number of patients who will not receive proper care will end up accumulating and a proportion of these patients will turn into new cases of acute ischemia. In conclusion, patients with stable chronic coronary syndrome during the current pandemic should receive optimal therapy and be warned of the importance of seeking urgent medical attention in the presence of symptoms of ischemic instability.

ACUTE CORONARY SYNDROMES

In the current context of the COVID-19 pandemic, there is no unanimous agreement to define the optimal treatment strategy for patients with ACS. We will be reviewing the information available accumulated over a very short period of time on the different treatment proposals reported followed by the position and recommendations from this group.

Classification

ACSs can be divided into: *a)* ST-segment elevation ACS including ST-segment elevation myocardial infarction (STEMI) and *b)* non-ST-segment elevation ACS including non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina.

Diagnosis

Two recommendations should be followed to minimize the risk of contagion. The first one should be social distancing and limited contact with patients during the physical examination or while performing the transthoracic echocardiogram to obtain the maximum amount of information while minimizing physical contact with the patient; the second recommendation is the use of coronary computed tomography angiography as a fast non-invasive imaging modality to confirm or discard the presence of coronary heart disease as the cause for the symptoms when appropriate.³ The main elements for diagnosis are:

- Suggestive symptoms.
- Twelve-lead electrocardiogram.
- Myocardial biomarkers.
- Coronary computed tomography angiography: when available, it should be considered in the case of reasonable doubt on the coronary origin of the symptoms. It speeds up the confirmation/discarding process, reduces hospital stay and use of hospital resources and minimizes stay in the cath lab and exposure to contagion for the heart team who work in the cath lab.

Management of STEMI

Primary percutaneous coronary intervention (pPCI) is the treatment of choice for coronary reperfusion. Fibrinolysis is spared for cases where percutaneous coronary intervention (PCI) is not available or when the patient transfer to a PCI capable hospital involves significant time delays.⁴ The COVID-19 pandemic has produced different points of view for the management of patients with STEMI; these different positions are indicative of the particular situations that medical societies are facing to design their recommendations.

Fibrinolysis as the strategy of choice

A report and the position adopted by opinion leaders recommend the use of fibrinolysis as the first reperfusion strategy in both uninfected patients and patients with suspicion or diagnosis of COVID-19. The PCI would be spared for cases of failed fibrinolysis and only if benefits exceed the possible risks.⁵ They recommend that patients with serious pneumonia due to SARS-CoV-2, unstable vital signs, and concurrent STEMI should receive support medical treatment only—no fibrinolysis or pPCI—until they have recovered from pneumonia. These recommendations are highly restrictive, do not anticipate the pPCI option and limit the possibility of bailout PCIs in selected cases.⁵

pPCI as the strategy of choice

Several medical societies are keeping to their usual recommendations during the current pandemic. Patients with STEMI (with or without suspicion of infection, with or without COVID-19) inescapably need medical attention and should receive pPCI as the reperfusion therapy, especially those with persistent angina or hemodynamic compromise; they also keep the bailout PCI option alive. They accept that fibrinolysis can be an alternative in patients with pneumonia due to SARS-CoV-2 who develop STEMI but remain stable.^{1,2,6} The Spanish Society of Cardiology (SEC) ranks pPCI as the preferred reperfusion strategy in most patients with severe pneumonia and difficulties moving or being transferred.⁷ At the present time, Spain is one of the countries with the highest contagion and mortality rates and its healthcare system has collapsed due to the excessive volume of patients with COVID-19; in the middle of this health crisis, consensus still favors the reperfusion of STEMI through pPCI.

Management of non-ST-segment elevation ACS

In general, the specific risk of complications of patients with NSTEMI or unstable angina should be identified to decide the best time to perform cardiac catheterization. Regardless of their risk, it is essential to know the patients' coronary anatomy and based on the findings assess the revascularization method.⁸ As with STEMI, this routine common practice has changed during the current pandemic and several of the position papers on the management of ST-segment elevation ACS have been replicated.

Medical therapy as the strategy of choice

The general recommendation is to know the state of contagion before referring patients to the cath lab. Patients without a diagnosis or suspicion of infection need to be tested to confirm or discard the presence of SARS-CoV-2. It is suggested that patients with suspicion of COVID-19 who have not been tested yet and

those who have already tested positive should receive medical therapy. The interventional procedure should be deferred until they have recovered or the risk of contagion has gone down.⁷ It is recommended that patients without suspicion of infection or without COVID-19 (common patients) undergo PCI only if they are high-risk patients or remain unstable during the course of conservative treatment. Urgent PCIs will be spared only for patients with hemodynamic compromise or malignant arrhythmias regardless of their state of infection.^{6,7}

PCI as the strategy of choice

Here the usual recommendations still stands, which is why high-and-intermediate risk patients should undergo PCI, regardless of their state of contagion.⁸ In low-risk patients with COVID-19 or with severe pneumonia and who remain unstable it is advised to consider medical therapy and defer the procedure. Early PCIs facilitate early hospital discharges. In patients with multivessel disease the PCI should be favored over coronary revascularization surgery. Patients admitted to hospitals without cath lab capabilities should not be transferred. In these cases, conservative treatment is advised followed by early hospital discharges.^{1,2}

CONSENSUS ELEMENTS

The following variables were taken into consideration while the recommendations of this consensus document were being designed:

- *Contagion.* When examined, patients who seek medical attention should be classified according to their current state of SARS-CoV-2 infection regardless of the presence of symptoms. A special subgroup are unstable patients with severe pneumonia who develop ACS.
- *Timeframe.* At different times and different speeds peaks and troughs in the number of patients with COVID-19 are expected to happen.
- *Geographic location.* More cases are expected in more heavily populated cities in particular the Mexico City metropolitan area, Guadalajara, Monterrey, and Puebla.
- *Healthcare system.* There are different healthcare models available in Mexico. In general, in private hospitals cath labs are opened around the clock. In the public system several secondary care centers have cath lab capabilities with different care plans for the management of ACS. Most tertiary care centers have pPCI programs available around the clock too.
- *Therapeutic effectiveness.* In the full spectrum of ACS, PCI is the treatment of choice. In patients with STEMI, fibrinolysis is a less effective alternative associated with a higher risk of bleeding complications. In patients with non-ST-segment elevation ACS, medical therapy in the acute phase is only intended to stabilize the atheromatous plaque and alleviate myocardial ischemia before the cath. lab. referral.
- *Risk profile.* In the full spectrum of ACS, it is essential to examine patients at increased risk of adverse cardiovascular events early. This group of patients benefits the most from invasive treatment.
- *Hospital stay.* Anticipating larger volumes of patients in a prolonged emergency situation, it is advised to shorten hospital stays to alleviate the work load, reduce the use of hospital resources, reduce the exposure of patients, relatives, medical

and paramedic personnel to a potentially contaminated environment, empty beds, and facilitate the ongoing rotation of patients.

- *Rooms and special catheterization laboratories.* According to the type, size, and resources of each hospital, whether public or private, a specific physical space should be spared to examine patients without COVID-19 or clinical suspicion away from patients with confirmed infections or a justified suspicion of infection. In public and private hospitals with at least 2 cath labs it is possible to use 1 cath lab for the specific care of patients with confirmed or suspected COVID-19 and the other one for the management of common patients. In public or private hospitals with only 1 cath lab available, the heart team should look for alternatives to perform the procedures while minimizing the risk of contagion. This can be done by splitting the care schedule depending on the patients' state of infection and only if the clinical indication for cardiac catheterization allows it (managing infected or suspicious patients in the morning, and uninfected or unsuspecting patients in the afternoon). Reducing the number of healthcare workers in the cath lab and organizing groups and shifts during specific timeframes helps too. Regardless of the number of cath labs available, it is a priority to observe the recommendations established for adequate protection of the heart team, which should be the smallest possible. Also, the cath lab should be disinfected before taking on the next patient.
- *Personal protective equipment.* The medical personnel looking after patients, whether infected or suspicious, should all have the necessary personal protective equipment and observe the protection measures recommended like those from the Interventional Cardiology Association and Heart Rhythm Association of the Spanish Society of Cardiology.⁹

RECOMMENDATIONS

The objective of this document is to guide the decision-making process on the coronary revascularization of patients with ACS during the health emergency declared due to the current SARS-CoV-2 pandemic. Considering the elements described above and anticipating an epidemiological model similar to the one seen in countries like ours, we recommend making slight modifications to the management of patients with ACS while continuing to use the pharmacoinvasive reperfusion strategy prevalent in Mexico.

STEMI

Cardiovascular risk

We recommend that pharmacoinvasive strategy should start by identifying patients with higher risk of complications. The presence of 1 or more of the following characteristics is indicative of high risk:

- Age > 75 years.
- Cardiogenic shock (whether associated or not to mechanical complications).
- Refractory angina.
- Ventricular tachyarrhythmias.
- Bradyarrhythmia requiring temporary pacemaker implantation.
- Electrocardiographic pattern of diffuse ischemia.

pPCI

We recommend public and private hospitals with cath lab capabilities and, in particular, tertiary care or reference centers to keep offering pPCI over fibrinolysis. This is completely justified by its higher rate of success, lower risk of complications, and shorter hospital stays (hospital discharges within 36 h - 48 h). The fibrinolysis proposal as the primary reperfusion method even in hospitals with cath lab is questionable.

Fibrinolysis

We still recommend its indication as the reperfusion method in non-PCI capable centers. Unlike conventional pharmacoinvasive strategy, the transfer of stable patients with successful fibrinolysis for early elective cardiac catheterization is ill-advised; these patients should be followed and monitored later in time. Only patients with failed fibrinolysis should be transferred and only in the presence of hemodynamic or electric instability. In patients with severe pneumonia due to COVID-19 it is a valid option even for PCI-capable centers in the presence of high and growing volumes of suspicious or confirmed cases. Also, in the absence of high-risk markers, especially in patients admitted within the first 3 hours after symptom onset and without contraindications for fibrinolysis.

Periodic adjustment of reperfusion method

We recommend that in cities, regions, and hospitals with large volumes of patients with COVID-19 or suspected cases, whether critical, growing or rapidly spiking, the hospital management should decide on the most adequate reperfusion method with the heart team and the resources available. The primary reperfusion strategy should adjust periodically based on the temporal and geographic pattern of the infection.

The algorithm shown on [figure 1](#) for the management of patients with STEMI during the current COVID-19 pandemic recommends pPCI as the method of choice for coronary reperfusion. The reperfusion strategy should change as the pandemic evolves with the necessary, periodic adjustments based on the modification criteria already described.

NSTEMACS

Regardless of the presence of SARS-CoV-2, low-risk patients who respond to medical therapy can be discharged from the hospital to be studied later in time if the risk of contagion is lower or if they have recovered from COVID-19. If the patient's coronary anatomy needs to be documented prior to hospital discharge, an option here is to perform a coronary computed tomography angiography and, based on the findings, plan the PCI or discharge the patient. Moderate-or-high risk patients (according to the criteria described above) and those who become unstable during the course of conservative treatment should be transferred to the cath lab regardless of their state of contagion.

Most concepts described for the management of STEMI are valid in these patients. PCI-capable public and private hospitals with experienced personnel and the necessary resources should keep the PCI option open in light of its high rate of success and short hospital stays. In patients with significant multivessel disease the hospital stay should be short and PCI revascularizations should be prioritized over coronary revascularization surgeries.

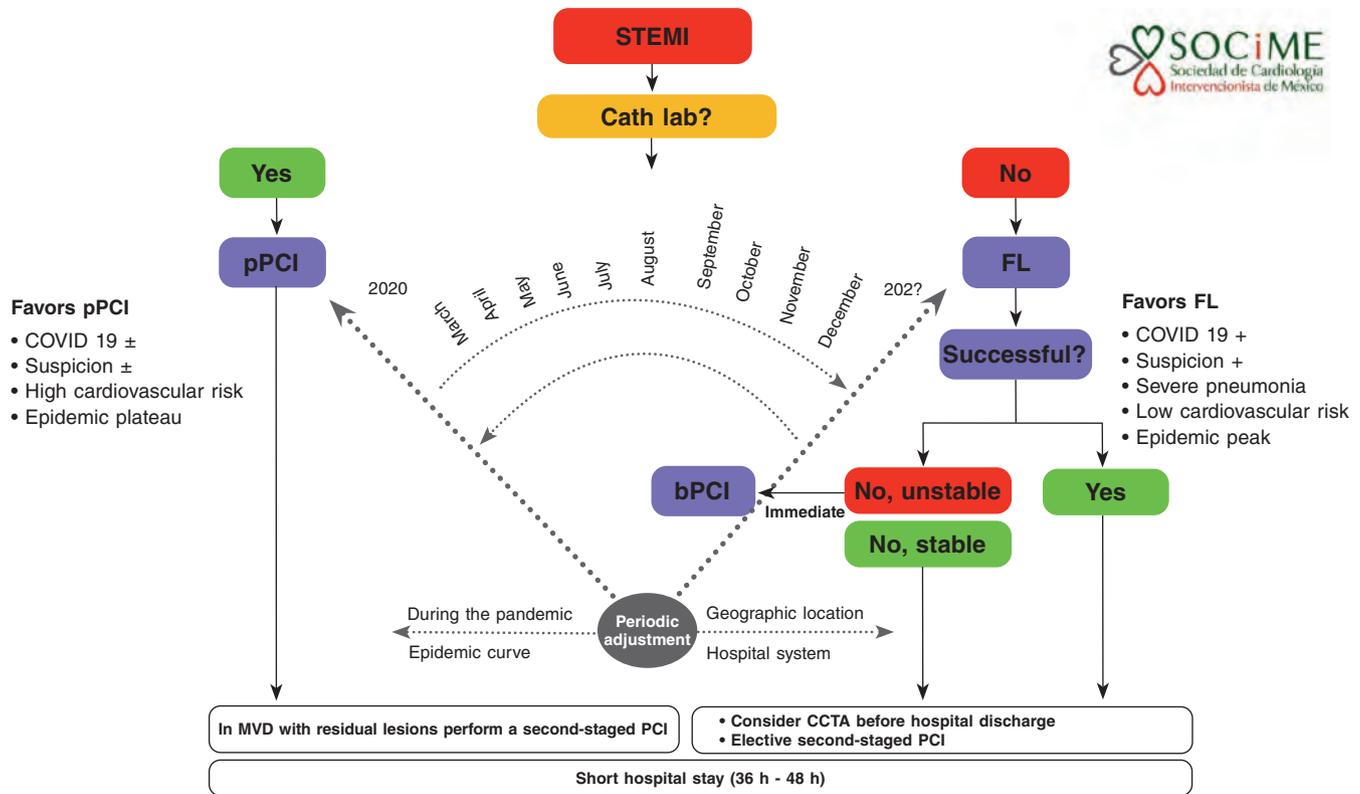


Figure 1. Therapeutic algorithm for the management of patients with STEMI during the current SARS-CoV-2 pandemic. The arrow thickness is indicative of the preferred therapy. +, present; ±, present or absent; bPCI: bailout percutaneous coronary intervention; CCTA, coronary computed tomography angiography; FL, fibrinolysis; MVD, multivessel coronary artery disease; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

In the algorithm shown on [figure 2](#) for the management of patients with NSTEMI during the current COVID-19 pandemic the use of PCI is recommended in high-risk patients. However, the reperfusion strategy should be dynamic as the pandemic evolves with periodic adjustments based on the modification criteria already described.

Cardiovascular complications in patients with COVID-19

Patients with COVID-19 can have clinical signs of myocardial damage and secondary complications. Myocardial damage with elevated high-sensitivity cardiac troponin levels (7.2%), cardiogenic shock (8.7%), and arrhythmias (16.7%) has been reported in some patients. In the absence of coronary heart disease, the gradual increase of high-sensitivity cardiac troponin levels is a predictor of mortality.¹⁰ Cases of type I STEMI and fulminant myocarditis have also been reported.¹¹

Most of the patients who develop complications are eligible for intensive therapy, and a high percentage of these may end up needing mechanical support of the ventricular function. The etiology of patients with cardiovascular complications can be coronary heart disease; this consideration will not be rare because the characteristics of patients more often affected are old age, overweight, high blood pressure, and diabetes mellitus. If the hypothesis of concomitant coronary heart disease is accepted there are two possible avenues: treat the case as that of a patient with NSTEMI and follow the corresponding algorithm or discard the presence of significant coronary heart disease using coronary computed tomography angiography.

In patients with severe pneumonia, myocardial damage, hemodynamic or electric instability, and suspicion of coronary heart disease, the medical team should decide on the adequacy (benefits exceeding risks, patients who can be saved) of transferring the patient to the cath lab or performing a coronary computed tomography angiography. In particular, the presence of left main coronary artery disease or disease of the proximal left anterior descending artery in a patient who can be saved supports the need to perform an urgent PCI ([figure 3](#)).

VALIDITY OF RECOMMENDATIONS

The epidemiological model is totally unpredictable under the current circumstances; the rate of contagion, number of confirmed cases, and mortality rates are different across cities, regions, countries, and continents. However, estimates from the Mexican Ministry of Public Health suggest a peak of cases and more hospitalizations in the metropolitan area of Mexico City and main cities of the nation from May through August 2020. The flattening of the curve of infection will still take several months. No definitive projection on this regard can be given at the present time.

These recommendations will remain effective as necessary. They will be re-evaluated periodically together with the Mexican Ministry of Public Health to discuss the right time to go back to normal.

CONFLICTS OF INTEREST

None reported.

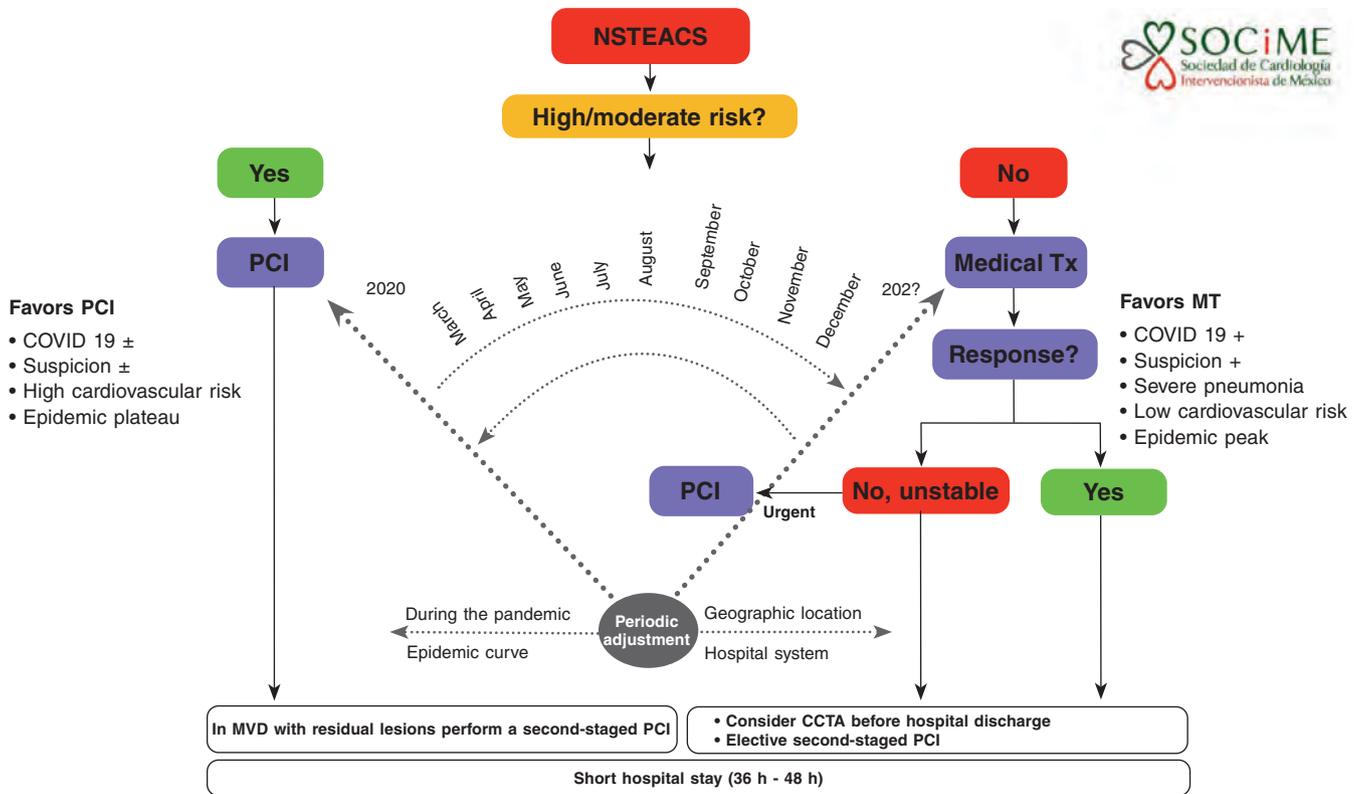


Figure 2. Algorithm for the management of patients with NSTEMACS during the current SARS-CoV-2 pandemic. The arrow thickness is indicative of the preferred therapy. +, present; ±, present or absent; CCTA, coronary computed tomography angiography; MT, medical therapy; MVD, multivessel coronary artery disease; NSTEMACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; Tx, treatment.

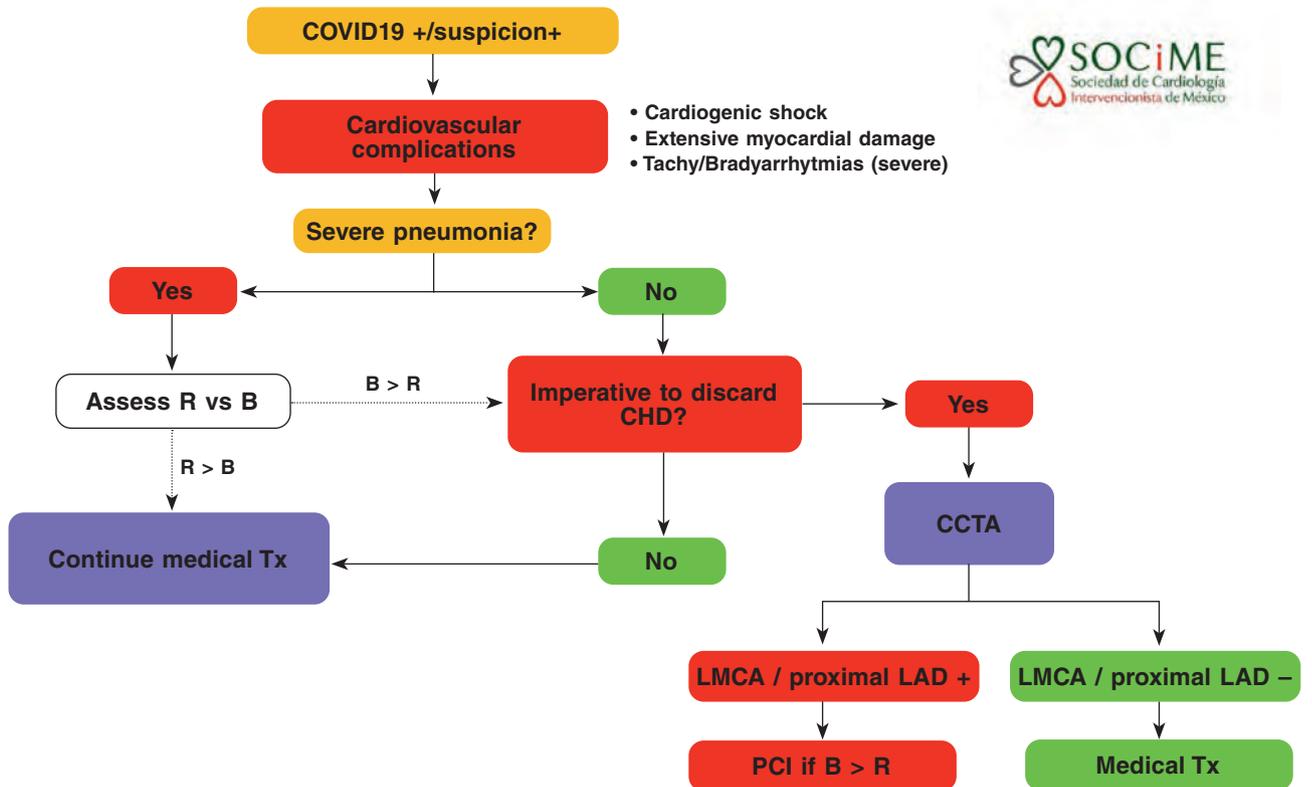


Figure 3. Diagnostic-therapeutic algorithm for the management of patients with COVID-19 or suspicion of COVID-19 infection with cardiovascular complications. B, benefits; CHD, coronary heart disease; CCTA, coronary computed tomography angiography; LAD, left anterior descending coronary artery; LMCA, left main coronary artery disease; R, risk; Tx, treatment.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Jorge Gaspar Hernández, General Manager of the Ignacio Chávez National Institute of Cardiology for his remarks on this manuscript.

EDITOR'S NOTE

This document is subject to further iterations based on the evolution of the current COVID-19 pandemic. This manuscript has undergone a process of internal review of exceptional priority by the editorial staff due to the special interest of disclosing the information contained herein to the scientific community. The editors wish to thank Permanyer Publications for its collaboration and commitment for the quick publication of this document.

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Specific indications for TAVI

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) is the most commonly used structural technique in the field of interventional cardiology. Initially, this procedure was only used in patients with severe symptomatic aortic stenosis and prohibitive risk for surgical aortic valve replacement. In just 1 decade, TAVI indications have extended to patients at intermediate surgical risk. More recently, the results of the PARTNER 3 and Evolut Low Risk clinical trials has opened that door for patients at low surgical risk. However, there are still some controversial indications that represent the boundaries of TAVI including patients at lower risk with bicuspid aortic valve, valve-in-valve procedures, pure aortic regurgitation or severe valvular heart disease after healed infective endocarditis. Our objective was to summarize the evidence available –mostly case series and retrospective registries– that supports the use of TAVI for these new indications.

Keywords: TAVI. Bicuspid aortic valve. Aortic regurgitation. Aortic bioprosthesis.

TAVI en indicaciones especiales

RESUMEN

El implante percutáneo de válvula aórtica (TAVI) es la técnica de intervencionismo estructural cardiaco más extendida. Inicialmente, el procedimiento se realizaba solo en pacientes con estenosis aórtica grave sintomática, con riesgo prohibitivo para el reemplazo valvular aórtico quirúrgico. En pocos años, esta técnica se extendió a pacientes con riesgo quirúrgico intermedio y, más recientemente, gracias a los resultados de los estudios PARTNER 3 y *Evolut Low Risk*, se ha abierto esta indicación para pacientes de bajo riesgo. Sin embargo, existen algunas indicaciones controvertidas que marcan la frontera en la evidencia del uso de TAVI, incluyendo pacientes con riesgo quirúrgico intermedio-bajo y válvula aórtica bicúspide, procedimientos válvula en válvula, casos de insuficiencia aórtica pura y pacientes con secuelas valvulares graves tras una endocarditis infecciosa «curada». Nuestro objetivo es resumir la evidencia disponible —fundamentalmente basada en series de casos y registros retrospectivos— referente al empleo de TAVI en estas nuevas indicaciones.

Palabras clave: TAVI. Válvula aórtica bicúspide. Insuficiencia aórtica. Bioprótesis aórtica.

Abbreviations

AoR: aortic regurgitation. **BAV:** bicuspid aortic valve. **IE:** infective endocarditis. **SAVR:** surgical aortic valve replacement. **SVD:** structural valve deterioration. **TAVI:** transcatheter aortic valve implantation. **ViV:** valve-in-valve.

INTRODUCTION

The growing incidence of age-related aortic stenosis (AS) has turned the aortic valve into the most commonly treated heart valve, both surgically and percutaneously, in Europe and the United States.¹ Since the first off-label transcatheter aortic valve implantation (TAVI) procedure back in 2002,² the international experience gained with the use of TAVI has grown. Parallel to this there has been an increase of alternative off-label indications for

this technology. These indications have encouraged the clinical practice guidelines to gradually include more recommendations. Universally accepted for high and intermediate surgical risk patients,³⁻⁶ TAVI has dramatically changed the management of AS over the last decade. However, the recent publication of the PARTNER 3⁷ and Evolut Low Risk⁸ trials that showed TAVI outcomes at the 1-year follow-up that were similar to those of traditional surgical aortic valve replacement (SAVR) raises the question of whether there are limits to this technology or if it will

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Online: 03-04-2020.

<https://doi.org/10.24875/RECICE.M20000109>

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ever become the gold standard treatment. The doubts on its long-term durability, something essential for its widespread indication in younger patients is increasingly seen as the sword of Damocles rather than the Achilles heel of this technology by surgical defenders blinded to the course of events.

Although it is beyond the scope of this work, it is worth mentioning that another current limitation of TAVI is the challenging trans-vascular approach. Although transfemoral TAVI is the gold standard, this approach is not feasible or too risky in around 15% of the patients.⁹ The transcatheter TAVI approach has had promising results –better than all the other transthoracic approaches– but are still far from the outcomes obtained with transfemoral cases.¹⁰ Importantly, a recent meta-analysis showed that the trans-subclavian approach may not only be an alternative route to transfemoral access but also a competitive one in certain patients with higher risk of femoral artery injury.¹¹

New indications and alternative approaches for TAVI have increased gradually preceded by its use as a compassionate alternative. In this study we describe the current boundaries of these indications by reviewing the main off-label uses of TAVI and the reported outcomes in such challenging scenarios.

SPECIFIC INDICATIONS FOR TAVI

There are several controversial TAVI indications today; however, we have decided to exclude certain uncommon indications and focus on the following ones: *a)* TAVI for bicuspid AS; *b)* TAVI for valve-in-valve (ViV) procedures; *c)* TAVI for pure aortic regurgitation (AoR); and *d)* TAVI for valvular severe dysfunction following healed infective endocarditis (IE).

TAVI for the management of bicuspid AS

Incidence and specific challenges of bicuspid AS

Bicuspid aortic valve (BAV) is the most common congenital valvular defect. It has been reported in up to 1% to 2% of the general population.¹² It is more common in younger patients with severe AS, but it is present in elderly patients as well. BAV is associated with increased mechanical stress, which predisposes to calcification and the development of AS.¹³ BAV stenosis has been considered an anatomical challenge for TAVI for the following reasons: *a)* the shape of the annulus is often extremely elliptical and tends to aortic dilation compared to the characteristic annular oval shape of calcified tricuspid aortic valve (TAV) that may be associated with greater leakage; *b)* BAVs usually have a higher cusp coaptation point that can be a confounding factor during the procedure and increase the risk of valve embolization (figure 1); and, *c)* the asymmetric distribution of calcium with a tendency to bulky formations increases the risk of paravalvular leak and annular rupture.¹⁴ All these elements should be taken into account when considering TAVI for patients with BAV since stent malposition is more common in patients with these abnormalities and may be associated with higher rates of paravalvular regurgitation, valvular dysfunction or early degeneration of the implanted valve.¹⁵

Current evidences of TAVI for the management of BAV

Patients with BAV have not been included in landmark trials of TAVI devices. Patients who need aortic valve replacement due to AS at a younger age (< 60 years) often have congenital BAV. For this reason, patients with BAV often have less comorbidities and

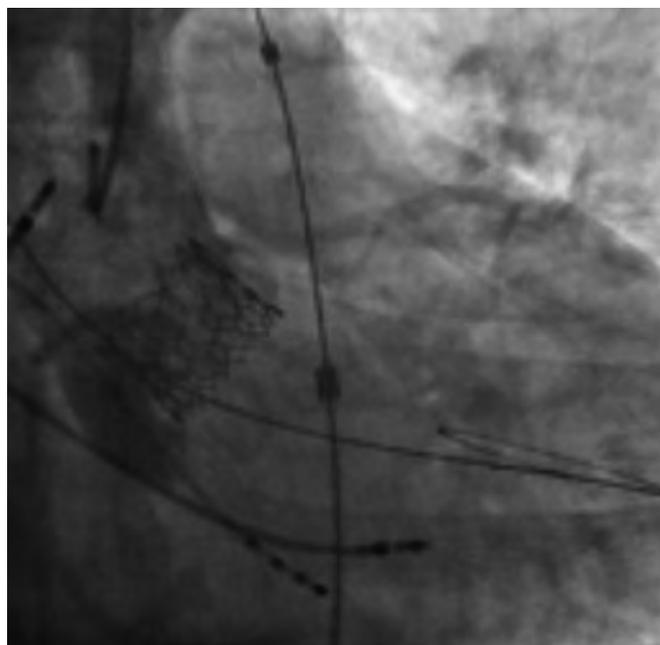


Figure 1. Example of balloon-expandable TAVI (Myval, Meril Lifesciences, India) in a bicuspid aortic stenosis. The relatively high position is due to the high coaptation level of the leaflets that is common of bicuspid aortic valves.

the heart team usually decides to perform SAVR. When TAVI is the preferred option, meticulous valve sizing and procedural planning are important to achieve good results.¹⁶ To this day, all the specific studies dedicated to analyze the different outcomes of TAVI in the management of patients with BAV and TAV have been retrospective studies. We identified 13 studies that proved the feasibility and safety of TAVI in BAV stenosis. The main baseline characteristics and procedural outcomes are shown on table 1 and table 2.¹⁶⁻²⁸ In their meta-analysis Quintana et al.²⁹ reviewed the results of studies that focused on early-generation devices mainly.¹⁶⁻²⁰ This analysis showed that the TAVI therapy was feasible and safe in BAV disease. The primary endpoint of the 1-year all-cause mortality revealed an 11.8% mortality rate in patients with BAV compared to 15.06% in patients with TAV. No differences were seen between the 2 groups (relative risk [RR], 1.03; 95% confidence interval [95%CI], 0.70-1.51). However, the BAV group was associated with less procedural success with the device and more significant valve regurgitation after TAVI compared to patients with TAV. Yoon et al.²² compared the procedural and clinical outcomes of patients with BAV versus TAV including new-generation devices. In the group that received early-generation devices, the BAV more commonly presented with aortic root injury (4.5% vs 0.0%; $P = .015$) when the balloon-expandable device was used and moderate-to-severe paravalvular leak (19.4% vs 10.5%; $P = .02$) when self-expanding devices were used. However, in patients with new-generation devices procedural results were similar with different valves. The 2-year cumulative all-cause mortality rates were similar between bicuspid and tricuspid AS (17.2% vs 19.4%; $P = .28$). Takagi et al.³⁰ conducted the last meta-analysis available to this day and showed no statistical differences in the rates of pacemaker implantation and early- and mid-term mortality (RR, 1.35; 95%CI, 0.94-1.93 and RR, 1.00; 95%CI, 0.77-1.31, respectively). However, the BAV group showed significantly more aortic valve regurgitation compared to the TAV group (RR, 1.42; 95%CI, 1.11-1.82). This setback was less common when using balloon-expandable devices compared to self-expandable ones. Maybe because of this, as shown on table 1, balloon-expandable devices have been the preferred options in most recent studies.

Table 1. Comparison between bicuspid and tricuspid aortic stenosis. Baseline data and procedural characteristics

Reference, year	N		Age (years)		STS score (%)		Logistic EuroSCORE (%)		TF approach (%)		Balloon-expandable (%)	
	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Hayashida et al., ¹⁷ 2013	21	208	82.0 ± 7.0	83.2 ± 6.5	N/A	N/A	19.9 ± 11.9	20.1 ± 11.4	61.9	50.5	52.4	83.7
Bauer et al., ¹⁸ 2014	38	1357	80.7 ± 6.6	81.8 ± 6.2	N/A	N/A	18.0 ± 10.0	20.0 ± 13.0	81.6	88.0	31.6	18.0
Costopoulos et al., ¹⁶ 2014	21	447	76.7 ± 7.1	79.8 ± 7.4	7.6 ± 4.2	7.8 ± 7.3	23.9 ± 12.0	24.4 ± 17.3	71.4	83.9	38.1	58.6
Kochman et al., ¹⁹ 2014	28	84	77.6 ± 5.5	79.1 ± 6.8	N/A	N/A	19.2 ± 9.0	18.8 ± 8.7	78.6	77.4	17.9	17.9
Liu et al., ²⁰ 2015	15	25	75.4 ± 5.7	75.8 ± 5.5	5.6 ± 4.1	7.5 ± 5.9	16.1 ± 11.1	21.8 ± 14.7	86.7	92.0	0.0	0.0
Sannino et al., ²¹ 2017	88	735	80.2 ± 8.4	81.8 ± 7.9	7.4 ± 3.9	7.6 ± 3.9	N/A	N/A	88.6	87.1	52.3	59.7
Yoon et al., ²² 2017	546	546	77.2 ± 8.2	77.2 ± 8.8	4.6 ± 4.6	4.3 ± 3.0	16.1 ± 12.0	16.9 ± 13.9	79.1	78.8	57.7	57.1
Arai et al., ²³ 2017	10	143	81.3 ± 5.1	82.6 ± 6.2	N/A	N/A	19.0 ± 12.5	18.1 ± 11.0	70.0	87.4	100.0	100.0
Liao et al., ²⁴ 2018	87	70	80.2 ± 8.4	81.8 ± 7.9	7.9 ± 4.0	8.6 ± 4.4	N/A	N/A	100.0	100.0	0.0	0.0
De Biase et al., ²⁵ 2018	83	166	81.4 ± 7.6	82.9 ± 5.7	5.1 ± 3.3	5.1 ± 2.9	N/A	N/A	98.8	98.8	60.2	36.7
Xiong et al., ²⁶ 2018	67	49	74.0 (68.0–77.0)	75.0 (68.0–79.0)	6.5 (4.4–9.3)	8.3 (5.2–9.5)	N/A	N/A	98.5	100.0	0.0	0.0
Kawamori et al., ²⁷ 2018	41	239	80 (70.5–83.0)	83 (78.0–87.0)	N/A	N/A	N/A	N/A	97.6	98.7	100.0	100.0
Makkar et al., ²⁸ 2019	2691	2691	74.0 (66.0–81.0)	74.0 (66.0–81.0)	4.9 ± 4.0	5.1 ± 4.2	N/A	N/A	93.6	93.9	100.0	100.0

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

BAV, bicuspid aortic valve; N/A, not available; STS score, Society of Thoracic Surgeons predicted risk of mortality; TAV, tricuspid aortic valve; TF, transfemoral.

Table 2. Comparison between bicuspid and tricuspid aortic stenosis. Main outcomes

Reference, year	Mean valve gradient (mmHg)		Valvular AoR > 2 (%)		Permanent pacemaker (%)		30-day mortality (%)	
	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Hayashida et al., ¹⁷ 2013	10.0 ± 3.4	9.7 ± 4.1	19.0	14.9	14.3	7.2	1 (4.8)	17 (8.2)
Bauer et al., ¹⁸ 2014	5.5 ± 7.1	5.9 ± 6.8	23.7	15.0	15.8	35.0	4 (10.5)	5 (11.0)
Costopoulos et al., ¹⁶ 2014	10.3 ± 5.7	10.5 ± 4.7	23.8	21.7	14.3	15.0	3 (14.3)	3.6 (3.6)
Kochman et al., ¹⁹ 2014	11.5 ± 6.4	10.4 ± 4.5	32.1	22.6	28.6	33.3	1 (3.6)	6 (7.1)
Liu et al., ²⁰ 2015	9.6 ± 3.1	11.0 ± 4.2	0.0	4.0	13.3	12.0	1 (6.7)	2 (8.0)
Sannino et al., ²¹ 2017	7.96 ± 4.15	8.5 ± 4.2	5.3	5.0	22.7	18.1	3 (3.4)	23 (3.1)
Yoon et al., ²² 2017	10.8 ± 6.7	10.2 ± 4.4	10.4	6.8	15.4	15.4	20 (3.7)	18 (3.3)
Arai et al., ²³ 2017	N/A	N/A	0.0	6.0	0.0	8.4	0 (0.0)	1 (0.7)
Liao et al., ²⁴ 2018	13.7 ± 8.4	13.0 ± 7.5	1.2	0.0	24.1	28.6	8 (9.2)	3 (4.3)
De Biase et al., ²⁵ 2018	10.0 ± 4.0	9.8 ± 4.5	3.6	2.4	14.5	10.2	4 (4.8)	5 (3.0)
Xiong et al., ²⁶ 2018	13.5 (10.0 - 17.0)	13.0 (10.0 - 18.0)	N/A	N/A	25.4	22.4	6 (9.0)	2 (4.1)
Kawamori et al., ²⁷ 2018	11.9 ± 4.2	10.8 ± 4.0	2.4	1.3	22.0	9.6	0 (0.0)	1 (0.4)
Makkar et al., ²⁸ 2019	N/A	N/A	N/A	N/A	9.1	7.5	66 (2.6)	63 (2.5)

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

AoR, aortic regurgitation; BAV, bicuspid aortic valve; N/A, not available; TAV, tricuspid aortic valve.

Will TAVI be the future gold standard treatment for the management of BAV?

TAVI has proven to be an excellent option for selected BAV cases, which is consistent with the data collected so far. In order to extend its indications, Elbadawi et al.³¹ compared TAVI to SAVR and showed similar in-hospital mortality rates (3.1% vs. 3.1%; odds ratio [OR], 1.00; 95%CI, 0.60-1.67). No differences between TAVI and SAVR were reported in the rates of procedural complications and early outcomes such as cardiac arrest, cardiogenic shock, acute kidney injury, cardiac tamponade or acute stroke. TAVI was associated with lower rates of acute myocardial infarction, post-operative bleeding complications, and shorter hospital stays. However, TAVI was associated with higher rates of complete heart block and permanent pacemaker implantation (13.8% vs 4.6%; OR, 3.32; 95%CI, 2.34-4.71; $P < .001$).

Keypoints: use of TAVI in the management of BAV

In conclusion, the use of TAVI in BAV seems like a good alternative regarding mortality and major complications. However, balloon-expandable devices may have a slightly higher rate of annular rupture and self-expandable devices a higher rate of pacemaker and paravalvular leak as in alternative scenarios. Dedicated randomized trials that compare TAVI versus SAVR are justified in the future and may open the way to a new gold standard treatment in younger patients with BAV.

TAVI for ViV procedures

Bioprosthetic structural valve deterioration

Bioprosthetic valves have limited durability compared to mechanical valves and eventually fail between 5 and 20 years after the intervention; however, when this happens they can be treated using ViV procedures instead of mechanical valves. Also, bioprosthetic valves do not require anticoagulation, which minimizes the risks associated with this procedure.^{32,33} These factors have led to a significant increase in the use of these procedures over the last 2 decades.

Structural valve deterioration (SVD) is an acquired intrinsic bioprosthetic valve abnormality defined as the deterioration of the leaflets or supporting structures that results in thickening, calcification, tearing or disruption of the prosthetic valve materials eventually leading to prosthetic valve hemodynamic dysfunction. SVD may present as stenosis, regurgitation or both. Mechanical stress, collagen fiber disruption, and tissue calcification are the main contributors to this process.³² Although there is not a standard definition of SVD,³³⁻³⁵ the growing use of TAVI for ViV procedures with certain cases wrongly indicated to treat pre-existing severe mismatch makes it necessary to establish clear diagnostic criteria on the indication for ViV³⁴. Dvir et al.³² proposed a practical definition of SVD in the valve-in-valve international data (VIVID) registry and gave recommendations on the timing of clinical and imaging assessment at the follow-up. This definition is built on different stages and each stage is associated with a specific recommendation to show SVD as a continuum instead of a binary categorical variable. Therefore, stage 1 is associated with early morphological changes in the leaflet without hemodynamic effects. Stage 2 SVD refers to the valve leaflets morphological abnormalities associated with hemodynamic dysfunction. Depending on the type of dysfunction this stage is divided into: stenosis (stage 2S) or regurgitation (stage 2R) since the clinical implications and progression of deterioration are different between these 2 failure modes. Investigators categorized a mixed moderate stenosis/regurgitation condition as Stage 2RS.

In this stage 2 SVD there are symptomatic patients who may be eligible for reintervention. The most severe stage of SVD (stage 3) is the development of severe stenosis and/or regurgitation.

Indication of ViV for the management of bioprosthetic SVD

Until the past decade, when SVD would reach stage 3, the standard of care for bioprosthetic valve deterioration was to replace the valve again. The ViV proof-of-concept was described by Walther et al. back in 2007.³⁶ Since then and due to its less invasive and more appealing nature for both patients and operators compared to having to perform open-heart surgery again, the rates of ViV procedures have grown rapidly³² even without the CE mark approval for some of the current devices. Relatively small series and some long registries on the devices used have been published since then. The results of the studies include over 20 cases of ViV procedures and are shown on table 3.³⁷⁻⁴⁹

Although in 2012 Dvir et al.⁴¹ suggested that the ViV procedure was technically demanding and should be spared for highly experienced centers, nowadays this procedure is performed in all TAVI-capable centers and –unlike Dvir et al. predicted– is probably not considered as one of the most complex scenarios anymore. However, operators need to be skilled on valve malapposition, retrieval techniques, implantation of a second TAVI device, and management of the feared coronary occlusion. During the screening stage, the heart team should take all these factors into consideration. Also, the mechanism of SVD should be assessed by cardiac imaging experts familiar with structural procedures and taken into consideration when having to choose the TAVI model and the right size.

New techniques and challenges for ViV procedures

Positioning during ViV procedures can be very challenging as it is predictive of the risk of coronary obstruction, which is more likely when the leaflets are sutured outside the sewing ring or in stentless valves.⁴⁹ Better devices and dedicated techniques are being rapidly developed to help operators achieve better outcomes including fracturing the ring during postdilatation to improve the transvalvular gradients of patients with prior small bioprosthetic valves and certain degree of mismatch⁵⁰ or the BASILICA technique (bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction).⁵¹ These procedures are based on short series of cases but are growing rapidly given their promising results.

A relatively new problem which will become eventually bigger is the TAVI-in-TAVI procedure. Little is known about the mid- and long-term durability of transcatheter aortic valves beyond the first decade of implantation.⁵² Although the transcatheter ViV procedure is now accepted as a good alternative to having to perform surgery again in high-risk patients with failed surgical bioprosthetic valves, the TAVI-in-TAVI procedure is associated with specific risks depending on the type of device used. On the one hand, supra-annular self-expandable valves may present a higher risk of coronary occlusion if treated with the current devices, which makes access to the coronary ostia even more challenging. On the other hand, intra-annular devices may have worse residual gradients after the ViV or a higher risk of annular rupture when postdilatation is performed. Overall, the scarce data available today regarding this new scenario seem favorable.^{52,53}

Keypoints: ViV

Despite the tendency to underestimate the risks of ViV or the long-term impact of poor acute hemodynamic results, the truth is

Table 3. Cases series (> 20 patients) and registries of aortic valve-in-valve procedures

Reference, year	N	THV	Age (years)	STS score (%)	Logistic EuroSCORE (%)	Procedural success (%)	Mean gradient after ViV (mmHg)	AoR > 2 (%)	PPI (%)	THV malap-position (%)	30-day mortality (%)	1-year mortality (%)
Eggebrecht et al., ³⁷ 2011	47	ES	79.8 ± 7.1	11.6 ± 8.5	35.0 ± 18.5	100	17.0 ± 10	2	N/A	8	17	N/A
Bedogni et al., ³⁸ 2011	25	CV	82.4 ± 3.2	8.2 ± 4.2	31.5 ± 14.8	100	13.8	0	12	N/A	12	16
Bapat et al., ³⁹ 2012	23	ES	76.9 (43-92)	7.6 ± 3.8	31.8 ± 15.3	100	9.1	0	0	4.3	0	12.5
Linke et al., ⁴⁰ 2012	27	CV	74.8 ± 8	N/A	31.3 ± 17	100	18 ± 8	7.4	3.7	3.7	7.4	12.5
Dvir et al., ⁴¹ 2012	202	CV/ES	77.7 ± 10.4	11.8 ± 9.9	31.1 ± 16.4	93.1	15.9 ± 8.6	5.0	7.4	15.3	8.4	14.2
Dvir et al., ⁴² 2014	459	CV/ES	77.6 ± 9.8	9.8 (6.2-16.1)	29 (19.1-42.3)	93.1	15.8 ± 8.9	5.4	8.3	15.3	7.6	16.8
Ihlberg et al., ⁴³ 2013	45	CV/ES	80.6 (61-91)	15.0 ± 10.8	35.4 ± 16.1	95.6	16.4 ± 8.7	2	7	2.2	4.4	11.9
Camboni et al., ⁴⁴ 2015	31	CV/ES/ME/SA	77.8 ± 6.3	20.9 ± 8.8%	N/A	88	16.1 ± 7.2	N/A	6	N/A	22.5	N/A
Webb et al., ⁴⁵ 2017	365	ES	78.9 ± 10.2	9.1 ± 4.7	12.3 ± 9.8	97.5*	17.6 (16.2 – 19.1)	1.9	1.9		2.7	12.4
Zenses et al., ⁴⁶ 2018	79	CV/ES/P	74.5 ± 11.0	N/A	10.2 ± 2.7	78.5	22.2 ± 9.3	3.9	3.8	N/A	N/A	N/A
de Freitas Campos Guimaraes et al., ⁴⁷ 2018	116	CV/ES	76 ± 11	8.0 ± 5.1%	N/A	94.8	18.5 ± 10.5	4.3	5.2	N/A	6.9	25.9 (3-years)
Tuzcu et al., ⁴⁸ 2018	1150	CV/ES	79 (74–85)	6.9 (4.5-10.8)	N/A	96.9*	16.0 (10.0-22.0)	3.5	3.0	< 1%	2.9	11.7
Holzamer et al., ⁴⁹ 2019	85	AN	77 ± 8	6.8 ± 6.0	11.4 ± 7.9	99	16 ± 8	10	1	N/A	5	8

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

* Not explicit in the text. Procedural success according to the Valve Academic Research Consortium (VARC) criteria.

AoR, aortic regurgitation; AN, ACURATE neo; CV, CoreValve; ES, Edwards Sapien; ME, Medtronic Engager; N/A, not available; P, Portico; PPI, permanent pacemaker implantation; SA, Symetis ACURATE; STS score, Society of Thoracic Surgeons predicted risk of mortality; THV, transcatheter heart valve; ViV, valve-in-valve.

that the ViV procedure is far from being a well-established technique despite the large number of cases performed to this day. To have optimal outcomes technical improvements and new devices are needed in both the transcatheter and surgical fields.

TAVI for the management of pure AoR

Mechanisms of AoR and current management

AoR is characterized by its prolonged silent clinical course. When patients with severe AoR become symptomatic, they present with volume overload related congestive heart failure, increased wall stress, and left ventricular dysfunction.¹ There are other differences compared to AS. On the one hand, the anatomy of patients with native aortic valve regurgitation is often challenging with dilated aortic root, dilated ascending aorta, and often an elliptical annulus.⁵⁴ On the other hand, patients with AoR are usually referred for valve replacement at a younger age due to the different mechanisms involved in the AoR like degenerative, congenital, rheumatic and, less commonly, infectious disease or radiotherapy.⁵⁵ For these reasons, SAVR is the standard therapy.¹

The role of TAVI in the management of patients with AoR

However, the advances made in the technology of the valves and the accumulated experience have led to the off-label use of TAVI for the management of inoperable or high-risk patients with AoR.⁵⁶ As a matter of fact, TAVI has been contraindicated for the management of pure AoR due to absent or scarce valve calcification, which makes fixing the device even more challenging.⁵⁷ Since Roy

et al.⁵⁵ published the first case series of TAVI for the management of pure native AoR other retrospective studies have been published trying to generate evidence and show the feasibility and safety of TAVI for this indication. As it occurs with other TAVI indications, performing a preoperative echocardiography and a three-dimensional multislice computed tomography should be mandatory. Careful assessment of the diameters of the annulus and sinus of Valsalva followed by the measurement of the ascending aortic diameter become essential. Valve sizing should match the perimeter and area too. However, proper annular contrast enhancement is often challenging during the computed tomography scan and the dimensions of the annulus can quickly change if the procedure is not performed shortly after the assessment of the images.

Table 4 and table 5 show the main registries on this topic.^{55,57-65} Studies have been arranged chronologically and, as Takagi et al.⁶⁶ did in their recent meta-analysis, the information has been classified into early- and new-generation devices with educational purposes.

Alternative TAVI devices for the management of AoR

The Medtronic CoreValve (Medtronic, United States) was the preferred option in most of the early reports of TAVR in patients with pure native AoR.^{60,67-74} Its self-expandable properties were thought to offer stability during implantation and guarantee valve fixation even in the absence of heavy calcification (figure 2). However, the regular need for ViV implantation and the moderate-to-high rates of postoperative AoR grade III-IV (table 5, results from Roy et al.⁵⁵ and Testa et al.⁵⁹) resulted in a modest change in the definition of device success according to the Valve Academic

Table 4. Cases series (> 20 patients) and registries of TAVI on the management of pure aortic regurgitation. Baseline clinical and echocardiographic data

Reference, year	N	THV	Age (years)	STS score (%)	Logistic EuroSCORE (%)	Mean LVEF (%)	Mean LVEDD (mm)	Significant MR* (%)
Roy et al., ⁵⁵ 2013	43	CV	75.3 ± 8.8	10.2 ± 5.3	26.9 ± 17.9	45.5 ± 12.9	59.4 ± 13.7	32.6
Seiffert et al., ⁵⁸ 2014	31	JE	73.8 ± 9.1	5.4 ± 3.6	23.6 ± 14.5	46.8 ± 16.1	N/A	20.0
Testa et al., ⁵⁹ 2014	26	CV	73 ± 10	13.1 ± 2	24 ± 8	45 ± 14	N/A	50.0
Frerker et al., ⁶⁰ 2015	22	CV/ES	80 ± 7.6	N/A	25 ± 18	N/A	N/A	N/A
Zhu et al., ⁶¹ 2016	33	JV	74.2 ± 5.2	N/A	24.4 ± 5.1	N/A	N/A	N/A
Yoon et al., ⁵⁷ EGD 2017	119	CV/ES	74.2 ± 13.1	7.6 ± 6.7	N/A	44.5 ± 14.3	62 ± 11	35.1
Yoon et al., ⁵⁷ NGD 2017	212	CV/ES/JE/JV/SA/DF/ME/LO/P	74.2 ± 11.6	6.2 ± 6.7	N/A	46.3 ± 14.8	60 ± 11	35.6
Sawaya et al., ⁶² 2017	78	CV/ES/JE/DF/LO	74 ± 10	6.7 ± 4.8	23.6 ± 14.5	42.7 ± 13.8	58.5 ± 10.2	43.3
Liu et al., ⁶³ 2018	43	JV	73.9 ± 5.7	N/A	25.5 ± 5.3	55.9 ± 10.8	60.5 ± 8.4	9.3
De Backer et al., ⁶⁴ EGD 2018	109	CV/ES	74 ± 13	6.9 ± 7.5	N/A	44 ± 15	N/A	42.9
De Backer et al., ⁶⁴ NGD 2018	145	CV/ES/JE/SA/DF/ME/LO/P	75 ± 10	6.2 ± 4.9	N/A	45 ± 15	N/A	43.5
Silaschi et al., ⁶⁵ 2018	30	JE	74.4 ± 9.3	17.7 ± 14.8	4.9 ± 3.5	49.6 ± 13.3	N/A	50.0

Data are expressed as mean ± standard deviation.

* Significant MR, mitral regurgitation (at least grade).

CV, CoreValve; DF, Direct Flow; EDG, early-generation devices; ES, Edwards Sapien; JV, J Valve; JE, JenaValve; LO, Lotus; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; ME, Medtronic Engager; MR, mitral regurgitation; N/A, not available; NGD, new-generation devices; P, Portico; SA, Symetis ACURATE; STS score, Society of Thoracic Surgeons predicted risk of mortality; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve.

Table 5. Cases series (> 20 patients) and registries of TAVI on the management of pure aortic regurgitation. Procedural and follow-up outcomes

Reference, year	Procedural success (%)	Conversion to open surgery	THV-in-THV (%)	Annulus rupture	Reintervention	PPI (%)	≥ moderate PVR	30-day mortality (%)
Roy et al., ⁵⁵ 2013	74.4	2.3	18.6	N/A	N/A	16.3	4.7	9.3
Seiffert et al., ⁵⁸ 2014	96.8	0.0	0.0	0.0	N/A	6.5	0.0	12.9
Testa et al., ⁵⁹ 2014	76.9	0.0	19.2	N/A	N/A	7.7	23.1	23.1
Frerker et al., ⁶⁰ 2015	81.8	N/A	N/A	N/A	N/A	27.3	N/A	22.7
Zhu et al., ⁶¹ 2016	93.9	3.0	N/A	N/A	N/A	6.1	3.0	3.0
Yoon et al., ⁵⁷ EGD 2017	61.3	3.4	24.4	1.7	5.0	17.5	18.8	13.4
Yoon et al., ⁵⁷ NGD 2017	81.1	3.8	12.7	1.4	3.8	18.6	4.2	9.4
Sawaya et al., ⁶² 2017	70.5	N/A	16.7	N/A	2.6	18.5	13.4	14.3
Liu et al., ⁶³ 2018	97.7	2.3	0.0	0.0	4.7	2.3	2.4	2.3
De Backer et al., ⁶⁴ EGD 2018	46.5	N/A	N/A	N/A	3.7	N/A	25.5	17.1
De Backer et al., ⁶⁴ NGD 2018	82.5	N/A	N/A	N/A	4.4	N/A	4.7	7.7
Silaschi et al., ⁶⁵ 2018	88.9	3.7	0.0	0.0	3.3	3.8	0.0	10.0

EGD, early-generation devices; N/A, not available; NGD, new-generation devices; PPI, permanent pacemaker implantation; PVR, paravalvular regurgitation; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve.

Research Consortium.³⁵ This was a heads-up on the limitations of this device for its use in the setting of this specific off-label indication.⁵⁴ Other self-expandable transcatheter valves such as the ACURATE neo (Boston Scientific, United States), Lotus (Boston Scientific, United States), Portico (Abbott, United States), and the balloon-expandable Edwards SAPIEN XT/S3 (Edwards Lifesciences, United States) have been used for the management of

AoR (table 4) with variable outcomes but poorer results compared to the management of patients with AS.

New devices have been developed for the management of patients with pure severe AoR. The JenaValve (JenaValve Technology, Germany) was the only new-generation repositionable valve with self-positioning geometry and specific fixation mechanisms with



Figure 2. Example of a self-expandable TAVI (Evolut R, Medtronic, United States) in pure aortic regurgitation. Note that in this case there is no residual aortic regurgitation in the angiographic assessment.

Conformité Européenne mark for the management of AoR. A nitinol stent frame that houses a trileaflet porcine pericardial valve with 3 feelers that allow the correct anatomical orientation of the valve plus a special clipping mechanism that fixes the device onto the native leaflets. The first report of a TAVR with the JenaValve included 5 patients with moderate or severe AoR and high surgical risk; procedural success was achieved in all cases and no death or stroke was reported at the 30-day follow-up.⁷⁵ A similar performance was observed in longer registries as shown on [table 4](#) and [table 5](#). However, this device is no longer in the market. The J-Valve system^{61,76} (JieCheng Medical Technology, China), not available in Europe yet, has 3 U-shaped and anatomically oriented device "graspers" for "self-positioning" purposes during valve prosthesis implantation and provides radial fixation by embracing the native valve leaflets in a "clip mechanism". The Direct Flow Medical Transcatheter Aortic Valve System (Direct Flow Medical, California) consists of 2 systems of rings (ventricular and aortic) that are independently inflated with a contrast-saline mixture during the deployment phase plus a polymer that solidifies and brings support while the device is being fixated in its final position. Schofer et al.⁷⁷ reported their experience with this device in 11 high-risk patients with 100% device success and an early safety rate of 91% according to VARC-2 criteria.³⁵

Keypoints: TAVI for the management of pure AoR

TAVR for the management of pure native AoR with early-generation devices has been associated with relatively high rates of procedural complications. The development of new-generation devices improved procedural outcomes with lower rates of second valve implantation need⁵⁷ or significant postoperative AoR (\geq grade 2).^{57,64} However, recent studies⁵⁷ prove that a significant reduction of the degree of AoR is not enough since postoperative AoR \geq 2 is associated with higher rates of re-hospitalization and all-cause mortality. This is indicative that there is still a long way to go

before reaching the level of evidence currently available for TAVI for the management of patients with AS. New devices on the pathophysiology of AoR are needed but for the time being TAVI should be only considered in selected cases of non-calcified AoR after clinical and imaging assessment.

TAVI for the management of severe valvular dysfunction after healed IE

Current relevance of IE

IE affects between 1 and 10 cases per 100000 individuals each year.^{78,79} The detection, management, and treatment have slightly improved in recent years, although a concomitant rise in its incidence has been reported.^{80,81} Also, the rates of mortality and complication remain stable.⁸¹ The life-threatening aspect of this entity is evident in its mortality rates (between 15% and 30%) depending on the patients' baseline conditions, the causative organism, and the presence of other complications like cerebrovascular events.⁷⁸ Approximately, half of the patients affected by IE require cardiac surgery to treat the infection or the associated complications. However, many of the patients with an indication for surgery due to residual valvular lesion are not eligible for surgery due to high surgical risk. When the aortic valve is damaged, TAVI may be a potential therapeutic option despite its current contraindication established by the guidelines due to risk of reinfection concerns. However, the damaged valve can be treated with TAVI once the infection has been resolved.⁷⁸

Experience with TAVI in the setting of healed IE with residual valvular damage

There are very few cases in the medical literature on the use of TAVI following IE. Back in 2013, Albu et al.⁸² described the first case of a healed IE related severe aortic homograft stenosis successfully treated with a self-expandable TAVI. In 2015, Nguyen et al.⁸³ described the first case of valve-in-valve procedure to treat a healed IE in a patient treated with TAVI inside a surgical bioprosthetic valve. Both cases had good clinical outcomes at the mid-term follow-up (6 and 12 months, respectively). There are no larger series that confirm the good results of TAVI in healed IE leaving dysfunctional valves. However, in a subanalysis of their long-term registry of surgical treatment in patients with AS, Pechlivanidis et al.⁸⁴ suggested the possibility of using transcatheter valves to treat patients who overcame an IE and were at very high risk for conventional surgery.

Evidences supporting the use of TAVI after healed IE

To our knowledge, the most complete review of potential candidates for TAVI following IE was the study conducted by Garcia-Granja et al.⁸⁵ They analyzed 182 patients treated with aortic valve surgery due to IE and looked for predictors of active local infection at the time of the intervention through explant tissue cultures. The main independent predictors of active local infection were diabetes mellitus, *Staphylococcus aureus*, and concomitant compromised mitral valve. In contrast, an interval between the diagnosis and the intervention of over 9 days was predictive of healed infection. Without predisposing criteria for active infection, the risk of positive cultures in the explanted tissue was \sim 3%. This hypothesis-generating research supports the use of TAVI in selected cases with healed infections but residual valve damage, high surgical risk, and no predisposing criteria for active local infection.

Keypoints: use of TAVI after healed IE

In patients who are not eligible for surgery but have a low risk of local infection according to the «IE team», TAVI may be an option to treat residual aortic valve damage. More evidence is still needed before knocking down the current contraindication of TAVI in this setting.

CONCLUSIONS

Although it may be controversial there is a growing interest in the off-label uses of TAVI devices to solve several uncovered clinical scenarios. However, the level of evidence is variable across these indications and several technological advances and controlled clinical trials are still needed. Although there is a large number of studies that support the use of TAVI in patients with bicuspid AS or SVD of a prior surgical bioprosthetic valve, the indication for the management of pure native AoR or healed IE with residual aortic valve dysfunction is, at least for now, under discussion as a last-resort procedure.

CONFLICTS OF INTEREST

None declared.

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Debate: Mechanical circulatory support in relation to coronary intervention. The interventional cardiologist perspective



A debate: Soporte circulatorio en relación al intervencionismo coronario. Perspectiva del cardiólogo intervencionista

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QUESTION: After the IABP-SHOCK II clinical trial, which would you say is the utility of the intra-aortic balloon pump (IABP)?

ANSWER: In my opinion and yet despite the results of the IABP-SHOCK II,¹ the intra-aortic balloon pump (IABP) still plays a significant role in the management of acute myocardial infarction (AMI) and complex percutaneous coronary intervention (PCI) with risks higher than normal.

In high-risk PCIs there is evidence of the benefits derived from using left ventricular assist devices. In the first place, the IABP has shown late benefits in the BCIS-I trial.² This study randomized patients treated with high-risk PCI—defined as a left ventricular ejection fraction < 30% and > 40% of the lesion related myocardium with intention-to-treat—assessed using scores ≥ 8 in the Jeopardy score. The early study found no significant differences in the primary endpoint at the 28-day follow-up. In the secondary endpoint a numerical difference was found in the mortality rate at the 6-month follow-up, although it was not statistically significant (4.6 in the IABP vs 7.4% in the control group; $P = .32$) probably due to the low number of patients included (301). However, at the 51-month follow-up,³ the mortality rate was significantly higher in the control group: 38% (12.1/100 patients/year) vs 27.8% (7.9/100 patients/year). The Kaplan-Meier curves showed a significant difference with a hazard ratio of 0.66 [95% confidence interval, 0.44-0.98; $P = .039$]. In our routine clinical practice, patients undergoing high-risk PCI (left main coronary artery with occluded right coronary artery, multivessel disease with depressed left ventricular function) without a technically complex lesion are treated with IABP support.

On the other hand, in the management of AMI there is no doubt that in the presence of mechanical complications like acute mitral regurgitation or interventricular communication, the IABP improves

the patient's condition as long as he is not in a situation of deep cardiogenic shock. This stabilizes the patient until he is in a better condition to undergo definitive surgery.

In the management of AMIs complicated with cardiogenic shock, the role of the IABP would be limited when the shock has already occurred. However, it may be useful for the early management of those stages when the patient is in a high-risk situation and is starting to show hemodynamic impairment (certain degree of hypotension and tachycardia, but no signs of poor target organ perfusion) to achieve an early stabilization. This is so because it is easy to implant in any critical care unit without having to transfer the patient, and thanks to its safety profile confirmed by its low rate of complications.

Q.: In the congress held by the American Heart Association back in 2019 several observational registries showed more adverse events and higher costs compared with the use of the Impella device compared to the IABP. However, these results may be due to the effect of multiple biases. What do you think of all this?

A.: These studies have been published in *JAMA* and provide different data on the management of patients with post-infarction cardiogenic shock in a retrospective registry.⁴ This was a very large registry of patients with different baseline characteristics despite the fact that propensity score matching was used. After a thorough reading and analysis of the final outcomes, the mortality rate of the group treated with IABP was clearly lower compared to the one reported by randomized studies on the management of AMI with cardiogenic shock. This is indicative of an early selection bias since it was not a randomized study. However, the group treated with a micro-axial pump had a similar mortality rate compared to the one described by the studies.

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Online: 05-06-2020.

<https://doi.org/10.24875/RECICE.M20000118>

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We should mention that neither one of the 2 devices showed clinical benefits in this situation compared to standard treatment. This means that the only information provided by that registry is that the least critically ill patients receive an IABP while the most critically ill ones receive a micro-axial flow device. The final outcome shows this early selection bias.

Q.: What is the evidence available on the use of the Impella device in high-risk interventional cardiac procedures? What is the routine clinical practice in your center? And in patients with infarction and cardiogenic shock?

A.: The Impella device has proven useful for the management of high-risk PCIs in the PROTECT II trial.⁵ This study randomized patients undergoing high-risk PCIs—defined as left main coronary artery disease or last patent vessel disease with an ejection fraction $\leq 35\%$ or 3-vessel disease with an ejection fraction $\leq 30\%$ —eligible to receive an IABP circulatory support device or an Impella 2.5 device. Regarding major cardiovascular events (all-cause mortality, myocardial infarction, stroke or new revascularization), the Impella 2.5 device obtained better results and even showed preventive properties in a multivariate study. If we analyze the study data thoroughly, we can see that its greatest advantage was the lower rate of new revascularizations in part due to the fact that with the Impella device we can treat more complex lesions during the index procedure.

In light of the results from these studies our indications for ventricular support in patients undergoing elective or high-risk PCIs (severe ventricular dysfunction with left main coronary artery disease plus right coronary artery occlusion or 3-vessel disease) are:

- Technically easy lesion: intra-aortic balloon pump.
- Technically complex lesion: Impella 2.5 device.

Q.: What escalation of mechanical circulatory support do you recommend in hemodynamically compromised patients or patients with post-infarction cardiogenic shock?

A.: The definition and fast detection of patients who have suffered an AMI is very important. In this sense, the Society for Cardiovascular Angiography and Intervention (SCAI) proposed a new classification of patients after AMI with a series of clinical, analytic, and hemodynamic criteria.⁶ This classification in stages has proven that there is a clinical correlation with the mortality rates shown by these patients.⁷ Thus, the stages of hemodynamic impairment can be described as:

- A (At risk): without hemodynamic impairment.
- B (Beginning): hypotension and tachycardia, without hypoperfusion.
- C (Classic): hypoperfusion without general impairment.
- D (Deteriorating): hypoperfusion with impairment, non-refractory.
- E (Extremis): refractory shock.

Currently, there are different types of hemodynamic support with different characteristics regarding the mechanism of action and the effects it has on the heart and coronary circulation.⁸ Every device

offers different hemodynamic support and is associated with a different rate of complications. That is why the risk-benefit ratio should be taken into consideration depending on each patient's hemodynamic impairment. In my view, the different devices may be indicated for the following stages:

- Intra-aortic balloon pump: stages A and B.
- Impella 2.5 device: stage B.
- Impella CP device, 5.0: stage C.
- Extracorporeal membrane oxygenation (ECMO): stages D and E.

In general, the degree of support required may be defined in a different way:

- Coronary support (refractory ischemia): intra-aortic balloon pump.
- Ventricular support (pulmonary edema): Impella device.
- Circulatory support (correct hypotension): ECMO.

CONFLICTS OF INTEREST

J. A. Gómez Hospital has received funding from Izasa Hospitals for his collaboration in the implantation of Impella devices and organizing sessions on left ventricular support.

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Debate: Mechanical circulatory support in relation to coronary intervention. Cardiologist's perspective from the cardiac intensive care unit



A debate: Soporte circulatorio en relación al intervencionismo coronario. Perspectiva del cardiólogo de la unidad de críticos

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QUESTION: After the IABP-SHOCK II clinical trial, which would you say is the utility of the intra-aortic balloon pump (IABP)?

ANSWER: The IABP-SHOCK II¹ did not show any benefits in the 30-day mortality rate or major complications rate when the IABP was compared to conventional therapy in patients with post-infarction cardiogenic shock undergoing primary percutaneous coronary intervention (PCI). No differences were found either in the mortality rate or quality of life of survivors in the studies conducted at 12-month² and 6 year-follow-up.³

European guidelines⁴ downgraded the systematic use of IABP to a class IIIb level of evidence leaving the indication IIa for the management of infarct related mechanical complications. This decreased the use of IABP in the routine clinical practice. However, it is still used in critical care units because it is easy to use, can be implanted quickly, and is cheaper compared to other devices.

Taking into account the limitations of these studies and although we do not use it systematically in our center like we used to years ago, we still implant it as the first-line strategy for the management of infarct related mechanical complications. Also, in patients with extensive acute myocardial infarction (IAM) and hemodynamic instability because it improves coronary perfusion and increases the cardiac output.

Q.: In the congress held by the American Heart Association back in 2019 several observational registries showed more adverse events and higher costs compared with the use of the Impella device compared to the IABP. However, these results may be due to the effect of multiple biases. What do you think of all this?

A.: These observational registries revealed a higher rate of adverse events, and higher costs associated with the use of the Impella device compared to the IABP. However, they have some

limitations: they mixed different types of Impella devices (2.5, CP, and 5) and different etiologies of cardiogenic shock. Also, in most of the patients the device was implanted after the primary percutaneous coronary intervention. In one of these registries that would later be published in *Circulation*,⁵ patients implanted electively with the Impella device in the cardiogenic shock setting were also included.

We have been getting more and more data that the management of cardiogenic shock through the creation of specialized units, invasive hemodynamic monitorization, and implantation of the Impella CP device prior to the PCI improves the results of revascularization and reduces the size of the infarction and the 30-day mortality rate in patients with post-infarction cardiogenic shock. Some studies like the Detroit shock initiative⁶ and the national cardiogenic shock initiative⁷ have already discussed this theory.

Currently, several randomized clinical trials are trying to come to terms with this hypothesis: the Danger shock trial⁸ (support with Impella CP prior to the PCI vs conventional therapy in the management of post-infarction cardiogenic shock), the RECOVER IV (Impella before PCI vs PCI without Impella in the management of infarction related cardiogenic shock), and the STEMI DTU (ClinicalTrials.gov NCT03947619) (Impella CP and PCI delayed 30 min. vs immediate PCI in patients with ST-segment elevation acute myocardial infarction of anterior location without shock). The latter is based on the results from a pilot study on safety and feasibility. The DTU-STEMI pilot trial⁹ proved that it is safe and feasible to perform a PCI 30 min. after LV (left ventricular) unloading with the Impella CP device in patients with anterior AMI without shock.

Regarding high-risk PCIs, the PROTECT-II trial¹⁰ that randomized 452 patients who underwent high-risk PCIs with IABP or Impella 2.5 support showed no differences in the cardiovascular events occurred at the 30- and 90-day follow-up. However, fewer

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Online: 05-06-2020.

<https://doi.org/10.24875/RECICE.M20000118>

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adverse events were seen at the 90-day follow-up in the Impella 2.5 group.

The PROTECT IV study is underway (Impella as support for high-risk PCI vs PCI without hemodynamic support). It will start in 2021 and it will be part of the clinical evidence for the class I recommendation for the Impella device in high-risk PCIs.

The results of the studies currently underway are promising because I think it is LV unloading prior to the PCI that will certainly improve the mortality of post-infarction cardiogenic shock. To this day and until proven wrong, I strongly believe that the Impella CP implanted prior to the PCI is the device of choice for the management of post-infarction cardiogenic shock.

Until we have more data available, I think high-risk PCIs should be handled individually based on the characteristics of the patients and the experience of the heart teams with these devices and in the management of complex PCIs.

Q.: Is your center savvy in the use of extracorporeal membrane oxygenation (ECMO)? What evidence exists for its use in the management of cardiogenic shock in patients with infarction? What studies would be needed in this context to consolidate its indication?

A.: Some of the advantages of the ECMO device are that it is easy to use and can be implanted quickly. Its main hemodynamic effect is an increased mean arterial blood pressure that is higher compared to other devices. However, this advantage is precisely the cause for its most important limitation: the problem of LV unloading in relation to an increased afterload. This increases myocardial oxygen demand and produces deleterious effects on the size of the infarction and its potential recovery. From the pathophysiological point of view, it is not a good device for the management of post-infarction cardiogenic shock.¹¹ Its basic role rests in its hemodynamic effect and improved organ perfusion; that is, it is indicated for patients in INTERMACS 1 situation. To overcome the limitation of inadequate LV unloading, the best option is to add an Impella device that is capable of producing the most powerful hemodynamic effect for LV unloading in ECMO.¹²

Our center is highly experienced in the use of ECMO for the management of cardiogenic shock of any known etiology. We use it for the management of patients with post-infarction deep cardiogenic shock (INTERMACS 1) in the coronary care unit before or after the primary percutaneous coronary intervention. In these patients we initially implant the IABP to improve LV unloading. If the balloon is insufficient, the next step is to add an Impella device.

There are no randomized studies available on the use of ECMO for the management of post-infarction cardiogenic shock. We'll have to wait for the results from other devices. If the hypotheses formulated prove right, ECMO will play a significant role in the management of patients with AMI in whom the Impella device is insufficient or in hospitalized patients with hemodynamic compromise used in combination with the Impella device to overcome the limitation of inadequate ventricular unloading.

Q.: What escalation of mechanical circulatory support do you recommend in hemodynamically compromised patients or patients with post-infarction shock?

A.: I think the first thing to do is to include cardiogenic shock in specialized units experienced in the management of these patients and use of this type of devices. The right selection of patients, invasive hemodynamic monitorization, and use of inotropes for

stabilization purposes is of paramount importance until early device implantation.

With the current data and taking into account the costs of the different devices and the complications associated there are different considerations to be made when choosing one device over the other:

- Patients with extensive infarction and pre-shock, mechanical complications or ventricular arrhythmias: IABP.
- Patients without deep shock (INTERMACS 2): Impella CP prior to the percutaneous coronary intervention and, if not enough support is achieved, add ECMO.
- Patients in deep shock (INTERMACS 1): ECMO combined with balloon or Impella device if there are problems unloading the left ventricle.

CONFLICTS OF INTEREST

None reported.

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Bail-out alcohol septal ablation in the management of obstructive hypertrophic cardiomyopathy and refractory electrical storm



Ablación septal con alcohol de rescate en miocardiopatía hipertrófica obstructiva y tormenta eléctrica refractaria

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CASE PRESENTATION

This is the case of a 51-year old male without a past medical history. One month before his admission he experienced fast heart palpitations associated with diaphoresis, nausea and vomit. Both the electrocardiogram and the Holter monitor showed recurring episodes of monomorphic ventricular tachycardia (figure 1). The physical examination confirmed the presence of an aortic ejection murmur exacerbated when performing the Valsalva maneuver. The transthoracic echocardiography showed obstructive asymmetric septal hypertrophy with a 32-mm maximum septal diameter (figure 2A), a 65-mmHg gradient in the left ventricular outflow tract, and systolic anterior motion of the mitral valve with moderate regurgitation. The cardiovascular magnetic resonance imaging confirmed the presence of extensive myocardial fibrosis as a risk factor of sudden death (figure 2B and video 1 of the supplementary data). Amiodarone and propranolol were prescribed, and an automatic defibrillator was implanted as a secondary prevention measure. The patient was readmitted to the hospital 4 months later with signs of electrical storm with multiple discharges provided by the device implanted. Deep

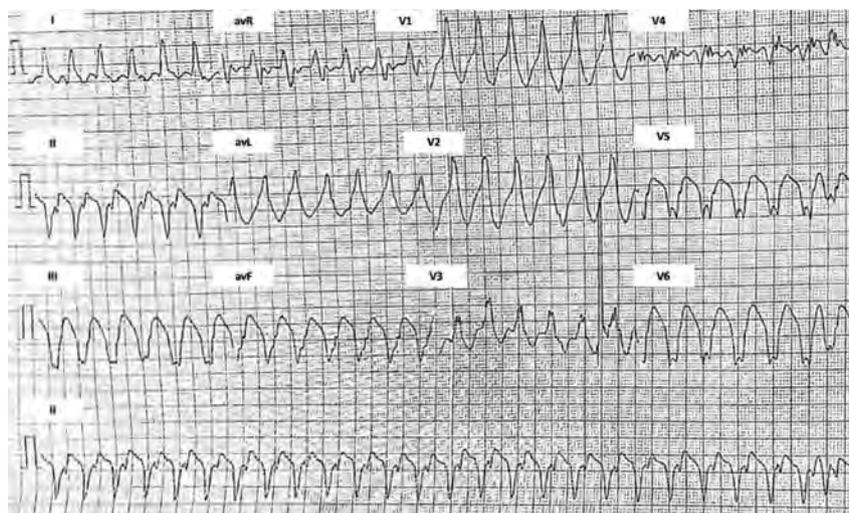


Figure 1. Initial electrocardiogram. Ventricular tachycardia originated at the mid-inferior septum of the left ventricle.

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Online: 13-11-2019.

<https://doi.org/10.24875/RECICE.M19000070>

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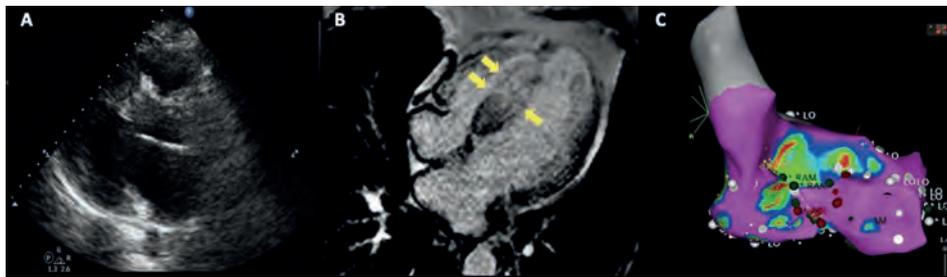


Figure 2. **A:** transthoracic echocardiography. Interventricular septum with a 32 mm diameter. **B:** magnetic resonance imaging showing late contrast (arrows). **C:** mapping of cardiac electrophysiology and ablation attempt of the septal macroreentrant. LO, voltage label; RAM, local electrogram label.

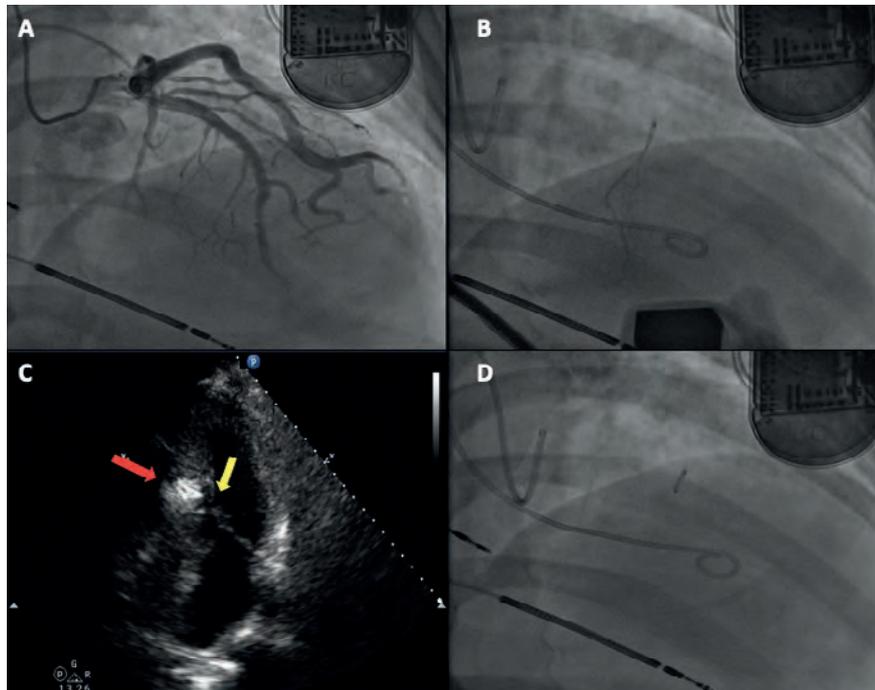


Figure 3. **A:** coronary angiography. **B:** injection of bubble contrast in the second septal branch. **C:** contrast enhancement of the susceptible septal region (arrow). **D:** over-the-wire balloon used for the administration of alcohol.

sedation, mechanical ventilation, and hemodynamic support were administered, and the stellate ganglion was blocked. However, the patient progression was poor with persistent episodes of ventricular tachycardia that triggered the mapping of cardiac electrophysiology using the CARTO 3 system (Biosense Webster, Israel). The ablation of a septal macroreentrant circuit of the left ventricle associated with the clinical ventricular tachycardia was unsuccessful (figure 2C).

A bail-out alcohol septal ablation procedure was attempted that showed a 65-mmHg intraventricular gradient. After the 110-mmHg extrasystole bubble contrast was injected to choose the target septal branch (figure 3) followed by the injection of 0.1 mL of alcohol per millimeter of contrasted septum. In the echocardiography a 23 mm contrasted septum was measured, and 2.3 mL of alcohol were administered in the second septal branch.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000070>.

Bail-out alcohol septal ablation in the management of obstructive hypertrophic cardiomyopathy and refractory electrical storm. How would I approach it?



Ablación septal con alcohol de rescate en miocardiopatía hipertrófica obstructiva y tormenta eléctrica refractaria. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

Authors describe the case of a 51-year old patient with obstructive hypertrophic cardiomyopathy with unusual clinical presentation and progression. The patient had repeated episodes of sustained monomorphic ventricular tachycardia (VT) that required defibrillator implantation in secondary prevention and pharmacological treatment with amiodarone and beta-blockers.

Afterwards, the patient experienced an arrhythmic storm with appropriate multiple discharges despite the antiarrhythmic medication. The stellate ganglion block was indicated. Modulating the sympathetic nervous system can be effective to suppress the arrhythmic storm, but I think of it as the last option. The first therapeutic strategy here would have been the electrophysiological study and the substrate-based ablation of VT. The ablation of recurring VT has a high rate of success with obstructive hypertrophic cardiomyopathies with apical aneurysm and a clear anatomical substrate. However, when this is not the case and there are several fibrotic areas like this patient's cardiovascular magnetic resonance (CMR) imaging showed, the utility of ablation is limited. According to the electrocardiogram and late gadolinium enhancement CMR imaging, the origin of VT could be septal. The authors describe that the intracardiac mapping showed septal macroreentrant whose ablation failed. The endocardium catheter ablation is expected to fail in cases like this when the focus is at deep intramyocardial location. If ablation through endocardial and epicardial accesses fails, the next step is trying alcohol septal ablation.

Back in 1989, Brugada et al.¹ described for the first time the successful management of refractory VTs using intracoronary injections of alcohol in humans. From that moment on, isolated cases and series of patients² have been published supporting the use of alcohol septal ablation as an effective alternative in these cases. However, recurrence is still high.²

When available a CT scan with contrast can be used to study the origin and distribution of septal arteries. Combining the CT scan imaging and the CMR imaging showing the fibrotic area we can identify the septal branches that irrigate the arrhythmogenic focus to plan the alcohol septal ablation procedure.³ This procedure should be planned by the electrophysiology, hemodynamics, and cardiac imaging teams combined. Using the venous access, the electrophysiologist introduces the catheters for mapping purposes and stimulates the VT. The interventionist performs a routine alcohol septal ablation procedure through 2 arterial accesses (right femoral of 7-Fr for the guide catheter and right radial of 5-Fr for the pigtail catheter) plus the simultaneous registry of pressures. In this patient, the CMR imaging showed late enhancement in the mid portion of intraventricular septum, so it was not probably the first but the second septal branch that irrigated the arrhythmogenic focus (figure 3A, figure 3B of the case presentation). After the coronary angiography, a long 0.014 in guidewire is introduced in the target septal branch and a short and relatively large coaxial balloon compared to the septal branch (at least in a 1.2:1 ratio). When the balloon has been inflated at low atmospheres inside the septal branch and the guidewire has been removed, 1-2 mL of echocardiographic contrast are injected through the balloon lumen to discard collaterals. Using the transthoracic echocardiography (TTE) it is verified that the target focus of the septum opacifies (where the origin of the VT would be); in this case, the medial-basal portion of the septum. At this point, VT is induced. The ideal scenario would be that with the inflation of the balloon and the corresponding ischemia, the VT was suppressed, suggestive that alcohol septal ablation may be effective. If this is not the case, the administration of 2-3 mL of a cold physiological saline solution through the balloon can be effective too. Then using ultrasound guidance alcohol is gradually injected through the balloon in less than 1 mL per 1 cm of septal thickness. After the alcohol infusion, the balloon is kept inflated for 10 minutes and the lack of complications in the coronary artery tree is verified; we often seen that the

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Online: 13-11-2019.

<https://doi.org/10.24875/RECICE.M19000071>

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septal branch treated has no flow. VT is re-induced again but if unsuccessful, the procedure is considered terminated. Not being able to induce VT is not a guarantee for future success. But if VT is actually induced, the procedure can be repeated using a different septal branch—the distal sub-branch of the first septal branch—to induce ischemia-necrosis in the edges of the area already treated.

While the procedure is being performed targeting the ablation of the focus of VT, the pressure gradient is being monitored. The procedure may also be useful to reduce the subaortic dynamic gradient, but we should remember that we need to wait for a full year before confirming that it has been effective. However, if the gradient does not fall in the cath. lab, we can use the procedure to test the first septal branch, inflate the balloon in its proximal sub-branch, for ultrasound-guided contrast infusion, to see if the basal septum opacifies in contact with the anterior mitral leaflet and to see what's happening with the gradient. If the gradient does fall, we would have confirmation that such septal branch is causing the gradient, which is important for an eventual procedure if the patient's functional class gets worse.

The most common complication is atrioventricular block that has a higher prevalence in alcohol septal ablation (ASA) procedures of VT compared to procedures to reduce the gradient: 35% vs 5% to 10%.² In the absence of complications, the patient will stay 2 days in the coronary unit with a temporary pacemaker and another 5 at the hospital ward with telemetry.

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Bail-out alcohol septal ablation in the management of obstructive hypertrophic cardiomyopathy and refractory electrical storm. Case resolution



Ablación septal con alcohol de rescate en miocardiopatía hipertrófica obstructiva y tormenta eléctrica refractaria. Resolución

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CASE RESOLUTION

The outcome was successful with a final 19-mmHg intraventricular gradient and after the extrasystole of 25 mmHg (figure 1). No more new events of ventricular tachycardia (VT) were reported, disease progression was good, and the patient remained asymptomatic at 3 months.

Sustained monomorphic VT in hypertrophic cardiomyopathy is a rare entity. These patients are considered eligible to receive an automated implantable-cardioverter defibrillator and antiarrhythmic drugs. Also, in cases of VT of focal origin, the mapping of cardiac

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Online: 13-11-2019.

<https://doi.org/10.24875/RECICE.M19000072>

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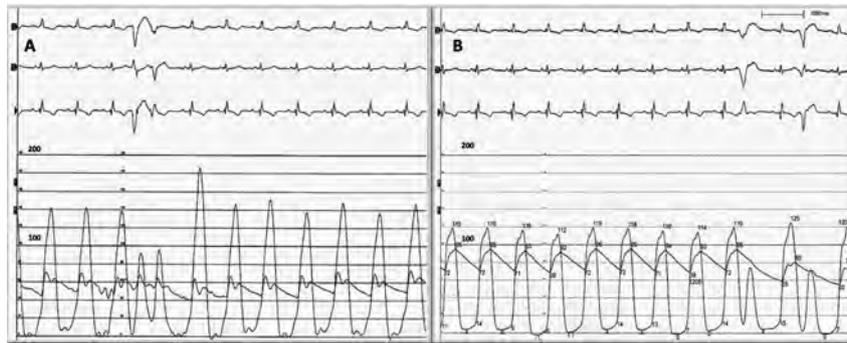


Figure 1. A: gradient between left ventricle and initial aorta. **B:** gradient between left ventricle and final aorta.

electrophysiology and ablation is indicated. In 1989, Brugada et al.¹ first published that in the management of patients in whom other options have failed, alcohol ablation of the coronary branches that irrigate the origin or route of VT is a valid therapeutic option to treat persistent tachycardia.

Our case is unique because it describes the role of septal ablation for arrhythmic and hemodynamic control purposes in a septal region where the maximum gradient and origin of VT were located. Even though septal ablation can be less effective in large scars and hypertrophies ≥ 30 mm, it can also be a successful procedure and replace myectomy in high risk patients or centers with low surgical experience with similar long-term mortality rates for both strategies. Bubble contrast echocardiography is effective to enhance the region perfused by the target branch with the corresponding lower use of alcohol and fluoroscopy. The ablation of VT in hypertrophic cardiomyopathy is successful in up to 80% of the cases²; however, sometimes its utility is limited because the ventricular wall is too thick and there is an unreachable deep intramural reentry circuit. Magnetic resonance imaging is useful in the electrophysiological search of the circuit and to help identify the size, location, and thickness of the scar. When radiofrequency ablation fails in the management of VT, as it was the case here, alcohol ablation can prevent recurrences and improve control.³ In conclusion, it is a good alternative to treat refractory VT during the management of hypertrophic cardiomyopathy.

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Pulmonary arteriovenous fistula as a possible cause for myocardial infarction



Fístula arteriovenosa pulmonar como posible causa de infarto de miocardio

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Figure 1.

Although the most common cause for coronary embolism is atrial fibrillation, we should take other conditions into consideration that, despite their low frequency of occurrence, need to be discarded to be able to establish a definitive treatment. Arteriovenous malformations like the case presented here are some of these conditions.

A 36-year-old woman with Rendu-Osler-Weber syndrome and recurrent and spontaneous epistaxis as the only personal medical history presented to the ER with oppression in her middle chest and pain radiating towards her left upper limb and back with concomitant vegetative symptoms. The electrocardiogram confirmed the presence of a subepicardial lesion in leads V2-V3 with high-sensitive troponin peak values of 9148 pg/mL.

A coronary angiography performed early confirmed the presence of a thrombus at the circumflex artery distal bifurcation (figure 1, arrow).

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Online: 05-02-2020.

<https://doi.org/10.24875/RECICE.M19000095>

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Figure 2.

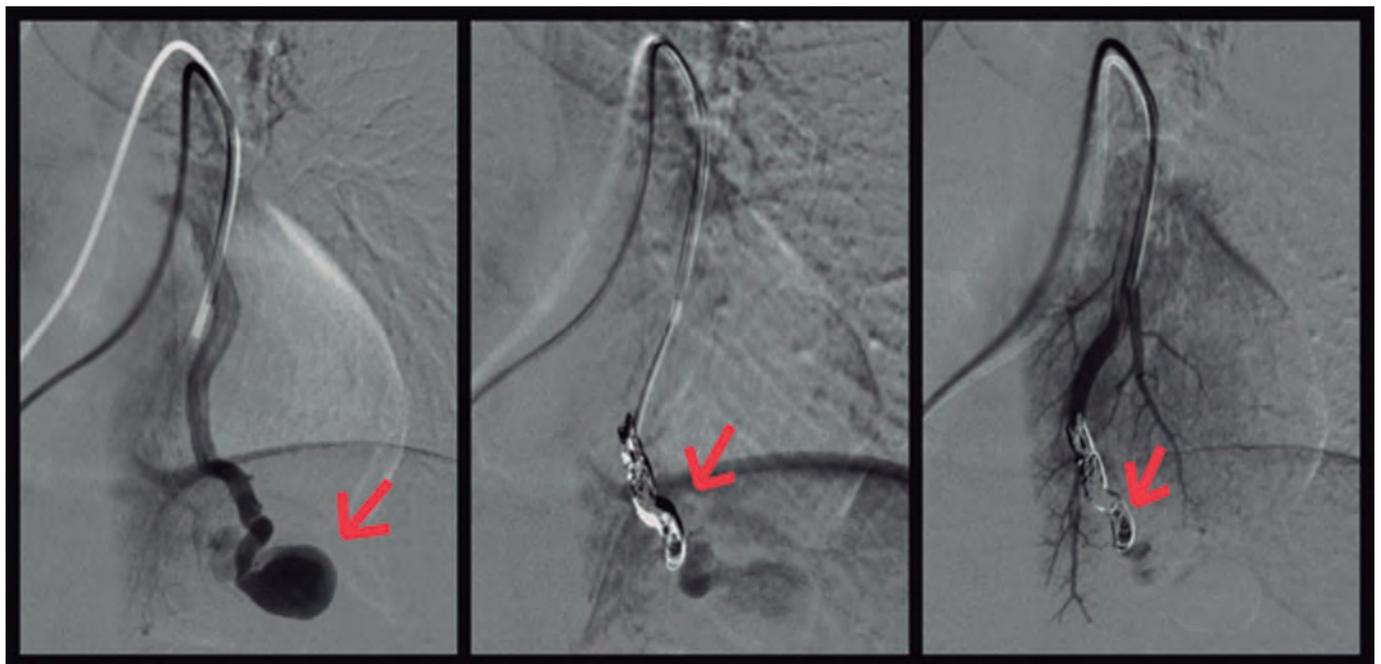


Figure 3.

To discard emboligenic source a Doppler ultrasound scan of the lower limbs was performed that revealed no signs of deep venous thrombosis. Given the patient's syndromic history, a thoracic computed tomography angiography was performed to look for pulmonary arteriovenous fistulas and found 2 of them: one located at the left pulmonary territory in the posterior basal segment (figure 2, arrow) and another smaller one in the homolateral lateral basal segment.

The interventional cardiovascular unit used selective microcatheterization of the segmental arteries afferent to the fistulas and coil embolization to close them (figure 3, arrows).

Percutaneous reconstruction of pulmonary trunk to solve stent embolization



Reconstrucción percutánea del tronco pulmonar para resolver la embolización de un stent

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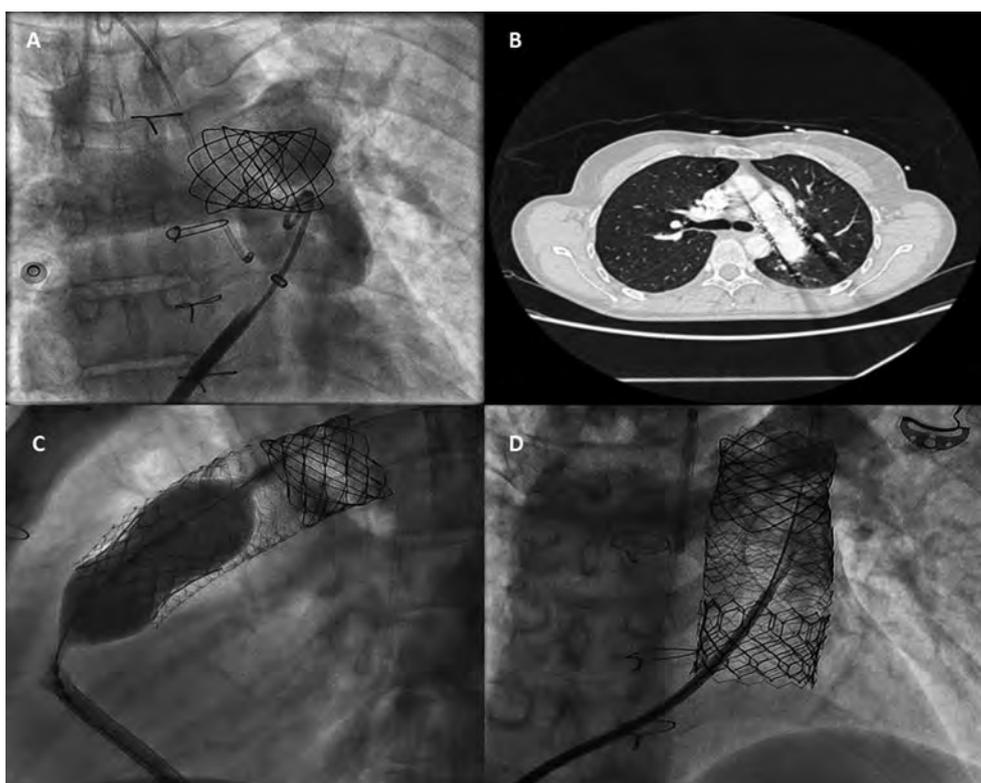


Figure 1.

A 48-year-old woman with congenital pulmonary stenosis who required surgical valvuloplasty in 1978 presented with progressive dyspnea. The cardiovascular magnetic resonance imaging performed confirmed the presence of dilated right ventricle, severe regurgitation, and pulmonary artery aneurysm (39 × 25 mm). The heart team decided to perform a transcatheter pulmonary valve implantation. During pre-stenting with an uncovered 15-25 mm × 47-55 mm CP Stent (NuMED, United States) mounted on a 25 mm balloon of the native right ventricular outflow tract, stent embolization with spontaneous anchoring to the left pulmonary artery occurred ([video 1 of the supplementary data](#), and [figure 1A](#)). Since the patient remained stable, a wait-and-see approach was decided to facilitate stent endothelialization. The stent ([figure 1B](#)) was used as the anchoring substrate 2 months apart of the proximal implantation for 2 longer Andrastent XXL 57 mm-stents (Andramed, Germany) on a 30 × 40 mm XL AndraBalloon to create a landing zone for the 29 mm

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Online: 27-01-2020.

<https://doi.org/10.24875/RECICE.M19000088>

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Sapien-3 valve. The rest of the procedure was successful (figure 1C). The patient remained asymptomatic, with no perfusion defects as confirmed by the ventilation/perfusion lung scan and a mean transvalvular gradient of 7 mmHg without any residual regurgitation at the 6-month follow-up (figure 1D).

In cases of aneurysmal pulmonary trunk and dilated native/non-calcified right ventricular outflow tract, the high risk of stent or valve migration may be prevented by the "planned" implantation of a first stent of smaller dimensions in a pulmonary branch. Then, sequential proximal stents may be anchored to this landing zone, which facilitates the reconstruction of pulmonary trunk with low risk of flow compromise in the jailed pulmonary branch. Further studies to assess this scenario are warranted.

CONFLICTS OF INTEREST

J.L. Zunzunegui is a proctor for Edwards Lifesciences.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M19000088>.

Use of radial access to create an arterio-arterial loop to facilitate the percutaneous closure of paravalvular aortic leak. Is it feasible?



Uso del acceso radial para crear un asa arterio-arterial para facilitar el cierre percutáneo de una fuga paravalvular aórtica. ¿Es posible?

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To the Editor,

Transcatheter paravalvular leak (PVL) closure through the implantation of occlusion devices has become an alternative to surgery.¹ The closure of aortic PVLs is usually performed through retrograde approach (via femoral artery and with echocardiographic and fluoroscopic guidance).² There are times that the antegrade approach is necessary (via femoral vein through transseptal puncture, rarely transapical approach). However, certain cases require additional support using an arteriovenous loop. This is often done through the snaring of a wire introduced into the left atrium with a catheter that is advanced through the interatrial septum (transseptal).³⁻⁴ We describe a non-reported approach so far: the transcatheter closure of paravalvular leak using an arterio-arterial loop by passing the wire through the bioprosthesis and using radial access to snare the wire.

An 89 year old male was examined in our hospital for dyspnea on exertion. He had a past medical history of surgical aortic valve replacement with a Hancock-II bioprosthesis (Medtronic, United States) back in 2013. The transthoracic echocardiography performed revealed the presence of severe aortic regurgitation. The transthoracic echocardiography (TEE) performed assessed the mechanism of regurgitation. The TEE confirmed the presence of a very eccentric, severely calcified and crescent shaped 6-7mm PVL located underneath the right coronary sinus (figure 1A,B).

According to the Society of Thoracic Surgeons risk calculator the estimated 30-day mortality surgical risk was 5.6% and the patient was considered mildly frail. The case was discussed by the heart team and a decision was made to use the transcatheter closure approach.

The closure of paravalvular leak was performed under general anesthesia and TEE guidance. The right femoral artery approach was used and the leak was crossed through the retrograde approach using a 5-Fr vertebral catheter and a hydrophilic guidewire. However, none of the catheters used (Judkins right 5-Fr, Multipurpose 5-Fr, Glidacath 4-Fr) could be advanced through the leak over the hydrophilic wire. It was decided to advance the hydrophilic

guidewire from the left ventricle, cross the biological prosthesis, and place it in the ascending aorta. The wire was snared using an 18-30 mm snare (EN Snare Endovascular Snare Systems, Inc., United States) advanced through the right radial artery. Thus, the arterio-arterial loop was created from the femoral artery and through the aortic leak, aortic bioprosthesis, and radial artery (figure 1C).

This extra support allowed the retrograde 5-Fr Torquevue sheath progression (figure 1D). A 10 × 5 mm Amplatzer Vascular Plug III device (Abbott Medical, United States) was successfully deployed. The TEE confirmed the good positioning and effective closure of the PVL (figure 1E and video 1 of the supplementary data). The patient was discharged 4 days later after treatment with dual antiplatelet therapy (aspirin and clopidogrel). The patient improved significantly at the 2-month follow-up and the transthoracic echocardiography performed revealed the presence of mild aortic regurgitation (figure 1F).

The aortic closure of PVL has been routinely performed using the retrograde approach and femoral access. When additional support is required, an arterio-venous loop can be performed. This requires femoral venous access, transseptal puncture, and snaring of the wire placed in the left atrium, which increases time and procedural complexity. However, in our case the arterio-arterial loop was created easy and fast through the radial access after the hydrophilic guidewire was placed in the ascending aorta. When the loop is created the support for the advancement of large sheaths grows significantly as our case confirmed and the occlusion device can be successfully deployed. It should be noted that these Amplatzer vascular plug III devices can be delivered through smaller sheaths (5- or 6-Fr), which is an important advantage of this occlusion device.

The percutaneous closure of aortic PVL using radial access to release the occlusion device has been reported here.⁵ In our case, due to the presence of a very eccentric, severely calcified, and crescent shaped leak, we decided to create the loop to increase support and advance the catheter to release the occlusion device. Another case of closure of aortic PVL using an arterio-arterial loop

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Online: 28-02-2020.

<https://doi.org/10.24875/RECICE.M20000101>

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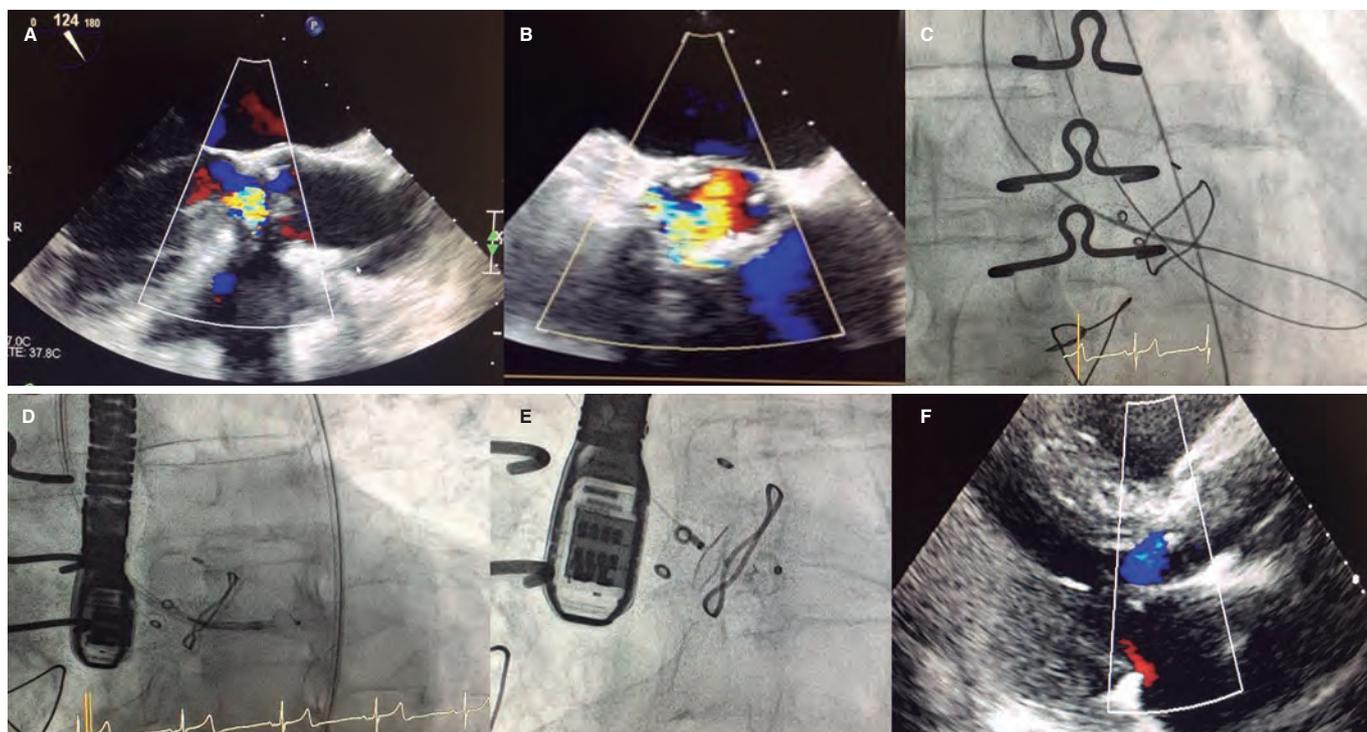


Figure 1. **A and B:** the transthoracic echocardiography X-plane view revealed severe aortic regurgitation from a crescent-shaped PVL located underneath the sinus of the right coronary artery in the anterior position and surrounded by mild aortic root calcification. Also, see video 1 of the supplementary data. **C:** arterio-arterial loop in the left ventricle using the radial access to create the loop. **D:** 5-Fr 90 cm sheath crossing the leak. **E:** 10 × 5 mm Amplatzer Vascular Plug III delivered. **F:** 2-month follow-up transthoracic echocardiography showing mild aortic regurgitation.

has been reported. Unlike our case, Estevez-Loureiro et al.⁶ performed the closure of an aortic PVL in a CoreValve transcatheter aortic valve implantation using an arterio-arterial loop through femoral access to create the loop and add extra support. While reducing vascular complications, radial access also provides a better angle for loop traction.

The use of an arteriovenous rail is well known among practitioners of complex structural interventions. This case illustrates a novel approach to create an arterio-arterial loop easy and fast through the radial access. This technique could be useful in other difficult structural heart interventions.

SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M20000101>.

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Transcatheter aortic valve implantation during the current COVID-19 pandemic. Recommendations from the ACI-SEC



Implante percutáneo de válvula aórtica durante la pandemia de COVID-19. Recomendaciones de la ACI-SEC

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To the Editor,

During the first few months of 2020, a severe acute respiratory syndrome outbreak due to coronavirus 2 (SARS-CoV-2) was announced worldwide. The WHO (World Health Organization) declared the global pandemic in March 11, 2020. After the United States, to this day Spain remains as the second country with the highest number of patients infected. Apart from the direct consequences of the coronavirus disease 2019 (COVID-19), the health-care system overload is negatively impacting the effective management of other severe conditions whose treatment can't wait.

During the current COVID-19 pandemic, patients with cardiovascular diseases are suffering diagnostic and treatment delays that are probably impacting cardiovascular mortality.¹ Scientific societies have issued several warnings on the management of the acute coronary syndrome and ST-segment elevation myocardial infarction.²

Symptomatic severe aortic stenosis (SSAS) has a poor short-term clinical outcome if untreated. As transcatheter aortic valve implantation (TAVI) has been established as the most common treatment option for the management of SSAS,³ recommendations on this therapy during the current pandemic are clinically relevant for physicians who are treating these patients.

In order to clarify how the COVID-19 pandemic may affect patients with SSAS who are eligible for TAVI the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) has issued the following 10 recommendations:

- In patients with SSAS > 70 who require treatment during the current COVID-19 pandemic, transfemoral TAVI should be the treatment of choice regardless of their surgical risk because this procedure is less invasive compared to the surgical aortic valve replacement. Also, it is associated with shorter hospital stays and a lower in-hospital COVID-19 infection rates.

- Patients eligible for TAVI are a high-risk population for COVID-19 infection mainly because they are older. For this reason, TAVI should be postponed in clinically stable patients with preserved left ventricular ejection fraction (figure 1).
- Stable patients with postponed TAVIs should be monitored closely (telemedicine can be useful) to detect any clinical destabilizations early and be able to act fast.
- In patients who need to undergo TAVI during the current pandemic, the procedure should be as minimalistic as possible (ie, without intubation or transesophageal monitoring) to shorten the hospital stay and minimize the risk of SARS-CoV-2 contagion.
- To reduce the need for new invasive procedures that could extend the hospital stay and increase the risk of SARS-CoV-2 contagion, devices that require fewer permanent pacemakers are advised.
- Try to minimize the rate of complications that could require additional procedures: vascular access should be assessed carefully and devices with small size sheaths should be considered (to avoid vascular complications). Also, special attention should be paid to prevent acute kidney injury from happening (avoiding the need for renal replacement therapy).
- In-hospital echocardiographic studies after the procedure should not be performed if deemed unnecessary to reduce the risk of COVID-19 infection at the echocardiography laboratory. A handheld echocardiographic device at the patient's bedside can be used to discard complications such as late pericardial effusion.
- If the procedure cannot be postponed for clinical reasons, always look for COVID-19 infection (polymerase chain reaction) before the procedure. If the polymerase chain reaction tests positive for COVID-19, the procedure should be postponed (figure 1).

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Online: 04-06-2020.

<https://doi.org/10.24875/RECICE.M20000137>

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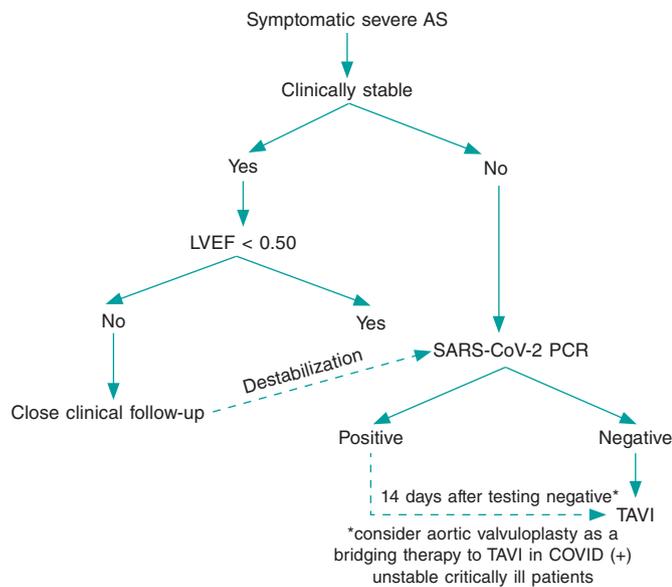


Figure 1. Proposed management of symptomatic severe aortic stenosis with TAVI during the current COVID-19 pandemic (Interventional Cardiology Association of the Spanish Society of Cardiology [ACI-SEC]). AS, aortic stenosis; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation; PCR, polymerase chain reaction.

- In patients with COVID-19 disease and a clear need for TAVI (asymptomatic COVID-19 disease with highly clinically unstable SSAS), the heart team involved in this procedure should be protected properly.⁴

- In critically unstable patients with COVID-19 disease in whom treatment for SSAS is contemplated, the percutaneous aortic valvuloplasty can be a valid option as a bridging therapy to TAVI.

CONFLICTS OF INTEREST

R. Moreno is associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. R. Moreno is a proctor for Acurate Neo, Lotus (Boston Scientific), and Allegra (New Vascular Therapy) valve devices. The remaining authors have not declared any conflicts of interest whatsoever.

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