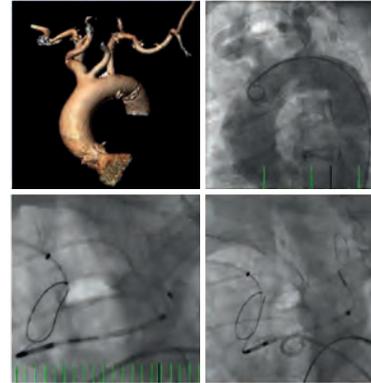


### Update on requirements and equipment in interventional cardiology



#### Material resources

- Physical space of  $\geq 200 \text{ m}^2$  (cath lab  $\geq 50 \text{ m}^2$ )
- High-risk conditions of sterility and air quality, class I
- Proper radiological equipment
- Digital image acquisition and storage system
- PCI equipment and intracoronary diagnostic systems
- Resuscitation equipment



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Microalbuminuria predicts contrast-induced nephropathy in patients with acute coronary syndrome

Use of subcutaneous nitroglycerin to facilitate transradial access in coronary procedures (NiSAR Study)

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# Translational research in the new era of percutaneous mitral valve interventions



## Investigación traslacional en la nueva era del intervencionismo mitral percutáneo

Juan F. Granada\*

Cardiovascular Research Foundation, Columbia University Medical Center, New York, NY, United States

### SEE RELATED ARTICLE:

<https://doi.org/10.24875/RECICE.M20000125>

Mitral regurgitation (MR) is one of the most prevalent valvular heart diseases in the world.<sup>1</sup> Although surgical mitral valve replacement has shown to improve clinical outcomes in patients with severe primary MR, surgery is still being denied in a significant number of patients due to their multiple clinical comorbidities.<sup>2</sup> The current clinical practice guidelines for the management of severe secondary MR recommend the surgical valve intervention only in cases where concomitant coronary revascularization is indicated.<sup>3</sup>

Transcatheter mitral valve repair using the edge-to-edge technique (MitraClip, Abbott Menlo Park, CA, United States) has shown to improve quality of life and reduce all-cause mortality in patients with heart failure and secondary MR refractory to the optimal medical treatment.<sup>4</sup> However, the level of MR reduction achieved by MitraClip is inferior compared to the surgical techniques, and its overall use is limited by several anatomical factors.<sup>5</sup> Transcatheter mitral valve implantation is emerging as a potential therapeutic alternative that could overcome some of the current limitations of edge-to-edge repair.<sup>6</sup> Due to their technical design features, most transcatheter mitral valve implantation systems use the surgical transapical approach. Limited experience has been gathered on the use of dedicated transseptal systems. Finally, complex anatomical features such as the possibility of left ventricular outflow tract obstruction and presence of mitral annular calcification have limited the fast clinical adoption of this technology.

The field of catheter-based mitral valve intervention is rapidly expanding, and translational experimental models are seriously needed for the proper validation of these technologies. Unlike aortic valve disease, MR is due to several pathological conditions that result in different anatomical substrates that are not easy to reproduce in experimental models. Catheter-based technologies are designed taking into consideration specific anatomical targets such as annular dilatation or chord elongation, which are also challenging to reproduce in experimental animal models. Significant differences exist between humans and animal models. In the first place, one of the most important challenges we face is annular size. Devices developed for human use are typically larger compared to the annulus seen in common experimental models, which at times, requires developing customized valve sizes. Secondly, the aortomitral curtain is particularly small, which often leads to device interaction with the aortic valve. Thirdly, the mitral tissue is thin and friable providing little support to technologies that require the use of anchors or pads to remain in position. Finally,

the left atrium is flat and shallow and provides little room for the validation of technologies via transseptal access.

The use of diseased animal models is not typically required to validate structural heart technologies and most of the validation work can be done on the bench or on healthy animal models. Healing and thrombogenicity of valve materials is particularly important and can be validated in healthy animals. The stability of the frame and durability of the leaflets can also be tested and is of particular significance in the transcatheter mitral valve implantation space. The mechanism of the deployment and delivery system can also be tested but, overall, the retention of the valve depends on the mechanism of anchoring used, which could be challenging due to the lack of structural support. In these cases, the surgical placement of the valves is needed for the long-term stability of the implant.

The use of diseased animal models is often spared to assess the efficacy of the device or test particular device features (ie, anchoring). Several animal species, primarily dogs suffer from primary MR due to leaflet prolapse and have been used to test several catheter-based technologies.<sup>7</sup> However, these models are expensive and difficult to provide. Several groups have already developed secondary MR models by inducing ischemia of the posteromedial papillary muscle.<sup>8-9</sup> These models have resulted in a high periprocedural mortality rate and moderate levels of clinically relevant MR. The study conducted by Rodríguez-Santamarta et al. recently published on *REC: Interventional Cardiology* presents a variation of this model by adding volume overload and creating an aorto-pulmonary fistula following the myocardial infarction of the circumflex artery.<sup>10</sup> The number of animals was small, but researchers were able to prove the feasibility of model development. In this study, the level of MR was moderate (at most) and other features associated with MR such as annular dilatation were present. These morphological features, although obvious on the image assessment, were subtle in nature and probably in their early stages compared to patients who suffer from severe MR.

The field of structural heart procedures is changing very rapidly, and experimental models are essential for the proper validation of these technologies. Healthy animal models are perhaps enough to test the mechanism of the device delivery system, healing, and durability. Diseased animal models can help validate device efficacy, mechanisms

\* **Corresponding author:** CRF-Skirball Center for Innovation, Cardiovascular Research Foundation, 8 Corporate Dr, Orangeburg, New York 10962, United States. E-mail address: [jgranada@crf.org](mailto:jgranada@crf.org).

Online: 05-11-2020.

<https://doi.org/10.24875/RECICE.M20000178>

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of anchoring, and the long-term stability of the device. However, due to the high anatomical variability seen in humans compared to animals, long-term results may be confusing and require careful analysis by multidisciplinary teams before starting the first tests in humans. A multi-modality approach is highly desirable in the validation process of structural heart technologies. Although animal data are key, proper validation including human tissue and imaging correlation studies may help minimize the misinterpretation of experimental signals and define the developmental pathway of structural heart technologies.

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

J. Granada is co-founder of Cephea Valve Technologies.

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# Elderly patients with comorbidities and acute coronary syndrome: *primum non nocere*?



## *Ancianos con comorbilidades y síndrome coronario agudo: ¿primum non nocere?*

Miquel Vives-Borràs<sup>a</sup> and Alessandro Sionis<sup>b,c,\*</sup>

<sup>a</sup> Servicio de Cardiología, Hospital Universitari Son Espases, Institut d'Investigació Sanitària Illes Balears (IdISBa), Palma de Mallorca, Islas Baleares, Spain

<sup>b</sup> Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, IIB-SantPau, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>c</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

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<https://doi.org/10.24875/RECICE.M20000147>

According to data from the National Statistics Institute, life expectancy has increased from 73.5 years in 1975 to 83.6 years in Spain in the year 2019. Also, the mean age of the population has gone up 10 years during this same period.<sup>1</sup> In this sense, the results from the study conducted by Dégano et al.<sup>2</sup> in 2013 come as no surprise. They already anticipated a strong increase in the rate of acute coronary syndrome (ACS) within the next 35 years when the Spanish population > 75 years will represent almost a quarter of the national census. This study anticipated that between 2013 and 2049, the cases of ACS in elderly patients would increase over 70%, but keep a discrete growth in patients under 75 years. These data are but a glimpse of a not so distant future when our patients will be older and their life expectancy longer. Also, the association between aging and comorbidity means that we will have to treat more complex patients.

Elderly patients with comorbidities are misrepresented in clinical trials studying the efficacy of both early invasive strategy for the management of non-ST-segment elevation acute coronary syndrome (NSTEMACS) and the most suitable antithrombotic treatment.<sup>3</sup> Therefore, despite the fact that clinical practice guidelines recommend early invasive strategy in most patients,<sup>4</sup> its generalization to these patients is controversial. It is often decided to individualize the decision-making process by weighing risks and benefits and taking into consideration the treating physician's perception on the possible complications. Hence, conducting clinical trials focused on this subpopulation as creating large registries representative of the actual clinical practice is of paramount importance.

In an article recently published by Pernias et al.<sup>5</sup> on *REC: Interventional Cardiology*, the authors present a wide registry of elderly patients with NSTEMACS conducted thanks to the collaborative work of different cardiology units from several Spanish autonomous communities. With over 7000 patients included, this study evaluated the impact of comorbidities on the indication to perform coronary angiographies. The 6 comorbidities studied (cerebrovascular disease, anemia, kidney disease, peripheral arteriopathy, chronic pulmonary disease, and diabetes mellitus) turned out to be

independent predictors of a non-invasive approach. Also, it was confirmed that patients with more comorbidities had lower the chances of undergoing an invasive strategy despite having higher GRACE scores.

The comorbidities reported in this study are associated with a worse prognosis in this clinical setting.<sup>6</sup> However, this does not necessarily involve low short-term life expectancy per se. Therefore, given the futility of an eventual revascularization a conservative strategy would not be justified. This clearly shows the need for a proper comprehensive geriatric assessment of these patients, since the accumulation of concomitant comorbidities is often followed by frailty, cognitive impairment, and functional dependency. These variables are key finding out why there is a paradoxically reverse correlation in these patients between the risk of ischemic events and the frequency of performing coronary angiographies. In this sense, we should mention the LONGEVO-SCA, a registry conducted in our setting that studied in detail the impact of frailty and geriatric syndromes on the therapeutic approach and vital prognosis of elderly patients with NSTEMACS. Important conclusions can be drawn from this registry, like the negative impact of frailty both on the prognosis of elderly patients with NSTEMACS and on the benefits of an invasive strategy.<sup>7,8</sup>

The usefulness of the invasive strategy in elderly patients is not well established. The randomized clinical trial After Eighty included 457 patients > 80 years with non-ST-elevation acute myocardial infarction (NSTEMI). It confirmed a lower incidence rate of the composite endpoint of death or cardiovascular events at the 1.5-year follow-up with the invasive strategy.<sup>9</sup> However, this clinical trial did not consider frailty and included less than 25% of the possible candidates, indicative of bias in favor of elderly patients in better general health conditions and with fewer comorbidities.<sup>9</sup> The MOSCA clinical trial<sup>10</sup> included 106 elderly patients with NSTEMI and comorbidities. Although there were fewer chances of death or ischemic events in this study at the 3-month follow-up in patients randomized to the invasive strategy, no benefits were seen with this strategy at the end of the follow-up (2.5 years).

\* **Corresponding author:** Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret 167, 08025 Barcelona, Spain.  
E-mail address: [asionis@santpau.cat](mailto:asionis@santpau.cat) (A. Sionis).

Online: 05-11-2020.

<https://doi.org/10.24875/RECICE.M20000167>

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Currently underway, the MOSCAFRAIL clinical trial<sup>11</sup> will assess the efficacy and safety of the invasive strategy and its prognostic effect within the first year after NSTEMI in elderly patients with confirmed frailty. This trial, that included over 10 tertiary and secondary Spanish hospitals, is a systematic geriatric and comorbidity study conducted with widely validated scales. Its results should provide valuable information and greatly impact clinical practice in the coming future.

Another controversial issue with studies of elderly patients with ACS is what clinical outcomes should be assessed. Most randomized and observational studies focus on "traditional" clinical outcomes like mortality or ischemic events. However, on many occasions there are no data on the impact on symptoms, perceived quality of life, and need for readmission, which may indicate better the clinical benefits of this population. In this sense, we should mention the After Eighty clinical trial found no differences regarding quality of life between patients treated with the invasive strategy and those treated conservatively.<sup>12</sup>

In conclusion, elderly patients with high comorbidities who are hospitalized due to NSTEMI are a common problem today and will remain so in the future. Given the scarce scientific evidence on the therapeutic approach of these patients, studies like the one conducted by Pernias et al.<sup>5</sup> improve our understanding of this complicated clinical scenario and remind us of the importance of collaborative research to conduct large registries that show the reality of this emerging problem in our setting.

#### FUNDING

No funding was received for this work.

#### CONFLICTS OF INTEREST

None reported.

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# Virtual vs face-to-face meetings. Can both of them coexist?



## *Analógicos frente a digitales: ¿es posible la convivencia de congresos?*

Armando Pérez de Prado\*

Servicio de Cardiología Intervencionista, Hospital Universitario de León, León, Spain

It comes as no surprise that the progression of medical training would eventually take a leap into the digital world where we would be able to access information without leaving our working place or the comfort of our homes. Our specialty, interventional cardiology, predominantly visual, has always benefited from the most advanced technology regarding communication. Actually, we have been doing this for years, even in our country: by the mid-1980s, the Madrid Interventional Course (MIC) organized by Dr. J.L. Delcán and Dr. E. García, was already broadcasting live cases via satellite to analyze and discuss new insights with larger audiences compared to those that can fit in a room. These days, live cases are an essential part of the meetings held in our setting (whether international like the ones organized by EuroPCR and TCT or national like the ones held by the *Società Italiana di Cardiologia Interventistica* [GISE] and the Interventional Cardiology Association of the Spanish Society of Cardiology [ACI-SEC])<sup>3</sup>. These cases are discussed remotely by panels of experts with a growing interaction with in-person and remote attendees thanks to specific computer tools and social media. But it is not only the broadcast of live cases which benefit from these advances. We have had access to information on late breaking clinical trials through the Internet many times even before in-person meeting where these trials are often presented. Also, we have had access to the recordings of many simultaneous sessions we couldn't attend in-person but can review later when we have the time.

The situation of the pandemic caused by the new SARS-CoV-2 coronavirus has accelerated this cross over to virtual meetings due to the impossibility of travelling to places and holding large in-person meetings.<sup>1</sup> The main in-person cardiology meetings scheduled for 2020 have been suspended or turned into virtual meetings. The two largest international meetings already mentioned, EuroPCR and TCT, have become virtual meetings. Also, mass meetings like the ones held by the American College of Cardiology, the American Heart Association or the European Society of Cardiology (ESC) have followed in the footsteps of this digital transition. Our sister societies, the Italian GISE and the Portuguese *Associação Portuguesa de Intervenção Cardiovascular* (APIC) have done the same thing. But, when these restrictions are lifted, will in-person activities like large face-to-face congresses and meetings be gone for good? Let us look at the pros and the cons of virtual and in-person meetings<sup>2</sup> (figure 1).

These are the basic strengths of virtual meetings:

- The speed at which these meetings are prepared is much faster compared to in-person meetings since there are many different tasks that the cardiology society does not need to do.

- Lower costs: it is obvious that reducing travel and accommodation expenses, renting fewer available spaces, etc. reduces the overall budget. A direct consequence of this is a lower impact on the environment thanks to lower mobility.
- Greater efficiency in the transmission of the message without time losses when going to the meeting or in-between sessions, possibility of increasing the capacity of the virtual rooms on demand and reviewing pre-recorded sessions on demand (even so, personal interaction will be gone).
- Better attendance control: computer tools facilitate the comprehensive registry of attendance to every session, time, origin, and interaction developed, etc., but not the quality. Although we cannot fully know to what extent these attendees' profit from these face-to-face meetings (exams may be an option?) leaving a device connected to these activities is no guarantee either.
- Universal access brings meetings to larger audiences erasing geographical borders: in the fully virtual EuroPCR of 2020 there were over 15 000 registrations (compared to 11 200 registrations in the 2019 in-person edition).<sup>3</sup> This phenomenon was even more evident in the ESC congress of 2020. This meeting still holds the registration record with 125 000 registrations from 213 different countries<sup>4</sup> compared to the previous year (33 500 registrations).<sup>5</sup> (figure 2). Can these figures be compared? Probably not because registration to these virtual editions was free of charge.
- Adaptation to changing situations: this virtual format allows us to accommodate meetings to travel limitations or potentially infectious situations like the one posed by the current pandemic.

The downsides of virtual meetings are:

- Dependency on technical factors: technical support systems are excellent, but still depend on variables like the Internet bandwidth, the quality of connectivity or the incompatibilities of presentations and videos. After 25 years of use of the DICOM standard for the communication and management of medical imaging we still have issues when we try to play video sequences in virtual meetings.
- To a great extent, the format of these sessions keeps the same structure as face-to-face meetings. The adaptation to the new

\* **Corresponding author:** Servicio de Cardiología Intervencionista, Hospital Universitario de León, Altos de Nava s/n, 24008 León, Spain.  
E-mail address: [aperez@secardiologia.es](mailto:aperez@secardiologia.es) (A. Pérez de Prado).

Online: 23-12-2020.

<https://doi.org/10.24875/RECICE.M20000183>

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Figure 1. Pros of virtual meetings compared to face-to-face meetings.



Courtesy of Dr. M. Roffi, on behalf of ESC

Figure 2. Registration comparison of the annual meetings held by the European Society of Cardiology back in 2019 and 2020.

virtual environment has been more cosmetic than a true reality with the implementation of several technological advances to mimic the in-person experience (avatars, virtual common rooms, chats to replace direct communication). However, fully developed specific methods of communication have not been implemented yet.

- More difficult personal interaction: asynchronous communication and other virtual borders like lack of types of nonverbal communication (beyond emoticons) complicate connectivity

among speakers, moderators, and audience. Speakers feel some kind of «digital loneliness» because they don't receive any feedback from the audience. In turn, the audience experience "digital fatigue" and they can't remain focused on anything for more than 30 minutes. New systems to encourage audience participation are desperately needed, particularly in the virtual format.

- Agendas, time zones, and time devoted to work: in these virtual meetings it is not unusual to find conflicting time

schedules since participants come from all across the world. It is not unusual either that these time schedules invade our spare time or affect our working day. The proliferation of these activities is associated with digital overload that has sometimes been referred to as «death-by-webinars».

- Program sustainability: although our political representatives can't wait to stop the private sector from funding our medical training programs, the truth is that this is crucial if we want to develop this kind of activity. If some of the activities that used to take place at face-to-face meetings are gone, will support still be the same? Isn't it more profitable to conduct sponsored meetings and not independent activities?

Those of us who have been trained in the "traditional" meeting environment have a hard time thinking that they can be totally replaced by the virtual format. Here are some of the reasons why:

- Attending a scientific meeting is a comprehensive experience that includes training as well as other activities: research coordination meetings, building up professional relations, consultancy and counseling, etc. It is almost impossible to conduct these activities outside the context of a scientific meeting.
- In this sense, attending a face-to-face meeting is time-bound. It is not always easy to disassociate attendance to these meetings from working or face-to-face obligations (especially when the meeting is held in our own town), but it is actually easier compared to virtual meetings. In our setting there are work permits that can be issued to attend training sessions: could this be applicable to virtual meetings particularly with the current extended time schedules of such events?<sup>6</sup>
- Most of the advantages seen in the broadcast of contents have long been part of face-to-face meetings. Consequently, most sessions are recorded for immediate broadcast and further reproduction. The same thing happens with in-person and remote audience interaction where the use of social media has proven very useful.

Will the digital gap between the analogical and the digital world, between immigrants and digital natives, between boomers and millennials grow? I don't think so. Their coexistence will prevail and bring us the best of both worlds: hybrid meetings. If these two worlds were actually ever there...

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

A. Pérez de Prado declared having received professional fees for his consultancy work or meetings held for iVascular, Boston Scientific, Terumo, BBraun, and Abbott totally unrelated to this article; he is the current president of the education and learning organization Fundación Epic.

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# Experimental model of mitral regurgitation in a porcine model



Miguel Rodríguez-Santamarta,<sup>a</sup> Rodrigo Estévez-Loureiro,<sup>b,c,\*</sup> Claudia Pérez Martínez,<sup>c</sup> José R. Altónaga,<sup>c</sup> Marta Regueiro Purriños,<sup>c</sup> Carlos Cuellas Ramón,<sup>a</sup> María López Benito,<sup>a</sup> Tomás Benito-González,<sup>a</sup> David Alonso Rodríguez,<sup>a</sup> David Viñuela Baragaño,<sup>d</sup> Javier Gualis Cardona,<sup>e</sup> José Manuel Gonzalo Orden,<sup>d</sup> Carlos Minguito-Carazo,<sup>a</sup> Elena Tundidor-Sanz,<sup>a</sup> Samuel del Castillo García,<sup>a</sup> Armando Pérez de Prado,<sup>c</sup> Mario Castaño Ruiz,<sup>e</sup> and Felipe Fernández-Vázquez<sup>c</sup>

<sup>a</sup> Servicio de Cardiología, Hospital Universitario de León, León, Spain

<sup>b</sup> Unidad de Cardiología Intervencionista, Hospital Universitario Álvaro Cunqueiro, Vigo, Pontevedra, Spain

<sup>c</sup> Unidad de Investigación Consolidada de Castilla y León (UIC104), Fundación Investigación Sanitaria en León, Universidad de León, Hospital Universitario de León, León, Spain

<sup>d</sup> Departamento de Veterinaria, Universidad de León, León, Spain

<sup>e</sup> Departamento de Cirugía Cardíaca, Hospital Universitario de León, León, Spain

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## ABSTRACT

**Introduction and objectives:** There is great interest in the development of devices for the percutaneous management of mitral regurgitation (MR). For this reason, having an experimental model that reproduces the conditions of the disease is of great importance. Our objective was to validate an experimental model of MR in a porcine model.

**Methods:** For the model creation phase 3, 2-month-old  $25 \pm 3$  kg large white pigs were used. An acute myocardial infarction was caused in the circumflex artery territory that hampered the perfusion of the posteromedial papillary muscle. Then, volume overload was induced in the animal by creating an arteriovenous shunt and connecting the aorta and the pulmonary artery using a Dacron tube. Echocardiography and magnetic resonance imaging were performed before the intervention and on week 8. Afterwards, the animal was euthanized to conduct the pathological study.

**Results:** One out of the 3 pigs died during the intervention due to ventricular fibrillation. The remaining 2 pigs survived the procedure and were euthanized as scheduled on week 8. In both cases a transmural infarction occurred, 1 at lateral level and the other one at posteroinferior level with moderate secondary mitral regurgitation. Ventricular dimensions and volumes increased and the overall contractility was maintained despite segmental alterations.

**Conclusions:** The experimental model of chronic MR based on the ischemic damage of the posteromedial papillary muscle associated with volume overload is feasible, safe and reproducible. Also, it can be very useful to test the safety and efficacy of future devices for the management of this condition.

**Keywords:** Mitral regurgitation. Experimental model. Porcine model.

## Modelo experimental de insuficiencia mitral en modelo animal porcino

## RESUMEN

**Introducción y objetivos:** Existe un creciente interés en el desarrollo de dispositivos para el tratamiento de la insuficiencia mitral (IM) de forma mínimamente invasiva. Para este propósito, disponer de un modelo experimental que reproduzca las condiciones de la enfermedad sería de gran utilidad. Nuestro objetivo fue validar un modelo experimental de IM en cerdos.

**Métodos:** Para esta fase de creación del modelo se han utilizado 3 cerdos de raza *large white*, de 2 meses de edad y un peso de  $25 \pm 3$  kg. Se provocó un infarto en el territorio de la arteria circunfleja que afectó la perfusión del músculo papilar posteromedial, y posteriormente se sometió al animal a una sobrecarga de volumen mediante creación de un *shunt* arteriovenoso, con la conexión de la aorta y la pulmonar mediante un tubo de dacrón. Se realizó análisis mediante ecocardiografía y resonancia magnética antes de la intervención y a las 8 semanas, y posteriormente el animal fue eutanasiado para realizar el estudio anatomopatológico.

\* **Corresponding author:** Unidad de Cardiología Intervencionista, Hospital Álvaro Cunqueiro, Estrada de Clara Campoamor 341, 36213 Vigo, Pontevedra, Spain.  
E-mail address: [roiestevez@hotmail.com](mailto:roiestevez@hotmail.com) (R. Estévez-Loureiro).

Received 31 January 2020. Accepted 3 April 2020. Online: 01-07-2020.

<https://doi.org/10.24875/RECICE.M20000125>

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**Resultados:** De los 3 cerdos, 1 falleció durante la intervención por fibrilación ventricular y los otros 2 sobrevivieron al procedimiento y fueron eutanasiados como estaba previsto a las 8 semanas. En ambos se produjo un infarto transmural, uno lateral y otro posteroinferior, con IM moderada secundaria. Las dimensiones y los volúmenes ventriculares aumentaron, y la contractilidad global se mantuvo a pesar de las alteraciones segmentarias.

**Conclusiones:** El modelo experimental de IM crónica basado en el daño isquémico del músculo papilar posteromedial asociado a una sobrecarga de volumen es factible, seguro y reproducible, y puede ser de gran utilidad para comprobar la seguridad y la eficacia de los futuros dispositivos para el tratamiento de esta afección.

**Palabras clave:** Insuficiencia mitral. Modelo experimental. Modelo porcino.

## Abbreviations

**MR:** mitral regurgitation.

## INTRODUCTION

Mitral valve repair surgery is the treatment of choice for the management of patients with severe mitral regurgitation (MR) who meet the criteria and indications proposed in the clinical practice guidelines.<sup>1</sup> However, almost 50% of the patients referred to surgery are not operated on,<sup>2,3</sup> mainly due to the presence of comorbidities, left ventricular dysfunction or age related issues.<sup>4</sup> In these cases, the use of transcatheter techniques has become a valid alternative.

Given the complexity of the mitral valve, there are several devices in the pipeline to reduce the degree of regurgitation using transcatheter approaches.<sup>5,6</sup> Of all the devices available, very few have been eventually used for the management of patients. Among these, only MitraClip—inspired in the Alfieri technique—has proven great clinical utility.<sup>7-9</sup>

That is why it is important to have an animal model of MR available to test the safety, efficacy, and tissue response of these new devices in a scenario that reproduces the future clinical situations we may encounter faithfully. Our objective was to assess the feasibility of creating an experimental model of MR capable of reproducing the actual conditions with an acceptable safety and efficacy profile.

## METHODS

### Animal model

Different experimental models have been described by the medical literature to induce MR by causing ischemic damage through the selective occlusion of the circumflex artery and rupture of a mitral chorda tendinae,<sup>10</sup> the production of ischemia in both the circumflex and right coronary arteries<sup>11</sup> or the production of selective ischemia in the marginal arteries that supply the papillary muscle.<sup>12</sup> A Spanish group studied the role of atrial infarction in ischemic MR and atrial and ventricular remodeling through the occlusion of the circumflex artery before or after the origin of the atrial branch.<sup>13</sup> The models based on the production of ischemic damage only caused moderate MR. Only the model designed by Cui et al.,<sup>10</sup> that combined mitral chordae tendinae ruptures with the corresponding volume overload, induced severe regurgitation. Our group designed a new model to induce MR by combining ischemic damage and the creation of an aortopulmonary shunt as the mechanism of volume overload.

To create this experimental model, 3 Large White domestic pigs were used. They were 2 months old and weighted  $25 \pm 3$  kg. All procedures were performed in full compliance with the national legislation in force (Royal Decree 53/2013 of February 1<sup>st</sup> on the basic standards for the protection of animals used for scientific purposes) and European Directive 2010/63/EU.

The echocardiographic studies were conducted using a Vivid I GE ultrasound system with 3S cardiac sector probe (1.5-4 MHz). Parasternal short-axis and long-axis slice planes and apical 4-chamber planes were acquired.

The magnetic resonance imaging study was conducted using a Signa HDx 3.0 T GE MR system through FIESTA balanced steady-state free precision multifarious sequences of specific cardiac planes (of 2, 3, and 4 chambers, and in the short axis) to assess both the anatomy and the cardiac function. All images were processed using the ReportCard 4.0 software package.

### Conceiving the experimental model

#### *Anesthetic procedure to perform the procedure destined to induce MR and magnetic resonance imaging study*

On the day of the surgery, anesthetic premedication was administered based on a combination of midazolam (0.35 mg/kg, Midazolam Normon, Normon), ketamine (5 mg/kg, Imalgene 1000, Merial), and methadone (0.1 mg/kg, Semfortan, Dechra) via intramuscular access. After confirming the correct sedation of the animals, preoxygenation with oxygen mask at 100% concentration was administered. Then, venoclysis was performed in the marginal atrial vein using a 20-gauge endovenous catheter followed by maintenance fluid therapy with lactated Ringer's solution at an infusion rate of 10 mL/kg per hour. Propofol (2-4 mg/kg, Propovet, Esteve) was used for the induction of anesthesia followed by conventional tracheal intubation. The maintenance anesthetic agent used was sevoflurane (Sevorane, Abbot) at a dose of 1-1.5 MAC. Fentanyl (Fentanest, Janssen) was the intraoperative analgesic used. It was administered through a slow IV bolus of 5 µg/kg and followed by the continuous infusion of a 6 µg/kg/hour dose during the entire procedure. Bail-out doses were administered if necessary.

Prior to the thoracotomy the neuromuscular blocking agent atracurium (Tracrium, Glaxo SmithKline) was administered intravenously at a dose of 0.25 mg/kg. This dose was repeated after 30 minutes if necessary.

As an additional analgesic measure and prior to performing the thoracotomy, intercostal nerve block was achieved using bupivacaine at 0.5% (Bupivacaine, Braun) at a dose of 2 mg/kg in 5 sites: the intercostal space of the surgical site, 2 cranial spaces, and 2 spaces immediately caudal to this one.

The anticoagulant therapy used was sodium heparin at a dose of 200 IU/kg via IV access. The antiarrhythmic therapy used was an infusion of amiodarone (Trangorex, Sanofi-Aventis) at a dose of 5 mg/kg every hour.

Volume controlled ventilation was used during the entire procedure. The ventilator parameters used were: inspired oxygen fraction (0.4), tidal volume (10 mL/kg) by controlling maximal inspiratory pressure and adjusting respiratory rate based on the volume per minute and partial pressure of carbon dioxide, inspiratory/expiratory ratio (1:2-1:3) (based on arterial oxygenation and arterial pressures), inspiratory pause time (10%), and positive end-expiratory pressure of 4 that gradually went up to 8 after the thoracotomy. Alveolar recruitment maneuvers were performed every 20 minutes to avoid alveolar collapse and atelectases.

Vital signs were monitored every 10 minutes and arterial blood-gas tests were performed by measuring the ventilator parameters during the procedure.

During the immediate postoperative 1.6 mg/kg of furosemide (Seguril, Aventis) and 4 mg/kg of carprofen (Rimadyl, Pfizer) were administered via IV access. The postoperative analgesic agent used was transdermal fentanyl (Durogesic, Janssen) at a dose of 50 µg/h within the first 72 hours followed by buprenorphine (Buprex, Life) at a dose of 0.01 mg/kg via subcutaneous access every 8 hours for 3 days. Also, oral carprofen (Rimadyl) was administered at a dose of 4 mg/kg every 24 hours as anti-inflammatory therapy for 5 days followed by a 9-day course of oral amoxicillin-clavulanic acid (Synulox, Pfizer) at a dose of 20 mg/kg every 12 hours as antibiotic therapy.

The protocol to perform the magnetic resonance imaging included the administration, on the day of the procedure, of anesthetic premedication: a combination of midazolam (0.35 mg/kg, Midazolam Normon) and ketamine (5 mg/kg, Imalgene 1000) via intramuscular access. Once the correct sedation of the animals was confirmed, they were transferred to the preparation area and preoxygenation with oxygen mask at 100% concentration was started. Then, venoclysis was performed in the marginal atrial vein using a 20-gauge endovenous catheter. Propofol (2-4 mg/kg, Propovet) was used for the induction of anesthesia followed by conventional tracheal intubation. Sevoflurane (Sevorane) at 1-1.5 CAM was used as maintenance anesthesia.

Mechanical ventilation followed the same parameters as during the entire procedure with periodic monitoring of the vital signs and arterial blood-gas tests.

### Inducing the infarction in the circumflex artery territory

After anesthetizing the animal, its thorax was opened, and the pericardium dissected to access the circumflex coronary artery and induce the infarction in this artery through surgical ligation. Prior to this an injection of contrast and echocardiographic study were used to see what branches of this artery were supplying the posteromedial papillary muscle. Once identified, ligation was attempted to occlude the 2 and 3 obtuse marginal arteries to avoid inducing a massive MR.

### Creation of an arteriovenous shunt

After the infarction volume overload was attempted through the creation of an arteriovenous shunt by connecting a branch of the pulmonary artery to the aorta using a Dacron tube graft. This procedure was performed with clamping and without extracorporeal circulation.

After performing both procedures the thorax was closed, and the pig was transferred to its storage facility for control and maintenance.

### Follow-up

The presence of MR and the effect of cardiac remodeling were assessed through echocardiographic and magnetic resonance imaging 8 weeks after the procedure and through ventriculography during euthanasia.

The degree of MR was assessed with an ultrasound scan using semi-quantitative methods (estimation of color area, vena contracta). In these ultrasound and MRI studies the volumes of the cardiac chambers (right and left ventricular diameters and volumes, left atrial diameters and volumes) and their function were measured.

### Anatomopathological study

At the 8-week follow-up, the animals were euthanized following the directives established by Royal Decree 53/2013 on animal protection.

A complete, organized, and systematic necropsy of each animal corpse was conducted to identify and diagnose any possible conditions associated with the procedure. The samples obtained were fixed in formaldehyde at 10% for histopathological study. In the macroscopic study of the heart, its weight was recorded and its cavities, walls, papillary muscles, mitral chordae tendinae, annulus, and valve leaflets analyzed. All the possible anomalies seen in these structures were documented photographically. Afterwards, the leaflets were extracted from their insertion location and up to their free borders including their chordae tendinae and they were fixed in formaldehyde at 10% and included in paraffin for histopathological study. Three µm thick serial sections were stained with the usual hematoxylin and eosin technique; the Van Gieson elastin stain protocol was used to study elastic and collagen fibers; the Masson trichrome stain protocol was used to differentiate muscular from collagen fibers; finally, the alcian-blue PAS staining protocol was used for the detection of mucopolysaccharides. The histopathological changes identified were semi-quantitatively assessed by establishing the different degrees of damage.

After collecting the leaflets to characterize the infarction, another 4 cross-sectional cuts were performed from the vertex of the heart towards its base. They were weighted and stained with triphenyltetrazolium chloride histochemical staining to enhance the viable area (red color) of the necrotic region (white color). For that purposes, the levels established were submerged in a solution of triphenyltetrazolium chloride (Sigma-Aldrich) at 1% in a phosphate buffered saline solution (pH 7.4) for 5 to 10 minutes at 37 °C, and then they were submerged in formaldehyde at 10%. The sections were photographed, and the areas measured using the Image J system. Samples of the infarction region, limit, and non-infarcted region were collected from every level, submerged in paraffin, and stained using the hematoxylin and eosin technique and the Masson trichrome stain protocol to characterize ischemic damage.

## RESULTS

The first animal died during the procedure due to an unresponsive ventricular fibrillation; the remaining 2 completed the 8-week follow-up without complications.

### Echocardiographic study

#### Animal #1

Echocardiographic data at baseline and at the 8-week follow-up from the parasternal short-axis and apical 4-chamber planes are shown on [table 1](#). In the baseline study, ventricular thickness at anteroseptal level was 10.6 mm and at posteroinferior level, 9 mm. The mitral valve was morphologically normal with thin normally moving leaflets and no regurgitation on the color Doppler ultrasound. At the 8-week follow-up there were segmental alterations of contractility that were seriously hypokinetic in the 3 segments of the lateral side with hypercontractility of the remaining segments. Also, a mitral valve with a thickened posterior leaflet and low motility, and moderate mitral regurgitation in the form of posteriorly directed eccentric regurgitation jet was seen too.

#### Animal #2

Echocardiographic data at baseline and at the 8-week follow-up are shown on [table 2](#). In the baseline study, ventricular thickness at anteroseptal level was 9 mm and at posteroinferior level, 6 mm. The mitral valve was morphologically normal with thin normally moving leaflets and no sign of regurgitation on the color Doppler ultrasound. At the 8-week follow-up, segmental alterations of contractility were seen in the medium and basal segments of the posterior side, a mitral valve with thickening of both leaflets, and moderate mitral regurgitation in the form of a mitral regurgitation central jet.

### Magnetic resonance imaging

The baseline study showed ventricles of normal dimensions, thickness, and also normal overall and segmental contractility for our cath lab in similar populations.

The 8-week follow-up revealed segmental alterations of contractility, lateral wall thinning, and fat transformation at posterior level in pig #1 and at posteroinferior level in pig #2 ([figure 1](#)). Ventricular volumes grew 10% and 7%, respectively.

The values found in this study are shown on [table 3](#) and [table 4](#).

### Anatomopathological study

#### Animal #1

The macroscopic examination revealed an infarction region in the lateral side from apical to basal level. The use of triphenyltetrazolium chloride stain confirmed the occurrence of a transparietal infarction ([figure 2](#)) whose size is shown on [table 1 of the supplementary data](#) together with the weight of each level.

The mitral valve showed a thickened posterior leaflet without damage to the anterior one. Microscopically, the posterior leaflet showed focal thickening with increased deposition of mucopolysaccharides and vascularization of the proximal part with distal reduction in the number of vessels. The infarction regions were

**Table 1.** Echocardiographic data at baseline and at the 8-week follow-up (animal #1)

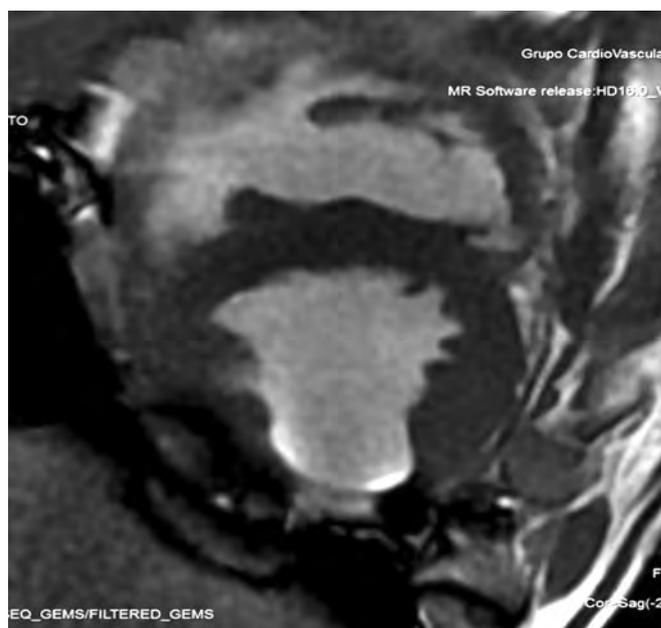
	LVEDD (mm)	LVESD (mm)	FS (%)	EF (%)	Color area (cm <sup>2</sup> )	Vena contracta (mm)
Baseline	46	30	34	62	0	0
8-week follow-up	49	32	34	60	4	4

EF, ejection fraction; FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

**Table 2.** Echocardiographic data at baseline and at the 8-week follow-up (animal #2)

	LVEDD (mm)	LVESD (mm)	FS (%)	EF (%)	Color area (cm <sup>2</sup> )	Vena contracta (mm)
Baseline	44	28	36	65	0	0
8-week follow-up	47	30	36	63	6	5

EF, ejection fraction; FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.



**Figure 1.** Magnetic resonance imaging of animal #2. Short axis of the left ventricle. Presence of fat transformation at posterior level.

histologically characterized by the presence of mature connective tissue including islets of cardiac muscle fibers and inflammatory cells.

#### Animal #2

The macroscopic evaluation revealed the presence of a transparietal infarction region in the posterior side damaging the medium and basal segments ([figure 3](#)) and papillary muscle ([figure 4](#)). The spread of this lesion into the different levels is shown on [table 2 of the supplementary data](#).

**Table 3.** MRI study at baseline and at the 8-week follow-up (animal #1)

	LVEDD (mm)	LVESD (mm)	LVEDV (ml)	LVESV (ml)	EF (%)	Left atrium (cm <sup>2</sup> )
Baseline	46	31	68	29	57	12
8-week follow-up	49	32	75	30	60	14

EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

**Table 4.** MRI study at baseline and at the 8-week follow-up (animal #2)

	LVEDD (mm)	LVESD (mm)	LVEDV (ml)	LVESV (ml)	EF (%)	Left atrium (cm <sup>2</sup> )
Baseline	42	29	58	29	50	10
8-week follow-up	44	31	62	30	52	11

EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

**Figure 2.** Animal #1. Presence of transparietal infarction areas from basal (A) to apical level (D). Triphenyltetrazolium chloride stain.

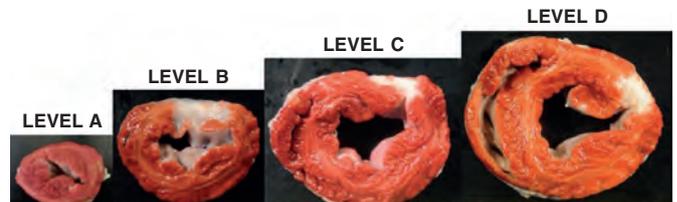
In the macroscopic examination, the mitral valve showed thickened leaflets with hemorrhages in their atrial surface (figure 1A of the supplementary data). Histologically and added to the already mentioned hemorrhages, both leaflets appeared thickened due to the deposition of mucopolysaccharides, especially in the middle layer (figure 1B,C of the supplementary data). Small caliber vessels were seen together with a mild inflammatory response figure 2 of the supplementary data. The infarction regions were characterized by the presence of mature connective tissue including islets of cardiac muscle fibers with similar characteristics compared to animal #1.

## DISCUSSION

Our group developed a safe and feasible experimental porcine model to induce ischemic MR after causing an infarction associated with volume overload by creating an aortopulmonary shunt.

Currently, several studies on experimental models (sheep and pigs, basically) have been conducted to induce and maintain MR. All of them have pros and cons and imitate different etiologies of MR such as dilated cardiomyopathy, ischemic MR, and even rupture of a mitral chorda tendinae.

In the model of ischemic MR, Llaneras et al.<sup>14</sup> were able to induce MR in sheep through obtuse marginal artery ligation. The authors

**Figure 3.** Animal #2. Presence of transparietal infarction areas from medium (B) to basal level (D). Triphenyltetrazolium chloride stain.**Figure 4.** Papillary muscle lesion. Lower part of level C. Triphenyltetrazolium chloride stain.

said that for this event to appear 2 prerequisites are required: a) the papillary muscle needs to be infarcted; b) the ventricle needs to be dilated. With just 1 of the 2 requirements no MR would be induced. In their results, the ligation of marginal arteries 2 and 3 induced a gradually developing MR. On the other hand, the ligation of marginal arteries 2, 3 plus the posterolateral artery led to the development of a massive MR with high lethality.

This model has been modified later on by inducing MR through the rupture of a mitral chordae tendinae and the association of an ischemic event in the territory of the circumflex artery by implanting an aneurysm.<sup>10</sup> This would induce an ischemic lesion with a dysfunctional papillary muscle and volume overload. However, the uncontrolled rupture of a mitral chorda tendinae may lead to a high mortality rate in animals when inducing massive MR, which is often poorly tolerated. The adverse events of the animals or if some of them died during the procedure was not reported in this study.

Considering the pros and cons of the models described, our objective was to create a sustainable model of ischemic MR that, according to the medical literature, seems to be reproducible. To that end, taking into consideration what has already been described in former studies, the model of ischemic damage to the posteromedial papillary muscle associated with volume overload seems to be the safest and most effective one. Since volume overload following the rupture of a chorda or the production of a major myocardial infarction can induce massive MR and severe deterioration of the animal, our objective was to create an arteriovenous shunt as a safe way to induce volume overload since former studies have proven that the creation of a systemic-to-pulmonary shunt induces biventricular remodeling.<sup>15</sup>

In our study we induced a small size acute myocardial infarction probably due to the isolated occlusion of the obtuse marginal arteries. Other authors occluded the marginal and posterolateral arteries too, which induced bigger acute myocardial infarctions, but at a price of a significantly higher mortality rate, which is why in our study we decided to occlude obtuse marginal arteries only.

Maybe the small size of the acute myocardial infarction was the cause for the moderate MR and discrete ventricular remodeling induced (10% and 7% increase in pigs #1 and #2) yet despite the segmental alterations of contractility seen. However, the possibility that an arteriovenous shunt of inadequate magnitude contributed to this cannot be discarded.

Finally, the possibility that in this model there is a mixed etiology for mitral regurgitation cannot be discarded either: the anatomopathological analyses revealed morphological anomalies in mitral leaflets, meaning that regurgitation would not be strictly functional only. This brings about new hypotheses on the repercussions of hemodynamic overload on mitral leaflets that may go beyond annular dilatation or the ischemic restriction of its movement.

### Limitations

The limitations of our study are associated with its small sample size, which is a problem when trying to draw definitive conclusions. However, we think it is very useful to disclose this new experimental model to induce ischemic MR through coronary ligation and volume overload by the creation of an aortopulmonary shunt. However, the results should be confirmed in future studies.

Whether ventricular remodeling impacts the creation of the aortopulmonary shunt is still unknown. In light of this study results, future phases of this model should analyze whether the magnitude of the shunt truly impacts ventricular remodeling.

Infarcts created through surgical ligation of the circumflex artery were small. Maybe the implantation of a coil or other occlusion devices into the proximal circumflex artery would have induced bigger infarctions. In any case, the study design anticipated the surgical approach since a thoracotomy would be needed to create the arteriovenous shunt.

Another possible limitation may be the short period of time animals were followed (8 weeks). This may explain why the remodeling process after the acute myocardial infarction was not completed, which is the reason why ventricular volumes did not reach greater dimensions.

### CONCLUSIONS

In our own early experience, the experimental model of chronic MR based on ischemic damage to the posteromedial papillary muscle and associated with volume overload is feasible, safe, and reproducible. It may be useful to assess the safety and efficacy profile of future devices for the management of this heart disease.

### FUNDING

This study was partially funded through a grant from the Regional Healthcare Management of Castille and León, Spain (GRS1396\_A\_16).

### CONFLICTS OF INTEREST

R. Estévez-Loureiro is a proctor for MitraClip and received a research grant from Abbott Vascular. A. Pérez de Prado participated and received funding for his consultancy job done for Boston Scientific and iVascular SL, and lectures given for Abbott, Braun Surgical, Terumo Medical Corporation, and Philips Volcano. The remaining authors declared no conflicts of interest whatsoever.

#### WHAT IS KNOWN ABOUT THE TOPIC?

- MR is the second most common valve disease. Mitral valve repair surgery is the standard treatment, but over 50% of the patients are not operated on due to their comorbidities.
- There are several devices available today to reduce the degree of regurgitation through transcatheter approaches. Also, there are several studies on experimental models to induce and maintain MR in order to test these devices. All of them have pros and cons and imitate different etiologies of MR such as dilated cardiomyopathy, ischemic MR, and even rupture of a mitral chorda tendinae.
- After studying the models already published, 2 are the prerequisites to induce a sustainable model of MR: ischemic lesion with damage to the papillary muscle, and ventricular dilatation.

#### WHAT DOES THIS STUDY ADD?

- A new experimental model to induce ischemic MR by combining the production of ischemic damage through the coronary occlusion of the branches supplying the papillary muscle and left ventricular volume overload with aortopulmonary shunt following the implantation of a Dacron tube graft between the aorta and a pulmonary branch.
- We should mention that none of the animals survived surgery and died at the follow-up, which is indicative of a feasible and safe model of ischemic MR.

### SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M20000125>.

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# Impact of comorbidities in the decision of using invasive management in elderly patients with NSTEMI

Vicente Pernias,<sup>a,b</sup> José María García Acuña,<sup>b,c</sup> Sergio Raposeiras-Roubín,<sup>d</sup> José A. Barrabés,<sup>b,e</sup> Alberto Cordero,<sup>f</sup> Manuel Martínez-Sellés,<sup>b,g</sup> Alfredo Bardají,<sup>h</sup> Pablo Díez-Villanueva,<sup>i</sup> Francisco Marín,<sup>b,j</sup> Juan M. Ruiz-Nodar,<sup>k</sup> Nuria Vicente-Ibarra,<sup>l</sup> Gonzalo L. Alonso Salinas,<sup>b,m</sup> Pedro Rigueiro,<sup>b,c</sup> Emad Abu-Assi,<sup>d</sup> Francesc Formiga,<sup>n</sup> Julio Núñez,<sup>a,b</sup> Eduardo Núñez,<sup>a,b</sup> Albert Ariza-Solé,<sup>o</sup> and Juan Sanchis<sup>a,b,\*</sup>

<sup>a</sup> Servicio de Cardiología, Hospital Clínico Universitario de Valencia, INCLIVA, Universidad de Valencia, Valencia, Spain

<sup>b</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

<sup>c</sup> Servicio de Cardiología, Hospital Clínico Universitario Gregorio Marañón, Universidad Complutense, Universidad Europea, Madrid, Spain

<sup>d</sup> Servicio de Cardiología, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain

<sup>e</sup> Servicio de Cardiología, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain

<sup>f</sup> Servicio de Cardiología, Hospital Clínico Universitario de San Juan, San Juan de Alicante, Alicante, Spain

<sup>g</sup> Servicio de Cardiología, Hospital Universitario Gregorio Marañón, Universidad Complutense, Universidad Europea, Madrid, Spain

<sup>h</sup> Servicio de Cardiología, Hospital Universitario de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili, Tarragona, Spain

<sup>i</sup> Servicio de Cardiología, Hospital Universitario de La Princesa, Madrid, Spain

<sup>j</sup> Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, El Palmar, Murcia, Spain

<sup>k</sup> Servicio de Cardiología, Hospital General Universitario de Alicante, Alicante, Spain

<sup>l</sup> Servicio de Cardiología, Hospital General de Elche, Elche, Alicante, Spain

<sup>m</sup> Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Madrid, Spain

<sup>n</sup> Servicio de Medicina Interna, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>o</sup> Servicio de Cardiología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

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## ABSTRACT

**Introduction and objectives:** The presence of comorbidities in elderly patients with non-ST-segment elevation acute coronary syndrome worsens its prognosis. The objective of the study was to analyze the impact of the burden of comorbidities in the decision of using invasive management in these patients.

**Methods:** A total of 7211 patients > 70 years old from 11 Spanish registries were included. Individual data were analyzed in a common database. We assessed the presence of 6 comorbidities and their association with coronary angiography during admission.

**Results:** The mean age was  $79 \pm 6$  years and the mean CRACE score was  $150 \pm 21$  points. A total of 1179 patients (16%) were treated conservatively. The presence of each comorbidity was associated with less invasive management (adjusted for predictive clinical variables): cerebrovascular disease (OR, 0.78; 95%CI, 0.64-0.95;  $P = .01$ ), anemia (OR, 0.64; 95%CI, 0.54-0.76;  $P < .0001$ ), chronic kidney disease (OR, 0.65; 95%CI, 0.56-0.75;  $P < .0001$ ), peripheral arterial disease (OR, 0.79; 95%CI, 0.65-0.96;  $P = .02$ ), chronic lung disease (OR, 0.85; 95%CI, 0.71-0.99;  $P = .05$ ), and diabetes mellitus (OR, 0.85; 95%CI, 0.74-0.98;  $P < .03$ ). The increase in the number of comorbidities (comorbidity burden) was associated with a reduction in coronary angiographies after adjusting for the GRACE score: 1 comorbidity (OR, 0.66; 95%CI, 0.54-0.81), 2 comorbidities (OR, 0.55; 95%CI, 0.45-0.69), 3 comorbidities (OR, 0.37; 95%CI, 0.29-0.47), 4 comorbidities (OR, 0.33; 95%CI, 0.24-0.45),  $\geq 5$  comorbidities (OR, 0.21; 95%CI, 0.12-0.36); all  $P$  values < .0001 compared to 0.

**Conclusions:** The number of coronary angiographies performed drops as the number of comorbidities increases in elderly patients with non-ST-segment elevation acute coronary syndrome. More studies are still needed to know what the best management of these patients should be.

**Keywords:** Comorbidities. Elderly. Acute coronary syndrome. Coronary angiography.

\* **Corresponding author:** Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Blasco Ibáñez 17, 46010 Valencia, Spain.

E-mail address: [sanchis\\_juafor@gva.es](mailto:sanchis_juafor@gva.es) [J. Sanchis].

Received 6 April 2020. Accepted 1 June 2020. Online: 21-09-2020.

<https://doi.org/10.24875/RECICE.M20000147>

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# Influencia de las comorbilidades en la decisión del tratamiento invasivo en ancianos con SCASEST

## RESUMEN

**Introducción y objetivos:** La comorbilidad en ancianos con síndrome coronario agudo sin elevación del segmento ST empeora el pronóstico. El objetivo fue analizar la influencia de la carga de comorbilidad en la decisión del tratamiento invasivo en ancianos con SCASEST.

**Métodos:** Se incluyeron 7.211 pacientes mayores de 70 años procedentes de 11 registros españoles. Los datos se analizaron en una base de datos conjunta. Se evaluó la presencia de 6 enfermedades simultáneas y su asociación con la realización de coronariografía durante el ingreso.

**Resultados:** La edad media fue de  $79 \pm 6$  años y la puntuación GRACE media fue de  $150 \pm 21$  puntos. Fueron tratados de manera conservadora 1.179 pacientes (16%). La presencia de cada enfermedad se asoció con un menor abordaje invasivo (ajustado por variables clínicas predictivas): enfermedad cerebrovascular (*odds ratio* [OR] = 0,78; intervalo de confianza del 95% [IC95%], 0,64-0,95;  $p = 0,01$ ), anemia (OR = 0,64; IC95%, 0,54-0,76;  $p < 0,0001$ ), insuficiencia renal (OR = 0,65; IC95%, 0,56-0,75;  $p < 0,0001$ ), arteriopatía periférica (OR = 0,79; IC95%, 0,65-0,96;  $p = 0,02$ ), enfermedad pulmonar crónica (OR = 0,85; IC95%, 0,71-0,99;  $p = 0,05$ ) y diabetes mellitus (OR = 0,85; IC95%, 0,74-0,98;  $p = 0,03$ ). Asimismo, el aumento del número de enfermedades (carga de comorbilidad) se asoció con menor realización de coronariografías, ajustado por la escala GRACE: 1 enfermedad (OR = 0,66; IC95%, 0,54-0,81); 2 (OR = 0,55; IC95%, 0,45-0,69); 3 (OR = 0,37; IC95%, 0,29-0,47); 4 (OR = 0,33; IC95%, 0,24-0,45);  $\geq 5$  (OR = 0,21; IC95%, 0,12-0,36); todos  $p < 0,0001$ , en comparación con ninguna enfermedad.

**Conclusiones:** Conforme aumenta la comorbilidad disminuye la realización de coronariografías en ancianos con síndrome coronario agudo sin elevación del segmento ST. Se necesitan estudios que investiguen la mejor estrategia diagnóstico-terapéutica en estos pacientes.

**Palabras clave:** Comorbilidad. Ancianos. Síndrome coronario agudo. Coronariografía.

## Abbreviations

**ACS:** acute coronary syndrome. **DM:** diabetes mellitus. **NSTEMACS:** non-ST-segment elevation acute coronary syndrome.

## INTRODUCTION

Population ageing leads to an increase in the number of elderly patients who suffer non-ST-segment elevation acute coronary syndrome (NSTEMACS). This population group, that has been misrepresented in large studies, has a great comorbidity burden that increases with age<sup>1</sup> and an important impact on prognosis.<sup>2-4</sup> The ideal therapeutic strategy for the management of these patients is still unknown. The benefit of an invasive strategy in elderly patients with NSTEMACS and comorbidities is still unclear.<sup>5-9</sup> In general, elderly patients with comorbidities undergo fewer coronary angiographies despite their worse prognosis.<sup>10</sup> This clinical practice—apparently in contrast with the recommendations published in the clinical practice guidelines<sup>11</sup>— seems to be based on the perception of a scarce benefit due to the worse intrinsic prognosis associated with comorbidities.

In this study the data of 11 Spanish NSTEMACS registries were collected to set up a common database with over 7000 elderly patients with NSTEMACS. In this preliminary analysis, the objective was to study the impact of comorbidities on the decision to go with invasive approach.

## METHODS

### Study design

The study was conducted from 11 cohorts of Spanish registries of patients with NSTEMACS (annex).<sup>2,12-20</sup> All cases were included in a single database of patients with chest pain and a diagnosis of NSTEMACS, > 70 years of age and with, at least, a 1-year follow-up.

The anthropometric and social-demographic data, main cardiovascular risk factors, and analytical and hemodynamic data at admission or during hospitalization were registered.

Patients were treated according to each center routine clinical practice and the decision to treat the NSTEMACS invasively, with or without a coronary angiography, was left to the discretion of the treating physician. The 6-month mortality GRACE risk score was determined in all the patients.<sup>21</sup>

A total of 6 conditions that proved to have a higher prognostic impact on elderly patients hospitalized due to acute coronary syndrome (ACS) in a previous study were included:<sup>22</sup> renal failure (glomerular filtration rate < 60mL/min/1.73m<sup>2</sup>), anemia (hemoglobin levels < 11 g/dL), diabetes mellitus (DM), cerebrovascular disease, peripheral arterial disease, and chronic pulmonary disease.

### Endpoints

The study primary endpoint was to assess how the presence of comorbidities impacted the decision to perform a coronary angiography during admission.

### Statistical analysis

Categorical variables were expressed as absolute values (percentages) and compared using the unpaired Student *t* test or the ANOVA. The continuous ones were expressed as mean  $\pm$  standard deviation and compared using the chi-square test.

Initially, the correlation between each disease and the performance of a coronary angiography through univariable analysis were assessed. Then, a first binary logistics regression model was conducted including the 6 conditions and the clinical variables associated with the performance of the coronary angiography in the univariable analysis. The odds ratio (OR) and the 95% confidence intervals (95%CI) were estimated. Afterwards, patients were classified according to their comorbidity burden, defined by the number of concomitant conditions (from 0 to 6). A second logistics regression model was conducted where comorbidity burden was adjusted for the predictive clinical variables in the previous analysis. Finally, a third logistics regression model was conducted where the comorbidity burden was adjusted based on the GRACE risk score. Differences were considered statistically significant with *P* values < .05

## RESULTS

A total of 7211 patients with a mean age of  $79 \pm 6$  years were included; 62% were males. Table 1 shows the population baseline characteristics. The prevalence of comorbidities was DM in 2874 patients (40%), chronic kidney disease in 3070 patients (42.6%), anemia in 1025 (14.2%), peripheral arterial disease in 1006 (14%), chronic pulmonary disease in 1161 (16%), and previous stroke in 831 (11.5%).

During admission 6032 patients (84%) underwent a coronary angiography. A total of 4339 patients (60%) were revascularized: 3848 (53%) of them through percutaneous coronary intervention and 491 (7%) through surgery. Patients on conservative management (1179, 16%) were predominantly women with higher scores in the GRACE score, and a past medical history of infarction or heart failure. Conversely, smoking and high levels of troponins or ST-segment depressions on the electrocardiogram performed at admission and a previous percutaneous coronary intervention were associated with a higher invasive approach (table 1). The GRACE risk score was lower in patients who underwent catheterization ( $147 \pm 19$  vs  $159 \pm 21$ ; *P* = .0001).

The presence of each of the 6 conditions studied was associated with fewer coronary angiographies performed: chronic kidney disease, 60.7% vs 39% (*P* = .0001); anemia, 23.2% vs 12.5% (*P* = .0001); DM, 44.3% vs 39% (*P* = .0001); cerebrovascular disease, 15.8% vs 10.7% (*P* = .0001); peripheral arterial disease, 16.6% vs 13.4% (*p* = .04); and chronic pulmonary disease, 17.8% vs 15.8% (*P* = .08) (table 1).

In the multivariable analysis adjusted for the main cardiovascular risk factors and clinical variables that were statistically significant in the univariable analysis, the 6 conditions associated with a lower probability of an indication for coronary angiography were: cerebrovascular disease, OR, 0.78 (IC95%, 0.64-0.95; *P* = .01); anemia, OR, 0.64 (IC95%, 0.54-0.76; *P* < .0001); chronic kidney disease, OR, 0.65 (IC95%, 0.56-0.75; *P* < .0001); peripheral arterial disease, OR, 0.79 (IC95%, 0.65-0.96; *P* = .02); chronic pulmonary disease, OR, 0.85 (IC95%, 0.71-0.99; *P* = .05); and DM, OR, 0.85 (IC95%, 0.74-0.98; *P* = .03). Table 2 shows the clinical variables associated with the indication for coronary angiography.

Comorbidity burden was defined as the number of present conditions (from 0 to 6). This was their distribution: 0 conditions, *N* = 1891 (26%); 1 condition, *N* = 2413 (33.5%); 2 conditions, *N* = 1638 (22.7%); 3 conditions, *N* = 879 (12.2%); 4 conditions, *N* = 314 (4.4%); and 5 or 6 conditions, *N* = 76 (1.1%). The analysis of the comorbidity burden adjusted for the clinical variables associated with the indication for coronary angiography showed a negative correlation between the number of conditions and the probability to perform a coronary angiography: 1 condition, OR, 0.66 (95%CI,

**Table 1.** Differences in the baseline characteristics based on the therapeutic approach

	All N = 7211	Conservative approach N = 1179 (16)	Invasive approach N = 6032 (84)	<i>P</i>
Age (years)	79 ± 6	82 ± 6	78 ± 5	.001
Males	4441 (61.6)	597 (50.6)	3844 (63.7)	.0001
Smoking	621 (8.6)	72 (6.1)	549 (9.1)	.0001
Hypertension	5723 (79.4)	943 (80)	4780 (79.2)	.58
Dyslipidemia	4262 (59)	609 (51.7)	3653 (60.6)	.0001
Previous myocardial infarction	1682 (23.3)	371 (31.7)	1308 (21.7)	.0001
Previous percutaneous coronary intervention	1334 (19)	175 (14.8)	1159 (19.2)	.0001
Previous coronary surgery	573 (7.9)	104 (8.8)	469 (7.8)	.24
Previous heart failure	641 (8.9)	198 (16.8)	443 (7.3)	.0001
Killip ≥ 2	1889 (26.2)	463 (39.3)	1426 (23.6)	.0001
ST-segment depression	2638 (36.6)	396 (33.6)	2242 (37.2)	.02
High troponin levels	5319 (73.7)	920 (78)	4399 (73)	.001
Left ventricular ejection fraction (%)	54 ± 11	54 ± 12	55 ± 11	.03
GRACE	150 ± 21	159 ± 21	147 ± 19	.0001
<b>Comorbidities</b>				
Anemia	1025 (14.2)	273 (23.2)	752 (12.5)	.0001
Peripheral arterial disease	1006 (14)	196 (16.6)	810 (13.4)	.04
Chronic pulmonary disease	1161 (16.1)	210 (17.8)	951 (15.8)	.08
Diabetes mellitus	2874 (39.9)	522 (44.3)	2352 (39)	.0001
Cerebrovascular disease	831 (11.5)	186 (15.8)	645 (10.7)	.0001
Chronic kidney disease	3070 (42.6)	716 (60.7)	2354 (39)	.0001

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

0.54-0.81); 2 conditions, OR, 0.55 (95%CI, 0.45-0.69); 3 conditions, OR, 0.37 (95%CI, 0.29-0.46); 4 conditions, OR, 0.32 (95%CI, 0.23-0.45); and 5 or 6 conditions, OR, 0.21 (95%CI, 0.12-0.37); All *P* values < .0001 compared to no condition.

With more conditions, higher GRACE risk scores (table 3). The negative correlation between the comorbidity burden and the performance of the coronary angiography was kept after adjusting for the GRACE risk score. Figure 1 shows that with more conditions, the probability to perform a coronary angiography increased too (figure 1A) despite the higher risk posed by higher GRACE risk scores (figure 1B, table 3).

## DISCUSSION

The main findings of our study were: a) the 6 conditions studied (cerebrovascular disease, anemia, chronic kidney disease,

**Table 2.** Results: multivariable analysis for the indication of a coronary angiography

Variable	OR	95%CI	P
Age (years)	0.89	0.88-0.91	.0001
Males	1.48	1.28-1.71	.0001
Dyslipidemia	1.44	1.26-1.66	.0001
Previous myocardial infarction	0.46	0.39-0.54	.0001
Previous heart failure	0.68	0.56-0.84	.0001
Previous percutaneous coronary intervention	1.91	1.55-2.34	.0001
Killip $\geq 2$	0.68	0.56-0.80	.0001
ST-segment depression	1.44	1.25-1.66	.0001
Left ventricular ejection fraction (by 5%)	0.98	0.98-0.99	.001
Anemia	0.64	0.54-0.76	.0001
Peripheral artery disease	0.79	0.65-0.96	.02
Chronic pulmonary disease	0.85	0.71-0.99	.05
Diabetes mellitus	0.85	0.74-0.98	.03
Cerebrovascular disease	0.78	0.64-0.95	.01
Chronic kidney disease	0.65	0.56-0.75	.0001

95%CI: 95% confidence interval; OR: odds ratio.

**Table 3.** Distribution of comorbidity burden and the score obtained in the GRACE risk score ( $P < .0001$  for the tendency)

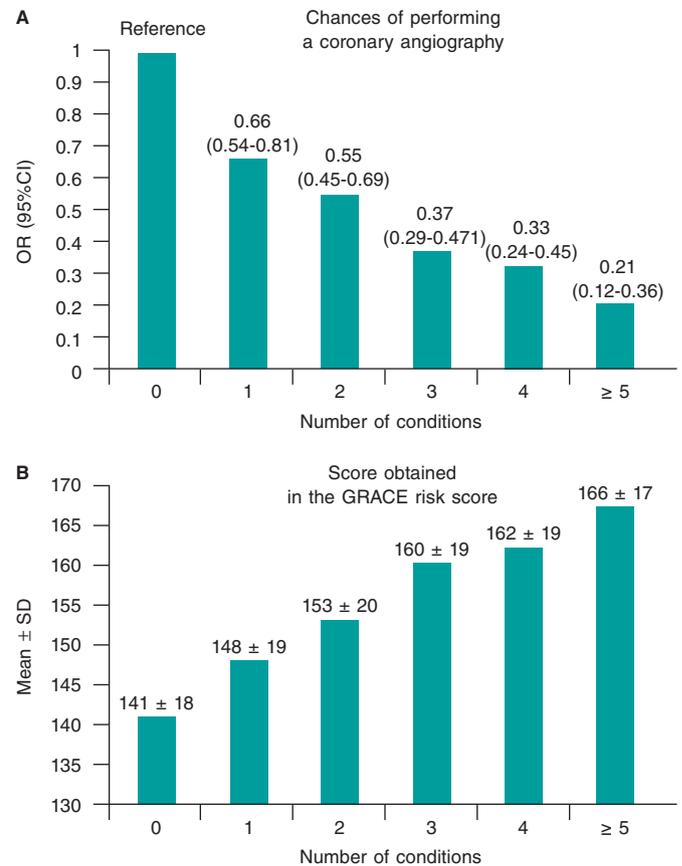
Conditions	N = 7211	GRACE risk score
0	1891 (26)	141 $\pm$ 18
1	2413 (33.5)	148 $\pm$ 19
2	1638 (22.7)	153 $\pm$ 20
3	879 (12.2)	160 $\pm$ 19
4	314 (4.4)	162 $\pm$ 19
$\geq 5$	76 (1.1)	166 $\pm$ 17

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

peripheral arterial disease, chronic pulmonary disease, and DM) were independently associated with a lower probability to use the invasive approach; b) with higher comorbidity burdens, considered as the number of concomitant conditions, lower chances of performing coronary angiographies.

There is a high prevalence of comorbidities in elderly patients with NSTEMI that greatly impacts prognosis in the short and mid-term.<sup>2,4</sup> The Charlson index is the most commonly used tool to assess comorbidities.<sup>23,24</sup> However, the analysis of the 6 conditions studied (chronic kidney disease, anemia, DM, cerebrovascular disease, peripheral arterial disease, and chronic pulmonary disease) has proven to be a useful risk stratification tool and have great predictive discriminatory capabilities that are similar to the Charlson index.<sup>22</sup>

Comorbidity burden is very important for the in-hospital management of NSTEMI.<sup>2,3,6,9,10</sup> Although the optimal therapeutic strategy for the

**Figure 1.** A: chances of undergoing a coronary angiography based on the number of concomitant conditions. The odds ratio (OR) with a 95% confidence interval (95%CI) can be seen. Analysis adjusted for the GRACE risk score. B: Representation of the correlation between comorbidity burden and the GRACE risk score. The mean  $\pm$  standard deviation (SD) of the GRACE risk score can be seen.

management of elderly patients with NSTEMI is still unknown, several studies show certain benefits with revascularization.<sup>5,7,8,25-30</sup>

Our study shows that with higher comorbidity burdens, lower chances of undergoing coronary angiographies. This may be due to the fact that comorbidities are seen as contraindications for the invasive approach.<sup>10</sup> However, the risk of suffering an acute myocardial infarction according to the GRACE risk score increases parallel to the number of concomitant conditions. Actually, these may be the patients who would benefit the most from an invasive approach.<sup>31,32</sup>

The presence of each one of these 6 conditions was independently associated with fewer invasive approaches. On the one hand, cerebrovascular disease and peripheral arterial disease are responsible for a greater spread of atherosclerotic disease.<sup>33</sup> Anemia has proven to be a powerful predictor of mortality in the ACS setting,<sup>34-36</sup> we used the 11 g/dL threshold as the cut-off value that had the greatest impact on mortality in former studies.<sup>34</sup> Its specific weight in the decision to administer conservative treatment may be justified by its clear association with the occurrence of hemorrhagic events in the ACS setting.<sup>37</sup> Chronic kidney disease is an expression of a greater spread of cardiovascular disease and is independently associated with more mortality after an ACS. There is a linear correlation between the risk of death due to cardiovascular causes and lower glomerular filtration rates.<sup>17,38</sup> DM is a powerful predictor of mortality, and not only due to cardiovascular causes. There is a clear correlation between DM and major adverse cardiovascular events, and these are

patients at very high risk.<sup>39</sup> Chronic pulmonary disease is associated with a worse short-term prognosis after an acute myocardial infarction. Also, in the management of NSTEMI it is associated with diagnostic delays, fewer invasive approaches, and a lower use of drugs for secondary prevention purposes.<sup>40</sup>

In the multivariable analysis, age, previous acute myocardial infarctions, previous heart failure, Killip class  $\geq 2$  at admission, and a reduced ejection fraction were associated with fewer invasive approaches. Elderly patients receive fewer evidence-based therapies. The older the age, the lower the rate of performing coronary angiographies.<sup>41</sup> On top of age, a past medical history of infarction, heart failure, a reduced ejection fraction, and scores  $\geq 2$  in the Killip classification are important aspects in the prognosis of ACS that, in general, translate into a worse ventricular function. Paradoxically, our findings suggest that the higher the risk, the lower the chances of performing a coronary angiography. Actually, these findings are consistent with former studies published.<sup>10,42</sup> It is possible that the perception of fewer benefits from revascularization or higher risk in the revascularization procedures may explain these results.<sup>2</sup> On the other hand, male sex, dyslipidemia, previous percutaneous coronary interventions, and ST-segment depressions at admission were associated with more invasive approaches. Several studies suggest that women undergo fewer invasive approaches compared to men despite the mortality benefits seen.<sup>43</sup> Previous angioplasties, ST-segment depressions, and dyslipidemia are probably interpreted as ischemic risk factors, which may explain their association with a higher frequency of invasive approaches.<sup>20,28,44</sup>

### Limitations

The main limitation of our study is that it is an observational registry with its corresponding selection bias and differences in the management of patients depending on the different centers involved. On the other hand, although the multivariable model was adjusted for percutaneous coronary intervention or previous coronary surgeries, it was not adjusted for previous coronary angiographies. It is possible that the previous knowledge of the coronary anatomy impacted the decision to perform fewer coronary angiographies in patients at higher risk.

### CONCLUSIONS

The presence of comorbidities greatly impacts the therapeutic decision in elderly patients with ACS. With more conditions, higher GRACE risk scores, and lower chances of indicating a coronary angiography.

This paradox of higher-risk and more conservative treatment justifies conducting new studies to determine the benefits of the invasive strategy in elderly patients with NSTEMI and comorbidities to establish the best therapeutic decision.

### FUNDING

This article was funded by a grant from the Carlos III Health Institute: CIBERCIV 16/11/00420, Madrid, Spain.

### CONFLICTS OF INTEREST

J. Sanchis is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. J. Núñez has received funding from Novartis, Vitor Pharma, and Boehringer Ingelheim, and a grant from Astra Zeneca and Vitor Pharma. J.A. Barrabés has received

funding for the educational activities conducted for AstraZeneca, and for his job as consultant for Bayer. The remaining authors did not declare any conflicts of interest whatsoever.

#### WHAT IS KNOWN ABOUT THE TOPIC?

- Elderly patients with NSTEMI have a higher comorbidity burden. Concomitant conditions are associated with worse prognosis. Elderly patients with comorbidities undergo fewer coronary angiographies despite their worse prognosis, which is in sharp contrast with the recommendations published in the clinical practice guidelines.

#### WHAT DOES THIS STUDY ADD?

- This analysis of a multicenter registry shows the correlation between comorbidity burden and invasive therapeutic approach in elderly patients with NSTEMI. With more concomitant conditions, higher GRACE risk scores, but lower chances of indicating a coronary angiography.

#### ANNEX. Registries included in the study.

Hospital Clínico Universitario, Valencia<sup>2</sup>

Hospital Universitario Joan XXIII, Tarragona<sup>12</sup>

Hospital Universitario de Bellvitge, Barcelona<sup>13</sup>

Hospital Ramón y Cajal, Madrid<sup>14</sup>

Hospital Universitario de San Juan, Alicante<sup>15</sup>

LONGEVO multicenter registry<sup>16</sup>

ACHILLES multicenter registry<sup>17</sup>

Hospital Álvaro Cunqueiro, Vigo<sup>18</sup>

Hospital Clínico Universitario, Santiago de Compostela<sup>19</sup>

Hospital Universitario Vall d'Hebron, Barcelona<sup>20</sup>

Hospital Universitario de La Princesa, Madrid\*

\*Unpublished data.

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# Microalbuminuria predicts contrast-induced nephropathy in patients with acute coronary syndrome

Yevgeniy Korolov,\* Ignacio Nogués, María Jimena Gambarte, María Sol Donato, María Graciana Ciambrone, Fedor Novo, and Claudio César Higa

Servicio de Cardiología, Departamento de Medicina Interna, Hospital Alemán, Buenos Aires, Argentine Republic



## ABSTRACT

**Introduction and objectives:** Between 10% and 25% of patients hospitalized due to an acute coronary syndrome develop acute kidney injury, a condition associated with higher morbidity and mortality rates. Scores have been developed to predict the occurrence of post-coronary angiography contrast-induced nephropathy (CIN) in patients with acute coronary syndrome. The objective of this study was to assess the association between microalbuminuria and post-coronary angiography CIN in patients with acute coronary syndrome.

**Methods:** Patients admitted with acute coronary syndrome in whom a coronary angiography was performed during their hospitalization and with urinary albumin-to-creatinine ratio (ACR) assessment within the first 24 hours were analyzed. The best ACR cutoff value for coronary angiography-induced CIN was determined using the C-statistic measure. The receiver operating characteristic (ROC) curves were built to compare between the predictive ability of the Mehran score alone and also in combination with the ACR.

**Results:** A total of 148 patients were analyzed. Median age was 64 years (56-73), 35% were women, mean creatinine clearance rate at admission was 86 mL/min (66-107) and the ACR was 5 mg/g (0-14). The analysis showed that 9.6% of the patients developed post-coronary angiography CIN with ACR levels  $\geq 20$  mg/g compared to 1.6% when these levels were  $< 20$  mg/g. The area under the ROC curve of the Mehran score to predict the development of post-coronary angiography CIN was 0.75 (95%CI, 0.68-0.81) and when the ACR was added it went up to 0.82 (95%CI, 0.76-0.87).

**Conclusions:** The ACR levels at admission were associated with the development of post-coronary angiography CIN and bring added value to an already validated predictive score. Therefore, the ACR should be used as a simple and accessible tool to detect and prevent this severe complication in patients with acute coronary syndrome.

**Keywords:** Contrast media. Coronary angiography. Microalbuminuria. Contrast-induced nephropathy. Urine albumin-to-creatinine ratio.

## La microalbuminuria predice el desarrollo de nefropatía inducida por contraste en pacientes con síndrome coronario agudo

### RESUMEN

**Introducción y objetivos:** Entre el 10 y el 25% de los pacientes hospitalizados por síndrome coronario agudo desarrollan insuficiencia renal aguda, lo que aumenta la morbimortalidad. Existen escalas para predecir la aparición de nefropatía inducida por contraste (NIC) tras la realización de una angiografía coronaria en pacientes con síndrome coronario agudo. El objetivo de este estudio fue evaluar la asociación entre el índice albúmina-creatinina (IAC) urinario y el desarrollo de NIC tras una angiografía coronaria en pacientes con síndrome coronario agudo.

**Métodos:** Se analizaron pacientes internados por síndrome coronario agudo a quienes se realizó angiografía coronaria durante el ingreso, con el cálculo del IAC en las primeras 24 horas. Se determinó el mejor valor de corte por curva ROC (Receiver Operating Characteristic) del IAC asociado a NIC. Se compararon las curvas ROC de la escala de Mehran sola y con el agregado de la variable de IAC.

**Resultados:** Se analizaron 148 pacientes. La mediana de la edad fue de 64 años (56-73), el 35% eran mujeres, el aclaramiento de creatinina fue de 86 ml/min (66-107) y el IAC de 5 mg/g (0-14). El 9,6% de los pacientes desarrollaron NIC tras la angiografía coronaria cuando su IAC fue  $\geq 20$  mg/g y el 1,6% cuando fue  $< 20$  mg/g. El área bajo la curva ROC de la escala de Mehran para predecir el desarrollo de NIC tras la angiografía coronaria fue de 0,75 (intervalo de confianza del 95% [IC95%], 0,68-0,81); cuando se agregó la variable de IAC fue de 0,82 (IC95%, 0,76-0,87).

\* **Corresponding author:** Servicio de Cardiología, Hospital Alemán, Avenida Pueyrredón 1640, Ciudad Autónoma de Buenos Aires C1118, Argentine Republic. E-mail address: [yeni\\_vin@yahoo.com.ar](mailto:yeni_vin@yahoo.com.ar) (Y. Korolov).

Received 26 December 2019. Accepted 14 May 2020. Online: 24-06-2020.

<https://doi.org/10.24875/RECICE.M20000139>

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**Conclusiones:** El IAC basal se asoció con el desarrollo de NIC tras la angiografía coronaria. Al añadirlo a la escala de Mehran aumentó la capacidad discriminativa. El IAC podría ser una herramienta de simple uso, bajo costo y amplia disponibilidad para detectar pacientes en riesgo de desarrollar NIC y adoptar medidas preventivas apropiadas.

**Palabras clave:** Contraste intravenoso. Angiografía coronaria. Microalbuminuria. Nefropatía inducida por contraste. Índice albúmina-creatinina urinario.

## Abbreviations

**ACR:** Albumin-to-creatinine ratio. **ACS:** Acute coronary syndrome. **AKI:** Acute kidney injury. **CIN:** Contrast-induced nephropathy.

## INTRODUCTION

Renal function impairment is associated with poor prognosis in patients with stable or acute coronary syndrome (ACS). One of the most common causes of acute kidney injury (AKI) in hospitalized patients is the nephropathy induced by the IV administration of contrast agents.<sup>1</sup> Its incidence varies between 1% and 6%, and increases considerably in high-risk conditions like in the ACS setting. The reported frequency of post-coronary angiography contrast-induced nephropathy (CIN) goes from 12% to 46% in patients with ACS.<sup>2,3</sup>

There are several potential causes that trigger CIN in patients without a past medical history of kidney failure such as hemodynamic instability, the IV administration of contrast agents, thromboembolic events, and adverse drug reactions, among others. Also, it is important to consider the type of contrast used, its osmolarity, the volume administered, and the lack of preventive measures.<sup>4-6</sup>

Because CIN is associated with poor prognosis in hospitalized patients, predictive scores have been designed to identify the most vulnerable patients who can develop this complication. The Mehran score is one of the most popular indices to estimate the chances of post-coronary angiography CIN.<sup>7</sup>

It is well-established that microalbuminuria is a predictor of kidney dysfunction mainly in diabetic and hypertensive patients.<sup>8-14</sup> Also, there is a correlation between high levels of microalbuminuria and the poor outcomes seen in patients with ACS.<sup>15-16</sup> Currently, microalbuminuria is estimated through the dosage of the albumin-to-creatinine ratio (ACR) through a simple urine sample.<sup>17</sup>

The objective of this study is to calculate microalbuminuria using the ACR as a predictive variable of post-coronary angiography CIN in patients with ACS.

## METHODS

### Population

Patients with ACS consecutively admitted to the coronary care unit of a community hospital were analyzed. Those undergoing an in-hospital coronary angiography with non-ionic, hyperosmolar IV contrast agents such as iopamidol, optiray or xenitix, were included in the study. The volume of IV contrast for each angiographic study was calculated retrospectively. It was estimated that

each injection of contrast material into the left coronary artery required an average 10 cc to 8 cc for the right coronary artery.

Patients with a past medical history of renal failure, macroalbuminuria, treatment with diuretics and patients with secondary angina were excluded from the study.

The urinary ACR was assessed in all patients included in the study using an immunoturbidimetric assay in simple urine samples within the first 24 hours after hospitalization.

### Definitions

IV contrast-induced nephropathy (CIN) was defined as an increase in serum creatinine levels  $\geq 25\%$  48 hours after performing the coronary angiography or an absolute increase of  $\geq 0.5$  mg/dL compared to levels at admission.

Microalbuminuria was defined as an abnormal urinary albumin excretion rate between 30 to 200 mg/min or 30 to 229 mg/day.

The study protocol was approved by the center review board and conducted in compliance with the Declaration of Helsinki, good clinical practice guidelines, and local regulatory requirements. Informed consents were obtained from all patients.

### Biochemical considerations

A urine sample collected within the first 24 hours after admission (preferably during morning hours) was centrifuged at 3000 rpm and stored at  $-20^{\circ}$  Celsius until biochemical analysis was conducted. The principle of the ACR test is immunoturbidimetry. This method is based on the reaction of human albumin antibodies to the antigen. Complexes are then measured after agglutination. The COBAS 6000 analyzer (ROCHE, Switzerland) was used to process the sample. The analytical detection limits of the assay were between 3 mg/g and 400 mg/g. The test variation coefficient was 3.8%.

### Statistical analysis

The Kolmogorov-Smirnov test was used to analyze the distribution of continuous variables and their kurtosis-skewness measures. Data were expressed as mean and standard deviation or as median with interquartile range (25%-75%) and compared using Student's *t* test or Mann-Whitney-Wilcoxon test for independent groups

according to their parametric or non-parametric distribution, respectively.

Discrete variables were expressed as percentages and compared using the chi-square test. The cross-product ratio was expressed as odds ratio (OR) with its 95% confidence interval (95%CI). The C-statistic measure was used to detect the best ACR cutoff value associated with the primary endpoint and compare the discrimination capacity of the Mehran score alone and with the ACR combined.

A multivariable regression analysis will be built to predict CIN including ACR and adjusted using the Mehran score.

Both the IBM SPSS Statistics version 19 software and the MedCalc version 11.6.1 software (Mariakerke, Belgium) were used for statistical analysis and to calculate and compare the C-statistic measure. To test the additional predictive value of ACR, the C-statistic measure was compared using the Mehran score alone and after adding the ACR information obtained.

## RESULTS

Out of a total of 397 patients diagnosed with ACS, 148 (59.4%) underwent a coronary angiography during hospitalization and this was the study population. The mean age was  $64 \pm 12$  years; 35% were women, 20% had diabetes, 54% dyslipidemia, 65% hypertension, and 42% were active smokers. The mean blood sugar levels on admission were 110 mg/dL (98-133 mg/dL), the median creatinine clearance rate (estimated using the MDRD) was 86 mL/min (66-107), and the ACR was 5 mg/g (0-14) (table 1). The patient comparison between these groups with or without CIN showed a higher rate of overweight and obesity, left bundle branch block, atrial fibrillation, and AMI Killip and Kimball class III-IV (table 2).

The C-statistic measure showed that the best CIN related ACR cutoff value was 20 mg/g. Twelve patients developed CIN (8.1%) and the ACR of 22% of the patients was  $>20$  mg/g. The rate of ACR  $> 20$  mg/g among patients without CIN was 2.9% and 11.3% ( $P = .01$ ) among patients with CIN. Contrast-induced nephropathy was significantly higher when the ACR was  $\geq 20$  mg/g compared to when it was  $< 20$  mg/g ( $\geq 9.6\%$  vs  $1.6\%$ , respectively,  $P < .001$ ). When the ACR was added to the Mehran score, its predictive power went up to 0.82 (95%CI, 0.76-0.87). (Figure 1).

Using a multivariable regression analysis model the ACR  $> 20$  mg/g turned out to be an independent predictor for CIN: OR, 3.2 (0.7-6.2);  $P = .01$ , adjusted by the Mehran score variables (age, women, body mass index, atrial fibrillation, Killip Class III-IV, and creatinine clearance rate).

## DISCUSSION

Our study proved the association between the ACR and the development of CIN in patients admitted with ACS.

Acute kidney injury in the ACS setting predisposes to more complications such as in-hospital and long-term mortality; therefore, predicting it is of critical clinical importance. A recent study reported that the rate of AKI was close to 17% in the ACS setting with significant peaks of cardiovascular complications. In this study, the ACR was not used as an early marker of AKI. The development of CIN was not specifically analyzed either as a post-coronary angiography complication.<sup>18-22</sup>

**Table 1.** Baseline characteristics of the patients

Total number of patients	N = 148
Age (years), median [25-75]	64 [56-73]
Women	35
Hypertension	65
Diabetes mellitus	20
Dyslipidemia	54
Smoking	42
Previous AMI	24.5
STEAMI	20.9
NSTEACS	79.1
Fasting blood glucose levels, mg/dL	110 [98-133]
Serum creatinine levels, mg/dL	0.9 [0.8-1.0]
Creatinine clearance rate, mL/min	86 [66-107]
Urinary albumin-to-creatinine ratio, mg/gr	5 [0-14]
CPK, IU/L	121 [73-264]
CK-MB, IU/L	16 [12-34]
Troponin T levels, ng/mL	0.01 [0.01-0.27]
Moderate to severe LVFSF impairment (EF < 40%)	5.79

Unless specified otherwise, data are expressed as % or mean and standard deviation. AMI, acute myocardial infarction; CK-MB, creatine kinase myocardial band; CPK, creatine phosphokinase; EF, ejection fraction; IQR, interquartile range; IU, international units; LVFSF, left ventricular shortening fraction; NSTEACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

Microalbuminuria calculated through the ACR obtained from a simple urine sample is also an established marker of endothelial dysfunction that has been validated to predict cardiovascular events and mortality in different clinical settings. A previous analysis of our group revealed that higher ACR levels are associated with significantly worse outcomes in patients with non-ST-segment elevation ACS, and with a higher rate of hard endpoints like mortality and/or non-fatal acute myocardial infarction at the long-term follow-up (12% vs 2.2%,  $P = /< .0001$ ).<sup>23</sup> Also, other authors proved its utility to assess the risk of developing AKI, mainly in the ACS setting or while being exposed to cardiac surgery.<sup>24</sup> Tziakas et al confirmed the significant correlation between AMI related higher ACR levels and the development of AKI after this event (area under the ROC curve 0.72; 95%CI, 0.67-0.77). However, the authors did not report on the clinical impact of this complication on the patient's clinical course or its association with the use of contrast during coronary angiography.<sup>25</sup>

Special attention should be paid to patients with post-angiographic AKI in the ACS setting. Several studies have shown that CIN negatively impacts the prognosis of hospitalized and long-term patients. In our population, mortality in patients with CIN was significantly higher compared to those without this disease (33% vs 1.8%).

The use of urinary ACR has been less studied in this context. Meng et al. reported that high microalbuminuria levels (ACR in

**Table 2.** Comparison of patients with and without contrast-induced nephropathy

	CIN - (136)	CIN + (12)	P
Age (years)	63.7 [55-74]	68 [61-76]	NS
Women	25.3	16.7	NS
Hypertensive	67.7	58.3	NS
Diabetic	20	33.3	NS
Body mass index	26 [24-29]	29 [25-31]	.05
Creatinine clearance rate mg/dL	85 [65-108]	74 [50-98]	NS
Blood glucose levels at admission, mg/dL	112 [100-142]	143 [108-209]	NS
Previous AMI	26	16	NS
Previous PCI	17	8.3	NS
Previous stroke or TIA	3.6	8.3	NS
NSTEACS	17.7	25	NS
STEMI	30.8	33.3	NS
Left bundle branch block	3.6	16.7	.02
Atrial fibrillation	0.9	8.3	.02
Killip and Kimball III-IV	4.1	22	.001

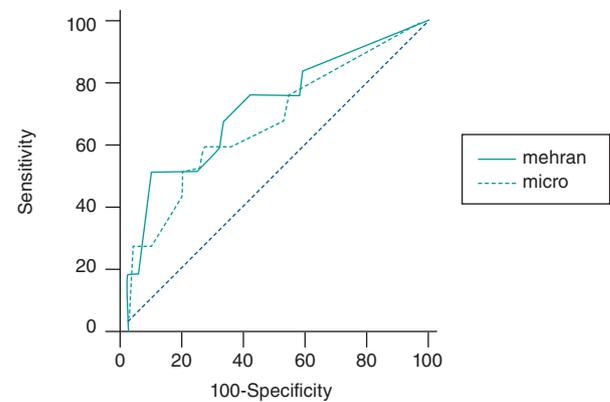
Unless specified otherwise, data are expressed as % or mean and standard deviation 25%-75%.

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARA II, angiotensin II receptor antagonists; ASA, acetylsalicylic acid; CK-MB, creatine kinase myocardial band; CPK, creatine phosphokinase; EF, ejection fraction; HR, heart rate; IQR, interquartile range; IU, international units; LVSF, left ventricular shortening fraction; NS, not significant; NSTEACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

between 30 mg/g and 300 mg/g) were associated significantly with the development of post-contrast acute kidney injury in patients undergoing coronary catheterization (12.1% vs. 5.0%;  $P = .005$ ). A key point here that distinguishes this study from ours is that they included patients with scheduled coronary angiographies only and out of the ACS setting.<sup>26</sup> Another relevant point is that the ACR cutoff value to develop CIN was determined from the analysis of the area under the ROC curve, and its value of 20 mg/g was even lower compared to the conventional standard threshold of 30 mg/g, a finding that was consistent with what other clinical studies reported.<sup>27</sup>

The rate of CIN and its impact on the clinical outcome of coronary patients triggered the development of predictive scores for this disease. One of the best known indices is the Mehran score that includes variables like age > 75 years, hypertension, functional class III/IV heart failure, diabetes mellitus, anemia, use of intra-aortic balloon pump, volume of contrast administered, and past medical history of renal dysfunction and is capable of identifying who the most vulnerable patients are to develop post-coronary angiography CIN (the area under the ROC curve was 0.75). Adding the ACR to this score showed an even greater discriminatory power to predict post-coronary angiography CIN in patients with ACS. This would prove the practical utility of adding this index as a variable to the Mehran score.

CIN, one of the most common causes for acute nephrotoxicity, is a multi-factor event. Among its causes we should mention the



**Figure 1.** Effect of albumin-to-creatinine ratio when added to the Mehran score. When the albumin-to-creatinine ratio was added to the Mehran score, its predictive power went up from 0.75 to 0.82 (95%CI, 0.76-0.87).

direct nephrotoxic effect of the contrast substances used during endovascular procedures on the renal endothelium and the development of acute tubular necrosis. It is estimated that the nephrotoxicity of hyperosmolar contrast enhanced by the hemodynamic alterations produced by the ongoing ACS could alter vascular resistance with changes in the regulation of the release and balance of vasoactive substances like adenosine, endothelin, and nitric oxide. The damage perpetuates the slowing down of renal perfusion, spinal hypoxemia, ischemic injury, and ultimately cell death. In addition to reducing the clearance of oxidative stress products, the lower glomerular filtration rate levels increase the concentration of inflammatory mediators triggering structural alterations at renal tubular epithelium level like edema, vacuolization, and death.<sup>28,29</sup>

We believe that these findings could help identify patients at high-risk of developing post-coronary angiography CIN in the ACS setting to promote preventive measures, behaviors, and strategies to avoid this complication.

### Limitations

First, one of the main limitations of our work is its single center nature. However, we should mention that the population included was representative and covered the entire spectrum of patients with ACS admitted to our coronary care unit, which secures the internal validity and representativeness of our study. Secondly, the under-powered sample may have conditioned the appearance of false negative results due to its alpha error or lower power and stopped us from performing a proper multivariable analysis. Finally, certain data such as the volume of contrast used in each study was calculated retrospectively with the usual biases of this type of analysis.

### CONCLUSIONS

The albumin-to-creatinine ratio, a recognized predictor of renal and endothelial dysfunction, was also a marker of CIN in patients with ACS with an added value when it was included in a widely validated clinical score. These results may be the beginning of a hypothesis-generating study to be confirmed prospectively at a multi-center level.

## FUNDING

No funding or grants were received for this work.

## CONFLICTS OF INTEREST

None declared.

## ACKNOWLEDGEMENTS

We wish to thank the entire staff of the Hospital Alemán Coronary Care Unit, particularly the nursing staff who helped collect the urine samples that were crucial to conduct this study.

### WHAT'S KNOWN ABOUT THE TOPIC?

- CIN is one of the most common causes for AKI in hospitalized patients. Microalbuminuria is an established marker of endothelial dysfunction and has been validated to predict cardiovascular events and mortality in different clinical settings. The ACR is useful to assess the risk of developing CIN basically in the ACS setting or while exposed to cardiac surgery.

### WHAT DOES THIS STUDY ADD?

- Our study proved the association that exists between the ACR and the development of post-coronary angiography CIN in patients admitted with ACS. The C-statistic measure showed that the best CIN related ACR cutoff value was 20 mg/g. The ACR brings an added value when included in the Mehran score to assess the risk of developing post-coronary angiography CIN in the ACS setting.

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# Use of subcutaneous nitroglycerin to facilitate transradial access in coronary procedures (NiSAR Study)

Santiago Coroleu,<sup>a,\*</sup> Jorge Allín,<sup>b,c</sup> Guillermo Migliaro,<sup>d,e</sup> Gustavo Leiva,<sup>d,e</sup> Pablo Baglioni,<sup>d,e</sup> Ignacio Nogués,<sup>d,e</sup> Cristian Rodríguez,<sup>a</sup> Brian Donato,<sup>d,e</sup> and José Álvarez<sup>d,e</sup>



<sup>a</sup> Servicio de Cardioangiología Intervencionista, Instituto de Cardiología, Santiago del Estero, Argentine

<sup>b</sup> Servicio de Cardioangiología Intervencionista, Sanatorio Nosti, Rafaela, Argentine

<sup>c</sup> Servicio de Cardioangiología Intervencionista, Sanatorio Esperanza, Esperanza, Argentine

<sup>d</sup> Servicio de Cardioangiología Intervencionista, Hospital Británico de Buenos Aires, Buenos Aires, Argentine

<sup>e</sup> Servicio de Cardioangiología Intervencionista, Hospital Alemán, Buenos Aires, Argentine

## ABSTRACT

**Introduction and objectives:** We assessed whether the routine use of subcutaneous nitroglycerin prior to a cannulation attempt improves transradial access significantly (the NiSAR study [subcutaneous nitroglycerin in radial access]).

**Methods:** Patients undergoing a coronary angiography were enrolled in a prospective, double-blind, multicenter, randomized trial in 2 groups (nitroglycerin group vs control group). The primary endpoints were the overall number of puncture attempts, access and procedural time, switch to transfemoral access, and local perceived discomfort score. The secondary endpoints were the pre- and post-anesthetic pulse score. A subgroup of patients underwent ultrasound scans performed through the radial artery.

**Results:** 736 patients were enrolled in the trial: 379 in the nitroglycerin group and 357 in control group. The average number of puncture attempts was similar (1.70 vs 1.76;  $P = .42$ ). Access and procedural time did not change significantly (61.1 s and 33.3 s vs 63 s and 33.4 s;  $P = .66$  and  $P = .64$ , respectively). No significant differences were found either between the 2 groups in the number of switches to transfemoral access (7.1% vs 8.4%;  $P = .52$ ). However, the average local perceived discomfort score and post-anesthetic pulse score were significantly better in the nitroglycerin group (2.34 vs 2.76;  $P < .001$  and 2.47 vs 2.22;  $P < .001$ ). The ultrasound scan performed through the radial artery showed post-anesthetic radial artery lumen diameters that were significantly higher in the nitroglycerin group in both the longitudinal (3.11 mm vs 2.43 mm;  $P = .002$ ) and cross-sectional planes (2.83 mm vs 2.41 mm;  $P = .002$ ). A trend towards fewer local hematomas in the nitroglycerin group was seen (6.1% vs 9.8%;  $P = .059$ ). Headaches were more common in the nitroglycerin group (3.2% vs 0.6%;  $P = .021$ ).

**Conclusions:** The routine use of subcutaneous nitroglycerin prior to radial puncture was not associated with fewer punctures or shorter access times. However, the lower local perceived discomfort and enlargement of the radial artery size would justify its daily use in the routine clinical practice to enhance the transradial experience for both patients and operators.

**Keywords:** Transradial access. Subcutaneous nitroglycerin. Radial spasm.

## Uso de nitroglicerina subcutánea para facilitar el acceso radial en procedimientos coronarios (Estudio NiSAR)

### RESUMEN

**Introducción y objetivos:** Se evaluó si la utilización sistemática de nitroglicerina subcutánea previa a cualquier intento de canulación podía mejorar de forma significativa el acceso transradial (nitroglicerina subcutánea acceso radial [NiSAR]).

**Métodos:** Se incluyeron todos los pacientes sometidos a angiografía coronaria en un estudio prospectivo, multicéntrico, doble ciego y aleatorizado, y se dividió la población en 2 grupos: grupo de nitroglicerina y grupo control. Los objetivos primarios del estudio fueron el número total de punciones radiales, el tiempo total de acceso y de procedimiento, la necesidad de cambio a acceso femoral y la puntuación de disconfort local. El objetivo secundario fue la evaluación del pulso antes y tras la anestesia. Además, un subgrupo de pacientes fue evaluado con ecografía de la arteria radial.

**Resultados:** Se incluyeron 736 pacientes: 379 en el grupo de nitroglicerina y 357 en el grupo C. El número promedio de intentos de punción radial fue similar (1,70 frente a 1,76;  $p = 0,42$ ). No hubo diferencias significativas en los 2 grupos con respecto al tiempo total del acceso y del procedimiento (61,1 y 33,3 s frente a 63 y 33,4 s;  $p = 0,66$  y  $p = 0,64$ , respectivamente). Tampoco se encontraron diferencias significativas entre los 2 grupos en la tasa de conversión a acceso femoral (7,1 en el grupo de nitroglicerina frente a 8,4% en el grupo C;  $p = 0,52$ ). Sin embargo, el índice de malestar local y el de pulso tras la anestesia fueron

\* Corresponding author: Av. Roca (S) 342, 4° Piso, 4200 Santiago del Estero, Argentine.

E-mail address: sfcoroleu@gmail.com [S. Coroleu].

Received 25 February 2020. Accepted 19 May 2020. Online: 23-06-2020.

<https://doi.org/10.24875/RECICE.M20000141>

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significativamente mejores en el grupo de nitroglicerina (2,34 frente a 2,76,  $p < 0,001$ ; 2,47 frente a 2,22,  $p < 0,001$ ). La ecografía mostró un diámetro radial significativamente mayor en el grupo de nitroglicerina tanto en la vista longitudinal (3,11 frente a 2,43 mm;  $p = 0,002$ ) como en la transversal (2,83 frente a 2,41 mm;  $p = 0,002$ ). Hubo una menor incidencia de hematoma en el antebrazo en el grupo de nitroglicerina (6,1 frente a 9,8%;  $p = 0,059$ ). La cefalea fue más frecuente en los pacientes del grupo de nitroglicerina (3,2 frente a 0,6%;  $p = 0,021$ ).

**Conclusiones:** El uso sistemático de nitroglicerina subcutánea previo a la punción radial no estuvo asociado a una reducción en el número de punciones ni en el tiempo de acceso, pero el menor malestar local y el aumento del calibre de la arteria radial podrían justificar su uso en la práctica clínica para mejorar la experiencia del acceso transradial tanto en el paciente como en el operador.

**Palabras clave:** Espasmo radial. Nitroglicerina subcutánea. Acceso radial.

## INTRODUCTION

Transradial access to perform coronary and peripheral procedures is becoming more successful compared to transfemoral access thanks to several advantages including more comfort as reported by the patients, early ambulation and discharge, less bleeding, and overall better outcomes.<sup>1-5</sup> However, the radial artery is more susceptible to spasm, which can stop the advance of the catheter, extend the duration of the procedure, and increase its difficulty.<sup>6</sup> Also, radial artery spasm has been identified as an independent predictor of radial access failure.<sup>7</sup>

When radial artery spasm occurs after an introducer sheath has been inserted, the intra-arterial administration of vasodilator drugs has proved to improve the conduit effectively.<sup>8</sup> Still, the subcutaneous administration of nitroglycerin relieves the spasm causing the reduction significantly and the eventual loss of pulse volume after several ineffective attempts to cannulate the radial artery.<sup>9</sup> Also, it enhances radial pulse palpation, and eventually makes the puncture of radial artery easier.<sup>10,11</sup>

Because the first puncture failure is a powerful predictor of radial artery spasm,<sup>12</sup> we conducted a double-blind, randomized, controlled trial in 4 Argentinian centers to see whether the routine subcutaneous administration of nitroglycerin prior to a cannulation attempt improved transradial access significantly (the NISAR study [subcutaneous nitroglycerin in radial access]).

Specifically, the primary endpoints of the study were to assess the number of radial artery puncture attempts, the time required to place the sheath introducer, the number of times that switching to transfemoral access was required, and the patients' tolerance to the procedure. The secondary endpoints included the assessment of the radial artery pulse and diameter and local and systemic complications.

## METHODS

### Patients and procedures

Patients undergoing a coronary angiography with evidence of myocardial ischemia were enrolled in a prospective, multicenter, and randomized clinical trial conducted in 4 Argentinian centers into 2 different groups based on the periradial subcutaneous administration of nitroglycerin. In the nitroglycerin group, 2% xylocaine (1 mL) was used followed by 200 mcg of nitroglycerin (2 mL). In control group, 2% xylocaine (1 mL) was followed by the infusion of a normal saline solution (2 mL) used as placebo. Trained nurses from each center prepared the syringes following

a 1:1 randomization scheme and making sure that their content was unknown to both the operators and the patients.

The coronary angiographies and revascularization procedures were performed using 5-Fr or 6-Fr diagnostic and guiding catheters as selected by the operators. In all cases a properly sized sheath introducer was inserted using the Seldinger or modified Seldinger technique. Five thousand units of heparin were consistently administered through a bolus injection with further additions to keep the activated clotting time between 250 and 300 seconds if a percutaneous coronary intervention was performed.

All procedures were performed after patients gave their informed consent by 8 skilled and experienced operators who had performed over 1500 transradial procedures. All operators used the right radial artery as the access of choice; the left radial artery was spared for cases with right radial artery occlusion and patients with left internal mammary artery graft. The Ethics Committee reviewed and approved this study. Patients' informed consent to publish was obtained.

### Outcome measures

The primary outcome measures were the overall number of puncture attempts, access, and procedural time, switch to transfemoral access, and local perceived discomfort score.

Access time was defined as the time elapsed between the administration of local anesthesia and the insertion of the radial sheath introducer. When the initial radial access could not be completed, the contralateral radial access was never tried and access site changed to the femoral access. The local perceived discomfort score was assessed by the patient after undergoing the procedure and graded according to a radial-related pain score between 0 = no pain and 10 = unbearable pain.

The secondary outcome measures were the pre- and post-anesthetic pulse score assessed by the operator by palpating the radial pulse before and 1 minute after the administration of local anesthesia and graded as: 1 = weak pulse; 2 = easily palpable pulse; 3 = strong pulse. Also, local and systemic complications including forearm hematomas, radial artery spasm, headaches, and symptomatic hypotension were recorded. Also, a subgroup of patients underwent a radial artery ultrasound scan both at the baseline and after the administration of anesthesia. Patients were examined in the supine position using a commercially available ultrasound system. The radial artery lumen diameter was measured on M-mode imaging in both the longitudinal and cross-sectional planes and 1 cm proximal to the radius styloid process. Three measures were taken in each plane and their values averaged.

**Table 1.** General characteristics of the patients

	Overall (N = 736)	Nitroglycerin group (N = 379)	Control group (N = 357)	P
Age (years)	64.9 ± 10.1	64.9 ± 10.1	65.1 ± 10.1	.80
Male gender	450 (61.1%)	230 (60.7%)	220 (61.6%)	.79
Body mass index	28.5 ± 4.2	28.5 ± 4.2	28.4 ± 4.2	.82
Active smoking	292 (39.7%)	153 (40.3%)	139 (38.9%)	.69
Hypertension	520 (70.6%)	277 (73.1%)	243 (68.1%)	.14
High cholesterol	365 (49.6%)	189 (49.8%)	176 (49.3%)	.88
Diabetes mellitus	168 (22.8%)	97 (25.6%)	71 (19.9%)	.07
<b>Clinical presentation</b>				
ST-segment elevation myocardial infarction	55 (7.5%)	28 (7.4%)	27 (7.6%)	
Non-ST-elevation acute myocardial infarction	285 (38.7%)	139 (36.7%)	146 (40.9%)	
Chronic stable angina	90 (12.2%)	51 (13.4%)	39 (10.9%)	.68
Silent ischemia	123 (16.7%)	67 (17.7%)	56 (15.7%)	
Preoperative assessment	64 (8.7%)	33 (8.7%)	31 (8.7%)	
First transradial access attempt	597 (81.1%)	307 (81%)	290 (81.2%)	.94
<b>Procedure</b>				
Coronary angiography	507 (68.9%)	259 (68.3%)	248 (69.5%)	
Percutaneous coronary intervention	24 (3.3%)	15 (3.9%)	9 (2.5%)	.55
Coronary angiography and <i>ad hoc</i> revascularization procedure	205 (27.9%)	105 (27.7%)	100 (28%)	

## Statistics

Continuous variables were compared using the Student *t* test. Categorical variables were compared using Pearson chi-square test. Data were expressed as mean ± standard deviation or frequency (percentage). Two-tailed *P* values < .05 were considered statistically significant.

## RESULTS

### Characteristics of patients and procedural details

Overall, 736 patients (450 men, age 65 ± 10 years) were enrolled in the trial: 379 (51.5%) in the nitroglycerin group and 357 (48.5%) in control group. Table 1 shows their general characteristics. Active smoking and diabetes mellitus were reported by 292 (39.7%) and 168 (22.8%) of the patients, respectively and 240 (46.1%) showed an unstable presentation. The radial access was the first access attempted in 597 patients (81.1%).

Procedural details are shown on table 2. In most cases, the radial artery was punctured with a 20G IV catheter using the modified Seldinger technique and a plastic-jacked mini-guidewire advanced through the artery lumen. Small and short sheath introducers were used in less than half of the patients.

### Outcomes

The average number of puncture attempts was similar in the nitroglycerin group compared to control group (1.70 vs 1.76;

*P* = .42). Access and procedural times did not change significantly in either one of the 2 groups (61.1 s and 33.3 s vs 63 s and 33.4 s; *P* = .66 and *P* = .64, respectively). No significant inter-group differences were found either in the rate of switch to transfemoral access (7.1% in the nitroglycerin group vs 8.4% in control group, *P* = .52).

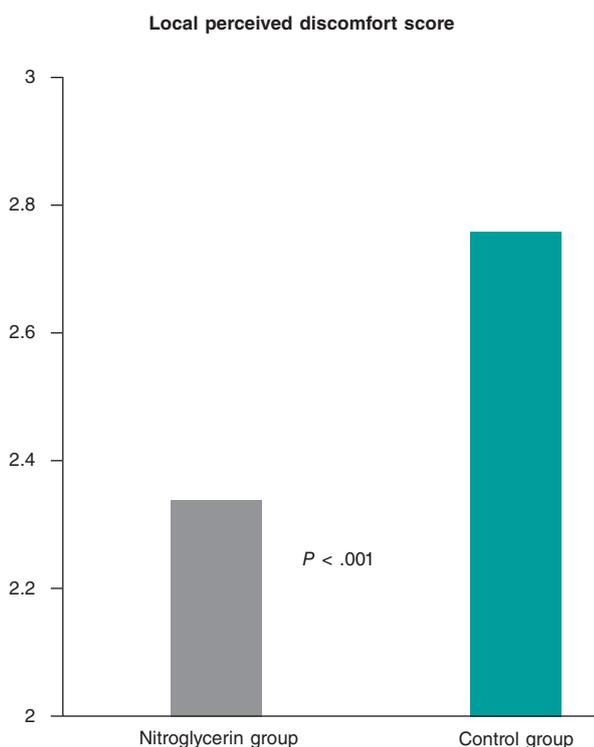
The main results of the patients and their local perceived discomfort score are shown on figure 1. The average local perceived discomfort score was significantly better in the nitroglycerin group (2.34 vs 2.76; *P* < .001) with a significantly higher rate of grade 0/1 (34.3% vs 25.2%; *P* = .088) and a lower rate of grade > 3 (33.5% vs 50.4%; *P* < .001).

Figure 2 shows the results of pre- and post-anesthetic pulse score assessment. No significant differences were seen in the pre-anesthetic pulse score. However, the post-anesthetic pulse score was significantly higher in the nitroglycerin group (2.47 vs 2.22, *P* < .001). The rate of post-anesthetic pulse score < 3 was significantly lower in the nitroglycerin group compared to group C (41.7% vs 57.1%, *P* < .001).

Radial artery ultrasound scans were performed in 70 patients; the results are shown on figure 3. No significant inter-group differences were seen at the baseline between the longitudinal (2.37 mm vs 2.34 mm; *P* = .84) and cross-sectional planes (2.31 mm vs 2.34 mm; *P* = .97). However, the post-anesthetic radial artery lumen diameter was significantly higher in the nitroglycerin group in both the longitudinal (3.11 mm vs 2.43 mm; *P* = .002) and cross-sectional planes (2.83 mm vs 2.41 mm; *P* = .002).

**Table 2.** Procedural details

	Overall (N = 736)	Nitroglycerin group (N = 379)	Control group (N = 357)	P
<i>Allen test result</i>				
Normal	659 (89.5%)	338 (89.2%)	321 (89.9%)	.94
Intermediate	66 (9%)	35 (9.2%)	31 (8.7%)	
Abnormal	11 (1.5%)	6 (1.6%)	5 (1.4%)	
<i>Radial puncture and introducer placement</i>				
20G IV catheter	719 (97.7%)	371 (97.9%)	348 (97.5%)	.71
0.021 in mini-guidewire	701 (95.2%)	364 (96%)	337 (94.4%)	.29
Plastic-jacketed mini-guidewire	684 (92.9%)	358 (94.4%)	326 (91.3%)	.10
Introducer length < 10 cm	292 (39.7%)	162 (42.7%)	130 (36.4%)	.08
Introducer size < 6-Fr	318 (43.2%)	166 (43.8%)	152 (42.5%)	.74
<i>Radial artery angiography</i>	271 (36.8%)	144 (38%)	127 (35.6%)	.50



**Figure 1.** Patients tolerance to the transradial procedure. The average local perceived discomfort score was significantly better in patients in whom nitroglycerin was administered subcutaneously compared to those in whom placebo was used (2.34 vs 2.76;  $P < .001$ ).

As shown on table 3, no significant differences in local complications were seen, although a trend towards a lower rate of local hematomas was seen in the nitroglycerin group (6.1% vs 9.8%  $P = .059$ ). Headaches were more common among patients from nitroglycerin groups (3.2% vs 0.6%,  $P = .021$ ).

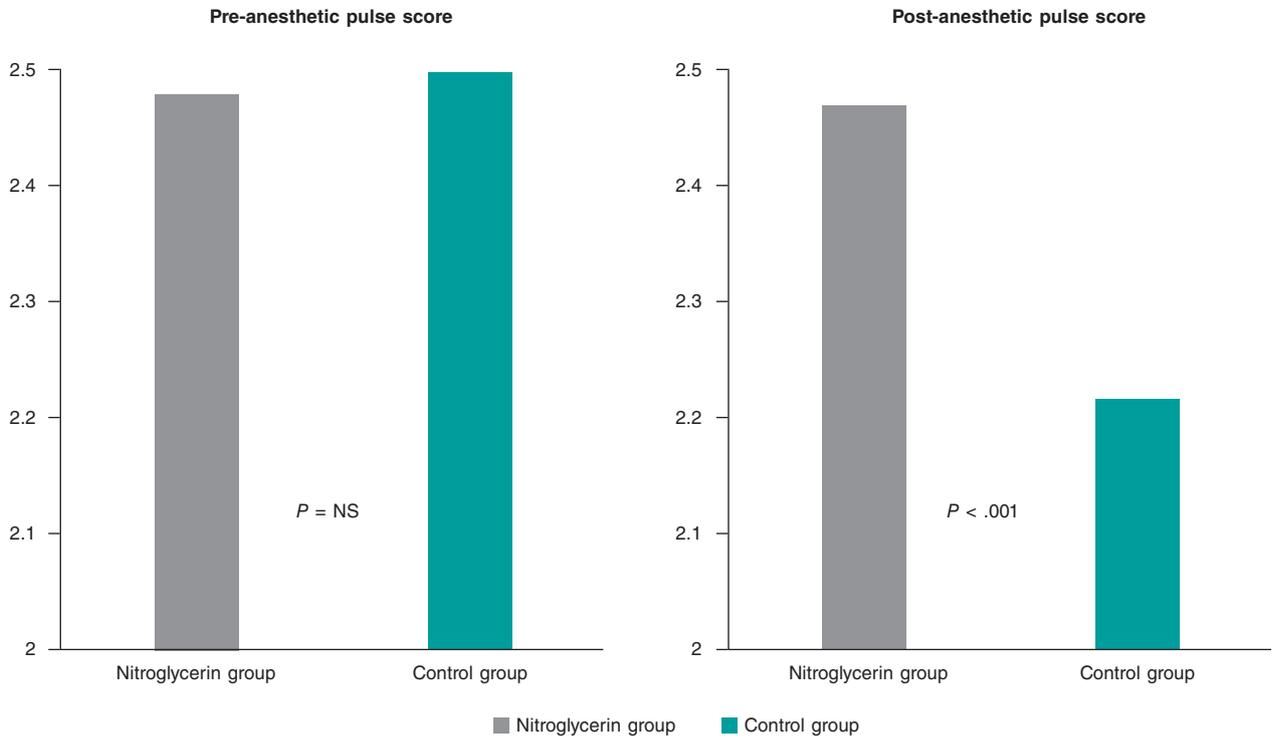
## DISCUSSION

The main findings of our study are that the subcutaneous administration of nitroglycerin plus the administration of a local anesthetic agent prior to radial artery puncture did not show any statistically significant differences in the number of punctures attempted, access and procedural time or switch to transfemoral access. However, it significantly improved: *a*) the patients' perceived comfort during the procedure; *b*) the radial artery pulse; and *c*) the radial artery size. Also, our data suggest a possible reduction in the occurrence of local hematomas. Also consistent with former studies, the subcutaneous use of nitroglycerin significantly increased the diameter of the radial artery in patients in whom an ultrasound scan was performed.<sup>10,13</sup>

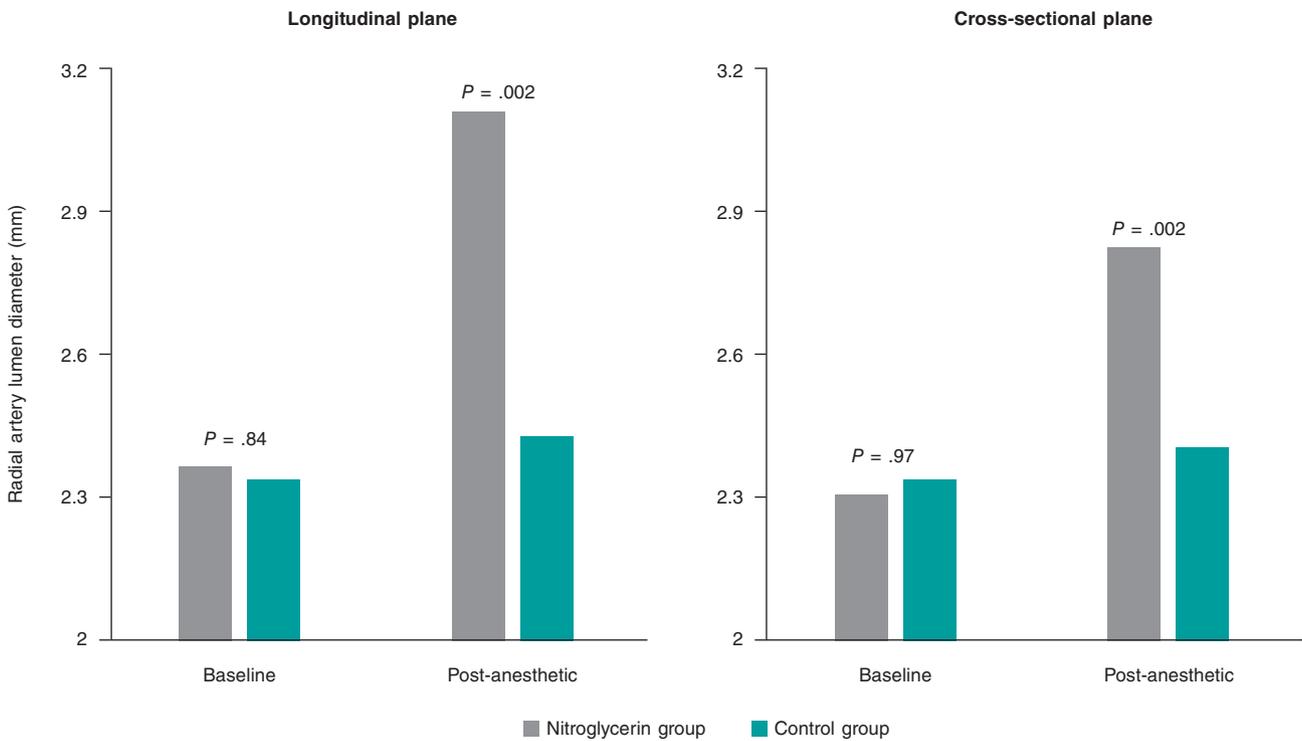
The radial artery spasm is the most common complication of transradial access in both coronary angiographies and procedures. It often holds up the regular course of the procedure impacting the patients' compliance and interfering with the cath lab proceedings.<sup>6,9</sup> Also, the occurrence of radial artery spasm before radial artery cannulation is even more frustrating to treat and may anticipate that the cannulation of the vessel will be impossible.

Multiple puncture attempts are the leading cause for radial artery spasm and may be a specific issue in the teaching environment.<sup>14,15</sup> Also, the administration of local anesthetics such as lidocaine has vasoconstrictive properties<sup>16</sup> and the radial artery has a relatively small diameter and a relatively thicker tunica media of smooth muscle cells, which leads to a high receptor-mediated vasomotion compared to other muscular arteries.<sup>17,18</sup> Conversely, the radial artery is particularly sensitive to nitroglycerin.<sup>19</sup>

Former studies have shown that nitroglycerin delivered through IV,<sup>20</sup> topical,<sup>21</sup> or intra-arterial<sup>16,22-24</sup> routes of administration determines the radial artery dilatation; current evidence with subcutaneous nitroglycerin to facilitate radial access suggests that it can be beneficial to increase the radial pulse and reduce the number of attempts. However, the evidence on this regard is scarce and based on small studies.<sup>10,11</sup> A review that assessed this issue also failed to find significant differences between both strategies.<sup>25</sup> Our study rigorously used a double-blind, randomized protocol to



**Figure 2.** Operator assessment of radial pulse. The left panel shows that no significant differences were found in the pre-anesthetic pulse score between patients in whom nitroglycerin was administered subcutaneously (nitroglycerin group) and those in whom placebo was used control group. The right panel shows that the post-anesthetic pulse score was significantly higher in the nitroglycerin group compared to control group (2.47 vs 2.22;  $P < .001$ ).



**Figure 3.** Radial artery ultrasound scan. No significant inter-group differences were seen at the baseline between the longitudinal (2.37 mm vs 2.34 mm;  $P = .84$ ) and the cross-sectional planes (2.31 mm vs 2.34 mm;  $P = .97$ ). However, the post-anesthetic radial artery lumen diameter was significantly higher in the nitroglycerin group compared to control group in both the longitudinal (3.11 mm vs 2.43 mm;  $P = .002$ ) and cross-sectional planes (2.83 mm vs 2.41 mm;  $P = .002$ ).

**Table 3.** Main local and systemic complications

	Overall (N = 736)	Nitroglycerin group (N = 379)	Control group (N = 357)	P
<i>Local complications</i>				
Forearm hematoma	58 (7.9%)	23 (6.1%)	35 (9.8%)	.059
Radial artery spasm	109 (14.8%)	49 (12.9%)	60 (16.8%)	.14
<i>Systemic complications</i>				
Headache	14 (1.9%)	12 (3.2%)	2 (0.6%)	.021
Symptomatic hypotension	16 (2.2%)	11 (2.9%)	5 (1.4%)	.25

assess the role of the subcutaneous administration of nitroglycerin prior to radial artery puncture. It concluded that its systematic use can improve the patient's perceived discomfort and make puncture easier for the operator but without reducing the number of punctures attempted or access time. Our findings are especially relevant in light of the improved safety associated with transradial access.<sup>26</sup>

The subcutaneous administration of nitroglycerin is a straightforward and inexpensive technique that allows a high concentration and long persistence of the vasoactive agent at the spasm site level without entering the bloodstream significantly.<sup>9</sup> As a matter of fact, in our study no significant differences were seen in the hemodynamic effect of patients who received subcutaneous nitroglycerin or placebo.

Also, the Doppler ultrasound scans performed on the radial artery pre- and post-nitroglycerin in a subgroup of patients triggered the new NISAR study (*Eco nitroglicerina subcutánea acceso radial*)—currently in its design phase—with echocardiographic evaluation of all the patients included.

### Limitations

All the patients of this study were taking standard anti-ischemic drugs including nitrates. We did not study the confounding effect of the vasodilation caused by these drugs. The inter-observer and inter-operator variabilities were not studied either. The Doppler ultrasound scan was used in a small subgroup of patients.

### CONCLUSIONS

The routine use of subcutaneous nitroglycerin prior to radial puncture was not associated with a lower number of punctures or shorter access times. However, the lower local perceived discomfort and improved radial artery size would justify its daily use in the routine clinical practice to enhance the transradial experience of both patients and operators.

### FUNDING

No funding was received for this work.

### CONFLICTS OF INTEREST

None declared.

### WHAT IS KNOWN ABOUT THE TOPIC?

- Radial artery spasm is still an issue; intra-arterial nitroglycerin and calcium blockers are systematically used after achieving radial access to prevent it. However, the use of subcutaneous nitroglycerin plus the administration of a local anesthetic agent prior to radial puncture is still controversial. This is so because the studies conducted so far on this issue are mostly scarce, small, and not randomized. This was confirmed in a review published back in 2018.

### WHAT DOES THIS STUDY ADD?

- The strength of our study is that it is the first prospective, randomized, multicenter, double-blind trial to assess this issue.
- Regarding the results from the trial and although some hard endpoints did not reach statistically significant differences, we believe that the fact that patients tolerated the procedure better, the increase seen in the pulse score and the radial artery diameter after the administration of subcutaneous nitroglycerin added to the simplicity, security and great availability of the procedure is indicative that this technique should be widely used.

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# Update on requirements and equipment in interventional cardiology. Consensus document by the Interventional Cardiology Association and the Ischemic Heart Disease and Acute Cardiac Care Association of the Spanish Society of Cardiology and the Spanish Association of Nursing in Cardiology



Raúl Moreno,<sup>a,\*</sup> Soledad Ojeda,<sup>b</sup> Rafael Romaguera,<sup>c</sup> Ignacio Cruz,<sup>d</sup> Belén Cid-Álvarez,<sup>e</sup> Oriol Rodríguez,<sup>f</sup> Armando Pérez de Prado,<sup>g</sup> José-Ramón López-Mínguez,<sup>h</sup> Cristóbal Urbano,<sup>i</sup> Eduardo Pinar,<sup>j</sup> Esteban López de Sá,<sup>a</sup> Francisco Javier Delgado,<sup>k</sup> Silvia Pérez Ortega,<sup>l</sup> and Ángel Cequier<sup>c</sup>

<sup>a</sup> Servicio de Cardiología, Hospital La Paz, Madrid, Spain

<sup>b</sup> Servicio de Cardiología, Hospital Reina Sofía, Córdoba, Spain

<sup>c</sup> Servicio de Cardiología, Hospital de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>d</sup> Servicio de Cardiología, Hospital Clínico, Salamanca, Spain

<sup>e</sup> Servicio de Cardiología, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain

<sup>f</sup> Servicio de Cardiología, Hospital German Trias i Pujol, Badalona, Barcelona, Spain

<sup>g</sup> Servicio de Cardiología, Complejo Hospitalario, León, Spain

<sup>h</sup> Servicio de Cardiología, Hospital Infanta Cristina, Badajoz, Spain

<sup>i</sup> Servicio de Cardiología, Hospital Regional, Málaga, Spain

<sup>j</sup> Servicio de Cardiología, Hospital Virgen de La Arrixaca, El Palmar, Murcia, Spain

<sup>k</sup> Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

<sup>l</sup> Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital Clínico, Barcelona, Spain

## ABSTRACT

Over the last two decades, several key advances have been made in the field of interventional cardiology including new techniques and treatments, organizational changes such as the management of acute myocardial infarction, and the arrival of satellite catheterization laboratories. All these advances require the updating of the requirements and equipment that are needed in an interventional cardiology unit. This consensus document by the Interventional Cardiology Association of the Spanish Society of Cardiology, the Ischemic Heart Disease and Acute Cardiac Care Association of the Spanish Society of Cardiology and the Spanish Association of Nursing in Cardiology which describes the recommendations that should be followed by percutaneous coronary intervention capable hospitals or centers intend to build interventional cardiology units. It also describes the requirements for provision, qualification of professionals, technological and material resource allocation, and aspects related to supervised catheterization laboratories and structural heart disease programs.

**Keywords:** Catheterization laboratory. Interventional cardiology. Acute myocardial infarction. Structural heart disease.

\* **Corresponding author:** Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Universitario La Paz, P.º de la Castellana 261, 28046 Madrid, Spain. E-mail address: [raulmorenog@hotmail.com](mailto:raulmorenog@hotmail.com) (R. Moreno).

Received 18 May 2020. Accepted 7 October 2020. Online: 22-12-2020.

<https://doi.org/10.24875/RECICE.M20000181>

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# Actualización de las recomendaciones sobre requisitos y equipamiento en cardiología intervencionista. 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 y la Asociación Española de Enfermería en Cardiología

## RESUMEN

En las últimas dos décadas han tenido lugar grandes avances en el campo de la cardiología intervencionista. Estos incluyen no solo nuevas técnicas y tratamientos, sino también cambios en la organización, como la atención continuada al infarto agudo de miocardio y la aparición de salas tuteladas. Todos estos avances hacen necesaria una actualización de los requisitos y del equipamiento necesarios en una unidad de hemodinámica y cardiología intervencionista. En este documento de consenso de la Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología, la Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares de la Sociedad Española de Cardiología, y la Asociación Española de Enfermería en Cardiología, se establecen las recomendaciones que deberían cumplir los centros hospitalarios donde esté instalada o se pretenda instalar una unidad de hemodinámica y cardiología intervencionista, los requisitos de dotación y cualificación de profesionales, las dotaciones tecnológicas y los materiales necesarios, y aspectos relacionados con las salas tuteladas y los programas de tratamiento de la cardiopatía estructural.

**Palabras clave:** Sala de cateterismo. Cardiología intervencionista. Infarto agudo de miocardio. Cardiopatía estructural.

## Abbreviations

**ACI-SEC:** Interventional Cardiology Association of the Spanish Society of Cardiology. **AEEC:** Spanish Association of Nursing in Cardiology. **PCI:** percutaneous coronary intervention. **PCT:** patient care technician. **TAVI:** transcatheter aortic valve implantation. **UIC:** unit of interventional cardiology.

## INTRODUCTION

Over the last 2 decades, interventional cardiology has been one of the fastest growing medical specialties. The invasive management of acute coronary syndrome, the optimization of short and long-term results of percutaneous coronary intervention (PCI) techniques, and the development of percutaneous techniques to treat a large number of structural heart disease cases have become very popular. This has facilitated the management of patients with cardiovascular diseases who require diagnostic or therapeutic invasive techniques at the unit of interventional cardiology (UIC) at one time or another.

Parallel to this increasing healthcare demand, we have seen another very significant increase in the number of UIC-capable centers, the need for material and human resources, and development of the technology used. Some rules and regulations have changed over the last few years. The latest clinical practice guidelines were published by the Spanish Society of Cardiology (SEC) 20 years ago,<sup>1</sup> and the very latest recommendations from the Spanish Ministry of Health were established almost 10 years ago.<sup>2</sup> That is why it seems necessary to update these recommendations, in our field, on the hemodynamic and interventional cardiology requirements and adapt them to the current situation where most UICs already have continuous infarction care plans and structural heart programs implemented. For this reason, the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC), the Spanish Society of Cardiology Working Group on Ischemic Heart Disease and Acute Cardiovascular Care, and the Spanish Association of Nursing in Cardiology (AEEC) have published this document.

## HOSPITAL REQUIREMENTS

This document divides cath labs into autonomous cath labs (run with medical personnel from the center) and satellite or supervised cath labs (run with personnel from other centers to secure the provision of healthcare).

These are the requirements for hospitals to qualify as PCI-capable centers (figure 1):

- Presence of a coronary care unit or cardiac surgery intensive care unit.
- Presence of a cardiology unit and on-call cardiologists are highly recommended as well.
- Ability to treat vascular complications surgically at the center or at a partner center with patient transfer times under 60 minutes.
- Access to a nephrology and dialysis unit.
- Access to a hematology unit and blood bank.
- Access to a radiological protection unit in or out of the hospital setting.

These requirements are applicable both to autonomous and satellite units. Regarding cardiac surgery, its existence *in situ* should not be considered a requirement *per se* for the center to qualify as a PCI-capable UIC.<sup>3</sup> Also, a protocol needs to be agreed upon

Hospital criteria	Human resources	Material resources
<ul style="list-style-type: none"> <li>• Coronary care unit or cardiac surgery intensive care unit</li> <li>• Vascular surgery unit</li> <li>• Cardiology unit</li> <li>• Nephrology unit</li> <li>• Blood bank</li> <li>• Radiation protection unit</li> </ul>	<ul style="list-style-type: none"> <li>• Head of the unit</li> <li>• Interventional cardiologists</li> <li>• Nurse supervisor</li> <li>• Nursing team</li> <li>• Patient care technician</li> <li>• Administrative clerk</li> <li>• Auxiliary health worker</li> </ul>	<ul style="list-style-type: none"> <li>• Physical space of <math>\geq 200</math> m<sup>2</sup> (cath lab <math>\geq 50</math> m<sup>2</sup>)</li> <li>• High-risk conditions of sterility and air quality, class I</li> <li>• Proper radiological equipment</li> <li>• Digital image acquisition and storage system</li> <li>• PCI equipment and intracoronary diagnostic systems</li> <li>• Resuscitation equipment</li> </ul>

**Figure 1.** Summary of hospital requirements regarding human and material resources that should become available at the interventional cardiology unit. PCI, percutaneous coronary intervention.

with a cardiac surgery unit to facilitate the transfer of patients for emergency surgeries in less than 60 min. Traditionally, structural heart procedures have not been deemed necessary to perform procedures such as valvuloplasties or percutaneous closures of interatrial defects. However, with the rise of structural heart procedures of higher risk and complexity like transcatheter aortic valve implantation (TAVI) or the management of mitral regurgitation using the MitraClip system, this question has gained popularity and the current clinical practice guidelines consider it necessary.

## HUMAN RESOURCES

### Chief, Director or Head of the UIC

The chief of the UIC should be a cardiologist accredited in the practice of interventional cardiology by the ACI-SEC. Although back in 2011, the Spanish Ministry of Health recommended, at least, more than 5 years of professional practice and over 500 procedures performed,<sup>2</sup> we believe the time has come to update these numbers. Therefore, we recommend over 1000 diagnostic procedures and over 500 therapeutic procedures performed.

The basic functions and responsibilities of the head of the UIC are:

- Coordinate healthcare, training and research activities at the UIC.
- Develop and establish procedural protocols, checklists, and outcome assessments.
- Plan the annual objectives of the activities that will be performed and manage the provision of healthcare, education, training, and research at the UIC. Also, elaborate plans with the annual needs of the UIC.
- Implement policies to provide the office material, devices or technologies needed to run the UIC properly.
- Promote the electronic registry of procedures and results and be in charge of sending it to the ACI-SEC annual registry.
- Facilitate the communication and coordination of actions with other cardiology and hospital units.
- See that the rules, regulations, and general policy of both the cardiology unit and the hospital are observed in line with both the cardiology unit and hospital board of directors.
- Draw up an annual report of the activities developed at the UIC.

- Design internal sessions for the training of medical staff and non-professional healthcare workers.
- Participate in the general sessions held at the UIC, especially in the medical-surgical sessions held by the heart team.
- Make sure that the rules and regulations on radiation protection are implemented and being observed. Also, make sure that the UIC personnel has completed the radiation protection courses required by law.
- Be an active leader in and out of the UIC.
- Periodic assessments of:
  - The quality of the clinical practice developed at the UIC by creating, reviewing, and updating the protocols of processes as well as diagnostic and therapeutic procedures.
  - The activity, productivity, cost, efficiency, and safety of all the activities developed at the UIC.
  - The degree of adherence to the goals set by the UIC with periodic follow-ups and problem solving approaches.

### Medical staff

As explained in the "Training and competences" section below, the UIC medical personnel should hold a valid degree as cardiology specialists issued in Spain, follow the recommendations established by the ACI-SEC regarding specific training in interventional cardiology,<sup>4</sup> and be in possession of the radiation protection course level 2.<sup>5</sup>

The functions and responsibilities of the interventional cardiologists who work at the UIC are:

- Perform the invasive procedures often performed in interventional cardiology.
- Perform evaluations of patients prior to performing any diagnostic or therapeutic invasive procedures including possible contraindications and individual risk assessments and confirm that the patients' legally required informed consent is duly signed.
- Make diagnostic and therapeutic decisions based on validated protocols and clinical pathways established by both the hospital and the cardiology unit.

- Know the different procedures included in the UIC repertoire as well as their indications, risks, and methodologies.
- Collaborate with the remaining UIC team and coordinators to achieve the goals set.
- Know how the equipment works, its indications, and functioning.
- Know which structural heart diseases are eligible for percutaneous treatment and its indications.
- When performing structural heart procedures, it is mandatory to know about techniques and procedures, indications, risks, and contraindications. Also, to be competent in the management of all potential complications that may occur.

The recommended number of cardiologists with full dedication to interventional cardiology to provide scheduled care at an UIC with just 1 cath lab and be able to cover vacations is 3. At UICs with 2 cath labs the recommended number of cardiologists with full dedication to interventional cardiology is 5. For every additional cath lab over 2, 1 interventional cardiologist should be added. This is applicable to supervised cath labs too in such a way that in those centers where the UIC acts as the reference to 1 or more supervised cath labs, the number of interventional cardiologists needed should increase by a factor of 1 for every supervised cath lab available. In any case, if the UIC has continuous infarction care plans implemented (on a 24 hour/day basis 365 days/year), the minimum number of interventional cardiologists required for its correct functioning is 4.<sup>6</sup> In order to guarantee the availability of continuous infarction care plans, in some centers (especially those with just 1 cath lab) it may be necessary to hire part-time interventional cardiologists who also work in other areas of cardiology.

The UIC accredited health professionals will facilitate and engage themselves in the development of training programs for both internal medicine residents (IMR) and internship recipients as long as the UIC is accredited to that effect. On the other hand, to perform special procedures, other health professionals who may not be part of the UIC such as cardiology specialists (echocardiography specialists or acute coronary care unit cardiologists) and anesthesiologists may be requested.

### Nurse supervision

Nurse supervisors should have an adequate level of experience and training in interventional cardiology, as well as other specific functions and responsibilities. It is advisable that they should be accredited as experts in interventional cardiology by the AEEC.<sup>7</sup> These are their responsibilities:

- Organize the UIC nursing staff.
- Supervise and coordinate the day's work together with the head of the UIC.
- Organize the management of patients before and after performing the procedures.
- Prepare and keep the areas involved in observation and care totally operational.
- Implement the hospital protocols and clinical practice guidelines on monitorization, drug therapy, pre- and postoperative

care while making sure that the patients' safety is guaranteed at all times.

- Develop and establish procedural protocols, checklists, and outcome assessments.
- Organize continuous education and training programs for the nursing staff.
- Assess the competence of health professionals.
- Take good care of equipment and tools.
- Make sure that tools and drugs are always available.

### Nursing staff

The minimum requirements for the nursing staff who work at the UIC are:

- Hold a bachelor's degree in nursing.
- Have UIC training and be trained in the kind of procedures performed in this setting at least in the management of diagnostic procedures and PCI techniques.
- Have a radiological protection degree (preferably the level 2 radiological protection course).<sup>5</sup>
- At least 50% of the nursing team needs to be accredited in interventional cardiology by SEC/ACI-SEC/AEEC.<sup>7</sup>

Also, the UIC nursing team needs to be competent in cardiovascular care in general and in the early management of patients, their mental preparedness, and be able to handle postprocedural monitorization. Also, they need to be experienced in the management of cardiovascular disease, critical coronary care unit, management of cardiovascular drugs, be skilled starting IVs, experienced using cardiovascular tools, competent in the use of interventional cardiology tools and skilled using them.<sup>2,8</sup>

Regarding their competences at the UIC, the nursing team can be divided into: instrument nurses, circulating nurses, and polygraph nurse specialists; still, the entire nursing team needs to be competent in the 3 areas described above. The team should also be skilled in preparing the patients before the procedure and immediate monitorization are tasks that should be performed by expert UIC nurses.

The number of nurses required for the proper functioning of the UIC depends on the type of procedure performed. In order to perform diagnostic studies and PCIs, the minimum number of nurses is 2 (in this case, the same nurse does both the circulating and polygraph monitoring tasks) being 3 the ideal number. At least 3 nurses are required to perform structural heart procedures. The AEEC estimates that for quality care purposes, the proper number of nurses at a cath lab should be 3 in order to cover the aforementioned instrument, circulating, and polygraph monitoring tasks.<sup>8</sup> In any case, at least 2 of these 3 nurses need to be experts in order to provide safe and quality care for the patients during and after cardiac catheterization.

### Radiology technicians

Since radiation protection training is mandatory for both the UIC medical staff and the nursing team, radiology technicians are not

considered essential workers at the UIC. Actually, most UICs simply don't have them among their staff. However, if they are among the UIC staff, they need to take regular care and maintenance of the radiology equipment and know the different software applications and quantitative coronary angiography systems. Also, they need to understand how non-angiographic imaging modalities (intracoronary ultrasound and optical coherence tomography) and physiological systems (intracardiac pressures and intracoronary pressure guidewires) work. Also, they need to make sure that radiation emissions are safe both for the patients and the healthcare personnel.

### Patient care technicians and non-professional healthcare workers

Patient care technicians (PCT) play an important role preparing the patients and helping the nursing team. At least 1 PCT needs to be present in UICs with 1 or 2 cath labs, and 2 PCTs in UICs with more than 2 cath labs.

The administrative personnel and auxiliary health workers are essential employees at the UIC. Administrative personnel handle medical appointments and all sorts of healthcare related documents. Auxiliary health workers are in charge of swiftly escorting the patients in and out of the hospital. At least 1 administrative clerk with full dedication to the UIC should be present in large volume centers with more than 1 cath lab. The cleaning personnel prepare the cath lab between cases while maintaining the proper hygienic conditions.

## TRAINING AND COMPETENCES

The SEC, through the ACI-SEC, has been implementing an internal accreditation system for healthcare professionals and training centers since 1998.<sup>4</sup> The requirements to access this accreditation system and the core curriculum update in interventional cardiology proposed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI)<sup>9</sup> are the basis of the recommendations described below.

### Interventional cardiology training

Training in interventional cardiology should guarantee an absolute knowledge of all diagnostic and therapeutic invasive techniques available. Over the last few decades, Spanish cardiologists have been treating not only coronary artery disease but also non-valvular<sup>10</sup> and valvular<sup>11,12</sup> structural heart diseases percutaneously. It is important to stress that interventional cardiologists are also involved in the comprehensive cardiac management of the patients including the indication for the procedure, evaluations using imaging modalities, the management of all possible complications, and clinical follow-up.

The prerequisites to obtain the professional accreditation in interventional cardiology are:

- Hold a medical degree as cardiology specialist issued by the Spanish Ministry of Education.
- Be well-trained in acute cardiac care to treat any possible complications and clinical impairment that may occur while procedures are being performed.
- Have a level 2 accreditation in radiological protection oriented towards the practice of interventional cardiology.<sup>5</sup>

- Be properly trained in both diagnostic and therapeutic interventional cardiology. According to the accreditation criteria established by ACI-SEC, training should take place over a 2-year period in a UIC licensed and registered to host this kind of training.<sup>4</sup> Since certain highly complex procedures are performed in a limited number of large volume centers, training can be carried out in more than 1 national accredited training centre or international center with a good professional reputation. Ideally, the UIC medical staff should be accredited and licensed for the practice of interventional cardiology. Also, they can be carrying out this training as specialists already hired by the UIC. At the ICU there can be 1 or more cardiologists at different levels of advanced training under the supervision of already accredited interventional cardiologists.
- To have performed, at least, 250 therapeutic coronary procedures, half of them as lead operator. These procedures should be properly documented and certified by the head of the UIC from the center where the training sessions are taking place.
- Master all manual and cognitive skills on the selection of patients, devices, equipment, tools, drugs, information, and writing of documents. In summary:
  - Coronary procedures: master all arterial and venous vascular accesses, hemostasis systems, and devices; PCIs for the management of simple lesions and acute coronary syndromes; and be experienced using complex techniques while performing PCIs including intravascular imaging, functional studies, treatment of bifurcations, chronic occlusions, calcified lesions, and implantation of circulatory mechanical support systems.
  - Direct participation in the primary angioplasty program for the management of infarction.
  - Have theoretical experience and practical knowledge as an assistant operator in structural heart procedures including transcatheter approaches for the management of different heart valve diseases and closures of septal defects, left atrial appendages, and paravalvular dehiscences.
- Know the care provided, and therapy administered to every patient before and after the procedure. Also keep a proper follow-up after hospital discharge.
- Have the capacity to treat all the possible complications that may occur associated with coronary procedures and coadjutant therapies.

### Training centers

In order to guarantee proper training in interventional cardiology, the clinical practice guidelines on the management of myocardial revascularization recommend<sup>13</sup> that training should be carried out in large volume centers with an independent UIC and a structured acute coronary syndrome care program on a 24/7 basis.

In Spain, the ACI-SEC has an accreditation program with training centers adapted to the reality of our context that establishes the following minimum requirements<sup>4</sup>:

- The UIC needs to be included in a cardiology unit accredited by the SEC and the National Specialty Commission for the training of cardiology specialists via IMR.

- The UIC needs to have at least 1 cath lab that should meet all the requirements anticipated by the current Spanish legislation and be certified by the center radiological protection unit including supervision by accredited personnel for manipulation and supervision purposes.
- The center should perform at least 500 PCIs every year. Centers that perform, on average, 500 PICs annually can train a specialist during the first year and a second specialist during the second year. However, centers that perform at least 1000 PCIs/year can train 2 specialists during the first year and 2 during the second year.
- The training program coordinator needs to be competent in all the cognitive and technical activities included in interventional cardiology with an overall historic volume of procedures performed non-inferior to 1000 PCIs and a mean annual activity of 200 PCIs.
- The UIC should offer satisfactory advanced training with enough cases with all the possible subgroups of risk and complexity including PCIs for the management of acute myocardial infarction.
- The presence of a heart team on-call (on a 24/7 basis) for the management of patients with acute coronary syndrome that may require emergency procedures is essential. Similarly, this service should be able to provide immediate care to patients who may experience complications resulting from interventional techniques and procedures.
- The UIC should observe a minimum level of activity and scientific curiosity in interventional cardiology.<sup>4</sup>
- Total area: at least 200 m<sup>2</sup>.
- Cath lab: it should have at least 50 m<sup>2</sup> of useful surface depending on the equipment included in it. The height of the ceiling should be at least 3 meters. Its design should be rectangular, and the walls need to be covered with lead. It should have an entry door for the patients separate from the door that gives access to the control zone. Both doors should also be covered with lead. The entry door to the cath lab needs to have a red light that should automatically turn on when x-rays are activated. The floor should be antielectrostatic.
- Control zone of the radiology equipment and polygraphy machine connected (ideally through a microphone amplifier circuit) to the examination room and separated from it by radiation shielding lead glass. Ideally, it should be located at the smaller side of the cath lab facing the patient table and opposite the radiology equipment. It can be individual for every cath lab or used with several cath labs.
- Technical room hosting the back-up equipment for the angiography system, polygraph, and transmission of images. The current equipment requires less space. Still, 10 m<sup>2</sup> are needed based on the specific needs of every manufacturer. It should have its own independent cooling system and all electric wires should be insulated.
- Reception area for patient preparedness and care. It can be an area adjacent to the cath lab or work as a day hospital does. It should be close to the examination rooms and used for pre- and postprocedural care. In the presence of outpatient catheter and PCI programs it is advisable to adapt this space as a day hospital to fit individual chairs or beds for privacy purposes. Every space should have its own individual monitoring system (electrocardiogram, arterial blood pressure, and oxygen saturation), gas outlets, and power sockets. This area needs to be monitored at all times by nurses and doctors in charge of the operations and procedures performed in such areas.
- Storage unit: since it is advisable to leave the fewest possible pieces of equipment at the cath lab (and always stored in specific surgical furniture and appliances) in order to secure the proper conditions of sterility and asepsis, the storage spaces should be big enough to store the material and equipment used during the procedures. Computerized storage control systems integrated into information and replacement systems are advisable and often used in an increasing number of UICs.
- Other zones intended to be part of this area: administrative area, waiting room and briefing room for families, medical report office, waiting room for the medical personnel, locker room for patients and medical personnel, and separate bathrooms.

### Keeping the accreditation

There is a direct correlation between results and the volume of PCIs performed per center and operator, both regarding PCIs in general and<sup>14</sup> in PCIs to treat infarctions.<sup>15</sup> In order to remain competent in performing PCIs to treat acute coronary syndrome, interventional cardiologists need to perform at least 75 PCIs every year. This represents a total of 400 PCIs performed each year by PCI-capable centers on a 24/7 basis). They also need to perform at least 75 PCIs each year to treat acute coronary syndromes (a total of at least 200 annual PCIs per center). Ideally, centers and operators with fewer PCIs performed should partner with larger volume centers.<sup>13</sup>

Under the current accreditation system, at the time this manuscript was being written, in order to maintain competency the ACI-SEC required that every 5 years, all accredited professionals will be compelled to justify the activity developed during this time. The applicants will need to prove that they performed at least a total of 75 annual PCIs documented and certified by the head of the UIC.<sup>4</sup>

## MATERIAL RESOURCES

### Physical space

The ideal location of the UIC is a place close or with easy access to the emergency unit and the cardiology unit hospitalization areas. The UIC should be built with the following physical spaces in mind:

### Conditions of sterility and air quality

UNE regulation 100713 dated September 2005 classified all UICs as high-risk areas<sup>16</sup>, class I, and categorized them traditionally as operating rooms type B (ISO class 7),<sup>17</sup> indicative that the air diffusion system recommended is turbulent flow.

According to UNE regulation 171340<sup>18</sup> which classifies hospital areas based on risk and type of ventilation/filtration used, cath labs are ranked as high-risk areas. The UICs built from 2012 onwards need to meet the aforementioned regulation to guarantee a sterile

**Table 1.** Conditions of sterility and quality of air that all current cath labs should meet

<ul style="list-style-type: none"> <li>Minimum advisable flow recirculation with 25 movements/hour of which <math>\geq 1200 \text{ m}^3/\text{h}</math> should be with fresh air from outside</li> </ul>
<ul style="list-style-type: none"> <li>Single air-handling unit</li> </ul>
<ul style="list-style-type: none"> <li>Recirculated air should be treated exactly the same as the outside air by the same air-conditioner</li> </ul>
<ul style="list-style-type: none"> <li>Periodic microbiological tests</li> </ul>
<ul style="list-style-type: none"> <li>Air velocity at the room occupancy area between 0.2 m/s and 0.3 m/s</li> </ul>
<ul style="list-style-type: none"> <li>Have, at least, 3 levels of filtration including these types of filters:               <ul style="list-style-type: none"> <li>Pre-filter EU4</li> <li>Air-conditioning EU9 air filter</li> <li>Final H13 filter in the surgical area</li> </ul> </li> </ul>

environment to be able to perform all kinds of minimally invasive procedures like TAVI, left atrial appendage closures, and use of the MitraClip system. Also, the conditions of sterility and asepsis allow us to use these UICs as conventional operating rooms too (for example, for the management of vascular complications). However, UICs built before this regulation became effective are not bound to it unless remodeled (table 1).

UICs should provide enough surgical coverage to perform procedures under conditions of sterility. The use of disposable material is also advised.<sup>19</sup> Under conditions of special risk of infection for healthcare personnel, personal protection equipment is advised.<sup>20</sup> In any case, all measures related to sterility at the cath lab and infection avoidance for the healthcare personnel should be discussed with both the preventive medicine and risk management units.

### Radiology equipment and clinical support systems

In general, the UIC radiological and additional equipment should include (figure 2):

- A 100 kW-standard X-ray generator.
- Flat-panel imaging digital detector with field sizes big enough to facilitate the use of coronary and structural techniques. Twenty inches is the recommended size.
- Collimation system.
- Anticollision systems are mandatory to avoid short range collisions with the patients. Also, a grid should be incorporated to the system.
- Ceiling or floor mounted motorized arm with iso centric tilt movement and possibility of cranial and caudal  $\geq \pm 40^\circ$  and lateral and oblique  $\geq \pm 90^\circ$  angulations without having to move table or patient.
- Examination table: low-attenuation carbon fiber board or equivalent with longitudinal and cross-sectional movement capabilities—automatic or manual—and electromagnetic system blocking system on the table. Vertical movement needs to be motorized. Also, it needs to include accessories and outlets to adapt additional components (injector pump, polygraph, consoles for coronary physiology monitoring, etc).



**Figure 2.** Equipment present at the cath lab. 1: patient table. 2: x-ray tube. 3: radiation shielding lead glass with upper leaded glass section and articulated adjustable arm mounted on the ceiling. 4: leaded skirt mounted on the table. 5: automated contrast media injector. 6: on/off ceiling light with adjustable articulated arm. 7: monitors. 8: infusion pumps. 9: anesthetic and respiratory equipment. 10: crash cart or code cart with defibrillator. 11: smart cabinet for material storage with automatic replacement. 12: table with the equipment needed to perform the procedure. 13: console of the pressure wire.

- Contrast injector: automatic injectors are advised but not required.
- Monitors: mounted on the ceiling and movable or adjustable for correct visualization. The monitor can be a single  $\geq 55$ -inch flat screen or multiple  $\geq 19$ -inch monitors. They need to show at least 3 different imaging sources such as real-time radiological images, the reference radiological image, polygraphy, echocardiogram, intracoronary ultrasound, optical coherence tomography, computerized tomography scan or fusion tools.
- Polygraph: it should display continuous ECG monitoring, invasive arterial pressure with at least 2 independent pressure transducers, oxygen saturation through pulse oximetry, cardiac output cable, hemodynamic wave data recording, and be capable of processing hemodynamic data (eg, valvular areas, vascular resistances, gradients, and cardiac output). It needs to be programmed with software that should allow the reception of the working list, the sending of information to a storage system, and the transmission of images with storage and post-processing editing capabilities. Ideally, it should be controlled from the examination table and the working station should be located in the control zone outside the cath lab.
- We should be able to generate final reports on the procedure performed including data from the Kerma-air product (KAP) and dose-area product (DAP) that will be included in the patient's medical history.
- Radiological contrast: iso-osmolar contrast media are advised since they are associated with a lower risk of contrast-induced nephropathy.
- Radiological protection systems:
  - Protective lead curtains for the examination table, at least where the table controls are located and on the side where

the procedure will be performed. The minimum lead cover should be 0.5 mm thick.

- Suspended and articulated transparent protection shield to protect the exposed medical personnel who participate in the procedure and remain close to the patient table. At the same time, it facilitates the visualization of the patient and should adapt to the patient contour.
- Radiological protection equipment for the medical staff: lead aprons, lead thyroid collar cover, lead glasses, and dose meters.
- Cold light operating lamp: hanging from the ceiling from an articulated arm and highly movable to light up specific sections of the surgical field.
- Intercommunicator between the examination room and the control room.
- Uninterruptible power supply systems for monitorization and life support purposes. Also, if possible, radiological equipment with enough power (15 min) to perform a fluoroscopy in case of possible power cuts.

### Image acquisition systems and storage

The image acquisition system should be digital with a proper dynamic range for routine clinical applications. It should cover the low doses of the different imaging modalities of x-rays and the higher doses of digital acquisition including the most demanding ones of the digital subtraction angiography. The frequency range in pulsed fluoroscopy or graphic representation should be of 30 or more images per second. It should allow processing, visualization, and digital storage.

This equipment needs to include coronary and ventricular quantification applications. Currently, there are applications available for quantitative computed tomography assessment to plan procedures, and fusion systems of transesophageal echocardiography plus digital angiography that can be useful when performing interventional procedures to treat structural heart diseases.

The images of every patient will be saved and stored permanently in a filing system compatible with multiple DICOM modality worklist services (digital imaging and communication on medicine) of cardiac images with integrated DICOM-3 services. These images need to be stored in the corresponding hospital or health service PACS (picture archiving and communication system) so that all studies can be seen and analyzed from the different working stations connected to this server. For that purpose, TCP/IP communications protocols (transmission control protocol/ internet protocol) are required. These protocols should be used in full compliance with data protection legislation. The capabilities of compact disc and digital versatile disc recording and reading are advisable in compliance with the DICOM standard anticipating the possibility of exporting images and angiographic series to other imaging formats.

For real-time image processing and simultaneous image acquisition purposes, a working station will be required for case review and analysis that will join the working station of the image acquisition system. It should be located in the same control zone as the x-ray and polygraph equipment.

### Resuscitation and life support systems

UICs should have specific resuscitation and life support systems:

- Crash carts or code carts: the entire UIC staff should be trained in cardiopulmonary resuscitation techniques. The cart should be placed at the patient's bedside and include the following components that should be reviewed periodically:
  - Defibrillator/monitor equipped with transcutaneous pacing capabilities.
  - Oxygen administration systems.
  - Orotracheal intubation equipment (laryngoscope and tubes).
  - Ventilation system.
  - Aspiration system.
  - Drugs required for hemodynamic drug support, sedation, and management of cardiorespiratory arrest.
- Ventilator.
- Infusion pumps.
- Temporary transvenous pacemaker insertion equipment (electrocatheter and generator).
- Pericardiocentesis kit.

### Specific material to perform coronary interventions

Added to the conventional material used to achieve diagnosis and perform coronary interventions (diagnostic catheters, guide catheters, angioplasty guidewires, angioplasty balloons, and coronary stents), it is advisable to have specific coronary stents available to treat coronary perforations, and plaque modification devices to treat nondilatable coronary lesions with conventional balloon or heavily calcified coronary lesions.<sup>21</sup>

### Intracoronary diagnostic tools

In a large number of patients, the use of pressure guidewires or intracoronary imaging modalities will be required as established by the latest clinical practice guidelines on the management of myocardial revascularization.<sup>13</sup>

Clinical practice guidelines consider pressure guidewires as the proper tool to identify hemodynamically relevant coronary lesions in stable patients (indication class I, level of evidence A) and guide revascularization in patients with multivessel disease (indication class IIa, level of evidence B).<sup>13</sup>

Also, clinical practice guidelines indicate the use of intracoronary imaging modalities (both intracoronary ultrasound and optical coherence tomography) to study the mechanisms of stent failure and for implant optimization purposes in selected patients (indication class IIa, level of evidence B). Also, intracoronary ultrasound is considered the imaging modality of choice to study the severity of left main coronary artery lesions and for result optimization purposes (indication class IIa, level of evidence B)<sup>13</sup>.

Therefore, we believe it is necessary for UICs to have functional assessment methods available (eg, pressure guidewires) and intracoronary imaging modalities as well.

### Circulatory support systems

Circulatory support systems are required at the UIC to approach complex angioplasties in high-risk patients and for the management of hemodynamically unstable patients or cardiogenic shock. Actually, this is very important in centers with continuous infarction care programs running, especially large volume centers and satellite cath labs without surgical coverage *in situ*. These systems can be:

- Intra-aortic counterpulsation balloon: catheters should be available at the UIC. However, the console can be stationed at the coronary care unit or cardiac surgery intensive care unit. It should be adaptable to any type of balloon, portable, and have a minimum power supply of 3 hours.
- Percutaneous left ventricular assist devices: the most commonly used one is transaortic microaxial blood pump. It is used for the management of patients with cardiogenic shock and to approach very high-risk PCIs. Its use should follow the recommendations established by the clinical practice guidelines.
- Venoarterial extracorporeal membrane oxygenation: this system is advisable in large volume centers that treat patients with refractory cardiogenic shock, cardiac arrest that remains unresponsive to cardiopulmonary resuscitation maneuvers, and refractory malignant ventricular arrhythmias.

## SPECIFIC CONSIDERATIONS

### Supervised cath labs

Over the last decade, the model of satellite or supervised cath labs in large volume center units has been widely implemented. The reason for this is to bring coronary intervention techniques to a larger number of centers so patients can have access to these services without detriment to the advantages that experienced tertiary levels bring. The characteristics of a satellite or supervised cath lab are:

- The interventional cardiology staff is stationed in another reference unit but still provides coverage to this center to perform the procedures required.
- The head of the satellite cath lab and the head of the reference UIC where the medical staff is stationed is the same person.
- In general, these satellite cath labs are implemented in level II hospitals without cardiac surgery *in situ*.

The requirements of these centers are:

- They should meet all remaining requirements and have the same support units as an autonomous cath lab.
- They require fewer medical staff and health professionals compared to the reference unit. Actually, 1 interventional cardiologist should be enough. At least 2 nurses should be available. However, 3 nurses are advisable per satellite cath lab and day of occupancy. The medical personnel should be stationed at the reference center. The nursing staff and auxiliary health workers

can be stationed at the hospital where the satellite cath lab is located.

- A prior written informed consent model needs to be implemented including the fact that emergency surgeries will be performed in a different partner center.
- Patient transfer time to the reference center when emergency surgery is required will not exceed 60 minutes.

A written agreement will need to be signed between the management of both centers for the provision of these services including a budget with all the expenses derived from buying the material required. These centers can be included in healthcare networks.

According to the legislation that regulates the planning and arrangement of the healthcare services provided by each Spanish autonomous community, satellite cath labs can have extraordinary continuous activity programs available on a 24/7 basis 365 days/year to provide urgent care especially within the framework of institutional infarction code programs. The implementation of these programs will be the sole responsibility of the reference UIC.

Structural heart procedures or urgent procedures will not be performed in the supervised cath lab. but in the reference center. However, very complex coronary procedures or interventions requiring special devices in clinically stable patients are ill-advised and they should be performed at the reference center.

### Optimization of the infarction care program (primary angioplasty program)

The requirements and needs of infarction care networks have already been described in detail.<sup>6</sup> In summary, hospitals with primary angioplasty programs require:

- A coronary care unit or general intensive care unit with levels of care 2 and 3 according to the Acute Cardiovascular Care Association.<sup>22</sup>
- Cardiologists on call physically present.
- A cardiac surgery unit capable of treating infarction related mechanical complications, or at least partnerships with centers with other cardiac surgery units, capable of transferring patients in less than 60 minutes.

Added to the material required to sustain life support and perform resuscitation maneuvers, UICs with infarction code care programs should include ventricular assist devices too. These UICs require a 24/7 on-call service throughout the year. The personal requirements for training and accreditation purposes are:

- At least 4 ACI-SEC- accredited interventional cardiologists in the on-call medical staff.
- A total of over 400 PCIs performed at the UIC every year. Also, each operator should perform at least 75 PCIs and 30 primary angioplasties each year.
- At least 2 nurses on-call and 1 PCT are required with proper training performing procedures *in situ* with the operators and expertise in the equipment used. It is advisable that the whole nursing staff should be part of the UIC.

- The quality of the program should be assessed using some sort of control mechanism including reperfusion times and mortality results. Similarly, it is advisable to participate in a regional or national registry to guarantee that the quality control process is properly carried out.

### Structural heart intervention programs

The specific recommendations to perform structural heart procedures are:

- To perform structural heart procedures, interventional cardiologists should have been accredited in hemodynamics and interventional cardiology by the ACI-SEC at an accredited center. This training qualifies the accredittee to be able to perform PCIs.
- At least 2 cath labs are required in centers that perform structural heart procedures, to be able to assist the infarction care network while long structural heart procedures are still underway.
- UICs capable of performing structural heart procedures should have enough room for the echocardiography specialist and anesthesiologist when required.
- Transesophageal echocardiography (ideally with a 3D probe) is required. The availability of intracardiac echocardiography at the UIC setting is not mandatory and its use is regulated by the recommendations established by the clinical practice guidelines.
- The availability of cardiac surgery in centers that perform structural heart procedures like such as valvuloplasties (mitral, aortic or pulmonary) or percutaneous closures of interatrial septal defects or other short circuits has traditionally not been considered a necessity. The general recommendations established for all UICs apply here too when these procedures need to be performed (possibility of patient transfer in less than 60 minutes to a center with cardiac surgery capabilities). These are also the recommendations established to approach the closure of left atrial appendage.<sup>23</sup> Regarding TAVI, developed by cardiology almost 20 years ago,<sup>24</sup> the current clinical practice guidelines require the availability of cardiac surgery at the treating center,<sup>25,26</sup> although these requirements may change in the future.<sup>27</sup> The recommendations established for the management of the MitraClip system regarding the need for surgery are similar to those established for TAVI.<sup>28</sup>
- Hybrid cath labs are not required, but if structural heart procedure is performed in an operating room, it should include all the necessary equipment for constant hemodynamic monitoring purposes, a kinescope, and high-quality fluoroscopy with possibility of a wide array of angles, projections, and image storage; a mobile C-arm would not be suitable here. In this case, the necessary equipment to perform PCIs, implant transvenous pacemakers, use different types of vascular introducers of different sizes and lengths, as well as bailout devices in cases of device migration, transseptal puncture equipment and pericardiocentesis kit, vascular closure devices, and devices to perform vascular interventions will also be required.
- High-resolution monitors are required for the simultaneous visualization of hemodynamic monitoring images (pressures, electrocardiogram, oxygen saturation). Also, they need to be

able to show images acquired using other imaging modalities like echocardiography.

- Two operators and 3 nurses are needed to perform structural heart procedures. In some cases, 1 echocardiography specialist and 1 anesthesiologist may be required. The presence of a cardiac or vascular surgeon may be required too to perform certain procedures.
- The head of the UIC or the coordinators of the structural heart program should be cardiologists with at least 1 year of specific training in structural heart procedures in a large volume centers, experienced in this kind of procedure. Also, they should have at least 5-year experience performing interventional procedures (both PCIs and noncoronary interventional techniques) including transseptal punctures, valvular procedures, and intracardiac device implantation and retrieval. If experience is limited with some of the techniques described, these procedures should be supervised until the proper experience has been gained.
- The number of procedures recommended for both the center and the operator is well-defined for TAVI: at least 50 per year.<sup>29</sup> This is the case with transfemoral TAVI, the only access of which there is evidence in randomized clinical trials as an alternative to aortic valve replacement surgery. Clinical practice guidelines are a little unclear regarding other techniques.<sup>30-32</sup> However, our recommendation is that at least 15 left atrial appendage closures and percutaneous mitral valve repairs and 10 percutaneous closures of interatrial septal defects should be performed every year.
- Centers capable of performing structural heart procedures will need to send the data from the procedures performed to the official registries of the ACI-SEC and the SEC. Also, data will be subject to the consequences that may arise from supervising these data.

### Latest programs: cardiac arrest code and management of acute pulmonary embolism

Over the last few years, the management of cardiac arrest and acute pulmonary embolism has improved significantly. Actually, interventional cardiology has progressively gained interest in these conditions.

Regarding cardiac arrest, performing emergency coronary angiographies to treat acute coronary syndrome can bring clinical benefits. Our recommendation is that patients with out-of-hospital cardiac arrests should be transferred to specific centers. Actually, this kind of care for this type of patient has become a customary practice for some hospitals and is now called "cardiac arrest code". Requirements for these centers are:

- Inclusion in an acute myocardial infarction care network.
- Cardiologists on call.
- Coronary care unit or cardiac surgery intensive care unit with circulatory support system implantation capabilities.
- Capability of performing therapeutic hypothermia.
- Neurology/neurophysiology unit.

Maastricht types III and IV controlled asystole organ donation programs are not required but highly recommended.

Regarding acute pulmonary embolism, more and more UICs have included the management of this condition in their repertoire using embolectomy catheters in hemodynamically compromised patients contraindicated for thrombolysis.

Based on experience and efficiency, both the cardiac arrest code and the management of pulmonary embolism should be handled by personnel from the continuous infarction care program-according to the internal reality of every hospital and the healthcare regulations of the department of health of the Spanish autonomous community concerned.

## CONCLUSION

Over the last few years, the wide invasive management of acute coronary syndrome, development of acute myocardial infarction care networks, creation of supervised cath labs, the arrival and development of new diagnostic and therapeutic coronary techniques and coronary interventions for the management of structural heart disease, as well as legislation changes have changed the equipment, and human resources associated with UICs. This document comes as a response to the need for adapting the current situation to the recommendations in our context regarding requirements in hemodynamics and interventional cardiology. In the future, the recommendations published in this document will need to be updated based on the future steps interventional cardiology may take.

## FUNDING

No funding.

## CONFLICTS OF INTEREST

The authors declared no conflicts of interest regarding this manuscript. R. Moreno is associate editor of *REC: Interventional Cardiology*; the editorial protocol of the journal was observed to guarantee an impartial manuscript handling.

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# Left main coronary artery percutaneous revascularization: *alea jacta est*

Fernando Lozano Ruiz-Poveda,\* José Abellán-Huerta, and Ignacio Sánchez-Pérez

Sección de Hemodinámica, Servicio de Cardiología, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain



## ABSTRACT

For many years, left main coronary artery disease has remained as the last frontier resisting percutaneous coronary intervention. Until recently, the most relevant clinical studies in this regard as well as clinical practice guidelines favored surgical revascularization almost as the only treatment pathway for the management of this condition. The changes that have occurred over the last 10 to 15 years since the appearance of drug-eluting stents and their technological advances have been extraordinary. This, added to the publication of randomized clinical trials that compared both revascularization modalities, has placed percutaneous coronary interventions at a similar level to surgery in a large number of patients. The anatomical, technical, and strategic aspects are essential for the percutaneous management of left main coronary artery lesions given their tremendous clinical variability. In this article we will be reviewing their anatomy, angiography, intracoronary diagnostic techniques, and different percutaneous revascularization strategies. As long as future clinical studies do not definitively favor percutaneous over surgical revascularization or vice versa, individual discussions on each particular case by the heart team and our patients' preferences should guide our clinical decision-making process.

**Keywords:** Coronary artery disease. Left main coronary artery. Percutaneous coronary intervention. Coronary artery bypass graft.

## Revascularización percutánea del tronco coronario izquierdo: *alea jacta est*

### RESUMEN

La enfermedad del tronco coronario izquierdo ha permanecido muchos años como la última frontera que se resistía al intervencionismo coronario percutáneo. Hasta hace poco tiempo, los estudios clínicos más relevantes en este campo, así como las guías clínicas, han sido favorables a la revascularización quirúrgica casi como forma exclusiva de tratamiento de esta patología. Los cambios ocurridos en los últimos 10-15 años, desde la aparición de los *stents* farmacológicos y su mejora tecnológica, han sido vertiginosos. La realización de estudios aleatorizados que han comparado ambas modalidades de revascularización ha llevado al intervencionismo percutáneo a la altura de la cirugía en un alto porcentaje de pacientes. Los aspectos anatómicos, técnicos y de estrategia son fundamentales en el tratamiento percutáneo de estas lesiones, dada su enorme variabilidad clínica. En tanto los estudios clínicos futuros no se decanten definitivamente a favor de la revascularización percutánea o de la quirúrgica, la discusión individualizada de cada caso en un equipo multidisciplinario y las preferencias de los pacientes deberían guiar la decisión clínica.

**Palabras clave:** Enfermedad coronaria. Tronco coronario izquierdo. Intervencionismo coronario percutáneo. Cirugía de revascularización coronaria.

### Abbreviations

**LAD:** left anterior descending coronary artery. **CABG:** coronary artery bypass graft. **LCx:** left circumflex artery. **FFR:** fractional flow reserve. **IVUS:** intravascular ultrasound. **LMCA:** left main coronary artery. **PCI:** percutaneous coronary intervention.

\* **Corresponding author:** Sección de Hemodinámica, Servicio de Cardiología, Hospital General Universitario de Ciudad Real, Obispo Rafael Torija s/n, 13005 Ciudad Real, Spain. E-mail address: [drlozano68@gmail.com](mailto:drlozano68@gmail.com) [F. Lozano Ruiz-Poveda].

Received 8 September 2020. Accepted 5 October 2020. Online: 22-12-2020.

<https://doi.org/10.24875/RECICE.M20000179>

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## INTRODUCTION

Significant left main coronary artery (LMCA) disease is present in 4% to 5% of all coronary angiographies.<sup>1</sup> Since the LMCA supplies over 75% of all the myocardial blood flow, the risk associated with its lesions is the highest of all possible coronary lesions. Without revascularization, its prognosis is poor and mortality rate can be up to 37% at 3-year follow-up.<sup>2</sup> Revascularization can be surgical or percutaneous, each one with its corresponding advantages and limitations. Assessing anatomic spread correctly, the complexity of coronary artery disease, the patient's comorbidities, and the operator's expertise in complex percutaneous coronary interventions (PCI) are key factors when choosing the right revascularization strategy. There are different models and scales to guide the selection of patients. However, none of them has become the leading model yet.<sup>3,4</sup>

## HISTORIC PERSPECTIVE

Coronary artery bypass graft (CABG) has been the standard of care for the management of patients with LMCA disease based on early clinical trials that proved its prognostic benefit in patients assigned to surgery compared to medical therapy.<sup>5</sup> Patients with severe LMCA disease were excluded from most of the early clinical trials and, until recently, no specific trial compared the results of surgery vs PCI as one of its endpoints.<sup>6,7</sup> Currently, there are randomized clinical trials that have confirmed the utility of the PCI to treat LMCA disease; actually, the American and European clinical guidelines consider it the recommended strategy in certain settings.<sup>8,9</sup> Approximately, 50% of this type of lesions are revascularized percutaneously in our setting with an annual 5% increase.<sup>10</sup>

## ANATOMIC CONSIDERATIONS

Anatomically speaking, the LMCA can be divided into 3 portions: ostial portion, mid-portion, and distal portion; the latter is a bifurcation with an angle that is typically wider compared to other coronary bifurcations ( $> 70^\circ$ ). It supplies at least 75% of the total coronary flow. The LMCA caliber is often  $5 \text{ mm} \pm 0.5 \text{ mm}$ <sup>11</sup> and its mean length is  $10.5 \text{ mm} \pm 5.3 \text{ mm}$ .<sup>12</sup> In up to 30% of the cases it originates a third branch, the ramus intermedius or bisector branch (figure 1).

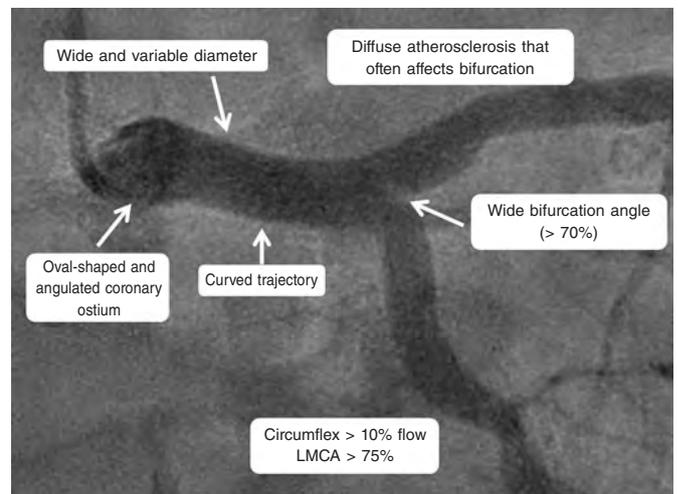
LMCA atherosclerotic disease is often diffuse. When the bifurcation is affected (in 70% of cases) there is also often presence of plaque at the beginning of the left anterior descending coronary artery (LAD) and left circumflex artery (LCx).<sup>11</sup> At times, the origin of both the LAD and the LCx is independent from the left coronary sinus without LMCA *per se* (0.41% to 0.67% of cases).<sup>13,14</sup> In 0.03% of patients, the origin of the LMCA is anomalous describing its trajectory between the aorta and the pulmonary artery, a pattern associated with a high risk of sudden death.<sup>14,15</sup>

## LEFT MAIN CORONARY ARTERY ASSESSMENT

### Angiography

The clinical practice guidelines of the European Society of Cardiology establish that the revascularization of the LMCA is indicated for patients with angiographic stenoses  $> 50\%$  and documented myocardial ischemia.<sup>16</sup> The practical problem here is that coronary angiography has limitations when evaluating LMCA disease with great intra and interobserver variability.<sup>17,18</sup>

Some ostial lesions can be overestimated due to catheter-induced overlapping and artifact or the presence of an associated spasm.



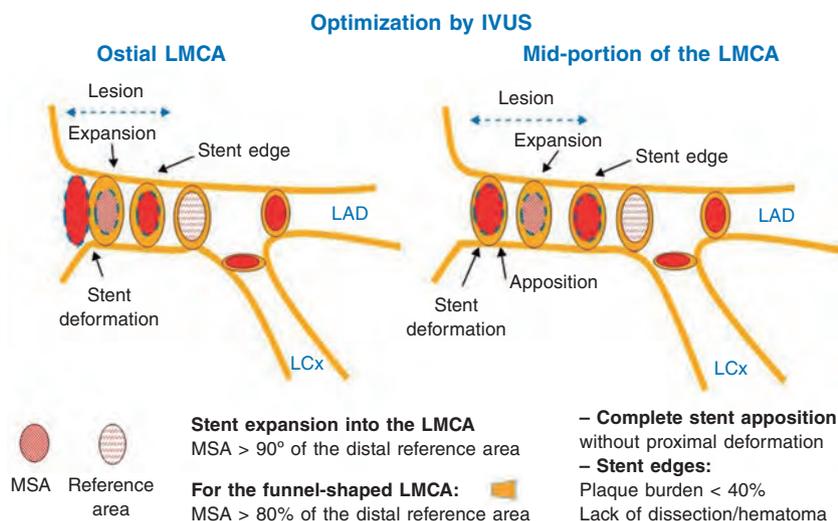
**Figure 1.** Main anatomical characteristics of the left main coronary artery (LMCA).

Consequently, distal lesions may be difficult to assess due to the often diffuse affectation of the bifurcation and lack of a healthy reference vessel. Damping and/or ventricularization of the pressure curve are indirect data of LMCA disease.<sup>19</sup>

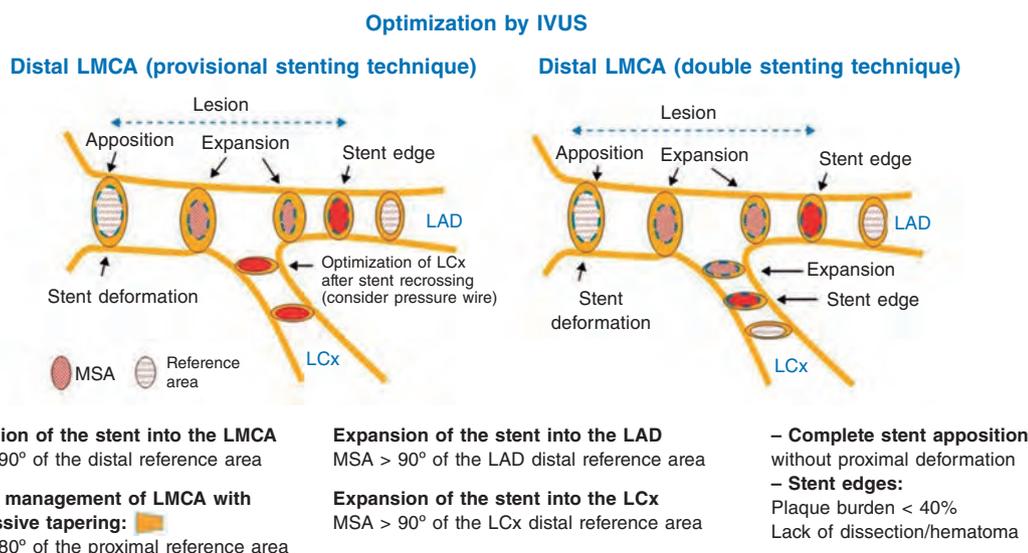
The correct assessment of the severity of LMCA disease is essential given the evidence that functionally nonsignificant lesions have a favorable prognosis without revascularization,<sup>20</sup> and the early graft failure seen in nonsignificant lesions.<sup>21</sup> In this regard, clinical practice guidelines accept the value of diagnostic imaging modalities like intravascular ultrasound (IVUS) and the pressure guidewire to estimate the severity of LMCA disease.

### Intracoronary imaging modalities

The IVUS provides information on the structure and anatomy of the LMCA as well as on the presence of plaque, its spread, composition, and classification. Several studies have determined a minimum lumen area (MLA)  $> 6 \text{ mm}^2$  as the cut-off value to establish severity.<sup>22,23</sup> The Spanish multicenter, prospective clinical trial LITRO proved that it was safe to delay the revascularizations of intermediate LMCA lesions with MLAs  $> 6 \text{ mm}^2$  with favorable results at the 2-year follow-up.<sup>24</sup> Also, the IVUS helps us determine whether the coronary ostia of LAD and LCx have significant disease. When revascularization is indicated, the IVUS provides information on the right size of the stent and the best strategy should be based on the anatomy and calcium load of the LMCA and proximal LAD/LCx; in lesions due to previous in-stent restenosis, the IVUS characterizes their etiology and the possible damage to the borders of the stent. The IVUS-guided PCI of the LMCA is beneficial compared to the angiography-guided PCI.<sup>25</sup> The need for stent postdilatation and the existence of distal dissection can be assessed too. Also, it can help us determine the need for stent implantation into the lateral branch or exclude the compromise of this branch after implanting a provisional stent.<sup>26</sup> Several parameters have been described for the optimization of IVUS-guided PCIs to treat LMCA disease (figure 2 and figure 3). A large metanalysis of patients from several Spanish registries confirmed that the use of IVUS is associated with better clinical progression, fewer deaths and infarctions, and particularly stent thrombosis. These findings are especially significant in LMCA distal lesions.<sup>27</sup> Other registries, a few minor clinical trials, and a combined analysis of them all confirm significant clinical benefit from IVUS-guided PCIs performed on the LMCA with fewer deaths, infarctions, and



**Figure 2.** Key points to optimize the percutaneous coronary interventions performed on the ostial and mid-portions of the left main coronary artery through intravascular ultrasound. IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery; MSA, minimum stent area. (Modified with permission from de la Torre Hernández et al.<sup>25</sup>)



**Figure 3.** Key points to optimize the percutaneous coronary interventions performed on the distal left main coronary artery through intravascular ultrasound. IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery; MSA, minimum stent area. (Modified with permission from de la Torre Hernández et al.<sup>25</sup>)

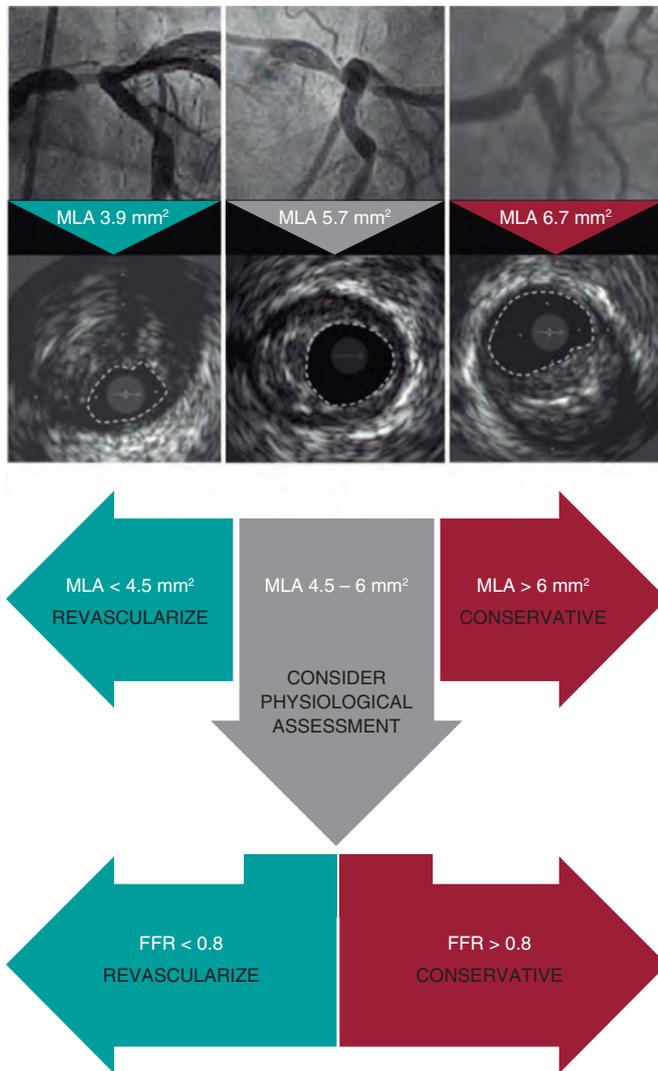
thrombosis.<sup>28</sup> The clinical practice guidelines of the European Society of Cardiology consider the use of IVUS to stratify the severity of all LMCA lesions as an indication type IIa B.<sup>16</sup>

The utility of the optical coherence tomography (OCT) for the management of the LMCA is somehow more limited, mainly because of the technical difficulty involved in completing contrast filling and the native area of ostial segments. Another downside of the OCT for the management of the LMCA is its limited penetration depth (2 mm to 3 mm) compared to IVUS (4 mm to 8 mm), and since the LMCA often has diameters between 3.5 mm and 4.5 mm the assessment can be wrong. The MLA cut-off value for the management of LMCA lesions with the OCT is still unknown. On the other hand, due to the different image acquisition of both imaging modalities, the thresholds established as cut-off values with the IVUS don't work with the OCT.

**Pressure wire**

The pressure guidewire provides valuable information to stratify the severity of LMCA disease.<sup>16,29</sup> In order to stop a presumably ostial disease from impacting measurement, pressures need to be equalized and measured using a guide catheter partially «desintubated» from the LMCA. Obtaining hyperemic indices from the LAD and the LCx leads to better overall assessments of the severity of LMCA disease. Also, it secures the decision-making process on the best therapeutic approach. Some authors suggest that IV adenosine is better than intracoronary adenosine to secure the condition of maximum hyperemia.<sup>4</sup>

Another important aspect when assessing the LMCA with the pressure guidewire is the physiological interdependence of the coronary tree that may change the values of fractional flow reserve (FFR).



**Figure 4.** Criteria for significant left main coronary artery disease. FFR, fractional flow reserve; MLA, minimum lumen area. (Modified with permission from Johnson et al.<sup>33</sup>)

In particular, the FFR has been reportedly overestimated in the presence of diffuse disease of the LAD and the LCx and underestimated in cases of significant lateral branch disease.<sup>30</sup> Therefore, in the presence of concomitant distal branch disease, measuring the FFR during controlled retrieval can be useful.<sup>30</sup>

Regarding the pathological threshold, it seems that delaying the PCI with FFR values  $> 0.8$  is safe.<sup>31</sup> Although the value of other pressure guidewire indices that don't require hyperemia like the instantaneous wave-free ratio (iFR) has not been fully assessed in the LMCA, a study proved that using the iFR to delay the revascularization of the LMCA is safe.<sup>32</sup> Currently, the multicenter clinical trial iLITRO (NCT03767621) is being conducted in Spain. This trial will probably shed light on the utility of the iFR and its pathological threshold in the management of LMCA lesions.

#### Integrating different techniques

Integrating the IVUS and the pressure guidewire in the assessment of the LMCA of angiographically dubious severity is advised as stated by an international consensus document from the European

Association of Percutaneous Cardiovascular Interventions<sup>33</sup> (figure 4). Therefore, in ambiguous LMCA lesions, MLAs  $> 6 \text{ mm}^2$  would be indicative of no revascularization, MLAs  $< 4.5 \text{ mm}^2$  to  $5 \text{ mm}^2$  would be indicative of revascularization, and MLAs between  $4.5 \text{ mm}^2$  to  $6 \text{ mm}^2$  would recommend the use of the FFR/iFR indices before making any decision.

### REVASCULARIZATION OF THE LEFT MAIN CORONARY ARTERY

#### Surgical revascularization

CABG has been the standard of care for patients with LMCA disease since traditional clinical trials confirmed its prognostic benefit in patients randomized to surgery vs medical therapy.<sup>5</sup> The CASS registry reported a 4-year survival rate in 88% of operated patients compared to 63% in non-revascularized patients.<sup>34</sup> Other studies confirmed that the mortality rate dropped to 65% with surgery.<sup>35</sup> This allows a complete revascularization regardless of the characteristics of proximal lesion and technical advances facilitate faster procedures without having to use extracorporeal blood pumps. The main setback is still the non-negligible peri and postoperative morbidity and mortality. Some studies have reported a mortality rate of between 5.5% to 8.5%, a need for ischemia-guided revascularization of 7.1% to 9.4%, and a rate of stroke of 3.1% to 5.1% at the 3-year follow-up.<sup>36</sup>

#### Percutaneous revascularization

The arrival of stents improved the results of PCI on the LMCA significantly. However, at the beginning, conventional stents fared worse compared to surgery with mortality rates of 14%, a left ventricular ejection fraction (LVEF)  $> 40\%$  and 78%, and a LVEF  $< 40\%$  at the 9-month follow-up.<sup>37</sup> With the arrival of drug-eluting stents, the rates of restenosis and adverse events dropped low enough to be able to compare PCI to CABG,<sup>38-41</sup> with event-free survival rates at the 1-year follow-up of 98% in patients with LVEF  $< 40\%$ .<sup>38</sup> In patients considered non-eligible for surgery (EuroSCORE  $> 6$  or Parsonnet  $> 15$ ), the mortality and survival rates without major adverse cardiovascular events were 3.5% and 75.3%, respectively, at the 6-month follow-up.<sup>42</sup> These studies already showed that the PCIs performed on the ostial and mid-portions of the LMCA seemed to have a better prognosis compared to those performed on the distal LMCA or that involved bifurcation. The arrival of new antiproliferative drugs, the development of better devices, and the use of new techniques and strategies to treat bifurcation improved results, efficacy, and the good prognosis of the PCIs performed on the LMCA in experienced centers.

#### Surgical vs percutaneous revascularization

Six landmark randomized clinical trials have compared percutaneous and surgical strategies (table 1). The first ones (LE MANS,<sup>43</sup> SYNTAX,<sup>44</sup> Boudriot et al.<sup>45</sup> and PRECOMBAT<sup>46</sup>) were conducted with first-generation drug-eluting stents and reported similar rates of a composite of death, infarction, and stroke for both strategies. The main differences were a higher rate of strokes in the CABG group and a higher rate of new revascularizations after the PCI. The two most recent clinical trials conducted so far, the EXCEL and NOBLE, used second-generation drug-eluting stents and included large cohorts of patients with less complex atherosclerotic disease, which may be indicative of the actual clinical practice.<sup>16,47</sup> The difference in results obtained by these studies was very controversial; differences were reported in the definition of endpoint and periprocedural infarction as possible determinants. Actually, unlike the EXCEL, the NOBLE trial excluded periprocedural infarction

**Table 1.** Main comparative studies between percutaneous and surgical revascularization

Study	Year	n	Mean SYNTAX score	Distal LMCA lesions	Type of stent	Endpoint (PCI vs CABG)	Secondary endpoints (PCI vs CABG)
LE MANS <sup>43</sup>	2008	105	n/a	58%	Conventional, first-generation covered stents	Change of LVEF at the 1-year follow-up: 3.3% ± 6.7% vs 0.5% ± 0.8%; <i>P</i> = .047	<ul style="list-style-type: none"> <li>Death, stroke, AMI or need for revascularization at the 10-year follow-up: 2.2% vs 62.5%; <i>P</i> = .42</li> <li>Death at the 10-year follow-up: 21.6% vs 30.2%; <i>P</i> = .41</li> <li>Stroke at the 10-year follow-up: 4.3% vs 6.3%; <i>P</i> = .58</li> <li>AMI at the 10-year follow-up: 8.7% vs 10.4%; <i>P</i> = .68</li> <li>Need for revascularization at the 10-year follow-up: 26.1% vs 31.3%; <i>P</i> = .39</li> </ul>
SYNTAX LM <sup>44</sup>	2010	705	30	61%	Taxus	Death, stroke, AMI or need for revascularization at the 1-year follow-up: 15.8% vs 13.6%; <i>P</i> = .44	<ul style="list-style-type: none"> <li>Death, stroke, AMI or need for revascularization at the 5-year follow-up: 36.9% vs 31%; <i>P</i> = .12</li> <li>Death/stroke/AMI at the 5-year follow-up: 19% vs 20.8%; <i>P</i> = .57</li> <li>Death at the 5-year follow-up: 12.8% vs 14.6%; <i>P</i> = .53</li> <li>Stroke at the 5-year follow-up: 1.5% vs 4.3%; <i>P</i> = .03</li> <li>AMI at the 5-year follow-up: 8.2% vs 4.8%; <i>P</i> = .10</li> <li>Need for revascularization at the 5-year follow-up: 26.7% vs 15.5%; <i>P</i> &lt; .001</li> </ul>
Boudriot et al. <sup>45</sup>	2011	201	23	72%	Cypher	Death, AMI or need for revascularization at the 1-year follow-up: 19.0% vs 13.9%; <i>P</i> for non-inferiority = .19	<ul style="list-style-type: none"> <li>Death or AMI at the 1-year follow-up: 5% vs 7.9%; <i>P</i> for non-inferiority &lt; .001</li> <li>Death at the 1-year follow-up: 2% vs 5%; <i>P</i> for non-inferiority &lt; .001</li> <li>AMI at the 1-year follow-up: 3% vs 3%; <i>P</i> for non-inferiority = .002</li> <li>Need for revascularization at the 1-year follow-up: 14% vs 5.9%; <i>P</i> for non-inferiority = .35</li> </ul>
PRECOMBAT <sup>46</sup>	2011	600	25	64%	Cypher	Death, stroke, AMI, ID-TLR at the 1-year follow-up: 8.7% vs 6.7%; <i>P</i> for non-inferiority = .01	<ul style="list-style-type: none"> <li>Death, stroke, AMI or ID-TLR at the 5-year follow-up: 17.5% vs 14.3%; <i>P</i> = .26</li> <li>Death, stroke, or AMI at the 5-year follow-up: 8.4% vs 9.6%; <i>P</i> = .66</li> <li>Death at the 5-year follow-up: 5.7% vs 7.9%; <i>P</i> = .32</li> <li>Stroke at the 5-year follow-up: 0.7% vs 0.7%; <i>P</i> = .99</li> <li>AMI at the 5-year follow-up: 2% vs 1.7%; <i>P</i> = .76</li> <li>Need for revascularization at the 5-year follow-up: 13% vs 7.3%; <i>P</i> = .02</li> </ul>
EXCEL <sup>16</sup>	2017	1905	21	81%	Xience	Death, stroke or AMI at the 3-year follow-up: 15.4% vs 14.7%; <i>P</i> for non-inferiority = .02; <i>P</i> for superiority = .98.	<ul style="list-style-type: none"> <li>Death, stroke, AMI or need for revascularization at the 3-year follow-up: 3.1% vs 19.1%; <i>P</i> for non-inferiority = .01</li> <li>Death at the 3-year follow-up: 8.2% vs 5.9%; <i>P</i> = .11</li> <li>Stroke at the 3-year follow-up: 2.3% vs 2.9%; <i>P</i> = .37</li> <li>AMI at the 3-year follow-up: 8.0% vs 8.3%; <i>P</i> = .64</li> <li>Need for revascularization at the 3-year follow-up: 12.6% vs 7.5%; <i>P</i> &lt; .001</li> </ul>
NOBLE <sup>38</sup>	2017	1201	22	81%	BioMatrix Other drug-eluting stents	Death, stroke, periprocedural AMI or need for revascularization at the 5-year follow-up: 29% vs 19%; <i>P</i> = .0066.	<ul style="list-style-type: none"> <li>Death at the 5-year follow-up: 12% vs 9%; <i>P</i> = .77</li> <li>Stroke at the 5-year follow-up: 5% vs 2%; <i>P</i> = .073</li> <li>Periprocedural AMI at the 5-year follow-up: 7% vs 2%; <i>P</i> = .004</li> <li>Need for revascularization at the 5-year follow-up: 16% vs 10%; <i>P</i> = .032</li> </ul>

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; ID-TLR, ischemia-driven target lesion revascularization; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; N/A, not applicable; PCI, percutaneous coronary intervention.

from the composite of primary events although its inclusion is recommended by the Academic Research Consortium and is part of the universal definition of myocardial infarction. It has been confirmed that periprocedural infarction is associated with a worse prognosis.<sup>16</sup> Also, the large difference seen in the rate of stent thrombosis (0.7% in the EXCEL trial vs 3% in the NOBLE) is indicative of the possible influence of the different type of stent used in each of these studies.

In general, the results of these studies suggest that when complete revascularization is achieved, both surgery and the PCI achieve similar results for the composite of death, infarction, and stroke at the 5-year follow-up.<sup>48</sup> However, there is an early benefit for the PCI in terms of periprocedural infarction and stroke that is

compensated by the higher risk of infarction at the long-term follow-up. The risk of requiring a new revascularization is evenly higher in patients treated with PCI compared to surgical patients.

Another issue that should be taken into consideration is the correlation between the results of the PCI and the SYNTAX score. The first clinical trials conducted on this topic already suggested that higher scores probably led to a better prognosis with CABG. Some meta-analyses have described that, overall, long-term cardiovascular mortality seems to be directly proportional to the angiographic complexity of LMCA disease. Therefore, patients with low SYNTAX scores had a better prognosis with PCI compared to patients with higher scores. Also, patients with high SYNTAX scores showed a non-significant tendency towards a higher 10-year survival rate

**Table 2.** Indication, level, and class of evidence of significant left main coronary artery disease according to the clinical practice guidelines established in 2018 by the European Society of Cardiology<sup>8</sup>

Left main coronary artery disease	Surgery		PCI	
	I	A	I	A
Low SYNTAX score (0-22)	I	A	I	A
Intermediate SYNTAX score (23-32)	I	A	IIa	A
High SYNTAX score ( $\geq 33$ )	I	A	III	B

with surgery compared to PCI.<sup>49,50</sup> One of the main setbacks of this score is that it only includes anatomical variables. Currently, there are other scales including angiographical, clinical, and even functional variables, but their utility as long-term prognostic markers of LMCA disease has not been properly studied yet.<sup>51</sup>

The current clinical practice guidelines on coronary revascularization<sup>16</sup> establish the indication for CABG or PCI based on the SYNTAX score (table 2). If complexity is low, the PCIs performed on the LMCA have the same indication as surgery (IA). The PCI is an alternative to surgery in patients with intermediate SYNTAX scores (IIa A) and greater evidence is needed in patients with high SYNTAX scores before clearly recommending PCI.

### Patient selection

The European clinical practice guidelines highlight the importance of the heart team in the decision-making process on which revascularization strategy should be used in stable patients with LMCA disease. This team should include clinical and interventional cardiologists and cardiac surgeons. However, in emergent procedures, surgery is not often a viable option due to the delay involved and the progressive worsening of prognosis in relation to ischemic time. Pappalardo et al.<sup>52</sup> described in-hospital mortality rates of 21% (basically due to multiorgan failure) in patients with acute myocardial infarction and acute occlusion of the LMCA. However, patients who survived hospitalization and were treated with PCI had a good prognosis with a 1-year survival rate of 89.5%.

In the remaining cases it would be desirable to avoid performing interventional procedures *ad hoc* after the diagnostic procedure. The different revascularization options should be discussed with the clinical cardiologist, the cardiac surgeon, and especially with the patient. The latter should also be objectively informed of the theoretical pros and cons of every technique and the specific results obtained by the treating center making him part of the decision-making process. Other clinical, anatomic and general factors should be taken into consideration too (table 3). Finally, if performing a PCI on the LMCA is considered the best option, the administration of the right premedication, assessment by the heart team, and procedural planning on the technique and materials that will be used are all associated with higher rates of success.

Since most clinical trials have been conducted in centers with coronary care units, performing PCIs on the LMCA in centers without these units has been controversial. However, since there is evidence of the good outcome of PCIs in centers without these units,<sup>53-55</sup> it is widely accepted that PCIs can be performed on the LMCA in these centers safely as long as an experienced medical team is in charge and the necessary technical equipment used. Also, the patient's informed consent needs to have been collected, and a previous protocol established for urgent transfers to hospitals with coronary care units in the hypothetical case that the patient may require urgent surgery.

**Table 3.** Factors impacting the modality of revascularization of the left main coronary artery

	In favor of PCI	In favor of CABG
General factors	<ul style="list-style-type: none"> <li>• Similar mortality</li> <li>• Safe in the short-term</li> <li>• Early recovery</li> <li>• Less invasive</li> </ul>	<ul style="list-style-type: none"> <li>• Similar mortality</li> <li>• Fewer revascularizations</li> <li>• Durability</li> <li>• Fewer spontaneous infarctions</li> </ul>
Clinical factors	<ul style="list-style-type: none"> <li>• Comorbidity: COPD, elderly, and frail, previous heart surgery, previous stroke, dialysis</li> <li>• Urgent revascularization</li> </ul>	<ul style="list-style-type: none"> <li>• Left ventricular systolic dysfunction</li> <li>• Concomitant valvular surgery</li> <li>• Impossibility of DAPT</li> <li>• Diabetes</li> </ul>
Anatomical factors	<ul style="list-style-type: none"> <li>• Ostial or mid-portion LMCA lesions</li> <li>• Isolated LMCA lesion</li> <li>• LMCA lesion and single-vessel disease</li> </ul>	<ul style="list-style-type: none"> <li>• LMCA lesion and 3-vessel disease</li> <li>• Complex lesions: calcified, very long, diffuse, previous restenosis</li> </ul>
Patients' preferences and needs		

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; LMCA, left main coronary artery; PCI, percutaneous coronary intervention.

### Operators and equipment

The PCIs performed on the LMCA should always be considered high-risk procedures. Actually, the experience of the operators is of paramount importance here. There is evidence that patients treated in high volume centers that perform procedures like this regularly have a better prognosis.<sup>56</sup>

The equipment should guarantee the proper assessment of the LMCA (IVUS, pressure guidewire). All kinds of materials that may be required to perform the angioplasty and handle all possible complications should be available too. Since it is a high-risk procedure, hemodynamic support devices and resources like the intra-aortic balloon pump and the Impella device (Abiomed, United States) are very important.

### ANGIOPLASTY OF THE LEFT MAIN CORONARY ARTERY

Prior to performing the procedure, it is essential to conduct a comprehensive analysis of the case to decide on the strategy, access route (radial or femoral), caliber of the introducer sheath (due to the presumable need for the double stenting technique, 7-Fr catheters via femoral access or "7 in 6-Fr" catheters via radial access are advised), and type of guide catheter. Although radial access has replaced femoral access in many cases, the PCIs performed on the LMCA are probably a niche where femoral access should be considered since obtaining the least support possible can be key here. Also, this access facilitates the use of larger caliber catheters and the possibility of quick hemodynamic support device implantation.

Damage to the distal LMCA or bifurcation complicates the procedure with more chances of needing 2 stents and a worse prognosis. Other factors associated with worse outcomes and prognoses are calcifications, smaller LMCA diameters, and the presence of non-ostial disease in the LAD or LCx.<sup>57</sup>

### Wiring and preparation of the lesion

The use of at least 2 angioplasty guidewires (for the 2 main vessels) will be the standard of use in the PCIs performed on the LMCA with notable exceptions like protected LMCA lesions if rotablation

is required or in some cases of isolated and ostial LMCA disease. Using 2 guidewires slightly changes the bifurcation angle, facilitates access to the lateral branch and maintains flow towards it. Using 2 guidewires also helps find this lateral branch in cases of occlusion. Actually, some authors advocate the use of the bailout technique with balloon when flow is compromised after stent implantation into the main vessel.<sup>58</sup> Predilatation of the main vessel should be avoided if both vessels have not been protected first due to the high risk of changing and moving the plaque, which could occlude the coronary ostium of a branch complicating further catheterizations.

The use of plaque bulking techniques (rotablation or laser, among other) to change the anatomy and facilitate the angioplasty can be considered. LMCA ostial lesions often consist of abundant calcification and large amounts of elastic muscle fibers, which is associated with a risk of elastic retraction of the lesion both after predilatation and stent implantation. On the other hand, the presence of fibrocalcific plaques can condition the use of cutting balloons as the first step and even rotablation, that has proven beneficial in angioplasties of bifurcated LMCAs prior to the implantation of drug-eluting stents.<sup>59,60</sup> When the lateral branch shows severe ostial or heavily calcified disease or access to it becomes complicated, predilatation with a non-compliant small-caliber balloon is advised.

### Stent selection

Two different scenarios should be looked into when choosing the right stent: whether only the LMCA or the bifurcation should be treated. Treating the LMCA may be justified only in cases of isolated ostial or mid-portion disease. In this situation, a stent of nominal size should be picked that should reproduce the size of the LMCA as much as possible. Another option would be to implant a stent of a smaller size and overexpand it with a high-pressure balloon of the right dimensions. Several platforms achieve large degrees of expansion without jeopardizing the integrity of its structure.<sup>61,62</sup> However, there is no clear evidence that stent overexpansion is a safe practice since it is subject to the suboptimal coverage of the intima layer due to metal-to-artery ratio reduction. Also, it can change the polymer or kinetics of the drug-eluting stent.

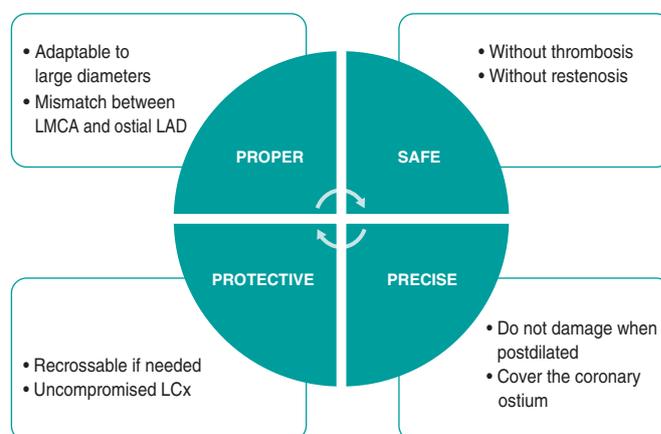
When the bifurcation should be treated, the stent implanted into the LMCA should cover the proximal portion of 1 of the 2 main vessels. Also, its size should match the proximal diameter of that main vessel. Another important aspect here is having to use the proximal optimization technique (POT) with a non-compliant balloon to adapt the stent proximal caliber to the LMCA. Recrossing towards the lateral branch or using the double stenting technique can be an option too.

Stents implanted into the LMCA are especially prone to proximal deformation because they are in continuous contact with the guide catheter, due to the need for using the POT, and because they scrape against other devices that come through after implantation.<sup>63</sup> Therefore, the resistance of every stent to longitudinal compression is a factor that should be taken into consideration during stent selection. Other fundamental characteristics that should be looked into when choosing the ideal stent to perform PCIs on the LMCA are the safety profile and precision provided by the stent (figure 5).

### Selection of the bifurcation technique

#### Non-complex bifurcation

When LMCA disease affects 1 bifurcation branch only or the LCx has a small caliber (< 2.5 mm), the best strategy is the provisional



**Figure 5.** Technical characteristics of the ideal stent to perform percutaneous coronary interventions on the left main coronary artery. LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery.

stenting technique with a single stent implanted from the LMCA towards the main vessel. In general, the LAD is the main vessel and only in some cases it would be the LCx. Afterwards, the use of the POT with a non-compliant balloon of the right size is routinely advised.

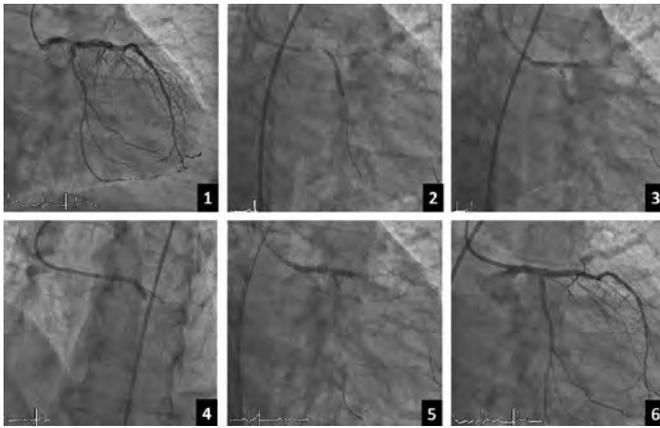
There are times when it is necessary to fully cover the length of the LMCA. In these cases, it is extremely important to be very precise when implanting the stent to treat the coronary ostium properly and avoid any significant stent protrusions into the aorta.

However, there is still controversy over whether it is necessary to always recross it towards the lateral branch and optimize it with the kissing balloon technique in the bifurcation after using the POT if the provisional stenting technique proves insufficient. The kissing balloon technique should be used with suboptimal final outcomes in the lateral branch, when the main vessel selected is the LCx, and when the future need for a PCI on the lateral branch cannot be discarded.<sup>4</sup>

#### Complex bifurcation

When disease affects both bifurcation branches significantly, the use of the double stenting technique should be considered. However, since different registries report that the rates of restenosis and new revascularizations are lower with the single stenting technique,<sup>38,64-66</sup> the early approach in many centers and in most complex bifurcations is often using the provisional stenting technique with the possibility of finishing using the double stenting technique, if necessary. With suboptimal results, the expert committee of the European Bifurcation Group recommends using double T stenting, the T and small protrusion (TAP) or the culotte technique as the bailout strategy after provisional stent implantation.<sup>67</sup> Once the second stent has been implanted into the lateral branch, individual dilatation in both branches is advised using non-compliant balloons to secure the ostial expansion of the stent of the LAD and the LCx followed by the kissing balloon technique. If it takes over a significant portion of the LMCA, a new proximal dilatation (re-POT) should be performed to optimize the result.

When the double stenting technique is used right away, this selection is often based on different factors: anatomical and angiographic variables, location of the lesion, intracoronary imaging modalities,



**Figure 6.** Example of double kissing crush stenting technique. 1: baseline angiography. 2: stent implanted towards the circumflex artery. 3: first kissing balloon inflation. 4: stent implanted towards the left anterior descending coronary artery. 5: second kissing balloon inflation. 6: angiography with final outcome.

damage to the LAD and LCx coronary ostia, clinical situation, and even the operator's skills in each technique. To this day, we still do not have enough evidence to know which is the best technique. Several algorithms and therapeutic strategies have been suggested based on the parameters mentioned above like the ones proposed by Fajadet et al.<sup>68</sup> or De Maria and Banning.<sup>69</sup> However, none of them has come out victorious maybe due to the huge variability of clinical and angiographic situations and the different experience reported by the different centers. The crush, modified crush, and culotte techniques are still the most widely used today. The double kissing crush technique seems to have good results as it is associated with a lower rate of target lesion failure or stent thrombosis at the 3-year follow-up (figure 6).<sup>70</sup>

### Result optimization

The IVUS, the OCT, and the guidewire pressure optimize the results of the angioplasties performed on the LMCA. There is evidence that the suboptimal result of these angioplasties performed on the LMCA is associated with a worse clinical prognosis.<sup>71</sup> Although the OCT shows the aforementioned limitations (limited penetration depth compared to the IVUS, possible inadequate filling), the truth is that both imaging modalities can detect significant findings like stent underexpansion, strut malapposition, border dissection, and degree of lateral branch involvement, which could require result optimization.

The imaging modality we have more evidence of in the optimization of angioplasty results of the LMCA is also IVUS that has an associated net clinical benefit.<sup>26,72,73</sup> The protocolized use of IVUS for optimization purposes seems to additionally improve the prognosis of these patients.<sup>30</sup> However, the ongoing clinical trial OPTIMAL (NCT04111770, Optimization of left main percutaneous coronary intervention with intravascular ultrasound randomized controlled trial), that will be recruiting 800 patients, will shed light on the prognostic effect of using IVUS in PCIs performed on the LMCA compared to angiography alone.

On the other hand, several studies have been conducted on the pressure guidewire and its value as a predictor of events in cases of provisional stent implantation by estimating the flow reserve towards the lateral branch.<sup>74</sup>

## MEDICAL THERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION AND FOLLOW-UP

Although angioplasties performed on bifurcations are a predictor of events,<sup>54,75</sup> currently, there is no evidence available to recommend a specific antiplatelet therapy in angioplasties performed on the LMCA. Therefore, treatment should be administered based on each patient's clinical presentation and ischemic and hemorrhagic risk profile. However, we should bear in mind that implanting a stent into the LMCA and performing a PCI on a bifurcation, especially when 2 stents are used, are criteria that add more ischemic risk to the profile of these patients.<sup>76-79</sup>

The reappearance of suggestive symptoms or documented ischemia justifies an invasive approach. The review coronary angiography performed at the 1-year follow-up in patients with angioplasty on the LMCA has a level IIB C indication according to European clinical practice guidelines,<sup>16</sup> and is not justified in all cases. The randomized clinical trial ANGELINE (Angiographic evaluation of left main coronary artery intervention) (NCT04604197) will bring more evidence on the potential advantages of the systematic angiographic review.

## CONCLUSIONS

The assessment of LMCA lesions is complex, which is why acquiring different angiographic views and using imaging modalities like IVUS or pressure guidewire is advised.

Currently, the SYNTAX score, the possibility of complete revascularization, and the patient's comorbidities are the main criteria that should guide the selection of percutaneous or surgical revascularization.

Regarding the PCIs performed on LMCA lesions, there are 2 different categories: isolated ostial or mid-portion LMCA lesions (technically easier to treat and with an excellent prognosis), and bifurcation lesions (with a more complex approach).

Optimizing the PCIs performed on the LMCA is essential using intravascular ultrasound and techniques and stents backed by the highest level of evidence in this setting followed by the proper pharmacological cover.

In conclusion, there is no doubt that PCIs performed on LMCA lesions crossed their own particular Rubicon a long time ago. *Alea jacta est* (which is Latin for "the die is cast") and, in the future, new randomized clinical trials on surgical or percutaneous revascularization and technical advances in both modalities will favor one over the other. In the meantime, revascularizations based on every individual patient and in close collaboration with the heart team should guide the routine practice of clinical cardiologists and interventional and cardiac surgeons.

## FUNDING

No funding declared.

## CONFLICTS OF INTEREST

The authors declared no conflicts of interest regarding the content of this manuscript.

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# Cerebral embolic protection device in TAVI after the REFLECT II clinical trial: does it change our strategy?

Luis Nombela-Franco\* and Gabriela Tirado-Conte

Instituto Cardiovascular, Hospital Clínico San Carlos, Instituto de Investigación del Hospital Clínico San Carlos (IdISSC), Madrid, Spain



## ABSTRACT

The occurrence of strokes after transcatheter aortic valve replacement is one of the most devastating complications. It has a multifactorial etiology and nearly half of the events occur during or immediately after the procedure. The use of periprocedural embolic protection devices to stop the emboli from reaching the cerebral vessels is a promising preventive strategy to reduce this complication. However, we still lack solid evidence supporting its systematic use. The REFLECT II clinical trial is a new randomized clinical trial that assessed the safety and efficacy profile of an embolic protection device in patients undergoing transcatheter aortic valve replacement.

**Keywords:** TAVI. Stroke. Embolic protection device. Prevention.

## Protección cerebral en el TAVI tras el estudio REFLECT II: ¿cambia nuestra estrategia?

## RESUMEN

El ictus después de un implante percutáneo de válvula aórtica es una de las complicaciones más devastadoras. Su etiología es multifactorial y en torno a la mitad de los casos ocurren durante el procedimiento o en el periodo inmediatamente posterior. El uso de dispositivos de protección embólica durante la intervención para prevenir que los émbolos alcancen los vasos cerebrales es una estrategia preventiva muy prometedora para reducir esta complicación. Sin embargo, la evidencia sólida que apoye su uso sistemático todavía es escasa. El estudio REFLECT II es un estudio aleatorizado que evalúa la seguridad y la eficacia de un dispositivo de protección embólica en pacientes que reciben un implante percutáneo de válvula aórtica.

**Palabras clave:** TAVI. Ictus. Sistemas de protección embólica. Prevención.

## Abbreviations

**CEPD:** cerebral embolic protection device. **TAVI:** transcatheter aortic valve implantation.

## INTRODUCTION

The occurrence of strokes after transcatheter aortic valve implantation (TAVI) is, if not the most significant, one of the most feared and devastating complications because of its impact on the patients' quality of life and mortality. Although it is not very common (~3%) its incidence rate has not gone down parallel to that of other complications with the development of this technique and the arrival of new devices despite the efforts and preventive measures adopted.<sup>1</sup> Several studies using magnetic resonance imaging and transcranial

Doppler ultrasound have proven that most strokes that occur after TAVI have an embolic origin from the aortic valve itself<sup>2</sup> and at least half of them are closely related to the procedure.<sup>3</sup> Therefore, cerebral embolic protection devices (CEPD) are used as a preventive strategy, often a mechanical barrier, to protect the cerebral vascular territory during the intervention. The results of the REFLECT II clinical trial (NCT 02536196) have recently been published. It is a randomized trial that assesses the safety and efficacy profile of the TriGUARD 3 CEPD (Keystone Heart Ltd, Caesarea, Israel) to reduce clinical events and minimize brain injuries during TAVI.<sup>4</sup>

\* **Corresponding author:** Instituto Cardiovascular, Hospital Clínico San Carlos, Instituto de Investigación del Hospital Clínico San Carlos (IdISSC), Prof. Martín Lagos s/n, 28040 Madrid, Spain.

E-mail address: [luisnombela@yahoo.com](mailto:luisnombela@yahoo.com) (L. Nombela-Franco).

Received 4 November 2020. Accepted 19 November 2020. Online: 11-01-2021.

<https://doi.org/10.24875/RECICE.M20000192>

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**Table 1.** Randomized clinical trials with cerebral embolic protection devices

Study	Year	Device	Total number of patients/ total number with CEPDs	Primary endpoint	Main results
EMBOL-X, Wendt et al. <sup>5</sup>	2015	EMBOL-X (Edwards Lifesciences, United States)	30/14	New brain injuries Volume of injuries	– No differences in new injuries (57% vs 68%; $P = .70$ ) or injury volume (88 mm <sup>3</sup> vs 168 mm <sup>3</sup> ; $P = .27$ )
DEFLECT III, Lansky et al. <sup>5</sup>	2015	TriGuard (Keystone Heart Ltd, Israel)	85/46	Safety and efficacy Safety endpoint: death, stroke, life-threatening hemorrhage, acute kidney injury (stage 2-3), major vascular complication	– Technical success rate: 88.9% – No differences in safety endpoint (21.7% vs 30.8%; $P = .34$ ) – Tendency to more new brain injuries (26.9% vs 11.5%) and less neurological deficit in the NIHSS (3.1% vs 15.4%) in the device group
MISTRAL-C, Van Mieghem et al. <sup>7</sup>	2016	SENTINEL (Boston Scientific, United States)	65/32	New brain injuries	– Success rate: 94%; material captured: 100% – No differences in the percentage of patients with new brain injuries – Smaller injury volume (95 mm <sup>3</sup> vs 197 mm <sup>3</sup> ; $P = .17$ ) and fewer patients with multiple injuries (0% vs 20%) in the device group
CLEAN-TAVI, Haussig et al. <sup>8</sup>	2016	SENTINEL (Boston Scientific, United States)	100/50	Number and volume of brain injuries	– Fewer brain injuries (4 vs 10; $P = .001$ ) in the device group – Smaller injury volume (242 mm <sup>3</sup> vs 527 mm <sup>3</sup> ; $P = .001$ ) in the device group – No differences in clinical events
SENTINEL, Kapadia et al. <sup>9</sup>	2017	SENTINEL (Boston Scientific, United States)	363/244	Clinical safety and efficacy (MACE) of CEPD during TAVI	– Success rate: 100%; material captured: 99% – No differences in clinical events (MACE, 7.3% vs 9.9%; $P = .41$ ) or in the volume of new brain injuries (103 mm <sup>3</sup> vs 178 mm <sup>3</sup> ; $P = .33$ ) – Lower incidence rate of early stroke (3.0% vs 8.2%; $P = .05$ ) in the device group
REFLECT II, Moses <sup>4</sup>	2020	TriGUARD 3 (Keystone Heart Ltd, Israel)	179/121	Safety endpoint (composite) after 30 days Efficacy endpoint (death or stroke, neurological deterioration, lack of brain injuries and volume) after 30 days	– Higher non-significant rate of the safety endpoint (15.9% vs 7.0%; $P = .11$ ) in the device group – Similar rate in the efficacy endpoint: • Mortality or stroke (9.8% vs 6.7%; $P = .47$ ) • Worse NIHSS (14.1% vs 7.6%; $P = .18$ ) • Brain injuries (85.0% vs 84.9%; $P = 1.00$ ) • Brain injury volume (215 mm <sup>3</sup> vs 188 mm <sup>3</sup> ; $P = .405$ )

CEPD, cerebral embolic protection device; MACE, major adverse cardiovascular events; NIHSS: National Institute of Health Stroke Scale; TAVI: transcatheter aortic valve implantation.

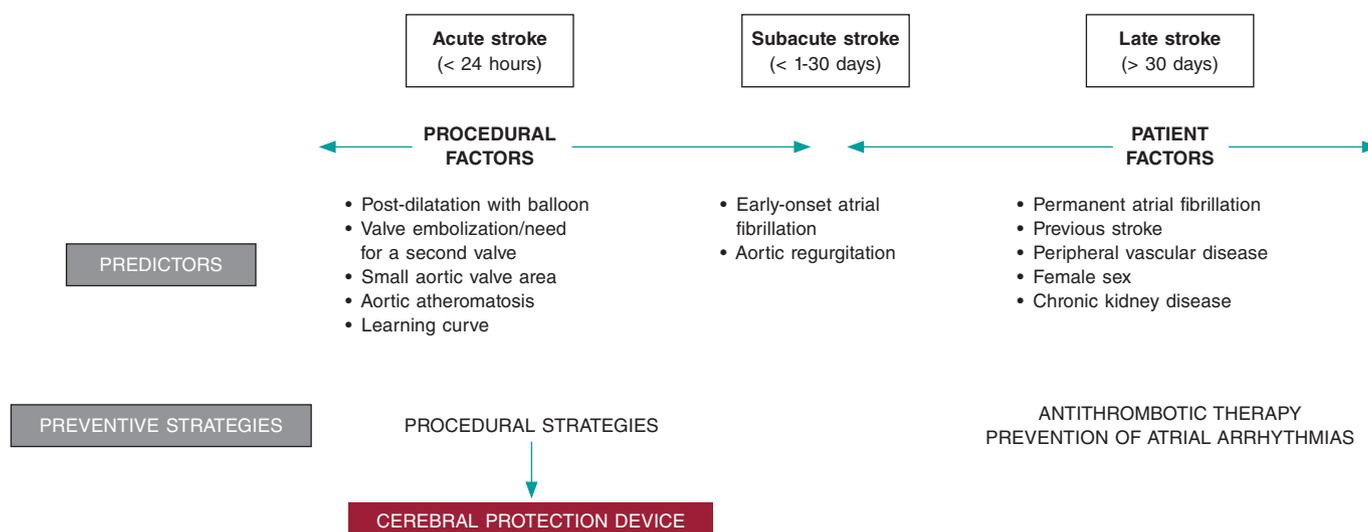
## THE REFLECT II CLINICAL TRIAL

It is a randomized clinical trial in a 2:1 allocation ratio (device vs control) with an estimated sample size of 225 patients. However, since it was completed prematurely it eventually included 179 patients (121 in the device group and 58 in the control group). The safety primary endpoint was a composite of death, stroke, life-threatening hemorrhage, acute kidney injury stage 2 or 3, major vascular complications or valvular reinterventions after 30 days. The efficacy endpoint by hierarchical order included death or stroke after 30 days, neurological deterioration according to the NIHSS (National Institute of Health Stroke Scale), lack of brain injuries, and total volume in the magnetic resonance imaging performed 2 to 5 days after the procedure. To study the safety primary endpoint, the data of 41 patients treated with the device in the early recruitment phase (162 vs 58) were included. To study the efficacy primary endpoint 63 patients of the control group from the previous DEFLECT III clinical trial (NCT02070731)<sup>5</sup> that also studied this device were included (121 vs 121 control patients). The pre-specified per protocol analysis of efficacy was established in patients with complete coverage of the 3 sections of their brain-stems, exclusively, which was finally achieved in 62 of them (59.3%). The baseline characteristics were well-balanced between both groups except for a higher percentage of patients with a past medical history of stroke in the device group. Although there were

not statistically significant differences in the safety primary endpoint, the percentage of events was higher in the device group (15.9% vs 7.0%;  $P = .11$ ) mainly due to a higher rate of life-threatening hemorrhages (5.7% vs 0%;  $P = .12$ ) and major vascular complications (7.0% vs 0%;  $P = .04$ ) associated with TAVI not with CEPD. The efficacy endpoint was also similar in both groups in all the events studied: mortality or stroke after 30 days (9.8% vs 6.7% in the control group;  $P = .475$ ), worse NIHSS score (14.1% vs 7.6%;  $P = .176$ ), brain injuries (85.0% vs 84.9%;  $P = 1.000$ ), and brain injury volume (215.4 mm<sup>3</sup> vs 188.1 mm<sup>3</sup>;  $P = .405$ ) (table 1). The overall brain injury volume of patients with complete cerebral protection was smaller in the pre-specified protocol analysis (145.7 mm<sup>3</sup> vs 188.1 mm<sup>3</sup>), although it was not statistically significant.

## REFLECTIONS ON THE REFLECT II CLINICAL TRIAL

Strokes post-TAVI are a complex problem with a multifactorial etiology. Several factors impact different moments during and after TAVI such as patient factors like atrial arrhythmias or previous cerebrovascular disease, procedural risk factors like embolisms or hemodynamic instability, and antithrombotic therapy (figure 1). CEPDs can reduce procedural strokes. Six randomized clinical trials have been conducted so far (including the DEFLECT III and the REFLECT II) with CEPDs in patients treated with TAVI (table 1).<sup>4-9</sup>



**Figure 1.** Risk factors for stroke after TAVI and possible preventive strategies.

This new trial confirmed the same limitations already reported by previous randomized clinical trials on CEPDs since it also included a small number of patients and rare events. Therefore, it did not have the statistical power required to study differences in clinical trials. Most primary endpoints went from surrogate endpoints to findings made by the imaging modalities (in general, rate and volume of new brain injuries in the magnetic resonance imaging).<sup>10</sup>

The REFLECT II is a complex clinical trial regarding design and analysis with different population groups to study safety and efficacy endpoints and several interconnected factors that can mask the possible benefits derived from the device. As it happened in previous trials, the implantation success rate was very high (> 90%) and without serious associated complications. We should mention that since this is a preventive strategy, safety should be of paramount importance and the number of complications associated with its use should be close to none. Regarding efficacy, we should consider that the percentage of patients with complete cerebral coverage was low (~ 60%) even though the device was designed to cover the 3 supra-aortic trunks. Whether the previous analysis of the CT scan performed at aortic arch and supra-aortic trunk level can contribute to a better selection of patients eligible for this device is still to be elucidated. In other studies, the percentage of patients with material captured inside the filters of the SENTINEL device (Boston Scientific, Corp., United States) has been systematically high (> 90%). Another limitation of this study is that the amount and nature of the embolized material remain unknown since the design of the device acts as a deflector stopping embolic material from entering the supra-aortic trunks. Finally, the neutral results obtained from analyzing the 4 efficacy endpoints recommend a selective use of CEPDs in patients of high-risk of sustaining embolic events (eg, heavily calcified aortic valve or bicuspid aortic valve, valve-in-valve procedures or previous strokes). We should mention that several observational studies with historic cohort comparison<sup>11</sup> and risk-propensity score-based registries<sup>12</sup> have confirmed a lower overall rate of in-hospital ischemic strokes (or within the first 72 hours). However, these studies have possible biases and limitations. Therefore, randomized clinical trials with enough statistical power are needed to be able to detect clinical differences and establish an ultimate indication for this preventive measure. Two ongoing randomized clinical trials [PROTECTED TAVR [NCT04149535] and BHF PROTECT-TAVI [ISRCTN16665769]] with large sample sizes and systematic evaluations by a neurologist will shed light on all these issues. The participation of neurologists to assess patients is an essential aspect in the design

of these studies that should help non-specialists find «silent» clinical events with possible neurological deterioration with clinical implications in the mid- and long-term follow-up, particularly of young patients with longer life expectancies.

The importance and impact of strokes post-TAVI is undisputed, and the ultimate goal should be to reduce their incidence rate. In most patients, the procedure itself causes the migration of embolic material towards the cerebral territory. The current evidence behind CEPDs comes from randomized clinical trials and is based on reducing the volume of silent brain injuries as a surrogate marker of cerebral disease. The clinical benefit of these devices relies on observational studies only, which is why their universal vs selective use to reduce clinical events is still under discussion. Future larger clinical trials with proper methodologies and enough statistical power are needed to find differences in clinical events. As a matter of fact, they will eventually set the pace for CEPDs in the prevention of strokes after TAVI.

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

L. Nombela-Franco is a proctor for Abbott Vascular and has received funding for his consulting work for Abbott Vascular, and Boston Scientific.

G. Tirado-Conte has reported no conflicts of interest.

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## Debate: Refractory angina. The Reducer device as a new therapeutic approach. Perspective from the clinic



### *A debate: Angina refractaria. El dispositivo Reducer como nueva alternativa terapéutica. Visión desde la clínica*

José R. González-Juanatey<sup>a,b,\*</sup>

<sup>a</sup> Servicio de Cardiología y Unidad de Cuidados Intensivos Cardiológicos, Hospital Clínico Universitario de Santiago de Compostela, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, A Coruña, Spain

<sup>b</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

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**QUESTION:** How often do you see nonrevascularizable patients with refractory angina today?

**ANSWER:** The prevalence of this complex entity has gone up thanks to the better prognosis of patients with ischemic heart disease due to changes of lifestyle, drugs, and coronary interventions. Among these, surgical revascularization and, in particular, percutaneous coronary interventions increase survival in the acute coronary syndrome setting. For its diagnosis, reversible myocardial ischemia that cannot be controlled with a combination of medical therapy, angioplasty, and myocardial revascularization surgery needs to be documented first. Although it is often due to severe stenosis of epicardial coronary arteries, it can be seen in non-atherosclerotic coronary artery diseases (spasm, microvascular disease, etc.) and myocardial diseases within the heart-brain axis including myocardial metabolism, and coronary microcirculation. Also, in the perception of pain until neuromodulatory pathways that can also be therapeutic targets in this clinical condition. Therefore, obstructive coronary disease is only one of the possible phenotypes in patients (women in particular) with angina or myocardial ischemia. There is no clear evidence associated with a higher mortality rate; however, the quality of life of rehospitalized patients is worse and health costs are higher.<sup>1,2</sup> Former studies<sup>1,3</sup> describe a prevalence of refractory angina (RA) of 5% to 10% in patients with chronic coronary syndromes; these studies often focus on nonrevascularizable patients with angina on non-optimized antianginal drug therapy excluding patients without stenosis of epicardial coronary arteries. These studies do not report either on possible cases of RA due to coronary microvascular dysfunction that actually seem to be most of the patients with RA.

**Q.:** Please explain to us briefly the diagnostic approach used for screening etiologies different from ischemia due to epicardial coronary artery disease such as microvascular ischemia, vasospasm or even noncardiac causes.

**A.:** Beyond the traditional idea of ischemia-angina where imbalance between myocardial oxygen supply and demand is the main pathophysiological mechanism, we should admit that, in many cases, ischemia is not followed by angina and that many ischemic patients have a constellation of symptoms that may worsen their quality of life.

To improve quality of life is the primary endpoint in patients with angina in the chronic ischemic heart disease setting since its presence or myocardial ischemia do not seem to increase mortality. In this sense, rather than making us question the prognostic value of systematic myocardial revascularization in patients with angina in the chronic coronary syndrome setting, the recent results of the ISCHEMIA clinical trial<sup>4</sup> should make us think of the need to conduct routine tests to detect ischemia. In this study, over 20% of the selected patients with angina/ischemia could not be randomized eventually for the lack of significant coronary stenoses. In this sense, it has been reported that nearly 40% of the patients with angina without coronary stenosis showed vasomotor response disturbances in coronary micro and macrocirculation. On the other hand, we should transcend the idea of hypoperfusion as the cause of angina and myocardial ischemia; the metabolic alterations of cardiomyocytes related to hypoxia can be due to peaks in the ischemia threshold as the adaptation of metabolism to hypoperfusion or decrease in metabolic situations of use of substrates of lower energy efficiency.<sup>1</sup>

\* **Corresponding author:** Servicio de Cardiología, Hospital Clínico Universitario, Travesía de A Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain. E-mail address: [jose.ramon.gonzalez.juanatey@sergas.es](mailto:jose.ramon.gonzalez.juanatey@sergas.es) [J.R. González-Juanatey].

Online: 22-12-2020.

<https://doi.org/10.24875/RECICE.M20000176>

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The diagnosis of microvascular angina is often achieved after discarding significant epicardial coronary stenosis; since segmental contractility alterations are rare on these patients' exercise echocardiography, we need specific techniques to assess coronary circulation/perfusion and confirm the diagnosis.

I'd like to add that angina, including RA, in the absence of significant coronary stenosis cannot be a diagnosis of exclusion. New protocols are needed to confirm not only the clinical signs and ischemia, but also the pathophysiological mechanisms involved. Only then the diagnostic and therapeutic strategy will be complete for each particular case.

**Q.:** Which are the best pharmacological strategies to treat refractory angina and how should drug escalation be done?

**A.:** I think that changing our management of nonrevascularizable patients with RA to improve their clinical situations is a priority. These patients often remain in some sort of diagnostic and therapeutic limbo. Disease exists beyond the possibilities of coronary dilatation. Therefore, only by knowing the pathophysiological substrate of angina in each particular case, we'll be able to establish protocols including new therapeutic, pharmacological or other modalities.<sup>5</sup>

The standard of care for the management of patients with RA is to discard and treat secondary causes by optimizing medical therapy and rehabilitation. These patients should be treated with antianginal drug therapy, beta-blockers, dihydropyridine calcium channel blockers, and sustained-release nitrates. In cases of persistent angina, ivabradine can be used in patients who are in sinus rhythm with heart rates  $\geq 70$  beats/minute. Also, the possible combination of ranolazine, trimetazidine, and nicorandil is another antianginal therapeutic option. Patients with RA without obstructive coronary lesions benefit from a better control of their angina when therapy is based on every particular patient and the results of intracoronary functional tests. Patients with microvascular angina, reduced coronary flow reserve, increased resistances, and a negative acetylcholine testing respond positively to treatment with beta-blockers, angiotensin-converting enzyme inhibitors, and statins. They are also responsive to rehabilitation programs to control their risk factors, physical exercise, and weight loss. Patients with EKG changes and angina as a response to the acetylcholine testing but without epicardial coronary spasm should be treated as if they had vasospastic angina: dihydropyridine calcium channel blockers and sustained-release nitrates are the drugs of choice associated with changes in the patient's lifestyle and control of their risk factors. Data available today show the efficacy of ranolazine plus traditional antianginal drugs in patients with microvascular angina; due to its mechanism of action, it should be considered a supplementary therapeutic option in this group of patients

**Q.:** Which non-invasive, non-pharmacological alternatives exist for these patients?

**A.:** As I already mentioned, patients with RA should join structured cardiac rehabilitation programs to change their lifestyle. Exercise adapted to each particular case has proven to improve ischemia and stimulate collateral circulation, coronary vascular function, and control the main cardiovascular risk factors. To control the symptoms, transcutaneous electrical nerve stimulation has been suggested. Extracorporeal shock waves can promote myocardial revascularization, and external counterpulsation generates diastolic retrograde aortic flow that increases the coronary diastolic and mean pressures. Also, retrograde flow improves myocardial perfusion after inducing flow-mediated coronary vasodilation and

stimulates angiogenesis. There is not a single solid piece of evidence on the utility of these techniques in patients with RA. Actually, they should be used based on each particular case strictly as compassionate use and only when the remaining therapeutic options have failed.<sup>1</sup>

**Q.:** What evidence do we have today on the Reducer device?

**A.:** Several invasive techniques have been developed to improve angina including neural stimulation, stellate ganglion block, myocardial laser revascularization, angiogenic stimulation with plasmid DNA, and implantation of CD34+ and CD133+ cells. The results of a recent meta-analysis on the intramyocardial injection of CD34+ have confirmed that it improves angina, the patients' functional capacity, and prognosis. However, for the time being these techniques are in research stage only.<sup>1</sup>

The description that an increased coronary sinus pressure induces myocardial flow redistribution in the ischemic regions of patients with RA is the basis of the Reducer device design (Neovasc Inc., Canada). It is a metal balloon-expandable percutaneous device that causes the focal the stenosis of coronary sinus rising its pressure and elevating it in the venules and capillaries too. This promotes the redistribution of flow bringing the endocardial/epicardial perfusion gradient back to normal.<sup>1</sup> Several studies confirm the safety profile of this technique and its benefits regarding symptom improvement; the early study results of 15 patients confirmed its long-term safety profile with 12-year patency in 10 of these patients and symptom improvement. However, device migration and coronary sinus perforation and bleeding have been reported; these are complications that should be taken into consideration when giving this device a clinical use. From my own point of view, the only randomized clinical trial published to this date, the COSIRA (Coronary sinus reducer for treatment of refractory angina)<sup>6</sup> offers modest efficacy results. A total of 104 patients with RA were randomized to receive the Reducer device or undergo a sham procedure. The patients who received the device improved their angina symptoms and quality of life. However, no significant changes were seen in the stability and frequency of angina or in the duration of exercise.

Several real-world registries confirm the efficacy and safety profile seen in the clinical trial with maximum clinical benefits reported after 4 months and maintained at the 2-year follow-up.<sup>7</sup> Improvements in inducible ischemia, functional capacity in the cardiopulmonary exercise testing, myocardial perfusion, and cardiac function have been reported. A special comment should be made on symptom efficacy and myocardial perfusion with the Reducer device in 8 patients with microvascular angina.<sup>1</sup>

Considering the time elapsed since the arrival of the Reducer device and the scarce quality of scientific evidence with just one randomized clinical trial available and a very qualitative primary endpoint (the assessment of the patient's self-reported angina), in my opinion, at least, 2 clinical trials should be conducted: the first one in patients with RA due to nonrevascularizable coronary lesions. The second one in patients with microvascular angina. The first study primary endpoint should include symptom improvement according to some objective test of overload and myocardial perfusion assessed through cardiac magnetic resonance imaging. The second study primary endpoint should also include these components plus the functional assessment of coronary microcirculation. In the meantime, I think it should only be used as compassionate use in quality high-volume PCI-capable centers for the management of patients with RA on an optimized therapeutic strategy and clinical follow-up including objective tests to assess ischemia and myocardial perfusion.

## FUNDING

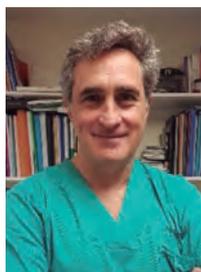
No funding was received for this work.

## CONFLICTS OF INTEREST

The authors declare no conflicts related to this work.

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## Debate: Refractory angina. The Reducer device as a new therapeutic approach. Perspective from interventional cardiology



### *A debate: Angina refractaria. El dispositivo Reducer como nueva alternativa terapéutica. Visión desde el intervencionismo*

Santiago Jiménez Valero\*

Sección de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario La Paz, Madrid, Spain

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**QUESTION:** How often do you see nonrevascularizable patients with refractory angina today?

**ANSWER:** Refractory angina is defined as chronic angina that cannot be controlled even with the use of optimal medical therapy and where all revascularization options have failed.<sup>1,2</sup> It is a common entity whose prevalence is on the rise due to the ageing of population and the improved prognosis of ischemic heart disease. It is estimated that between 5% and 10% of the patients with chronic ischemic heart disease can develop refractory angina. Its annual incidence rate is between 50 000 and 100 000 cases in the United States and between 30 000 and 50 000 cases in Europe.<sup>1,2</sup> On the other hand, we know that around 10% of all coronary angiographies performed indicate that it is not possible to give efficient options of revascularization. According to the activity registry in interventional cardiology in Spain from 2019,<sup>3</sup> this figure would be up to 15 000 patients each year, and it is reasonable to think that a significant percentage can suffer refractory angina.

These patients often remain asymptomatic which negatively impacts their quality of life and. Actually, to this day, we still do not have effective therapeutic options to offer. Multidisciplinary approach is crucial here (cardiology, family medicine, cardiac rehabilitation, psychology, pain management units, etc.). Also, we should consider the use of non-pharmacological therapies like spinal cord or subcutaneous stimulation, external counterpulsation or use the coronary sinus reducer device as well as keep looking into other alternatives like new drugs, cardiac shock wave therapy or use of progenitor cells.<sup>1,2</sup>

**Q.:** Please explain to us briefly the diagnostic approach used for screening etiologies different from ischemia due to epicardial coronary artery disease such as microvascular ischemia, vasospasm or even noncardiac causes.

**A.:** The diagnosis of refractory angina is mainly clinical, but it is important to show that there is a correlation between symptoms and ischemia. That is why it is essential to confirm the presence of myocardial ischemia, if possible, through imaging modalities like stress echocardiography, pharmacological stress echocardiography, single-photon emission tomography or magnetic resonance imaging. If no ischemia is seen on these imaging modalities, other possible causes for the symptoms should be considered like esophageal spasm or osteomuscular etiology. In the presence of ischemia, we need to know the coronary anatomy preferably through a coronary angiography before discussing any revascularization options. Information should be analyzed by the heart team including experienced interventional cardiologists and cardiac surgeons to determine the possibilities of percutaneous or surgical revascularization.

There are 2 groups of patients without revascularization options: the largest one, with advanced coronary disease (diffuse disease, small-caliber distal beds, chronic total coronary occlusions non-eligible for percutaneous coronary intervention, coronary artery bypass graft deterioration...); and that of patients with angina and myocardial ischemia without obstructive coronary lesions. In these patients it would be good to perform a functional study with microvascular dysfunction and coronary spasm testing (coronary reserve, index of microvascular resistance, absolute coronary flow, acetylcholine test) to facilitate targeted therapies with better symptom control.

**Q.:** What evidence do we have today on the Reducer device?

**A.:** It is a new option for patients with refractory angina with a different mechanism of action over the cardiac venous system. This mechanism developed over 60 years ago by Claude S. Beck<sup>4</sup> is based on creating coronary sinus (CS) stenosis to generate a pressure gradient that is transmitted retrogradely to venules and

\* **Corresponding author:** Paseo de la Castellana 261, 28046 Madrid, Madrid, Spain.  
E-mail address: [sjvcardio@yahoo.es](mailto:sjvcardio@yahoo.es) (S. Jiménez Valero).

Online: 22-12-2020.

<https://doi.org/10.24875/RECICE.M20000176>

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capillaries, which translates into an improved subendocardial perfusion, probably due to collateral recruitment through the venous plexus and Thebesian veins.

The first experience with humans was reported back in 2007. In 2015 the COSIRA multicenter, randomized, double-blind, sham-controlled clinical trial<sup>5</sup> was published. It included a total of 104 patients with refractory angina and functional class III or IV according to the Canadian Cardiovascular Society (CCS) with ischemia seen on the dobutamine stress echocardiography and without any revascularization options after assessment by the medical team assessment. The primary endpoint was to reduce, at least, 2 CSS functional class degrees of severity of angina at the 6-month follow-up. The Reducer device was superior to the sham procedure (35% vs 15%;  $P = .024$ ), improved, at least, 1 CSS functional class degree of angina in 71% of the patients vs 42%, and improved parameters like duration of exercise or quality of life.

Also, there is evidence of the results of the REDUCE registry<sup>6</sup>—similar to those reported by the COSIRA trial—in the routine clinical practice on the improvement of, at least, 1 CSS functional degree of angina in 81% of the patients, better parameters of quality of life, greater distances covered in the six-minute walk test, and lower the need for antianginal drugs. The REDUCER-1 registry results of 195 patients presented at Euro-PCR 2019 showed that clinical benefit remained at the 2-year follow-up.<sup>7</sup>

Overall, in all the studies published it was effective in up to 75% of the patients.<sup>8</sup> The reasons why some patients remain unresponsive to therapy are still not known, but they could be associated with lack of device endothelialization or with an alternative venous drain through other territories.

An important conclusion we can draw from the accumulated experience is that the implantation of the Reducer device is viable and safe<sup>5-8</sup> with serious complications (like CS dissection or perforation or device embolization) in less than 2% of the cases. The 10-plus-year follow-up of the early patients has confirmed its patency and lack of structural alterations in the long-term. No CS thrombosis has ever been reported after implantation.

Magnetic resonance imaging study supports the hypothesis of an increased subendocardial perfusion as the mechanism of action by showing that in ischemic areas the correlation between the myocardial perfusion reserve index and the endocardial reserve index—that remains low at baseline—increases after implantation. Also, myocardial perfusion improves when reducing the myocardial ischemic burden, improving the longitudinal and circumferential strain and systolic function without microstructural alterations or effect on the diastolic function.<sup>9</sup>

With the accumulated evidence, the last clinical practice guidelines on the management of chronic coronary occlusions of 2019 established by the European Society of Cardiology (ESC) included, for the very first time, the implantation of the Reducer device in patients with refractory angina with the same level of recommendation (IIb, level of evidence B) than other previous non-pharmacological options like external counterpulsation or spinal cord stimulation.<sup>10</sup>

**Q.:** How is the selection process of the most eligible candidates for this technique?

**A.:** In my opinion, most patients with symptomatic refractory angina are potential candidates despite the optimal medical therapy without percutaneous or surgical revascularization options after assessment by the heart team and with myocardial ischemia in the left main coronary artery territory as seen on the imaging

modalities.<sup>6</sup> Due to vein drain anatomy of the right coronary artery territory through the middle and small cardiac veins that drain into the CS very close to its ostium, this drainage would not be affected by the implant. For this reason, the Reducer device would not be the right option for patients with ischemia in the right coronary artery territory only. Thanks to its mechanism of action, it may be an interesting option for patients with ischemia due to microvascular disease without lesions in the epicardial coronary arteries. Although information is still limited in this context information, the early data are positive.<sup>11</sup>

One contraindication would be the presence of left ventricular pacing electrodes through the CS for resynchronization purposes, which is why its indication should be carefully studied in patients with ventricular dysfunction who may be candidates to such therapy.

Patients with refractory angina can also be candidates to other non-pharmacological therapies like external counterpulsation or neurostimulation. Although they have been available for decades, these techniques have been underused for different reasons like the perception of the lack of efficacy or placebo effect or lack of solid scientific evidence. Randomized clinical trials are needed to compare these different techniques and establish the best way to approach the management of these patients.

**Q.:** Can you please give us a brief technical description of this procedure?

**A.:** The implantation of the Reducer device is easy on the technical level<sup>12,13</sup> and successful in over 95% of the cases. The device is implanted under local anesthesia via right jugular vein as the access of choice and preferably under vascular ultrasound guidance. A 6-Fr introducer sheath is used followed by the advancement of a multipurpose catheter until the right atrium while keeping the mean pressure < 15 mmHg (with higher pressures the implantation is ill-advised since the pressure of the CS is already high at the baseline level). Afterwards, the CS undergoes selective catheterization by carefully advancing the multipurpose catheter and avoiding small-caliber branches like the left marginal ones or the vein of Marshall. There are times that a highly developed or fenestrated Thebesian valve can make selective catheterization difficult. A venography of CS is performed through the multipurpose catheter to see its size, the origin of lateral branches, and the presence of valves (like Vieussens valve that can complicate the implant).

If the procedure is continued, heparin is administered, and the guidewire is placed distal to the CS. Then, the introducer sheath is changed for a 9-Fr sheath to advance the guide catheter and deliver the device in the location previously indicated by the venography (2-4 cm from the origin of CS avoiding the jailing of lateral branches). The device consists of a stainless-steel balloon-expandable stent whose balloon has the shape of a sand clock that leaves a central waist of 3 mm. It is implanted through the inflation of a second balloon for 30 to 60 seconds at 4 to 6 atm, adjusting its size to the actual diameters of CS of 9.5 mm to 13 mm. During inflation oversizing is attempted (10% to 20%) to reduce the risk of embolization and facilitate neointimal coverage. Once implanted, the balloon is carefully removed until the guide catheter making sure that the Reducer device remains stable. Lastly, a new venography is performed to check the position of the device and lack of complications. The patient can be discharged early on after the procedure and dual antiplatelet therapy is advised for, at least, a month. The effect is evident with device endothelialization, which creates a coronary sinus (CS) stenosis, which is why it is necessary to wait between 4 and 6 weeks to determine its efficacy.

In conclusion, the CS Reducer device is a new technique for the management of refractory angina. It improves myocardial perfusion

acting from the cardiac venous system. Clinical results confirm its efficacy and safety profile, the technique is easy to use, and its indication has already been established in the clinical practice guidelines. Clinical evidence still needs to grow with more patients, longer follow-up periods, comparisons to other therapies, and further research on the mechanisms of nonrespondent patients. Nonetheless, the Reducer device is a new tool in the interventional cardiology armamentarium that can be an option for patients with refractory angina without revascularization options.

## FUNDING

No funding.

## CONFLICTS OF INTEREST

None declared.

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# Cardiovascular interventions live: show or training? The professional perspective: the LIVE study



## *Intervenciones cardiovasculares en directo, ¿educación o espectáculo? Valoración de los profesionales en el estudio LIVE*

Iván J. Núñez-Gil,<sup>a,\*</sup> Jesús María Aranzaz,<sup>b</sup> Marian Bas,<sup>a</sup> Gisela Feltes,<sup>c</sup> Carlos Macaya,<sup>a</sup> and Antonio Fernández-Ortiz<sup>a</sup>

<sup>a</sup> Instituto Cardiovascular, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

<sup>b</sup> Servicio de Medicina Preventiva, Hospital Ramón y Cajal, Madrid, Spain

<sup>c</sup> Servicio de Cardiología, Hospital Nuestra Señora de América, Madrid, Spain

### To the Editor,

Over the last few years the number of procedures that have been broadcast live—often at medical meetings—has been growing exponentially. Still, this is a controversial issue.<sup>1,2</sup> In cardiology, the very first case of a coronary angioplasty broadcast live took place in Zurich back in 1980.<sup>1,2</sup>

Some say that there is a potential risk for patients, and they share different arguments claiming that live broadcasts may bring no educational benefits at all compared to cases already filmed or recorded. Added to the technical complexity involved, there would be more pressure to the operators themselves. However, others are true defenders of these broadcasts mentioning their educational value when performed correctly with selected cases claiming that this should not be detrimental at all to results or safety.<sup>3,4</sup> Thus, the VERITAS study compared 60 transcatheter aortic valve implantation (TAVI) broadcasts to 42 similar control procedures and concluded that, if performed by experienced operators, broadcasting TAVI procedures live is safe and results are similar to the usual ones.<sup>4</sup>

Also, consensus documents have been published with recommendations, and several meetings have been held and hosted by the European Society of Cardiology (VITAL-Live<sup>2</sup>) to define how courses with live cases should work.<sup>3</sup>

The primary endpoint of this study was to know the expert opinion on the procedures that are broadcast live in medical meetings and those that are performed for the general public. The study secondary endpoint was to conduct a stratified analysis based on the professional profile (sex, years of experience, field of expertise, etc.) A brief survey in English and Google-forms format was e-mailed to 360 health professionals (from the specialties of cardiology, hemodynamics, electrophysiology, cardiac surgery, and anesthesia) of different countries. The scores given were ranked from 1 to 5 being 1 the worst score of all and 5 the best score of all (more safety and more educational value). Respondents sent back the survey in September 16, 2019 and no further reminders were sent.

Ninety-nine valid responses were received within a month: 65% on the same day the survey was sent. Eighty-two-point-eight per cent were males, mostly specialists with extensive training (83.8%), and the remaining ones were fellows (16.2%). The age profile was the following one: 26.3% of the participants were between 25 and 35 years old, 46.5% were between 36 and 45 years old, and 27.3% > 45 years old. The most predominant group were interventional cardiologists (60.6%), electrophysiologists (5.1%), and cardiac surgeons (2%); 30.3% of the participants were from other medical specialties (clinicians, experts in cardiovascular imaging, etc.) (table 1).

Respondents from different countries participated: Canada, 1; Cuba, 1; Check Republic, 1; Ecuador, 1; Germany, 1; Italy, 14; Korea, 1; Mexico, 1; The Netherlands, 2; Spain, 69; Uruguay, 1; United States, 2; and not specified, 4.

Most respondents (90.9%) said they had attended, at least, 1 course with live cases; 45.5% did so as operators too. Thirty-nine-point-four per cent had attended between 2 and 3 of these courses within the last year, and 22.2% had attended more than 3. The average score on the educational value of the live cases seen in medical courses was  $4.02 \pm 0.90$ . The average safety score was  $3.55 \pm 1$ . The average score of live educational cases was  $2.72 \pm 1.22$  (figure 1). Among the factors considered most relevant by the respondents to give this or that score were potential distractions (54.2%), different management than usual (46.9%), overall educational value (38.5%), and impact on funding (24%).

Regarding the specific guidelines or recommendations to organize or host courses with live cases, only 19.2% had read documents on this regard.

The suggestions to improve safety were to minimize distractions by training operators and moderators and include highly experienced health professionals to avoid questions and discussions with the operators during the case that would only be allowed before or after performing the procedure.

\* Corresponding author: Cardiología Intervencionista, Hospital Clínico San Carlos, Prof. Martín Lagos s/n, 28041 Madrid, Spain.  
E-mail address: [ibnsky@yahoo.es](mailto:ibnsky@yahoo.es) (I.J. Núñez-Gil).

Received 24 January 2020. Accepted 17 April 2020. Online: 29-06-2020.

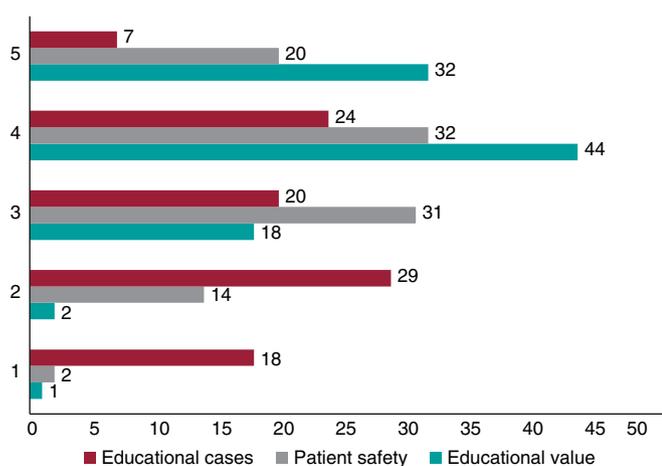
<https://doi.org/10.24875/RECICE.M20000127>

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**Table 1.** Scores given based on the professional profile

Professional profile	Educational value		Patient safety		Live cases for the general public	
Interventionists* (N = 67)	4.12 ± 0.78	P = .11	3.63 ± 0.99	P = .25	2.76 ± 1.25	P = .66
Non-interventionists (N = 32)	3.81 ± 1.09		3.38 ± 1.10		2.65 ± 1.17	
Males (N = 82)	3.96 ± 0.92	P = .17	3.51 ± 1.03	P = .48	2.54 ± 1.22	P = .14
Women (N = 17)	4.29 ± 0.77		3.71 ± 1.04		3.12 ± 1.16	
≤ 45 years old (N = 72)	4.15 ± 0.81	P = .01	3.68 ± 0.97	P = .03	2.75 ± 1.19	P = .73
> 45 years old (N = 27)	3.67 ± 1.03		3.19 ± 1.11		2.65 ± 1.32	
Residents or fellows (N = 16)	4.19 ± 0.65	P = .42	3.75 ± 1.00	P = .39	2.81 ± 1.27	P = .75
Attending physicians (N = 83)	3.99 ± 0.94		3.51 ± 1.04		2.71 ± 1.22	
Participated as an operator (N = 45)	4.02 ± 0.96	P = .98	3.51 ± 0.99	P = .76	2.69 ± 1.20	P = .79
Was never an operator (N = 54)	4.02 ± 0.85		3.57 ± 1.07		2.75 ± 1.25	

\* Including interventional cardiologists, electrophysiologists, and surgeons.



**Figure 1.** Scores given by the respondents of the survey to the educational value of live cases broadcast in medical meetings (green), their safety (gray), and level of acceptance of those with educational purposes for the general public (red), between 1 and 5, from lowest to highest level of agreement.

Also, it is important to adapt oneself to the clinical practice guidelines without changing the approach by just being in a live case, avoid very complex cases, and use checklists. As a matter of fact, this may be a very appropriate scenario for the current simulation techniques that have already become very popular technological advances like computers, phantom models, etc.

Health professionals are much more critical on the procedures that are broadcast live with general educational purposes; some even do not recommend them openly and question their educational value compared to pre-filmed or pre-recorded cases. However, we should mention here that nobody identified any possible medical-legal risks for the health professionals. The potential detriment to the patient's confidentiality or intimacy was not mentioned either.

The low response rate (27.5%) and heterogeneous sample used were some of the study limitations. Also, no parameters were built to report on how representative the results were, which may have induced a certain selection bias since only highly interested health professionals were surveyed. However, this was just an exploratory study for the sake of scientific reflection.

In conclusion, the participants of the LIVE study agreed on the benefits of this type of courses with live cases for medical training purposes for their educational value while keeping the patient safe. However, the broadcast of these courses to the general population did not achieve the same level of acceptance, which is why other curricular approaches were suggested.

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

None.

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# Anomalous origin of left circumflex artery from the right pulmonary artery of an adult



## Origen anómalo de la arteria circunfleja en la arteria pulmonar derecha en un adulto

Carlos Eduardo Vergara-Uzcategui, Rafael Vera Urquiza, Pablo Salinas,\* and Iván J. Núñez-Gil

Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Clínico San Carlos, Madrid, Spain

### To the Editor,

The anomalous origin of coronary arteries is a rare entity (overall rate < 1 for every 300 000 live births), and often appears concomitantly with other congenital heart defects.<sup>1</sup> The anomalous origin of the left circumflex artery (LCx) from the right coronary artery (RCA), the right sinus of Valsalva or the separate origin of the left anterior descending coronary artery (LAD) and LCx all have been reported.<sup>2,3</sup> However, an anomalous origin of the LCx from the pulmonary artery (PA) or its branches is extremely rare.<sup>4</sup>

A 39-year-old male presented with palpitations and atypical chest pain of 12-hour duration in a context of vomits, diarrhea, and abdominal pain. Three weeks prior to admission he had reported the presence of catarrhal symptoms. Prior to the current admission the patient recounted several episodes of chest tightness while performing high-intensity physical exercise. The patient's past medical history included a non-dysfunctional bicuspid aortic valve and aortic coarctation. Coarctation was initially corrected (1995) with a subclavian artery-to-descending aorta bypass graft. Ten years later he underwent further surgical repair using an interposition tube graft. A diagnosis of acute myocarditis was considered likely. Upon admission the electrocardiogram showed sinus rhythm with normal progression of R waves and no repolarization abnormalities. The creatine kinase myocardial band (CK-MB) and troponin I levels were positive. Other laboratory tests looked normal too. The echocardiogram showed normal left ventricular contractility, bicuspid aortic valve without stenosis or regurgitation, normal right ventricle, normal pulmonary pressure, and normal gradients in the left anterior descending coronary artery. The cardiovascular magnetic resonance (CMR) imaging performed confirmed the absence of myocardial edema or late gadolinium enhancement of the left ventricle. The coronary computed tomography angiography (CCTA) performed revealed the anomalous origin of the LCx from the right PA without coronary atherosclerosis (figure 1). The CCTA confirmed the presence of isolated coronary artery ectasia of the LAD originating from the left sinus, normal non-dominant RCA, and a dominant LCx originating from the right PA with retrograde filling receiving collateral circulation from both the LAD and the RCA (figure 2). The therapeutic options were discussed with the heart team and the patient who refused surgery. Therefore, medical therapy was the strategy of choice. Patient's informed consent to diagnostic tests and consent to publish were granted.

The anomalous origin of the LCx from PA or any of its branches is often accompanied by heart conditions like aortic coarctation, patent ductus arteriosus, Tetralogy of Fallot, aortopulmonary

window, truncus arteriosus, subaortic fibrous membrane stenosis, ventricular septal defect, and pulmonary valve stenosis.<sup>1,2</sup>

Clinical presentation depends on age. In some cases it is symptomatic within the first week of life. In others, it is asymptomatic until adulthood or presents with sudden cardiac death (SCD).<sup>2</sup> Depending on coronary collateralization, the clinical course may be silent.<sup>5</sup> In our case, the diagnosis was an incidental finding despite having 2 aortic surgeries. The patient had no prior coronary angiograms as he had undergone surgery at 13 and 23 years old.

In patients who undergo a coronary angiography due to ischemic heart disease, this anomaly can be incidentally noted. Few adult cases have been reported with different presentations like new-onset angina, dyspnea, abnormal ischemic changes on the electrocardiogram, abnormal stress electrocardiography, nuclear scintigraphy or single-photon emission computed tomography.<sup>2,6</sup> Our patient reported chest tightness while performing high-intensity physical exercise. Cardiac arrest has been reported as a very rare presentation in adults.<sup>1,4</sup>

SCD can occur after myocardial ischemia during exercise or ventricular arrhythmias triggered by ventricular scar tissue.<sup>4</sup> Endothelial injury of the anomalous coronary artery with subsequent sudden coronary spasm or modification in the physiology of blood circulation have been proposed as probable pathophysiological mechanisms to explain ischemia and SCD in patients with coronary arteries of anomalous origins.<sup>3</sup>

The gold standard for diagnosis here is coronary angiography that allows good visualization of collateral vessels and the degree of shunting,<sup>1,5</sup> and allows us to exclude concomitant atherosclerotic disease.<sup>6</sup> CMR or CCTA imaging give us the correct anatomical location of the coronary origin. The CCTA has better spatial resolution, but the CMR can give us information on the direction of flow in an anomalous vessel, on myocardial viability and perfusion.<sup>1,3,5,6</sup>

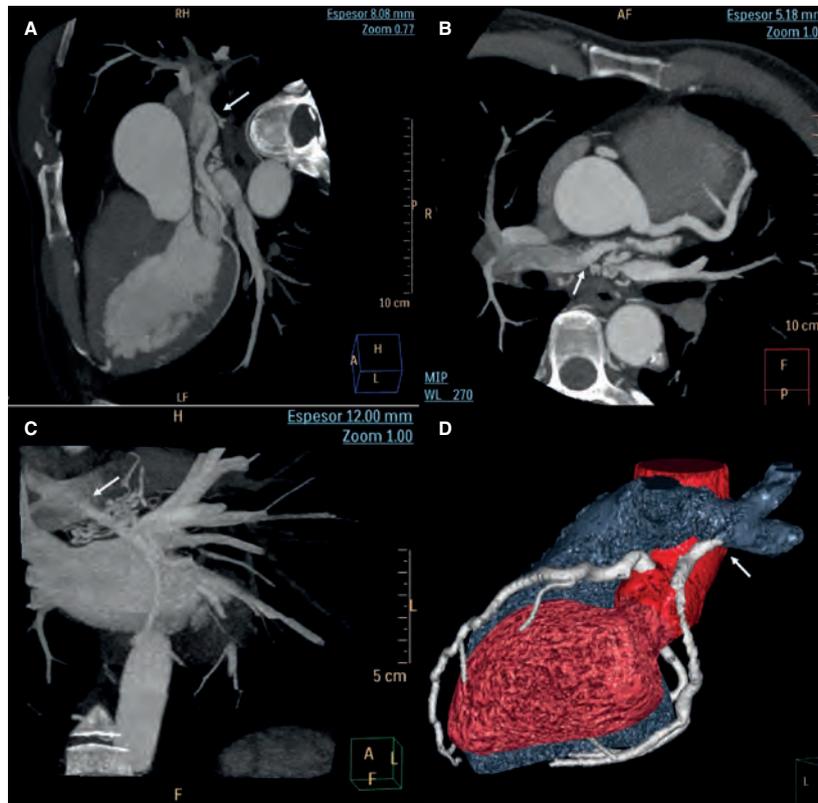
Some criteria for surgical treatment are the presence of anginal symptoms, the ventricular area supplied by the artery, and homo-coronary and/or hetero-coronary collateral vessels.<sup>5</sup> In this patient a conservative approach was decided due to the patient's refusal to undergo surgical treatment and in view of the absence of clear signs of ischemia and late enhancement on the CMR. Surgical options can include the simple ligation of the anomalous vessel, reimplantation of the anomalous vessel into the aorta, a coronary artery bypass graft or transpulmonary artery aortocoronary reconnection.<sup>2</sup> At the 12-month follow-up our patient has no cardiac symptom at all.

\* Corresponding author: Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Clínico San Carlos, Prof. Martín Lagos s/n, 28040 Madrid, Spain. E-mail address: salinas.pablo@gmail.com (P. Salinas).

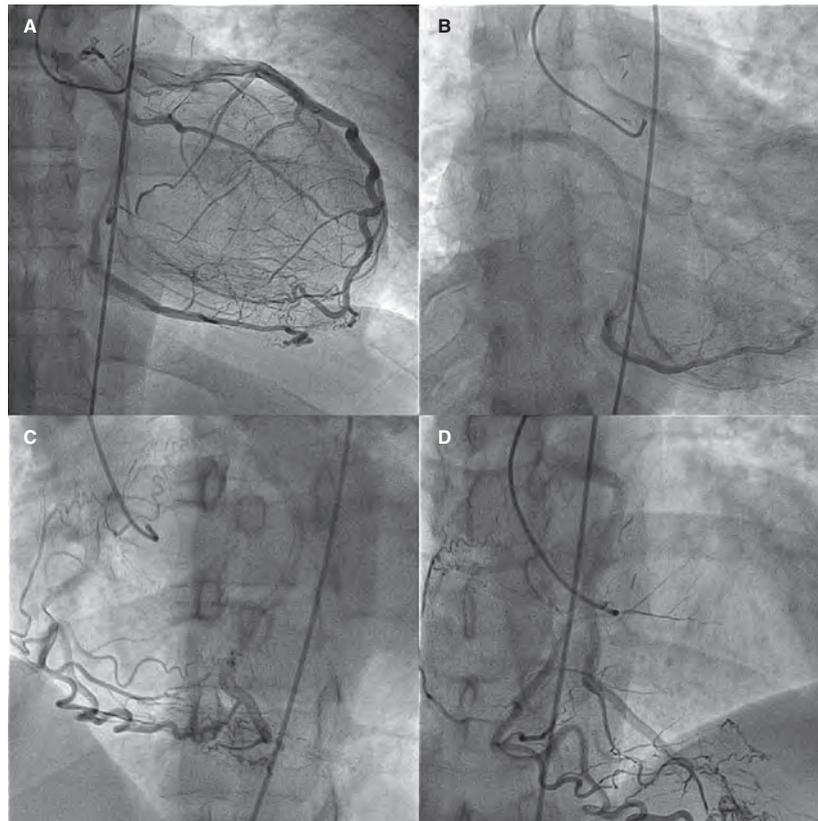
Received 8 April 2020. Accepted 22 April 2020. Online: 05-06-2020.

<https://doi.org/10.24875/RECICE.M20000128>

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**Figure 1.** Maximum intensity projection images of coronary computed tomography angiography (A, B, C) and volume-rendering imaging (D) showing the anomalous origin of the left circumflex artery coming from the right pulmonary artery (arrow) with posterior trajectory.



**Figure 2.** Coronary angiography in the (A) anteroposterior, (B) caudal, (C) left anterior oblique and (D) cranial projections showing the independent origin of left anterior descending coronary artery that supplies collateral circulation and retrograde filling to the left circumflex artery that originates in the right pulmonary artery, and the right coronary artery of normal origin that supplies collateral circulation and retrograde filling to the left circumflex artery.

**FUNDING**

No funding was received for this work.

**CONFLICTS OF INTEREST**

The authors declare no conflicts related to this work.

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## Transcatheter aortic valve migration in aortic regurgitation following left ventricular assist device



### *Migración de prótesis aórtica transcatóter en insuficiencia aórtica por asistencia ventricular*

Agustín Albarrán González-Trevilla,<sup>a,\*</sup> Nicolás Manuel Maneiro Melón,<sup>a</sup> Julio García Tejada,<sup>a</sup> María Teresa Velázquez Martín,<sup>a</sup> María Dolores García-Cosío Carmena,<sup>b,c</sup> and Fernando Sarnago Cebada<sup>a</sup>

<sup>a</sup> Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), Madrid, Spain

<sup>b</sup> Unidad de Insuficiencia Cardíaca y Trasplante Cardíaco, Servicio de Cardiología, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), Madrid, Spain

<sup>c</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

**To the Editor,**

Moderate-to-severe aortic regurgitation (AR) is a common complication of patients treated with continuous-flow left ventricular assist devices (CF-LVAD) that affects 35% of these patients at 5 years.<sup>1</sup> The risk factors associated with its appearance are the absence of valvular opening, the time of progression, the presence of aortic or mitral regurgitation prior to implantation, and female sex.<sup>2</sup> AR causes left ventricular overload and inefficient recirculation flow through the pump. Observational studies have reported that post-implantation AR is not associated with a higher mortality rate. However, it has been reported that the cardiac function deteriorates requiring some type of procedure in 33% of the patients who develop it.<sup>3</sup>

The implantation of percutaneous devices, in particular transcatheter aortic valve implantation (TAVI), has become the therapeutic alternative in this subgroup of patients in whom surgery is ill-advised because of their risk and possible future procedures.<sup>4</sup> Although evidence is scarce on this regard, it has been described as an

effective technique with disappearance of significant AR after the procedure and in the mid-term follow-up.<sup>5</sup>

This is the case of a 54-year-old woman with idiopathic dilated cardiomyopathy in situation of advanced heart failure who received the Heartmate III CF-LVAD (Abbot, Chicago, United States) as the destination therapy. The transthoracic echocardiogram performed prior to implantation showed severe ventricular dysfunction, a non-dysfunctional right ventricle, mild AR, and moderate mitral regurgitation. Five months after the implant the patient was admitted due to heart failure. The new echocardiogram performed revealed the lack of aortic valve opening with leaflets without relevant morphologic abnormalities but with reduced mobility when closing, and severe systolic-diastolic AR (figure 1A). Although the ramp test performed with right heart catheterization showed fewer revolutions, the patient remained seriously symptomatic with persistent AR, which is why TAVI was decided in a multidisciplinary session. The computed tomography performed revealed the presence of a noncalcified aortic valve with a 25 mm × 21 mm annulus, a 73 mm perimeter, and 26 mm × 27 mm sinus

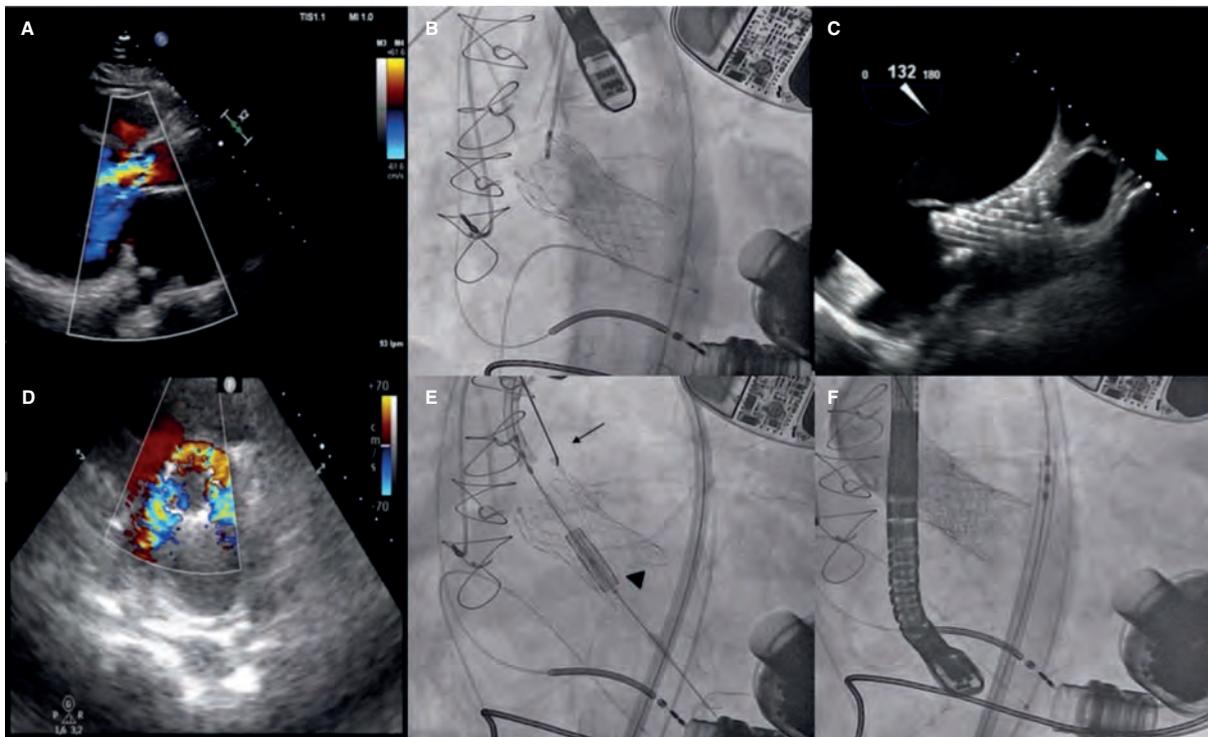
\* **Corresponding author:** Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain.

E-mail address: [agustin.albarran@hotmail.com](mailto:agustin.albarran@hotmail.com) [A. Albarrán González-Trevilla].

Received 20 April 2020. Accepted 18 May 2020. Online: 28-07-2020.

<https://doi.org/10.24875/RECICE.M20000140>

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**Figure 1.** **A:** transthoracic echocardiogram prior to the implant. Continuous severe aortic regurgitation. **B:** aortic angiography. Early results after Evolut R 26 mm valve implantation. **C:** transesophageal echocardiogram after the implant. Valve migration towards the left ventricle. **D:** transesophageal echocardiogram after the implant. Severe aortic regurgitation. **E:** fluoroscopy. Repositioning of the Evolut R 26 mm valve using snare catheter system (arrow). Edwards SAPIEN 3 23 mm valve advanced for valve-in-valve implantation (arrowhead). **F:** aortic angiography. Valve-in-valve implantation final result.

parameters. The Evolut R 26 mm system (Medtronic, Minneapolis, United States) was used following technical advice and given the dimensions of the root at sinus level. Informed consent to publish was granted verbally.

The procedure was performed via femoral access. Assist only stopped during implantation to avoid suction effect. The early results were satisfactory, and the valve remained in a normal position with mild paravalvular AR (figure 1B).

In the early progression, the patient developed cardiogenic shock, and required vasoactive drugs at high doses. The transesophageal echocardiogram confirmed the apical displacement of the valve with severe paravalvular regurgitation (figure 1C,D). Under this situation, it was decided to perform an emergent valve-in-valve implantation procedure. Using the radial access, a snare catheter was advanced in order to capture the Evolute valve and traction it until it would be placed it in its early location. Afterwards, an Edwards SAPIEN 3 23 mm valve (Edwards Lifesciences, Irvine, United States) was implanted via femoral access and the valve-in-valve procedure was performed with 2 mL inflation volume above nominal value (figure 1E,F). The transesophageal echocardiogram performed after the implant revealed the presence of mild paravalvular AR. The patient's clinical progression was good and uneventful. Eighteen months later the good results still remain with mild paravalvular AR. The patient is now a New York Heart Association functional class II patient.

TAVI in patients with AR and CF-LVAD is a procedure with characteristics that are especially risky. Together with paravalvular leak, the migration of the device is the main complication of this technique. It is a classic complication of TAVI in the management of pure AR where there is fewer calcification and valve anchoring is more complicated. And all of it adds to the apical suction of the pump.

In order to prevent migration, it has been suggested to oversize the valve in relation to the annulus (15% to 20% for balloon-expandable valves and 20% to 25% for self-expandable valves), and use recapturable self-expandable systems<sup>6</sup> to allow a more controlled release and reduce the revolutions of the device during implantation. In our case, oversizing was discarded due to the presence of a small aortic root with the corresponding risk of rupture.

In conclusion, TAVI for the management of patients with AR and CF-LVAD is an effective procedure with good mid-term results. The peculiarities of this context require careful planning and implantation to reduce complications such as valvular migration. The recapture of the valve and valve-in-valve implantation are effective techniques to solve this complication and avoid surgery.

#### FUNDING

No funding.

#### CONFLICTS OF INTEREST

None declared.

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## Effects of the COVID-19 pandemic on the population over 75 years old with coronary artery disease. The EPIC SIERRA 75 registry



### Efectos de la pandemia de COVID-19 en la población mayor de 75 años con enfermedad coronaria. Registro EPIC SIERRA 75

José M. de la Torre-Hernández,<sup>a,\*</sup> Pilar Carrillo Sáez,<sup>b</sup> Jesús M. Jiménez Mazuecos,<sup>c</sup> Alejandro Gutiérrez Barrios,<sup>d</sup> Belén Cid Álvarez,<sup>e</sup> and Armando Pérez de Prado<sup>f</sup>

<sup>a</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Cantabria, Spain

<sup>b</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario San Juan de Alicante, San Juan de Alicante, Alicante, Spain

<sup>c</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Complejo Hospitalario Universitario, Albacete, Spain

<sup>d</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Hospital Universitario Puerta del Mar, Cádiz, Spain

<sup>e</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

<sup>f</sup> Unidad de Cardiología Intervencionista, Servicio de Cardiología, Complejo Asistencial Universitario de León, León, Spain

#### To the Editor,

The negative impact of the SARS-CoV-2 pandemic on public health is due not only to the infection itself, but also to the effects of confinement and the negative impact of the population's perceptions on the risks involved when visiting medical facilities for health reasons. Proof of this are the repeated observations of an obvious reduction in the number of patients treated of myocardial infarctions during the pandemic.<sup>1,2</sup> It is highly plausible that what we saw with ischemic heart disease happened with other conditions as well whether cardiovascular or not.

It is well known that older populations and patients with vascular risk factors and/or cardiovascular disease have been the ones most severely affected by the pandemic.<sup>3</sup>

In this study we evaluated the impact of the pandemic on the population of patients over 75 years of age with known coronary artery disease. For this purpose, a subgroup of all the patients recruited in the ongoing prospective EPIC SIERRA 75 registry published at ClinicalTrials.gov (identifier: NCT03567733) were included in this study. The EPIC SIERRA 75 is a prospective registry that included patients over 75 years with percutaneous revascularization of de novo coronary artery lesions using a new-generation drug-eluting stent. Those with cardiogenic shock or whose life expectancy was < 1 year were excluded from the study. Recruitment started back in June 2018 in 35 Spanish hospitals and 7 Portuguese centers.

For the purpose of the present study, a subgroup of patients registered in the EPIC SIERRA 75 study from 24 hospitals were selected. The follow-up was updated and it covered the entire official 2-month period of confinement through direct phone calls with the patients and/or their relatives who answered a specifically designed questionnaire. Additionally, all electronic health records available in corresponding hospital units have been reviewed. The EPIC SIERRA 75 registry received the approval of each of the clinical research ethics committees of the participating centers. All patients granted informed consent prior to their inclusion in the registry.

A total of 709 patients who underwent a percutaneous coronary intervention within the 18 months prior to the pandemic were included. A total of 17 of these patients died during the 12.5 months  $\pm$  3.4 months of median follow-up prior to confinement. This means that 692 patients were followed during the outbreak period. The patients' clinical characteristics are shown on [table 1](#).

During this period, 11 (1.6%) confirmed cases of COVID-19 have been reported. Therefore, the incidence of COVID-19 was higher compared to that of the general population during such period (1.6% vs 0.4%).<sup>4</sup> This incidence varies across different regions in Spain, meaning that this comparison could be affected by the territorial distribution of the patients.

These patients were  $81.2 \pm 5$  years old and 36.3% were females ( $P = .6$  and  $P = .9$  compared to the rest of the patients, respectively). Two patients (18%) died at the hospital, an 80-year-old man and a

\* Corresponding author: Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Universitario Marqués de Valdecilla, Valdecilla Sur 1ª Planta, Avda. Valdecilla 25, 39008 Santander, Cantabria, Spain.

E-mail addresses: [he1thj@humv.es](mailto:he1thj@humv.es); [chematorre60@gmail.com](mailto:chematorre60@gmail.com) (J.M. de la Torre-Hernández).

Received 17 July 2020. Accepted 3 September 2020. Online: 27-10-2020.

<https://doi.org/10.24875/RECICE.M20000171>

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**Table 1.** Clinical data

	<b>N = 692</b>
Age, years	80.8 ± 4.2
Females	256 (37%)
Hypertension	585 (84.5%)
Diabetes	298 (43%)
Previous ACS	519 (75%)
Previous PCI	692 (100%)
<b>Status during the outbreak (confinement)</b>	
Cardiac symptoms	91 (13.1%)
Stable angina	21
Dyspnea	82
Syncope	6
Unstable conditions*	43 (6.2%)
Admitted to the hospital	22 (3.2%)
ACS	4 (0.6%)
Revascularization	4 (0.6%)
Dead	7 (1%)
Medical visits cancelled	119 (17%)
Contacted	108/119 (90%)
Treatment discontinuation	17 (2.4%)
Additional anxiolytics	61 (9%)
COVID-19 +	11 (1.6%)
Admitted	8
Intensive care	0
Dead	2
Suspected COVID-19	8 (1.1%)

\* Cardiovascular, respiratory, GI, and urological and renal disorders. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

76-year-old woman, after a hospital stay of 1 and 7 days, respectively. The mortality rate seems to be much higher than that the one seen in the overall population affected by COVID-19.<sup>4</sup> We should mention that none of the 11 patients received treatment in the intensive care unit. Although there were 8 cases (1.2%) of highly suspected but eventually unconfirmed COVID-19, no one died.

During the 2-month period of confinement, the patients developed symptoms and clinical events as shown on [table 1](#). Thirteen per cent of the patients were symptomatic and 6.2% remained unstable

due to this or that condition being half of them admitted to hospitals. Four cases of acute coronary syndrome were reported (2 with ST-segment elevation and another 2 with non-ST-segment elevation) and 4 patients required revascularization (3 required percutaneous coronary interventions and 1 required surgery). Overall, 7 (1%) patients died during this period. The etiologies found were 2 in-hospital COVID-19 diseases, 1 in-home myocardial infarction, 2 in-hospital strokes, 1 in-hospital intestinal ischemia and 1 with multiple pathologies reported at a nursing home. The monthly mortality rate during this period was 2.6 times higher than the one seen during the months prior to the pandemic (3.5 vs 1.36 dead patients/month). Outpatient medical visits were cancelled in 17% of the patients, but most of them were contacted by their doctors. Therapeutic adherence remained high, but many patients required anxiolytics, though these are self-reported data and should be interpreted with caution.

We can conclude that this population of patients over 75 years with coronary artery disease who had been revascularized before the pandemic was associated with high cardiovascular and total morbidity and mortality rates with probably more prevalent COVID-19 compared to the overall population. The mortality rate of COVID-19 patients was very high but no patients were ever treated in the intensive care unit.

As a future reference for upcoming pandemics, healthcare systems must intensify the protection of this vulnerable population not only against contagion but also against other adverse health effects indirectly derived from the pandemic.

## FUNDING

The EPIC SIERRA 75 registry was funded by Abbott Laboratories. This sub-analysis received no specific funding.

## CONFLICTS OF INTEREST

J.M. de la Torre-Hernández is editor-in-chief of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. No conflicts of interest to disclose by the remaining authors.

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# Percutaneous management of recurrent prosthetic valve thrombosis



## Tratamiento percutáneo de trombosis valvular protésica recurrente

Francisco Pomar Domingo,\* Margarita Gudín Uriel, Pau Federico Zaragoza, Luis Martínez Ortiz de Urbina, Teresa Castelló Viquer, and Enrique Peris Domingo

Servicio de Cardiología, Hospital Universitario La Ribera, Alzira, Valencia, Spain

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<https://doi.org/10.24875/RECICE.M20000148>

<https://doi.org/10.24875/RECICE.M20000133>

### CASE PRESENTATION

Prosthetic valve thrombosis (PVT) is a complication associated with a high morbimortality rate. Yet despite anticoagulation, the rate of PVT is between 0.5% and 8%.<sup>1</sup> The management of this disease depends on various factors like the size and location of the thrombus, the degree of valvular obstruction or dysfunction, the symptoms at presentation, and the patient's hemodynamic status. Therapeutic options include surgery and fibrinolysis. Both have given good results, but they are not always effective and are associated with a high risk of complications.

This is the case of a 55-year-old woman with rheumatic myocardopathy treated with aortic and mitral valve replacement using the bidisco ATS 27 mechanical heart valve (Medtronic ATS Medical, Inc, Plymouth, Minnesota, United States) and Sorin Overline 29 device (Sorin Biomedica Cardio SpA, Saluggia, Italy), respectively. The patient granted consent to publish her case, respecting her right to privacy and the protection of personal data. Two months after surgery the patient was showing signs of dyspnea (New York Heart Association functional class III) and she was diagnosed with obstructive thrombosis of the prosthetic mitral valve. The transesophageal echocardiography (TEE) performed revealed the presence of a mass compatible with a thrombus attached to the atrial side of the valve. Both discs were blocked in an intermediate position causing severe stenosis and mitral regurgitation. The patient was treated with surgery with extraction of the thrombotic material and left atrial appendage occlusion. The transthoracic echocardiography performed after the surgery confirmed the normal movement of the valve. The patient was discharged without symptoms on oral anticoagulation and acetylsalicylic acid (100 mg/day).

Although anticoagulation was kept within the recommended range (INR, 3-3.5), 3 months later the patient was re-admitted with signs of dyspnea (New York Heart Association functional class III). The TEE revealed the presence of an increased mean mitral gradient (18 mmHg). The anterior disc was blocked in the closed position, but the other one moved normal and with no signs of significant mitral regurgitation. The TEE also revealed the presence of a highly mobile, linear, thin mass (< 1 mm) compatible with a Lambl's excrescence attached to the atrial side of the valve. Also, there were slightly mobile, echo-dense, and sessile masses (maximum diameter, 4 mm; area, 0.29 cm<sup>2</sup>) compatible with thrombi and attached to the atrial side of the valve.



Figure 1. Mitral valve prior to the intervention with a blocked anterior disc in the close position (asterisk).

\* Corresponding author: Unidad de Hemodinámica, Servicio de Cardiología, Hospital Universitario La Ribera, Carretera de Corbera km 1, 46600 Alzira, Valencia, Spain. E-mail address: [pomar\\_fra@gva.es](mailto:pomar_fra@gva.es) (F. Pomar Domingo).

Received 19 April 2020. Accepted 6 May 2020. Online: 22-09-2020.

<https://doi.org/10.24875/RECICE.M20000132>

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The patient was treated with IV thrombolysis with alteplase followed by 48 hours of IV infusion of unfractionated heparin. The new TEE performed after fibrinolysis revealed the presence of small residual thrombi (maximum diameter, 3 mm; area, 0.17 cm<sup>2</sup>) and persistent fixation of the anterior disc in the closed position (figure 1).

After the failed fibrinolysis attempt and given the high risk for a new surgery, the percutaneous manipulation of the valve was decided as the therapeutic option.

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

None declared.

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# Percutaneous management of recurrent prosthetic valve thrombosis. How would I approach it?

## *Tratamiento percutáneo de trombosis valvular protésica recurrente. ¿Cómo lo haría?*

Bruno García del Blanco<sup>a,b,\*</sup>

<sup>a</sup> Unidad de Cardiología Intervencionista, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>b</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

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<https://doi.org/10.24875/RECICE.M20000132>

<https://doi.org/10.24875/RECICE.M20000133>

## HOW WOULD I APPROACH IT?

Currently, the management of thrombosis refractory to IV anticoagulant therapy of heart valves is limited: reintervention or fibrinolysis. Both procedures bring acceptable immediate results, but logically reintervention has a greater impact on the patient's recovery. Also, the treatment of choice will be influenced by a series of parameters including hemorrhagic risk, the patient's clinical status, the size of the thrombus, other concomitant findings in the imaging study, etc.

The female patient of this case is young with a mechanical prosthesis in the mitral and aortic position and a second episode of mitral valve thrombosis with serious clinical repercussions. Also, it is a case refractory to pharmacological treatment after reintervention due a first thrombosis of acute presentation (< 3 months after the intervention). This makes us have to consider 2 important details before moving on with the possible percutaneous treatment: could this be a case of endocarditis with an added thrombus? and also, is this the case of a patient with some sort of refractoriness to antithrombotic treatment? I am exposing this because, in both cases, the percutaneous therapeutic strategy did not seem like the optimal strategy to me. Since thrombotic content was not massive here, the first step in the percutaneous strategy should have been to regain the mobility of the prosthetic valve hemidisks. It is somehow logical to think of regaining their movement: the best fibrinolytic agent is flow and the movement of the valve. Also, it is the cause of symptom onset. Percutaneous treatment has the limitation of the potential embolization of the attached thrombotic material. The idea of the percutaneous manipulation of the prosthetic valve discs was already described by Jabbour et al.<sup>1</sup> back in 1996 as bridging therapy to reintervention. However, the greater experienced ever reported in the current medical literature is Hariram's<sup>2</sup> who described 5 cases of immobile prosthetic discs that were manipulated or limited in their atrial side using a Judkins Right guide catheter through a Mullins transseptal introducer sheath. The consensus achieved at the congress held by the American College of Cardiology in 2018 introduced the first case of a young female patient in whom transseptal access was also used to insert a deflectable Agilis introducer sheath (Abbott Cardiovascular, Sta. Clara, United States) by contacting an Amplatz Super Stiff guidewire (Boston Scientific, Marlborough, MA, United States) directly into the prosthetic valve. None of the cases reported developed embolic complications and all of them regained the disc movement in the mitral position. We have no further information on these patients' clinical progression.

\* **Corresponding author:** Unidad de Cardiología Intervencionista, Hospital Universitari Vall d'Hebron, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail address: [brunogb51@gmail.com](mailto:brunogb51@gmail.com) (B. García del Blanco).

Received 9 June 2020. Accepted 12 June 2020. Online: 22-09-2020.

<https://doi.org/10.24875/RECICE.M20000148>

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In our setting it seemed reasonable for me to suggest the following percutaneous access: radial access to control the central arterial pressure with a 5-Fr pigtail catheter (it is still a mark for transseptal access), venous access to perform a transseptal puncture trying a preferably posterior puncture with the deflectable Agilis NxT introducer sheath (Abbott Cardiovascular, Sta. Clara, United States), and contralateral venous access to guide the transseptal access with an intracavitary ultrasound. Both the puncture and the regain of disc mobility can be performed through transesophageal ultrasound guidance, which also facilitates residual thrombus comparison after finishing the maneuver. The patient's clinical status is key regarding the decision of using one technique over the other. Theoretically speaking, a Judkins Right guide catheter (due to the location of the immobile disc) followed by active aspiration (a 50 mL Luer-Lock syringe directly connected to the catheter that a second operator can traction to perform the aspiration) can be used to safely cross the valve and smoothly impact the atrial surface of the prosthesis, the annulus or the disc until mobility is regained. We should not forget that the procedure should be performed with anticoagulation to keep the activated clotting time, at least, above 250 seconds in a patient operated on and who has been treated with fibrinolysis; that is why transseptal guidance seems important to me. Although according to the image the size of thrombosis seems limited, I would be suggesting protection against possible cerebral embolizations with a Sentinel device (Boston Scientific, Marlborough, MA, United States) via right radial access. Protection with a balloon inflated at left subclavian and other visceral branch level like the mesenteric branches seems optional to me given the size of the current thrombus. If the maneuver with the Judkins Right guide catheter fails, I think it would be safer to try with catheter tips of different shapes and, eventually, with a second pigtail catheter mounted over a guidewire to change the curve rather than the strategy of using guidewires to impact the discs. It is essential that the neuroradiology and angioradiology teams of our center are involved in this process.

We should mention that in the case presented here it is expected that percutaneous resolution will be a bridging therapy until the endothelialization of the area of the prosthetic valve annulus can stop a third thrombosis from happening. Currently, pharmacological treatment with vitamin K antagonists is the right one. Due to the pathogenesis of this type of thrombosis where the intrinsic pathway is activated, antiplatelet therapy does not seem to play a key role and direct anticoagulants are ill-advised to prevent prosthetic valve thrombosis from happening (the REALIGN study). Finally, it is obvious that a strict clinical follow-up is required including a transesophageal ultrasound 1 month after the procedure with regular assessments of the international normalized ratio (to keep it between 3 and 3.5). The recurrence of thrombosis would make us have to rethink a third mitral valve replacement surgery and reconsider the type of prosthetic valve used. Biological valves in the mitral position are associated with a lower rate of thrombosis compared to mechanical prostheses. The downside of early degeneration in young patients should be compensated with that of recurrent prosthetic valve thrombosis. Also, thrombosis on a biological valve would be eligible for treatment with transcatheter valve implantation.<sup>3</sup>

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

None declared.

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# Percutaneous management of recurrent prosthetic valve thrombosis. Case resolution



## *Tratamiento percutáneo de trombosis valvular protésica recurrente. Resolución*

Francisco Pomar Domingo,\* Margarita Gudín Uriel, Pau Federico Zaragoza, Luis Martínez Ortiz de Urbina, Teresa Castelló Viguer, and Enrique Peris Domingo

Servicio de Cardiología, Hospital Universitario La Ribera, Alzira, Valencia, Spain

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\* **Corresponding author:** Unidad de Hemodinámica, Servicio de Cardiología, Hospital Universitario La Ribera, Carretera de Corbera km 1, 46600 Alzira, Valencia, Spain. E-mail address: [pomar\\_fra@gva.es](mailto:pomar_fra@gva.es) (F. Pomar Domingo).

Received 19 April 2020. Accepted 6 May 2020. Online: 22-09-2020.

<https://doi.org/10.24875/RECICE.M20000133>

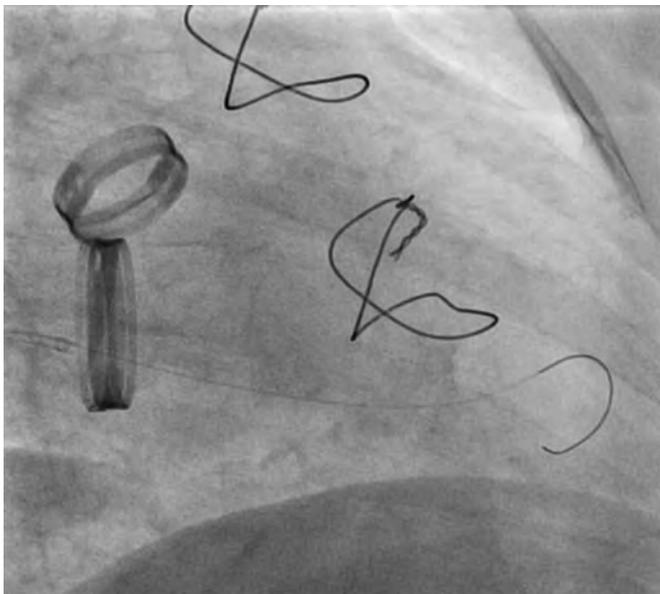
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## CASE RESOLUTION

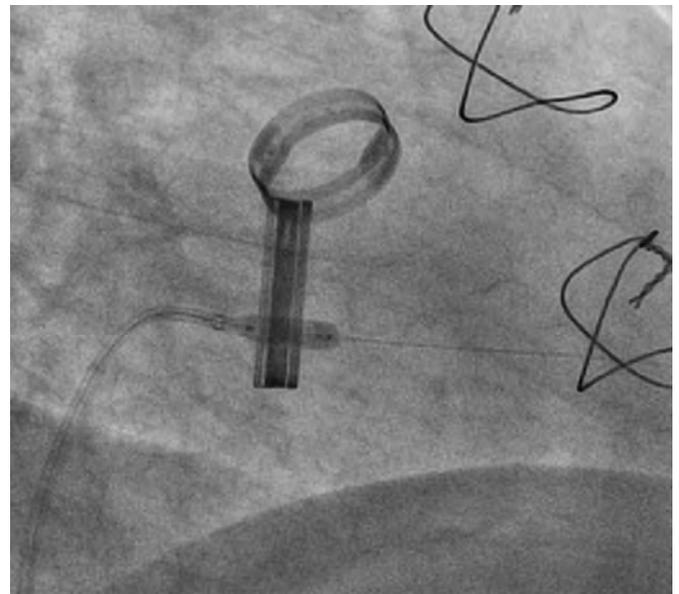
Our patient, with recurrent prosthetic valve thrombosis (PVT) and a thrombus area  $< 0.8 \text{ cm}^2$  was treated with thrombolysis but without clinical or echocardiographic improvement. It was considered that a third cardiac surgery would be too risky. Since the thrombotic load was not high, we decided to proceed with the percutaneous manipulation of the valve using the technique described by Jabbour et al.<sup>1</sup> in a patient with acute thrombosis of a tilting-disc aortic valve. This patient was treated with percutaneous manipulation of the disc trapped using a rigid catheter. Hariram<sup>2</sup> also reported on a series of 5 patients with mitral PVT and failed fibrinolytic therapy successfully treated through percutaneous manipulation of the valve using a 6 Fr-Judkins guide catheter.

In our case, the procedure was performed under general anesthesia with fluoroscopy and transesophageal echocardiography guidance. The right femoral vein was used as the access site. The transseptal puncture was performed using a Mullins introducer sheath and a Brockenbrough needle in the superior-posterior portion of the oval fossa. After the IV administration of sodium heparin (100 IU/kg) and mounted over a 0.032 in J guidewire a 3.5/6-Fr EBU guide catheter (Medtronic Launcher; Minneapolis, United States) was successfully inserted into the left atrium.

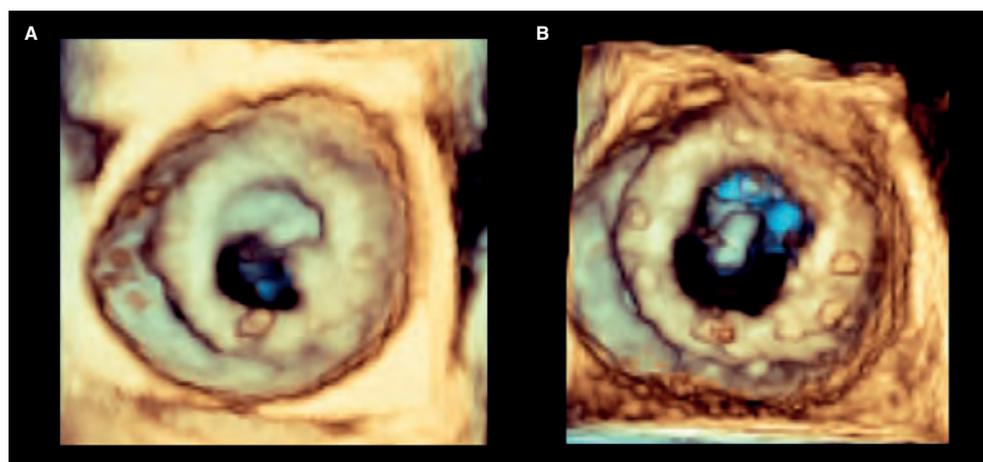
Since the disc was blocked in an almost completely closed position ([video 1 of the supplementary data](#)), we decided to take a less aggressive approach than the one described by Jabbour et al.<sup>1</sup> and instead of manipulating the disc with the guide catheter we decided to use a balloon catheter. Therefore, the guide catheter was mounted over a 0.014 in Balance Middleweight guidewire and advanced towards the left cavities. Although the guidewire advanced towards the left ventricle through the space left by the moving disc when opening, after several attempts it was successfully advanced through the small space left between the blocked disc and the prosthetic annulus ([figure 1](#)) ([video 2 of the supplementary data](#)). While the tip of the guidewire was resting on the apex, a 5.0 mm  $\times$  15 mm NC Euphonia noncompliant



**Figure 1.** Guidewire entering the left ventricle.



**Figure 2.** Balloon catheter inflated at mitral annular level.



**Figure 3.** Mitral valve before (A) and after the intervention (B). The complete opening of both discs can be seen after the percutaneous intervention.

balloon (Medtronic) was smoothly advanced and inflated several times at mitral annular level until the blocked disc was fully released (figure 2) (videos 3 and 4 of the supplementary data). The transesophageal echocardiography performed postprocedurally confirmed the normalization of valvular function with a mean gradient of 5 mmHg and a proper movement of both discs (figure 3). The patient was extubated immediately after the intervention without complications or further thromboembolic or hemorrhagic events. She was discharged 2 days after the procedure and remained on oral anticoagulants and acetylsalicylic acid. A systematic study conducted discarded coagulation alterations and the patient remained asymptomatic at the 12-month follow-up.

The percutaneous manipulation of a mechanical valve with PVT can be a therapeutic option in patients with low thrombotic load in whom thrombolysis is contraindicated or ineffective or in whom surgery is not feasible. However, although in our case there were no complications there is a high risk of embolic events inherent to any percutaneous manipulation of a PVT, which is why carotid filters should be considered to minimize such risk.

## FUNDING

No funding was received for this work.

## CONFLICTS OF INTEREST

None declared.

## SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M20000133>.

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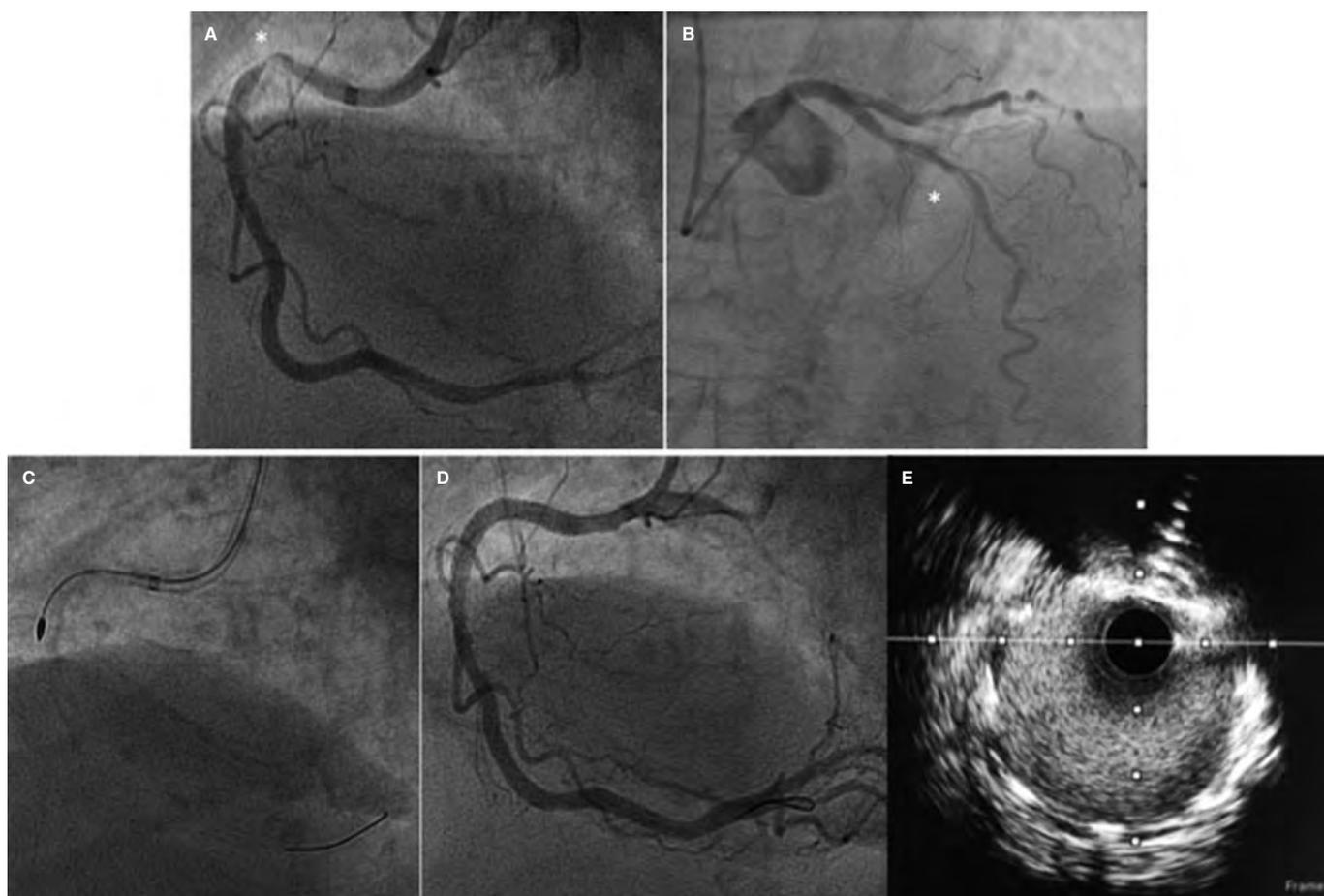
## Left main coronary artery perforation after rotational atherectomy



### *Perforación del tronco coronario izquierdo tras aterectomía rotacional*

Alfonso Jurado-Román,\* Guillermo Galeote, Santiago Jiménez-Valero, Sandra Ofelia Rosillo, Raúl Moreno, and José Luis López-Sendón

Servicio de Cardiología, Hospital Universitario La Paz, Madrid, Spain



**Figure 1.**

Eighty-five-year-old woman with unstable angina with serious and heavily calcified lesions in proximal right coronary arteries (figure 1A, asterisk) and proximal and mid left anterior descending coronary artery (figure 1B, asterisk).

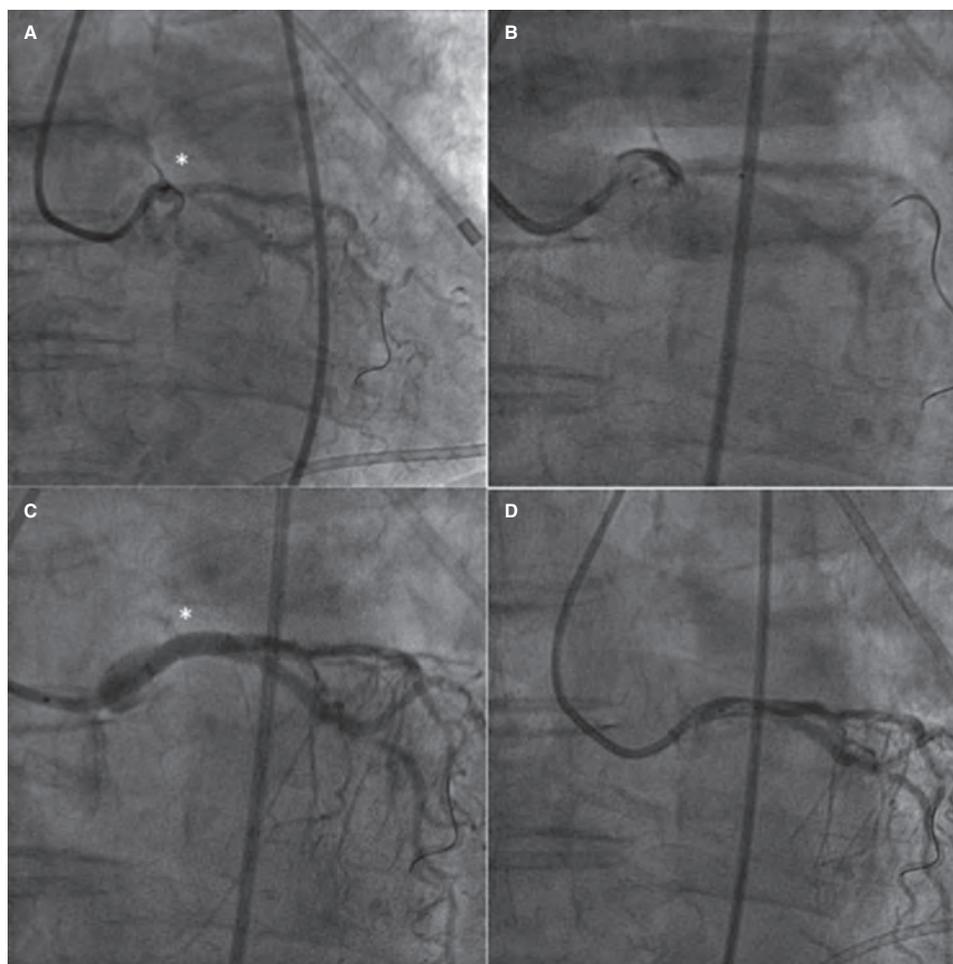
Rotational atherectomy was performed in the right coronary artery using the RotaPro system (Boston Scientific, United States) (figure 1C) and a drug-eluting stent was implanted with good results (figure 1D) as confirmed by the intracoronary ultrasound (figure 1E). Informed consent was obtained from the patient.

\* **Corresponding author:** Servicio de Cardiología, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.  
E-mail address: [alfonsojuradoroman@gmail.com](mailto:alfonsojuradoroman@gmail.com) (A. Jurado-Román).

Received 5 December 2019. Accepted 23 January 2020. Online: 24-03-2020.

<https://doi.org/10.24875/RECICE.M20000100>

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**Figure 2.**

After the catheterization of the left main coronary artery (LMCA) the left anterior descending coronary artery was crossed. A 1.5 mm olive-shaped burr was advanced in the DynaGlide mode towards the LMCA, which is when the guide catheter was extubated and an Ellis type III perforation occurred in the LMCA (figure 2A, asterisk; video 1 of the supplementary data); it is possible that an unnoticed deformation of the guidewire moved the burr towards the vessel wall. The patient showed cardiac tamponade that was treated with pericardiocentesis. A 4 × 15 mm PK-Papyrus covered coronary stent (Biotronik, Germany) was implanted in the LMCA without jailing the bifurcation (figure 2B). However, a discrete leak of contrast still occurred (figure 2C, asterisk). After postdilatation with a 4.5 mm balloon, the perforation was sealed (figure 2D; video 2 of the supplementary data). The disease progression of the patient was favorable.

Coronary perforations at LMCA level are rare, but they can be lethal. Prolonged balloon inflations in this location are not well tolerated, which is why proceeding to implant the covered stent fast may be the best alternative. To our knowledge, this is the first perforation of the LMCA ever reported with rotational atherectomy resolved with a Papyrus stent.

## FUNDING

No funding.

## 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.

## SUPPLEMENTARY DATA



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M20000100>.

# Deployment of cerebral protection device in complex anatomy

## Posicionamiento del dispositivo de protección cerebral en anatomía compleja

Héctor Cubero-Gallego,\* Pablo Avanzas, Raquel del Valle, Isaac Pascual, Daniel Hernández-Vaquero, and César Morís

Área del Corazón, Hospital Universitario Central de Asturias, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Universidad de Oviedo, Oviedo, Asturias, Spain

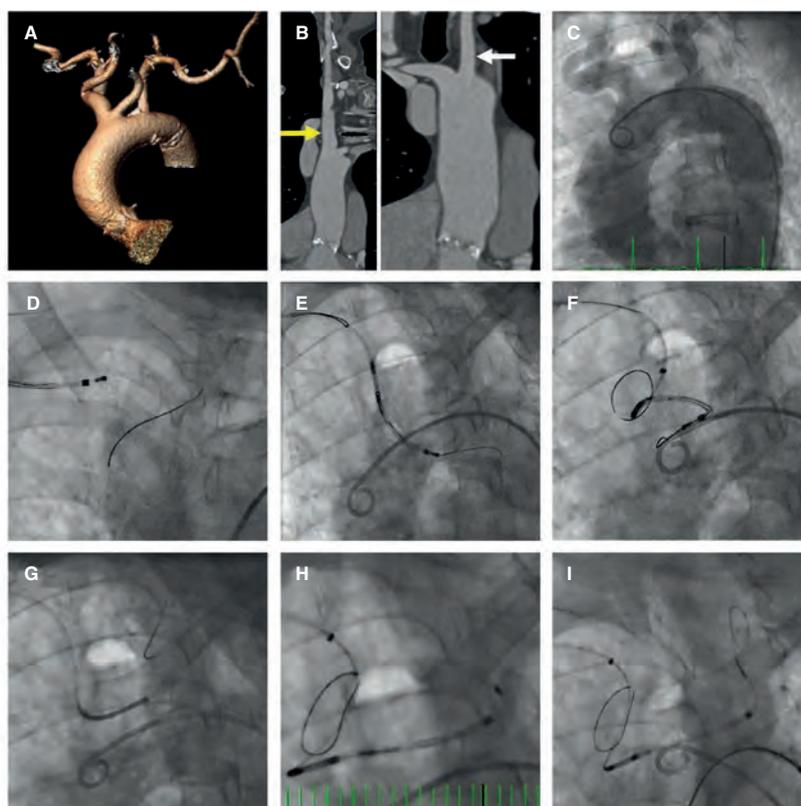


Figure 1.

An 84-year-old female with severe aortic stenosis and previous non-disabling stroke was referred to undergo transcatheter aortic valve replacement (TAVR). The 3D computed tomography performed revealed the presence of a type 9 aortic arch with severe tortuosity (figure 1A). It was decided to protect the supra-aortic branches with suitable diameters to be able to use the Sentinel Cerebral Protection System (Boston Scientific, Marlborough, MA, United States). Manipulation length in the left common carotid artery (LCCA) was of, at least, 8 cm which is the distance between the proximal filter and the Sentinel distal edge. Figure 1B: yellow arrow: brachiocephalic trunk, 12 mm-diameter. White arrow: LCCA, 7 mm-diameter. This cerebral protection device (CPD) has a proximal filter for brachiocephalic trunk diameters between 9.0 mm and 15 mm and a distal filter for LCCA diameters between 6.5 mm and 10 mm. The angiography of the aortic arch is shown on figure 1C. This dual-system-filter basket was tried unsuccessfully over a 0.014 in guidewire despite the use of an articulating sheath (figure 1D-F). After several attempts, a multipurpose catheter was used to engage the LCCA (figure 1G). Using a 300 cm 0.014 in guidewire, the multipurpose catheter was exchanged for the CPD which allowed its suitable deployment (figures 1H,I). The TAVR was performed successfully and the CPD was retrieved (video 1 of the supplementary data). Informed consent was obtained from the patient.

\* Corresponding author: Área del Corazón, Hospital Universitario Central de Asturias, Avda. Roma s/n, 33011 Oviedo, Asturias, Spain.  
E-mail address: [hektorkubero@hotmail.com](mailto:hektorkubero@hotmail.com) [H. Cubero-Gallego].

Received 21 January 2020. Accepted 10 March 2020. Online: 23-04-2020.

<https://doi.org/10.24875/RECICE.M20000112>

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The major concern is how to balance the risk of stroke after TAVR and the risk of manipulation with guidewires/catheters in supra-aortic arteries. Thus, the rigorous study of the computed tomography scan is the key factor for strategic planning purposes. This was an alternative approach to achieve the placement of a Sentinel device using a multipurpose catheter in a complex aortic arch.

#### **FUNDING**

No funding was received for this work.

#### **CONFLICTS OF INTEREST**

None declared.

#### **SUPPLEMENTARY DATA**



Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.24875/RECICE.M20000112>.

# Magmaris bioresorbable stent: cardiac CT follow-up

## Stent bioabsorbible Magmaris: seguimiento por cardio-TC

Lydia Bos,<sup>a,\*</sup> Victor Agudelo,<sup>b</sup> and David Viladés<sup>a</sup>

<sup>a</sup> Unidad de Imagen Cardíaca, Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>b</sup> Unidad de Hemodinámica, Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

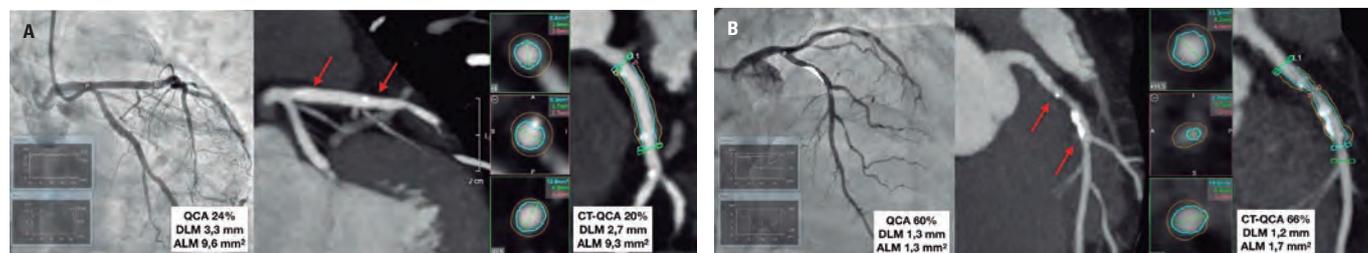


Figure 1.

Fifty-five-year-old male with signs of angina and anterior ischemia as seen on the single-photon emission computed tomography. The invasive coronary angiography performed confirmed the presence of significant stenosis in the proximal left anterior descending coronary artery (LAD). A percutaneous coronary intervention was attempted using a 3.5 x 20 mm Magmaris bioresorbable scaffold. At the 12-month follow-up and as part of a clinical research protocol, both the control invasive coronary angiography and cardiac computed tomography (cardiac CT) performed confirmed the good correlation between the minimum lumen diameter (MLD) and the minimum lumen area (MLA). The quantitative coronary angiography (QCA) performed showed the same results (figure 1A; note that in the cardiac CT the 2 hyperintense points pointed with red arrows show the location of the borders of the stent.)

A second 65-year-old male with previous ischemic heart disease underwent an invasive coronary angiography due to new-onset angina that revealed the presence of a significant stenosis in the proximal LAD. A percutaneous coronary intervention was performed using a 3.5 x 15 mm Magmaris scaffold. At the 12-month follow-up, the angina symptoms relapsed with a positive ergometric test to moderate load. The cardiac CT revealed the presence of moderate in-stent restenosis that was later confirmed and treated percutaneously. Also, in this clinical scenario a good correlation was seen between the diameters and the areas measured with both imaging modalities (figure 1B).

Both cases suggest that cardiac CT can be a useful tool in the follow-up of patients who are carriers of a Magmaris bioresorbable scaffold, especially in patients with larger diameters implanted in not severely calcified lesions. This may be applicable to other types of polylactic acid-based devices if the new generations of devices achieve enough clinical evidence. The present study was conducted in accordance with the Helsinki Declaration Code of Ethics. The patients granted their verbal and written consent to the diagnostic tests, and to the data analysis and processing.

### FUNDING

No funding was received for this work.

### CONFLICTS OF INTEREST

None declared.

### ACKNOWLEDGEMENTS

The authors wish to thank the funding from Canon Medical through an unconditional grant.

\* Corresponding author: Sant Quintí 89, 08041 Barcelona, Spain.

E-mail address: lidiabore@gmail.com (L. Bos).

Received 25 February 2020. Accepted 13 March 2020. Online: 06-06-2020.

<https://doi.org/10.24875/RECICE.M20000115>

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