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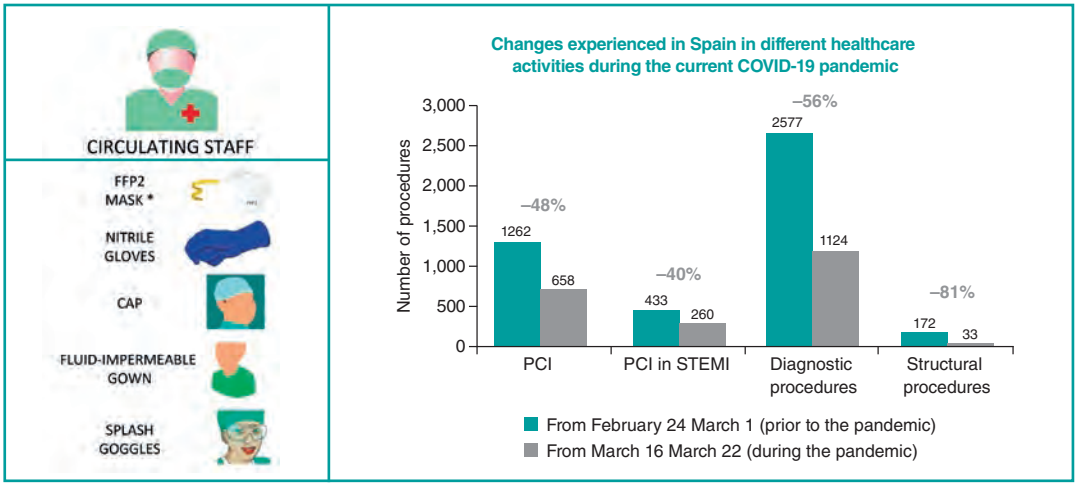

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Editorial

Emergence of a new technique to treat calcified coronary lesions

Ha surgido una nueva técnica para el tratamiento de lesiones calcificadas

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Over the last few years, the risk profile of patients referred to receive a coronary angiography has deteriorated and angiographic findings as well. Therefore, the progressive aging of the population and the development of better techniques to address the complexity of the different angiographic scenarios have conditioned the current situation of percutaneous coronary interventions. The balance between demand and supply in this field is in an ongoing expansion. The management of these delicate situations—which is often competence of cardiac surgery—requires profound knowledge of dedicated techniques and a precise clinical judgment.[1-3] This population is often discarded for coronary artery bypass graft surgery. There are times that even percutaneous treatment is denied because of a high clinical risk or unfavorable angiographic profile.

According to different series,[4] to this day complex calcified coronary lesions are a common finding in up to 25% to 30% of all percutaneous coronary interventions. De Maria et al.[5] published a review on the management of calcified lesions. They portrayed an accurate, contemporary big picture on the treatment of these lesions. The review basically focused on the technologies in intravascular imaging and tools available to solve today's technical complexities. The authors emphasize that today the objective of percutaneous coronary intervention when treating these lesions is to modify the plaque. If it fails to do so, the procedure is more likely to fail also in the clinical and technical aspects. Clinically because there would be more major complications, and technically because the result would compromise stent expansion and apposition, with the resulting increase in the rates of in-stent restenosis and thrombosis, etc.[6,7]

Intracoronary lithotripsy (ICL) is the latest technology available for the management of severely calcified lesions. Its mechanism of action has been well described in the document. Basically, ultrasound energy interacts with the atherosclerotic plaque causing vibrations that crack and tear the calcified components of superficial and deep layers. Compared to ablation techniques, since it is based on balloons, it is easy to use and there is a short learning curve. This, together with an early apparent evidence of efficacy, suggests that it will soon become the standard of care for the management of many severely calcified lesions. Similarly, this effect on deep calcium is an important benefit of ICL compared to other plaque-modifying techniques. Compared to rotational and orbital atherectomies, both of which reduce the plaque burden, ICL does not ablate or reduce it but cracks it supposedly improving stent apposition and expansion. The long-term follow-up will confirm whether this is enough to see long-term benefits.

In a recent article published in *REC: Interventional Cardiology*, Vilalta del Olmo et al.[8] commented on their first experience with an ICL device in a high-risk population. Their data provide useful information to assess the role, safety, and feasibility profile of ICL in high-risk patients not included in other studies. The authors report on procedural success and the short-term clinical outcomes of a non-randomized registry. The data published show the utility of ICL improving the clinical and angiographic results of complex patients with advanced, diffuse, multivessel, and calcified atherosclerotic disease. Their patients often presented with critical conditions such as acute coronary syndrome or left ventricular dysfunction.

Since they recruited their first patient, many things have changed and new information has come to light. By performing OCTs in 31 patients, Ali et al.[9] confirmed that ICL cracks the calcified arch in 43% of the patients with multiple fractures caused in over 25% of the cases. According to these authors, the efficacy of this technique is proportional to the burden of calcium with a higher rate of calcium fractures (77%) in cases with a higher degree of coronary calcifications. Serious safety issues or technical complications (coronary perforations, important dissections or slow flow/no reflow) have not been reported in the studies. Unlike former reports,[10] Vilalta del Olmo et al.[8] share encouraging data on a high-risk population with results that are as good as those from other authors.

Although the use of ICL has grown rapidly, the experience published on this device is limited, especially that coming from randomized clinical trials, and some considerations should be made on this regard. The first one is that the navigation capabilities of the device are an important limitation of this technique. Although Vilalta del Olmo et al.[8] reported that the ICL balloon crossing rate was 100%, our data show that 89% of the lesions required preconditioning with balloon angioplasty (62%) or rotational atherectomy (27%). Therefore, with the current design of the

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ICL device, in most cases a coadjuvant technique is required prior to the ICL so it can be used effectively which increases the cost of both procedures. Secondly, since the population of the Disrupt CAD II clinical trial[10] included stable patients with concentric lesions, the role of this technique in unstable patients and eccentric calcified lesions should be studied in a randomized controlled trial. Although it is a registry with a small sample size, the data from Vilalta del Olmo et al.[8] are encouraging on this regard. In the third place, life often outruns science. Although it is a friendly, easy to use technique, randomized clinical trials should be performed to select the patients and establish the indications. For instance, because of the simultaneous presence of compression and decompression forces (pull and push) and the fact that flow is compromised with ICL, its role should be studied in detail in different clinical and angiographic contexts like ST-segment elevation myocardial infarction, chronic total coronary occlusion via subintimal pathway, patients with pacemakers, etc. Other contexts suggested are patients with in-stent restenosis or to facilitate transfemoral access in patients with transcatheter aortic valve implantation. The fourth consideration to make is closely associated with the previous one and is inherent to any new technique: the lack of data on its use and long-term benefit. With the ICL rapid expansion we run the risk of using it in non-studied settings making it a useless and unsafe technique that may increase the rate of complications or lead to worse results. For example, a few isolated clinical cases have been reported on the role of ICL on in-stent restenosis due to stent underexpansion. The study conducted by Vilalta del Olmo et al.[8] did not report on any of this. Maybe the underlying mechanism of restenosis may explain the oberved differences (underexpansion, malapposition, neoatherosclerosis, etc.). Nevertheless, we still need time to study these issues in randomized and controlled clinical trials. ICL balloon tears have also been reported with the resulting added risk.[11] In the fifth place, a very important aspect is that ICL may complement other plaque-modifying techniques; its use is feasible and safe with different angioplasty balloons (non-compliant balloons, cutting balloons, and other), rotational atherectomy, etc.[12]

In conclusion, the ICL is a new, attractive, easy-to-learn and use technique for the management of calcified lesions. Randomized clinical trials and further data are needed to establish its indications and benefits. In the coming future this technique will probably simplify the complex procedures associated with percutaneous coronary interventions and improve the outcomes of patients.

CONFLICTS OF INTEREST

None reported.

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Editorial

Cardiovascular reparative and regenerative medicine: state-of-the-art

Medicina reparadora y regenerativa cardiovascular: estado de la cuestión

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INTRODUCTION

Therapies for the management of heart failure have been responsible for the great benefit experienced by the population in terms of hope and quality of life. However, they are nothing more than palliative measures that have not resolved the tissue destruction due to this problem whose malignity causes 20 million cardiac deaths worldwide every year.[1] Reparative and regenerative medicine was born over 2 decades ago as a biological response to the pressing need for innovation in this field. Its objective is to orchestrate diagnostic tools and therapeutic strategies to restore the molecular, cellular, and tissue health of the cardiac organs damaged.[2]

Although we can categorically say that the adult heart has a limited capacity for regeneration that depends on the formation of new cardiac muscle, endothelial and smooth muscle cells from a reservoir of existing heart stem cells,[3] we can also say that this capacity is marginal and insufficient to repair cardiac organs after sustaining ischemic, toxic, valvular or inherited damage,[4] even after physiological aging.[5] On the contrary, the myocardium major repair response consists of cellular hypertrophy, in some cases, and replacement of damaged functional tissue by more or less dense fibrous tissue (scar) in most cases. Process that causes the adverse ventricular remodeling that defines the advanced stages of heart failure (systolic ventricular disfunction and cardiac cavity dilatation) of both ischemic and non-ischemic origin (figure 1).

FUNDAMENTALS OF PATHOBIOLOGY AND PRECLINICAL EXPERIENCES

Ever since the 1990s, different types of cells have been studied in the lab in small and large animal models; in chronological order: skeletal myoblasts, hematopoietic end endothelial cells (in most cases harvested from the bone marrow), mesenchymal cells (harvested from bone marrow or adipose tissue), cardiac cells and, recently, embryonic or adult somatic induced pluripotent stem cells.[6] All these types of cells have been studied mostly in ischemic heart disease models. In some cases, they have been explored in their allogenic origin of healthy donors of the same species (unlike autologous stem cells that are harvested from the same recipient). As years have gone by, new products have appeared with regenerative or reparative capabilities. Added to gene therapy that has coexisted with cell therapy almost since the beginning, "non-cellular" products have been developed (growth factors, cytokines, proteins or types of ribonucleic acid—microARN). Many of them contained in microvesicles or exosomes that release stem cells or adult cells when they suffer an aggression. These products together with tissue engineering platforms (nanoparticles, gels, and matrices), have recently become part of regenerative medicine; and clinical research is still in its infancy.

Lab experiments and animal model experimentation have been useful because they have proved that: *a)* the process of myocardial and vascular repair is incredibly complex, both on the molecular, cellular, and tissue levels, which to this day, it is mostly unknown; *b)* the contribution made by cardiac stem cells to this process is marginal as it is the re-entry process of mature cardiomyocytes to the cellular cycle; *c)* the beneficial effects of the different products in the myocardium are due to the effect of the proteins and cytokines released by the cells administered (paracrine effect). They are not due to cellular fusion, proliferation or differentiation of these cells into cardiomyocytes, endothelial cells or smooth muscle cells (this has only been confirmed with pluripotent and embryonic cells that are still not used in clinical research); and *d)* these positive effects include protection from apoptosis, reduced fibrous tissue resulting from myocardial damage, modulation of the inflammation that precedes or is associated with such damage, creation of new blood vessels or formation of small amounts of cardiomyocytes (figure 1).

However, as in other areas of cardiovascular research,[7] there has also been a significant "translational gap" in regenerative medicine, and the closer animal research has been to human clinical features the lower the impact of the therapies applied. For example, a meta-analysis of 80 studies showed that in small animal models, the average reduction of the infarction size with different products was 11%.[8] However, in large animals, this reduction was only 5%, and it is well-known that in humans it is between 2% and 4%.[9] This discrepancy in the results obtained in animals and humans is partly explained by the complexity of cellular processes that regulate cardiac repair, the enormous size difference among species, and the amount of cells (or products) needed to revert it. Other areas with room for improvement and other concepts that require further study regarding preclinical research are doses, administration times, and combination of products. Lastly, the

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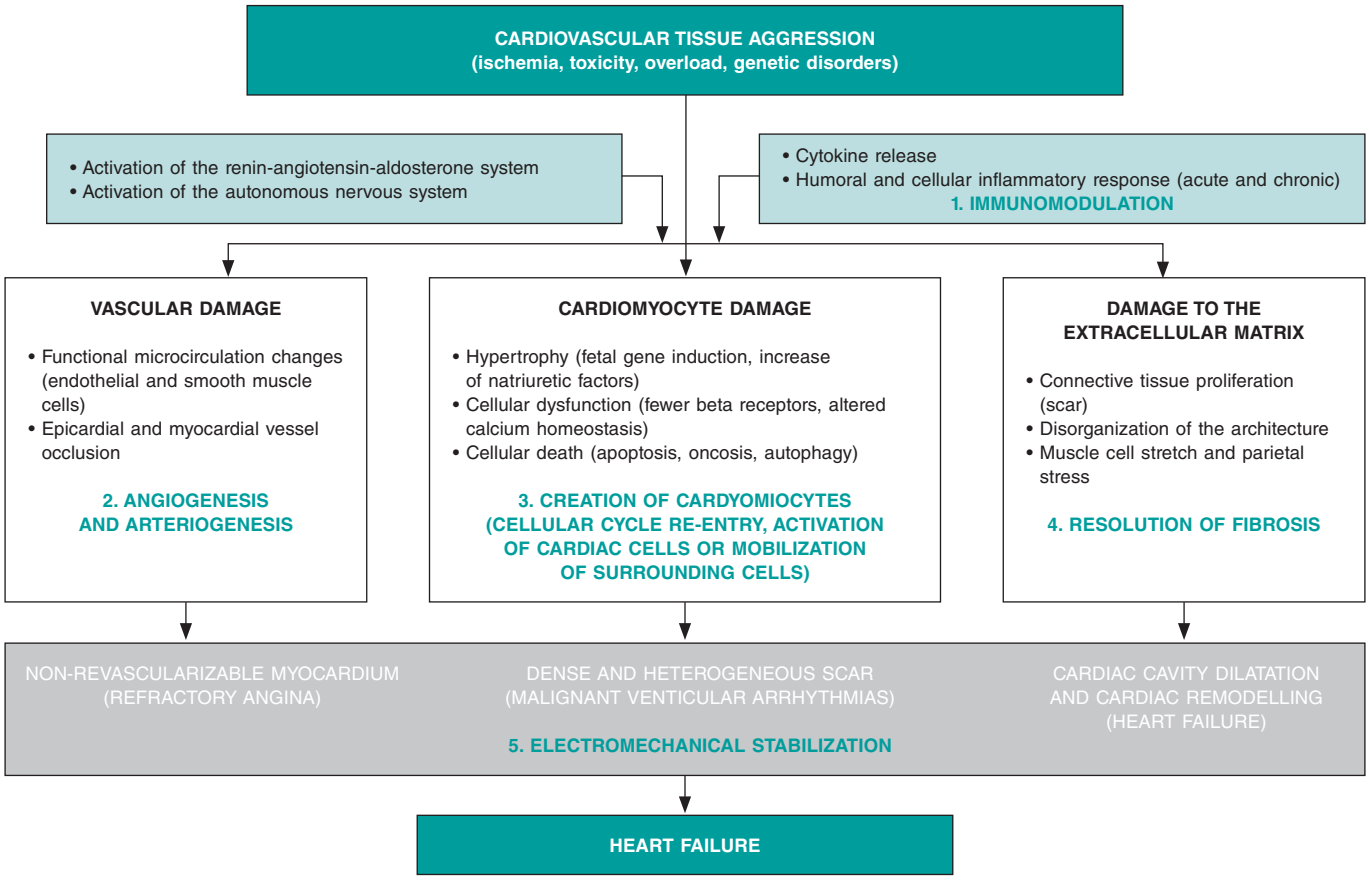

Figure 1. Common biopathological mechanisms indicative of myocardial damage in its vascular, muscular, extracellular components due to different types of tissue damage including the role of neurohormonal compensatory mechanisms and inflammatory response. The bottom shows the 3 main componentes of heart failure (angina, ventricular arrhythmias and ventricular remodelling). In green, the 5 beneficial action mechanisms confirmed by basic, preclinical research through which reparative and regenerative therapies work.

rigor of clinical research is not always thoroughly applied to animal research. This means that it is required to standardize animal models and protocols to obtain and prepare repair products and develop multicenter, randomized and previously registered studies.[2]

CLINICAL EVIDENCE

The pressing need for innovation in the management of heart failure promoted research in human regenerative therapies early on. Phase I and pilot studies would soon be followed by clinical trials with small numbers of patients. Some products reached phase III in clinical research, particularly in patients with acute myocardial infarction, refractory angina or ischemic and non-ischemic heart failure. Of all the evidence available to this day these conclusions can be drawn: *a)* except for exceptional well-identified cases (ventricular arrhythmias with initial cellular types), all products administered in humans have proven safe and no cases of rejection (not even with allogenic products), oncogenesis, worsening of the patients' cardiovascular status or major complications during the administration have been reported; *b)* the real clinical efficacy of these therapies has not been undeniably confirmed through hard endpoints. While some studies have shown neutral results, others have confirmed a reduction of the infarction size, increased myocardial perfusion or ejection fraction, and better soft endpoints; *c)* the most promising scenarios are heart failure with systolic ventricular dysfunction and refractory angina; and *d)* a large and very sophisticated array of administration strategies, including surgical, has been developed (mostly percutaneous) to allow the injection of biological materials in certain cardiac regions using conventional or special catheters and navigational systems to accurately guide the administration.

Like the preclinical setting, the clinical evidence available allows us to identify some of the variables that should be confirmed and better defined before conducting large-scale clinical trials; among them, the selection of the type of product, the total dose, and the optimal administration time for every particular condition. Also, comparative studies of products, repeated administration, and improvement of myocardial retention in the products infused or injected. All these aspects should be rigorously analyzed through basic and preclinical research before conducting new studies in humans. At this point, the rigorous design of clinical trials with well-defined endpoints, adequate sample sizes, and strict regulatory control should be mentioned here.

INTERNATIONAL ALLIANCES AND SPECIFIC WORKING GROUPS

As part of the development of regenerative medicine, and to go deeper in its study and organize and structure a still marginal research, 2 main organizations have been created:

- The international consortium TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes).[10] This consortium includes over top 100 international research working groups in this field. It is an worldwide, collaborative consortium network for the writing of position papers and recommendations, the rigorous promotion in all settings (scientific, institutional, and social), and for the design and development of coordinated and efficient clinical and preclinical research projects.

- The Working Group on Cardiovascular Regenerative and Reparative Medicine,[11] is part of the European Society of Cardiology (ESC). It is a dynamic body founded on the pillars of training, education, research, congress participation, and field support as defined by the ESC rules and regulations.

The common initial objective of both associations is to analyze the evidence available on cardiovascular regenerative and reparative medicine, establish future research lines, and ultimately, facilitate the development of therapies to improve the patients' cardiovascular health.

CONCLUSIONS

Although the clinical efficacy of regenerative and reparative medicine has not been confirmed yet to be able to include it in the routine clinical practice, it has overwhelmingly contributed to broaden our knowledge on the molecular biological, cellular, and tissue processes that govern functional loss, homeostasis, and cardiovascular system repair. By analyzing and planning future studies using multicenter, multidisciplinary, coordinated, evidence-based, rigorous methodology we will be closer to obtaining therapies capable of partially or totally reversing irreversible myocardial tissue damage and improving cardiovascular health.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever.

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Editorial

Health innovation in Spain. A real challenge, an actual need

Innovación sanitaria en España. Un auténtico reto, una auténtica necesidad

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Talking about innovation can be confusing. The term "innovation" is used to refer to many different things and proof of this is the large number of different definitions currently available. In any case, innovation is almost a magical word often hiding huge expectations of possible solutions to the great challenges posed by society and that have a dramatic impact on healthcare. We present some of the current trends and reflections affecting the Spanish healthcare system providers.

INNOVATION: GENERATING THE PRODUCT

At this point in time, talking about lists in relation to research and development (R+D) and its situation in Spain is an obvious and overused argument these days. Figures are well-known, have already been confirmed, are widely accepted, and have showed room for improvement over the last few decades: our country ranks high in research but runs low on R+D funding (high efficiency), especially in the private sector (mainly related to the business structure of small and medium-sized enterprises) but innovation still lags behind. Coming to terms with the specific weight of the different possible causes for this gap between research and innovation (culture, funding, education, regulation, etc.) is even harder.[1]

The impact of a disadvantaged situation in innovation is relevant: we do not invent, so we never own what we need (understood as a product manufactured and marketed by Spanish companies), which means we have to import it. Regarding health—where the impact of technology and drugs is huge—the effect the trade balance may have is considerable. Undubitably, this is a field where the activity of the Spanish healthcare system as a country that generates products, patents or companies may have a significant economic impact.[2,3]

INNOVATION: INTRODUCING THE PRODUCT

Advances in medicine are the key to improve disease management and prevention. The speed at which new products like drugs, devices, machines, diagnostic procedures, etc. are available is now greater than ever. These advances are considered innovation and they become part of the therapeutic arsenal available after an often very expensive process of development where proprietary companies make big investments. The cost of these new products is sometimes considerable and their benefits in terms of incremental net health benefit do not usually match costs and are often limited. Two examples of striking innovations that have recently impacted the media because of their potential cost are the CAR T-cell therapy and proton radiotherapy. Another recent example of great therapeutic innovation is the curative treatment of hepatitis C. The total artificial heart is unquestionably relevant innovation in cardiology. The developing speed of technologies like 3D printing, artificial intelligence, big data, digital health or tele-healthcare forces us to understand what they are good for before implementing them in health organizations and also to assess their impact in the system. In these innovations, price, complexity, conditions of use, and effects greatly condition their use.

INNOVATION: USING THE PRODUCT

Management experts have been anticipating the arrival of a sustainable prevention healthcare model for decades because of the constant growth of healthcare spending due to a number of reasons: higher costs in healthcare innovation, increased chronicity and longevity, and greater expectations from the population.

Patients live longer but they also remain sick longer, and every month of life gained equals higher costs. Although this statement has several exceptions, it forces us to identify those patients who can live disease-free for longer, or, at least, not dependant on the healthcare system. Also, it shows what innovations bring real value both in general and particular terms. Precision medicine and innovation in management play a big role. Both concepts can be considered a spectral continuum in the decision-making process. On the other hand, knowing that these innovations are cost-effective is no longer enough; now it is required to know what their real impact is on population health outcomes like quality of life and disease progression. This is how the Spanish healthcare system is moving forward with the great challenge posed by value-based medicine.[4]

INNOVATION: ORGANIZATION AND HEALTH PROFESSIONALS

There are 3 different scenarios regarding innovation: production, introduction, and use. These 3 settings require 3 different fields of

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expert knowledge —innovation manager, health professional, and healthcare manager— with significant overlapping that still coincides in information systems and new data management. In this context, the great expectations generated by big data and artificial intelligence should not be a surprise. These are true innovations to help us make decisions, prioritize efforts, speed up healthcare processes, reduce the load of tasks with no added value for health professionals, and eventually focus on personal attention.[5]

Beyond the traditional concept of product understood as technology—devices or drugs—healthcare providers have always been involved by generating solutions in their setting adapted to their working framework and using the existing resources based on process innovation. Healthcare providers can change the way things are done, most of the time intuitively, and then adapt them to their setting thanks to years of experience. They often give their opinion on current needs and possible solutions to different settings. They also happen to be right most of the time.

This may be an organizational innovation we must face: to hear what health professionals have to say to share the decision-making process with them. Also, to support them in complex priority decision-making processes caused by limited resources in a society with growing well-being demands. It is the healthcare institutions that need to move towards more intelligent and collaborative ecosystems to promote a culture of innovation. Innovative ideas have always been there; time has come to listen to the people who had these ideas, evaluate them rigorously, focus on the impact they have on health outcomes, and promote innovation.[6-8]

FUTURE PERSPECTIVES

The road towards innovation is a long one and changing the productive model and the culture of an entire country is a huge challenge. However, over the last few decades, it has been proven that we can change the Spanish model of producing science together. Why not do the same thing with innovation?

Let's give ourselves the time and opportunity to innovate in health, instead of letting others do the job. Let's be us who, with our own knowledge, improve our healthcare system, one of the world's most efficient healthcare systems now facing huge challenges ahead.[9]

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CONFLICTS OF INTEREST

None declared.

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Original article

Intracoronary lithotripsy in a high-risk real-world population. First experience in severely calcified, complex coronary lesions

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ABSTRACT

Introduction and objectives: Complex calcified lesions can affect stent expansion and lead to stent failure and adverse outcomes. Intracoronary lithotripsy (ICL) has emerged as a new tool that enables calcium modification. The Disrupt CAD II clinical trial has recently evaluated the safety and feasibility of ICL in patients with stable coronary disease and calcified coronary lesions. Although its use has increased rapidly, the experience already reported with this new device is limited. We report the results in real-life complex patients with heavy coronary calcification.
Methods: From October 2018 to March 2019, 25 patients (37 calcified lesions) were treated in 2 Spanish centers, which accounted for 2.7% of the patients treated with percutaneous coronary intervention.
Results: The device and clinical success rates were 84% and 95%, respectively. No procedure-related complications were seen. The crossing rate of the ICL balloon was 100% and balloon rupture during inflation occurred in 8%. The ICL was performed in a subset of highly complex lesions like left main coronary artery lesions and chronic total coronary occlusions. Compared to the Disrupt CAD II trial, our patients were younger but their clinical scenario was worse with a higher prevalence of diabetes (68%), renal failure (22%), and up to 76% suffered from acute coronary syndrome. The ICL failed to reach proper expansion in 3 out of 4 cases of stent underexpansion. The procedure was performed safely, and clinical and device success were high with no in-hospital mortality. One patient died of non-cardiac causes at the 30-day follow-up.
Conclusions: The ICL-assisted percutaneous coronary intervention was performed safely and effectively in a real-life cohort of patients with calcified and highly complex lesions.

Keywords: Lithotripsy. Calcium. Shockwave.

Litotricia intracoronaria en pacientes de la vida real: primera experiencia en lesiones complejas y gravemente calcificadas

RESUMEN

Introducción y objetivos: Las lesiones coronarias calcificadas pueden impedir una correcta expansión del *stent* que en ocasiones conduce a eventos adversos. La litotricia intracoronaria es una nueva herramienta de modificación de la placa, cuyas seguridad y viabilidad en pacientes con enfermedad coronaria estable han sido evaluadas en el ensayo Disrupt CAD II. Aunque su uso ha aumentado rápidamente, hasta el momento solo se han comunicado casos aislados en escenarios concretos. Se presentan los resultados en pacientes clínicamente complejos de la vida real con calcificación coronaria grave.
Métodos: Entre octubre de 2018 y marzo de 2019 se trató a 25 pacientes (37 lesiones) en 2 centros españoles, lo que representa el 2,7% de los pacientes tratados con intervención coronaria percutánea.
Resultados: Las tasas de éxito clínico y del dispositivo fueron del 84 y el 95%, y no se observaron complicaciones relacionadas con el procedimiento. En todos los casos se consiguió cruzar la lesión con el balón de litotricia intracoronaria, si bien en el 8% de los casos se rompió el balón durante el inflado. Se trataron con éxito lesiones complejas, como oclusiones coronarias totales y estenosis del tronco común. En comparación con el estudio Disrupt CAD II, nuestros pacientes eran más jóvenes, pero tenían peor

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escenario clínico, con mayor prevalencia de diabetes (68%) e insuficiencia renal (22%), y hasta el 76% se presentó como síndrome coronario agudo. En 3 de 4 pacientes con infraexpansión de *stent* tratados con litotricia intracoronaria no se consiguió una expansión adecuada tras el procedimiento. No hubo complicaciones ni mortalidad hospitalaria. Un paciente falleció por causa no cardiaca a los 30 días de seguimiento.
Conclusiones: La litotricia intracoronaria se ha demostrado efectiva y segura en una cohorte de pacientes complejos de la vida real con lesiones calcificadas.

Palabras clave: Litotricia intracoronaria. Calcio. Ondas de choque.

Abbreviations

CTO: chronic total coronary occlusion. **ICL:** intracoronary lithotripsy. **OCT:** optical coherence tomography. **PCI:** percutaneous coronary intervention.

INTRODUCTION

Percutaneous coronary intervention (PCI) in calcified coronary lesions is often challenging and may be associated with suboptimal stent expansion and apposition both related to stent failure due to stent thrombosis and in-stent restenosis.[1-3] The balloon angioplasty used in calcified lesions increases the risk of dissection of non-calcified segments usually without significant modification of calcified plaques and often without a proper luminal gain.[4] The management of this subset of lesions is complex and often requires complex techniques such as rotational atherectomy or excimer laser coronary atherectomy.

Intracoronary lithotripsy (ICL) (Shockwave Medical, Freemont, CA, United States) has emerged as a new tool to modify calcium by applying a diffuse acoustic pulse through a balloon inflated at 4 to 6 atmospheres without damage to endovascular soft tissues. The multicenter, prospective, single-arm Disrupt CAD II clinical trial[5] has recently evaluated the safety and feasibility of the ICL system prior to stent implantation in 120 patients with coronary artery disease and calcified coronary lesions. This study showed that the ICL appeared feasible with favorable initial success and complication rates in selected patients.[5] Although its use has grown rapidly among interventional cardiologists and there are many case reports on the medical literature available to us, the experience already reported on this new device is quite limited. We present the initial results of lithotripsy-assisted PCIs in a real-life cohort of high-risk patients with complex, calcified lesions.

METHODS

Patient population and data collection

Two-center, prospective, observational registry including all consecutive PCI cases that required ICL prior to stent implantation to the operator's discretion from October 2018 to March 2019. The baseline characteristics and procedural and in-hospital outcomes were prospectively recorded.

Intracoronary lithotripsy procedure

The ICL system is a portable and rechargeable generator connected to the ICL catheter. The catheter consists of a rapid exchange semi-compliant 12-mm balloon with 2 radiopaque emitters mounted inside available in 2.5, 3.0, 3.5, and 4 mm diameters. The catheter is compatible with a 6-Fr guiding catheter with a crossing profile range of 0.042 in and it is placed across the calcified lesion through a 0.014 in guidewire. Once in position, the balloon is inflated at 4 atmospheres to make intimate contact with the vessel wall and facilitate an efficient the transfer of energy. An electrical discharge from the emitters vaporizes the fluid inside the balloon generating sonic pressure waves that create a localized field effect. The ICL catheter is connected to a generator preprogrammed to deliver 10 pulses at a rate of 1 pulse per second. Each catheter can administer a maximum of 80 pulses. The sonic pulses through the soft vascular tissue cause selective microfractures at the intimal and medial calcium level of the vessel wall. After the pulse emission and the corresponding modification of calcium, the balloon is inflated up to 6 atmospheres to maximize luminal gain.

Definitions and outcomes

The use of the ICL catheter was based on the presence of a significant and severely calcified lesion (70% stenosis in an epicardial coronary vessel) on the angiography or intravascular imaging.

Coronary calcified lesions were defined by: *a)* the presence of radiopacities prior to contrast injection often involving both sides of the arterial wall; *b)* the presence of ≥ 270 degrees of calcium on at least one single cross-section on the intravascular ultrasound or optical coherence tomography (OCT); or *c)* subsets of calcified lesions with previous failed revascularization attempts.

According to the Disrupt CAD II trial criteria,[5] lithotripsy delivery was considered successful when it facilitated stent delivery with < 50% residual stenosis and without any serious angiographic complications like severe dissection, perforation, slow flow or persistent no-reflow. In addition, clinical success was defined as residual stenosis < 50% after stenting without any evidence of in-hospital adverse events. We also assessed procedural complications such as PCI-related myocardial infarction (type 4a myocardial infarction, defined according to the fourth universal definition of myocardial infarction),[6] and in-hospital and 30-day outcomes.

Statistical analysis

Categorical variables were expressed as number (percentage) and continuous variables as mean ± standard deviation or median according to their distribution. We analyzed all data using the STATA statistical package version 15.0 (StataCorp LP, College Station, Texas, United States).

Table 1. Baseline characteristics (per patient)

Clinical characteristics	N = 25
Age, years	71 ± 9
Male sex	17 (68)
Diabetes	17 (68)
Renal failure	7 (28)
Peripheral vascular disease	8 (32)
Previous PCI	14 (56)
Previous CABG	3 (12)
LVEF	49 ± 17
ACS on admission	19 (76)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
Data are expressed as no. (%) or mean ± standard deviation.

RESULTS

Patients

Between October 2018 and March 2019, 25 patients with 37 calcified lesions were treated, which amounted to 2.7% of the patients treated with PCIs in both centers. The baseline characteristics of the patients are shown on table 1. Mean age was 71 ± 9 years and 68% of the patients were males. The traditional cardiovascular risk factors were common and the vast majority of patients had undergone a previous revascularization (PCI or coronary artery bypass graft). The indication for PCI was acute coronary syndrome in most cases (76%), all of them non–ST-elevation myocardial infarctions.

Procedural characteristics

Procedural characteristics are shown on table 2. The mean SYNTAX score (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) was 19.3 ± 2, and the left anterior descending artery was the most-treated vessel. A non-negligible proportion of complex coronary artery lesions like chronic total coronary occlusions (CTO), bifurcation and ostial lesions, and stent underexpansion were also treated.

The ICL was used after a failed attempt of balloon pre-dilatation in 62% of the lesions, of which 10% showed balloon rupture. Ten lesions (27%) had previously been treated with rotational atherectomy. Only one lithotripsy catheter per lesion was required, and the mean number of pulses was 46 ± 19. The crossing rate of the lithotripsy balloon was 100% in pre-dilated and non-pre-dilated lesions, and the ICL balloon rupture occurred in 3 cases (8%) with no associated complications. An OCT prior to the ICL therapy was performed in a small percentage of cases (10%) to the operator's discretion. All stents implanted were drug-eluting stents and successful angiographic result according to the definition was achieved in 95% of cases.

Intracoronary lithotripsy in complex lesions

A subset of complex lesions was also treated with lithotripsy balloon (table 2). Success rate was 100% for left main coronary artery revascularizations, 100% for CTOs, and 86% for bifurcations.

Table 2. Procedural characteristics

Lesion characteristics	N = 37
Protected LMCA	1 (3)
Unprotected LMCA	4 (11)
LAD	17 (46)
LCx	3 (8)
RCA	12 (32)
Syntax Score	19.3 ± 2
Stent underexpansion treatment	4 (11)
Ostial lesions	13 (35)
Bifurcation lesion	13 (35)
CTO	3 (8)
Lesion severity by QCA	**N = 37**
Pre-PCI diameter stenosis	81.6 ± 2.5
Post-PCI diameter stenosis	15.9 ± 3.4
Pre-PCI area stenosis	84.6 ± 3.8
Post-PCI area stenosis	21.6 ± 3.5
Total lesion length, mm	20.7 ± 3
Mean luminal diameter, mm	0.77 ± 0.1
Procedural characteristics	**N = 25**
Radial access	15 (60)
Mechanical support Impella device	5 (20)
Fluoroscopy time, min	31.5 ± 4.8
Contrast, mL	212 ± 28
Number of vessels treated (per patient)	1.3 ± 0.5
Number of lesions treated (per patient)	1.7 ± 0.8
PCI characteristics	**N = 37**
Pre-ICL balloon pre-dilatation	23 (62)
Pre-ICL rotational atherectomy	10 (27)
Pre-ICL cutting balloon	2 (5)
ICL number of pulses	46 ± 19
ICL balloon rupture	3 (8%)
Number of stents implanted	1.2 ± 0.6
Stent diameter, mm	3.3 ± 1
Stent length, mm	23.1 ± 10
Angiographical success	35 (95)

CTO, chronic total coronary occlusion; ICL, intracoronary lithotripsy; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RCA, right coronary artery.
Data are expressed as no. (%) or mean ± standard deviation.

Left main coronary artery lesions

Five patients with left main *coronary artery* lesions were treated with the ICL balloon. Four were unprotected lesions and were treated under hemodynamic support using the Impella device (all of them showed a severely depressed ejection fraction and/or a right coronary artery chronic total occlusion). Device and clinical success were achieved in all cases.

Bifurcation lesions

Seven lesions treated involved bifurcations, 4 were treated using a provisional stenting technique, and 3 cases were treated using the 2-stent technique (V stenting).

Chronic total coronary occlusions

The CTOs of 3 patients were treated using the ICL with complete success in all of them. The first patient had a severely calcified aorto-ostial lesion in the right coronary artery, a Japanese chronic total coronary occlusion score (Japanese Multicenter CTO Registry) of 2 (presence of calcification ≥ 20 mm in length). After unsuccessful pre-dilation using 2 balloons (1 of them ruptured) the ICL was performed and good balloon expansion was achieved without need for post-dilatation prior to the stenting. The second successfully treated CTO case involved the mid portion of the left anterior descending coronary artery (bifurcation according to the Medina classification 1,1,1), Japanese CTO score of 2 (calcification ≥ 20 mm in length) that had been treated with rotational atherectomy prior to the ICL. The third case was the CTO of a distal right coronary artery involving bifurcation (according to the Medina classification 1,0,0) and a Japanese CTO score of 3 (blunt-tip entry, calcification ≥ 20 mm in length). The artery was dilated using 5 balloons, some of which ruptured before performing the ICL. Lesion expansion was completed with a cutting balloon after the ICL, which allwed proper stent implantation.

Stent underexpansion

Four cases of stent underexpansion were treated, but results after the ICL were only successful in one case. There was 1 case that needed additional very high-pressure balloon dilatation (up to 40 atmospheres) for proper expansion, and 2 cases that remained unexpanded even after very high-pressure balloon dilatation (up to 40 atmospheres), and in-stent rotational atherectomy with 1.75 and 2.00 mm burrs.

In-hospital and 30-day outcomes

The procedure was performed safely in all cases. Both the clinical and device success were high with no in-hospital mortality. One patient died of non-cardiac causes at the 30-day follow-up (sepsis due to spontaneous bacterial peritonitis in the presence of hepatic cirrhosis). Procedural, in-hospital, and 30-day outcomes are shown on table 3.

Table 3. In-hospital and 30-day outcomes

Clinical outcomes	N = 25
Procedural complications	
Dissection	0 (0)
Perforation	0 (0)
No-reflow	0 (0)
Type 4a acute myocardial infarction	3 (12)
In-hospital mortality	0 (0)
30-d myocardial infarction	0 (0)
30-d target-vessel revascularization	0 (0)
30-d stent thrombosis	0 (0)
30-d mortality	0 (0)
Cardiac death	0 (0)
Non-cardiac death	1 (4)

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

DISCUSSION

We present our initial experience with ICL in a cohort of real-life clinically complex patients with heavy coronary artery calcification and showed that the ICL is feasible with favorable initial outcomes and low complication rates.

Debulking techniques like rotational atherectomy, orbital atherectomy or excimer laser coronary atherectomy are commonly used to treat calcified coronary lesions. Back in 2018, in Spain up to 1517 patients were treated with rotational atherectomy and 88 with excimer laser coronary atherectomy.[7] Recently, the ICL has emerged as an attractive option for the management of patients with severely calcified coronary lesions. Nevertheless, the experience reported on this new technique is still limited. The recently published single-arm Disrupt CAD II clinical trial confirmed the safety and performance of ICL to treat calcified coronary lesions.[5] However, the clinical characteristics of the patients enrolled in this trial show a relatively low-risk population. Complex calcified coronary lesions are a common thing and they amount to 25% to 30% of all PCIs performed.[3] Among our population, 2.7% of patients were considered eligible to receive ICL therapy, indicative of a highly demanding indication criterion. Compared to the Disrupt CAD II clinical trial[5] our patients were younger but had a worse clinical scenario with a higher prevalence of diabetes (68% vs 32%) and renal failure (22% vs 9%), and up to 76% had suffered an acute coronary syndrome (none in the Disrupt CAD II trial). Another recent report described the initial experience with ICL in a cohort of 26 patients with calcified coronary lesions with findings for the clinical characteristics and results similar to the Disrupt CAD II.[8]

Regarding the procedure, it should be noted that the crossing rate for the ICL balloon was 100% despite a high percentage of plaque preparation was required (62% balloon pre-dilatation, 27% rotational atherectomy). Recently, the combination of rotational atherectomy and ICL has been described as RotaTripsy, suggestive that these 2 calcium debulking techniques may be complementary, since rotational atherectomy facilitates the ICL balloon crossing, and the latter facilitates proper expansion in the presence of circumferential deep calcium plaques.[9] The device success rate was 84% (100% in the Disrupt CAD II linical trial) and the clinical success rate was 95% (94% in the Disrupt CAD II trial). And most important of all, no major procedural complications were seen, which is consistent with the Disrupt CAD II trial results. The rupture of the ICL balloon during inflation occurred in 3 cases (12%) without associated complications, yet the rupture of the balloon has been described in a case report resulting in a type C coronary dissection; the interventional cardiologist needs to be aware of this lithotripsy-related potential complication.[10] Intravascular imaging were

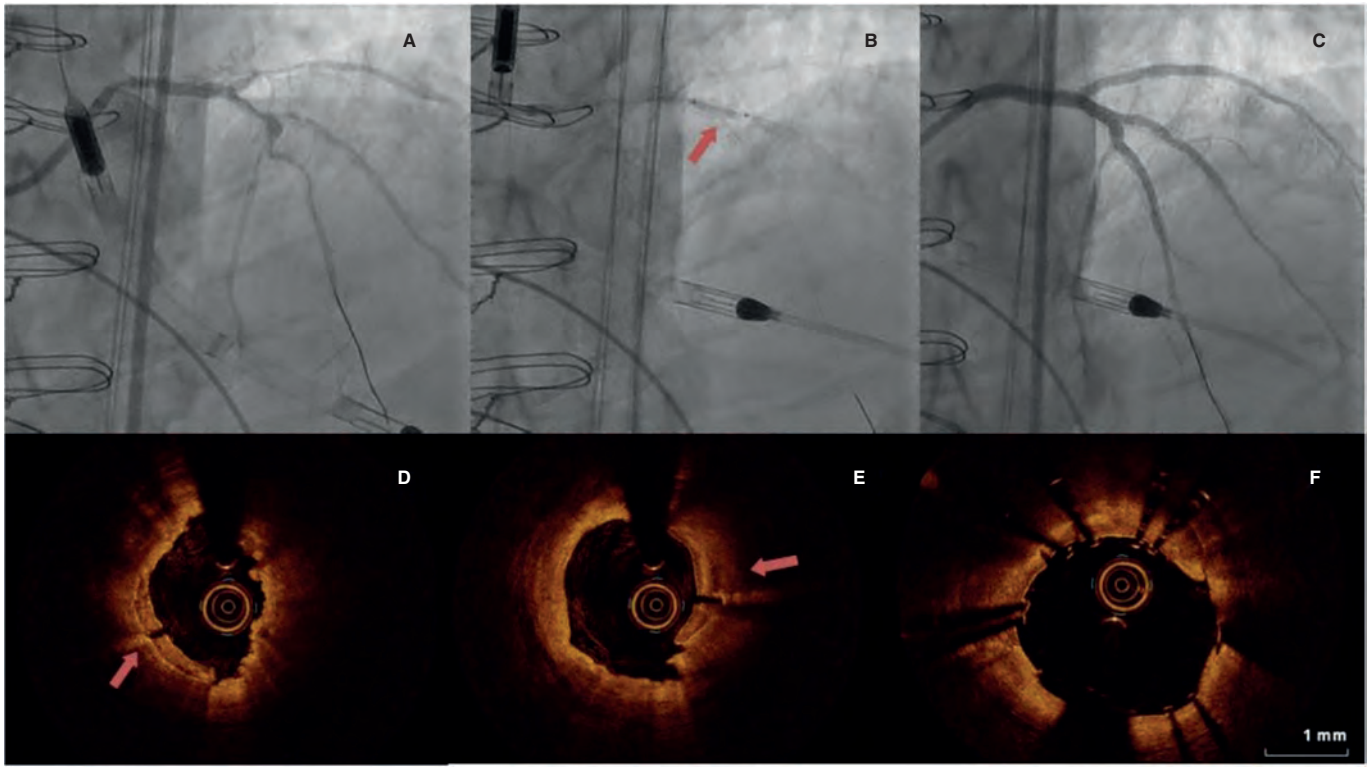

Figure 1. Intracoronary lithotripsy, angiography, and optical coherence tomography. Patient with severe coronary artery heart disease with severely depressed left ventricular ejection fraction previously treated with coronary artery bypass graft (venous graft-left anterior descending coronary artery, currently occluded). Treatment of left main coronary artery, left anterior descending artery, and diagonal branches. **A:** pre-intracoronary lithotripsy angiography. **B:** Impella-assisted PCI of left anterior descending coronary artery. Arrow indicates inflated lithotripsy balloon. **C:** successful final angiographic result after stenting. **D, E** and **F:** optical coherence tomography cross-sectional images of a post-lithotripsy calcified lesion. Red arrows indicate calcium microfractures after intracoronary lithotripsy.

performed in few cases probably because the operator thought it would be difficult to cross an especially severe and calcified lesion with the OCT or IVUS catheter. Consistent with the results of the Disrupt CAD I and II clinical trials and OCT substudy,[5,11] it was confirmed that the modification of calcium and the presence of fractures lead to an acute area gain and favorable stent expansion in the lesions assessed through OCT in our series. Figure 1 shows the coronary angiography and OCT of one complex patient treated with ICL; the red arrows seen on figure 1D,E indicate calcium fractures after the ICL.

We used the ICL in a subset of highly complex lesions like left main coronary artery stenosis, CTO, stent underexpansion, and bifurcation lesions.

Five complex patients with calcified left main coronary artery and severe stenosis were treated with ICL; mechanical support with the Impella device was needed in 4 patients due to a depressed left ventricular ejection fraction. Recently, a case report with 2 patients that were successfully treated with ICL in a left main coronary artery stenosis has also been published.[12] The ICL seems like a safe treatment option to treat calcified left main coronary artery stenoses even in technically complex cases that require hemodynamic support, a clinical scenario where the use of rotational atherectomy or excimer laser coronary atherectomy is rare.

Three patients with CTO lesions were successfully treated with ICL. Treatment of CTO with ICL has been previously described in 2 case reports. The first one was a patient with a CTO in the proximal right coronary artery. In this case, the ICL allowed the reverse controlled antegrade/retrograde tracking at the location of heavy calcification at the site of the chronic occlusion.[13] The second case was a patient with a proximal right coronary artery CTO due to heavily calcified in-stent restenosis. The ICL achieved good lesion expansion prior to stent implantation.[14] If performed properly, the ICL can be an alternative to other debulking techniques in heavily calcified CTO lesions to guarantee proper lesion expansion.

Several case reports of stent underexpansion due to heavily calcified lesions successfully treated with ICL have been reported recently.[15,16] Surprisingly, in our series the ICL failed to achieve proper stent expansion in 3 out of the 4 cases attempted. The management of stent underexpansion using ICL should be performed with extra caution because sound waves can damage the metallic structure of the stent.

The management of calcified bifurcation lesions is often complex due to the high risk of side branch occlusion when applying debulking techniques such as rotational atherectomy or excimer laser coronary atherectomy because the treatment cannot be performed using a guidewire for side branch protection purposes.[17,18] The ICL allows us to treat the main branch bifurcation with a guidewire in the side branch to guarantee quick access in case of flow impairment just like conventional procedures do.

Compared to atherectomy or specialty balloons, the ICL is said to offer several potential advantages[5] and requires no specific training as the device is delivered similar to the standard catheter-based PCI. ICL therapy is balloon based, and, therefore, the risk of atheromatous embolization may be lower compared to free debulking

devices; according to the Disrupt CAD I (19) or Disrupt CAD II trial[5] results, none of the patients from our series experienced no-reflow events and the rate of periprocedural myocardial infarction was relatively low. Whereas standard and specialty balloons are inflated at high atmospheric pressure to modify calcium, the ICL is typically performed at low atmospheric pressure balloon inflation, thus minimizing mechanical vascular trauma. Lastly, side-branch protection using a guidewire may be easily performed using ICL, without running the risk of wire entrapment or severing associated with rotational or orbital atherectomy. However, there is no evidence regarding stent restenosis of lesions treated with ICL therapy. New studies like the Disrupt CAD III trial that has just begun and will be recruiting up to 400 patients with a 2-year follow-up are needed to determine long-term outcomes.

Limitations

This 2-center experience using the ICL balloon has the limitations inherent to an observational study with a small sample size, which limits drawing conclusions especially in subgroups of high-risk lesions treated with ICL. However, in our opinion, it may contribute by adding more evidence supporting the use of ICL. This study did not have a comparison group either among existing plaque-modifying techniques.

CONCLUSIONS

In our own experience, the ICL-enhanced PCI was performed safely and effectively in a real-life cohort of complex patients with severely calcified and highly complex lesions.

CONFLICTS OF INTEREST

The authors of the manuscript declared no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Calcified lesions continue to be a challenge for interventional cardiologists since poor plaque preparation prevents proper stent expansion, which leads to a higher rate of periprocedural complications and long-term adverse events.
- The ICL balloon is a new plaque modification tool whose safety and efficacy in patients with stable coronary heart disease has recently been evaluated in a cohort of 120 patients in the Disrupt CAD II clinical trial.
- The use of the ICL balloon has grown rapidly in the cardiac catheterization laboratories. However, to this day extensive series in real-life patients have not been reported yet.

WHAT DOES THIS STUDY ADD?

- We present the results of the ICL balloon in real-life patients referred to undergo coronary angioplasty.
- Although the size of the sample in our series was not big enough to draw any conclusions, the patients included were clinically complex and a high percentage of acute coronary syndromes and technically complex interventions (left main coronary artery lesions, bifurcation lesions, CTOs and stent underexpansion) was reported.
- The procedure was performed safely and successfully in a large percentage of cases (95%). In-hospital mortality was zero and only one patient died at the 30-day follow-up (due to non-cardiac reasons).

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Original article

Impact of the COVID-19 pandemic on interventional cardiology activity in Spain

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ABSTRACT

Introduction and objectives: The COVID-19 epidemic and the declaration of the state of alarm have led to a decrease in healthcare activity in interventional cardiology units. The objective of this study is to quantify these changes in activity, with special interest in the treatment of patients with ST-segment elevation myocardial infarction (STEMI).
Methods: A telematic survey of 81 centers involved in STEMI networks in the 17 autonomous communities of Spain. Information was collected on diagnostic activity, percutaneous coronary intervention (PCI), structural interventions, and PCI in STEMI on changes in the organization of STEMI networks, and on the prevalence of COVID-19 among interventional cardiologists. Data was compared for the week of February 24 through March 1 (before the outbreak) and for the week of March 16 through March 22 (during the outbreak).
Results: Response has been obtained from 73 centers (90%). A very significant decrease in the number of diagnostic procedures (–56%), PCI (–48%), structural interventions (–81%) and PCI in STEMI (–40%) has been observed. A slight increase in the use of pharmacological thrombolysis has been reported, although primary angioplasty remains the leading reperfusion strategy. Up to 5% of interventional cardiologists (17) had COVID-19.
Conclusions: An important reduction in the activity in interventional cardiology has been observed during the COVID-19 epidemic. Likewise, a great decrease has been detected in the number of patients treated in the STEMI networks, with the risk of increased morbidity and mortality that this represents. Scientific societies and health authorities have to promote that patients presenting STEMI compatible symptoms proceed with no delay to access the health system to receive reperfusion treatment in an appropriate way.

Keywords: STEMI network. COVID-19. Primary angioplasty. Survey. Pandemic.

Impacto de la pandemia de COVID-19 sobre la actividad asistencial en cardiología intervencionista en España

RESUMEN

Introducción y objetivos: La epidemia de COVID-19 y la declaración del estado de alarma han propiciado una disminución en la actividad en la cardiología intervencionista. El objetivo de este estudio es cuantificar esta disminución, con especial interés en el funcionamiento del código infarto.

[◊] *Annex 1 shows the participant centers and researchers in charge of each particular center.*

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Métodos: Se realizó una encuesta telemática a 81 centros de las 17 comunidades autónomas españolas con procedimientos de código infarto. Se recogió información sobre la actividad diagnóstica, el intervencionismo coronario, el intervencionismo estructural y el intervencionismo en el seno del infarto agudo de miocardio con elevación del segmento ST (IAMCEST) sobre cambios en la organización de las redes del infarto y sobre la afección por COVID-19 de las plantillas de cardiología intervencionista. Se compararon 2 periodos: uno entre el 24 de febrero y el 1 de marzo (antes del inicio de la pandemia en Spain) y el otro entre el 16 y el 22 de marzo (durante la pandemia).
Resultados: Se obtuvo respuesta de 73 centros (90%) que evidenció una disminución significativa en el número de procedimientos diagnósticos (–56%), terapéuticos coronarios (–48%), terapéuticos estructurales (–81%) y en el seno del IAMCEST (–40%). Se indicó un leve incremento en el uso de trombolisis. Se diagnosticó infección por COVID-19 en 17 cardiólogos intervencionistas (5%).
Conclusiones: Se observó una reducción importante de la actividad asistencial durante la epidemia de COVID-19 y una gran disminución en el número de pacientes tratados con IAMCEST, con el riesgo de incremento de morbimortalidad que esto supone. Las sociedades científicas y autoridades sanitarias deberían promover que los pacientes con síntomas compatibles con IAMCEST demanden asistencia al sistema sanitario para poder recibir el tratamiento de reperfusión de forma adecuada.

Palabras clave: Código Infarto. COVID-19. Angioplastia primaria. Encuesta. Pandemia.

Abbreviations

ACI-SEC: Interventional Cardiology Association of the Spanish Society of Cardiology. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

The COVID-19 pandemic caused by the SARS-CoV-2 virus has seriously overloaded the Spanish healthcare system. On March 14, 2020 a national state of emergency was declared in Spain with a special call to house confinement in an attempt to stop the progression of the pandemic.[1] As a consequence, the management of other conditions, among them cardiovascular diseases, has changed. This can be especially significant when it comes to the urgent management of myocardial infarction that, in our country, has been the responsibility of specialized networks for quite some time with primary percutaneous coronary intervention as first-line therapeutic option.[2] The Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) has taken a proactive approach under the current circumstances with the publication of 2 consensus documents; on the one hand, a document on the invasive approach of ischemic and structural heart disease.[3] On the other hand, another document on the management of catheterization laboratories for the performance of cardiac invasive procedures.[4]

ACI-SEC Working Group on the Infarction Code has developed different actions to promote specialized networks for the management of myocardial infarction and percutaneous coronary intervention as first-line of therapy for patients with ST-segment elevation myocardial infarction (STEMI). One of the main actions taken is the Infarction Code Registry. During 2019 and for 3 months this registry collected data from 5241 consecutive patients in whom the infarction code had been activated in 81 public centers from specific care networks in the 17 Spanish autonomous communities. Using the specific infrastructure of this registry, ACI-SEC has conducted a survey to quantify the degree of damage caused by the COVID-19 pandemic to the catheterization laboratories of our country with special attention to how the infarction code actually works.

METHODS

A remote survey was conducted among 81 centers that participated in the Infarction Code Registry. Almost all centers were part of the specific infarction care networks (only one center did not participate in the survey). The survey was sent back on March 24 and answers were received until March 30; the content of the survey is shown on figure 1.

The primary objective can be divided into 3 main points: *a)* quantify the changes in the volume of patients assisted by the healthcare system: diagnostic procedures, therapeutic coronary interventional procedures, therapeutic procedures for the management of structural heart disease, and therapeutic procedures in the STEMI setting; *b)* assess the changes caused to the activity of the infarction code by the COVID-19 pandemic; and c) assess the impact of COVID-19 on interventional cardiologists health status and activity.

Data on the activity displayed were collected during the week of February 24 through March 1 (prior to the start of the pandemic in our country) and during the week of March 16 through March 22 (during the pandemic). We should mention that during the first week there was a local festivity in Andalusia (February 28) and in Canary Islands (February 25) and during the second week there was another local festivity (March 19) in the autonomous communities of Castile-La Mancha, Region of Murcia, Chartered Community of Navarre, Valencian Community, Basque Country, and Galicia.

RESULTS

Data from 73 centers were received (90% of the total). The nationwide overall data showed a significant reduction in the number of diagnostic procedures (–56%), therapeutic coronary interventional procedures (–48%), structural therapeutic procedures (–81%), and procedures performed in the STEMI setting (–40%). Overall data and data by autonomous communities are shown on table 1, table 2, table 3, table 4, and figure 2. The overall data for Spain is shown on figure 3.

From March 16 through March 22 a total of 40 centers (56%) followed a center specific protocol for the management of patients with COVID-19. On the other hand, in 13 centers (18%) a specific protocol from the infarction code network was followed for the management of patients with COVID-19.

Name of the center (fill in with hospital name):

Changes in the activity of the unit. Register the name of procedures performed each week

	Diagnostic procedures, n	Overall PCI, n	PCI in STEMI, n	TAVI, n	Occlusions (left atrial appendage, ASD, FOP, etc.), n	MitraClip, n
Week February 24 to March 1						
Week March 16 to March 22						

Changes in the Infarction Code Program affecting the center. Fill in box with an "x" Yes/No

	Yes	No
We did not see any major changes		
My center internal protocol on the Infarction Code and COVID-19 has been activated		
A protocol has been activated at AC level with respect to Infarction Code and COVID-19		
More thrombolysis performed since there is no guarantee of proper transfers in a timely manner		
More thrombolysis performed on cases with suspicion/confirmation of COVID-19		
More thrombolysis performed for elective treatments in patients who do not go to an AMI Code-capable center and need to be transferred		
More thrombolysis performed in all cases		
There has been a change in the volume of patients treated, so after pPCI (in my center), patients without complications were transferred to different centers (private, public, etc.)		
There has been a change in the volume of patients treated, so some selected cases that used to be performed in my center are now being transferred to a different hospital (private, public, etc.)		
There has been a change in the volume of patients treated, so the pPCIs that used to be performed in my center are now being transferred to a different Infarction Code-capable hospital (concentration of cases.)		

Medical personnel affected by COVID-19. Register the number of infected doctors in every situation and the overall number of doctors in the unit

	Number of infected doctors	Overall number of doctors in the unit
Some members of the medical team are on sick leave after diagnosis has been confirmed		
Some members of the medical team are on isolation due to close contact		
Some members of the medical team are not in the unit because they are assisting other patients with COVID-19		

Figure 1. Questionnaire filled out by each center. AC, autonomous communities; AMI, acute myocardial infarction; ASD, atrial septal defect; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; pPCI, primary percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; STEMI, ST-segment elevation myocardial infarction.

We saw a slight change in the indication for reperfusion treatment in 2 centers (in the Community of Madrid and the Basque Country) that indicated a greater use of thrombolysis due to the inability to transfer patients to the infarction code center in a timely manner; 4 centers (2 in the Region of Murcia, 1 in the Community of Madrid, and 1 in Aragon) reported a greater use of thrombolysis in cases of patients with suspicion or confirmation of COVID-19; finally 3 centers (1 in Aragon, 1 in the Community of Madrid, and 1 in the Region of Murcia) reported a greater use of thrombolysis for elective treatment in patients admitted to non-PCI centers and who required transfer to a different center.

Some hospitals reported a change in the management before percutaneous coronary interventions hadbeen detected, in such a way that in 14 centers (1 in the Community of Madrid, 8 in Catalonia, 1 in Castile and León, 3 in Andalusia, and 1 in the Balearic Islands) the patients treated with uncomplicated percutaneous coronary intervention were transferred to other centers for their follow-up; in 4 centers (2 in the Community of Madrid and 2 in Catalonia) some selected cases that used to be treated at the center were treated somewhere else; in 4 centers (1 in the Valencian Community, 1 in the Basque Country and 2 in the Community of Madrid) there was a change in the volume of patients to the extent that all cases of percutaneous coronary intervention that used to be performed at the center were performed somewhere else.

Finally, on the degree of infection of the interventional cardiologists who perform percutaneous coronary interventions, of a total of 339 healthcare workers 17 were infected with COVID-19 (5%), 10 needed isolation because they had been in close contact (3%), and 27 quit interventional cardiology related practices to assist patients with COVID-19 (8%).

DISCUSSION

The results of this study show a significant decrease of interventional cardiology procedures performed after the COVID-19 pandemic was declared in our country. The 40% decrease in interventional procedures performed in the STEMI setting is particularly disturbing. Also, we should mention here the implementation of local or regional protocols to assist these patients in many centers and, last but not least, the significantly high rate of contagion among healthcare workers. We anticipate that with the progression of the pandemic this activity will gradually drop in

Table 1. Variation in the number of diagnostic procedures performed by autonomous community*

Autonomous Community	Weekly diagnostic procedures performed prior to the COVID-19 pandemic	Weekly diagnostic procedures performed during the COVID-19 pandemic	Variation, %
Andalusia	460	254	–45
Aragon	68	31	–54
Principality of Asturias	87	34	–61
Balearic Islands	54	36	–33
Canary Islands	36	37	–23
Cantabria	42	9	–79
Castile-La Mancha	103	47	–54
Castile and León	141	63	–55
Catalonia	410	136	–67
Community of Madrid	327	102	–69
Chartered Community of Navarre	39	15	–62
Region of Murcia	70	48	–31
Valencian Community	342	134	–61
Basque Country	138	52	–62
Extremadura	77	36	–53
Galicia	161	81	–50
La Rioja	22	9	–59
Total	2577	1124	–56

* During the week prior to the COVID-19 pandemic there was a local festivity in the middle of the week in Andalusia (February 28) and Canary Islands (February 25) and during the COVID-19 pandemic week there was a local festivity in the autonomous communities of Galicia, Region of Murcia, Chartered Community of Navarre, Basque Country, and Valencian Community (March 19).

Table 2. Variation in the number of therapeutic coronary interventional procedures by autonomous community*

Autonomous community	Weekly therapeutic coronary interventional procedures before the COVID-19 pandemic	Weekly therapeutic coronary interventional procedures during the COVID-19 pandemic	Variation, %
Andalusia	240	152	–37
Aragon	35	23	–34
Principality of Asturias	36	16	–56
Balearic Islands	27	17	–37
Canary Islands	16	25	56
Cantabria	16	4	–75
Castile-La Mancha	64	18	–72
Castile and León	71	40	–44
Catalonia	209	94	–55
Community of Madrid	143	49	–66
Chartered Community of Navarre	14	6	–57
Region of Murcia	46	21	–54
Valencian Community	165	78	–53
Basque Country	60	38	–37
Extremadura	46	20	–57
Galicia	64	52	–19
La Rioja	10	5	–50
Total	1262	658	–48

* During the week prior to the COVID-19 pandemic there was a local festivity in the middle of the week in Andalusia (February 28) and Canary Islands (February 25) and during the COVID-19 pandemic week there was a local festivity in the autonomous communities of Galicia, Region of Murcia, Chartered Community of Navarre, Basque Country, and Valencian Community (March 19).

several centers and many more healthcare workers will be infected with COVID-19.

Back in 2018 a total of 21261 interventional procedures were performed in our country in the STEMI setting.[2] During the COVID-19 pandemic patients still suffer from STEMI. A recent study on the management of infarctions in Hong Kong, China during the COVID-19 pandemic showed that the time elapsed between the infarction until care was received delayed significantly with median times since symptom onset until the first medical contact of 318 min on average. In the cases managed before the pandemic, median time was only 82 minutes.[5] Our data confirm that added to this additional delay, there is a significant number of patients with STEMI who don't seek medical attention. The reason may be that they are afraid of being infected at the hospitals. This is especially worrying since many patients with STEMI end up with sudden death due to early ventricular fibrillation and never have the chance to be treated.[6] The remaining times until reperfusion—including in-hospital times—were also significantly delayed in the Hong Kong study.[5] We can expect something similar to happen here in Spain.

We are therefore faced with a very unfavorable scenario in patients with STEMI. On the one hand, many will not seek medical attention and, on the other , for those who seek it, time to reperfusion will be longer than usual. In this situation, STEMI driven mortality is expected to grow, due to an increase in sudden out-oh-hospital death and longer ischemia times. Besides, the lack of or the delay in reperfusion will increase the incidence of heart failure, cardiogenic shock, and infarct related mechanical complications.[7] Scientific societies and health authorities need to take strong action to minimize this excess of cardiovascular morbimortality that is expected during the current pandemic. The population needs to be told that seeking medical attention in health centers is safe, that protection against contagion is guaranteed, and that infarction-like symptoms or other serious conditions (strokes, pulmonary embolisms, aorta dissections) require urgent medical attention.

We cannot rule out the possibility that STEMI are being misdiagnosed in patients who go to the hospital seeking medical attention since the healthcare activity displayed these days is focused on the management of patients with COVID-19. Therefore, for staff who are working in the emergency services during this pandemic,

Table 3. Variation in the number of procedures in the STEMI setting by autonomous community*

Autonomous community	Weekly procedures in the STEMI setting before the COVID-19 pandemic	Weekly procedures in the STEMI setting during the COVID-19 pandemic	Variation, %
Andalusia	88	39	–56
Aragon	12	7	–42
Principality of Asturias	16	7	–56
Balearic Islands	8	5	–38
Canary Islands	2	8	300
Cantabria	6	3	–50
Castile-La Mancha	15	5	–67
Castile and León	23	12	–48
Catalonia	74	55	–26
Community of Madrid	55	29	–47
Chartered Community of Navarre	8	4	–50
Region of Murcia	7	9	29
Valencian Community	61	32	–48
Basque Country	13	14	8
Extremadura	13	2	–85
Galicia	28	25	–11
La Rioja	4	4	0
Total	433	260	–40

STEMI, ST-segment elevation myocardial infarction.
* During the week prior to the COVID-19 pandemic there was a local festivity in the middle of the week in Andalusia (February 28) and Canary Islands (February 25) and during the COVID-19 pandemic week there was a local festivity in the autonomous communities of Galicia, Region of Murcia, Chartered Community of Navarre, Basque Country, and Valencian Community (March 19).

Table 4. Variation in the number of structural interventional procedures by autonomous community*

Autonomous community	Weekly structural interventional procedures before the COVID-19 pandemic	Weekly structural interventional procedures during the COVID-19 pandemic	Variation, %
Andalusia	30	10	–67
Aragon	5	1	–80
Principality of Asturias	3	0	–100
Balearic Islands	9	0	–100
Canary Islands	0	2	-
Cantabria	2	0	–100
Castile-La Mancha	6	0	–100
Castile and León	15	5	–67
Catalonia	24	3	–88
Community of Madrid	29	1	–97
Chartered Community of Navarre	0	2	-
Region of Murcia	3	0	–100
Valencian Community	22	3	–86
Basque Country	9	1	–89
Extremadura	2	0	–100
Galicia	13	5	–62
La Rioja	0	0	-
Total	172	33	–81

The procedures included are transcatheter aortic valve implantation, appendage occlusion, closures of interatrial and intraventricular communications, foramen ovale, perivalvular leaks, mitral or tricuspid clip device.
* During the week prior to the COVID-19 pandemic there was a local festivity in the middle of the week in Andalusia (February 28) and Canary Islands (February 25) and during the COVID-19 pandemic week there was a local festivity in the autonomous communities of Galicia, Region of Murcia, Chartered Community of Navarre, Basque Country, and Valencian Community (March 19).

we should emphasise the importance of the correct and early diagnosis of STEMI. The best revascularization option today is still percutaneous coronary intervention that has consistently proven to reduce mortality, reinfarction, stroke, and mechanical complications compared to thrombolysis.[7] The ACI-SEC and the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology have both proposed an algorithm where percutaneous coronary intervention should be the treatment of choice. Also, patients with anticipated time delays until mechanical reperfusion should be treated with thrombolysis. Patients with COVID-19 who present at the hospital 3 hours before symptom onset who are hemodynamically stable and have no contraindication for thrombolysis should receive thrombolytic treatment.[3]

Another disturbing piece of information is the reduction in the number of non-emergent diagnostic and interventional procedures not related to STEMI being performed. These procedures will need to be rescheduled after the peak number of patients hospitalized with COVID-19 has been reached. Also, the lack of intensive care unit beds (most filled with patients with COVID-19) can reduce the capacity to perform cardiac surgeries and treat patients with surgical indications. This anticipates more interventional procedures being performed in complex patients who would have required surgical treatment in other circumstances.

Finally, we should mention that up to 5% of interventional cardiologists who participated in the infarction code program have presented COVID-19, in addition to those who remain under confinement or those who are attending COVID-19 patients outside the interventional cardiology units. This scenario is probably applicable to nurses and other healthcare workers at the cathlab. It is essential to protect all healthcare workers with the appropriate personal protection equipment to avoid exposure to COVID-19. Weekly shifts could also be established to reduce the risk of simultaneous contagion of several members of the unit

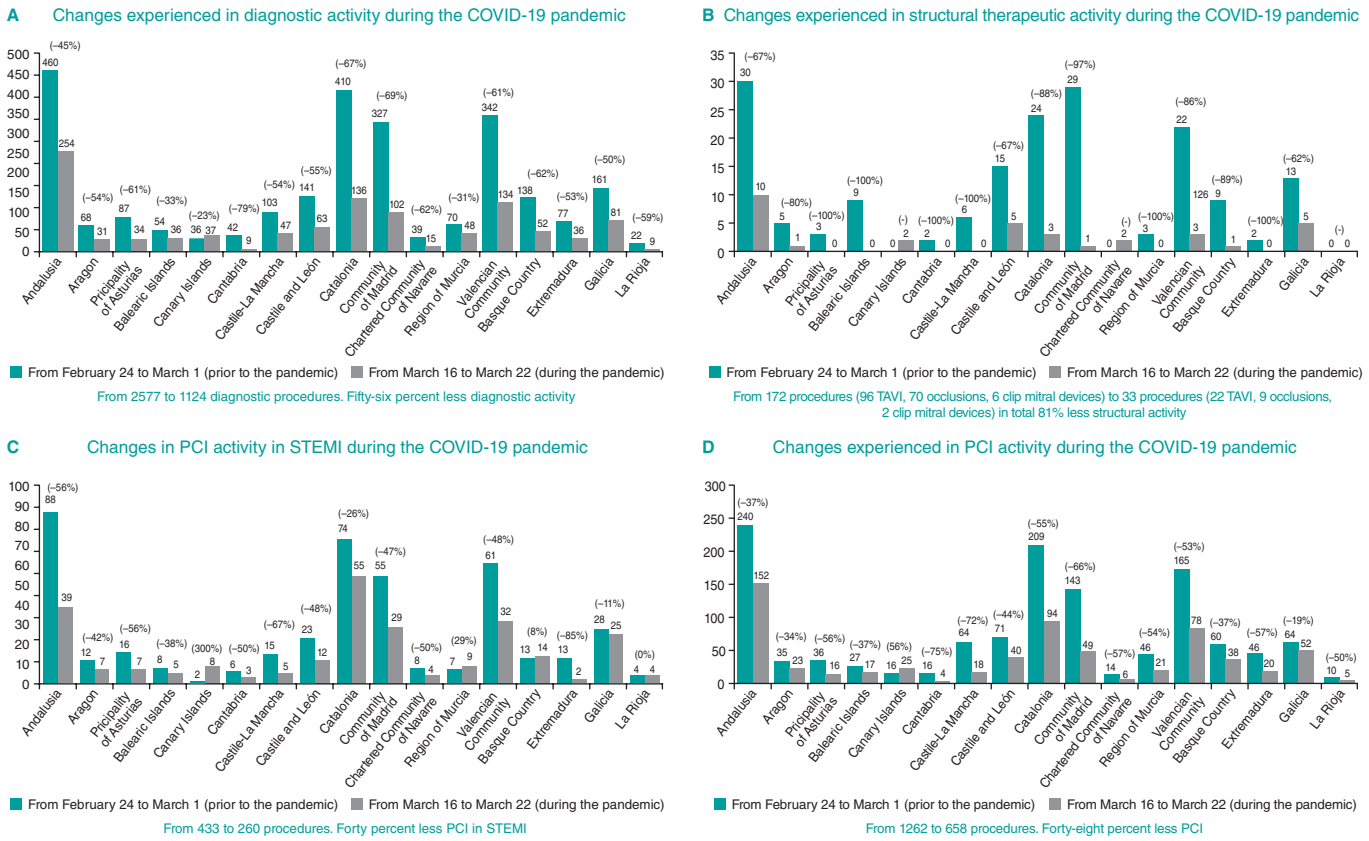

Figure 2. Changes experienced in Spain in different healthcare activities during the current COVID-19 pandemic on an AC basis. **A:** changes experienced in diagnostic activity; **B:** changes experienced in structural therapeutic activity; **C:** changes experienced in PCI activity in the STEMI setting; **D:** changes experienced in PCI activity. AC, autonomous communities; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TAVI, transcatheter aortic valve implantation.

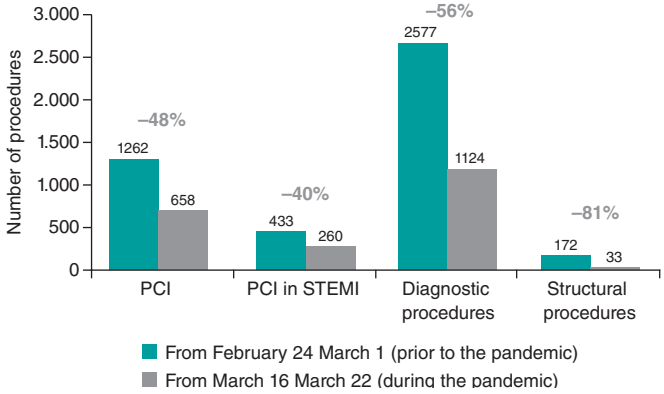

Figure 3. Changes experienced in Spain in different healthcare activities during the current COVID-19 pandemic. STEMI, ST-segment elevation myocardial infarction.

given that these procedures require a very high level of specialization and cannot be performed by other healthcare workers.

Limitations

Although this is a retrospective analysis, the parameters of activity have been well-established in all interventional cardiology units An important limitation is the unavailability of infarction assistance times, patients' clinical characteristics and in-hospital complications. However, as already mentioned, a study has confirmed that reperfusion times are being delayed significantly.[5] Another limitation is that some autonomous communities have had local festivities that may have altered the number of elective procedures performed. Even so, the great reduction of activity seen cannot be attributed to this fact alone since other autonomous communities without any local festivities have also seen their production reduced. Also, STEMI is managed independently regardless of whether there is a local festivity or not. Lastly, there are 8 centers whose activity has not been reported. In Canary Islands there is data for only 50% of centers. Despite the number, the volume of cases reported by those centers is low and only represents less than 5% of all percutaneous coronary interventions performed in the infarction setting.[2]

CONCLUSIONS

This study analyzes the significant reduction of healthcare in interventional cardiology that is being sustained during the current COVID-19 pandemic. Similarly, a great reduction in the number of STEMI patients treated has been observed with the corresponding risk of higher morbimortality. Scientific societies and health authorities need to take strong actionso patients with STEMI-like symptoms can seek medical attention and be properly diagnosed and receive reperfusion treatment.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest whatsoever. R. Moreno is associate editor of *Rev Esp Cardiol.* The journal's

editorial procedure to ensure impartial handling of the manuscript has been followed.

EDITOR'S NOTE

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.

WHAT IS KNOWN ABOUT THE TOPIC?

- Percutaneous coronary intervention is the treatment of choice for patients with STEMI. A recent study conducted in Hong Kong, China during the current COVID-19 pandemic showed it takes longer than usual for patients with infarction to seek medical attention after symptom onset. There is no information available on the number of patients treated during the pandemic compared to the number treated in normal conditions.

WHAT DOES THIS STUDY ADD?

- The COVID-19 pandemic has significantly reducedthe number of STEMI patients treated. Also, a significant reduction of elective coronary and structural procedures has been confirmed. This dramatic reduction in the performance of elective procedures may have an impact on future organization and care. Finally, yet despite how serious the current situation is, infarction code systems are still working adequately.

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Annex 1. Participant centers and researcher in charge in each particular center

Andalusia	
Hospital Universitario Virgen del Rocío	Manuel Villa
Hospital Universitario Virgen Macarena	Rafael Ruiz
Hospital Universitario Regional de Málaga	Carlos Sánchez
Hospital Universitario Virgen de la Victoria	Antonio Jesús Muñoz
Hospital Costa del Sol	Luís Iñigo
Hospital Universitario de Jaén	Juan Herrador
Hospital Universitario Juan Ramón Jiménez	Antonio Gómez
Hospital Universitario Virgen de las Nieves	Eduardo Molina
Hospital Universitario San Cecilio	Juan Caballero
Hospital Universitario Reina Sofía	Soledad Ojeda
Hospital Punta de Europa	Mérida Cárdenas
Hospital Universitario Puerta del Mar	Livia Gheorghe
Hospital Universitario de Jerez de la Frontera	Jesús Oneto
Hospital Universitario Torrecárdenas	Félix Valencia
Aragon	
Hospital Clínico Universitario Lozano Blesa	José Ramón Ruiz
Hospital Universitario Miguel Servet	Juan Sánchez Rubio
Principality of Asturias	
Hospital Universitario Central de Asturias	Pablo Avanzas
Hospital de Cabueñes	Juan Rondan
Balearic Islands	
Hospital Universitari Son Espases	Vicente Peral
Policlínica Nuestra Señora del Rosario	Lucía Vera
Canary Islands	
Hospital Universitario de Canarias	Francisco Bosa
Hospital Universitario Ntra. Sra. de Candelaria	Julio Hernández
Cantabria	
Hospital Universitario Marqués de Valdecilla	José María de la Torre Hernández

(Continued)

Annex 1. Participant centers and researcher in charge in each particular center *(continuation)*

Castile-La Mancha	
Complejo Hospitalario de Toledo	José Moreu
Hospital General de Ciudad Real	Fernando Lozano
Hospital General Universitario de Albacete	Jesús Jiménez
Hospital Universitario de Guadalajara	Enrique Novo
Castile and León	
Hospital de León	Armando Pérez de Prado
Hospital Clínico Universitario de Valladolid	Ignacio Amat
Hospital Universitario de Salamanca	Ignacio Cruz
Catalonia	
Hospital Universitari Bellvitge	Joan Antoni Gómez
Hospital de la Santa Creu i Sant Pau	Joan García Picart
Hospital Universitario Vall d'Hebrón	Bruno García
Hospital Clínic de Barcelona	Salvatore Brugaletta
Hospital Universitari Germans Trias i Pujol	Oriol Rodríguez
Hospital del Mar	Neus Salvatella
Hospital Universitari Joan XXIII	Mohsen Mohandes
Hospital Universitari de Girona Dr. Josep Trueta	Xavier Oliva
Hospital Universitari Arnau de Vilanova	Joan Casanova
Hospital Universitari Mútua de Terrassa	Juan Francisco Muñoz
Community of Madrid	
Hospital Universitario Fundación Jiménez Díaz	Juan Franco
Hospital Clínico San Carlos	Pablo Salinas
Hospital General Universitario Gregorio Marañón	Jaime Elízaga
Hospital Universitario 12 de Octubre	Fernando Sarnago
Hospital Universitario La Paz	Santiago Jiménez
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Original article

Multicenter experience with a second-generation fully-retrievable and repositionable transcatheter aortic valve

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ABSTRACT

Introduction and objectives: The Lotus Valve device (Boston Scientific) is a second-generation fully-retrievable and repositionable transcatheter aortic valve. We report the initial multicenter experience with the Lotus valve in the management of patients with severe aortic stenosis.
Methods: Observational study that described the short and long-term results of implanting the Lotus valve in 8 Spanish and Portuguese centers from March 2014 through April 2016.
Results: The study included 102 patients (mean age 80.4 ± 6.1 years; STS score 5.2% ± 3.3%) with severe symptomatic aortic stenosis (mean aortic valve area 0.66 ± 0.17 cm^2, aortic gradients 74.3 / 45.6 mmHg). The valve was successfully implanted in 100 patients (98%), with significant improvement in both the peak and mean aortic valve gradients and with only one patient showing moderate paravalvular regurgitation. Upon hospital discharge, mortality rate was 3.9% while the stroke rate was 2.9%. No cases of valve embolization, ectopic valve deployment or additional valve implantation (valve-in-valve) were seen. Thirty-three patients (32.3%) received a permanent pacemaker.
Conclusions: The Lotus Valve System is effective and safe for the management of patients with severe symptomatic aortic stenosis. In particular, considering the low rate of periprosthetic regurgitation and lack of complications like embolization or ectopic valve deployment; however at the expense of a high pacemaker implantation rate.

Keywords: Transcatheter Aortic Valve. Aortic Stenosis.

Experiencia multicéntrica con prótesis valvular aórtica transcatéter de segunda generación reposicionable y recuperable

RESUMEN

Introducción y objetivos: El dispositivo Lotus (Boston Scientific, Estados Unidos) es una prótesis valvular aórtica transcatéter de segunda generación, completamente recuperable y reposicionable. Se presenta la experiencia inicial con la prótesis Lotus en un registro multicéntrico.
Métodos: Estudio observacional que reporta los resultados a corto y largo plazo del implante transfemoral de prótesis Lotus entre marzo de 2014 y abril de 2016 en 8 centros de España y Portugal.
Resultados: Se incluyeron 102 pacientes (edad media 80,4 ± 6,1 años, índice STS medio 5,2% ± 3,3%) con estenosis aórtica grave sintomática (área valvular media 0,66 ± 0,17 cm^2, gradientes 74,3/45,6 mmHg). Se implantó con éxito el dispositivo en 100 pacientes (98%), con mejoría significativa de los gradientes máximo y medio valvular, y un solo caso de regurgitación periprotésica moderada. No hubo ninguna embolización ni necesidad de implante de una nueva prótesis intravalvular. Hasta el alta hospitalaria, la mortalidad fue del 3,9% y la tasa de ictus fue del 2,9%. En 33 pacientes (32,3%) fue necesario el implante de marcapasos definitivo.

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Conclusiones: La válvula Lotus es eficaz y segura para el tratamiento de pacientes con estenosis aórtica grave sintomática. Destacan la escasa tasa de insuficiencia periprotésica y la ausencia de complicaciones derivadas del mal posicionamiento o la embolización de la prótesis, a costa de un alta incidencia de implante de marcapasos.

Palabras clave: Prótesis aórtica transcatéter. Estenosis aórtica.

Abbreviations

AR: aortic regurgitation. **AS:** aortic stenosis. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a therapeutic option in patients with severe symptomatic aortic stenosis (AS) that has proven to be non-inferior to surgical aortic valve replacement even in low-risk patients.[1-8]

However, TAVI-related persistent complications can have a negative impact on the short and medium-long-term results including periprosthetic aortic regurgitation (AR)—associated with more in-hospital and medium and long-term mortality after TAVI.[9-12] Several factors have been associated with the development of periprosthetic regurgitation like valve underexpansion following the severe calcification of the aortic annulus or valve malapposition. The latter is a factor associated with other complications like valve embolization. In order to minimize these setbacks, innovative, second-generation, fully or partially repositionable devices have been developed.

The Lotus device (Boston Scientific, United States) is a fully retrievable and repositionable second-generation transcatheter aortic valve. It has been designed to minimize the risk of complications related to valve malapposition, in particular periprosthetic AR and valve embolization.[13]

The objective of this study is to present the initial experience in Spain and Portugal in the management of AS with the Lotus valve.

METHODS

Patient selection

This observational study included all consecutive patients with severe AS treated with transfemoral Lotus valve implantation between March 2014 and April 2016 in Spanish and Portuguese centers that disclosed their databases voluntarily. All patients had symptomatic, severe AS (aortic valve area < 1 cm^2) or with left ventricular dysfunction according to the recommendations from the European Society of Cardiology guidelines on the management of valvular heart disease;[14] in any case, the indication was established according to the local protocols of each center after each particular case was individually assessed by the heart team. Surgical risk was assessed using the STS risk score.[15] However, its value was not considered an inclusion or exclusion criterion in the registry because in the selection of patients, clinical and anatomical aspects not found in the surgical risk scores were also considered (porcelain aorta, patency of mammary artery bypass graft, hostile chest, etc.).

Study variables

The patients' main baseline clinical and echocardiographic variables, procedural details, and clinical and echocardiographic results until hospital discharge were gathered. Special attention was paid to peri- and postoperative complications. Data mining was prospective in every center, although there was no common protocol for it or for the allocation of clinical and echocardiographic results. Each center disclosed its own database and they were all compiled in a single database.

The clinical assessment and diagnostic tests prior to the implant were similar to those of common recommendations.[14] A few variables were not systematically collected in all the centers and, therefore, not included in the study final analysis.

Regarding procedural data, the main variables studied were the performance or not of a prior valvuloplasty, the device total or partial recapture, the need for post-dilation, the degree of valvular regurgitation, and postoperative transvalvular gradients. Finally, a comparison was drawn between mean and peak gradients and the prevalence of moderate AR before and after device implantation.

Procedural complications were gathered according to the recommendations established in the Valve Academic Research Consortium 2 consensus document.[16] The following complications were analyzed: mortality, strokes, hemorrhagic complications, major and minor vascular complications, definitive pacemaker implantation, renal failure, echocardiographic data suggestive of prosthetic valve dysfunction (mean valve gradient > 20 mmHg, effective valvular area < 0.9-1.1 cm^2, Doppler velocity index < 0.35, and moderate or severe AR). The combined efficacy parameter used this definition established according to the criteria of the Valve Academic Research Consortium 2: proper single valve implantation + lack of in-hospital mortality + lack of mean gradient > 20 mmHg, aortic valve area ≥ 1.2 cm^2, Doppler velocity index < 0.35 or moderate or severe AR. The combined initial safety parameter (until hospital discharge) was defined as: lack of all-cause mortality, stroke, life-threatening bleeding, stage 2-3 renal failure, coronary obstruction requiring intervention, major vascular complication or valve dysfunction requiring reintervention.

Finally, patients were followed retrospectively 3 years after finishing the registry recruitment phase, and clinical (mortality and cardiovascular events) and echocardiographic parameters were collected.

Boston Scientific has not been involved in the design or development of this study whatsoever.

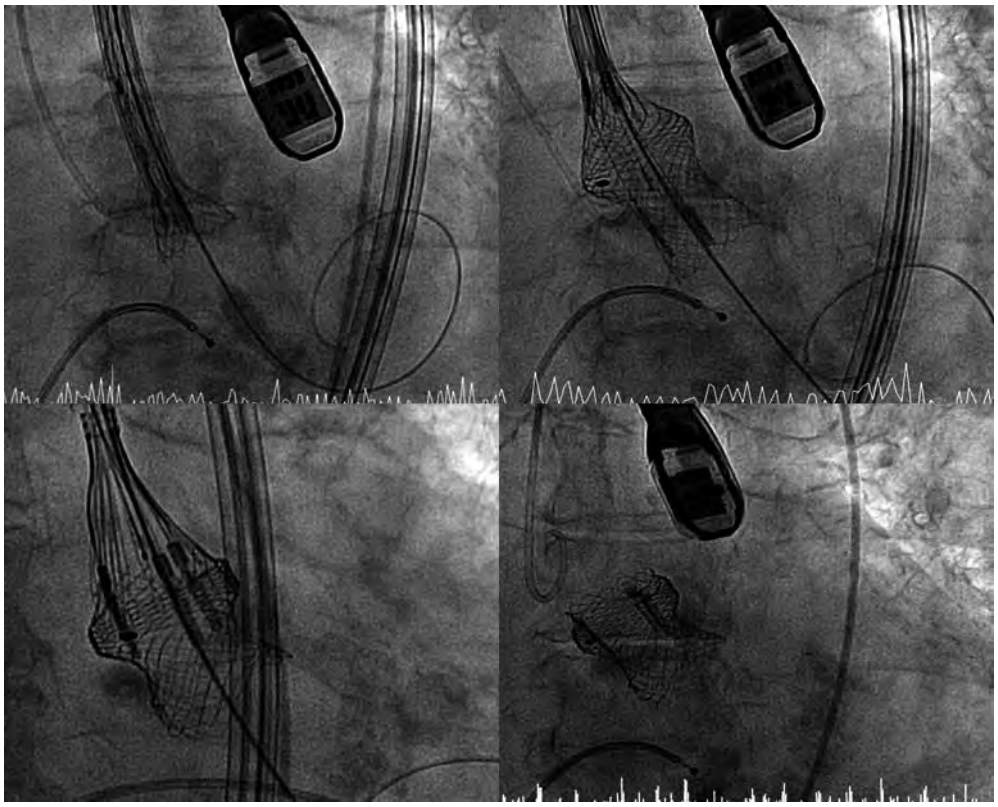

Figure 1. Lotus valve implantation procedure.

Description of the device

The Lotus device used in the registry is a bovine pericardial heart valve (3 cusps) mounted on a nitinol frame, preloaded, and deployed through a controlled mechanical expansion system. It measures 72 mm before expansion and 19 mm after implantation. There are 3 diameters available: 23 mm, 25 mm, and 27 mm. The Lotus Edge valve available today has a more flexible deployment catheter, an easier implantation system, and can be implanted through a 14-Fr expandable introducer.

The delivery system and the introducer sheath have been designed to facilitate a precise and predictable delivery to guarantee the valve early functionality, and the possibility of non-traumatic repositioning and retrieval at any time prior to the definitive delivery of the valve. The device has a sealing system (urethane membrane) designed to minimize the rate of paravalvular regurgitation.

Procedure

Implantation was performed according to the method described in the medical literature.[13] It was performed in the cardiac catheterization laboratory under general anesthesia or deep sedation, in a sterile environment, following the operator's preferences, and with or without transesophageal echocardiography guidance.

Transfemoral access was used in all cases using a fully percutaneous technique or surgical exposure. An 18-Fr introducer was advanced for the 23 mm-valve (minimum diameter required: 6 mm) and a 20-Fr introducer for the 25 mm and 27 mm-valves (minimum diameter required: 6.5 mm) towards the descending aorta. The native aortic valve was crossed using the routine technique. Before using the guidewire to cross to the left ventricle, a temporary transvenous pacemaker was implanted.

The Safari high-support guidewire was used (0.035 in guidewire, 260 cm) (Boston Scientific). The decision to perform a prior balloon valvuloplasty was left to the operator's discretion.

To implant the device, the delivery system is steered, and the radiopaque marker is positioned towards the aorta external region to facilitate the advancement of the catheter thanks to its adapted morphology. After crossing the native aortic valve and without the need for cardiac pacing, the valve is expanded. The proper anchoring of the valve support systems and positioning of the valve are confirmed. Finally, it is delivered and the system removed (figure 1).

In the absence of significant atrioventricular conduction disturbances, the temporary pacemaker was removed 24-48 hours after the procedure. The indications for the definitive pacemaker were established by the local protocols of each center. Antithrombotic treatment at discharge was dual antiplatelet therapy with acetylsalicylic acid and clopidogrel during the first 3-6 months, except for cases with indications for chronic oral anticoagulation.

Statistical analysis

Statistical analysis was performed using the SPSS 22 statistical software package (SPSS Inc., United States). Categorical variables were expressed as percentages, and quantitative variables as mean ± standard deviation or median (interquartile range). Continuous variables were compared using the Student *t* test for paired data, and categorical variables were compared using the chi-square test.

RESULTS

Baseline characteristics of the patients

A total of 102 patients were included from 5 Spanish centers and 3 Portuguese centers (table 1). Baseline characteristics are shown on table 2. Mean age was 80.4 ± 6.1 years, 52.9% were women, and the STS score was 5.4% (3.7-7.7).

Most patients had preserved systolic function and they were all diagnosed with severe AS with a mean indexed valve area of 0.66 ± 0.17 cm^2/m^2 and peak and mean aortic gradients of 74.3 ± 23.7 and 45.6 ± 15.7 mmHg, respectively; 22% of the patients had moderate AR too (≥ 2).

Table 1. Participant hospitals in the study and number of patients per hospital

Hospital Universitario La Paz, Madrid, Spain	33 (32.4%)
Policlínica Gipuzkoa, San Sebastián, Spain	19 (18.6%)
Hospital Universitari Vall d'Hebron, Barcelona, Spain	7 (6.9%)
Hospital Virgen de las Nieves, Granada, Spain	8 (7.8%)
Hospital Puerta del Mar, Cádiz, Spain	6 (5.9%)
Centro Hospitalar de Vila Nova de Gaia, Oporto, Portugal	8 (7.8%)
Centro Hospitalar de Lisboa Central, Lisbon, Portugal	10 (9.8%)
Hospital Santa Cruz, Lisbon, Portugal	11 (10.8%)

Procedural characteristics

Procedural characteristics are shown on table 3. General anesthesia was used, and the procedure was transesophageal echocardiogram-guided in most patients. Implantation was performed using transfemoral access; in 91.2% of the cases x-ray-guided percutaneous punctures and closures were performed.

The size of the valve was decided based on the dimensions of the annular area and perimeter based on the computed tomography scan performed in each center. Valve pre-dilation was performed in 19.6% of the patients, and no patient was post-dilated.

Before the definite implantation the device had to be repositioned in 12 procedures (11.8%) and the valve fully recaptured in 1 occasion because the patient showed severe periprosthetic regurgitation due to valve malapposition; the same device was successfully re-implanted in this patient.

Table 2. Baseline characteristics of patients (N = 102)

Age (years)	80.4 ± 6.1
Feminine sex	54 (52.9%)
Coronary artery disease	44 (43.1%)
Percutaneous revascularization	24 (54.5%)
Surgical revascularization	11 (25%)
No revascularization	9 (20.5%)
Cerebrovascular disease prior to TAVI	8 (7.8%)
Chronic kidney disease (CrCl < 60 mL/min)	37 (36.3%)
Without dialysis	33 (32.4%)
With dialysis	4 (3.9%)
Atrial fibrillation prior to TAVI	42 (41.2%)
Paroxysmal	13 (12.7%)
Permanent	29 (28.5%)
Ventricular function prior to TAVI (N = 82)	
> 50%	65 (79.3%)
30%-50%	9 (11%)
< 30%	8 (9.8%)
STS score	5.4% (3.7-7.735)
Pacemaker prior to TAVI	11 (10.8%)

CrCl, creatinine clearance; TAVI, transcatheter aortic valve implantation.

Procedural results

The valve was successfully implanted in 100 patients (98%), except for 2 patients due to major vascular complications: one case of a ruptured iliac artery that required surgical intervention (with good progression) and another case of aortic rupture prior to device implantation (the patient eventually died). In all the cases where the native aortic valve was accessed, the device was successfully implanted.

After the implant there was a significant reduction of transvalvular mean and peak gradients and the percentage of significant AR ($P < .001$) (figure 2). There was paravalvular leak grade 2 in 1 case, but no serious leaks whatsoever. In this case, a large annulus is described (a 27 mm diameter measured through CAT scan exceeding the upper limits recommended by the manufacturer). The main cause for the moderate paravalvular leak reported may have been a moderate oversized valve with respect to the annular size.

There were no complications associated with the valve malapposition and there was only 1 case of perioperative thromboembolic coronary occlusion. It soon resolved rusing coronary thromboaspiration and balloon angioplasty without any major adverse events (with intraoperative infarction but no death or worsening of the left ventricular ejection fraction after the procedure).

Complications are shown on table 4. In-hospital mortality was 3.9% (4 patients). As reported, 1 patient died of a ruptured aorta prior to device implantation. This patient had a porcelain aorta and the perioperative transesophageal echocardiogram performed showed plaque ulceration in the aortic wall. The second patient died of cardiogenic shock 4 days after admission; he showed ventricular dysfunction and left bundle branch block prior to device implantation. However, there were no complications during the procedure. The third patient suffered a perioperative ischemic stroke, and had a long hospital stay. He eventually died 74 days after admission of nosocomial infection. Finally, the fourth patient had a past medical history of hepatic failure and presented with liver failure and hemodynamic instability. He died within the first 30 days following the intervention.

The rate of perioperative stroke was 2.9%, and the rate of major vascular complications was 3.9%. There were 2 ruptured aortas with cardiac tamponade. In 1 case the patient died and in the other, the patient required conversion to sternotomy and surgery with good disease progression. The other 2 major complications were a

Table 3. Procedural characteristics

Procedural characteristics (N = 102)	
General anesthesia	94 (92.1%)
Perioperative transesophageal echocardiogram	94 (92.1%)
Transfemoral access	102 (100%)
Surgical exposure	8 (7.8%)
Percutaneous	94 (92.1%)
ProGlide closure system	38 (37.2%)
Prostar closure system	56 (54.9%)
Pre-dilation	20 (19.6%)
Repositioning	
Partial	12 (11.8%)
Complete	1 (1%)
Post-dilation	0
Valve size	
23 mm	43 (42.1%)
25 mm	27 (26.5%)
27 mm	32 (31.4%)

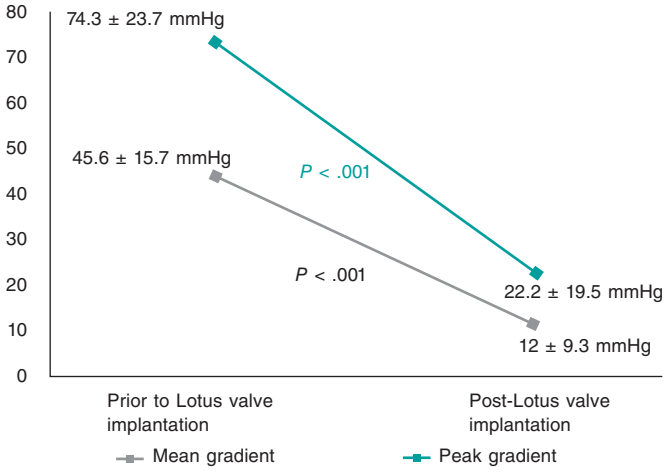

Figure 2. Gradients before and after valve implantation.

ruptured iliac artery and a retroperitoneal hematoma that required intervention with good disease progression.

The rate of successful implantation defined according to the Valve Academic Research Consortium 2 criteria, was 93.1% (95 out of the 102 patients included), since 4 patients died. In 1 patient the device was not implanted due to a major vascular complication, another patient had a mean gradient > 20 mmHg after implantation, and another showed moderate AR. The combined initial safety parameter (until hospital discharge) reached 90.2% of the cases (92 out of the 102 patients included).

A definitive pacemaker was implanted prior to hospital discharge in 33 out of the 91 patients who did not carry a pacemaker prior to device implantation (36.3%).

Table 4. Procedural results

Procedural results (VARCS2 criteria) (N = 102)	
Successful implantation	100 (98%)
Hospital stay (days)	
Mean	12.8 ± 16.5
Median	8.5 ± 4.5
Device malapposition	0
Migration	0
Embolization	0
Valve-in-valve	0
Coronary occlusion	1 (1%)
Periprosthetic aortic regurgitation (grade)	
0	81 (79.4%)
1	20 (19.6%)
2	1 (1%)
3	0
In-hospital mortality	4 (3.9%)
Stroke	3 (2.9%)
Disabling	2 (1.9%)
Non-disabling	1 (1%)
Bleeding	5 (4.9%)
Life-threatening	3 (2.9%)
Major	1 (1%)
Minor	1 (1%)
Renal failure	
Stage 2	5 (4.9%)
Stage 3	2 (2%)
Vascular complications	11 (10.8%)
Major	4 (3.9%)
Minor	7 (6.9%)
Conversion to open surgery	1 (1%)
Definitive pacemaker implantation	33 (36.3%)
Combined efficacy parameter	95 (93.1%)
Combined safety parameter	92 (90.2%)

VARC2, Valve Academic Research Consortium 2.

Follow-up

Out of the 92 patients who reached the combined initial safety parameter, it was possible to analyze the 3-year follow-up results in 57 of them (62%) with a mean age of 80 ± 6 years and a median follow-up of 37 months (22-47).

The 1-year mortality was 10.5% (6 patients). Two patients died of endocarditis: 1 case of mitral valve endocarditis (a patient with

Table 5. Studies published on the Lotus valve

Series	Number of patients	Successful implantation	Mortality	Periprosthetic aortic regurgitation ≥ 2	Pacemaker
Reprise II[17,18]	120	100%	4.2%	1%	28.6%
Rampat et al.[19]	228	99.1%	1.8%	0.8%	31.8%
De Backer et al.[20]	154	100%	1.9%	0.6%	27.9%
Wöhrle et al.[21]	26	100%	0	0	26.9%
RESPOND[23]	1014	98.1%	2.9%	0.3%	34.6%
Current series	102	98%	3.9%	1%	36.3%

severe mitral regurgitation prior to TAVI) 10 months after the procedure, and another case of aortic valve endocarditis 3 months after the implant. The 4 remaining patients died of non-cardiac causes (1 patient died of metabolic encephalopathy and 3 of sepsis of a different origin). The 3-year mortality rate was 35.1% (20 patients): 6 patients (10.5% of the total) died of cardiac causes, 10 of non-cardiac causes, and 4 for unknown reasons.

Regarding the echocardiographic parameters, the persistence of good long-terms results was seen without significant variations of the valvular gradients post-TAVI (mean gradient of 12 ± 9.3 mmHg at discharge vs 12.4 ± 6.8 mmHg at the 3-year follow-up; peak gradient of 22 ± 19.5 mmHg at discharge vs 24.5 ± 13.2 mmHg at the 3-year follow-up). However, valve thrombosis was seen in 2 patients (3.5%), both diagnosed in a routine echocardiographic examination without any associated clinical events. One case was an early thrombosis that occurred 2 months after device implantation in an 87-year-old patient with severe ventricular dysfunction and implantation of a 27-mm Lotus valve on dual antiplatelet therapy at hospital discharge. The other was a case of very late thrombosis —46 months after device implantation— in a 71-year-old patient with moderate ventricular dysfunction and implantation of a 23-mm Lotus valve. Both patients improved with anticoagulant medication. No cases of periprosthetic aortic regurgitation grade > 1 were reported at the follow-up, and no patient required reintervention.

DISCUSSION

This is the first study to report on real-life results of the Lotus valve (Boston Scientific) in the Iberian Peninsula. They are similar to the results published in former studies and registries (table 5),[17-23] in particular the results of the RESPOND study.[23] It should be mentioned the low rate of periprosthetic regurgitation (1% moderate and 0% severe), the lack of complications related to the valve malapposition, and no need for post-dilation despite a low rate of pre-dilation. Three factors are responsible for these results:

- The possibility of fully or partially repositioning and recapturing the device, thus facilitating a more accurate positioning of the valve.

- The presence of great valvular radial strength. It has a controlled mechanical expansion mechanism, not a self-expanding one (while the device is released from the delivery system, the nitinol frame shortens and expands always in a totally reversible way).

- The presence of a new sealing system (urethane membrane) adapted to the annulus irregular surface to minimize perivalvular regurgitation and also in heavily calcified and irregular annuli.

In our population in-hospital mortality (3.9%) is similar to that of the Reprise II trial[15] and a little higher compared to that of the landmark registry published to this day of 1014 patients: the RESPOND clinical trial.[23] However, results are hardly comparable due to the different populations included, especially the high-risk population of the Reprise II like that of recruitment centers. This is so because in the RESPOND trial the participant centers had a huge experience in Lotus valve implantation. Our registry included an intermediate-risk population (STS score of 4%-8%), similar to that of the PARTNER 2,[6] and in our study all-cause mortality was consistent with the one reported in such trial (3.9% at 30 days). If we take into account the importance of the learning curve when analyzing the results of new devices and the fact that our registry included centers with < 10 years of experience, in-hospital mortality was relatively low. In our series, cardiovascular mortality was 3%.

One of the advantages of this device is that it guarantees the patient's hemodynamic stability during the entire procedure. First, no cardiac pacing is required during implantation. Second, the leaflets start to function very early on and before the valve shortens because they are attached to the device most distal portion, thus avoiding hypotension periods. Third, it can be implanted directly without pre-dilation with certain frequency because it has tremendous radial strength. In our registry, only 19.6% of the patients were pre-dilated, fewer patients compared to the RESPOND trial (53.9%).

The rate of significant periprosthetic AR (grade ≥ 2) was fairly low with similar results to those of former studies published on the Lotus valve (table 5). Moderate periprosthetic regurgitation was seen in one patient only, but it was not serious. Moderate-severe periprosthetic AR (grade ≥ 2) has been associated with worst post-TAVI results and higher short and long-term mortality rate.[9-12] The PARTNER 2 clinical trial revealed a 30-day rate of moderate-severe periprosthetic AR of 3.7%. The 2-year mortality rate in these patients was higher compared to those with grade 0-1 periprosthetic regurgitation ($P < .001$).[6] Our registry and the Reprise II trial 1-year follow-up confirmed that the results seen during the first 30 days are kept in time including the low 1-year rate of significant periprosthetic regurgitation.[18] The possibility of valve repositioning and retrieval prior to the device implantation reduces other valve malapposition-related complications. No cases of device embolization were seen in our population, and no patient required valve-in-valve implantation, which increases the device safety profile.

In our registry the rate of strokes was 2.9% (3 patients, of these 2 suffered disabling strokes) similar to that of the RESPOND trial[23] (overall strokes: 3%; disabling strokes: 2.2%). However, due to the lack of a systematic neurological exam before and after the procedure and an event adjudication committee we cannot draw

definitive conclusions or compare the rate of this complication between our registry and other studies.

The rate of major vascular complications is not different from the one published in other series and with other devices.

The issue that still needs to be addressed with the Lotus valve is the rate of definitive pacemaker implantation. As previous studies report, around 30% of the cases require a definitive pacemaker, yet the reason for it is still not clear. Several factors have been proposed in association with this complication. The Reprise II trial suggested overstretching—defined as a ≥ 10% ratio between the valve theoretical area and the annular area or left ventricular outflow tract measured through CAT scan[21]—as the main independent predictive factor of pacemaker implantation. This, added to the higher rate of pacemaker implantation of some self-expandable valves[24] and cases of valve deeper implants[25] leads us to think that the occurrence of conduction disturbances may be associated with excessive mechanical stress in areas where the conduction system passes through like the aortomitral junction.[26] Also, better valve size selection based on data from the CAT scan, technique modifications for higher valve implantation depths, and the arrival of the LOTUS Edge device may reduce the rate of this complication. Compared to the former Lotus valve system generation, the LOTUS Edge valve is easier to deliver, has a more flexible catheter, and is easier to follow-up. The Depth Guard delivery technology and the radiopaque markers added contribute to simplify the release. Depth Guard technology has been designed to minimize valve implantation depths, thus reducing its interaction with the left ventricular infundibulum. By reducing contact with the left ventricular infundibulum, the rates of definitive pacemaker implantation go down.

In conclusion, the results already published of the REPRISE III trial on a randomized comparison between the Lotus valve and the CoreValve self-expandable aortic valve (Medtronic, United States) are very interesting.[27] The results available validate those from our registry regarding the safety and efficacy profile of the Lotus valve. No significant differences were seen at the 2-year follow-up either regarding the mortality and stroke rates compared to the CoreValve. Also consistent with our results, a lower rate of moderate-severe periprosthetic AR with the Lotus valve at the 2-year follow-up (0.3% with Lotus vs 3.8% with CoreValve; $P < .01$) and device embolization (0.0% with Lotus vs 2.0% with CoreValve; $P < .01$) was seen. However, there was a higher need for pacemaker implantation (41.7% with Lotus vs 26.1% with CoreValve; $P < .01$) and a higher rate (3%) of valve thrombosis at the long-term follow-up in our registry and in the REPRISE III trial.

CONCLUSIONS

This is the first study to describe the safety and functioning data of the Lotus valve in Spain and Portugal. Our results confirm those obtained by former studies and indicate that the Lotus valve is a safe and effective alternative for patients with symptomatic and severe AS. In particular, a low rate of periprosthetic AR after device implantation at the expense of a high rate of pacemaker implantation was reported.

Limitations

The study main limitations are probably the lack of a comparison group, and the non-negligible percentage of patients lost to follow-up since the study main initial objective was to assess the in-hospital results of device implantation. Second, the device available today is the LOTUS Edge valve that still has the advantages of the original Lotus valve plus an improved catheter and delivery system. Lastly, another limitation is the lack of a common predefined protocol for patient inclusion and result collection although it was prospective in each center.

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 also a proctor for Boston Scientific.

WHAT DOES THIS STUDY ADD?

- The experience with this kind of device in our setting is still limited. The relevance of this study is that this is the first description of the safety and functioning data of the Lotus valve in Spain and Portugal. Our results confirm those of former studies: high successful implantation rate, low mortality, and low rate of periprosthetic aortic regurgitation at the expense of a high rate of pacemaker implantation. Also, our registry reported on the long-term follow-up results (3 years), making it even more relevant because there are very few data in the medical literature on the durability of this valve.

WHAT IS KNOWN ABOUT THE TOPIC?

- Despite the always growing experience in the percutaneous management of severe aortic stenosis, we still face TAVI-related complications. They can have a negative impact on the short and mid-long-term results, in particular periprosthetic aortic regurgitation. The Lotus is a fully retrievable and repositionable second-generation, transcatheter, aortic valve with good initial efficacy and safety results in former studies and registries. Also, it showed fewer major complications like periprosthetic aortic regurgitation or device malapposition.

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Original article

Time trend in transcatheter aortic valve implantation: an analysis of the Spanish TAVI registry

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ABSTRACT

Introduction and objectives: This study primary endpoint was to present the in-hospital all-cause mortality of the Spanish TAVI registry from its inception until 2018. Secondary endpoints included other in-hospital clinical events, 30-day all-cause mortality, and an assessment of the time trend of this registry.
Methods: All consecutive patients included in the Spanish TAVI registry were analyzed. In this time-based analysis, the population was been divided into patients treated before 2014 (cohort A: 2009-2013) and patients treated between 2014 and 2018 (cohort B).
Results: From August 2007 to June 2018, 7180 patients were included. The mean age was 81.2 ± 6.5 years and 53% were women. The logistic EuroSCORE was 12% (8-20). Transfemoral access was used in 89%. In-hospital and 30-day all-cause mortality was 4.7% and 5.7%, respectively. On the time-based analyses during the hospital stay, the rate of myocardial infarction, stroke, need

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for pacemakers, tamponade, coronary obstruction, and vascular complications was similar between both groups. However, cohort B showed less need for conversion to surgery and malapposition of the valve. Also, the implant success rate increased from 93% to 96% (P < .001). In-hospital and 30-day all-cause mortality was significantly lower in cohort B, ([OR, 0.65; IC95%, 0.48-0.86; P = .003] and [OR, 0.71; IC95%, 0.54-0.92; P = .002], respectively).
Conclusions: The time trend analysis of the Spanish TAVI registry showed a change in the patients' clinical profile and an improvement in the in-hospital clinical outcomes and 30-day all-cause mortality in patients treated more recently.

Keywords: Transcatheter Treatment of the Aortic Valve. Records. Severe Aortic Stenosis.

Evolución temporal en el tratamiento transcatéter de la estenosis aórtica: análisis del registro español de TAVI

RESUMEN

Introducción y objetivos: El objetivo primario de este estudio fue presentar la mortalidad total intrahospitalaria del registro español de implante percutáneo de válvula aórtica (TAVI) desde su inicio hasta el año 2018, y como objetivos secundarios otros eventos clínicos intrahospitalarios, la mortalidad total a los 30 días y la evaluación de cuál ha sido la evolución temporal de este registro.
Métodos: Fueron analizados todos los pacientes consecutivos incluidos en el registro español de TAVI. En este análisis temporal se dividió la población en pacientes tratados antes de 2014 (cohorte A: 2009-2013) y pacientes tratados entre los años 2014 y 2018 (cohorte B).
Resultados: Desde agosto de 2007 hasta junio de 2018 se incluyeron 7.180 pacientes. La edad media fue de 81,2 ± 6,5 años y el 53% eran mujeres. El EuroSCORE logístico fue del 12% (8-20). Se utilizó un acceso transfemoral en el 89%. La mortalidad total intrahospitalaria fue del 4,7% y a los 30 días fue del 5,7%. En el análisis temporal durante la fase hospitalaria, las tasas de infarto, accidente cerebrovascular, necesidad de marcapasos, taponamiento, obstrucción coronaria y complicaciones vasculares fueron similares en ambos grupos. Sin embargo, en la cohorte B se observó una reducción de la necesidad de conversión a cirugía y de malaposición de la válvula, y además la tasa de éxito del implante fue mayor (93 frente a 96%; p < 0,001). La mortalidad por cualquier causa ajustada tanto intrahospitalaria como a los 30 días, fue significativamente menor en la cohorte B (*odds ratio* [OR] = 0,65; intervalo de confianza del 95% [IC95%], 0,48-0,86; p = 0,003; y OR = 0,71; IC95%, 0,54-0,92; p = 0,002, respectivamente).
Conclusiones: En el análisis temporal del registro español de TAVI se observan un cambio en el perfil clínico de los pacientes y una mejora en la evolución clínica tanto intrahospitalaria como a los 30 días en los pacientes tratados en los últimos años.

Palabras clave: Tratamiento transcatéter de la válvula aórtica. Registros. Estenosis aórtica grave.

Abbreviations

TAVI: transcatheter aortic valve implantation.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is the best therapeutic option today for most elderly patients with severe, degenerative aortic stenosis.[1-4] The evidence that supports this indication comes from rigorous randomized clinical trials conducted with balloon expandable valves[5-7] like self-expandable valves.[8-10] In this sense, this technique has recently consolidated after the publication of the initial results of new studies conducted in low-risk patients.[11,12]

Over the years, the implantation technique and the type of patients have changed.[13,14] These factors together with the new generations of valves including technical improvements have reduced the occurrence of major cardiovascular and cerebral events both in-hospital and in the long-term follow-up.[15,16] In the French TAVI registry (n = 16 969 patients) surgical risk was lower in the patients treated, a greater simplification of the technique via transfemoral access, and a lower short-term mortality rate over the last few years (2013-2015) compared to the first period studied (2010-2012). However, these differences were not found in the time trend analysis of the English registry (n = 3980).

The study primary endpoint was to present the in-hospital all-cause mortality rate of the Spanish TAVI registry from its inception until 2018. Secondary endpoints included other in-hospital clinical events, 30-day overall mortality, and a time trend analysis in 2 well-defined time periods: from August 2007 through December 2013 (cohort A), and from January 2014 through June 2018 (cohort B) by assessing the differences seen in the baseline clinical characteristics and the appearance of clinical events between both groups.

METHODS

The Spanish TAVI registry has been promoted by the board of directors of the Section of Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology. Since 2010, all Spanish TAVI-capable centers are invited every year to participate in this registry and enter data from all the patients with severe, aortic stenosis treated with TAVI. These data come from the units of cardiology and cardiac surgery and are entered into a periodically reviewed online dedicated database. Although there is not

such a thing as a formal audit, the data entered in the registry are systematically reviewed to look for inconsistencies or lack of data; the review is conducted by a database expert who contacts the centers to solve any incidents found. Over the years 46 Spanish centers have participated in the registry (annex 1 of the supplementary data) and although it started back in 2010, 232 patients treated between 2007 and 2009 have been entered retrospectively and included in the analysis.

In this study all consecutive patients included in the Spanish TAVI registry were analyzed. In the time trend analysis, the population was divided into patients treated before 2014 (cohort A: 2009-2013) and those treated between 2014 and 2018 (cohort B) since 2014 was the year when the new generation of the 2 most popular valves in our country were implanted for the first time: the Edwards and the CoreValve.

Study variables

Events were defined according to the recommendations established by the Valve Academic Research Consortium[17] in cohort A, and according to the recommendations designed by the Valve Academic Research Consortium II[18] in cohort B. High surgical risk was defined as a logistic EuroSCORE value > 20% and as a Society of Thoracic Surgeons' risk model value > 8%.

Statistical analysis

After confirming the variables normal distribution (Kolmogorov-Smirnov normality test), quantitative data were expressed as mean ± standard deviation or median and interquartile range, as appropriate. Qualitative data were expressed as absolute value and percentage. To assess the predictors of in-hospital mortality, the multivariable logistics regression model was used. Variables with probability values < 0.1 in the univariable analysis or clinically relevant were included in the analyses. To assess the predictors of 30-day mortality the Cox backward stepwise regression model was used. Survival curve was obtained using the Kaplan-Meier method. Two-tailed *P*-values < .05 were considered statistically significant. The statistical analysis was performed using the statistical software SPSS.[19]

RESULTS

Total results

Baseline and procedural characteristics

From August 2007 through June 2018, 180 patients were included in the Spanish TAVI registry.[7] Mean age was 81.2 ± 6.5 years and 53% were women. Logistics EuroSCORE was 12% (8-20). Transfemoral access was used in 89% of the cases in 78% of which percutaneous puncture was used and surgical dissection in the remaining cases. The most commonly used valve was the CoreValve self-expandable system (49%) very closely followed by the balloon-expandable Edwards valve (46%). The most common valve size was number 26. The rate of successful device implantation was 94% (table 1 and table 2).

In-hospital and follow-up complications

The rates of in-hospital acute myocardial infarction, stroke, vascular complications, and hemorrhages were 0.9%, 1.9%, 10.7%, and 7.6%, respectively. Pacemaker implantation was required in 14% of the cases. The rates of overall in-hospital mortality and 30-day mortality were 4.7% and 5.7%, respectively (table 3).

Results of the time trend analysis

Baseline and procedural characteristics

No differences were found between the groups regarding the patients' mean age and sex. However, cohort B had more cardiovascular risk factors and surgeries performed prior to mitral valve implantation, but less peripheral vascular disease. Although the rate of coronary artery disease was similar in both groups, previous surgical coronary revascularizations were less common in cohort B. Creatinine clearance values were higher in cohort B. Regarding the clinical situation, the presence of severe symptoms (functional class III-IV) both for dyspnea (New York Heart Association) and angina (Canadian classification) was significantly lower in cohort B. Surgical risk was significantly lower in cohort B according to the logistics EuroSCORE and the Society of Thoracic Surgeons' risk model. There were fewer inoperable patients or high surgical risk patients in cohort B as well. In this group, the severity of stenosis was lower (larger indexed valve area, lower transvalvular mean gradient) and annular diameter was larger. Regarding the route of access, the use of transfemoral approach started to grow back in 2014 (from 83% to 94%) mainly because the use of transapical access dropped from 14% to 3%. The type of valve used was almost exclusively the Edwards SAPIEN XT while the CoreValve was used in cohort A. In cohort B the new generations of these valves were used (Edwards SAPIEN 3 and Evolut R) as well as other types of self-expandable valves like the Portico (4.1%), the ACURATE neo (2.6%). and the Lotus valve (1.4%). The most common size of the valves was 26 mm in both groups. The rate of predilatation decreased in cohort B, but the rate of postdilatation grew. The rate of successful implantation increased significantly over the last period from 93% (cohort A) to 96% (cohort B). The working space where the TAVI was performed changed as well; although the cardiac catheterization laboratory was the most common working space in both cohorts fewer valves were implanted in the operating room and more valve were implanted in hybrid operating rooms in cohort B.

In-hospital and 30-day follow-up events

The length of hospital admission was reduced significantly in cohort B. In the hospital stage, the rates of acute myocardial infarction, stroke, need for pacemaker, and coronary obstruction were similar in both groups. However, the conversion rate to surgery (figure 1) and valve malapposition dropped significantly in patients treated from 2014. No inter-group differences were found regarding vascular complications. However, the overall rate of hemorrhages and renal complications were higher in cohort B. In-hospital all-cause mortality was significantly lower in cohort B with a 47% reduction (odds ratio [OR], 0.65; 95% confidence interval [95%CI], 0.48-0.86; P = .003).

Mortality rate dropped 32% at the 30-day clinical follow-up in cohort B (6.9 vs 4.7%) (OR, 0,71; 95%CI, 0.54-0.92; P = .002) (figure 2 and figure 3). The 30-day mortality predictors are shown on table 4.

DISCUSSION

The main findings of this study were: *a)* in Spain there is a time trend in the type of patients treated with TAVI through the years; *b)* there have been changes, transfemoral access has become

Table 1. Baseline clinical and echocardiographic characteristics of the study patients

Baseline characteristics	All patients (n = 7180)	Cohort A (years 2009-2013) (n = 3075)	Cohort B (years 2014-2018) (n = 4105)	*P*
Clinical characteristics				
Age	81.2 ± 6.5 7171	81.0 ± 6.4 3075	81.2 ± 6.7 4096	.19
Women	3796 / 7166 (53.0)	1636 / 3075 (53.2)	2160 / 4091 (52.8)	.79
Weight, kg	72.6 ± 14 7087	70.9 ± 13 3069	72.1 ± 14 4018	< .001
Height, cm	160 ± 9 6714	159 ± 9 2879	160 ± 9 3835	< .001
Body mass index	28.01 ± 4.9 6838	27.99 ± 4.9 2879	28.16 ± 4.9 3959	.143
Hypertension	5728 / 7081 (80.9)	2437 / 3073 (79.3)	3291 / 4008 (82.1)	.003
Dyslipidemia	3903 / 6698 (58.3)	1586 / 2875 (55.1)	2317 / 3823 (60.6)	< .001
Diabetes mellitus	2447 / 6752 (36.2)	998 / 2875 (34.7)	1449 / 3877 (37.4)	.02
Past medical history				
Previous stroke	764 / 6797 (11.3)	342 / 2879 (11.9)	422 / 3918 (10.7)	.15
Peripheral vascular disease	1009 / 6903 (14.6)	484 / 3071 (15.7)	525 / 3832 (13.7)	.02
Coronary artery disease	2090 / 7105 (29.4)	1231 / 3075 (40.0)	1576 / 4030 (39.1)	.43
Previous AMI	919 / 6565 (13.9)	396 / 2878 (13.7)	523 / 3687 (14.2)	.62
Previous PCI	1476 / 6879 (21.4)	651 / 3065 (21.2)	825 / 3814 (21.6)	.70
Previous revascularization surgery	645 / 6689 (9.6)	336 / 3059 (10.9)	309 / 3630 (8.5)	.001
Previous aortic valve replacement	210 / 4245 (4.9)	44 / 931 (4.7)	166 / 3314 (5.0)	.73
Previous mitral valve replacement	81 / 4245 (1.1)	6 / 931 (0.6)	75 / 3314 (2.3)	.001
Atrial fibrillation	1905 / 7037 (27.1)	855 / 3067 (27.9)	1050 / 3970 (26.4)	.18
Pacemaker	520 / 7037 (7.3)	216 / 3067 (7.0)	304 / 3970 (7.6)	.33
Creatinine clearance (mL/min/1.73 m^2)	55 ± 25 6638	50 ± 47 2874	58 ± 27 3764	< .001
Class III-IV dyspnea	4726 / 6810 (69.4)	2136 / 2877 (74.2)	2590 / 3933 (66.8)	< .001
Class III-IV angina	567 / 7062 (8.0)	303 / 3073 (9.8)	264 / 3989 (7)	< .001
Logistic EuroSCORE	12 (8-20) 6738	14 (9-22) 3027	11 (7-18) 3711	< .001
STS score	5 (3-9) 3190	7 (4-18) 1024	5 (3-7) 2166	< .001
High surgical risk	2010 (28.0%)	1139 (37%)	871 (22%)	< .001
Surgical contraindication	1854 / 7180 (25.8)	971 / 3075 (31.6)	883 / 4105 (21.5)	< .001
Preprocedural echocardiographic data				
LVEF (%)	56.9 ± 13 6927	56.9 ± 14 3056	56.8 ± 13 3871	.66
Mean aortic transvalvular gradient, mmHg	48 ± 15 6599	49 ± 15 3026	47 ± 15 3573	< .001
Peak aortic transvalvular gradient, mmHg	79 ± 23 6606	81 ± 23 3033	77 ± 23 3573	< .001
Indexed valve area, cm^2	0.65 ± 0.2 4267	0.62 ± 0.2 1679	0.68 ± 0.2 2588	< .001
Pulmonary artery pressure, mmHg	47 ± 18 3046	48 ± 16 1188	47 ± 20 1858	.17
Diameter of aortic annulus, mm	23.2 ± 3 3935	22.9 ± 2 1224	23.2 ± 3 2711	.001
Grade III-IV mitral regurgitation	410 / 5857 (7.0)	159 / 2368 (6.7)	251 / 3489 (7.2)	.48
Grade III-IV aortic regurgitation	121 / 3172 (3.8)	56 / 691 (8.1)	65 / 2481 (2.6)	< .001

AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons' risk model.

Table 2. Procedural characteristics

	All patients (n = 7180)	Cohort A (years 2009-2013) (n = 3075)	Cohort B (years 2014-2018) (n = 4105)	*P*
Access				< .001
Transaortic	56 / 7180 (0.8)	28 / 3075 (0.9)	28 / 4105 (0.7)	
Subclavian axillary	144 / 7180 (2.0)	58 / 3075 (1.8)	86 / 4105 (2.0)	
Transapical	568 / 7180 (7.9)	431 / 3075 (14.0)	137 / 4105 (3.3)	
Transfemoral	6412 / 7180 (89.3)	2558 / 3075 (83.2)	3804 / 4105 (92.6)	
Access route				.57
Dissection	1378 / 6225 (22.1)	526 / 2417 (21.7)	852 / 3808 (22.4)	
Puncture	4847 / 6225 (77.8)	1891 / 2417 (78.2)	2956 / 3808 (77.6)	
Type of valve				< .0001
Engager	5 / 7180 (0.1)	0 / 3075 (0)	5 / 4105 (0.1)	
Direct Flow	8 / 7180 (0.1)	3 / 3075 (0.1)	5 / 4105 (0.1)	
Allegra	5 / 7180 (0.1)	0 / 3075 (0.1)	16 / 4105 (0.4)	
Lotus	60 / 7180 (0.8)	1 / 3075 (0.03)	59 / 4105 (1.4)	
Symetis	105 / 7180 (1.5)	0 / 3075 (0)	105 / 4105 (2.6)	
Portico	172 / 7180 (2.4)	0 / 3075 (0)	172 / 4105 (4.1)	
Edwards	3309 / 7180 (46.1)	1468 / 3075 (47.7)	1841 / 4105 (44.8)	
CoreValve	3516 / 7180 (48.9)	1603 / 3075 (52.1)	1913 / 4105 (46.6)	
Valve size				< .001
23	1746 / 6712 (26.0)	742 / 2865 (25.9)	1004 / 3847 (26.1)	
26	2742 / 6712 (40.9)	1402 / 2865 (48.9)	1340 / 3847 (34.8)	
29	1791 / 6712 (26.7)	681 / 2865 (23.8)	1110 / 3847 (28.8)	
> 29	247 / 6712 (3.6)	37 / 2865 (1.2)	210 / 3847 (5.4)	
Other sizes	186 / 6712 (2.7)	3 / 865 (0.04)	183 / 3847 (4.7)	
Predilatation	2072 / 3748 (55.3)	707 / 809 (87.4)	1365 / 2939 (46.4)	< .0001
Posdilatation	1457 / 6767 (21.5)	561 / 3071 (18.3)	897 / 3696 (24.3)	< .0001
Room				< .0001
Operating room	288 / 7180 (4.0)	223 / 3075 (7.2)	65 / 4105 (1.5)	
Catheterization laboratory	6575 / 7180 (91.6)	2759 / 3075 (89.7)	3816 / 4105 (92.5)	
Hybrid room	317 / 7180 (4.4)	93 / 3075 (3.0)	224 / 4105 (5.4)	
Duration, minutes (mean ± standard deviation)	105 ± 45	106 ± 47	105 ± 43	.48
Median	95 (72-121) 5514	95 (72-122) 2834	95 (72-120) 2680	.94
Length of hospital admission, days (mean ± standard deviation)	8.3 ± 8	8.6 ± 8	8.0 ± 7	.002
Median	6 (5-9) 6459	6 (5-9) 2751	6 (4-8) 3708	.15
Successful implantation	6778 / 7153 (94.8)	2848 / 3062 (93.0)	3930 / 4091 (96.1)	< .001

widely used, postdilatation has increased, and the rates of valve malapposition and conversion to surgery have dropped. And the most important thing of all, there has been a significant increase in the rate of successful implantation since 2014; and *c)* there is a significant reduction of in-hospital and 30-day all-cause mortality in patients treated from 2014.

Differences in baseline characteristics

This study saw a time change in the risk profile of patients treated with TAVI in Spain. The percentage of high-risk patients over the first period was 37% vs 22% from 2014 onwards. These findings are consistent with those reported in the time analysis of the French registry[15] where the logistics EuroSCORE dropped from 21.7 ± 14.2% to 17.9 ± 12.3%. In this sense, the facts that may explain these findings are the appearance of randomized clinical trials that use TAVI in lower-risk patients.[2,7] From 2015 to 2016 the results from the NOTION (The Nordic Aortic Valve Intervention) and PARTNER II (Placement of Aortic Transcatheter Valves) clinical trials—on low-and-intermediate risk patients—were published. The NOTION trial did not find any significant differences between patients treated with TAVI or surgical aortic valve replacement regarding the composite

Table 3. In-hospital events

	All	Cohort A (years 2009-2013) (n = 3075)	Cohort B (years 2014-2018) (n = 4105)	*P*	Non-adjusted OR	Adjusted OR	*P*
Conversion to surgery	58 / 7076 (0.8)	34 / 3005 (1.1)	24 / 4062 (0.6)	.013	0.52 (0.31-0.88)	0.49 (0.24-0.98)	.04
Tamponade	57 / 6899 (0.8)	19 / 2900 (0.7)	38 / 3999 (1.0)	.18	1.45 (0.83-2.56)	2.17 (1.08-3.85)	.03
Coronary obstruction	23 / 6889 (0.3)	12 / 2897 (0.4)	11 / 3992 (0.3)	.33	0.66 (0.29-1.52)	0.69 (0.28-1.69)	.42
Malapposition Migration Embolization Unknown	153 / 6884 (2.2) 119 / 6884 (1.7) 12 / 6884 (0.2) 22 / 6884 (0.3)	92 / 2897 (3.2) 76 / 2897 (2.5) 2 / 2897 (0.1) 14 / 2897 (0.2)	61 / 3987 (1.5) 43 / 3987 (1) 10 / 3987 (0.2) 8 / 3987 (0.1)	< .001	0.47 (0.34-0.66)	0.46 (0.32-0.66)	.001
AMI	64 / 7055 (0.9)	28 / 3053 (0.9)	36 / 4001 (0.9)	.94	0.98 (0.60-1.61)	0.97 (0.53-1.79)	.93
Vascular complications	769 / 7055 (10.7)	268 / 3053 (8.8)	501 / 4001 (12.5)	< .001	1.49 (1.27-1.72)	1.18 (0.98-1.41)	.09
Hemorrhages	544 / 7054 (7.6)	169 / 3053 (5.5)	375 / 4001 (9.4)	< .001	1.75 (1.47-2.13)	1.79 (1.43-2.22)	< .001
Renal complications	377 / 7054 (5.3)	140 / 3053 (4.6)	237 / 4001 (5.9)	.01	1.32 (1.05-1.61)	1.32 (1.03-1.69)	.028
Stroke	133 / 7055 (1.9)	55 / 3053 (1.8)	78 / 4001 (1.9)	.65	1.09 (0.76-1.54)	0.84 (0.55-1.28)	.43
Pacemaker	1016 / 7092 (14.3)	416 / 3053 (13.6)	600 / 4001 (15.0)	.14	1.11 (0.96-1.27)	0.99 (0.84-1.16)	.91
In-hospital mortality	340 / 7054 (4.7)	200 / 3053 (6.6)	140 / 4001 (3.5)	< .001	0.52 (0.41-0.65)	0.65 (0.48-0.86)	.003

AMI, acute myocardial infarction; OR, odds ratio.

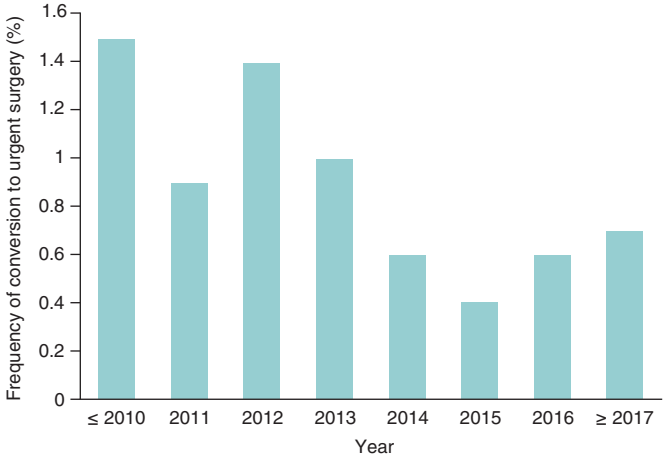
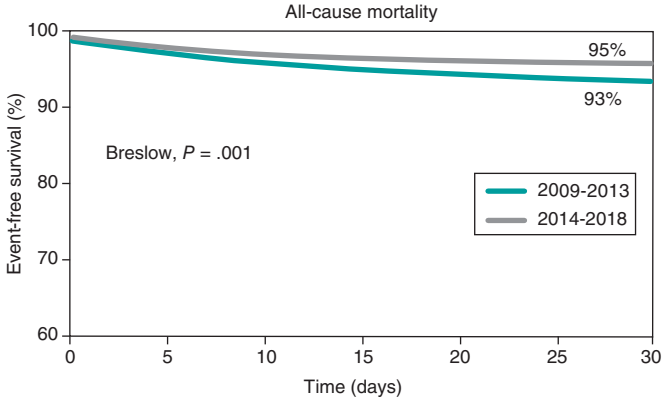
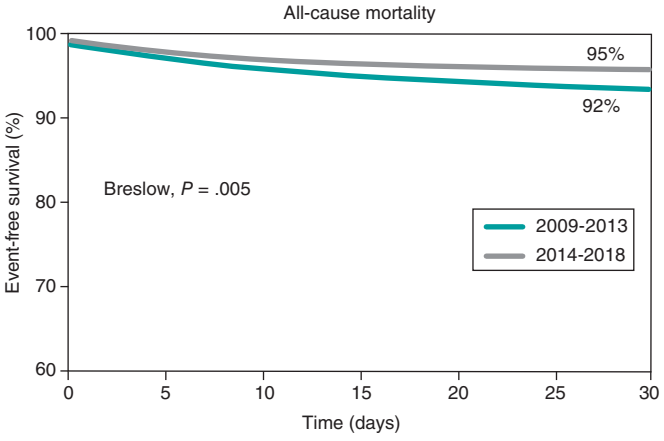


Figure 1. Conversion rate to urgent surgery through the years.



Procedures performed between 2009 and 2013: 2689
Procedures performed between 2014 and 2018: 2817

Figure 2. Survival rate at the 1-year follow-up of patients included in the Spanish TAVI registry treated in 2009-2013 and 2014-2018.



Procedures performed between 2009 and 2013: 1000
Procedures performed between 2014 and 2018: 625

Figure 3. Survival rate at the 1-year follow-up of high surgical risk patients only treated in 2009-2013 and 2014-2018.

endpoint of death, stroke or acute myocardial infarction at the 1 and 5-year follow-up. The PARTNER II clinical trial[7] randomized 2032 intermediate risk patients to be treated with TAVI or surgery. No significant differences were found in the primary endpoint of all-cause mortality or disabling stroke at the 2-year follow-up. However, when only the cohort treated with transfemoral access was studied, TAVI showed significantly lower rates of death and disabling stroke.

Procedural differences

This study describes the time changes that seem to impact the higher rate of successful implantation, a factor closely related to mortality. The difference found would be fewere cases of malapposition. Also, an increase of transfemoral access has been reported. All these changes are explained by the greater

Table 4. Independent predictors of mortality at the 30-day follow-up

Variables predictors of death at the 30-day follow-up	Univariate OR (95%CI)	*P*	Adjusted multivariate OR (95%CI) before the procedure	*P*	Adjusted multivariate OR (95%CI) before and after the procedure	*P*
Preoperative						
Years 2014-2018	0.52 (0.41-0.65)	< .001	0.59 (0.46-0.76)	< .001	0.71 (0.54-0.92)	.01
Body mass index	0.97 (0.95-0.99)	.007				
Dyslipidemia	0.93 (0.74-0.93)	.54	0.94 (0.74-1.21)	.64	0.89 (0.69-1.14)	.35
Creatinine clearance	0.99 (0.98-0.99)	< .001	*		*	
Peripheral vascular disease	1.49 (1.13-1.97)	.005	*		*	
Mean aortic gradient, mmHg	1.003 (0.99-1.01)	.47	1.002 (0.99-1.01)	.57	1.003 (0.99-1.01)	.54
Grade III-IV mitral regurgitation	1.98 (1.34-2.92)	.001	*		*	
Grade III-IV aortic regurgitation	2.06 (1.01-4.19)	.05	*		*	
Grade III-IV angina	1.08 (0.73-1.61)	.69	1.16 (0.76-1.78)	.50	1.16 (0.74-1.81)	.52
Grade III-IV dyspnea	1.48 (1.13-1.96)	.005	*		*	
Surgical risk	1.38 (1.09-1.74)	.007	1.33 (1.03-1.71)	.029	1.26 (0.96-1.64)	.09
Postoperative						
Transfemoral access	0.50 (0.38-0.66)	< .001			0.49 (0.36-0.67)	< .001
Successful implantation	0.10 (0.08-0.13)	< .001			0.11 (0.09-0.15)	< .001

95%CI, 95% confidence interval; OR, odds ratio.
*These variables were not part the model because they are used to estimate surgical risk.

experience gained with the implantation technique that is focused on simplification and the improvements made in valve design. All through 2014, a new generation of valves (Edwards SAPIEN 3 and Evolut R) were implanted for the first time with technical breakthroughs like the smaller release system and greater use of transfemoral access seen in cohort B. The introduction of the outer skirt was associated with a lower rate of perivalvular leak, higher procedural success, and less need for valve overexpansion. This reduces potentially the rate of annular tear and need for conversion to surgery (a high mortality procedure). Also, in the case of the Evolut R valve the introduction of a fully retrievable platform may have lowered the rate of valve malapposition and increased the rate of successful implantation seen from 2014.

Reduced mortality

Back in 2013 the data of 1416 patients included in the years 2010 and 2011 in the Spanish TAVI registry were published.[19] In this analysis the rate of successful implantation was 94% and the in-hospital mortality rate 8%. In this study the overall mortality rate was 4.7%. A remarkable aspect of the Spanish registry time analysis is that it shows a clear mortality reduction over the second period studied (cohort B) regardless of the patients' baseline characteristics. These results are consistent with the French registry time analysis that showed reduced in-hospital and 30-day mortality in the patients included in the 2013-2015 period.[15] On the contrary, in the English registry time analysis[16] from 2007 through 2012, no differences were found in the patients' baseline characteristics or surgical risk studied through those years. However, there was a higher percentage of patients with ventricular dysfunction. In this registry, mortality reduction and shorter hospital stays were only seen over the first 2 years of follow-up in the patients treated back in 2012. The authors explain these results by the greater experience gained in the better selection of patients who may benefit the most from TAVI, something that may have also affected the results of this study.

In this registry, as it occurred in the French one, there was a higher rate of tamponade over the last period studied. However, the conversion rate to surgery was lower, suggestive that the consolidation of the procedure and the early diagnosis of complications may have influenced the results.

A remarkable aspect is the higher overall rate of hemorrhages and renal dysfunction seen in cohort B. These results should be interpreted with caution because there are no data on the severity and cause for these events. However, given the reduced mortality seen in this period, it can be concluded that there is no significant increase of major hemorrhages, although this is just speculation due to the lack of data on this regard.

Limitations

The main limitation of this study is that it is a registry whose data have not been audited externally. Also, it is a voluntary registry that does not include all Spanish centers with TAVI-capabilities. Certain variables appear in 50% of the patients, which is something exceptional if we consider that most variables are present in 90% of the cases. The degree and causes for vascular complications (hemorrhage and renal failure) are not available and data should be interpreted with caution. On the other hand, the change in the adjudication of events derived from the different definition used over the first and second periods (Valve Academic Research Consortium and Valve Academic Research Consortium II, respectively) may vary in some patients although this would be an exception.

CONCLUSIONS

This study shows the better risk profile and more successful implantation rate of patients treated over the last few years. This has reduced in-hospital and 30-day all-cause mortality.

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The Section of Hemodynamics and Interventional Cardiology of the Spanish Society of Cardiology sponsors the maintenance and exploitation of the database.

CONFLICTS OF INTEREST

R. Trillo-Nouche is a proctor of TAVI valves for Medtronic and Boston Scientific. M. Pan has participated and received funds for the lectures given on behalf of Abbott, Terumo Medical Corporation, and Philips Volcano. R. Moreno is an associate editor of *REC: Interventional Cardiology*; the editorial protocol of the journal was observed to guarantee an impartial manuscript handling. R. Moreno has participated and received funds for lectures, counsel, and congress attendance on behalf of Edwards Lifesciences, and is a proctor of the Lotus and ACURATE neo valves (both from Boston Scientific). Also, R. Moreno has participated and received funds for the lectures, counsel, and congress attendance on behalf of Boston Scientific, and is a proctor of the Allegra valve from New Vascular Therapy. I. Amat-Santos is a proctor of Boston Scientific. R. Romaguera has participated and received funds from Medtronic and Palex Medical. A. Pérez de Prado has participated and received funds for counseling provided to Boston Scientifice iVascular, and for the lectures given on behalf of Abbott, B Braun Surgical, Terumo Medical Corporation, and Philips Volcano. L. Nombela-Franco is a proctor for Abbott and has participated and received funds for lectures given on behalf of Edwards Lifesciences. F. Alfonso is an associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. J.M. de la Torre Hernández is the editor-in-chief of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- In national registries like the French one, a time change in the clinical profile and progression of patients treated with TAVI has been confirmed. However, these findings have not been made in the time analysis of the English registry.

WHAT DOES THIS STUDY ADD?

- The main contribution of this study is the publication of all data from our national database. Also, that results will be included in the medical literature and that the time change seen in the profile of patients and clinical results is indicative of a growing experience with the implantation technique and improvements in valve design

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000104.

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Special article

Consensus document of the Interventional Cardiology and Heart Rhythm Associations of the Spanish Society of Cardiology on the management of invasive cardiac procedure rooms during the COVID-19 coronavirus outbreak

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ABSTRACT

During March 2020, the SARS-CoV-2 virus spread throughout Europe, with the spread being especially intense in Italy and Spain. Given the emergency created by the COVID-19 outbreak, routine activity has been altered in most cardiac catheterization and electrophysiology labs. Health staff working in these areas are faced with performing procedures in patients with a confirmed diagnosis of COVID-19 or with uncertainty in unconfirmed cases. This article is a consensus document of the Interventional Cardiology Association and Heart Rhythm Association of the Spanish Society of Cardiology and aims to provide information to health care professionals working in these invasive cardiology facilities (cardiac catheterization and electrophysiology labs, pacemaker implantation) in order to guarantee quality patient care and adequate levels of infection prevention.

Keywords: Interventional Cardiology. Electrophysiology. Infection. Prevention. COVID-19. Coronavirus. Pandemic.

Gestión de salas de procedimientos invasivos cardiológicos durante el brote de coronavirus COVID-19. Documento de consenso de la Asociación de Cardiología Intervencionista y la Asociación del Ritmo Cardiaco de la Sociedad Española de Cardiología

RESUMEN

Durante marzo de 2020, el virus SARS-CoV-2 se ha extendido por toda Europa, con especial intensidad en Italia y España. Ante la emergencia creada por el brote de COVID-19, la inmensa mayoría de las salas de hemodinámica y electrofisiología han visto alterada su actividad habitual. Además se enfrentan a la realización de procedimientos en pacientes con diagnóstico confirmado de COVID-19 o con la incertidumbre en casos no confirmados. El presente texto es un documento de consenso de la Asociación de Cardiología Intervencionista y la Asociación del Ritmo Cardiaco de la Sociedad Española de Cardiología que pretende dar información al personal sanitario de estas instalaciones de cardiología invasiva (hemodinámica y electrofisiología y marcapasos) para garantizar una atención de calidad a los pacientes así como unos niveles los niveles adecuados de prevención de la infección.

Palabras clave: Cardiología intervencionista. Electrofisiología. Infección. Prevención. COVID-19. Coronavirus. Pandemia.

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INTRODUCTION

On 31 December 2019, the authorities of the People's Republic of China informed the World Health Organization of several cases of pneumonia of unknown cause in Wuhan, a city located in the Chinese province of Hubei. One week later, they confirmed that the cases were due to a new coronavirus, named SARS-CoV-2. During February, the virus spread through northern Italy and subsequently throughout the rest of Europe, including Spain, where measures to contain the spread were initiated on 10 March, 2020. On 13 March, 2020, the Spanish Government issued a decree (article 116.2 of the Spanish Constitution) declaring a state of alarm with immediate effect. The decree involves changes to the organization of health care installations, staff, and services. In line with the new legal situation, the respective health departments of the autonomous communities modified the regulations generally affecting the availability of health staff (eg, working hours, granting of leave, holidays or days off, exemptions), clinical care, and procedures, often restricting activity to emergency care. The Interventional Cardiology Association and the Heart Rhythm Association of the Spanish Society of Cardiology understand the need to make our commitment public and to adapt our practice to the best practices in the current regulatory context.

Like other viruses in the coronavirus family, this pathogen causes various clinical manifestations encompassed within the term COVID-19, which include respiratory illness ranging from the common cold to severe pneumonia with respiratory distress syndrome, septic shock, and multiorgan failure.[1] Moreover, prognosis is poor in patients with prior cardiovascular disease and COVID-19 infection.[2] Most cases of COVID-19 notified to data have been mild, but the virus is highly contagious, mandating measures to be taken in all health care and nonhealth care settings.

Faced with the emergency created by the COVID-19 outbreak, the vast majority of cardiac catheterization and electrophysiology labs have experienced changes in their day-to-day running. Health care staff working in these areas are faced with performing procedures in patients with a confirmed diagnosis of COVID-19 and with uncertainty in those with unconfirmed infection. In addition, interventional cardiology units are generally closed units with the same team members working closely together in these areas, representing a risk for health care delivery if quarantines are declared in entire units.

The present article is a consensus document aiming to provide information to health staff in these invasive cardiology installations (cardiac catheterization, electrophysiology, and pacemakers) to guarantee delivery of quality patient care. The document also aims to provide information on how to ensure adequate levels of protection against infection among family members, persons living with infected individuals, workers in health care centers, health care workers attending infected individuals, and the remainder of the population in general.

STAFF MANAGEMENT AND INDICATIONS FOR PROCEDURES

We recommend that each unit take the appropriate measures to separate workers into groups so that possible quarantines can be applied to groups within each unit rather than the unit as a whole.

In elective patients, we recommend considering delaying procedures whenever possible.

APPROACH TO THE PATIENT BEFORE ENTRY TO THE LAB

The following steps are recommended before patients enter cardiac catheterization and electrophysiology labs (figure 1):

- Maximal coordination to minimize pre- and postprocedure waiting times in waiting areas.
- Use of surgical masks in all patients while they wait.
- Questioning of all patients about respiratory symptoms, fever, and close contacts before entry to the lab; we also recommend temperature-taking in all patients.

APPROACH TO PATIENTS WITHOUT CONFIRMATION OF COVID-19 INFECTION

Given the current panorama and the possibility of having to treat asymptomatic patients or those with undiagnosed infection, we recommend taking maximal protection measures,[3] especially in patients referred from the emergency department. Procedures involving manipulation of the airway and/or esophagus should also be considered high risk. The following measures are recommended:

- Patients: surgical mask before entry to the lab.
- Physicians and nurses: hand-washing, sterile fluid-impermeable gowns, sterile gloves, splash goggles, cap covering hair, and surgical mask.
- Cardiologists or circulating nurses: splash goggles, gloves, cap, and surgical mask.

In patients with respiratory symptoms in areas of community transmission, those with confirmed contacts and those who may require transesophageal echocardiography, manual ventilation, intubation, or any other type of airway manipulation, we recommend that the approach to infection prevention be the same as that used in patients being tested for COVID-19 infection or with confirmed infection (see next section). The approach to unstable patients, especially those with ST-segment elevation, should also be the same as that in patients with confirmed COVID-19 infection.

APPROACH TO PATIENTS WITH SUSPECTED OR CONFIRMED COVID-19 INFECTION

In patients with suspected or confirmed COVID-19 infection, we recommend the following measures:

- Consider procedures involving airway and/or esophageal manipulation as very high risk.
- Allow only essential staff to enter the lab.
- Keep doors shut at all times.
- Prepare drugs before patient entry to the lab.
- Avoid leaving the lab with contaminated equipment (eg, gown, gloves, mask, etc.) to collect material (eg, stents, catheters, etc) and consequently try to predict the necessary material as much as possible.

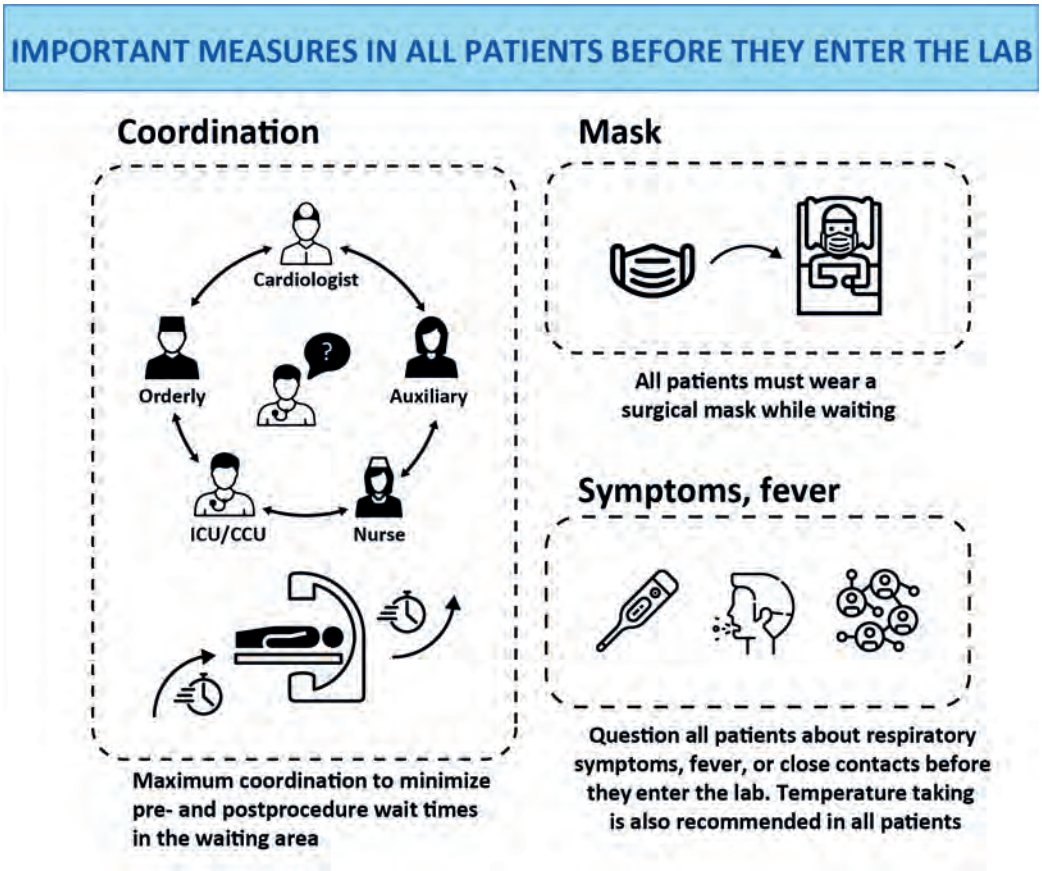

Figure 1. Important measures in all patients before they enter the lab. CCU, Cardiac/Coronary Care Unit; ICU, Intensive Care Unit.

Material

The recommended material is shown figure 2 and is described below:

- Patients: surgical mask. It is important to stress that FFP2 masks are personal protection masks and not barrier masks. The air expelled by these masks is contaminated and so they should not be worn by infected patients. Patients should wear a face mask that acts as a barrier to secretions.

- Physicians and nurses: hand-washing, coated fluid-impermeable gown with cuff (if the gown is not fluid-impermeable, a plastic apron should be added), 2 pairs of gloves (whose use is recommended by some local authorities), splash goggles or conventional goggles and face shield, cap, and high filtration efficiency FFP2 mask if available[4] (for procedures such as placement of implantable cardioverter-defibrillators, pacemakers and transcatheter prostheses, a surgical mask should be placed over the FFP2 mask). Closed work shoes are recommended or, if unavailable, boots.

- Cardiologists or circulating nurses: gloves, cap, fluid-impermeable gown and FFP2 face mask (if available).

Recommended steps for moving patients from the gurney to the operating table

Staff responsible for transferring patients with COVID-19 infection from the gurney to the operating table must wear previously placed individual personal protection equipment, including fluid-impermeable gown, cap, cuff-covering gloves, goggles and FFP2 mask (if available). On finishing the transfer, staff must undress as follows, remembering not to remove the mask under any circumstances while inside the lab.

How to dress

The steps for dressing are described below (figure 3).

Outside the lab

- Do not wear jewelry.

- Tie hair back (if necessary).

- Put on lead apron.

- Perform correct hand hygiene using routine method.

- Place FFP2 mask. The rubber bands should be placed in the following way: the bottom bands in the upper part of the neck and the top bands on the top of the head. Then adjust the height of the mask at the bridge of the nose and cheeks to isolate them and prevent leaks.[5]

- Place splash goggles.

- Place the cap.

Figure 2. Protective equipment for health care professionals in COVID-19+ patients in cardiac catheterization and electrophysiology labs. * For implantation of pacemaketers, implantable cardioverter-defibrillators and transcatheter prostheses, place a surgical mask over the FFP2 mask. FFP2, filtering face piece type 2.

- Perform second hand-washing, with use of alcohol-based hand sanitizer and rubbing.
- Put on the first pair of gloves.
- Put on the gown.

Inside the lab

- Roll the second pair of gloves over your fist.

How to undress

We recommend that staff undress as shown in figure 3 and described below.

Inside the lab

- As you remove the gown, peel off the outer pair of gloves at the same time[6] and discard into a group III container (do not push the gown down into the container to avoid releasing aerosol, which could be contaminated).

Outside the lab

- Remove cap.
- Peel off the second pair of gloves.
- Wash hands.
- Remove splash goggles with eyes closed.
- Remove the mask by lifting the elastic bands. Under no circumstances touch the front of the mask (which should be assumed to be contaminated).
- Wash hands.

If only 1 pair of gloves are worn, first remove them, taking extreme care to avoid contact with the contaminated surface. Then remove the gown by grasping the inside of the gown, taking maximal caution to avoid skin contact with the outer surface.[7]

Important: Contaminated gowns and gloves (outer ones) should never leave the lab. Staff should never be inside the lab without an FFP2 mask, as a minimum precaution. Masks must always be placed before entering the lab and must not be removed until after staff have left the lab.

After completion of the procedure

After the end of the procedure:

- We recommend disinfecting goggles with wipes impregnated with a wide spectrum biocidal agent to disinfect surfaces. Leave them wet and air dry. Use gloves to disinfect, due to the toxicity of the wipes and potential contamination of surfaces.
- Discard all material used in the procedure in a group III container for biomedical waste and then seal the container.
- Consider changing scrubs.
- Patients must wear a surgical mask during transfer to the ward or referral center and the orderly or physician (if required) must wear an FFP2 mask.

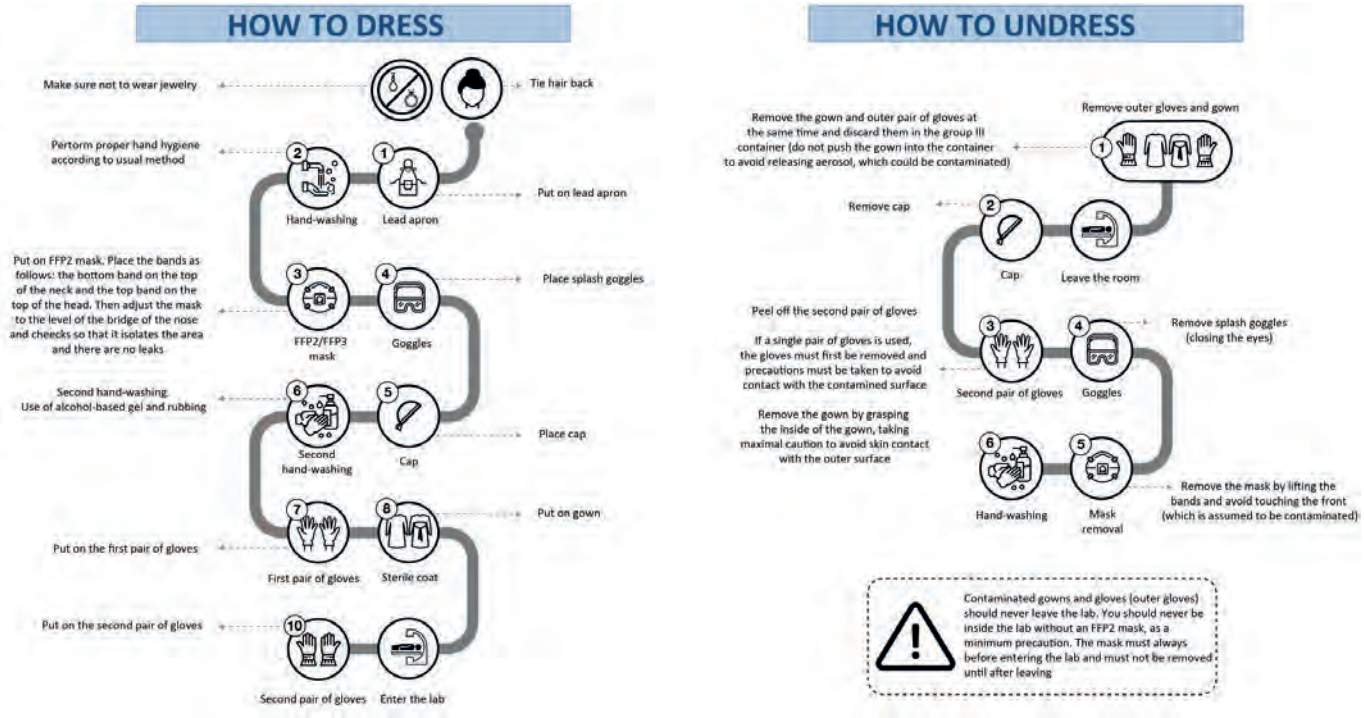

Figure 3. Guidelines on how health staff in cardiac catheterization and electrophysiology labs should dress and undress. FFP, filtering face piece.

Lab cleaning

We recommend the following cleaning measures:

- Labs should be cleaned by following specific procedures for contact and drip isolation in each center. For example, by using sodium hypochlorite at a concentration of 1000 parts per million, leaving it in contact with the surface for 5 minutes.
- Cleaning cloths should be discarded (disposable).
- Cleaners should be equipped with personal protection equipment.
- After lab cleaning, consider cleaning all areas where the infected patient has been in contact with an ultraviolet-disinfectant robot.
- Labs should be cleaned at least 1 hour after the procedure, rather than immediately, to allow aerosol deposition.

SPECIAL SITUATIONS: SEVERELY ILL PATIENTS

If oxygen is required, a mask should be placed over the nasal cannula or oxygen mask.

We discourage the use of nebulizers in patients with COVID-19 and also advise against the use of noninvasive positive pressure ventilation (continuous positive airway pressure [CPAP] and bilevel positive airway pressure [BiPAP]).

In patients requiring intubation and mechanical ventilation or cardiopulmonary resuscitation, extreme care should be taken to apply preventive measures due to the high risk of droplet release.

ROUTINE CARDIOLOGY DRUGS IN PATIENTS WITH COVID-19

Angiotensin converting-enzyme inhibitors/angiotensin II receptor antagonists

There is no evidence to support the hypothesis that these drugs may cause deleterious effects during COVID-19 infection. In contrast, there is much evidence of their cardiovascular benefits in specific populations. Therefore, unless there is a change in current evidence, we advise against their withdrawal unless there is hemodynamic instability.[8]

Antithrombotic agents

Any inflammatory process increases platelet reactivity. However, there is no current evidence to support any use other than routine use during COVID-19 infection. Therefore, the use of antithrombotic and antiplatelet agents should continue to be considered according to the patient's clinical situation and bleeding risk.

CONFLICTS OF INTEREST

None declared.

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EDITOR'S NOTE

This manuscript has undergone an especially rapid internal review by the editorial team due to the strong interest in

disseminating the information among the scientific community. The editors thank Permanyer Publications for their collaboration and commitment to the prompt publication of this document.

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REC Interv Cardiol. 2020;2(2):112-117

Special article

Considerations on the invasive management of ischemic and structural heart disease during the COVID-19 coronavirus outbreak. Consensus statement of the Interventional Cardiology Association and the Ischemic Heart Disease and Acute Cardiac Care Association of the Spanish Society of Cardiology

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ABSTRACT

The current COVID-19 outbreak is forcing healthcare workers to continuously reconsider the proper indications for cardiac catheterization. Human and material resources optimization, infection prevention for patients and healthcare workers, and transfer times force a rethink of the previously established protocols. This article is a consensus statement of the Interventional Cardiology Association and the Ischemic Heart Disease Association of the Spanish Society of Cardiology and aims to provide information to healthcare workers on the indications of diagnostic or therapeutic cardiac catheterization during the current COVID-19 pandemic.

Keywords: Myocardial infarction. Interventional cardiology. Angioplasty. Infection. Prevention. COVID-19. Coronavirus. Pandemic.

Consideraciones sobre el abordaje invasivo de la cardiopatía isquémica y estructural durante el brote de coronavirus COVID-19. Documento de consenso de la Asociación de Cardiología Intervencionista y la Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares de la Sociedad Española de Cardiología

RESUMEN

El brote actual de COVID-19 está obligando a los profesionales sanitarios a replantear de forma continua las indicaciones de cateterismo cardiaco. La optimización de recursos materiales y humanos, la prevención de contagios a profesionales y pacientes, así como la gestión de los tiempos de traslado, hace totalmente necesario reformular los protocolos previamente establecidos. El presente texto es un documento de consenso de la Asociación de Cardiología Intervencionista y la Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares de la Sociedad Española de Cardiología que pretende dar información al personal sanitario sobre las indicaciones de cateterismo diagnóstico o terapéutico durante la pandemia actual de COVID-19.

Palabras clave: Infarto. Cardiología intervencionista. Angioplastia. Infección. Prevención. COVID-19. Coronavirus. Pandemia.

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INTRODUCTION

The current outbreak of COVID-19 has caused all healthcare providers have to rethink the indications for cardiac catheterization on an ongoing basis. The optimization of material and human resources, the prevention of contagions to healthcare providers and patients, and management during patient transfers makes it absolutely necessary to reformulate the protocols previously established. This consensus document has been agreed by the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (ACI-SEC) and the Spanish Society of Cardiology Working Group on Ischemic Heart Disease and Acute Cardiovascular Care. It includes indications to perform cardiac catheterizations under the current situation. It is difficult to foresee the evolution of this pandemic and its health impact, which will probably force us to readjust this document based on the particular situation and dynamic of each center. It is important to emphasize that when the actual situation is over, we recommend going back to the indications included in the clinical practice guidelines published by the European Society of Cardiology.[1]

In order to perform cardiac catheterizations our advice is to follow the recommendations on prevention and management included in the consensus document published by the ACI-SEC and the Heart Rhythm Association of the Spanish Society of Cardiology.[2]

ELECTIVE PROCEDURES

Indication for elective procedures in the catheterization laboratory should be based on individual assessments of the risk of contagion/benefit from the intervention ratio. In the current situation postponing all elective procedures seems the most reasonable thing to do to minimize the possibility of contagion of disease-free patients (and people they may have been in contact with) in a setting of high prevalence of COVID-19 infection such as hospitals. Similarly, performing right catheterizations during this pandemic is ill-advised.

If the cath lab has enough material and human resources, the non-emergent catheterizations of already hospitalized patients without suspicion of COVID-19 or COVID-19-negative patients may be an option to promote early discharges (ie, a study to characterize dilated cardiomyopathy in a patient admitted with an index episode of heart failure).

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Differential diagnosis

A key element to be taken into consideration when indicating a cardiac catheterization in a patient with acute coronary syndrome (ACS) is the high prevalence of heart disease in patients admitted due to COVID-19,[3] the significantly high troponin levels (8% to 12% higher) seen in confirmed cases of COVID-19 but without ACS yet,[4] and the possibility that myocarditis complicates the COVID-19 infection.[5] This highlights the importance of clinical judgement before establishing a diagnosis of ACS/acute myocardial infarction. In general, in patients hospitalized due to COVID-19 infection who experience high cardiac enzyme levels of coronary origin and remain asymptomatic we recommend following a conservative approach. Coronary angiography should be spared for cases of high suspicion of high-risk ACS, medical treatment-resistant recurrent ischemia, and when the patient's vital prognosis following the infection anticipates good prognosis.

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Figure 1 shows the approach suggested for patients with non-ST-segment elevation acute coronary syndrome (NSTEACS). In patients hospitalized due to NSTEACS with suspicion of COVID-19 we recommend running the diagnostic test before performing the cardiac catheterization to assess the risk/benefit ratio of the procedure. The current clinical guidelines on revascularization recommend an early invasive strategy (< 24 h) in patients with at least 1 criterion of high risk and in < 72 h in patients with at least 1 criterion of intermediate risk.[6] In most of the patients with NSTEACS this interval should be enough to confirm or discard the infection. The procedure should be postponed if the patient's clinical situation allows it in cases where the diagnostic test is not available yet. On the contrary, in patients with NSTEACS but with persistent ischemia or high-risk criteria like recurrent angina, diffuse ST-segment changes suggestive of left main coronary artery or ventricular dysfunction performing the catheterization within the first 2 hours may be an option, taking the necessary protective measures to avoid transmitting the infection.

Patients negative for COVID-19 undergoing the procedure should be discharged early from the hospital.

In patients admitted to centers without a cath. lab. who need to be transferred, it is advisable, if possible, to follow a conservative approach and early discharge except for high-risk criteria or poor disease progression.

In selected patients with acute myocardial infarction —especially type 2[7]— the conservative approach is the one recommended initially.

Revascularization in NSTEACS and multivessel disease

In patients with NSTEACS and multivessel disease and an indication for complete revascularization who remain hospitalized in centers where surgeries have been postponed, we recommend performing it within the same procedure to reduce hospital stay and avoid having to perform another procedure in the cath. lab.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

The reperfusion treatment during the management of ST-segment elevation elevation myocardial infarction (STEMI) of < 12 hour-duration since symptom onset should be the primary percutaneous coronary intervention (pPCI) because it reduces the rates of mortality, reinfarction, stroke,[1] and mechanical complications compared to fibrinolysis. Also, a significant percentage of patients undergoing pPCI can be discharged early and don't require further invasive examinations which simplifies the management of these patients. This reduces the hospital stay and avoids collapsing the entire healthcare system. Nevertheless, during the COVID-19 pandemic the following key points should be taken into consideration:

- Due to the current care overload sustained by the ERs of our healthcare system, transfer times can take longer than usual in many cases.

- The transfer of patients with suspicion or confirmation of COVID-19 should take place safely and with infection under control. Also, after the transfer the ambulance should be properly disinfected. Therefore, the logistics required to guarantee safe transfers can also delay the entire process.

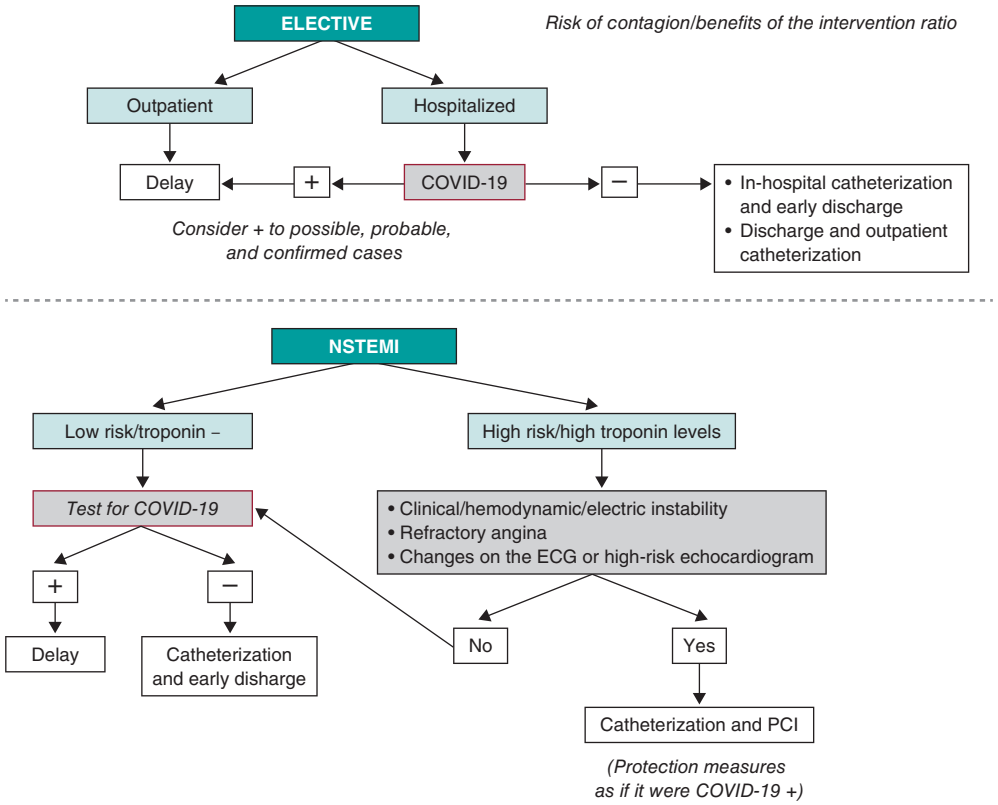

Figure 1. Algorithm for the management of elective patients and non-ST-segment elevation myocardial infarction (NSTEMI). ECG, electrocardiogram; PCI, percutaneous coronary intervention.

- Despite the preventive measures implemented to avoid transmitting the infection, the transfer of patients with an active infection for COVID-19 to a different center can infect the healthcare providers and, most important of all, other patients hospitalized and who are especially vulnerable to the disease.

- In patients already diagnosed with COVID-19 and in poor clinical state (especially patients hospitalized in intensive care units) with STEMI, repefusion treatment may yield no clinical benefits.

Reperfusion strategy

Figure 2 shows the management of STEMI. The ACI-SEC and the Spanish Society of Cardiology Working Group on Ischemic Heart Disease and Acute Cardiovascular Care recommend that the percutaneous coronary intervention should be the reperfusion strategy of choice in most cases. Fibrinolysis should be spared for cases diagnosed in non-PCI capable centers that meet one of the following requirements:

- Estimated time to the pPCI > 120 min.

- Patients who have tested positive to COVID-19 with poor clinical state that makes transfer difficult.

- Patients who have tested positive to COVID-19 with low hemorrhagic risk and symptoms of < 3 hour-duration.

In cases where fibrinolysis may be an option, the lack of contraindications and the administration of the drug in < 10 min from diagnosis should be guaranteed.[1] Then, depending on the patient's clinical state and the availability of beds in the ICU of the destination hospital, transfer to a center with cath. lab. capabilities may be considered. The rule of thumb here is to avoid transferring patients with confirmed reperfusion and good disease progression.

After the percutaneous coronary intervention, it is recommended that each patient be taken to their referring centers. However, the patients' clinical situation and bed availability of each center should be individualized in each case.

Other considerations

As a general rule we recommend leaving the number of centers that are part of the infarction code program untouched. Although demand from out-of-hospital emergency medical services may change significantly during the COVID-19 pandemic, a hospitalized patient may have an indication for an urgent cardiac catheterization. In the current situation, transferring this patient to a different center may be more problematic than performing the procedure at the center where the patient is already hospitalized. Our recommendation here is that no PCI capable center should avoid treating infarctions.

Other clinical considerations:

- The diagnosis of STEMI in patients with complete left bundle-branch block is still complex to this day despite the use of different electrocardiographic criteria.[8] Therefore, in patients with suspicion or confirmation of COVID-19 who require transfer for reperfusion we recommend agreeing on the diagnosis as much as possible to avoid unnecessary transfers.

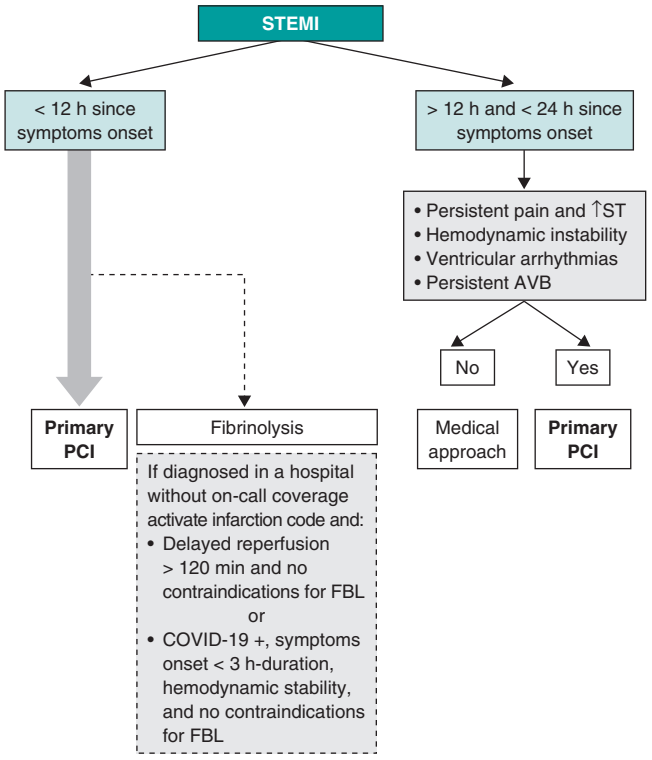

Figure 2. Algorithm for the management of patients with ST-segment elevation myocardial infarction (STEMI). AVB, atrioventricular block; FBL, fibrinolysis; PCI, percutaneous coronary intervention.

- The management of patients with recovered sudden death without overt electrocardiographic criteria of STEMI is still controversial. Although a recent randomized clinical trial showed that these patients don't benefit from an immediate coronary angiography,[9] it is still being performed in most centers. However, due to their clinical situation—if infected—these patients are extremely prone to secreting microdroplets and infecting the healthcare providers. At the same time they are very vulnerable to infection if they are not already infected. For this reason, immediate PCIs are ill-advised in these patients.

- In patients with STEMI without cardiogenic shock and multivessel disease the overall recommendation is to perform a complete revascularization.[10] However, in the current situation, we believe that the management of STEMI should be as simple as possible. In this sense, we believe that in most of these patients the management of non-culprit lesions should be postponed until the outbreak of COVID-19 is over. On the other hand, in patients with a clear need for complete revascularization at admission, we recommend the study of all lesions within the same procedure during the acute phase.

CARDIOGENIC SHOCK

In situations of acute coronary syndrome related cardiogenic shock, cardiac catheterization is indicated. The management of critically ill patients is especially complex because intubation, aspiration, and CPR maneuvers can prompt respiratory secretions in the form of aerosols and increase the exposure of the healthcare providers. All critically ill patients should be treated as patients with COVID-19.

The following key points should be taken into consideration:

- As in the rest of patients with cardiogenic shock, only the culprit vessel should be revascularized.[11]

- If intubation is necessary and possible, it should be performed before entering the cath. lab. and in the best conditions possible to comply with all COVID-19 prevention recommendations.

- Connection to a ventilator —a closed system— is recommended prior to manual ventilation with an ambu-bag. If ventilation with manual resuscitation is necessary, the use of high-efficiency particulate air (HEPA) filters between the tube and the bag is recommended.

- The extracorporeal membrane oxygenation (ECMO) machine used by the heart team should be purged at all times before the arrival of patients to reduce the possibility of infection and speed up the whole process. In patients with COVID-19 with cardiogenic shock, ECMO can be used as the first-line therapy compared to other devices like the Impella ventricular support system or the intra-aortic balloon pump counterpulsation.

STRUCTURAL HEART INTERVENTIONS

In general, all structural heart interventions should be postponed until the pandemic is under control. We should remember that most of these procedures require several days at the hospital, but at the same time the ICU/coronary unit beds may become necessary for patients with COVID-19. Also, in some cases structural heart interventions are performed under general anesthesia and intubation or on transesophageal echocardiography monitoring. All of them high-risk situations for the infection of patients and healthcare providers. On the other hand, patients undergoing structural heart interventions are often old and therefore especially susceptible to nosocomial infection due to COVID-19.

Other urgent procedures like aortic valvuloplasty or transcatheter aortic valve implantation in patients with angina at rest, recurrent syncope or refractory heart failure can be performed.

DRUGS

Regarding the drugs commonly used at the catheterization laboratory such as antithrombotic therapies, the recommendations are basically the same regardless of whether the patient has been infected with COVID-19 or not.

The medication to treat patients with COVID-19 may interact with the most common drugs currently used at the cath lab.[12]

Figure 3 shows the most commonly used drugs in cardiology both in the context of ACS and stable coronary artery disease.

Antiplatelet therapy

- Adiro: no evidence of significant interactions.

- Oral $P2Y_{12}$ platelet receptor antagonits: prioritize prasugrel. Concomitant treatment with lopinavir/ritonavir or darunavir/cobicistat increases the effect of ticagrelor and can reduce the effect of clopidogrel.

- Cangrelor: no evidence of significant interactions.

- Tirofiban: no evidence of significant interactions.

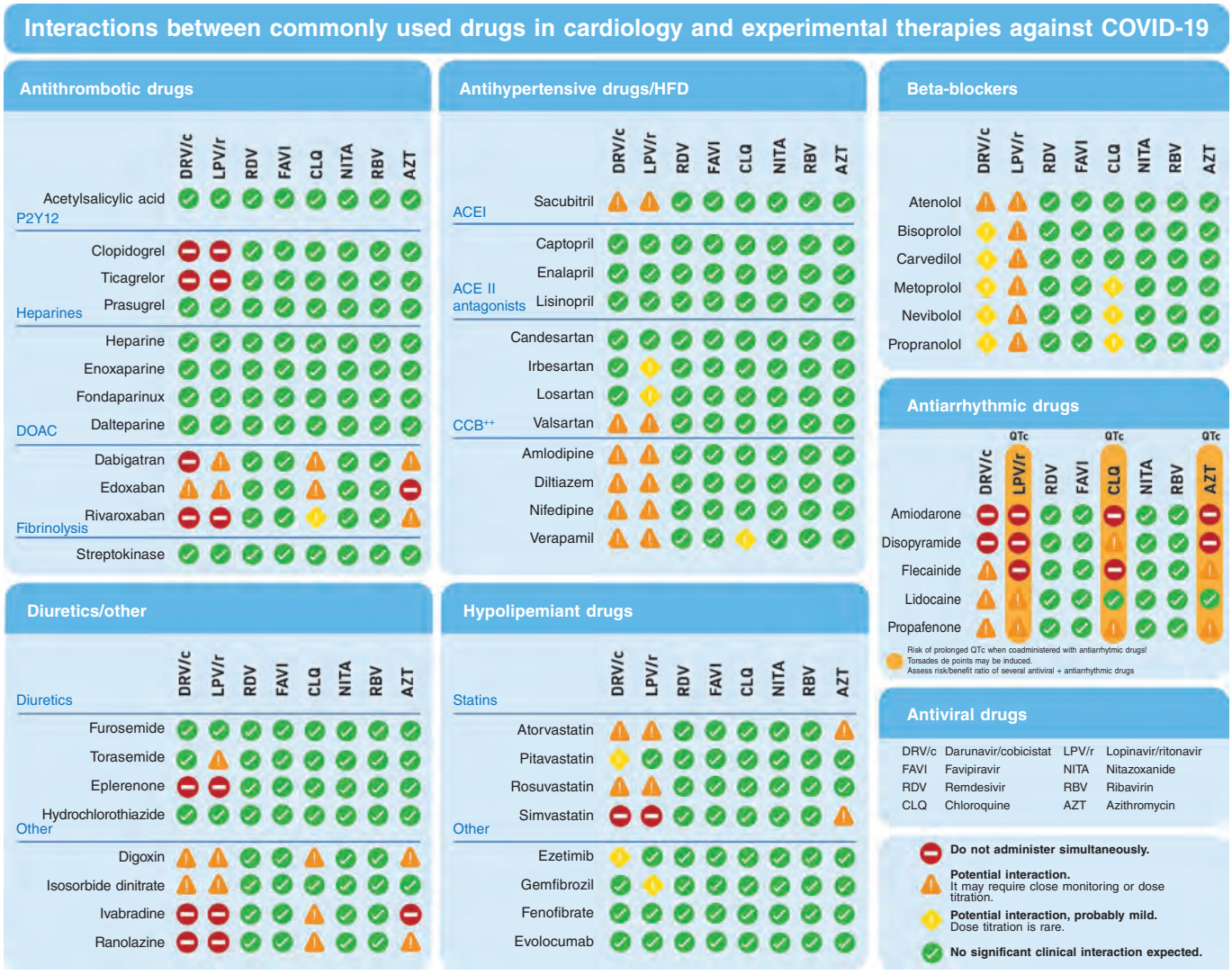

Figure 3. Possible interactions between the most commonly used drugs in cardiology and the possible treatments used against COVID-19. ACE II, angiotensin-converting enzyme antagonists; ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; DOAC, direct-acting oral anticoagulants; HFD, heart failure drugs.

Anticoagulant drugs

- Unfractionated heparin: no evidence of significant interactions.
- Bivalirudin: no evidence of significant interactions.
- Enoxaparin: no evidence of significant interactions.
- Fondaparinux: no evidence of significant interactions.

Analgesics/sedatives

- Fentanyl/morphine: potential interactions; prioritize morphine.
- Midazolam: it should not be administered orally. It can be IV administered with special caution.

Inotropes and vasopressors

- Adrenaline: no evidence of significant interactions.
- Dobutamine: no evidence of significant interactions.
- Noradrenaline: no evidence of significant interactions.
- Dopamine: no evidence of significant interactions.

Other

- Nitroglycerin: no evidence of significant interactions.
- Verapamil: potential interactions. Administer and use with special caution and close monitoring.
- Furosemide: no evidence of significant interactions.

CONCLUSIONS

The current outbreak of COVID-19 has made us rethink the invasive approach to ischemic and structural heart disease. The recommendation of the Spanish Society of Cardiology Working Groups on Cardiac Catheterization and Interventional Cardiology and Ischemic Heart Disease and Acute Cardiovascular Care is to postpone all non-emergent procedures to avoid the infection of patients and healthcare providers and minimize the collapse of the healthcare system. However, the percutaneous coronary intervention should still be used for the management of ST-segment elevation myocardial infarction unless prescribed otherwise.

CONFLICTS OF INTEREST

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

EDITOR'S NOTE

This manuscript has undergone an especially rapid internal review by the editorial team due to the strong interest indisseminating the information among the scientific community. The editors thank Permanyer Publications for their collaboration and commitment to the prompt publication of this document.

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Special article

Percutaneous management of tricuspid regurgitation. Image-guided step-by-step MitraClip procedure

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ABSTRACT

Severe tricuspid regurgitation is independently associated with an increased mortality. Recent studies show that surgery for isolated tricuspid valve (TV) is still associated with the highest surgical risk of all valve procedures. Percutaneous treatments for the management of tricuspid regurgitation have become an alternative to surgery in select patients of high surgical risk. To this day, the most widely used device is MitraClip in the tricuspid position. We reviewed the different devices used today for transcatheter treatments paying special attention to MitraClip. We describe the basic standpoints on transesophageal echocardiography screening and step-by-step procedure for the implantation of the clip. This document stands as a guide to systematize tricuspid valve assessments and the steps involved in device implantation to achieve successful procedures.

Keywords: Tricuspid regurgitation. Transesophageal echocardiography. Transcatheter tricuspid valve repair.

Tratamiento percutáneo de la insuficiencia tricuspídea. Procedimiento detallado guiado por imagen con MitraClip

RESUMEN

La insuficiencia tricuspídea se asocia de manera independiente con un aumento de la mortalidad. Investigaciones recientes demuestran que la cirugía aislada de la válvula tricúspide presenta la mortalidad quirúrgica más alta dentro de los procedimientos valvulares. Las terapias percutáneas han surgido como una alternativa a la cirugía en pacientes seleccionados de alto riesgo quirúrgico. El dispositivo MitraClip en posición tricuspídea ha sido el más empleado. El propósito de este artículo es revisar los diferentes dispositivos transcatéter para el tratamiento de la insuficiencia tricuspídea, con especial énfasis en el MitraClip. Se describirán las vistas básicas de la exploración por imagen y el procedimiento paso a paso para la inserción del clip. Este documento pretende ser una guía para la sistematización de la evaluación de la válvula tricúspide y los pasos del implante del dispositivo para asegurar el éxito del procedimiento.

Palabras clave: Insuficiencia tricuspídea. Ecocardiograma transesofágico. Reparación tricuspídea transcatéter.

Abbreviations

RV: right ventricle. **TTE:** transthoracic echocardiogram. **TEE:** transesophageal echocardiogram. **TR:** tricuspid regurgitation. **TV:** tricuspid valve.

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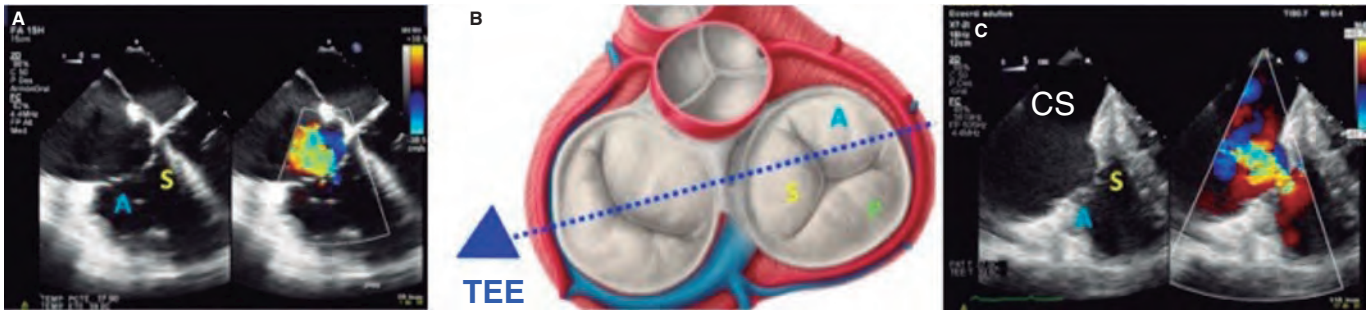


Figure 1. A: mid-esophageal 4-chamber view showing the septal leaflet and the anterior leaflet. **B:** imaginary view in the 4-chamber view. **C:** deep transesophageal view. A, anterior; TEE, transesophageal echocardiogram; S, septal; CS, coronary sinus.

INTRODUCTION

Although traditionally tricuspid valve disease has been considered a less serious condition compared to left-sided valvular heart disease, nearly 2 million patients in the United States suffer from moderate tricuspid regurgitation (TR). However, less than 10 000 patients are treated with surgery each year. Functional TR amounts to 90% of all cases of TR and is often due to tricuspid valve (TV) annular dilation (mainly in the anteroposterior diameter) and right ventricle (RV) dilation due to progressive left heart disease.[1] TV has been considered "the forgotten valve" for years. This problem may be explained because it was believed that TR was well-tolerated and decreased after treatment of the left-sided valvular heart disease. However, patients with significant TR and heart failure often remain very symptomatic.[2] The presence of moderate or severe TR is associated with a higher mortality rate regardless of other variables like the ejection fraction or pulmonary pressures. Mortality rate is > 25% per year.[3-5]

Current data confirm that repairing the TV while performing left heart cavity surgery is safe. However, reinterventions due to persistent TR are associated with high morbidity and mortality rates.[6] Recent studies show that isolated TV surgery is still the valve surgery that is most associated with higher surgical risk and mortality rates between 8.8% and 9.7%.[7] Therefore, the percutaneous therapies for the management of TR are an alternative to conventional surgery for patients who, until recently, were eligible for conservative medical treatment only for being high surgical risk patients.

Depending on the repair anatomical target, devices can be divided into coaptation, valve annuloplasty, and replacement devices (whether in the orthotopic or heterotopic position). The most widely used technique is the edge-to-edge repair with the MitraClip device (Abbott Vascular, Santa Clara, United States) in the tricuspid position. The TriValve registry[8] included over 650 procedures with the MitraClip device (66% of all percutaneous procedures performed on the TV). This article has 2 objectives: first, to propose a protocol for the echocardiographic assessment of TV in patients with TR to decide on the suitability and feasibility of performing tricuspid repair with this system and guiding the procedure on a step-by-step basis; and second, to review briefly other transcatheter percutaneous devices available today that have already become clinically relevant.

TRICUSPID VALVE IMAGING FOR INTERVENTIONAL PROCEDURES

All patients eligible for tricuspid percutaneous procedures should initially be treated with a transthoracic echocardiogram (TTE). If the valve can be repaired using the edge-to-edge technique, a more advanced assessment using the transesophageal echocardiogram (TEE) should be performed.

TVs that clearly interfere with pacemaker or implantable defibrillator leads, leaflet perforation, severe restriction or significant thickening should not be considered favorable on the TTE. The traditional views for TV assessment through TTE are the parasternal view on the TV modified long axis, the short axis, the modified apical 4-chamber view, and the subcostal view in the short axis.

TEE assessments are crucial to decide whether a procedure using this device is feasible or not. Anatomy should be adequate, yet images should have enough quality to guide the procedure; at times, anatomical variants or the presence of intracardiac prosthetic material can make the procedure unfeasible. The current TEE guidelines established by the American Society of Echocardiography include additional images for TV assessment purposes.[9] Multiplane rotations and multiple views are important for correct leaflet identification including adjacent structures used as reference.[10]

TRICUSPID VALVE ASSESSMENT THROUGH TRANSESOPHAGEAL ECHOCARDIOGRAM

The essential views for a detailed assessment of the TV regarding transcatheter procedures are:

1. Mid-esophageal 4-chamber view at 0°. The septal leaflet (adjacent to the aorta) and the anterior leaflet (adjacent to the RV free wall) can be seen when the transducer is in anteflexion position (figure 1). The posterior leaflet can be seen when it is in the retroflexion position.

To optimize the images of the right heart structures, the transducer should be turned clockwise. The artifacts of the septum and aortic or mitral valves can block the view of the septal leaflet. Tricuspid annulus is measured in this view with open flap-like cusps at the end of the diastole.

2. Mid-esophageal view of the RV inflow and outflow tract (intercommissural tricuspid view) between 60° and 90°. It shows the imaginary line from the anteroseptal (A-S) commissure up to the posteroseptal (P-S) commissure. The anterior leaflet close to the aorta and the posterior leaflet on the lateral side can be seen (video 1 of the supplementary data). This is the reference view to obtain biplanar images for the assessment of the septal leaflet. By bringing the cursor close to the aorta (X-plane tool), the orthogonal view shows the A-S coaptation and the anterior and septal leaflets.

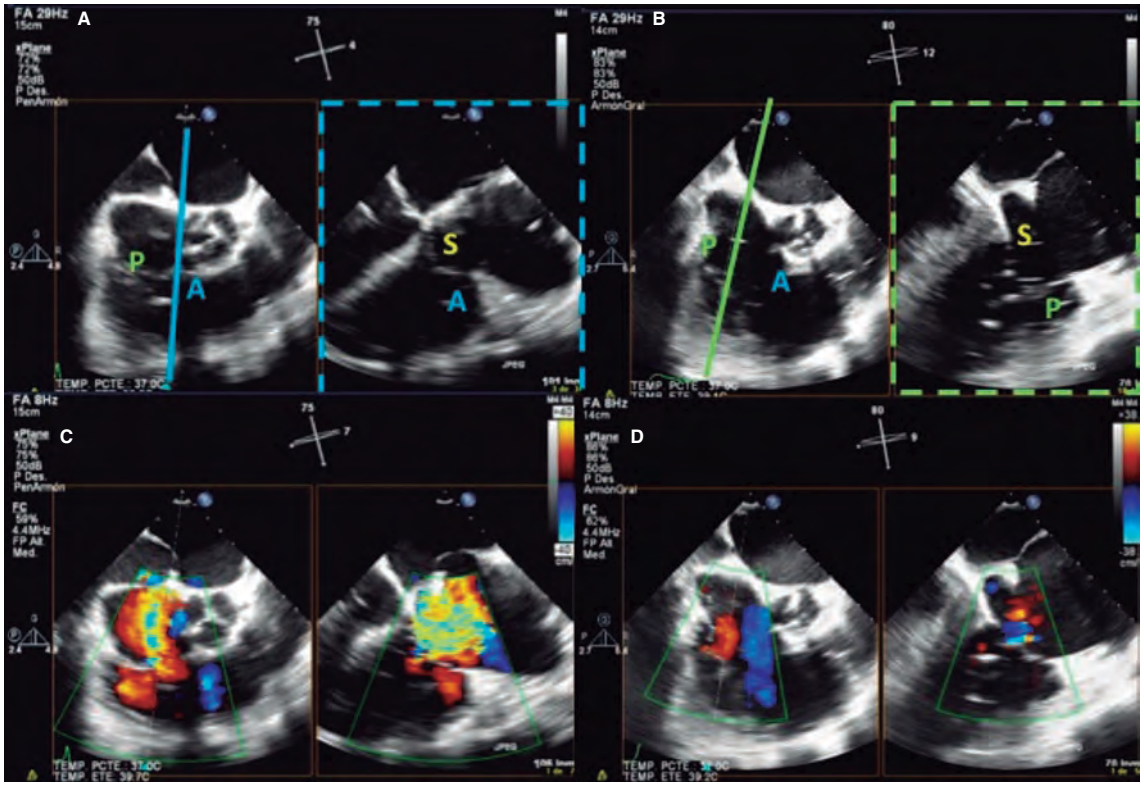


Figure 2. Intercommissural mid-esophageal view. **A:** when placing the cursor next to the aorta, the orthogonal view shows the anteroseptal coaptation line. **B:** by moving the cursor towards the most lateral region, the orthogonal view is acquired showing the posteroseptal coaptation line. **C and D:** color biplanar imaging showing the origin of regurgitation jet. A, anterior; P, posterior; S, septal.

By moving it away from the aorta towards the lateral position, the view shows the P-S coaptation and the posterior and septal leaflets. The same views should be acquired using the Doppler color technique (figure 2) to see whether the origin of the regurgitant jet is of anterolateral or P-S predominance.

Also, these views are useful to measure the length of the leaflets, see coaptation defects, assess the movement of the leaflets, and see the presence of strings that can make the procedure difficult. The presence of serious restrictions in the movement of the septal leaflet limits the performance of the procedure with the current device.

3. Deep esophageal 4-chamber view at 0°. Since the right inferior border of the heart is close to the diaphragm, the deepest insertion of the TEE transducer reaches the distal esophagus, close to the gastroesophageal junction; it may be that this view will only show the right atrium and coronary sinus and no images of the left atrium (figure 1). This prevents left heart structure-related artifacts from happening like the acoustic shadowing that the mitral prosthetic material can cause on the septal leaflet. This is the optimal view to acquire 3D volumes.

4. Transgastric view. These views are acquired by advancing the transducer towards the stomach. Starting at the baseline transgastric short axis and by rotating the transducer between 20° and 40° and making small clockwise rotations with anteversion, the optimal view to see the 3 tricuspid leaflets is acquired (TV short axis). This is the only 2D (bidimensional) view to see the 3 cusps and commissures simultaneously with the posterior leaflet in the nearby field, the anterior leaflet in the distant field, and the septal one adjacent to the septum (figure 3 and video 2 of the supplementary data). Images need to be optimized to make sure we are positioned on the tip of the leaflets and parallel to the valvular view. To do this we can start with a 2-chamber transgastric view of the RV at around 90°-110°. By using the X-plane tool to place the cursor on the tip of the leaflets, the orthogonal view will be acquired (that will be the TV short axis). This view provides a great deal of information on the TV:

- Number of leaflets: there are usually 3, but we may find valves with several scallops and even 4 cusps in up to 40% of the patients.[11]

- Portion of the valve occupying each leaflet: it is very useful to make a graphic representation of what part of the circumference occupies each leaflet.

- Location of the regurgitant jet origin: the leaflets distal edge needs to be approached for a correct visualization of the coaptation defect in the short axis.

The impact of 3D images is not as powerful when performing procedures on the TV compared to the mitral valve. Lang et al.[12] suggest a standard image visualization to see a frontal view of the TV by placing the septal leaflet in the inferior position (at the 6:00 hour position). These recommendations were established at the end of the last decade when there were no transcatheter procedures and the surgical view was trying to be replicated. Rotating the image 90° with the aortic valve in the 11:00 hour position is currently the preferred option. This should improve our understanding of the anatomy of the TV by creating a common language between cardiac imaging specialists and interventional cardiologists.

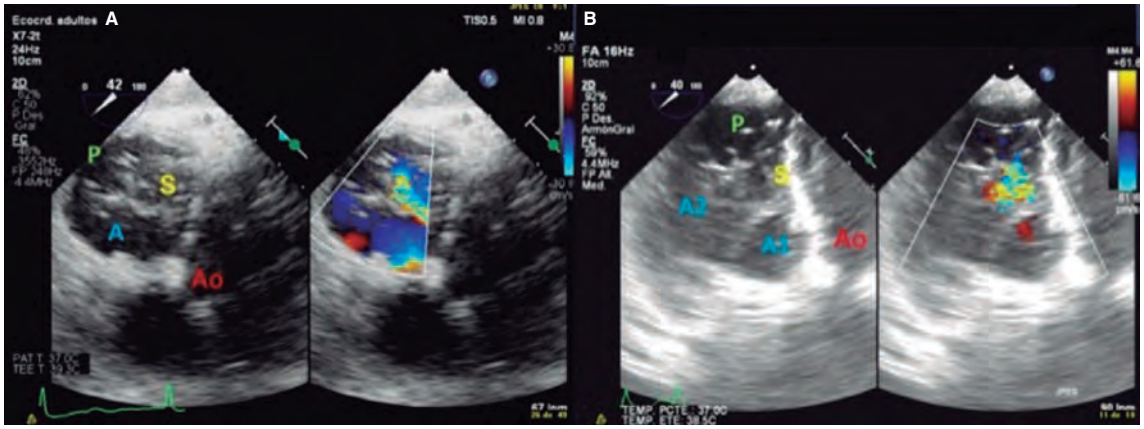


Figure 3. Transgastric view. **A:** transgastric short axis view of a tricuspid valve with 3 cusps. **B:** transgastric short axis view of an anatomical variant with 2 scallops in the anterior leaflet. A: anterior; A1, scallop 1 of the anterior leaflet; A2, scallop 1 of the anterior leaflet; Ao, aorta; P, posterior; S, septal.

The quantitative analysis of leaflets and annulus is performed through multiplanar reconstructions of 3D views.[13] By placing orthogonal views on the tricuspid annulus at the leaflet insertion site, the TV short axis is acquired. After precise adjustment the annular diameters and area dimensions can be obtained (figure 1 of the supplementary data).

The new classification of TR with new degrees of massive and torrential severity can be crucial for the adequate classification of patients and to assess the procedural final results.[14]

KEY TRANSESOPHAGEAL ECHOCARDIOGRAM VIEWS FOR TRICUSPID VALVE CLIP REPAIR

There are 4 key TEE views to guide the TV clip implantation: 4-chamber, bicommissural, transgastic, and grasping views (capture of tricuspid leaflets inside the device). The former views have already been described; we will now focus on the latter.

Grasping view

This is the view that better shows the leaflets that should be treated and the clip with wide open arms. Finding the best grasping view for clip implantation in the tricuspid position is one of the most complex and important steps during the procedure. The first limitation to find it is that, unlike what happens in the mitral valve, there are no clear anatomical references to guarantee the perpendicularity of the clip with respect to the leaflets. That is why a correct alignment at transgastric level is critical. After finding this alignment, the transducer is removed to look for the grasping view at mid-esophageal level.

The most common strategy is to place a clip between the A and S leaflets and towards the TV most central region. To acquire the grasping view and see the A and S leaflets we should start at the intercommissural view and the multiplanar view, and the grasping view will often be found at around 160° (figure 4). Another option is to perform a TEE transducer sweep from 0° to 180° until finding a direct grasping view to actually see the leaflets and the clip with wide open arms. In any case, every patient should be handled individually since the TV has more anatomical variations than the mitral valve. Also, the angle between the intercommissural view and the coaptation line of the A and S leaflets can be < 90° and mislead the multiplanar assumptions. The real-time 3D TEE can be useful to guide the clip, but not so much with mitral procedures.

STEP-BY-STEP PROCEDURE

In most cases, the MitraClip implantation in the tricuspid position is performed through femoral access under general anesthesia. It is monitored through fluoroscopy and TEE; the combination of the 2 is essential to achieve optimal results. This is the step-by-step procedure with the key data that should be assessed through imaging modality:

1. Percutaneous access through the right femoral vein using the Seldinger technique. A high-support guidewire is inserted through a 7-Fr introducer sheath towards the superior vena cava (SVC) and after access pre-dilation, the guide catheter (GC) is advanced towards the right atrium.

2. The GC is inserted similar to the way it is done in the mitral valve procedure and the handle is ± rotated approximately 180° in the direction (−). The GC is also rotated 180° counterclockwise to face the anterior region. Once in the right atrium, the dilator and the guidewire are removed, and the catheter is softly aspirated to avoid air embolism. The rotation is then released (−).

3. At this point, the procedure can be performed in 2 different ways. The first is using the handle (+) to increase the GC cuve and point directly at the TV. In this case, the clip catheter is normally inserted into the GC (blue line with blue line) while the GC guarantees the correct positioning of the device to perform leaflet grasping. In the second way, the most widely used, the clip catheter is inserted misaligned (90° counterclockwise or 180°; the authors of this article prefer the 180° misalignment). This technique facilitates the straddling (of the clip radiopaque markers on the GC) of the clip catheter on the GC (this should be done towards the SVC to avoid damaging surrounding structures). After reaching the straddling position, the A or M wheel (depending on the patient's anatomy) will deflect the tip of the clip towards the target TV region. This technique allows a more versatile range of motion with the device to avoid orientation or distance issues between the tip of the GC and the TV target area. Over the next few steps we will be describing the GC-clip catheter misalignment technique. From the echocardiographic standpoint, these steps are monitored in the 90°-110° bicaval view with biplane trying to not damage any anatomical structures.

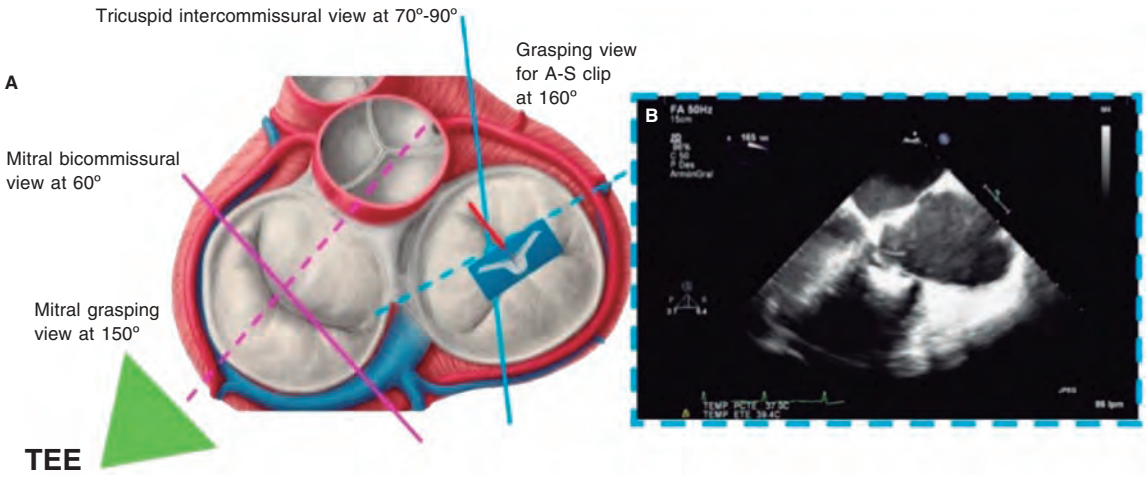


Figure 4. Search for the grasping view for the clip in the anteroseptal (A-S) position with respect to the center of the tricuspid valve. **A:** grasping view for A-S clip (discontinuous blue line). **B:** transesophageal echocardiogram (TEE) at 160° showing the clip with wide open arms and the anterior and septal leaflets resting on them.

4. Once the straddling position has been reached, the A or M wheel (or a combination of the 2) is activated to deflect the clip towards the TV. The wheel selected will depend on the trajectory of the clip. The objective is to achieve the most perpendicular trajectory possible to the TV and avoid, as much as possible, the catheter from coming too close to the interatrial septum (called septal hugging). This circumstance will make the clip point at the TV lateral region. Fluoroscopy in the 45° left, anterior, oblique view is used to see the tip of the clip move towards the left of the screen, away from the septum, pointing towards the operator (figure 2 of the supplementary data). Echocardiographic monitoring will then move from the bicaval to the intercommissural view.

5. When the clip remains perpendicular on the TV, the GC clockwise rotation will move the clip towards the septal position. The GC counterclockwise rotation will move it towards the lateral region. The stabilizer advancement will bring the clip closer to the A-S commissure. After retraction, it will pass to the P-S commissure. This will allow complete range of motion and guarantee the correct location of the grasping (figure 5).

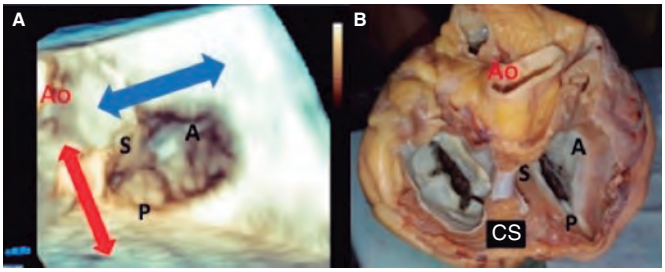


Figure 5. A: transesophageal echocardiogram in 3D zoom mode; periprocedural frontal view. The guide catheter can move inside the right atrium towards the aortic valve by advancing the entire system (red arrow) or towards the posterior leaflet by retracting it; the movement towards the septum (blue arrow) is possible through clockwise rotation of the guide catheter, and towards the right ventricle free wall through counterclockwise rotation. **B:** explanted heart, anatomic view. A, anterior; Ao, aorta; P, posterior; S, septal; CS, coronary sinus.

6. When the desired position has been achieved, the clip opens and perpendicularity is assessed. This should be done by using a 2D TEE in the transgastric short axis or by 3D zooming in the atrial view. The clip should be rotated smoothly so that it remains completely perpendicular to the desired grasping site (figure 6 and video 3 of the supplementary data).

7. Afterwards, the clip closes at 60° and is advanced slowly towards the RV just underneath the leaflets to avoid interfering with RV strings or structures. It is advisable to perform this maneuver through fluoroscopy guidance in a 30° right, anterior, oblique view (RV long axis). This fluoroscopic view will confirm that the clip describes a straight trajectory and maintains its perpendicularity. Fine tuning the rotation of the clip can be made while advancing towards the RV, but it should not be done underneath the leaflets (to avoid string interference). Then, the clip slowly opens at 120° to later retract and guarantee the capture of the leaflets (figure 3 of the supplementary data and video 4 of the supplementary data).

8. Back in the RV, the perpendicularity of the clip with respect to the target coaptation line should be confirmed on the transgastric short axis view. Then, the grasping view should be looked for, that is, the view that better shows the target leaflets and the clip with wide open arms. It is essential to have good ultrasound imaging during grasping to guarantee the correct insertion of the leaflets and the perpendicularity of the arms of the clip. Repeated suboptimal captures of the leaflets should be avoided to not cause excessive damage (TV leaflets are thinner and more fragile compared to the mitral valve leaflets) (figure 7).

9. Once the leaflets have been captured, their insertion should be confirmed through multiple 2D TEE views. Also, the presence of tissue bridges should be verified (though 3D TEE views). Multiplane is very useful for assessment purposes. A TTE or an intracardiac echocardiography should be used in cases of uncertain leaflet insertion. The TV mean gradient should be measured to discard stenosis; in general, mean gradients > 3 mmHg are not recommended (figure 8).

10. Standard release of the clip. Once it has been completely released, the degree and location of residual TR and need for new clip implantation should be assessed. The position of the new clips will depend on the location and amount of residual TR jets.

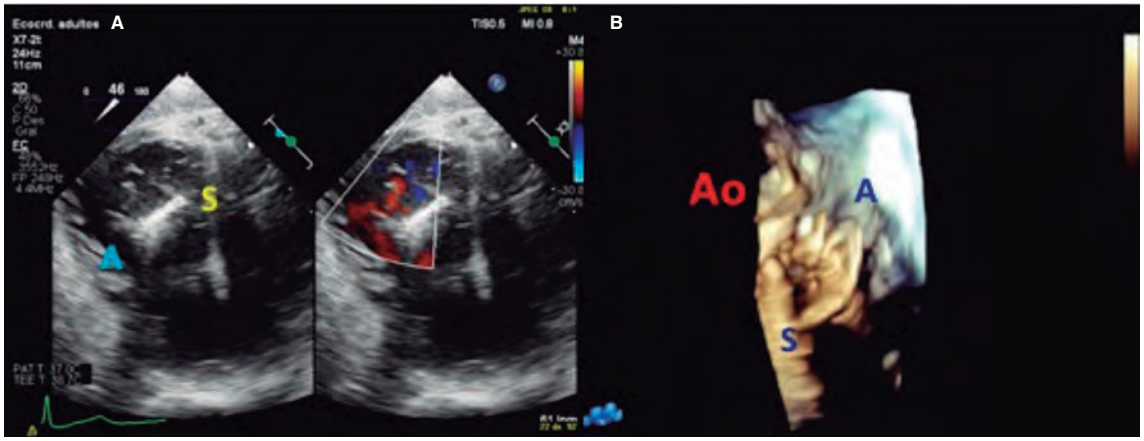


Figure 6. With the clip on the tricuspid annulus the transgastric short axis (**A**) or 3D zoom (**B**) should be used to steer the clip. A, anterior; Ao, aorta; S, septal.

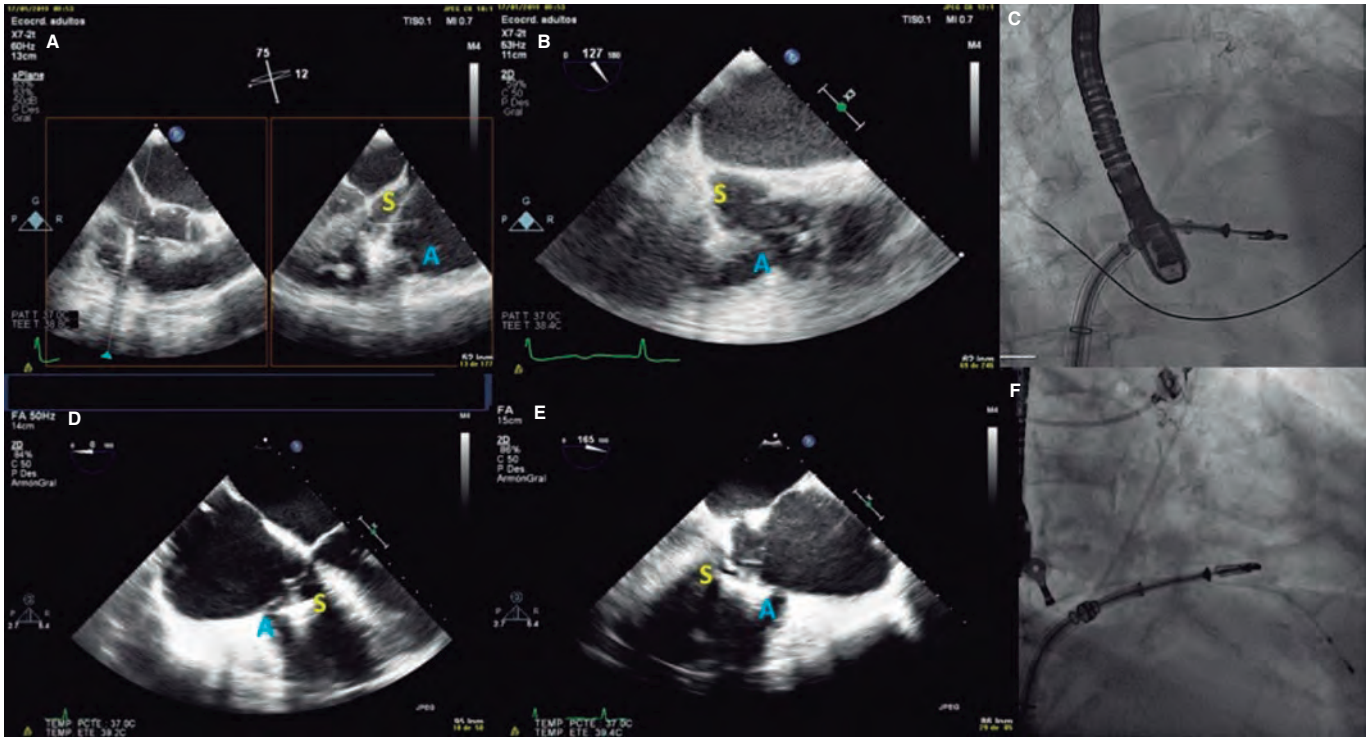


Figure 7. Examples of grasping view. **A and D:** patient 1, grasping from the intercommissural view at 75° and from the direct grasping view at 125°. **B and E:** patient 2, direct grasping view acquired at 0° and 160°. **C and F:** right, anterior, oblique projection to steer the movement of the clip. A, anterior; S, septal.

Since MitraClip XTR was introduced for the first time, most procedures have been performed using this device. It allows easier captures even when there are coaptation defects among the leaflets. The step-by-step procedure described here refers to the standard MitraClip device used today in mitral procedures. A modification of the Mitraclip device (in the GC) will soon be available to facilitate the steering and positioning of the clip (with excellent results in the 30-day assessment in the TRILUMINATE trial.[15]) This new version will replace the device mitral version. The steps will change too. Similarly, we will have a new iteration of the system within the next few months (TriClip).

There are several technical possibilities for clip implantation in the TV; the strategy can vary depending on the surface occupied by each leaflet and the location of the regurgitation jet. For the management of A-S coaptation defects, implanting the clip as close as possible to the center of the valve maximizes the reduction of TR. In patients with large coaptation defects, the most common

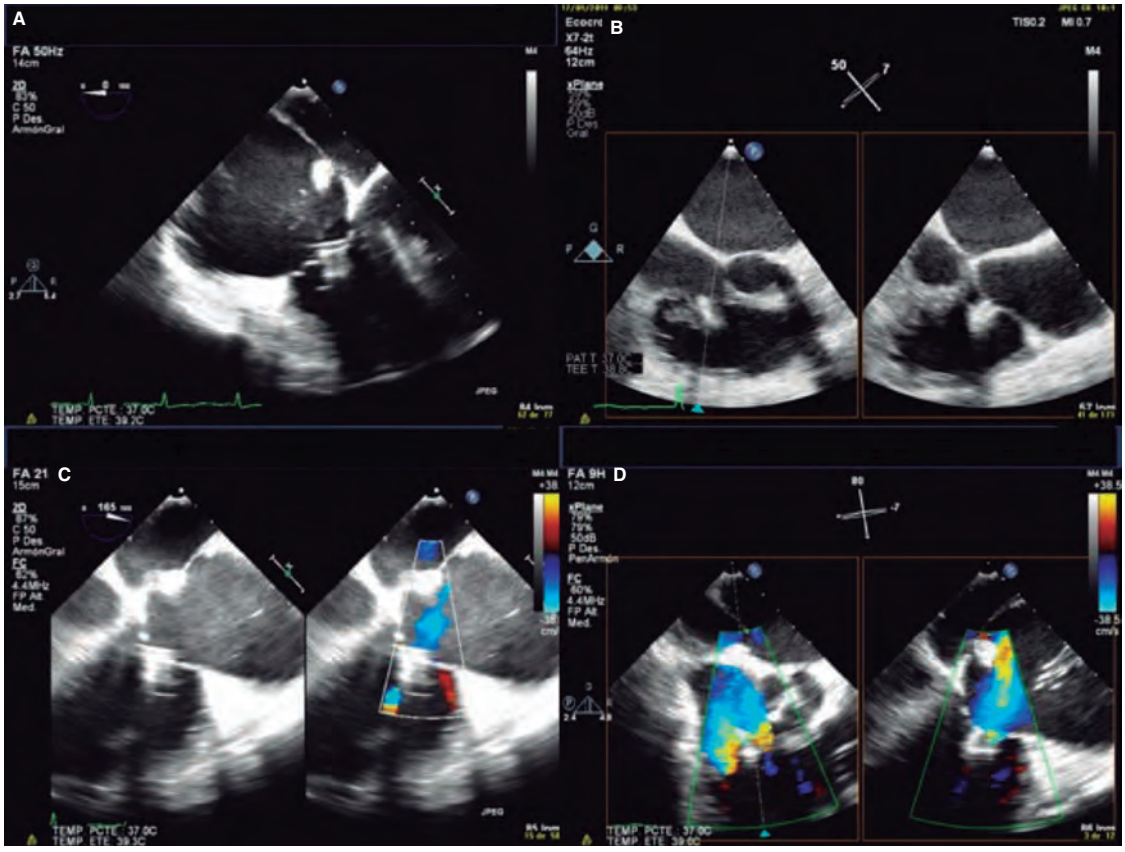


Figure 8. **A-D:** grasping assessment in multiple views for leaflet insertion assessment and reduction of tricuspid regurgitation.

Table 1. Criteria to identify the ideal candidates for tricuspid repair with the MitraClip device

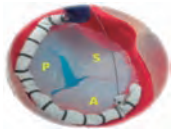
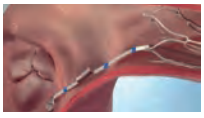
Optimal	Possible	Exceptional
Secondary TR with normal leaflets	Secondary TR with normal appearance of the leaflets or primary TR with valve prolapse	Significant leaflet thickening (rheumatic) or severe valve shortening or destruction or prolapse
Small coaptation defect (< 3-4 mm) and good leaflet mobility	Moderate coaptation defect (4-7.2 mm), reduced leaflet mobility	Large coaptation defect (> 7.2 mm) or severe leaflet restriction
Good TEE window	Enough echocardiographic window to see the leaflets	Insufficient echocardiographic window to see the leaflets
Without PM or ICD leads	Presence of PM or ICD leads without significant leaflet or clip interaction	PM or ICD lead-induced TR
Normal-moderately depressed RV function Normal size or moderately dilated RV	Moderately reduced RV function, moderate RV dilation	Severely reduced RV function or severe RV dilation
Normal pulmonary systolic pressure	< 60 mmHg-65 mmHg and pulmonary resistances < 4 WU	> 60 mmHg-65 mmHg or pulmonary resistances < 4 WU

ICD, implantable cardioverter-defibrillator; PM, pacemaker; RV, right ventricle; TEE, transesophageal echocardiogram; TR, tricuspid regurgitation; WU, Wood units.
Reproduced with permission from Hausleiter et al.[17].

strategy is to treat the A-S coaptation line using several clips and avoid the bicuspidization of the TV (video 5 of the supplementary data). An alternative to this can be to implant a first clip between the anterior and septal leaflets plus a second clip between the posterior and septal leaflets to create a triple-orifice TV (figure 4 of the supplementary data). In this sense, the triple-orifice technique can be superior to the A-S bicuspidization one because it achieves a direct reduction of coaptation defects and counteracts annular dilation by exerting traction forces in the annular anterior and posterior regions. However, the analysis of both strategies did not find any differences between the 2 regarding TR or clinical improvement.[16]

The selection of patients for tricuspid valve repair should include a combination of clinical, hemodynamic, and anatomical characteristics. Table 1 shows the criteria that define the optimal candidates who are eligible for TR repair using the MitraClip device.[17] It should be emphasized that all patients should have symptomatic TR despite receiving optimal medical treatment, high surgical risk, and severe TR.

Table 2. Transcatheter tricuspid percutaneous repair devices

	Characteristics	Strengths	Challenges
Coaptation devices			
 MitraClip	Bicuspidation or triple-orifice of the TV First series published	Wide experience in the mitral valve Easy to use for the operators	Vascular access route Modified implant technique Valve configuration with 3 leaflets Not for annular dilation
 Pascal	Similar to the TriClip device Bicuspidation or triple-orifice of the TV Advantage of the spacer for grasping	Probably easy to use for the operators Similar to the TriClip device	Modified implant technique Valve configuration with 3 leaflets Not for annular dilation
Annuloplasty devices			
 Trialign	Bicuspidation of the TV (posterior commissure) First series reported Pending study for CE marking	Surgical history High safety profile	Risk of damage to leaflets or right coronary artery Difficult technique TEE-guided Properties of the valve tissue
 Cardioband	Flexible annuloplasty annulus First cases ever reported in humans	Surgical history	Little experience in the mitral valve Risk of damage to right coronary artery
 TriCinch	Simple indirect annuloplasty Pending study for CE marking	Surgical history High safety profile Fully retrievable before stenting	Risk of damage to right coronary artery Dilation of the inferior vena cava

CE, European conformity; TEE, transesophageal echocardiogram; TV, tricuspid valve.

The echocardiographic predictors of success during TR repair with the MitraClip device recently published are: the location of the jet in the A-S coaptation line or central region, and the coaptation defect between leaflets < 7.2 mm are the best predictors with the NTR device.[17] Procedural success is also essential because it is a variable independently associated with better prognosis.[8,18]

OTHER TRANSCATHETER DEVICES TO TREAT TRICUSPID REGURGITATION

Table 2 and table 3 show other transcatheter devices for the management of TR.

Edge-to-edge repair devices

Pascal

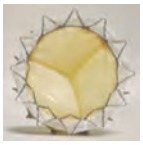
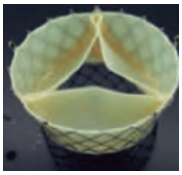
This device is used for edge-to-edge repair by capturing the leaflets of the TV. This device uses clasps (metal blades to capture the leaflets) and paddles (arms that go into the leaflets) to gently grasp the leaflets against a spacer. The clasps move independently for better leaflet capture in the device, while the spacer increases the coaptation surface reducing leaflet stress. The complete system is 22-Fr and the device can be fully elongated favoring its interaction with subvalvular apparatus. The procedure is TEE-guided through transfemoral access and under general anesthesia. Under TEE and fluoroscopy guidance, the device is steered towards the TV and implanted similar to the MitraClip. In a recent communication, the early experience with the Pascal repair system for TR repair was reported. Out of 12 patients treated, 92% reduced their TR in, at least, 1 degree, and all of them improved their functional class at the 30-day follow-up.[19] This early experience is encouraging, but more data are needed before using this device in a larger community of patients.

Annuloplasty devices

Trialign

The Trialign device (Mitralign Inc., Tewksbury, Massachusetts) is a transjugular suture-based annuloplasty system to reduce the tricuspid annular diameter through plicated leaflet tissue. During the procedure a pair of polyester sutures are released into the tricuspid annulus next to the anteroposterior and P-S commissures. It is then cinched using a polyester suture that obliterates the tricuspid posterior leaflet and fixates to the atrial side. The results of the SCOUT trial[20] have already been published on the successful implantation of a pair of sutures in 14 out of 16 patients (87.5%).

Table 3. Transcatheter tricuspid valve replacement percutaneous devices

Devices	Characteristics	Strengths	Challenges
 GATE	Nitinol self-expandable orthotopic valve Leaflet capture and annular expansion	Abolition of TR Similar to surgical experience Catheter-based valve system, easy to use for the operators	Vascular access route Preoperative planning Voluminous device Defect in the conduction system
 TricValve	Prevents the retrograde flow from TR into the cava veins Nitinol self-expandable valve with special design for the SVC and IVC	Easy to implant Symptomatic improvement	Vascular access route Preoperative planning No surgical history Anatomical restrictions Long-term effect of atrial ventricularization
 Tricento	Prevents the retrograde flow from TR into the cava veins Self-expandable stent from the SVC towards the cava vein Biological bicuspid valve towards the right atrium preventing flow towards the cava veins	Easy to implant Symptomatic improvement	Vascular access route Preoperative planning No surgical history Anatomical restrictions Individual design Long-term effect of atrial ventricularization

IVC, inferior vena cava; SVC, superior vena cava; TR, tricuspid regurgitation.

The mean reduction after the procedure was 37% in the tricuspid annulus and 59% in the regurgitant orifice area. A pair of sutures can be implanted in the anterior annulus to optimize the final outcome. There was no perioperative mortality and quality of life tests improved at the 1-month follow-up.

Cardioband

The Cardioband system (Edwards LifeSciences, CA, United States) is a percutaneous direct annuloplasty device for TV repair. It is implanted into the tricuspid annulus by a series of anchors that pass through the annulus and into the baseline RV myocardium following the natural shape of the annulus and sparing the septal region where it meets the atrioventricular node. Afterwards, it is cinched using TEE-guidance and the annular septal-lateral diameter is reduced.

The 6-month data of the TRI-REPAIR trial[21] have been published. It included 30 patients and procedure technical success was 100%. There was a 9% reduction of the annular septal-lateral diameter, and a 50% reduction of the PISA (proximal isovelocity surface area) at the 6-month follow-up. Eighty-eight percent of the patients had New York Heart Association (NYHA) functional class I-II and improved results in the quality of life tests.

TriCinch

The TriCinch (4Tech Cardio, Galway, Ireland) is an annuloplasty device with a deflectable catheter and a coil system in its distal end that anchors to the tricuspid annulus. This anchoring generates traction in the entire annulus through a band connected to it. The anchor is implanted in the pericardial space to avoid detachment at follow-up. Fixation site is in the middle region of the anterior tricuspid annulus under fluoroscopy and echocardiographic guidance. Then the catheter is tightened to cinch the tricuspid annulus, reduce its A-S dimension, and improve leaflet coaptation. Lastly, a self-expandable nitinol stent is released inside the inferior vena cava (IVC) to secure the system and keep the tension applied. The implantation of the TriCinch device preserves the native anatomy and facilitates other future treatment options. The experience with animals confirms the safety and efficacy profile of this device.[22]

Valve replacement devices

The transcatheter replacement of the TV can be orthotopic or heterotopic. The first experiences with this technique used aortic valves for percutaneous implantation in the tricuspid position. The "valve-in-valve" or "valve-in-ring" percutaneous implantation of an aortic valve in the tricuspid position is more common. Acceptable short-term results with these procedures have been reported.[23] However, the development of transcatheter tricuspid valve replacement systems in native TV is much more interesting.

GATE

The GATE bioprosthesis (NaviGATE Cardiac Structures, Lake Forest, CA, United States) is the only device available today experienced clinically in humans as compassionate use. Also, it is the only device that allows fully orthotopic transcatheter tricuspid valve replacements. It is a xenopericardial leaflet bioprosthesis inserted into a self-expandable nitinol scaffold. The nitinol stent is wider in the ventricular region, giving it a tronco-conical morphology that reduces the transvalvular gradient and minimizes the outflow tract obstruction (since very little material protrudes towards the

ventricle). It can be implanted using the jugular approach or the right atrium through minithoracotomy; the femoral access is still under development. The necessary size for the jugular access is ≥ 14 mm because a 42-Fr introducer sheath is used. In both cases, at least 7 cm are necessary from the annular entry site to steer the device (which should be angulated 70º) so that it is perfectly coaxial to the annular plane.

The prosthesis is available in 5 different sizes (36 mm, 40 mm, 44 mm, 48 mm, and 52 mm). A slight oversizing (from 5% to 10%) with respect to the annular dimensions is advisable. To select the device size, it is required to measure the annulus using TEE and computed tomography scan. On the CAT scan, the distance between the annulus to the right coronary artery is a very important feature to avoid damage and have guidance during the procedure. The x-ray projection imaging of the implant is also derived from the CAT scan.

To this day, very few implants have been performed worldwide and always with compassionate use. Recently, the experience of the University of Columbia with 5 consecutive procedures has been published.[24] Procedural success was 100% and the route of access was minithoracotomy in all cases. Only 1 patient died within the first 30 days after the procedure. Successful implantation was associated with improved RV remodeling, increased cardiac output, and a better NYHA functional class in most patients.

CAVI

The objective of CAVI (caval valve implantation) is to avoid return flow from TR to the cava veins. This means that the devices *per se* do not eliminate TR. They improve systemic venous congestion instead. The procedure is performed by implanting valves (in the early experience, non-dedicated balloon-expandable valves) into the origin of the IVC and SVC. The implant can be simple (IVC only) or double depending on the anatomical characteristics of the venous system drainage into the right atrium. There a special self-expandable CAVI device available too, the TricValve (P&F Products Features Vertriebs, Vienna, Austria), that consists of a nitinol stent specifically designed for low-pressure circulation. The largest sizes available are 38 mm and 43 mm for the SVC and IVC, respectively. This means that the optimal diameters of the anchoring area should be ≤ 35 mm (from 28 mm to 43 mm).

Both valves are released using the transfemoral access in a 27-Fr dedicated catheter. The IVC device is released with the portion covered inside the right atrium and the waist inside the diaphragm hiatus to allow the drainage of venous hepatic system. Although it has been the first transcatheter device ever used, it poses some problems because it does not correct TR. The long-term impact of the ventricularization of the right atrium, the persistent overload of the right atrium and RV, the persistent low cardiac output state, and the impact on the function of the RV prevent a more widespread use of this technique. The consequences of thrombotic complications remain unknown too.

Tricento

The Tricento device (NTV AG, Muri, Switzerland) is a sophisticated CAVI concept. It consists of a bicaval, anchored, covered stent with an element of the lateral bicuspid valve made out of a porcine pericardium that only requires a low closing pressure. The nitinol stent has radiopaque markers to allow precise positioning and orientation during implantation. Using the transfemoral approach, the device is released through a 24-Fr catheter. The Tricento is fully repositionable and retrievable until it is completely released. Because of the patients' great anatomical variability, the stent should be individualized. Once again, the idea is to avoid return flow from TR towards the cava veins. However, all the main setbacks of the CAVI concept are applicable here.

CONCLUSION

There are several transcatheter therapies under development for the management of TR. This article standardized the basic echocardiographic views available for the selection of patients. Also, it stands as a guide for the TV implantation of MitraClip, the most widely used device today. Given the non-stop advance of these devices and cardiac imaging, both imaging and interventional protocols will be jointly developed.

CONFLICTS OF INTEREST

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

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000091.

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Review article

Current options for the management of calcified lesions

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ABSTRACT

Severe coronary calcium increases the complexity of percutaneous coronary interventions. It may affect the adequate preparation of the lesion, proper stent expansion and apposition and increase the risk of stent thrombosis and restenosis. The techniques available for the management of severe calcified lesions can be divided into 2 groups: non-balloon and balloon-based technologies. Rotational atherectomy has been the predominant technique to treat severe calcified lesions. As a matter of fact, there are new devices available that facilitate the modification of the plaque such as the new lithoplasty balloon that involves the use of high-energy mechanical pulses to crack coronary calcium. Coronary lithoplasty is an easy technique with a short learning curve that seems to be more effective on deep calcium by increasing luminal compliance. This may revolutionize the standard approach for the management of severe calcified coronary lesions. Also, the role of intravascular imaging is essential to select the most appropriate plaque-modification device and assess the optimal stent result. This review provides an overview of the techniques available and evidence on the currently approved devices to treat calcified lesions.

Keywords: Rotational atherectomy. Orbital atherectomy. Excimer laser. Coronary lithoplasty.

Opciones actuales para el tratamiento de las lesiones calcificadas

RESUMEN

El calcio coronario aumenta la complejidad del intervencionismo coronario percutáneo. La calcificación grave dificulta la preparación de la lesión, impide la adecuada expansión y la aposición del *stent*, y aumenta el riesgo de trombosis y de reestenosis. Las técnicas de modificación de placa se pueden dividir en 2 tipos según el tipo de dispositivo: sin balón y con balón. La aterectomía rotacional ha sido la técnica por excelencia para el tratamiento de lesiones gravemente calcificadas. Actualmente existen nuevos dispositivos que facilitan la preparación de la lesión, como el novedoso balón de litoplastia, que utiliza pulsos de alta energía mecánica para fragmentar el calcio coronario. La litoplastia coronaria es una técnica sencilla, con una curva de aprendizaje corta, que parece tener efecto sobre el calcio profundo y aumentar la distensibilidad luminal, lo que podría suponer un gran cambio en el enfoque del tratamiento de las lesiones calcificadas. Cabe destacar la relevancia de la imagen intravascular al seleccionar el dispositivo de modificación de placa más adecuado, así como para evaluar el resultado final del *stent*. Esta revisión proporciona una visión general sobre las técnicas disponibles y la evidencia de los dispositivos aprobados para el tratamiento de las lesiones calcificadas.

Palabras clave: Aterectomía rotacional. Aterectomía orbital. Láser de excímeros. Litoplastia coronaria.

Abbreviations

CL: coronary lithoplasty. **ELCA:** excimer laser coronary atherectomy. **IVUS:** intravascular ultrasound. **OA:** orbital atherectomy. **OCT:** optical coherence tomography. **PCI:** percutaneous coronary intervention. **RA:** rotational atherectomy. **SCCL:** severely calcified coronary lesion.

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INTRODUCTION

Severely calcified coronary lesions (SCCL) pose a tremendous challenge to perform successful percutaneous coronary interventions (PCI).[1] Old age, diabetes mellitus, chronic kidney disease, and smoking are associated with increased coronary calcification.[2] Coronary calcium can be underestimated on the fluoroscopy and coronary angiography, and it is necessary to use intravascular imaging modalities such as the intravascular ultrasound (IVUS) and optical coherence tomography (OCT) for an accurate assessment of the severity and characterization of the plaque.[3]

Severe coronary calcification increases the complexity of the PCI.[4] It can affect the crossing of the lesion, the proper stent expansion and apposition, damage the drug-eluting polymer, increase the risk of stent thrombosis and restenosis, and have a negative impact on short and long-term results.[5] The optimal approach for the management of SCCL requires being knowledgable of a number of factors: the characteristics of the lesion, calcium distribution, intravascular imaging modalities, and the mechanism of action of every plaque-modification device.[6]

To this day, plaque-modification techniques can be divided into 2 groups based on the type of device used: with and without balloon.[6,7] Among the procedures with devices based on technologies without balloon we should mention rotational atherectomy ([RA], Rotablator and ROTAPro; Boston Scientific, United States), orbital atherectomy ([OA], Diamondback 360; Cardiovascular Systems, Inc., United States), and RA with excimer laser (CVX-300 Excimer Laser System, Philips, United States).[8,9] Among the procedures with devices based on technologies with balloon we find the cutting balloon (WOLVERINE, Boston Scientific, United States) and the scoring balloon. The most important ones are AngioSculpt (Biotronik, Germany), Scoreflex (OrbusNeich, China), and NSE Alpha (B. Braun, Germany); the ultra-high pressure non-compliant (NC) balloon, OPN (SIS Medical AG, Switzerland); and the coronary lithoplasty device ([CL], Shockwave Medical, Inc., United States).[8,9]

The widespread use of these techniques and devices has been limited due to the risk of complications, the degree of technical difficulty, the operator's experience, and the corresponding use of health resources. This review focuses on the techniques and evidence available today for the devices approved for the management of SCCLs.

ROTATIONAL ATHERECTOMY

Definition

RA is an endovascular procedure to modify atherosclerotic plaque by advancing a diamond-coated rotating metal olive-shaped burr.[10,11]

Operating principles

The RA device (Boston Scientific, United States) consists of an elliptical diamond crystal-coated olive-shaped burr rotating at high speed and performing differential cutting as it moves forward (figure 1 of the supplementary data). The RA pulverizes the plaque fibrocalcific components while preserving the adjacent elastic tissue by releasing microparticles into distal coronary circulation.[7,10]

The burr has different sizes (from 1.25 mm to 2.5 mm) and is mounted on a drive shaft connected to a console that supplies rotational energy. It has 3 connections (inside a single cable with 3 outputs connected to the console): a tachometer cable, a power connector, and a compressed air/nitrogen connection. From the console, the compressed air/nitrogen provides pressure for the rotation of the engine at selected revolutions. Similarly, there is a physiological saline solution connection to which heparin and vasodilators can be added to lubricate the sheath and cool the engine down (figure 1 of the supplementary data). A 0.5:0.6 ratio between the burr and the vessel is advisable. The olive-shaped burr is advanced on a 0.009 in specific guidewire (RotaWire, Boston Scientific, United States).[10,11] It should be mentioned that the RotaWire guidewire has different length diameters: the cable measures 0.009 inches and the radiopaque segment, 0.014 inches. The burr is compatible with the 0.009 in guidewire proximal segment. There are 2 different versions of RotaWire available (RotaWire Extra Support and RotaWire Floppy) used depending on the characteristics of the plaque and the support required.[10,11] (figure 1 of the supplementary data).

The rotational speed recommended is between 135 000 rpm and 180 000 rpm. Decelerations > 5000 rpm should be avoided. The burr should be advanced gradually with easy back-and-forth moves and rotablation time should be < 20 seconds with pauses in between each cycle. Once rotablation has been performed, the olive-shaped burr is removed and the Dynaglide mode is activated. Unless there is a technical issue, deceleration is usually indicative of a significant resistance to the advancement of the burr due to lesion severity and calcification and makes a distinctive sound. It is advisable to carefully listen while the RA is being performed because deceleration can be indicative of the risk of burr entrapment.[7,10,11] (table 1).

There is an update of this device, the ROTAPro, that facilitates manipulation by a single operator and provides an improved user interface with integrated controls in the advancement device. The pedal has been replaced by a button located on top of the burr advancement control. There is another button at the back of the device to activate the Dynaglide mode. The console is smaller, has a digital screen and requires less configuration time (figure 2 of the supplementary data).

Indications

The main indication for RA is for the treatment of SCCLs that are non-dilatable through conventional methods by modifying the plaque, which facilitates the proper stent expansion and apposition.[10,11] (figure 1).

The following factors significantly impact the outcomes of RA: calcium eccentricity, luminal area, and burr size. The optimal scenario to achieve proper luminal gain is a concentric lesion with a circumferential distribution of calcium and a minimal lumen area smaller than the burr size.[7] Another more controversial indication is for the management of stent restenosis due to stent underexpansion. Eccentric lesions with significant tortuosity are less eligible for RA treatment since there is a higher risk of complications.[9]

The RA can be used as the primary strategy for the modification of calcified lesions or as a bailout strategy after a failed balloon predilation attempt of the lesion.[9] It is a safe technique in both cases. However, the primary strategy is associated with shorter procedural and fluoroscopy times, fewer contrast volume, and less predilation balloons being used.[10] (table 1).

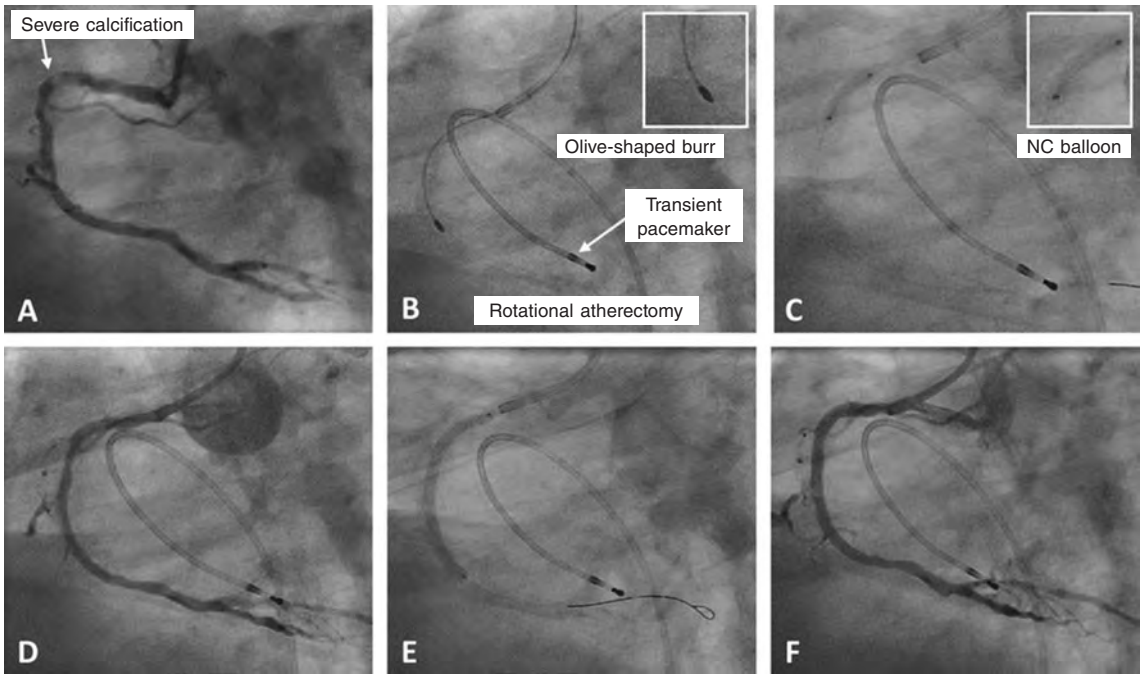

Figure 1. Case of rotational atherectomy on calcified lesion in right coronary artery. **A:** baseline angiography. **B:** rotablation of calcified lesion using a 1.5 mm olive-shaped burr. **C:** predilation with a 3 × 12 mm non-compliant balloon. **D:** angiographic result after rotablation. **E:** implantation of a 3 × 38 mm drug-eluting stent. **F:** final angiographic result after postdilation. NC, non-compliant balloon.

Clinical data

Currently the systematic use of RA is controversial because its clinical benefit has not been clearly demonstrated yet.[12-15] The ROTAXUS clinical trial[16] included 240 patients with moderate-severe calcification who were randomized to RA plus drug-eluting stent or balloon predilation plus drug-eluting stent. The RA had a higher success rate and initial luminal gain (1.56 ± 0.43 vs 1.44 ± 0.49 mm; P = .01), and there was a greater late stent luminal loss at the 9-month follow-up (0.44 ± 0.58 vs 0.31 ± 0.52 mm; P = .04). No significant differences were found regarding the rate of stent restenosis or thrombosis, need for new target lesion revascularization or rate of major adverse cardiovascular events (MACE) at the 9-month follow-up.[16]

The PREPARE-CALC clinical trial[17] included 200 patients with SCCLs randomized on a 1:1 ratio to receive treatment with cutting/scoring balloon or RA. No significant differences were seen regarding complications between the 2 groups. However, there was a higher procedural success rate with the RA and a lower percentage of residual stenosis (98% vs 81%; P = .0001). No significant differences were seen between the groups regarding the stent luminal loss or clinical outcomes at the 9-month follow-up.[17]

The ROTATE multicenter registry[18] included 1176 patients with SCCLs treated with RA plus drug-eluting stent. The rate of MACE at 1-year follow-up was 16%. The European multicenter RA registry included data from 963 patients. Clinical success rate was 92%, mortality rate was 12.5% and the rate of MACE at 1-year follow-up was 17% (results presented at the EuroPCR 2019 congress).[19]

Complications

The most dreaded complications of RA are burr entrapment, perforation, and coronary dissection (table 2).[10,20]

Two different types of burr entrapment can be distinguished: *a)* lesion entrapment (the burr cannot be moved forward or backwards) and *b)* distal entrapment (the burr cannot be removed but it can be moved forward). Several factors like significant lesions and very small burrs can predispose to this complication. In cases of burr entrapment, it is not advisable to activate rotablation or the Dynaglide mode.[10,11] To solve this complication, these maneuvers can be performed: *a)* controlled push and traction with catheter active intubation; *b)* cut the device catheter and advance the guide catheter extension as much as possible to pull with maximum strength; or *c)* place a second guide catheter through which a second guidewire and a balloon are advanced to release the burr.[11] This is a very serious complication that sometimes requires emergent surgery.[21]

Significant tortuosity and the lack of proper guide catheter coaxiality in the management of ostial lesion can lead to coronary dissections and increase the risk of perforation.[10,11]

The slow-flow/no-reflow phenomenon is a relatively common complication, although its incidence has dropped to 2.6% after improving the technique and with the operator's growing experience.[7,21] This phenomenon is more likely to happen in long and significant lesions where multiple ablations are performed and in the presence of a poor distal vessel. It is due to the embolization of residues towards microvasculature.[11] It can be prevented through short rotablation cycles by using small burrs at first, pausing between cycles, and controlling the flow angiographically.

Table 1. General characteristics of plaque-modification devices based on technologies without balloon

	Rotational atherectomy	Orbital atherectomy	Excimer laser coronary atherectomy
Operating principles			
Type of device	High-speed rotating olive-shaped burr	Crown at high-speed elliptical rotation	High energy light catheter
Mechanism of action	Antegrade differential cutting	Antegrade and retrograde differential sanding	Photoablation
Learning curve	Long	Long	Long
Device size	1.25-2.5 mm olive-shaped burr	1.25 mm crown	0.9-2 mm catheter
Compatible catheter	6-8-Fr	6-Fr	5-8-Fr
Type of guidewire	0.009/0.0014 in RotaWire	0.012/0.014 in ViperWire	0.014 in guidewire
Console	Small without pedal (ROTAPro)	Small without pedal	Large with pedal
Indications			
Main indication	Plaque-modification	Plaque-modification	Lesions hard to cross, like chronic total coronary occlusion
Optimal calcium location	Luminal	Luminal	Luminal
Stent restenosis	Yes	Yes	Yes
Complications			
Dissection	Moderate risk	Moderate risk	Moderate risk
Perforation	Moderate risk	Moderate risk	Moderate risk
Slow-flow/no-reflow	Moderate risk	Moderate risk	Moderate risk
Burr/crown entrapment	Moderate risk	Low risk	N/A
Practical advices			
Speed	135 000-180 000	80 000-120 000	N/A
Device-vessel ratio	0.5:0.6	N/A	0.5:0.6
Recommendations	Pecking motion Short cycles Pauses in between cycles Avoid significant tortuosity	Continuous and slow back-and-forth moves Short cycles Pauses in between cycles	Requires the continuous infusion of fluid

N/A, non-applicable.

Table 2. Complications of rotational atherectomy, strategy of prevention, and treatment

	Strategy of prevention	Treatment
Slow-flow/no-reflow	Use smaller burrs Avoid high rotation speeds Do short cycles with pauses in between	Intracoronary administration of nitrates, nitroprusside, adenosine Keep the right perfusion in the presence of hypotension
Dissection	Regarding lesions at segments with significant toruosity	In the presence of significant dissection, it is advisable to stop performing the atherectomy The standard management of dissection is advised
Perforation	Regarding the selection of large burrs, significant vessel tortuosity, and the selection of inadequate rotation speeds	Standard treatment advised (including the use of drug-eluting stents and urgent pericardiocentesis)
Burr entrapment	Rare complication; it can usually be avoided with an adequate selection of cases and performing the technique the right way	Perform controlled back-and-forth moves Position a second guidewire to advance a balloon to release the burr Increase support through active intubation or the use of a catheter extension to increase traction Cardiac surgery may be necessary

Once diagnosis has been established, it is treated with fluid therapy, local vasodilators at distal levels, vasoactive amines in the presence of hypotension, and atropine in the presence of bradycardia.[10,11]

ORBITAL ATHERECTOMY

Definition

OA is an endovascular procedure to modify atherosclerotic plaque by using a diamond-coated crown whose mechanism of action consists of the antegrade and retrograde modification of the plaque.[7]

Operating principles

The standard OA device is the Diamondback 360 (Cardiovascular Systems, Inc., United States). It consists of a one size only diamond-coated crown (1.25 mm) connected to a drive shaft and controller and powered by a pneumatic console (figure 3 of the supplementary data). The crown is advanced on a specific 0.012/0.014 in guidewire (ViperWire; Cardiovascular Systems, Inc., St. Paul, MN, United States). The centrifugal force generated during rotation compresses the crown against the plaque eventually cracking it and increasing distensibility.[22,23]

The OA mechanism of action is the elliptical rotation of the crown that gradually increases orbital diameter as rotation speed increases from 80 000 rpm to 120 000 rpm.[22] Increasing the orbit with higher rotation speeds allows the differential sanding of calcified lesions in vessels of up to 3.5 mm using the 1.25 mm crown.[7] For optimal results, the crown needs to be moved slowly and gradually through the lesion at a speed of 1-3 mm/s, which facilitates greater luminal gain and a lower rate of complications compared to higher moving speeds.[7,22]

The OA effect is time-dependent; 30 second-cycles are advisable with 30 second-pauses in between them.[22] The continuous infusion of a lubricant solution (ViperSlide) is required to minimize thermal lesions during OA; also, 18 mL/min of fluid are administered to cool the device down and eliminate residue, thus reducing ischemia and distal embolization.[22,24]

The Micro Crown system (Cardiovascular Systems, Inc., United States) is available for use. It is a technological advancement to improve the effectiveness of OA. It consists of a newly designed drive shaft to facilitate easier advances of the crown towards the lesion. It facilitates plaque modification at slower speeds (50 000 rpm-70 000 rpm)[9,22] (table 1).

Indications

The main indication of OA is for the management of calcified lesions non-dilatable using conventional methods to modify the plaque, increase vessel distensibility, and facilitate the proper stent expansion.[22,23] With the new OA Micro Crown system ostial and subocclusive lesions can be treated.[9] (table 1).

Clinical data

The ORBIT I clinical trial[25] included 50 patients and confirmed the safety and efficacy of OA for the management of calcified lesions. Procedural success was achieved in 94% of the patients and the rate of MACE was 8% at 6-month follow-up.

The ORBIT II clinical trial[26] included 443 patients. Procedural success was achieved in 98.6% of the patients, the rate of significant dissections was 2.3%, and the rate of MACE was 10.4% at the 30-day follow-up. The 3-year follow-up results showed a rate of MACE of 23.5%.[27]

The COAST clinical trial[28] that used the new Micro Crown system included 100 patients. Procedural success was achieved in 85% of the patients, and the rate of MACE was 22.2% at the 1-year follow-up. The ECLIPSE trial (NCT03108456) is being conducted now and will include 2000 patients with SCCLs randomized to OA plus drug-eluting stent or balloon predilation plus drug-eluting stent.

Complications

Complications are similar to those reported for RA. However, compared to RA, since the OA performs antegrade and retrograde sanding, it reduces the chances of crown entrapment in the lesion. The residues produced are smaller and they don't alter coronary flow during its application, thus reducing the risk of slow-flow/no-reflow phenomenon and thermal lesion of coronary endothelium.[7,24] Coronary perforation is one of the most serious complications of OA (between 0.7% and 2%).[26-28] OA is not advisavke when coronary anatomy shows significant tortuosity (> 90° angulations).

EXCIMER LASER CORONARY ATHERECTOMY

Definition

Excimer laser coronary atherectomy (ELCA) is an endovascular procedure for the management of significant and calcified lesions non-dilatable with the usual techniques. It uses a photochemical, photothermal, and photomechanical mechanism of action derived from applying high-energy light.[29,30]

Operating principles

The Philips CVX-300 ELCA system uses xenon chloride and emits pulses of ultraviolet (UV) light at a 308-nm wavelength. The UV pulses generated only penetrate 50 µm deep, which disintegrates the calcified plaque through a mechanism of ablation without damage to the middle or adventitia layers (figure 4 of the supplementary data).[31] There are 4 different sizes of ELCA monorail catheter available (0.9, 0.14, 1.7 and 2.0 mm) that can be advanced on a 0.014 in guidewire. The right size is selected on a 0.5:0.6[7] ratio between catheter and vessel.

Photomechanical effect occurs when the laser acts on a liquid environment (saline solution, contrast, or blood) with the corresponding release of expansion bubbles that act on the atherosclerotic plaque.[32] Slowly moving the device forward promotes an increased luminal gain at lesion level. The number of pulses, length and total time of ELCA treatment should be individualized depending on the characteristics of the lesion. The particles generated have a diameter < 10 µm so they are reabsorbed by the reticuloendothelial system, thus avoiding microvascular obstruction[31] (table 1).

Indications

The clinical use of ELCA es limited. Its main indication is for the management of lesions that are non-dilatable through conventional methods. It is rarely used as a first-line strategy for the management of SCCLs, but it is the only option when the lesion cannot be crossed with a microcatheter or with the RotaWire/ViperWire guidewires, as it occurs with chronic occlusions.[33,34]

Other more controversial indications are for the management of non-dilatable stent restenosis using the routine methods due to stent underexpansion,[35] ostial lesions, saphenous vein graft occlusions,[36] and lesions with thrombotic content.[37-39] This technique should be avoided in the presence of unprotected left main coronary artery disease, significant tortuosity, and in bifurcated lesions (table 1).

Clinical data

The data available on the medical literature come from randomized studies (balloon predilation vs ELCA) are old and did not show any significant differences regarding results.[29,30,40]

In acute myocardial infarction, the results of the multicenter CARMEL clinical trial[39] that included 151 patients with thrombotic lesions showed a device success rate in 95% of the cases. The multicenter CORAL registry[36] included 98 patients with significant stenosis of the saphenous vein graft and the rate of MACE was 18.4% at the 30-day follow-up.

A study that included 81 lesions of stent restenosis due to stent underexpansion confirmed the superiority of ELCA over predilation with high-pressure balloon; the OCT confirmed the ELCA-induced crack of calcium behind the struts.[35]

Complications

The potential complications of ELCA are similar to the ones reported for RA and OA. The main ones are coronary dissections and coronary perforations with incidence rates of 7% and 0.5%-8%, respectively.[29,30,33] However, improvements in its design, the use of a technique with continuous infusion of a saline solution, and the use of smaller caliber catheters has reduced the rate of complications.[33,34]

CORONARY LITHOPLASTY

Definition

CL is an innovative technique that uses high-energy mechanical pulses administered through a semi-compliant balloon that modiy the plaque by cracking coronary calcium.[41,42]

Operating principles

The device available is the Coronary Rx Lithoplasty System (Shockwave Medical, Inc., United States). The lithoplasty balloon (LB) is a single use 12 mm-long angioplasty balloon with diameters that go from 2.5 mm to 4 mm that is advanced on a 0.014 in guidewire.[42,43] It emits pulses of circumferential acoustic pressure to treat concentric calcified lesions (figure 5 of the supplementary data).

The LB is inflated at calcified lesion level at a pressure of 4 atm and 1 Hz shockwaves are administered.[43,44] Mechanical energy is transmitted to the lesion when the LB contacts the artery intima layer cracking the calcium in the superficial and deep layers of the vessel wall.[7] This facilitates the proper stent expansion and apposition.[7,42,43]

Once the LB is on the lesion, it is connected to an external unit that generates pulsatile mechanical waves (figure 5 of the supplementary data). It is advisable that the LB size and vessel keep a 1:1 ratio between them.[41,42] The LB is initially inflated at a pressure of 4 atm and 10 pulses are administered (around 10 seconds are required). Then, the LB is inflated at a 6 atm pressure and then it is deflated to restore the flow. New cycles are then applied; a total of 8 therapies (80 pulses) per balloon and lesion can be administered.[42,43] Due to its size, if the length of the lesion is > 12 mm, the LB can be repositioned to treat the lesion entirely. The use of the LB is easy, learning curve is short, and makes PCI easier[7,42] (table 3).

Indications

The main indication of CL is for the management of concentric, calcified lesions with a circumferential distribution of calcium.[41,42] It seems to be more effective on the deepest calcium compared to other plaque-modification techniques.[45-47] LC is effective in large caliber vessels since there are lithoplasty balloons of up to 4mm in diameter. This device can be used in bifurcated lesions since 2 guidewires can be released during the procedure for lateral branch protection. Similarly, the LB seems safe and effective in the presence of significant tortuosity, stent restenosis due to underexpansion,[48,49] and calcification involving the left main coronary artery with severe left ventricular dysfunction[50,51] (table 3). Another more controversial indication can be for the management of SCCLs in the context of an ST-segment elevation acute myocardial infarction[52] (figure 2).

Clinical data

The DISRUPT CAD I was a premarket clinical trial that confirmed the safety and efficacy of CL for the management of SCCLs before stent implantation; the rate of MACE at the 6-month follow-up was 8%.[45] The DISRUPT CAD II clinical trial that included 120 patients confirmed the safety profile of CL before stent implantation with a rate of MACE of 7.6% at the 30-day follow-up.[46] However, larger studies with longer follow-up periods are needed to confirm these results. The DISRUPT CAD III (NCT03595176) is a multicenter clinical trial with an estimate recruitment of 392 patients that will be analyzing the safety and efficacy of LB to obtain the Food and Drug Administration approval to use this device in the United States (table 4).

Complications

Perioperative complications (dissection and perforation) are uncertain. Although the device has proven successful in the short-term, there are few real-world data published on the use of LBs. It seems that the calcium crack caused by the LB remains *in situ* without causing distal embolization, which reduces the rate of the slow-flow/no-reflow phenomenon.[7,42,43]

Table 3. General characteristics of plaque-modification devices based on technologies with balloon

	Coronary lithoplasty	Cutting/scoring balloon	Ultra-high-pressure balloon
Operating principles			
Technology	Semi-compliant balloon that emits high-energy mechanical pulses	NC balloon with microblades/semi-compliant balloon with spiral struts	Double-layer NC balloon
Mechanism of action	Lithotripsy/Calcium cracking	Cutting of the plaque luminal surface	It allows inflation at 35-40 atm
Learning curve	Short	Short	Short
Device size	2.5-4 mm	2.75-3.5 mm/2.0-3.5 mm	1.5-4.5 mm
Compatible catheter	6-Fr	6-Fr	6-Fr
Indications			
Main indication	Preparation of calcified lesions	Stent restenosis	Stent optimization
Optimal calcium location	Luminal with circumferential distribution	Luminal	Luminal
Stent restenosis	Yes	Yes	Yes
Complications			
Difficulty crossing	Yes. Improved with the new generation LB	Yes/no	Yes
Dissection	Low risk	Moderate risk	Moderate risk
Perforation	Low risk	Low risk	Low risk
Slow-flow/no-reflow	Low risk	Low risk	Low risk
Practical advices			
Pulses administered	Up to 80 pulses (8 cycles)	N/A	N/A
Device-vessel ratio	1:1	0.8:1	1:1
Recommendations	Inflation at 4 atm, 10 pulses; then up to 6 atm and deflation Useful with tortuosity Useful in bifurcations	Slow and gradual inflation	Slow and gradual inflation It allows stent postdilation at high atm

LB, lithoplasty balloon; N/A, non-applicable; NC, non-compliant balloon.

OTHER TECHNIQUES AND DEVICES

Non-compliant balloon

The NC balloon sustains very few size changes event at high pressures. This facilitates focusing its power on a given point to dilate calcified lesions without causing excessive dilatation in other vessel segments. It is often used for stent postdilation and to guarantee proper stent expansion and apposition.[53] However, caution is required because the use of NC balloons for the management of SCCLs can cause coronary perforations and dissections of stent borders when used with postdilation purposes.[53]

Ultra-high-pressure balloon

The ultra-high-pressure balloon is a double-layer system that facilitates the balloon uniform expansion and reduces the risk of fracture and coronary perforation.[54] The OPN device (SIS Medical AG, Switzerland) provides pressures of up to 35-40 atm without tearing the balloon (table 3). These characteristics facilitate the management of stent underexpansion when other options have failed. The main limitation of this type of balloon is its crossing profile due to its greater rigidity and double-layer technology.[7,54]

Cutting balloon and scoring balloon

The WOLVERINE cutting balloon (Boston Scientific, Marlborough, MA, United States) consists of a NC balloon with 3 micro-blades longitudinally arranged on its surface. These blades create incisions inside the calcified lesion during balloon inflation; sequential inflation up to 6 atm is advisable.[55] The main limitations are its crossing profile and the risk of dissection and coronary perforation (table 3). The balloon crossing profile and navigability have improved with the new generation of devices: the AngioSculpt, Scoreflex, and NSE Alpha scoring balloons (table 3). It consists of a low-profile semi-compliant balloon surrounded by 3 nitinol spiral struts for better anchoring to the plaque, fewer chances of balloon gliding, and lower risk of dissection and perforation.[56]

COMBINING THE TECHNIQUES

The combination of RA plus cutting balloon for the management of SCCLs facilitates calcium cracking and better stent expansion and apposition.[57]

The RASER technique consists of combining ELCA plus RA or OA.[58] This combination can be used in lesions that don't allow the

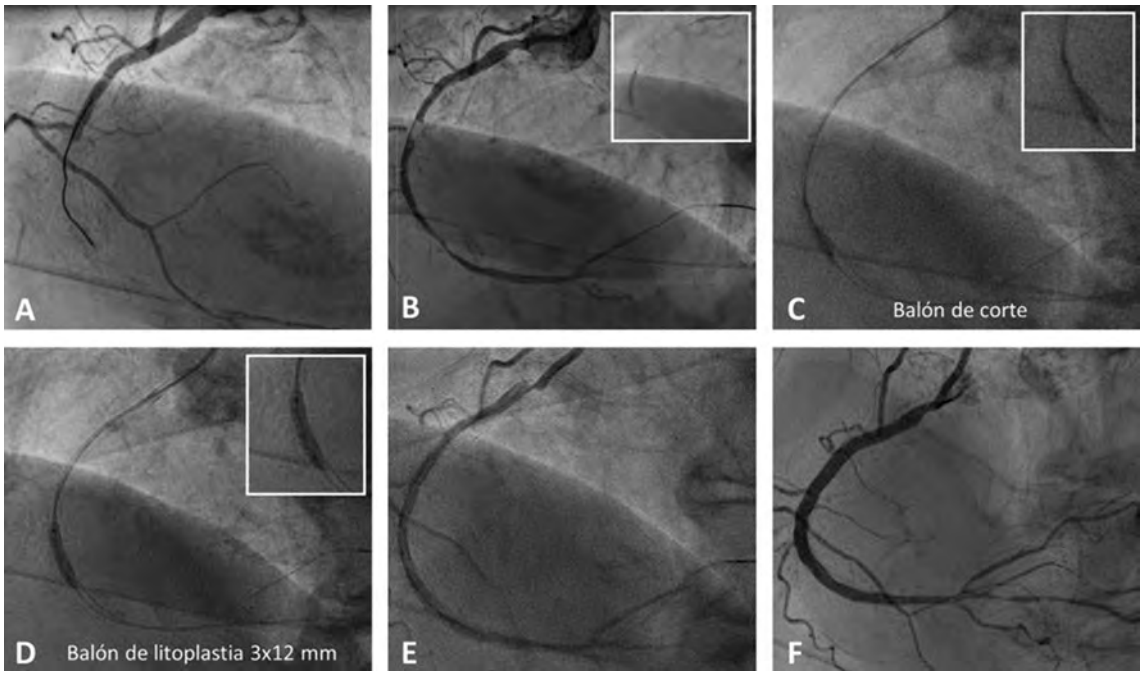

Figure 2. Case of coronary lithoplasty in a patient with inferior ST-segment elevation acute coronary syndrome. **A:** baseline angiography. **B:** result after predilation with a 2 × 15 mm semi-compliant balloon. **C:** failed predilation with a 2.5 × 8 mm non-compliant balloon and a 2.5 × 6 mm cutting balloon. **D:** coronary lithotripsy with a 3 × 12 mm lithoplasty balloon. **E:** angiographic result after coronary lithoplasty. **F:** final result after the implantation of 2 overlapping drug-eluting stents (2.75 × 33 mm and 3 × 38 mm) and postdilation with a 3 × 12 mm non-compliant balloon.

advancement of a microcatheter. The laser can do enough plaque modification to eventually advance the microcatheter and change it for a RotaWire/ViperWire guidewire to perform the RA or OA and achieve the proper stent expansion.[58]

The combination RA plus CL (RotaTripsy technique) has been described recently.[59] It can be useful in very serious and calcified lesions with circumferential distribution of calcium. In this type of lesions where the LB is hard to release on the target lesion, the RA can initially modify the plaque to advance the LB, thus increasing luminal distensibility for a proper stent expansion.[59]

INTRAVASCULAR IMAGING IN CALCIFIED LESIONS

Intravascular imaging modalities (IVUS and OCT) improve the identification of SCCLs and provide thorough assessments of the calcium load, distribution, and eccentricity.[7,42]

Thanks to the ultrasound deeper penetration, IVUS can detect calcified deposits at the deepest layers of the vessel wall. However, due to the acoustic shadowing, only the calcic arch can be seen and no information on its thickness.[60,61] The OCT has greater spatial resolution and higher definition. Calcium is seen as an attenuation region with a well-established luminal border. Compared to the IVUS it is a more precise technique to define calcium load because it provides information on the different degrees of calcic arch and the area, thickness, length, and volume of calcium distribution.[42,61-63]

Intravascular imaging is essential before selecting the plaque-modification device and to assess the stent final outcome. The OCT has greater sensitivity to detect stent underexpansion and malapposition and to assess the outcomes after postdilation.[7,61]

CONCLUSIONS

Coronary calcification is associated with complex lesions and patients with significant comorbidities, which is a predictor of poor prognosis in the short and long-term. More complex patients with more calcified lesions are being treated these days. This means plaque preparation is key in these cases to promote a proper stent expansion and apposition and avoid stent restenosis and thrombosis.

The ideal plaque-modification device is easy to use and implement,safe and effective during the procedure, and with good short and long-term results. With the appearance of CL and the upgrade of Rotablator and the cutting balloon, this field has a bright future ahead. There are many devices available today that can be classified into plaque-modification techniques with and without balloon.

We still lack much evidence from randomized studies and real-world registries to know what the exact role of each of these techniques is, and what benefit can be derived from combining them because they may be complementary, not exclusive. Regardless of the plaque-modification technique used, it is advisable to perform intravascular imaging to guarantee the proper stent expansion and apposition.

CONFLICTS OF INTEREST

None reported.

Table 4. Characteristics and results of the main studies on different plaque-modification techniques

Study and year	Number of patients and treatment groups	Characteristics of the lesion	Study results	
Rotational atherectomy				
ROTAXUS[16] (2014)	240 patients RA + stent vs standard PCI	Lesion with moderate-severe calcification	Luminal loss in the stent at the 9-month follow-up Rate of MACE at the 9-month follow-up	0.44 vs 0.31 mm; *P* = .04 24.2% vs 28.3%; *P* = .46
PREPARE-CALC[17] (2018)	200 patients Cutting/scoring balloon vs RA	Severely calcified lesion	Luminal loss at the 9-month follow-up Target lesion revascularization	0.16 ± 0.39 vs 0.22 ± 0.40 mm; *P* = .21 7% vs 2%; *P* = .17
ROTATE[18] (2016)	1176 patients RA + drug-eluting stent	Severely calcified lesion	Rate of MACE at the 1-year follow-up Rate of MACE at the 2-year follow-up	16% 24.9%
European RA Registry[19] (2019)	963 patients	Severely calcified lesion	Clinical success Rate of MACE at the 1-year follow-up	92% 17%
Orbital atherectomy				
ORBIT I[25] (2013)	50 patients	Calcified lesion	Procedural success Rate of MACE at the 6-month follow-up	94% 8%
ORBIT II[26,27] (2014)	443 patients	Severely calcified lesion	Procedural success Rate of MACE at the 1 and 3-year follow-up	98.6% 16.4% and 23.5%
COAST[28] (2017)	100 patients Micro Crown OA	Severely calcified lesion	Procedural success Rate of MACE at the 1-year follow-up	85% 22.2%
Coronary atherectomy with excimer laser				
AMRO[29] (1996)	308 patients (157/151) Standard PCI/laser	Severely calcified lesion/ stent restenosis	Luminal gain at the 6-month follow-up Rate of MACE at the 6-month follow-up	0.48 vs 0.44 mm; *P* = .34 29.9 vs 33.1%; *P* = .55
LAVA[30] (1997)	215 patients (98/117) Standard PCI/laser	Severely calcified lesion/ stent restenosis	Procedural success at the 1-year follow-up	96.9% vs 96.6%; *P* = .88 No significant differences
ERBAC[40] (1997)	222/232/231 patients Standard PCI vs ELCA vs RA	Lesion with moderate-severe calcification	Procedural success Target lesion revascularization	80% vs 77% vs 89%; *P* = .0019 32% vs 46% vs 42.4%; *P* = .013
Coronary lithoplasty				
DISRUPT CAD I[44] (2019)	60 patients	Severely calcified lesion	Angiographic success Rate of MACE at the 6-month follow-up	100% 8.3%
DISRUPT CAD II[45] (2019)	120 patients	Severely calcified lesion	Angiographic success Rate of MACE at the 30-day follow-up	100% 7.6%

AMRO, Amsterdam-Rotterdam trial; COAST; Coronary Orbital Atherectomy System Study; ELCA, excimer laser coronary atherectomy; ERBAC: Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison; LAVA, Laser Angioplasty Versus Angioplasty; MACE, major cardiovascular adverse events; OA, orbital atherectomy; PCI, percutaneous coronary intervention; RA, rotational atherectomy; ROTAXUS, Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000087.

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Debate: Angiography-derived FFR. The pressure guidewire perspective

A debate: RFF derivada de la angiografía. Perspectiva desde la guía de presión

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QUESTION: Compared to the pressure guidewire what possible advantages does coronary angiography-derived fractional flow reserve (FFRangio) have and what is the current clinical evidence?

ANSWER: Different physiological indices have been developed lately from the 3D reconstruction of the angiogram based on 2 projections and the application of fluid dynamics algorithms. These indices estimate fractional flow reserve (FFR) semi-invasively because, although they are based on percutaneous coronary angiography with contrast, pressure guidewires or drugs are not necessary in the coronary artery.

The most widely studied software package to obtain these indices is the one designed by Medis (QAngio XA 3D, Medis Medical Imaging System, The Netherlands), but there are others in the pipeline.[1] The actual software allows us to obtain the baseline quantitative flow ratio (QFR) (fixed QFR [fQFR]). There is another one that adds the speed of the flow of contrast to the estimate (contrast QFR [cQFR]) by quantifying the TIMI frame count. It can also obtain the adenosine-flow QFR (aQFR) with the administration of adenosine and the residual QFR after a hypothetic percutaneous treatment of the lesion.

To this day, the current studies on FFRangio basically focus on analyzing its match (especially that of cQFR) with FFR or the instantaneous wave-free ratio (iFR) obtained using invasive techniques. A study confirmed the modest diagnostic association with the nuclear test,[2] but similar to the FFR obtained invasively.

Most of the current evidence shows excellent QFR-FFR matches (> 90%) with the cut-off value of 0.80 with areas under the ROC curve > 0.90.

Two recent meta-analyses reviewed 1721 and 969 vessels studied.[3,4] In one of them[3] with a 87% match (95% confidence interval [95%CI], 85-89) without any significant differences between the QFR predictive value obtained online and the one estimated at the core lab. The cQFR-iFR match has proven similar to that of the FFR obtained invasively with mismatch classifications of 20%.[5]

To this day, no follow-up studies or event analyses have reviewed the clinical safety of guiding the intervention with FFRangio compared to FFR.

The theoretical advantages of using FFRangio are:

- It is less invasive. It avoids complications associated with passing the intracoronary guidewire trough the lesion that, though scarce, can still happen.
- It does not require vasodilators. The availability of new non-hyperemic indices does not require the use of drugs with pressure guidewires either.
- Time of assessment is significantly shorter. In the FAVOR II China study, the difference was 4.8 minutes (95%CI, 3.5-6) versus 7 minutes (95%CI, 5.0-10) ($P < .001$).[6] However, this difference of less than 3 minutes is questionable as a practical advantage and should be evaluated in the routine clinical practice.
- Saving costs in intracoronary guidewires and vasodilators; however, no study on costs has been conducted so far and the costs of the software have not been considered either (a "pay per use" model per study conducted after the initial payment plus updates has been suggested). This may require acquiring additional hardware.
- It facilitates the offline functional assessment of non-culprit lesions, thus avoiding new procedures especially of angiographies performed after the infarction acute phase.

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Q.: Which do you think are the technical limitations of FFRangio?

A.: FFRangio is nothing but a sophisticated analysis of quantitative angiography. Conceptually, it has the limitation of any functional estimate that uses imaging modalities. In theory, it does not consider factors that may impact the functional repercussion of stenosis or the possible benefit of revascularization such as the size of the irrigated area, the existence of collateral circulation, microvascular damage or myocardial necrosis. Technically, it requires a good angiography which is not always easy to obtain. *A posteriori* analyses are not always available either. A retrospective study of lesions that performed invasive estimates of FFR (which can be a selection bias of the best angiograms) showed that in 10.3% of the vessels (59 out of 575) the QFR could not be determined due to quality problems in the angiography or in the visualization of the lesion.[7]

I think the main limitation is the need to use software for measuring purposes. It is well known that the biggest obstacle for the generalization of functional assessments is the interventionist's trust in his own visual assessment, especially with highly stenotic lesions.[8] Outlining the borders of the lesion has a subjective component that, as it happens with visual assessment, can overestimate the lesion and reduce the value of the FFR obtained.

The good results obtained in the studies come from centers experienced in physiology and trained in quantitative angiography and FFRangio. The software provider has designed an education-certification system to learn how to use it. In its current iteration it is still far from being fully automatic, which may be misunderstood after reading the studies published. It is yet to be determined whether the hemodynamic situation, the flow of contrast infused, and the way of acquiring angiographic imaging can alter the value of the QFR obtained.

Q.: Which should be the most appropriate indications for FFRangio with the current state of evidence and which do you think will be its mid-term indications?

A.: I think it is too early to make clinical decisions based on the FFRangio. The match reported in the studies will not necessarily happen in the real clinical practice in all centers, subgroups of patients, and angiograms.

As it occurs with other approaches to FFR, obtaining extreme values may lead to stop using pressure guidewires with matches > 95% (cQFR values < 0.71 or > 0.90),[9] although this issue is still under discussion.

In a study of cQFR-invasive FFR match in non-culprit lesions in patients with ST-segment elevation myocardial infarction, a hybrid strategy consisting of using the pressure guidewire only with QFR values between 0.75 and 0.85 would have avoided 58.5% of the pressure guidewires, with a matching classification in 96% of the lesions.[10]

Patients treated with a primary angioplasty in the acute phase of the infarction could avoid second procedures in the presence of multivessel disease by just assessing the FFRangio.

The HAWKEYE clinical trial[11] found that cQFR cut-off values > 0.89 after stent implantation were associated with better prognosis after interventions with drug-eluting stents. In this case the cQFR may be a substitute, in some circumstances, of the optimization of angioplasty with imaging modalities.

Q.: In your opinion, which study or studies would be necessary to bring this technique to the same level as the pressure guidewire? Do you think this will happen anytime soon?

A.: First thing we need is large studies with a large number of patients and centers to show whether it is safe to generalize the decision of revascularizing a lesion or a patient based on the FFRangio. It needs to be confirmed whether the tool actually works. Also, that it does so in most clinical settings, not only in expert hands or clinical trials. To my knowledge, the measures of QFR shown by the studies published so far have been performed by experts, not by interventionists, technicians, or nurses in each case.

Although the visual assessment of angiographic stenoses is the most popular method to decide whether to revascularize or not, there is solid evidence on its important limitations. Although with limitations, establishing functional assessment as the reference method in the clinical practice has improved objectivity and accuracy in the identification of the cases that may benefit the most from revascularization, thus avoiding unnecessary interventions.

The return to quantitative angiography, even if perfected, must ensure that it does not recede on the ground gained due to an increase in randomness in decision making.

As we saw in the case of hyperemic indices, the publication of the results of clinical trials comparing the occurrence of events based on the use of this or that technique and, above all, generalization to other manufacturers of FFRangio can favor its adoption—maybe even full replacement—in the near future.

The FAVOR III Europe-Japan clinical trial (NCT03729739) will randomize 2000 patients with intermediate lesions and stable angina or after revascularization of the infarct related artery to analyze the non-inferiority of guiding revascularization with cQFR values versus FFR values obtained using pressure guidewires.

If FFRangio proves useful and is applicable it should increase the number of physiology-guided revascularizations, and not just through visual assessment. Taking into account the reasons not to use functional assessment,[8] this increase should be triggered by a change of mentality in the interventionist and clinician rather than by the greater ease of this technique.

CONFLICTS OF INTEREST

None reported.

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Debate: Angiography-derived FFR. The angiographic perspective

A debate: RFF derivada de la angiografía. Perspectiva desde la angiografía

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QUESTION: Compared to the pressure guidewire what possible advantages does coronary angiography-derived fractional flow reserve (FFRangio) have and what is the current clinical evidence?

ANSWER: Guidewire pressure-derived fractional flow reserve (FFR) is the most highly validated physiological index for the analysis of coronary stenoses.[1,2] Despite the large scientific evidence supporting its prognostic impact on the assessment of patients with coronary artery disease and great cost-effective ratio, its use, though on the rise, is still not very popular.[3] And this is so even despite the fact that only one third of the intermediate angiographic lesions considered significant through visual assessment are eventually confirmed as significant at the physiological analysis.[4,5] The main reasons are that performing the FFR requires advancing a guidewire—which is not the best thing to do from the standpoint of maneuverability—through a coronary artery that has some degree of atheromatous disease. Also, to assess hyperemia, it requires the administration of drugs that can have undesirable effects effects.[6]

In order to solve these issues, easier non-hyperemic indices such as the instantaneous wave-free ratio (iFR), the diastolic pressure ratio (dPR), and the resting full-cycle ratio (RFR)[7] have been developed. They all avoid using drugs, but require the advancement of an intracoronary guidewire. FFRangio can be performed using different software, such as the quantitative flow ratio (QFR; Medis, The Netherlands) and others in the pipeline like the 3D-CA (HeartFlow, United States) which provides the same information only with the angiography without having to advance the guidewire or use drugs, which is precisely their main advantage. Similarly, there are different software available to perform this analysis using computed tomography that have already generated evidence;[8] they are based on 3D reconstruction and computational fluid dynamics.[9] They have proved to match the FFR adequately in different contexts[10,11] with a cut-off value of 0.80, an apparently higher accuracy of iFR,[12,13] and an adequate intra- and inter-observer reproducibility in centralized analyses.[14]

The FAVOR pilot study,[15] that gained the CE marking for the QFR software back in 2017, recruited 88 patients with stable coronary artery disease and non-ostial lesions, and proved the good correlation between the QFR and the FFR. Also, it proved that the values of FFRangio in situations of hyperemia (with adenosine [aQFR]) did not increase diagnostic accuracy compared to measurements without hyperemia (only with the administration of contrast [cQFR]), which means that the use of drugs can be avoided. These results have also been confirmed in a recent meta-analysis conducted by Westra et al.[16] that only included prospective registries. It showed he high negative predictive value of FFRangio that would avoid unnecessary delayed procedures.

Q.: Which do you think are the technical limitations of FFRangio?

A.: One in 5 vessels cannot be analyzed accurately with the FFRangio when the study is performed retrospectively, that is, without an optimal angiography based on easy recommendations including 2 projections of the vessel under study with, at least, a 25º difference and a recording at 15 images per second. When performed this way, images can be analyzed more precisely in up to 90% of the vessels. However, the software available is still limited with ostial or bifurcation lesions. Other than the aforementioned, the factor that often slows down a correct analysis is the crossing of vessels in the studied lesion, which explains why when the images are specifically acquired, the possibility of performing the analysis is much higher. As a matter of fact, integrating this type of software online in the catheterization laboratory is essential to obtain FFRangio values and angiographic acquisition simultaneously and correct the latter when inadequate. This is so because with offline analyses the quality of angiography cannot be changed. Another factor that can be misleading and should be taken into consideration is that, although the contour of the vessel is acquired automatically, manual corrections can still be made. To minimize the impact of this subjective factor operators need to have proper training and certification in this technique. Finally, although evidence is scarce on this regard, we should ask ourselves to what extent variations in microcirculation that affect coronary flow (like in the infarct related artery or in stable patients with significant microvascular abnormalities) can also impact the results of the FFRangio analysis. In return, this

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software asseses the entire length of the vessel, not only individual lesions, to decide what part of the vessel should be treated in cases of tandem lesions to be more precise and effective therapeutically speaking (QIMERA-1, NCT04200469).

Q.: Which should be the most appropriate indications for FFRangio with the current state of evidence and which do you think will be its mid-term indications?

A.: From my own perspective, one of the most practical, efficient, and cost-effective uses will be to assess non-culprit lesions in the myocardial infarction setting.[14,17] Although, as I mentioned at the beginning, complete revascularization with pressure guidewire has proven useful in this context, the truth is that when dealing with culprit artery revascularizations the clinical context is often that of an emergency. Therefore, no treatment is administered or physiological assessment of the lesions performed in the remaining vessels. This leads to a second procedure with the resulting risks and costs that, in many cases, can be avoided since FFRangio assessments rules out significance in over 50% of the lesions. Actually, when a second procedure is performed, the most common finding is that, according to the FFR angio, the severity of the stenoses observed in non-culprit arteries often improves compared to the acute phase. As a matter of fact, the QIMERA pilot study[14] confirmed that in patients with cQFR values < 0.82 in non-culprit arteries during the first procedure, the delayed procedure could be avoided without assuming any risks.[14]

Q.: In your opinion, which study or studies would be necessary to bring this technique to the same level as the pressure guidewire? Do you think this will happen anytime soon?

A.: We will probably need several prospective and controlled studies that compare both tools in different clinical settings: infarctions, stable patients, pre- and post-angioplasties, etc. In this sense, our group simply conducted a prospective comparison among different non-hyperemic tools (RFR and QFR versus FFR)—to be published shortly—proving that there is a better correlation between QFR and FFR. Therefore, these strategies that do not require advancing a coronary guidewire for physiological assessment will probably be widely used. However, other technological achievements still need to be made first.

On the other hand, I don't believe one technique will end up replacing the other in the mid-term. Actually, evidence suggests that a combination of both can be very useful. Thus, with QFR values < 0.75 or > 0.85 it would not make sense to run more physiological tests (avoiding 60% of pressure guidewires). Regarding the gray values in that area a guidewire-based non-hyperemic index may be used, which could reach sensitivity and specificity values of 97%, both consistent with an analysis conducted by our group of over 100 lesions with a 94.5% positive predictive value and a 98.5% negative predictive value. This combined approach would avoid the administration of adenosine to 100% of the patients and minimize the need to advance an intracoronary guidewire. According to the interventional cardiologists surveyed, this is the main setback for the physiological assessment of lesions.[18]

CONFLICTS OF INTEREST

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REC Interv Cardiol. 2020;2(2):145-149

Clinical case

An unusual cause of cardiogenic shock

Una causa inusual de shock cardiogénico

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CASE PRESENTATION

The incidence of ST-segment elevation acute myocardial infarction (STEMI) complicated with cardiogenic shock is between 5% and 8% and hospital and long-term mortality is up to three times higher compared to uncomplicated STEMI.

The leading cause of STEMI is the sudden rupture of an atherosclerotic plaque, but there are other less common causes such as cardiac myxoma-induced embolization which, same as it happens with atherosclerotic events, can lead to hemodynamic instability and cardiogenic shock.

We hereby present the case of a 61-year-old male with a past medical history of arterial hypertension and diabetes mellitus type 2 who experienced sudden loss of consciousness in his house; after remaining in this state for 10 minutes, the emergency medical team examined the patient and confirmed that the patient was experiencing confusional state and was hemodynamically unstable (arterial blood pressure, 60/40 mmHg). It was decided to proceed with orotracheal intubation and initiate the infusion of norepinephrine. The electrocardiogram performed confirmed the depression of the ST-segment of up to 5 mm at the inferior-lateral side, which is why the infarction code was activated and the patient was transferred to our center to perform a primary angioplasty procedure.

Upon arrival to the cath lab, the patient remained in a state of cardiogenic shock and complete atrioventricular block. A temporary pacemaker was urgently implanted through the right femoral vein and an Impella CP device (AbioMed, Danvers, Massachusetts, United States) was placed in the left ventricle through the left femoral artery. The coronary angiography was performed using the right femoral access and showed an acute embolic-like occlusion of the middle of the circumflex and distal right coronary arteries (figure 1A,B). Thrombus aspiration was performed in both arteries, and abundant thrombotic material was extracted. A simple angioplasty procedure was performed on the distal right coronary artery with suboptimal recovery of epicardial flow (Thrombolysis in Myocardial Infarction ≤ 2) (figure 1C,D).

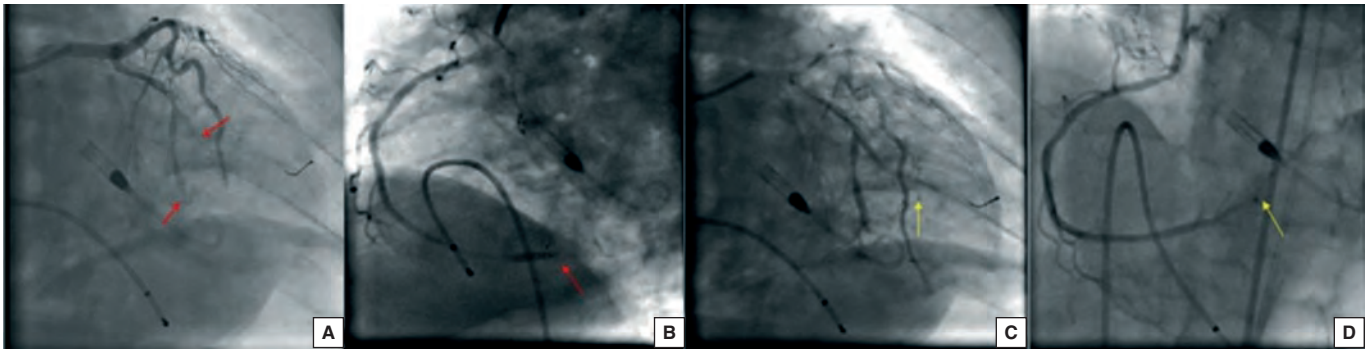

Figure 1. A: the arrows point at the embolization of the distal circumflex artery. **B:** the arrow points at the embolization of the distal right coronary artery. **C-D**: the arrows point at the outcomes of the interventional procedure.

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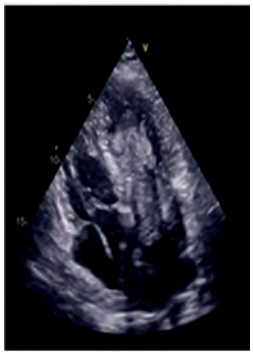

Figure 2. Mass displaced towards the left ventricle.

After the procedure, the transthoracic echocardiography performed revealed the presence of an intracavitary mass attached to the left atrial ceiling and spreading towards the left ventricle (figure 2). Given the images available and the patient's persistent hemodynamic instability despite the vasoactive drugs administered at maximum doses and percutaneous circulatory support, the heart team was activated and a decision was made to implant a extracorporeal oxygenation membrane system percutaneously and remove the Impella CP device.

Prior to the patient's admission to the cardiac intensive care unit, the computed tomography scan performed on the patient's brain revealed the total occlusion of intracranial arteries and diffuse cerebral edema. During the patient's stay at the cardiac intensive care unit, he remained in a state of refractory cardiogenic shock; the new transthoracic echocardiography performed revealed the presence of a tumor in the left atrium causing a double severe mitral lesion (regurgitation and stenosis), and severe left ventricular dysfunction.

An unusual cause of cardiogenic shock. How would I approach it?

Una causa inusual de shock cardiogénico. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

The authors hereby present the clinical case of a 61-year-old male who suffered a seizure in his home, was assessed by the EMT, and then transferred to his reference center where one primary angioplasty was performed with a diagnosis of inferior-lateral ST-segment elevation acute myocardial infarction in a situation of cardiogenic shock (CS) and further treatment with vasoactive amines and orotracheal intubation. Upon arrival to the cath. lab and since the CS was persistent, as a first-line therapy, it was decided to implant the circulatory mechanical assist Impella CP device (AbioMed, Danvers, Massachusetts, United States). Then a coronary angiography confirmed the embolic occlusion of the circumflex and right coronary arteries that resolved partially after thrombus aspiration and simple angioplasty. However, since hemodynamic instability was persistent and a left intracavitary mass was found on the echocardiography after the interventional procedure, it was decided to remove the Impella CP device and proceed to use extracorporeal membrane oxygenation (ECMO).

This is a very interesting case, not only because finding multiple coronary embolisms as the cause for the CS is exceptionally rare, but also because of the learning we acquired from the initial management of the patient such as:

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- From the "door to balloon" to the "shock to support". Considering the patient's situation when he got to the cath lab, it was prioritized to proceed with the patient's hemodynamic stabilization through the implantation of the Impella CP device before the interventional procedure (that was performed immediately after device implantation). Although we still don't have clinical trials that endorse this practice, several authors have confirmed significant mortality rate reductions in patients with CS using a protocol that prioritizes reducing the time elapsed from the medical contact to the implantation of the circulatory mechanical assist device and without significant increases of the time elapsed until the opening of the artery.[1]

- Performing an emergent echocardiography was essential for diagnostic purposes and in order to guide the therapeutic attitude. We should emphasize here that the early echocardiographic assessment of a patient with CS is crucial to be able to rule out any mechanical complications and guide the implantation of a circulatory mechanical assist device.

- Therapeutic scalation and upgrade. As already described when talking about the evolution of the patient, the persistence of the situation of CS led to a therapeutic scalation from the Impella CP device to ECMO. We should not forget here how important it is to perform an ongoing and thorough assessment of the patient with CS and have action protocols available and adapted to the reality of each particular center (figure 1) in order to offer the best therapeutic option in each particular case.

Interestingly enough, although in this case finding a mass that was spreading towards the left ventricle led to removing the Impella CP device (due to possible interactions because of its intraventricular location), in patients with CS and severe left ventricular dysfunction, keeping the Impella CP device plus ECMO has proven to be beneficial for prognostic purposes since the Impella CP device is a system to unload the ventricle, and avoid the phenomenon of overload, stasis, and thrombus formation.

Finally, the computed tomography scan performed on the patient prior to his intensive care unit admission revealed the complete occlusion of different intracranial arteries with diffuse cerebral edema, echocardiographic data of tumor-induced double mitral lesion, and significant systolic dysfunction. At this point, in order to answer the question "how would I approach it?" in a patient with such a complex clinical situation, several issues should be taken into consideration:

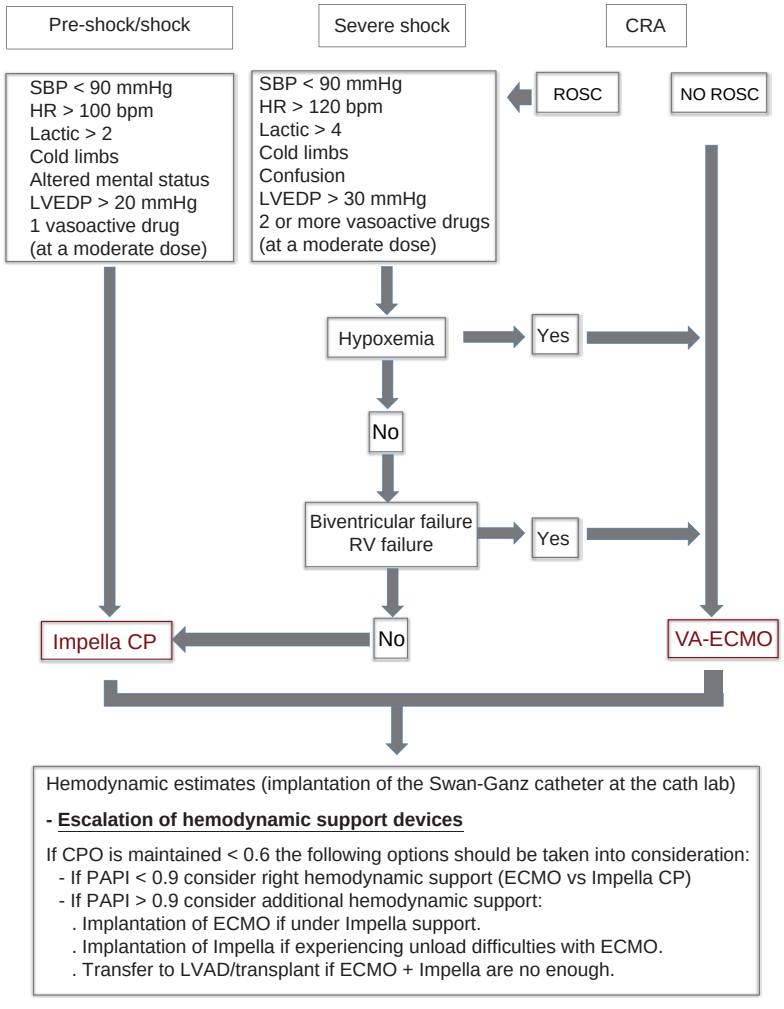

Figure 1. Action protocol for the management of cardiogenic shock at the Hospital Clínico Universitario de Santiago de Compostela, Spain. CPO, cardiac power output; CRA, cardiopulmonary arrest; ECMO, extracorporeal membrane oxygenation; HR, heart rate; bpm, beats per minute; LVAD, left ventricular assist device; LVEDP, left ventricular end-diastolic pressure; PAPI, pulmonary artery pulsatility index; ROSC, return of spontaneous circulation; RV, right ventricle; SBP, systolic blood pressure.

- The characterization of the intracavitary mass. Both the echocardiographic description and the image acquired suggest the diagnosis of myxoma: 80% of them anchor to the left atrium and 16% develop embolic phenomena that are more common in large villous tumors (irregular and jelly-like, similar to the capture of the echocardiography shown).[2] The main diagnostic doubt here has to do with the image of a thrombus. Different series recommend performing computed tomography scan, magnetic resonance imaging or both before establishing differential diagnosis. In this case, given the general situation of the patient, we could consider completing the study of characterization by performing one transesophageal echocardiography. Although the definitive diagnosis is always histological with the study of the surgical piece, the analysis of the fragments extracted in the thrombectomy may help.

- The neurologic prognosis is key to decide the therapeutic attitude. With the data provided by the computed tomography scan (and for the lack of data from the magnetic resonance imaging and the angiography, which by the way were difficult to perform considering the situation of the patient), it does not seem plausible to perform an invasive approach using the thrombectomy. Also, the hemorrhagic risk of a patient on ECMO contraindicates thrombolysis. Therefore, we can only maintain anticoagulation, establish anti-edema measures, and make thorough assessments to determine the patient's neurological prognosis before indicating the surgical resection of the mass.

- The management of a large mass that has become occluded and then caused a severe double mitral lesion that, in turn, jeopardizes hemodynamic instability should be urgent surgical resection. However, in a patient with refractory CS on ECMO, severe systolic dysfunction due to extensive ongoing acute myocardial infarction, and diffuse cerebral edema, the risk/benefit ratio should be taken into serious consideration. Several contemporary series on the surgical management of primary tumors recommend performing minimally invasive surgery,[3] although in all of them patients with large tumors or hemodynamic instability have been excluded. Therefore, if the resection of the mass is to be performed, we should choose conventional surgery, in hypothermia with total cardiopulmonary arrest, and under neurological protective measures.

In sum, this is a complex case, one of those that do not see the inside of a clinical trial or that do not fall within the recommendations established by the clinical practice guidelines. It is not easy to establish this or that therapeutic attitude with a clear-cut image of the whole situation in a type of patient where the decision-making process has a lot to do with the evolution of the patient who also needs bedside monitoring. Common sense and the best clinical judgement should be the rule of thumb here. It will be very interesting to know the outcome.

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An unusual cause of cardiogenic shock. Case resolution

Una causa inusual de shock cardiogénico. Resolución

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CASE RESOLUTION

The evolution of the patient was not favorable, brain death was declared 24 h after admission, and the patient was eventually declared dead. The microscopic analysis of the coronary aspirate revealed the presence of mesenchymal tissue with myxoid changes consistent with tumor embolism (figure 1) whereas the macroscopic piece confirmed the diagnosis of atrial myxoma (figure 2, arrow).

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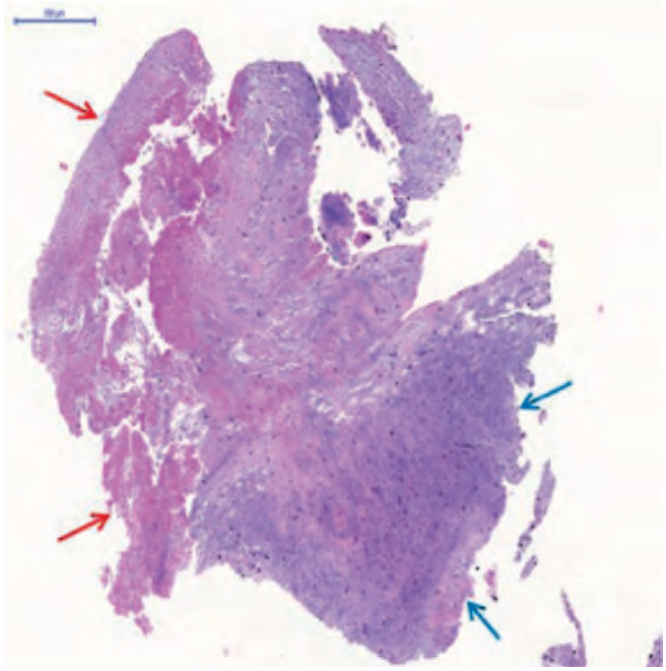

Figure 1. The red arrows point at the fibrinoid tissue. The blue arrows point at the mesenchymal tissue with myxoid changes.

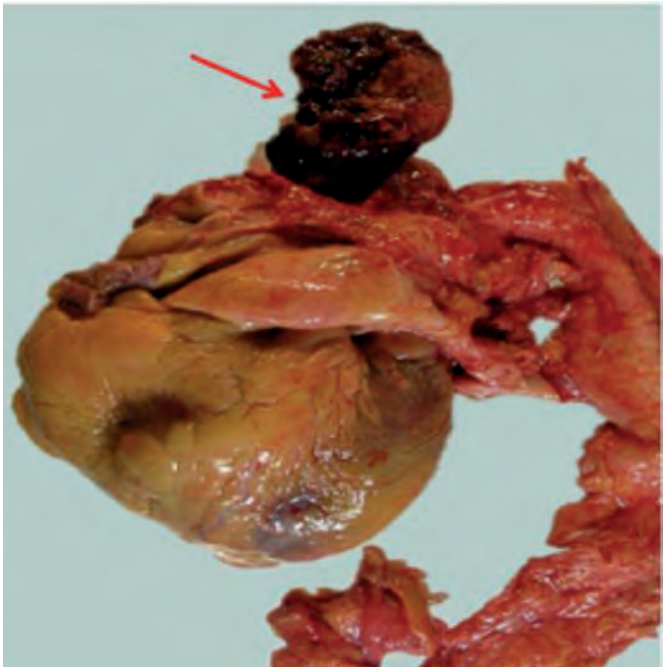

Figure 2. Atrial myxoma, macroscopic piece.

Although they are regarded as benign tumors, cardiac myxomas can lead to life-threatening events. Among their different ways of presentation, coronary embolism is one of the least common of all (0.06%). One possible explanation to this low incidence can be found in the anatomical-functional characteristics such as the existing straight angles between the aortic root and the coronary ostia, the protection of coronary arteries by the cusps of the aortic valve, and the coronary filling during ventricular diastole.

The shape of the tumors is one of the leading predictors of embolization, and papillary or villous myxomas are thought to have the highest potential to cause embolisms. According to the medical literature available, the right coronary artery is the most common location of embolization; however, there is an interesting percentage of normal coronary arteries on the angiography[1] probably attributed to the fact that the myxomatous histology of the tumor favors greater fragmentation, distal spread, and spontaneous resolution. The clinical signs of tumor embolism go from silent events to ST-segment elevation acute myocardial infarctions (STEMI) complicated with cardiogenic shock, as it was our case, and the emergent therapy here is similar to the management of atherosclerotic coronary syndromes.

We should emphasize that the use of mechanical circulatory assist devices in the setting of STEMI-related cardiogenic shock is not recommended systematically (evidence IIbC) since, to this day, we still have not seen any improvements in the short or long-term mortality rate.[2] However, its use may be an option on a per-patient basis in to achieve hemodynamical stability, guarantee the proper perfusion of vital organs or as bridging therapy for the recovery of myocardial function.

Given the presence of complete atrioventricular block and severe hypotension, in our case we considered implanting the Impella CP device (AbioMed, Danvers, Massachusetts, United States), which was the device that provided the highest utility since it does not require arterial pulse or an electrocardiographic registry to operate; however, performing a transthoracic echocardiography prior to the implantation of the device could have been decisive for diagnostic purposes and to re-think what was the best therapeutic strategy to use since, probably, the clinical situation of the patient was not only due to the STEMI, but also to the obstructive effect of the mass and the systemic embolization that may have exacerbated after the implantation of the device.

With this case we learned that performing a transthoracic echocardiography in a patient with cardiogenic shock before approaching other therapeutic attitudes is essential. Also, that the delay involved should not care at all given the benefits derived from finding possible contraindications as it happened with our case.

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Clinical trial review

ISCHEMIA trial: what is the role of revascularization in patients with chronic coronary syndromes?

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ABSTRACT

The primary endpoint of the ISCHEMIA trial, whose results were presented at the *American Heart Association* congress back in 2019, was to determine whether an initial invasive strategy of cardiac catheterization and successful revascularization plus optimal medical treatment would reduce the primary composite endpoint of cardiovascular death or myocardial infarction in patients with chronic coronary syndrome compared to an initial conservative strategy of optimal medical treatment. Out of 5179 patients, 2588 were randomized to receive an invasive strategy and 2591 to receive conservative strategy. At the 4-year follow-up, the primary endpoint showed no significant differences between both groups revolutionizing mass media. In our opinion, we should be cautious when interpreting the results of a study that has not been published yet. There is no doubt, however, that the ISCHEMIA trial deals with an important matter, that the most powerful medical treatment was able to modify the natural history of this disease in patients with chronic coronary syndrome.

Keywords: Chronic coronary syndrome. Conservative strategy. Invasive strategy.

Estudio ISCHEMIA: ¿cuál es el papel de la revascularización en pacientes con síndromes coronarios crónicos?

RESUMEN

El estudio ISCHEMIA, cuyos resultados se presentaron en el congreso de la *American Heart Association* en 2019, tiene como objetivo principal determinar si una estrategia invasiva inicial de cateterización cardiaca y revascularización exitosa, junto con el tratamiento médico óptimo, reduce el objetivo primario combinado de muerte cardiovascular o infarto de miocardio en pacientes con síndrome coronario crónico, en comparación con una estrategia conservadora inicial de tratamiento médico óptimo. De 5.179 pacientes, se aleatorizaron 2.588 para seguir una estrategia invasiva y 2.591 para una estrategia conservadora. A los 4 años de seguimiento, el objetivo primario no mostró diferencias significativas entre ambos grupos, lo que generó un gran revuelo mediático. En nuestra opinión, debemos ser prudentes al interpretar los resultados de un estudio aún sin publicar. No obstante, es innegable que el estudio ISCHEMIA aborda la importante cuestión de que el tratamiento médico más potente en pacientes con síndrome coronario crónico ha demostrado modificar la evolución natural de la enfermedad.

Palabras clave: Estrategia conservadora. Estrategia invasiva. Síndrome coronario crónico.

Abbreviations

CCS: chronic coronary syndrome. **CS:** conservative strategy. **IS:** invasive strategy. **OMT:** optimal medical treatment. **PCI:** percutaneous coronary intervention.

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INTRODUCTION

According to current recommendations of the clinical practice guidelines for the management of patients with chronic coronary syndromes (CCS), the optimal medical treatment (OMT) is a fundamental therapy to improve symptoms, reduce the progression of atherosclerosis, and prevent the occurrence of atherothrombotic events. Coronary revascularization has a significant role in the management of these patients as an adjuvant therapy of OMT. Similarly, traditional studies have proven that symptoms subside, and prognosis improves.[1-3] However, current studies question the benefits of routine revascularization in patients with CCS because of the similar mortality and myocardial infarction rates seen in patients who received OMT with and without percutaneous coronary intervention (PCI) in the COURAGE clinical trial;[4] and with and without PCI or surgical coronary revascularization in the BARI 2D trial.[5] These studies share common characteristics that the researchers of the ISCHEMIA trial (NCT01471522) have taken into account when designing their study: *a)* there is a selection bias in both studies since randomization takes place after knowing coronary anatomy; *b)* among the inclusion criteria no minimal threshold of myocardial ischemia is required; and *c)* only covered stents were used in a very small number of patients.

STUDY DESIGN AND ENDPOINTS

The ISCHEMIA trial original primary endpoint was to determine whether an initial invasive strategy (IS) of cardiac catheterization and successful revascularization (with PCI or surgical revascularization) plus OMT would reduce the composite primary endpoint of cardiovascular death or myocardial infarction in patients with CCS and moderate or severe ischemia (with medically controllable or absent symptoms) compared to an initial conservative strategy (CS) of OMT, with catheterization spared for cases where OMT failed (figure 1). Secondary endpoints were cardiovascular death or myocardial infarction and objectives of quality of life. The study was initiated back in 2012 but, in June 2017, an independent panel of experts from the National Heart, Lung, and Blood Institute (NHLBI) changed the study double primary endpoint for a composite endpoint of 5 variables: cardiovascular death, myocardial infarction, resuscitated cardiac arrest, and unstable angina or heart failure related hospitalization.[6] Median follow-up was 3.3 years.

The most interesting aspects of the study design are:

1. The degree of ischemia to assess whether a patient met the study requirements was established according to predefined criteria through one of the following additional studies: nuclear medicine test, stress echocardiogram, cardiac magnetic resonance or ergometry.

2. The main exclusion criteria were the presence of recent heart failure, acute coronary syndrome or revascularization, left ventricle ejection fraction < 35%, left main coronary artery stenosis > 50% (the study required a computed tomography [CT] scan prior to randomization) or the presence of unstable angina at the beginning of the study despite maximal medical treatment.

RESULTS

Of a total of 8518 patients screened, 5179 were randomized to receive an IS (n = 2588) or CS (n = 2591) with a median follow-up of 3.3 years (figure 1). The baseline characteristics between both groups did not vary significantly.[7,8] Mean age was 64 years old

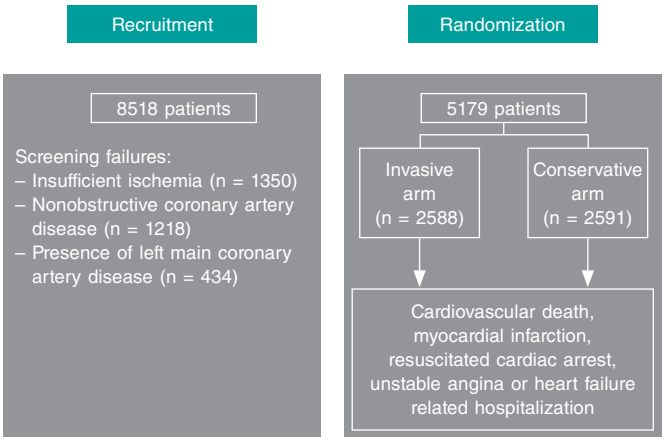

Figure 1. Flow of patients from inclusion until randomization.

and 23% of the patients recruited were women. The mean ejection fraction was 60%. In 75% of the patients ischemia imaging test was used while ergometry was used in the remaining 25%. A core laboratory determined that 54% of randomized patients had severe ischemia, 33% moderate ischemia, 12% mild or no ischemia, and 1% ischemia that could not be interpreted. Eighty percent of the patients of the IS arm were revascularized; 74% with PCI and the remaining ones with coronary revascularization surgery. Two thirds of the non-revascularized patients had significant coronary artery disease, and one third nonrevascularizable extensive coronary artery disease.

The study met its 4-year primary endpoint in 15.5% and 13.6% of the patients from the CS and IS group, respectively without any significant differences (adjusted hazard ratio [HR], 0.93 [0.8-1.08]; P = .34). There was a tendency towards a higher rate of events within the first 6 months in the IS arm that reversed in favor of such arm at the 2-year follow-up. Regarding myocardial infarction, the spontaneous one was reduced in the IS arm (adjusted HR, 0.67 [0.53-0.83]; P < .01) while the perioperative infarction was increased in this arm (adjusted HR, 2.98 [1.87-4.74]; P < .01).

COMMENT

The ISCHEMIA trial was presented in 3 late-breaking clinical trial sessions held in Philadelphia by the American Heart Association congress back in November 2019: clinical outcomes, objectives of quality of life, and results in patients with end-stage renal disease.[7] Ever since, the media has made a big deal out of it[9] by reporting on the preoccupation of different associations of patients following a message delivered on the news: «thousands of patients are receiving unnecessary procedures».

In our opinion, we should be cautious when interpreting the results of a popular study that still unpublished. What is undeniable—and researchers should take credit for it—is that the ISCHEMIA trial discussed an important issue: the management of patients with stable coronary artery disease (now called CCS) with the most powerful medical treatment that was able to modify the natural history of this disease.

There are 4 main issues we should take away from this study.

1. It was a very difficult study to conduct where the recruitment of patients was slow in most participant centers. Before reaching 50% of the events estimated for the study primary

endpoint, such primary endpoint had to be changed to increase the number of events, which is a non-desirable practice when designing a study.[10]

2. Inclusion criteria were very rigorous. To recruit a patient the presence of coronary artery disease had to be confirmed through a CT scan (anatomical study) followed by the presence of significant ischemia (functional study, 50% of randomized patients through nuclear medicine test), something rare in the management of these patients in our setting.

3. On the other hand, the ISCHEMIA was a trial on the management of patients with stable coronary artery disease, not on revascularization vs no revascularization as it was announced by the media at one point. This is very clear if we consider the following data: only 80% of the patients from the IS group were revascularized and up to 23% of those assigned to the CS group were revascularized. The ISCHEMIA was not a PCI trial either since only 74% of the patients revascularized were treated with this technique while coronary revascularization surgery was performed in the remaining cases. This means that 1 in 5 patients from the IS group was not revascularized, but 1 in 4 patients from the CS group was.

4. The study main results confirm that when both strategies are compared there are similar risks of presenting the composite endpoint of cardiovascular death, myocardial infarction, resuscitated cardiac arrest and unstable angina or heart failure related hospitalization. Analyzing the remaining study endpoints, it can be said that the CS has a lower risk of perioperative myocardial infarction (for obvious reasons) or heart failure related hospitalization. However, the initial invasive strategy has a lower risk of spontaneous myocardial infarction and unstable angina related hospitalization, and is associated with an undeniable symptomatic relief and improved quality of life in patients with angina symptoms. On the analysis of adverse events, it is obvious that perioperative myocardial infarction does not have the same prognostic value as spontaneous myocardial infarction. Also, the spontaneous myocardial infarction curves and primary assessment criterion vary at the end of the follow-up. This favors the revascularization strategy yet despite the great deal of patients of the CS group who were revascularized, meaning that it will important to see the long-term results.

In conclusion, the ISCHEMIA is a historic clinical trial that reinstates the importance of aggressive medical treatment in patients with stable coronary artery disease. However, before claiming victory against revascularization the improved quality of life provided by revascularization and the inherent limitations of an unpublished study, some of which have already been discussed, should not be forgotten.

CONFLICTS OF INTEREST

None reported.

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iFR variations during coronary angioplasty

Variaciones del iFR durante la angioplastia coronaria

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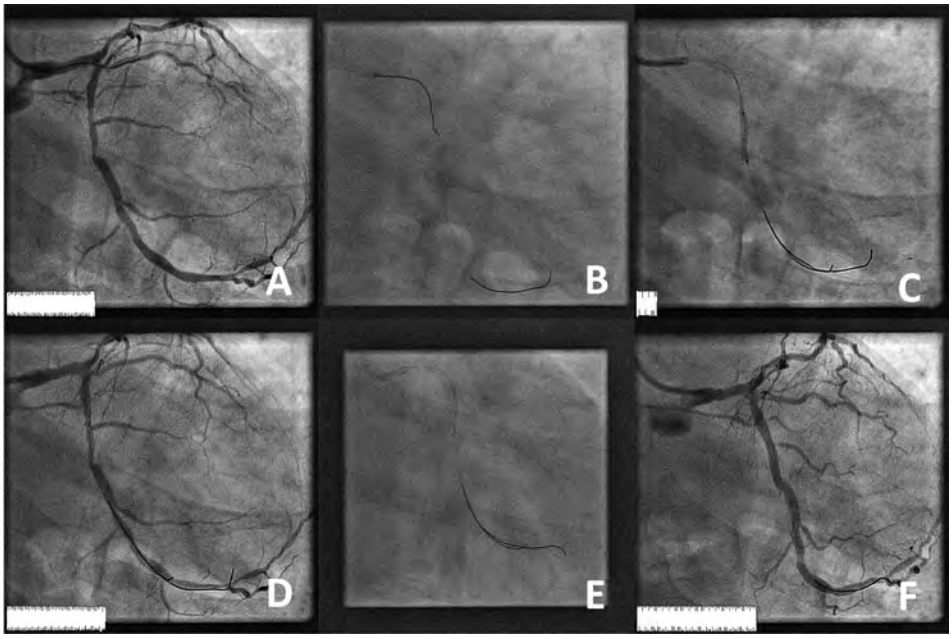

Figure 1.

A fifty-five year-old hypertensive and former smoker male admitted with signs of typical chest pain, left bundle brunch block, and normal troponin levels. The angiography revealed 2-vessel, left circumflex and right coronary artery disease. The latter was treated with a stent and for the circumflex coronary artery an instantaneous wave-free ratio (iFR)-guided intervention was decided. Then, a second conventional guidewire was used for stabilization purposes. Figure 1A shows initial angiography (video 1 of the supplementary data), equalization of proximal and distal pressures (figure 1B and figure 2A), plain balloon angioplasty and iFR wedge pressure determination (figure 1C and figure 2D), angiographic result after balloon-angioplasty (figure 1D), iFR determination after balloon angioplasty (figure 1E and figure 2E,F), and final result (figure 1F, figure 2G,H and video 1 of the supplementary data).

Figure 2A shows equalization, positive iFR after the lesion (figure 2B), sudden iFR change during the pullback suggestive of focal stenosis (figure 2C), iFR during balloon inflation without antegrade flow (iFR wedge pressure) (figure 2D), iFR 1 minute after the angioplasty (figure 2E), 4 minutes later without maneuvers or drugs (figure 2F), final iFR and iFR pullback, respectively, after stenting (figure 2G,H).

The still low iFR (0.63) immediately after balloon angioplasty was probably due to microcirculation and collateral flow. Thus, flow increase after the angioplasty balloon deflation is expected following arteriole compensatory vasodilation. This compensatory increased flow elevates the translesional pressure gradient resulting in lower iFR values than expected after lesion treatment. However, the iFR

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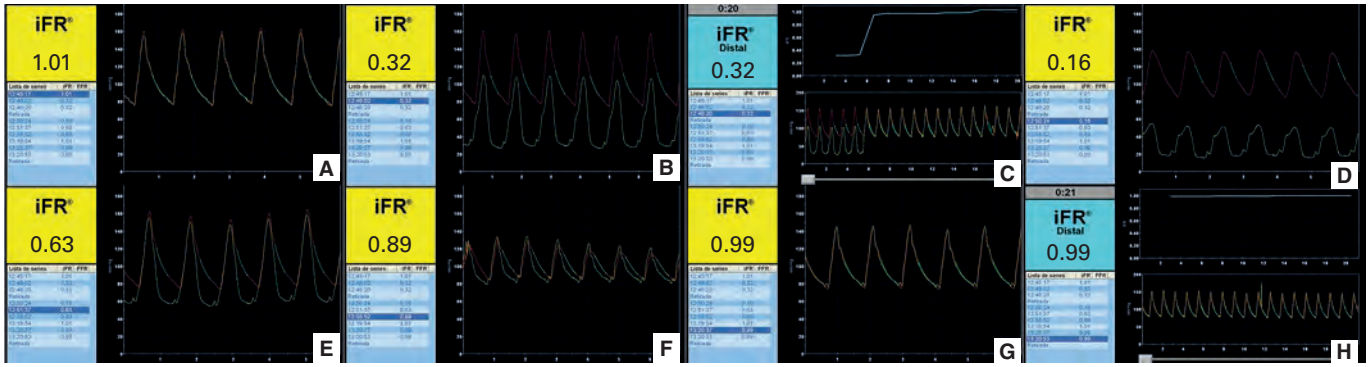

Figure 2.

increased 4 minutes later (from 0.63 to 0.89), a reasonable time to recover the conditions at rest including the baseline vascular arteriolar tone, confirming the good physiological result of balloon-angioplasty.

In conclusion, resting physiological indexes need to be performed carefully and timely to avoid bias and issues when interpreting the results.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000075.

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Spontaneous coronary dissection extension induced by optical coherence tomography imaging

Extensión de una disección coronaria espontánea causada por estudio con tomografía de coherencia óptica

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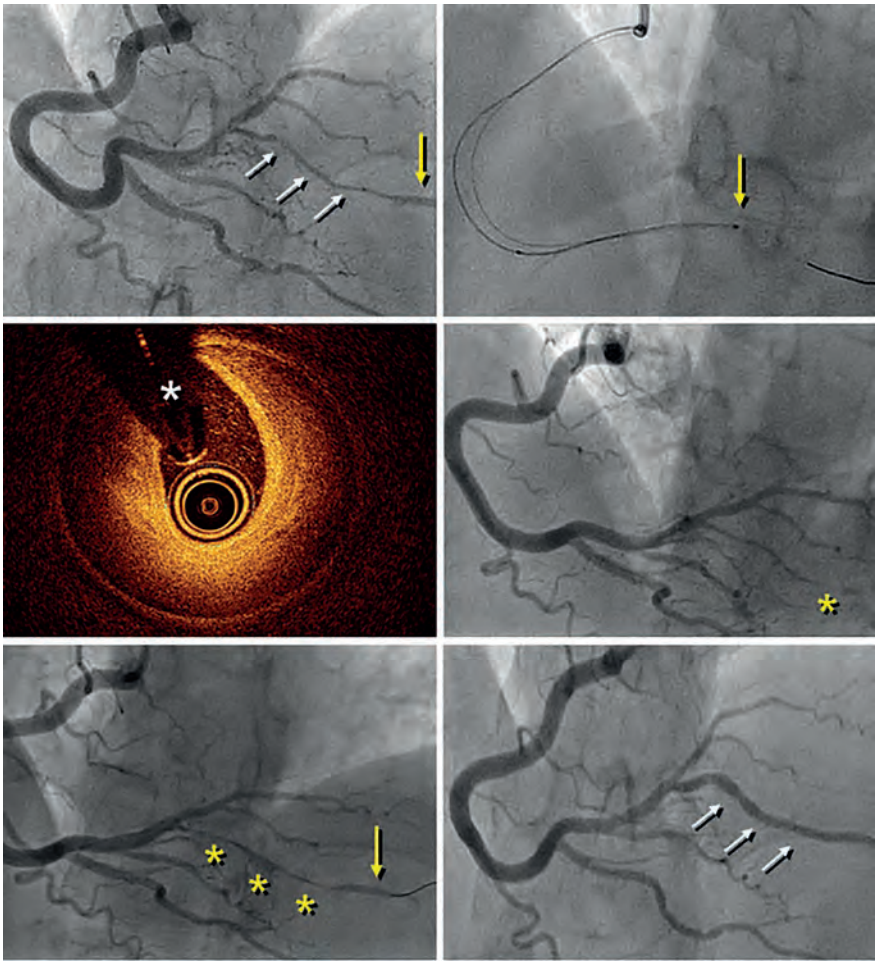

Figure 1.

A 41-year-old woman presented with an inferolateral ST-segment elevation myocardial infarction. Coronary angiography confirmed the presence of a long narrowing involving the right coronary artery posterolateral branch (figure 1A, white arrows). Spontaneous coronary artery dissection was suspected and optical coherence tomography (OCT) imaging was considered by the operator for confirmation

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purposes. Advancing the OCT catheter was difficult due to lack of support and it was decided to only interrogate the proximal aspect of the branch (figure 1B, arrow). OCT revealed the presence of an intramural hematoma without entry tear (figure 1C; asterisks denote wire artefact). At that moment the patient complained of chest pain that remained after removing the OCT catheter. The presence of functional branch occlusion (figure 1D, asterisk), with Thrombolysis in Myocardial Infarction (TIMI) grade 1 flow, was confirmed. Coronary flow was re-established through gentle dilation (4 atm) using a 1.5 mm balloon. Final TIMI grade 2 flow was achieved (figure 1E, asterisks) and the patient became asymptomatic. Her subsequent clinical course was uneventful. Coronary angiography performed 3 months later confirmed the complete healing of the dissected segment (figure 1F, arrows).

Diagnosing spontaneous coronary artery dissection can be challenging in the absence of the classical dual-lumen pattern. OCT imaging is considered safe and, therefore, recommended for selected patients to confirm the diagnosis. Our findings illustrate that extra care is required while acquiring images in these frail and disrupted vessels. OCT should only be considered when the diagnosis remains unclear, and the acquisition of images in very distal and small vessels should be avoided.

CONFLICTS OF INTEREST

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

TR Band modification for distal transradial access hemostasis

Modificación de TR Band para la hemostasia del acceso radial distal

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To the Editor,

Distal transradial access (dTRA) has been postulated as a new alternative to traditional left transradial access for coronary angiography.[1] Its main advantages are reduced time to hemostasis, increased comfort during the procedure—both for patient and operator—and preservation of proximal access for future interventions.

Traditionally, hemostasis with the dTRA has been done manually or using conventional radial bands with the limitation of instability causing increased or ineffective compression due to anatomical mismatch. The PreludeSYNC DISTAL[2] is the first dTRA hemostatic band with the setback of having multiple devices for a reasonably similar access.

The TR Band is a compression device designed to assist in radial artery hemostasis after performing a transradial procedure. The transparent structure is designed for visual control and selective compression of the radial artery featuring dual compression balloons through air titration. Also, it has a rigid transparent plastic support to guarantee compression. This plastic support avoids the correct apposition in the anatomical snuffbox if used for dTRA compression purposes (figure 1A,B).

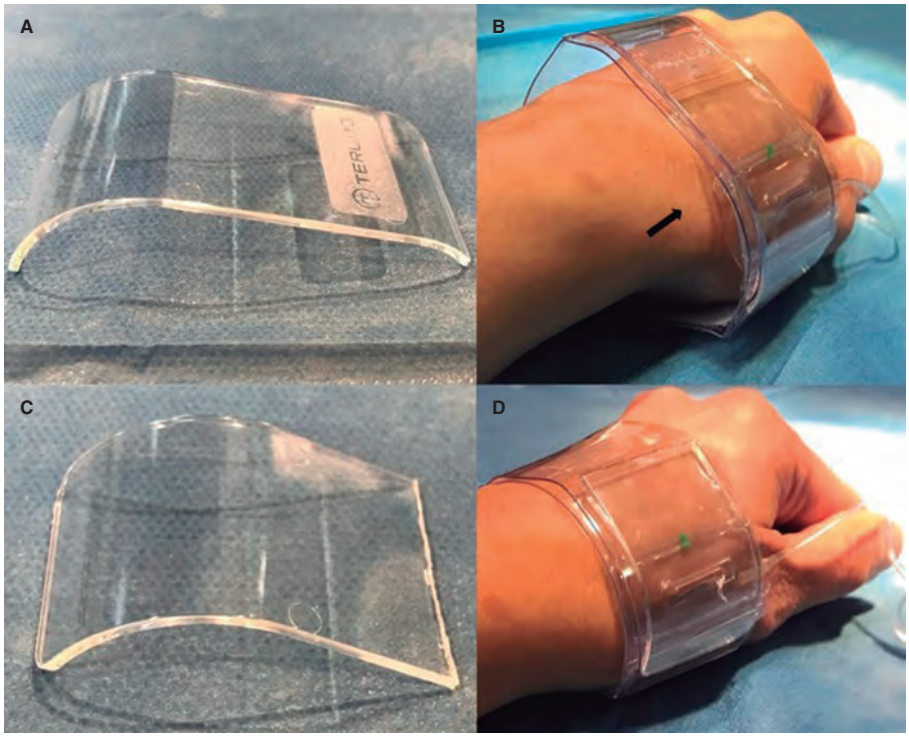

Figure 1. A-B: incomplete apposition in the anatomical snuffbox of the unmodified TR Band. **C-D:** complete apposition in the anatomical snuffbox after cutting through the middle of this rigid transparent plastic.

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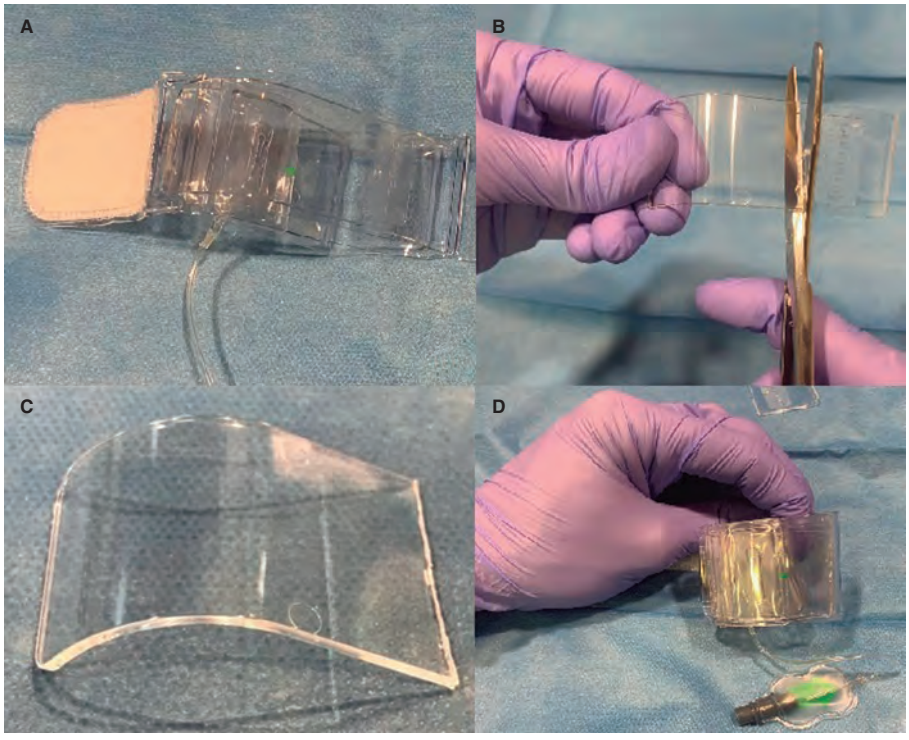

Figure 2. Modification process of the TR Band.

Cutting through the middle of this rigid transparent plastic (using surgical scissors, figure 2, video 1 of the supplementary data) facilitates the right apposition of the splint, and maximizes the effectiveness of compression in dTRA. The visibility of the puncture site is guaranteed, allowing the adjustment of the pressure depending on each patient's individual condition, while distributing the pressure evenly in the compression zone. The local effects of the remaining plastic shards are avoided by covering the plastic structure (figure 1C,D).

We have performed 96 cases of dTRA to date. In every procedure, punctures were ultrasound-guided[3] to minimize damage to the artery during the process. This modification of the TR Band was used as a hemostatis method in 90 out of a total of 96 patients treated with dTRA. The cases where it could not be used were patients with too thick a wrist for the TR Band to fit correctly and safely (6 patients). Thus, it was decided to perform manual compression of the distal radial artery to avoid possible complications associated with any accidental moves of the TR Band. No bleeding, hematomas or vascular complications were reported.

Other authors have suggested[3-5] further modifications of the TR Band by completely removing the rigid transparent plastic support with good results. Although it is an equally acceptable alternative worth taking into account, in our own experience we have not seen that the patient's anatomical characteristics are a limiting factor to apply our modification. The main advantages are a greater stability achieved during device placement and a more homogeneous pressure distribution. The rates of success of the entire removal of the plastic splint are similar compared to our own results (94.9% vs 93.75%).[4]

This off-label modification allows an effective and secure compression when using the dTRA with the most widely used device today. It can be an alternative to manual compression or dedicated devices. In our own experience it can bring more stability compared to the complete removal of the plastic splint. Puncturing the snuffbox is still not widely used in our routine clinical practice, and safe modifications of devices available can help both logistically and economically generalize the technique.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000089.

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Coronary perforation after intracoronary lithotripsy in a chronic total coronary occlusion

Perforación coronaria tras aplicación de litotricia intravascular en una oclusión total crónica

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To the Editor,

The management of chronic total coronary occlusions (CTO) has improved significantly over the last decade and reached success rates close to 85%-90% in contemporary registries.[1] However, angiographically severe coronary calcifications are a common limitation of CTOs making revascularization more difficult.[2]

Intracoronary lithotripsy seems to be a safe and effective alternative for the management of severely calcified coronary lesions through the administration of pulsatile mechanical energy. This energy generates a pressure high enough to crack the intimal and medial calcium while minimizing mechanical damage to the remaining vascular tissues.[3]

We present the case of a 77 year-old-male with a CTO in the mid left anterior descending coronary artery who underwent elective percutaneous coronary intervention. The distal left anterior descending coronary artery received retrograde flow through the septal collaterals from the right coronary artery (figure 1A).

The initial antegrade approach with guidewire escalation using the Sion (Asahi-Intecc, Abbott Vascular, United States), Gaia-Second (Asahi-Intecc, Abbott Vascular), and Progress-200T (Abbott Vascular) guidewires failed with progression through the subintimal space (figure 1B). Then the retrograde access was used. It facilitated the advance of a Fielder XT-R guidewire (Asahi-Intecc, Abbott Vascular) towards the proximal left anterior descending coronary artery and re-entry into the antegrade guide catheter. However, it was impossible to advance the Corsair-Pro (Asahi-Intecc, Abbott Vascular) and Turnpike (Teleflex, United States) microcatheters through the occlusion distal stump due to the heavy calcification at that point despite the balloon trapping of the retrograde guidewire into the guide catheter (figure 1C), so a second procedure was attempted 1 week later. This time the Corsair-Pro microcatheter was easily advanced using the retrograde access and the arterioarterial loop was completed using the RG-3 (Asahi-Intecc, Abbot Vascular) guidewire as shown on figure 1D.

Then, the CTO was predilated using 2.0 mm and 2.5 mm semicompliant balloons (figure 2A,B) that were properly expanded.

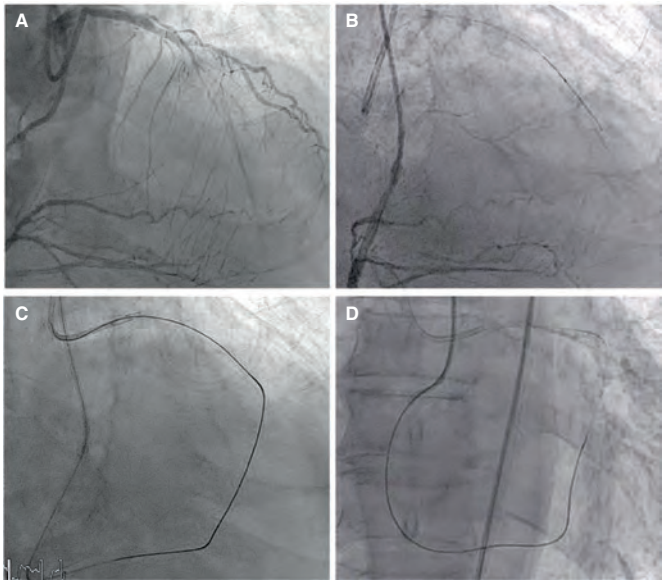

Figure 1. A: chronic total coronary occlusion of the mid left anterior descending coronary artery. **B:** failed initial antegrade approach with subintimal progression of the guidewire. **C:** impossibility to advance the microcatheter retrogradely through the occlusion. **D:** creation of the arterioarterial loop using a RG3 guidewire in a second retrograde attempt.

Considering the heavy coronary calcification and the previous difficulties, it was decided to perform an adjuvant intracoronary lithotripsy as the next step to crack the calcified plaque. In the procedure, non-compliant balloons were not used.

A 2.5/12 mm Shockwave lithotripsy balloon (Shockwave-Medical, United States) was advanced towards the mid left anterior descending coronary artery. After the balloon was inflated at a low pressure of 4 atm, 2 series of 10 acoustic shock waves were applied (figure 2C) with postdilatation at 6 atm following the technical specifications. The subsequent angiographic injection revealed the

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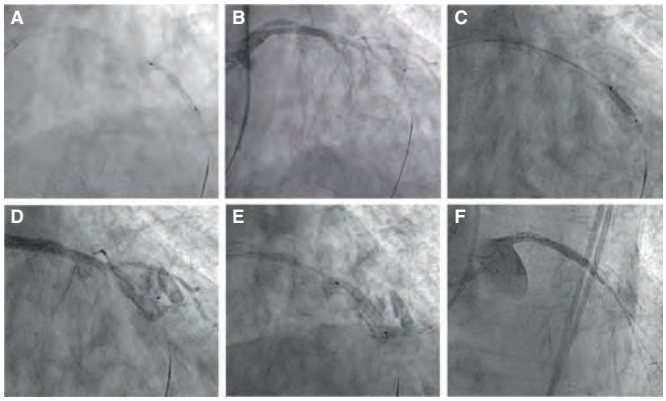

Figure 2. A: predilatation of the chronic total coronary occlusion using a 2.5 mm semicompliant balloon that proved ineffective **(B).** After the inflation of the Shockwave balloon in the mid left anterior descending coronary artery and the administration of the lithotripsy **(C)** an Ellis type III coronary perforation occurred **(D)** that was sealed using a Papyrus covered coronary stent **(E). F:** final result with flow restoration up to the level of the occlusion.

presence of an Ellis type III coronary perforation (figure 2D) that was controlled by implanting a 3.0/22 mm Papyrus covered coronary stent (Biotronik, Switzerland) (figure 2E), and a 3.0/22mm Onyx drug-eluting stent (Medtronic, United States) proximally overlapped. However, this did not restore flow to the distal left anterior descending coronary artery (figure 2F).

Intracoronary lithotripsy is an attractive therapeutic alternative for the management of severely calcified coronary lesions. It has been used in isolated cases of CTO,[4,5] but for the time being there are no solid clinical data supporting its efficacy and safety in this specific context. However, this technique may be associated to potentially serious complications like coronary perforations and deep dissections[6] reported in up to 13% of the vessels treated with lithotripsy at the optical coherence tomography assessment.[7]

In our patient the guidewire possibly advanced through the true lumen in the first retrograde attempt and the severe calcification of the CTO prevented the advance of the catheter. In the second attempt, the easier and less difficult advance of the microcatheter was possibly associated with the subintimal progression of the guidewire with posterior re-entry into the true lumen that facilitated the completion of the arterioarterial loop. Although no intracoronary imaging modality was performed for confirmation purposes, inflating the lithotripsy balloon and delivering of high-pressure pulsatile energy in the subintimal plane may have caused the tear of the coronary adventitia.

This case is indicative of the need to be more thorough in the assessment of the safety of coronary lithotripsy in the management of CTOs. From our standpoint, it is important to confirm the intraluminal position of the guidewire before using this technology, especially in complex lesions like CTOs. Hence, we think it is advisable to guide the application of intracoronary lithotripsy with intracoronary imaging modalities if feasible.

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