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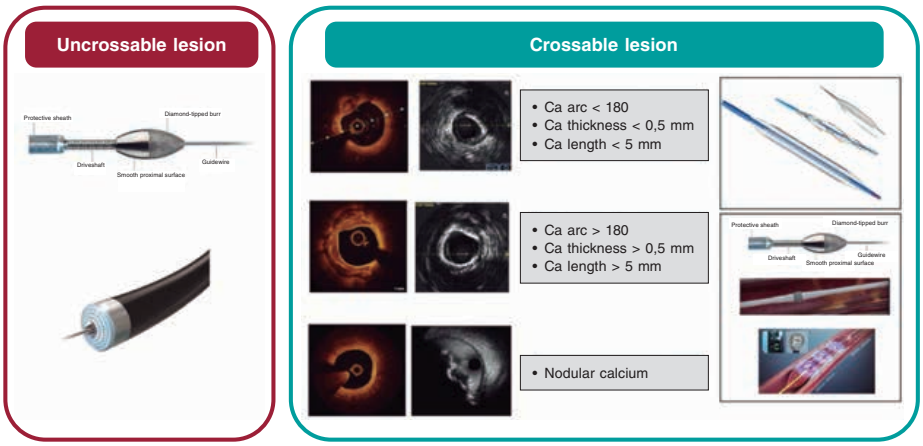

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CONTENTS

VOLUME 4, ISSUE 3, JULY-SEPTEMBER 2022

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Editorial

The need for a Spanish registry of interventional procedures to treat congenital heart disease and standards for center accreditation

La necesidad de un registro español de intervencionismo en cardiopatías congénitas y de estándares para la capacitación de centros

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Over the last 3 decades, the percutaneous treatment of congenital heart diseases has made significant progress. Currently, it is the therapy of choice to treat many of these diseases like atrioventricular septal defects, pulmonary valve stenosis or coarctation of the aorta. Multiple procedures throughout the life of a patient are required to treat complex heart disease like stenting and, more recently, percutaneous valves, which have become additional alternatives to surgery.

Since 1990, cath lab activity is regulated in the registries published by the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC).[1] In the annual publications of these registries there is a small section dedicated to congenital heart disease in the adult population with details on the activity performed, but without an in-depth analysis of the outcomes, complications or mortality.

The ACI-SEC and the Spanish Society of Pediatric Cardiology and Congenital Heart Disease Working Group on Hemodynamics have joined forces—for the first time in our country—to conduct a registry of the procedures performed in patients of all ages with congenital heart disease since the fetal stage until the adult age with the collaboration of pediatric and adult cardiologists.[2] The Spanish Society of Cardiovascular and Endovascular Surgery has recently published a registry of surgical procedures performed in patients with congenital heart disease from 2019, and retrospectively, of the past 8 years.[3] Therefore, we should mention that, to this date, in Spain, we have surgical and percutaneous activity registries in the specific field of congenital heart disease.

In the first official report from the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry—recently published in *REC: Interventional Cardiology*—Ballesteros Tejerizo et al.[2] reported the activity of 16 public centers, 7 of which have exclusive dedication to pediatric patients in an unaudited voluntary registry through an online database. The number of participant centers can be representative of pediatric activity. However, this seems like a very low number of hospitals to be representative enough of the activity developed in adult congenital heart disease. As a matter of fact, by 2014, there were already 24 PCI-capable centers with specialized consultations on the management of congenital heart diseases.[4] Also, other centers perform interventional procedures to treat simple congenital heart disease like interatrial shunt and patent foramen ovale closures without specialized consultations. These 2 aspects can explain the huge difference seen between the ACI-SEC national registry that reported a total of 1341 interventional procedures performed in the adult population compared to the 367 procedures reported in this registry.[2,5] This low representativity of interventional procedures in adult patients should be included in future registries to get an actual snapshot of the activity performed in this field.

The higher rate of almost 5% reported in the activity performed in the management of congenital heart disease in 2000—the pandemic year—compared to 2019 is not easy to explain either even though fewer hospitals (2) participated that year. This contrasts with other registries—like the Italian one—where 6 out of the 11 participant centers saw how their activity dropped over 50%, especially among adults and teenagers.[6] Also, during the pandemic, patients with congenital heart disease were a susceptible population with a higher morbidity and mortality risk due to appointment cancellations, and delays in the diagnosis and treatment of complications.[7]

Another significant and debatable aspect is the definition of congenital heart disease included in the registry. The patent foramen ovale can be present in over 25% of the general population and has become part of the interventional procedures performed to treat congenital heart disease. In fact, it is the most prevalent one among the adult population. However, interventional procedures to treat bicuspid aortic valve— considered the most common congenital heart disease and present in 1% to 2% of the general population—was not included in this registry. Although valve disease following calcification often occurs at a younger age compared to the tricuspid aortic valve—at around 50 to 60 years old—current registries show that transcatheter aortic valve implantation is performed in 4% to 5% of the patients with bicuspid aortic valve.[8] Also, bearing in mind that 4241 percutaneous aortic valves were implanted in Spain, it somehow seems logical to agree that nearly 190 were implanted in the bicuspid aortic valve, but this figure was never reported in this registry.

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The pulmonary angioplasty section includes interventional procedures on pulmonary branches, the native right ventricular outflow tract, and prosthetic valve conduits. These are different procedures regarding complexity and potential complication, which is why they should be included in separate sections.

We should mention the low rates of serious complications (2%), and mortality (0.1%) reported, which are similar to the ones reported by the best international registries. The exception to this was interventricular shunt closure with a high rate of complications reported—over 10%—which emphasizes the technical difficulty of this procedure.

The availability of a national registry on pediatric percutaneous procedures and adult congenital procedures with a prospective database is essential for patients, and their families. Also, for doctors who treat and advice patients on the risks and outcomes of a given procedure, and for interventional cardiologists to improve their clinical practice. It allows us to analyze results and draw comparisons among hospitals, autonomous communities, and even countries to eventually implement process management upgrades.

Also, this is closely associated with the need for establishing the optimal conditions to perform percutaneous procedures to treat congenital heart disease, and with the accreditation of both centers and interventional cardiologists. A consensus document was drafted on the need to establish the infrastructure standards and experience that both centers and interventional cardiologists should have by the different working groups and associations on pediatric and adult congenital heart disease, and the European Society of Cardiology.[9] Two different levels of centers were established based on the number of procedures performed each year. Therefore, in level 1 centers, the lead operator should perform, at least, 70 procedures with, at least, 10 percutaneous valve implantations, 10 angioplasties, and stenting to treat coarctations of the aorta, pulmonary arteries, surgical conduits or baffles (for a total of 10 in any of these areas). Also, the second operator should perform ≥ 30 procedures (over 100 in 1 year). Level 2 centers would need to perform over 60 procedures each year. Although these figures can seem arbitrary, it is essential to perform a high volume of procedures per center, and have onsite cardiac surgery teams expert in the management of congenital heart disease to solve potential and emergency complications that may arise. Heart teams including several specialties and experience in this field are required too. Therefore, this type of procedures should only focus on interventional cardiologists and experienced centers to obtain optimal results.

The future of structural and congenital heart procedures is guaranteed and looks bright thanks to the technological advances made in this field that will invariably improve the quality of life and increase the survival rate of patients with heart disease. Although there is large room for improvement in the quality of data curation for future registries, the first Spanish registry on interventional procedures for the management of congenital heart disease is a major first leap that should be interpreted as a snapshot of the state of interventional procedures to treat congenital heart disease, the activity, and results obtained nationwide. This will help standardize procedures and obtain excellent results.

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CONFLICTS OF INTEREST

None reported.

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Editorial

Bayesian vs frequentist statistics: afraid of losing the reference?

Estadística bayesiana frente a frecuentista: ¿temor a la pérdida del referente?

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While on his first hospital duty, a second-year cardiology resident receives a message in his pager about a patient who has just been admitted to the emergency room with chest pain. Specifically, he is asked to discard that the pain is of coronary origin. The resident questions the patient on his symptoms, examines his risk factors, and analyzes the electrocardiogram (ECG). With the ECG data, the qualitative information of pain provided by the patient, together with his past medical history, the presence of coronary pain is eventually discarded. The patient's past medical history reads «the symptoms described by the patient, the presence of hypertension as the only risk factor, and the lack of specific changes on the ECG suggest that the chances of coronary pain are extremely low». Intuitively, the resident considers that the chances the pain is due to coronary artery disease (CAD) with the data available (qualitative data of pain, risk factors, ECG) is lower than, let's say, 5%. In other words, the resident instinctively concludes that:

$$p(CAD|qualitative\ data,\ risk\ factors,\ ECG) < .05,$$

that is, the probability of having CAD according to all the above-mentioned information (qualitative data, risk factors, and ECG) is < 5%.

However, before the patient is discharged, the resident decides to consult with the fifth-year cardiology resident who is at the Coronary Care Unit. He arrives to the emergency room and asks the patient about his symptoms, examines his medical history, and crosschecks his ECG once again. The much more experienced fifth-year resident considers that, although there are no risk factors other than hypertension, certain characteristics of the pain could have a coronary origin. And not only that, the analysis of the ECG reveals minimal repolarization alterations that appear as a mild—almost unnoticeable—rectification of the ST-segment. Intuitively, the resident considers that the chances that the pain is due to coronary artery disease (CAD) is undoubtedly > 5%, and possibly > 20%. In other words, the fifth-year resident intuitively concludes that:

$$p(CAD|qualitative\ data,\ risk\ factors,\ ECG) > .02$$

that is, the probability of having CAD according to all the information provided above (qualitative data, risk factors, and ECG) is > 20%.

With this early assessment, the fifth-year resident decides to perform a transthoracic echocardiogram (TTE) that reveals alterations in segmental contractility. With this new information available, the resident believes that the chances that the pain is of coronary origin have increased significantly:

$$p(CAD|qualitative\ data,\ risk\ factors,\ ECG,\ TTE) > .05$$

The intuition of a moderate-high probability of the coronary origin of the pain plus the information provided by the TTE suggest that high-sensitivity troponin (Tp) level should be tested, as Tp appears slightly elevated. Therefore, the intuitive probability that the patient's chest pain is of coronary origin increases even more:

$$p(EC|qualitative\ data,\ risk\ factors,\ ECG,\ TTE,\ Tp) > .08$$

The previous example—though rather simplistic—illustrates several factors associated with conditioned probability and, more specifically, with traditional Bayes' theorem.

Firstly, it illustrates how Bayes' theorem is possibly a very appropriate mathematical approach to update our natural and intuitive decision making in medicine: we take an effect—which is what we find at the patient's bedside—(chest pain), and make a decision on its cause with diagnostic, prognostic or treatment purposes, and then intuitively assign a probability to the cause under consideration (coronary artery disease). We do this with the information available we believe to be the effects of this cause while considering other variables closely associated with the cause such as the characteristics of pain, the ECG, the risk factors, etc.

Secondly, it illustrates how different sources of information added sequentially provide a more accurate definition on the probability of a given cause, always intuitively. And not only that, in the routine clinical practice, interpreting different sources of information varies

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from observer to observer, which will determine that the probability assigned to a given cause will vary significantly among observers. Here the clinician's experience undoubtedly plays a key role.

This example also indirectly illustrates how difficult it is to obtain numerical—though approximate—estimates of the actual probability of the real cause for the effect (CAD) from the effects seen and other variables associated with this cause. As Armero et al.[1] state in an article recently published in *REC: Interventional Cardiology*, the accurate probability estimate of the example would require solving the equation of Bayes' theorem:

$$p(CAD|information\ available) = \frac{p\ (information\ available|CAC)\ p(CAD)}{p\ (information\ available}$$

where information available, in the example, would be the qualitative data of pain, the risk factors, the ECG, etc. But here is where problems begin. Like Armero et al.[1] say, the first problem is to obtain the prior distribution to estimate probabilities. Although estimates can be made on the probability of CAD in a population based on its prevalence or on the probabilities of hypertensive patients or on the probabilities of having an abnormal ECG, estimating the probability of the qualitative data of pain doesn't have a clear distribution on which to lean on. Like Armero et al.[1] say the second problem is implementing an analytical expression for the posterior distribution of parameters and estimating the function of verisimilitude. Again, although the probability of knowing that a hypertensive patient has CAD or that an ECG shows certain characteristics of coronary artery disease is feasible, the problem becomes more complicated when several sources of information are combined; what are the chances of having chest pain with certain characteristics in a hypertensive patient with a given ECG knowing that he's got CAD? Although it is true that distribution samples can be simulated, the analytical method becomes complicated and—as Armero et al.[1] say—interpretation probably stops being intuitive.

We should also add the problem of «expert knowledge» to the mix for the definition of prior distribution. Like the example illustrates, knowledge can depend on the expert's interpretation. But also, to a great extent, prior knowledge can significantly be affected by publication bias or it can be erroneous, which is why the associated informative distribution will give rise to biased probability estimates.

Due to all of this, although it is very possible that doctors can use Bayes' theorem naturally for his decision-making process regarding diagnosis, prognosis, and treatment, this does not seem to have translated into a significantly wider use of this methodology in research. In an exercise of indirect approach to corroborate the this, we used PubMed to analyze «clinical trial» or «randomized clinical trial» publications in the cardiovascular field over the last 10 years. Then, we selected those where the term «Bayesian» was included somewhere in the text field. Like figure 1 shows—although it has increased significantly over the last few years—the overall rate of possible use of Bayesian methodology in clinical trials in the cardiovascular field is well under 7‰.

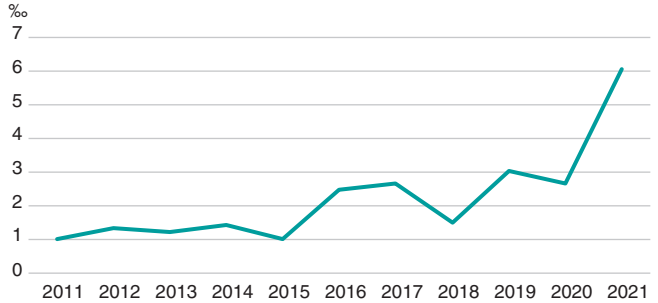

Figure 1. Clinical trials published over the last 10 years in the cardiovascular field with possible Bayesian methodology (for every 1000 cardiovascular publications).

If, like Armero et al.[1] say, the Bayesian protocol is easy-to-use, robust, and conceptually powerful, why is it used so marginally compared to frequentist statistics? We believe there are several reasons for this. In the first place, frequentist statistics was the first ever used to answer research questions in medicine possibly because right from the start the most common probability distributions had already been perfectly defined, and it was easy to apply the inferential method for decision-making based on such distributions with perfectly defined parameters. However, analytical and computer problems associated with the use of Bayes' theorem to estimate probabilities were not initially resolved. Secondly, because of the simplicity of being able to make decisions on whether a treatment, diagnostic method, procedure, etc. is effective or not based on the selection of P value < .05 so popular in the frequentist method also referred to by Armero et al. Finally, because the Bayesian conception of probability allocation to parameters and being able to establish direct probabilistic assessments means that the parameter is not an immovable fixed reference anymore. From the analytical standpoint this is a change of paradigm we are not used to. But maybe this loss also generates certain anxiety: parameters are not unchangeable anymore.

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CONFLICTS OF INTEREST

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Editorial

The role of percutaneous tricuspid regurgitation interventions in the current clinical practice: tackling a heterogenous disease

El papel de las intervenciones percutáneas en la insuficiencia tricuspídea en la práctica actual: abordando una enfermedad heterogénea

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Severe tricuspid regurgitation (TR) is known to be independently associated with adverse prognosis.[1] Its importance is further emphasized by the prevalence of this entity, particularly in the aging population.[2] Until the past few years, surgical management was the only available effective treatment for isolated severe TR. Operative mortality, nonetheless, remains high.[3] Moreover, surgery is associated with a 45% recurrence rate after 5 years,[4] and recent data suggest that surgery may not improve the survival rate in isolated severe cases of TR.[5] Accordingly, guidelines recommend TR surgery as a class 1 indication only with concomitant left-sided valvular surgery.[6] Conversely, patients with prohibitive surgical risk managed conservatively were shown to have dismal outcomes.[7] Fortunately, the emergence of percutaneous devices expanded the horizon of TR treatment.

TACKLING THE MULTI-MECHANISTIC PATHOLOGY

TR is the product of various pathophysiological mechanisms including right ventricular (RV) dilatation with consequential leaflet tethering, tricuspid annular dilatation with subsequent mal-coaptation, atrial fibrillation causing further annular dilation through atrial enlargement, and abnormalities in the tricuspid valve leaflets and apparatus. At a certain point, regurgitation itself becomes an etiology through a vicious circle of RV and atrial remodeling. Accordingly, numerous percutaneous devices are being developed for transcatheter tricuspid valve repair (TTVr) and replacement (TTVR). They can be classified according to their mechanism—leaflet approximation, direct suture or ring annuloplasty and valve implantation that can be orthotopic—implantation in the anatomic tricuspid location or heterotopic implantation in the cavoatrial junction. The long-term stability of the orthotopic valve may be compromised due to the structural changes of the valvular apparatus over time that faces increased postoperative afterload. Some valves minimize this effect by not entirely relying on radial forces such as the Lux-Valve (Ningbo Jenscare Biotechnology, China) that attaches to the septum. Of note, a shortcoming of the Lux-valve is the thoracotomy requirement. An approach to relief RV pressure due to increased afterload is the Trisol valve (TriSol Medical, Israel) that induces leaflet coaptation by using a dome-shaped structure that enables larger RV closing volume. Additional orthotopic valves like the Intrepid (Medtronic, United States)—that received the Food and Drug Administration Breakthrough Device designation—and the Evoque (Edwards Lifesciences, United States) are showing encouraging results. Heterotopic valve implantation had been reported as double-valve implantation (inferior and superior vena cava), as well as single valve solely into the inferior vena cava. Nevertheless, the vena cavae can show substantial dynamic variations in size as well, particularly in self-expanding valves applying radial force on the compliant vessel, whereas right atrial enlargement can generate a funnel-shaped cavoatrial junction, thus increasing the risk of valve migration. Since the procedure results in the ventricularization of the right atrium, persistent overload can cause morphological changes and adversely impact the cardiac function.

Additional anatomical considerations play a role in device selection including the course of the right coronary artery, proximity to the atrioventricular node, and or/bundle of His (in this regard, the NaviGate valve—NaviGate Cardiac Structures, United States—has short graspers, and termed atrial winglets to prevent compression of the conduction system[8]), the dimensions of the inferior vena cava and its orientation relative to the right atrium (that can impact device stability and introduce difficulties achieving coaxiality), the size of the tricuspid annulus (large annuli may be modified as with the TriCinch—4Tech Cardio, Ireland—,[9] that mimics the Kay procedure), the distance between the tricuspid annulus and the RV apex, the size of the iliac vein (eg, the Cardiovalve—Cardiovalve, Israel—and the Evoque utilize a relatively low profile), the presence of an intracardiac shunt, short leaflet length (with an insufficient grasping area), thickened nonpliable leaflets, coaptation gap and depth (usually over ~7mm is a predictor of leaflet approximation failure), tethering severity, the tenting area and height, the location of the regurgitant jet, the number of leaflets (eg, 3 or 4), a proper annular shelf, and the juxtaposed noncoronary sinus relative to the device anchoring to the anterior and septal leaflet commissures (that may be compromised by the anchoring mechanism).

Multiple factors must, therefore, be taken into observed when considering a patient for TTVr/TTVR, and a thorough evaluation is warranted. In advanced stages of the disease manifesting as severe

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RV enlargement, considerable tethering or very large annuli, TTVr and TTVR may not be technically feasible. The anatomical characteristics can exceed the device capabilities, eg, the maximum length of Cardioband (Edwards Lifesciences, United States) tricuspid system is 120 mm. Even if the intervention is technically possible with advanced disease, irreversible damage to the RV structure and function may impede clinical improvement. Nevertheless, the point of no return is not clear, and patients with RV dysfunction and pulmonary hypertension have the potential to improve.[10]

Finally, the patient's characteristics must be reviewed as certain trials excluded patients with specific comorbidities like chronic kidney disease or systolic pulmonary artery pressure > 70 mmHg.

OUTCOMES OF PERCUTANEOUS TRICUSPID VALVE INTERVENTIONS

TriValve is the largest TTVr registry available predominantly describing edge-to-edge repair with MitraClip (Abbott Vascular, United States) in the tricuspid position. Use of MitraClip was described as bicuspidization of the tricuspid valve,[11] by approximating the posterior or anterior leaflet to the septal leaflet (while anterior to the posterior leaflet clipping may distort the valvular apparatus). Devices operating with similar mechanisms are the TriClip (Abbott Structural Heart, United States), and the PASCAL (Edwards Lifesciences, United States).

Table 1. Outcome data with transcatheter tricuspid valve devices

	Leaflet approximation devices					Annuloplasty devices				
Device (company) or procedure	MitraClip (Abbott Vascular, United States)[12]	TriClip (Abbott Structural Heart, United States)[13]	PASCAL (Edwards Lifesciences, United States)[14]	TriCinch (4Tech Cardio, Ireland)[9]	Mistral (Mitralix, Israel)[15]	FORMA (Edwards Lifesciences, United States)[16]	Millipede (Boston Scientific, United States)[17]	Cardioband (Edwards Lifesciences, United States)[18,19]	Trialign (Mitralign, United States)[20]	PASTA[21]
No.	249	85	34	1	7	29	2	30	15	1
TR grade improvement after 30 days			Yes		Yes	Yes	Yes	Yes	Yes	
Significant improvement in QoL measures after 30 days			Yes		Yes	Yes		No	Yes	
Mortality after 30 days			0%		0%	0%		6.7%	0%	
TR grade improvement after 6 months		Yes		Yes				Yes		
Significant improvement in QoL measures after 6 months		Yes		Yes				Yes		No
Mortality after 6 months		5%		0%				10%		0%
TR grade improvement after 1 year	Yes	Yes				Yes (N = 16)				
Significant improvement in QoL measures after 1 year	Yes	Yes				Yes (N = 16)				
Mortality after 1 year	20%	7.1%				0% (N = 16)				
TR grade improvement after 2 years								Yes		
Significant improvement in QoL measures after 2 years								Yes		
Mortality after 2 years								26.7%		

(Continues)

Table 1. Outcome data with transcatheter tricuspid valve devices *(Continued)*

	Orthotopic valve implantation						Heterotopic valve implantation		
Device (company)	NaviGate (NaviGate Cardiac Structures, United States)[22]	Trisol (TriSol Medical, Israel)[23,*]	Lux-Valve (Ningbo Jenscare Biotechnology, China)[24,25]	Evoque (Edwards Lifesciences, United States)[26]	Cardiovalve (Cardiovalve, Israel)[27]	Intrepid (Medtronic, United States), NCT04433065*	TricValve (P+F Products + Features, Austria)[28]	Sapien in ring (Edwards Lifesciences, United States)[28]	Tricento (New Valve Technology, Switzerland)[29]
No.	5		12	25	1		7	14	1
TR grade improvement after 30 days			Yes	Yes					
Significant improvement in QoL measures after 30 days			Yes	Yes					
Mortality after 30 days			8.3%	0%					
TR grade improvement after 6 months	Yes								
Significant improvement in QoL measures after 6 months	Yes								Yes
Mortality after 6 months	0%								0%
TR grade improvement after 1 year			Yes					No	
Significant improvement in QoL measures after 1 year			Yes					No	
Mortality after 1 year			16.6%					57%	
TR grade improvement after 2 years					Yes				
Significant improvement in QoL measures after 2 years					Yes				
Mortality after 2 years					0%				

* No clinical follow-up data available yet.
QoL, quality of life; TR, tricuspid regurgitation.

Patients from studies describing the various devices were heterogenous and vary significantly from one to the other. Also, the 30-day mortality rate ranges from 0% to 13% with significant improvement in TR grade, and in the quality of life according to published data (table 1). Notable longer-term outcomes include a 20% mortality rate at 1-year follow-up in the MitraClip cohort,[12] and a 26% mortality rate after 2 years in the Cardioband cohort.[18] Currently, prospective efficacy data mostly rely on quality-of-life scores and TR grade. However, it was shown that patients with procedural failure have a significantly higher mortality rate,[30] suggestive that patients would fare worse without the procedure. Moreover, a registry-based propensity-matched study that compared TTVr to conservative treatment showed symptomatic and survival benefits.[31] Currently, 3 TTVr devices have received the CE marking: Cardioband, TriClip, and PASCAL system for the management of TR, but none have been approved by the U.S. Food and Drug Administration. Consequently, most percutaneous tricuspid interventions are applicable in trial settings or as compassionate use.

In conclusion, TTVR/TTVr devices are becoming considerably more viable options. Surgical, and most certainly, conservative treatment of patients with severe TR are not ideal choices and expanding treatment possibilities towards percutaneous approaches is, therefore, an obvious choice. Results from ongoing trials have been anticipated, which will hopefully be followed by the approval of additional devices.

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A. Latib has served on advisory boards or as consultant for Medtronic, Boston Scientific, Edwards Lifesciences, Abbott, and VDYNE. The remaining authors have no relations to disclose.

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Original article

Spanish cardiac catheterization in congenital heart diseases registry. First official report from the ACI-SEC and the GTH-SECPCC (2020)

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ABSTRACT

***Introduction and objectives*:** The Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) and the Spanish Society of Pediatric Cardiology Working Group on Interventional Cardiology (GTH-SECPCC) introduce their annual activity report for 2020, the starting year of the pandemic of coronavirus disease (COVID-19).
***Methods*:** All Spanish centers with cath labs and interventional activity in congenital heart diseases were invited to participate. Data were collected online, and analyzed by an external company together with members from the ACI-SEC and the GTH-SECPCC.
***Results*:** A total of 16 centers participated (all of them public) including 30 cath labs experienced in the management of congenital heart diseases, 7 of them (23.3%) dedicated exclusively to pediatric patients. A total of 1046 diagnostic studies, and 1468 interventional cardiac catheterizations were registered. The interventional procedures were considered successful in 93.4% of the cases with rates of major procedural complications and mortality of 2%, and 0.1%, respectively. The most frequent procedures were atrial septal defect closure (377 cases), pulmonary angioplasty (244 cases), and the percutaneous closure of the patent ductus arteriosus (199 cases).
***Conclusions*:** This report is the first publication from the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry. The data recorded are conditioned by the COVID-19 pandemic. Diagnostic cardiac catheterization still plays a key role in this field. Most interventional techniques have reported excellent security and efficacy rates.

Keywords: Congenital heart disease. Cardiac catheterization. Atrial septal defect closure. Coronavirus. COVID-19.

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Registro Español de Intervencionismo en Cardiopatías Congénitas. Primer Informe Oficial de la ACI-SEC y el GTH-SECPCC (2020)

RESUMEN

***Introducción y objetivos*:** La Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC) y el Grupo de Trabajo de Hemodinámica de la Sociedad Española de Cardiología Pediátrica y Cardiopatías Congénitas (GTH-SECPCC) presentan el informe de actividad hemodinámica en cardiopatías congénitas de 2020, año de inicio de la pandemia de la enfermedad coronavírica de 2019 (COVID-19).
***Métodos*:** Se invitó a participar a los centros españoles con laboratorio de hemodinámica y actividad intervencionista en cardiopatías congénitas. La recogida de datos se realizó telemáticamente; una empresa externa, junto con miembros de la ACI-SEC y el GTH-SECPCC, los analizó.
***Resultados*:** Participaron 16 centros (todos públicos), que acumulan 30 salas de hemodinámica con actividad en cardiopatías congénitas, 7 (23,3%) de ellas con dedicación exclusiva a pacientes pediátricos. Se registraron 1.046 estudios diagnósticos y 1.468 cateterismos intervencionistas. Los procedimientos terapéuticos fueron exitosos en el 94,9%, con una tasa de complicaciones mayores del 2% y una mortalidad del 0,1%. Las técnicas más frecuentes fueron el cierre de comunicación interauricular (377 casos), la angioplastia pulmonar (244 casos) y el cierre de *ductus* arterioso (199 casos).
Conclusiones: El presente trabajo representa la primera publicación del Registro Español de Intervencionismo en Cardiopatías Congénitas. La casuística registrada está condicionada por la pandemia de la COVID-19. Los cateterismos diagnósticos siguen teniendo un papel relevante en esta actividad. Para la mayoría de las técnicas intervencionistas se han reportado excelentes datos de seguridad y eficacia.

Palabras clave: Cardiopatía congénita. Cateterismo cardiaco. Cierre de comunicación interauricular. Coronavirus. COVID-19.

INTRODUCTION

Interventional activity in the management of congenital heart disease in Spain has not been properly evaluated or analyzed to date. The collaboration between the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (ACI-SEC) and the Spanish Society of Pediatric Cardiology and Congenital Heart Disease Working Group on Hemodynamics (GTH-SECPCC) has reactivated and updated a registry that includes all procedures performed in patients, of any age, with congenital heart disease since their fetal stage up to their adult age.

The first report resulting from this new stage of the registry included the activity developed in 2019 and was presented in the 31st Annual Congress of ACI-SEC that was held online back in December 3-4 of 2020, and in the online administrative meeting of GT-SECPCC held in December 11, 2020.

The current report presented in this article includes the activity developed in 2020 and is the first one to be published; all the information obtained is extremely useful not only to know the volume and results of this activity, but also for the analysis of the implementation of different interventional techniques in Spain and put them in an international context. The continuity of this work will bring us knowledge of its progress in the coming years.

The provision of data was voluntary and took place through an online database. An external company handled and analyzed all the data collected. Members from the ACI-SEC and the GTH-SECPCC boards of directors were involved in the follow-up and process of revising this database; the involvement of both scientific societies—essential to conduct the registry—initiates a very desirable collaboration that should strengthen synergies among interventional cardiologists who work in adult and pediatric areas.

METHODS

This registry includes diagnostic and interventional procedural data from most Spanish centers with significant interventional activity in the field of congenital heart diseases. The submission of data has not been audited and is voluntary. It was conducted through an online questionnaire that only the person responsible from each center can access through ACI-SEC website.[1] An external company (Tride, Spain) handled and analyzed the results from the registry in collaboration with members from ACI-SEC and the GTH-SECPCC boards of directors. In case of conflicting data or outside the routine clinical practice, the lead investigator of each center was contacted to verify the information submitted. Given the methodological characteristics of the study and since it was an activity registry only no approval was necessary from any ethics committees. No informed consent was needed either.

RESULTS

Resources and infrastructure

A total of 16 hospitals participated in this registry, all of them from the public healthcare network (annex 1). A total of 30 cath labs with activity in the management of congenital heart disease were included, 7 of which (23.3%) were for pediatric use only. The regular number of days a month dedicated to performing interventional procedures to treat congenital heart diseases in each hospital had a median of 7.5 (4-15) days. However, in 14 (87.5 %) of these centers, emergency cath lab care has become available on a 24-hour basis for patients of any age with congenital heart diseases.

With regard to the medical personnel, a total of 50 interventional cardiologists are involved in this activity 26 of whom (52%) are trained in adult interventional cardiology and 24 (48%) in pediatric interventional cardiology.

Diagnostic procedures

A total of 1043 diagnostic studies were conducted; 55 (5.3%) in infants < 1 month of age; 111 (10.7%) in patients between 1 month and 1 year, 486 (46.7%) cardiac catheterizations in patients between 1 and 18 years of age, and 399 (37.4%) in patients over 18 years of age.

Table 1. Number of interventional procedures performed and distribution by age groups

Variable	Total	Fetal	< 1 month	1 month through 1 year	1 through 18 years	> 18 years
Interventional procedures	1458	1 (0.1)	141 (9.6)	257 (17.6)	694 (47.6)	365 (25.0)
Congenital aortic valvuloplasty	45	1 (2.2)	7 (15.6)	18 (40.0)	16 (25.6)	3 (6.7)
Congenital pulmonary valvuloplasty	97	0	33 (34.0)	28 (28.9)	25 (25.8)	11 (11.3)
Congenital mitral valvuloplasty	1	-	0	0	1 (100)	0
Pulmonary angioplasty	244	-	11 (4.5)	50 (20.5)	143 (58.6)	40 (16.4)
Aortic angioplasty	109	-	3 (2.8)	25 (22.9)	40 (36.7)	41 (37.6)
Other angioplasties	91	-	22 (24.2)	20 (22.0)	35 (38.5)	14 (15.4)
Closure of interatrial communication/patent foramen ovale	377	-	-	2 (0.5)[a]	155 (41.1)	220 (58.4)
Closure of the patent ductus arteriosus	189	-	7 (3.7)	42 (22.2)	132 (69.8)	8 (4.2)
Closure of interventricular communication	39	-	-	3 (7.6)[a]	29 (74.3)	7 (17.9)
Other occlusions	106	-	3 (2.8)	19 (17.9)	54 (50.9)	30 (28.3)
Removal of foreign body	34	-	2 (5.9)	3 (8.8)	23 (67.6)	6 (17.6)
Atrial septostomy and transseptal puncture	68	-	56 (82.4)	2 (2.9)	10 (14.7)	0
Transcatheter aortic valve implantation	58	-	-	-	29 (50.0)[b]	29 (50.0)

[a] In this case, data < 1 month, and from 1 month through 1 year were not reported separately, which is why the value is < 1 year of age.
[b] Data correspond to patients under 18 only, which is why the value is exclusive to this group only.
Data are expressed as no. or percentage (%).

With regard to the type of studies conducted, only 69 (6.6%) were categorized as emergency studies and the remaining ones as scheduled studies. Only 1 serious complication (cardiac tamponade) and no deaths were reported in this group.

Interventional procedures

A total of 1458 therapeutic cardiac catheterizations grouped into 13 different categories and distributed based on age and frequency were reported: only 1 case (0.1%) during the fetal stage, 141 (9.7%) in infants < 1 month, 257 (17.6%) in patients between 1 month and 1 year, 694 (47.6%) in patients between 1 and 18 years of age, and 367 (25.1%) in patients over 18 years of age (table 1).

A total of 132 of these procedures (9%) were categorized as emergency procedures. A total of 30 serious events directly associated with cardiac catheterization were reported (table 2) including 2 deaths (a 0.1% mortality rate). Also, 17 cases of device embolization were reported 5 of which required surgery.

Percutaneous valvuloplasties

A total of 45 aortic valvuloplasties performed on congenital aortic stenoses were reported including the only case of fetal cardiac intervention in the registry, 25 of these (55.6%) were performed in patients < 1 year 7 of whom (15.6%) were < 1 month, and only 3 (6.7%) were performed in patients > 18 years of age. In 82% of the procedures, the native valves that had not been treated previously were dilated. The procedural success rate was 93.3%, and only 1 death and 1 case of severe aortic regurgitation after dilatation were reported.

A total of 97 pulmonary valvuloplasties were reported. The most numerous age range reported with 61 cases (72.9%) was that of patients < 1 year, 33 of whom (34%) were infants < 1 month, and 11 (11.3%) were patients > 18 years of age. In 95 cases (97.9%) data on the type of valves treated were reported: 80 (84.2%) were native valves, 9 of which (9.4%) were imperforated; only in 3 of these valves ductal stenting was performed to optimize pulmonary output in association with perforation and valvuloplasty. A total of 87 procedures (89.7%) were considered successful. A total of 2 major complications—cardiac tamponade, and arrhythmia with hemodynamic repercussion—were reported. Finally, only 1 case of mitral valvuloplasty was reported on a valve previously treated that turned out a success.

Percutaneous angioplasties

Pulmonary angioplasty is the group with the most cases in this section with 244 cardiac catheterizations; 143 of these (58.6%) were performed in patients between 1 and 18 years of age being this age range the most common one for this procedure. The anatomical substrate of angioplasty was the dilation of branch pulmonary arteries in 176 cases (72.1%), native outflow tract in 38 (15.5%), and the surgical implantation of a pulmonary artery conduit in 30 cases (12.2%). The technical data of 209 procedures were reported (overall percentage, 85.7%): in 55% of these procedures the angioplasty was performed with stenting while in the remaining 45% conventional balloon dilatation was used; no dilatations with cutting balloons were reported. The success rate was 91.4%, and 4 major complications were reported: 2 cases of device embolization, 1 vascular dissection, and 1 case of severe arrhythmia.

A total of 109 aortic angioplasties were reported: in this case the age group with more dilatations was that of patients > 18 years of age with 41 cases (37.6%). A total of 70 procedures (64.2%) were reinterventions while 39 (35.7%) were procedures to treat the native aortic valves. The technical data of 100 cases (overall percentage, 91.7%) were reported with the following distribution: conventional balloon angioplasty, 33%; bare-metal stent implantation, 36%; covered stent implantation, 21%; and redilation of balloon-expandable stent, 10%. A total of 105 procedures (96.3%) were successful.

Table 2. Distribution of complications and deaths reported for each interventional procedure

Interventional procedure	N	Major complications and deaths
Congenital aortic valvuloplasty	45	2 (4.4) 1 severe aortic regurgitation, 1 death
Congenital pulmonary valvuloplasty	97	2 (2.1) 1 case of severe arrhythmia, 1 tamponade
Congenital mitral valvuloplasty	1	0
Pulmonary angioplasty	244	4 (1.6) 2 embolizations, 1 case of severe arrhythmia, 1 arterial dissection
Aortic angioplasty	109	1 (0.9) 1 femoral artery pseudoaneurysm
Other angioplasties	91	3 (3.3) 1 arterial dissection, 1 neurological event, 1 death
Closure of interatrial communication/patent foramen ovale	377[a] (330)	6 (1.8) 5 embolizations, 1 removal due to massive residual shunt
Closure of the patent ductus arteriosus	189	5 (2.6) 5 embolizations
Closure of interventricular communication	39	4 (10.2) 3 embolizations, 1 case of severe arrhythmia
Other occlusions	106[b] (100)	0
Removal of foreign body	34	0
Atrial septostomy and transseptal puncture	68	1 (1.5) 1 embolization
Transcatheter aortic valve implantation	58[c] (53)	2 (2.8) 1 embolization, 1 coronary artery compression
Total	1.458[d] (1.401)	30 (2.0)

[a] Percentages estimated over 330 cases reported.
[b] Percentages estimated over 100 cases reported.
[c] Percentages estimated over 53 cases reported.
[d] Percentages estimated over 1401 cases reported.
Data are expressed as no. or percentage (%).

Only 1 case of major complication was reported (1 arterial pseudoaneurysm that required thrombin therapy).

A total of 91 cardiac catheterizations associated with other angioplasties were reported; in this section the anatomical substrate was reported in 63 cases only (69.2%) with special attention to the dilation of the patent ductus arteriosus in 21 cases (33.3%), and surgical fistulae in 5 (7.9%). The success rate reported in this group was 89%; 1 death associated with cardiac catheterization, 1 vascular dissection, and 1 serious neurological event were reported as well.

Shunt closures and other closing procedures

Closure of interatrial communication (CIAC) was the most widely performed interventional procedure in the registry with 377 cases; 220 of these closures (58.4%) were performed in patients > 18 years of age. The type of anatomy of the defect was reported in 374 cases (99.2%): on the one hand, simple CIAC with a single hole, borders > 5 mm, and nonaneurysmal septum in 125 cases (33.4%). On the other hand, complex CIAC and patent foramen ovale in 83 and 166 cases (22.1% and 44.3%, respectively). The most widely used imaging modality to guide the closure was transesophageal ultrasound in 298 procedures (79%) followed by intravascular ultrasound in 56 (14.8%). Angiographic measurement during balloon inflation was used in 79 closures (20.9%). Results were reported in 330 cardiac catheterizations (87.5%) being successful in 97.6% of them; out of the 5 embolizations registered only 1 required surgical bailout.

A total of 199 closures of the patent ductus arteriosus were collected, 132 of which (66.3%) were performed in patients between 1 and 18 years of age, 10 closures (5%) were performed in premature patients, and 8 (4%) in patients > 18 years of age. Occlusion devices were used in 85.2% of the cases reported, and coil-type occlusion devices in the remaining ones. The antegrade venous access was the most widely used of all (69.3%). The success rate reached 96.5% with 5 cases of device embolization, 1 of these eventually requiring surgery.

The third group of shunt closures studied was the closure of interventricular communication (CIVC) including 39 cases, 32 of which (80%) were performed in patients < 18 years of age. This was the distribution of the IVC by anatomical substrate in the 38 closures (97.4%) that included this variable: perimembranous in 26 cases (68.4%), postoperative in 7 (18.4%), and muscular in 5 (13.1%). With regard to the technical data of the procedure, in 56.7% of the cases occluder devices were used while coil-type devices with a controlled release mechanism were used in the remaining ones (40.3%). Only 2 were hybrid procedures. Only 31 cases (79.4%) were considered successful associated with 4 major complications: 3 embolizations (1 of these required surgical bailout), and 1 case of severe arrhythmia as a type of atrioventricular block that prevented the delivery of the occluder device.

Also, data from other occluder devices were collected for a total of 106 cases including the closure of aortopulmonary collaterals in 41 cases (38.6%), the closure of venous collaterals in 18 (16.9%), and the closure of coronary fistulae in 28 cases (26.4%). The materials most widely used were occluder devices (48.5%) followed by coil-type occluder devices (29.1%), and particles (13.5%). The success rate reported reached 99%.

Atrial septostomy

A total of 68 procedures were collected, 56 of which (82.4%) were performed in infants < 1 month. Echocardiography was used as imaging modality guidance in 43 cases (63.3%), and x-ray images in 30 (44.1%). A total of 57 cases (83.8%) were treated with Rashkind balloon atrial septostomy. Also, 8 procedures of septal perforation with radiofrequency, and 7 procedures of septal stenting were reported. The success rate reported reached 100%.

Transcatheter aortic valve implantation

A total of 58 procedures were reported, 29 of which (50%) were performed in patients > 18 years of age. Of these, a total of 55 valves were implanted in the pulmonary position, 2 in the mitral position, and 1 in the tricuspid position. The results of 53 cases (91.4%) were reported with a success rate of 100% and 2 major complications without associated mortality: 1 embolization (that was solved percutaneously) and 1 coronary artery compression.

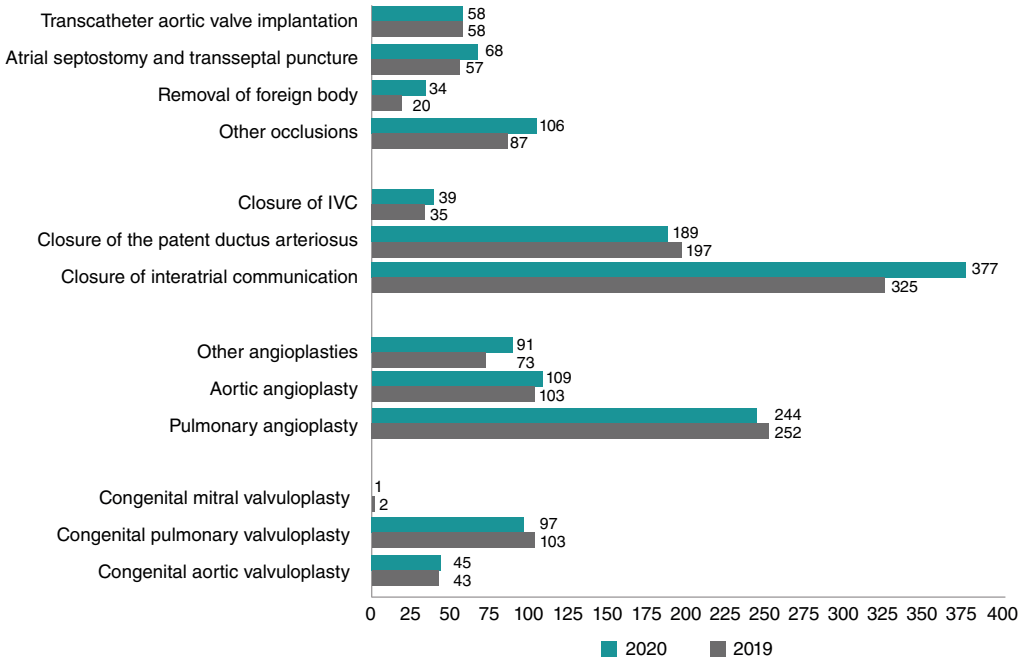

Figure 1. Comparison between the number of interventional procedures performed in 2019 and 2020. IVC, interventricular communication.

DISCUSSION

This study is the first one to report on the amount of interventional activity developed in our country for the management of congenital heart disease including pediatric and adult patients. The continuity of this registry and the collaboration between the ACI-SEC and the GTH-SECPCP will improve the quality of this registry in the coming years, and study its evolution in time.

The year 2020 was defined by the COVID-19 pandemic, which also conditioned the way care was provided for the management of cardiovascular disease.[2,3] In its annual activity report, the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology Registry of 2020[4] revealed that the reduction in the activity reported was actually not as significant as the one described within the first weeks of confinement, which would confirm a rebound in the activity reported after the first wave of the pandemic. In this registry, the volume of structural heart procedures like transcatheter aortic valve implantation did not fall that much while the volume of procedures like patent foramen ovale actually increased. In line with this trend, we also present a comparison of the data available from the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry from 2019 and 2020 (figure 1). This comparison shows a slight increase in the number of all interventional procedures performed compared to the previous year with an overall increase of 4.1%. We should mention that in the 2019 registry the participation of hospitals dropped (2 centers left the registry) compared to 2020, which puts this information into context.

Diagnostic cardiac catheterization provides relevant anatomical and hemodynamic information to guide the treatment required by patients with congenital heart disease through different stages of the disease. Despite the continuous development of other diagnostic techniques in this field, its significance can be seen in the volume of diagnostic procedures reported (1401 cases), which represent 41.6% of the overall number of cardiac catheterizations included in the registry.

Data from 1458 interventional procedures were collected of which 1093 cases (74.9%) correspond to patients < 18 years of age meaning that this activity is basically performed in the pediatric setting m. Only in the closure of interatrial communication, age range > 18 years was the one that accumulated more cases (overall percentage, 58.4%). On the other hand, only 1 interventional procedure (aortic valvuloplasty) was reported during the fetal stage, indicative that the number of patients treated with prenatal percutaneous therapy in our country is still limited.[5]

Over the last few years different studies have analyzed the risk of serious adverse events associated with cardiac catheterizations performed in pediatric and adult patients with congenital heart diseases;[6,7,8] given the variability of its methodology, the rate of serious adverse events also varies (from 2.5% to 7%) and for this same reason, the mortality rate reported is between 0.1% and 2%. In this registry, results and complications were reported in 96% of all interventional procedures performed. In addition, the rates of serious adverse events (2%) and mortality (0.1%) are consistent with those reported in previously cited international studies. Device embolizations—that mostly solved percutaneously—are among the complications most widely reported.

On the other hand, the overall effectiveness of interventional procedures is close to 94.9% (table 3). The least effective technique (79.4%) is the CIVC that is also associated with a high rate of complications (10.2%). All this could be interpreted as a demonstration of how difficulty and demanding it is to perform this procedure. Recently, the experience in our country with the CIVC using the Nit-Occlud device (PFM AG, Germany)—a coil-type device with a controlled release mechanism—has been published.[9] It includes the experience of 16 national centers in the management of 116 patients with an 89% efficacy and a rate of major complications of 6.9%.

With regard to valvuloplasties, percutaneous dilatation is the most widely accepted technique to treat congenital pulmonary valvular stenosis. Its efficacy reported in this registry (89.7%) may have been conditioned by certain unfavorable anatomical or genetic scenarios

Tabla 3. Summary of the efficacy of interventional procedures reported

Interventional procedure	N	Success	Infectious
Congenital aortic valvuloplasty	45	42 (93.3)	3 (6.7)
Congenital pulmonary valvuloplasty	97	87 (89.7)	10 (10.3)
Congenital mitral valvuloplasty	1	1 (100)	0
Pulmonary angioplasty	244	223 (91.4)	21 (8.6)
Aortic angioplasty	109	105 (96.3)	4 (3.7)
Other angioplasties	91	81 (89.0)	10 (11.0)
Closure of interatrial communication/ patent foramen ovale	377[a] (330)	322 (97.6)	8 (2.4)
Closure of the patent ductus arteriosus	189	184 (97.4)	5 (2.6)
Closure of interventricular communication	39	31 (79.4)	8 (20.5)
Other occlusions	106[b] (100)	99 (99.0)	1 (1.0)
Removal of foreign body	34	33 (97.1)	1 (2.9)
Atrial septostomy and transseptal puncture	68	68 (100)	0
Transcatheter aortic valve implantation	58[c] (53)	53 (100)	0
Total	1.458[d] (1401)	1330 (94.9)	71 (5.0)

[a] Percentage estimated over 330 cases reported.
[b] Percentage estimated over 100 cases reported.
[c] Percentage estimated over 53 cases reported.
[d] Percentage estimated over 1401 cases reported.
Data are expressed as no. or percentage (%).

disregarded during data duration. In primary care of congenital aortic stenosis there is still an unsolved ongoing debate on whether to go surgical or percutaneous.[10] The results reported on the aortic valvuloplasties performed (with a 93.3% efficacy) back up the convenience of using the percutaneous option in our setting. Finally, we should mention that, to this date, mitral valve valvuloplasty is an unusual technique in the congenital heart disease setting.

Within percutaneous angioplasties, the most widely used procedure was the dilation of branch pulmonary arteries that was also the second most widely performed interventional procedure of all in the registry. On the technique used, we should mention that no cutting balloon was used; instead, stent implantation was predominant. The cases reported of aortic angioplasty were mainly reinterventions and only a third treated the native aortic valve. Angioplasty with stenting was the most widely used procedure. Also, bare-metal stent implantation was more common compared to covered stent implantation.

Closure of interatrial communication (CIAC) is the interventional procedure with most cases reported in the registry especially the closure of the patent foramen ovale. The evidence published over the last few years on its utility in the prevention of strokes anticipates its growth in the years ahead.[11,12] Transesophageal ultrasound is the most widely used imaging modality to guide the closure of interatrial shunts compared to intravascular ultrasound that is a minority.

Regarding the closure of the patent ductus arteriosus, the use of occluder devices is predominant. In the pediatric setting, the implementation of this technique in premature patients could grow significantly within the next few years after the publication of different studies that support its safety and efficacy profile.[13,14]

The evolution of both the technique and the indications for transcatheter pulmonary valve implantation, as well as the availability of new valves[15,16] widen the number of anatomical scenarios eligible for this procedure. Therefore, it is expected that more patients with right ventricular outflow tract dysfunction will be treated with interventional procedures.

Limitations

The comparison between data collected from this Cardiac Catheterization in Congenital Heart Diseases Registry and data from the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology Registry (both from 2020)[4] reveals a significant underestimate of some interventional procedures performed in patients > 18 years of age. This would undermine the percentual distribution reported for such procedures between children and adults. Future registries should correct this deficiency and open participation to all centers from our country with some kind of interventional activity to patients with congenital heart diseases, especially adults.

From the methodological point of view, the success parameters of some interventional procedures have not been predefined assuming a uniform criterion in all participant centers. On the other hand, grouping certain techniques like the angioplasty of branch pulmonary arteries, the pulmonary artery conduit, and the native outflow tract can be a confounding factor regarding the assessment of its technical peculiarities and results. Finally, extending the information included on the latest techniques available adds a new asset to the registry and should be reevaluated in future editions.

CONCLUSIONS

This study is the first publication of the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry thanks to the collaboration of the ACI-SEC and the GTH-SECPCC.

Diagnostic cardiac catheterization still plays a key role in the management of patients with congenital heart disease. The most widely used interventional procedures are the CIAC, the angioplasty of branch pulmonary arteries, and the closure of the patent ductus arteriosus. The efficacy and safety data reported on the different interventional techniques used are consistent with the medical literature available. The complications most widely described are embolizations. The CIVC is a technique associated with the lowest success rate and the highest rate of complications in our setting.

Future editions of this registry should encourage the participation of hospitals from our country with interventional activity in the management of congenital heart disease and make the resulting information as truthful and honest as possible.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to data curation and the process of revising this study. F. Ballesteros Tejerizo, F. Coserría

Sánchez, and R. Romaguera were also involved in the drafting of this manuscript.

CONFLICT OF INTERESTS

R. Romaguera, and S. Ojeda Pineda are associate editors of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. The remaining authors had no competing interests to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

- Cardiac catheterization is the cornerstone for the management of patients with congenital heart disease.
- Excellent success rates have been reported in the medical literature available on the use of interventional techniques with limited morbidity and mortality rates too.
- In Spain, numerous centers offer interventional procedures to patients with congenital heart diseases both in the pediatric and in the adult settings.
- The national, multicenter studies on the interventional activity developed for the management of congenital heart diseases published to this date are scarce and only include certain techniques or are limited by age segments.

WHAT DOES THIS STUDY ADD?

- This is the first publication that evaluates the interventional activity developed in Spain to treat congenital heart disease in patients of any age.
- Based on the data submitted, diagnostic cardiac catheterization still plays a key role in the management of patients with congenital heart diseases with a significant number of procedures being performed.
- The interventional techniques that comprise a greater number of cases in our setting are the closure of interventricular communication (CIVC), the angioplasty of branch pulmonary arteries, and the closure of the patent ductus arteriosus.
- The efficacy and safety results reported on the different techniques used are consistent with the data previously published in the international medical literature.
- The type of complication most frequently associated with cardiac catheterization is device embolization.

ANNEX 1

List of centers that participated in the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry

Complexo Hospitalario Universitario, A Coruña
Hospital Universitario 12 de Octubre (Instituto Pediátrico del Corazón), Madrid
Hospital Universitario Ramón y Cajal, Madrid
Hospital Universitario Reina Sofía, Córdoba
Hospital Universitario de Cruces, Barakaldo, Bilbao
Hospital Universitario La Paz, Madrid
Hospital Universitario Son Espases, Palma de Mallorca
Hospital Universitario Virgen de la Arrixaca, Murcia
Hospital Universitario y Politécnico La Fe, Valencia
Hospital Universitario Gregorio Marañón, Madrid
Hospital Universitario Virgen de las Nieves, Granada
Hospital Universitario Virgen del Rocío, Sevilla
Hospital Clínico Universitario de Valladolid, Valladolid
Hospital Regional Universitario de Málaga (Materno-Infantil), Málaga
Hospital Universitari Vall de Hebrón, Barcelona
Hospital Miguel Servet, Zaragoza

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Original article

Percutaneous closure of ventricular septal defect with the KONAR-MF device

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ABSTRACT

Introduction and objectives: Percutaneous closure of ventricular septal defect (VSD) can be an alternative to surgery reducing length of stay, and complications. The high risk of atrioventricular block (AVB) involved during percutaneous closure has encouraged the development of new devices such as the KONAR-MF (Lifetech, China). This device is very flexible and has a low radial force that adapts to the anatomy of the VSD without exerting any pressure to the adjacent structures. This is our early experience with this new device.
Methods: Retrospective review of patients and VSD closure procedures using the KONAR-MF device at 2 Spanish centers from February 2020—date of the first implantation in our country—through September 2021.
Results: A total of 7 closure procedures of VSD were performed being the device successfully implanted in 6 of the 7 patients. A total of 4 native perimembranous VSDs and 3 residual VSDs after tetralogy of Fallot repair were reported. The size of the VSD measured through transesophageal echocardiography and angiography was consistent in all the cases except for 1. In this patient device embolization occurred. At the follow-up [1.2 months (IQR, 0.9-15.5), (maximum 17 months)] we saw worsening atrioventricular conduction in a patient with a previous AVB who required a pacemaker. The immediate residual shunt rate was 83% (5/6) with persistent residual shunt beyond the 1-month follow-up in 1 patient (16%). All patients were discharged from the hospital within the first 48 hours following the intervention.
Conclusions: The percutaneous closure of VSD with the KONAR-MF device is a feasible alternative to surgery in selected patients. An adequate anatomical evaluation of the VSD is one of the keys of successful procedures. The implantation of this device is no stranger to complications like AVB or device embolization.

Keywords: Ventricular septal defect. Catheterizations in congenital heart disease. Ventricular septal defect. Closure devices.

Cierre percutáneo de comunicación interventricular con el dispositivo KONAR-MF

RESUMEN

Introducción y objetivos: El cierre percutáneo de la comunicación interventricular (CIV) puede ser una alternativa a la cirugía y reduce el tiempo de hospitalización y las complicaciones. El alto riesgo de bloqueo auriculoventricular (BAV) en el cierre percutáneo ha incentivado el desarrollo de nuevos dispositivos, como el KONAR-MF (Lifetech, China), muy flexible y con poca fuerza radial para adaptarse a la anatomía de la CIV sin presionar las estructuras adyacentes. Se presenta la experiencia inicial con este nuevo dispositivo.
Métodos: Revisión retrospectiva de pacientes y procedimientos de implante del dispositivo KONAR-MF, en 2 centros españoles, desde febrero de 2020, fecha del primer implante en nuestro país, hasta septiembre de 2021.
Resultados: Se han realizado 7 procedimientos de cierre de CIV con KONAR-MF, implantándolo con éxito en 6 de los casos. Fueron 4 CIV perimembranosas nativas y 3 CIV residuales tras reparación de tetralogía de Fallot. El tamaño de la CIV medido por ecocardiografía transesofágica y angiografía fue concordante en todos los casos salvo en uno; en este paciente se produjo una embolización del dispositivo. En el seguimiento (1,2 meses [rango intercuartílico: 0,9-15,5], máximo 17 meses) se observó un empeoramiento de la conducción auriculoventricular en un paciente con BAV previo, que precisó marcapasos. La tasa de *shunt* residual inmediato fue del 83% (5/6), persistiendo el *shunt* residual más allá del mes de seguimiento en 1 paciente (16%). Todos los pacientes recibieron el alta hospitalaria en las primeras 48 horas tras la intervención.

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Conclusiones: El cierre percutáneo de CIV con el dispositivo KONAR-MF es una alternativa factible a la cirugía en pacientes seleccionados, siendo la adecuada valoración anatómica de la CIV una de las claves para el éxito del procedimiento. El implante de este dispositivo no está exento de complicaciones, como el BAV y la embolización.

Palabras clave: Comunicación interventricular. Intervencionismo en cardiopatías congénitas. Dispositivos de cierre de comunicación interventricular.

Abbreviations

AVB: atrioventricular block. **TOE:** transesophageal echocardiography. **VSD:** ventricular septal defect.

INTRODUCTION

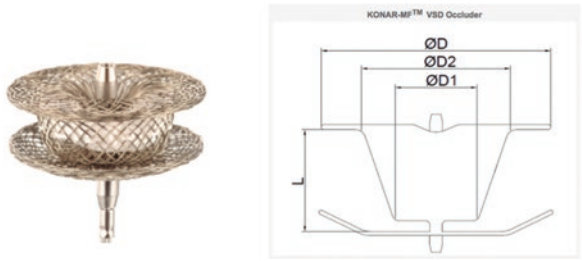
Ventricular septal defect (VSD) is one of the most common congenital heart diseases. Its prevalence is 5.3 cases for every 1000 live births.[1] It can occur in isolation or as part of a more complex congenital heart disease. Standard therapy is surgical closure with very low morbidity and mortality rates. However, it is no stranger to complications.

Percutaneous closure can be an alternative to surgery in selected anatomies, thus reducing the length of hospital stay, and complications. Both percutaneous and surgical closures have a potential risk of atrioventricular block (AVB)—< 2% for surgical closure, and 0.5% to 6.8% for percutaneous closure.[2-5] The high risk of AVB has led to the development of new and more flexible sheaths and devices to close the VSD with less radial strength that minimize the risk of damage to the cardiac conduction system. In this context, the KONAR-MF VSD device occluder (Lifetech, China) was developed. It obtained the CE marking in Europe back in May 2018. It is a low profile, nitinol, self-expanding device with little radial strength and high flexibility in order to adapt to the anatomy of the VSD without exerting any pressure to the adjacent structures. The device is made of 2 discs united at its waist that has a polytetrafluoroethylene membrane. The right disc is simple while the left one has 1 cone attached to it similar the devices that are used to close the ductus arteriosus (figure 1). Each disc has a screw so it can be anchored to the delivery system in such a way that it can be implanted via antegrade (venous) and retrograde (arterial) access. The device comes in several sizes from 5 mm to 14 mm. It is suitable for different VSDs of different sizes, and anatomies (figure 1). The specific sheaths of the delivery system—5-Fr to 7-Fr—are also very flexible, which reduces pressure to the cardiac conduction system during the device implantation maneuvers. Also, it can be implanted through a 7-Fr or 8-Fr guide catheter.

This is the early experience of 2 Spanish centers using this new device for the closure of VSD.

METHODS

Retrospective review of patients treated with the VSD KONAR-MF occluder device at 2 Spanish centers: Hospital Universitario Ramón y Cajal, Madrid, and Hospital Universitario La Fe, Valencia from February 2020—date of the first implantation procedure in our country—through September 2021. Patients were selected if they had suitable anatomies for percutaneous closure, that is, proper distance to the aortic valve (> 2 mm), lack of posterior prolongation (enough distance to the tricuspid valve), and proportionate size of the devices available. Since this was a short retrospective review, no control group was included.



Cat. No	D Disc Diameter (mm)	D1 Waist Diameter RV Side (mm)	D2 Waist Diameter LV Side (mm)	L Waist Length (mm)	Recommended Delivery Sheath (Fr.)
LT-MFO-5-3	10	3	5	4	4-5F
LT-MFO-6-4	10	4	6		4-5F
LT-MFO-7-5	12	5	7		4-5F
LT-MFO-8-6	12	6	8		4-5F
LT-MFO-9-7	14	7	9		6F
LT-MFO-10-8	14	8	10		6F
LT-MFO-12-10	16	10	12		7F
LT-MFO-14-12	18	12	14		7F

Figure 1. KONAR-MF device (Lifetech, China) with the table of measures available. Data from the device instructions for use.

The patients' demographic, clinical, and anthropometric data were collected, as well as the echocardiographic anatomy of the defect, the hemodynamic variables of the procedure, and the immediate complications or at the follow-up.

Definitions

Residual shunt was defined as the presence of flow on the color Doppler echocardiography around the device. Flow was categorized into mild (1 mm to 2 mm), moderate (2 mm to 4 mm), or severe (> 4 mm). The presence of flow inside the device was called intradevice shunt and was considered less significant compared to mild shunt.

Complications were categorized as minor or major:

- Major complications: death, potentially fatal adverse events, events requiring surgery (embolization, myocardial perforation, vascular rupture, severe residual shunt, severe hemolysis, valvular damage, persistent AVB).

Table 1. General description of patients treated with percutaneous closure of VSD

Patient	Sex	Age (years)	Weight (kg)	Qp/Qs ratio	Anatomy	Size of VSD on the TEE (LV/RD)	Size of VSD on the angiography (LV/RV)	Device	X-ray imaging time (min)
1	F	8	29.3	1.53	PM	6/4	6/5	7/5	21.2
2	F	14	57.2	1.71	PM	ND	8/4.5	8/6	50.4
3	M	19	59	1.5	PR	10/7	11/8	12/10	27
4	F	26	64	2.08	PR	10/7	11/8	12/10	42.3
5	M	9	23	1.58	PM	8/5	4/2	6/4	143
6	M	16	54	2.25	PR	9/8	11/8	12/10	25
7	M	13	51.2	1.66	PM	7/4	7/5	8/6	22

F, feminine; LV, left ventricle; M, masculine; NA, not available; PM, perimembranous; PR, postoperative residual; Qp, pulmonary cardiac output; Qs, systemic cardiac output; RV, right ventricle; TEE, transesophageal echocardiography; VSD, ventricular septal defect.

- Minor complications: complications that solve spontaneously or with medical therapy and don't have fatal outcomes (issues with vascular access, mild hemolysis solved with medical therapy, complete transient AVB or other conduction abnormalities that do not require pacemaker implantation, fever, neurapraxias, etc.)

Device implantation was considered successful in the absence of major complications, and severe residual shunt within the next 24 hours.

Description of the procedure

Previous diagnostic cardiac catheterization, and transesophageal echocardiography (TEE) were performed in all the patients. The patients referred for closure had hemodynamic repercussions due to VSD (left ventricular dilatation). Also, the presence of a Qp/Qs ratio ≥ 1.5 was confirmed through a cardiac catheterization performed under general anesthesia while the patient remained intubated.

The size of the device was determined based on the measures of VSD obtained on the TEE, and left ventriculography. The device was 1 mm to 3 mm larger than the defect (figure 2).

The VSD probing technique, and the device positioning and delivery are not substantially different compared to those used in other device occluders widely discussed in the medical literature.[6-9] The interventional procedure was performed under TEE guidance, and the device was released after being properly deployed without severe residual shunt.

Follow-up after closure of ventricular septal defect

Follow-up visits were conducted 1 month, 6 months, and 1 year after closure. After that time, depending on the patient's baseline condition and clinical situation, follow-up was conducted every 6 or 12 months. Anamnesis, physical examination, electrocardiogram, and echocardiography were performed in these visits. Blood tests were also added to the mix in cases of suspected hemolysis. In the presence of any other symptoms or pathological findings in any of the tests performed, additional studies were conducted like Holter, ergometry or further imaging modalities.

Ethical aspects

In compliance with the current legislation, and since this was a retrospective case review it was not necessary to obtain the patients' informed consent or approval by the ethics committees of the participant centers.

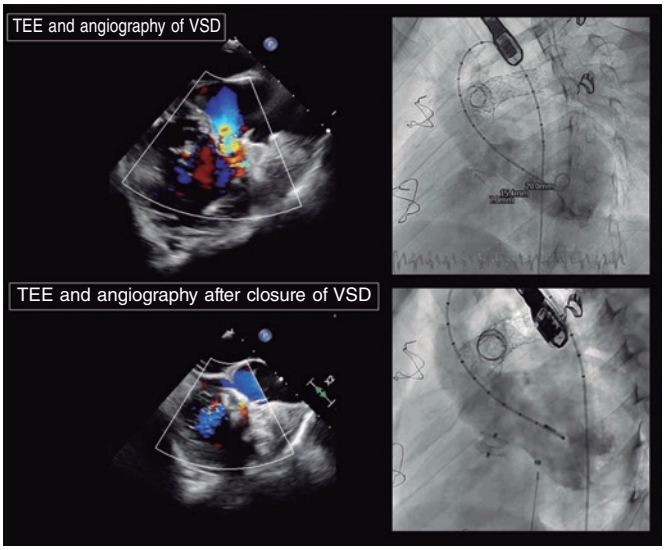


Figure 2. Ventricular septal defect (VSD) in a patch in a patient with tetralogy of Fallot. The upper images reveal the presence of the defect both on the transesophageal echocardiography (TEE), and the angiography. The lower images—also from TEE and angiography—reveal the defect being closed after KONAR-MF device implantation (Lifetech, China).

RESULTS

From February 2020 through June 2021, a total of 7 consecutive procedures of VSD closure were performed at the 2 centers using the KONAR-MF device by successfully implanting this device in 6 out of the 7 patients. Table 1 shows the overall description of the patients. Cases were restrictive defects (native or postoperative) with echocardiographic data of hemodynamic repercussion (left ventricular dilatation) without clinical translation in patients > 8 years.

The anatomy of VSD was:

- Native perimembranonus VSD in 4 patients (2 with aneurysmal tissue that partially closed the VSD) without associated disease in 3 patients while the fourth had been treated of coarctation of aorta.

- Residual VSD residual after repair of tetralogy of Fallot in 3 patients.

The size of the VSD measured on the TEE and angiography was consistent in all the cases except for 1 with a small VSD covered by an aneurysm.

In all the patients, vascular approach was attempted via femoral access (artery and vein); in 6 of them closure was performed via antegrade access, and in 1 patient via retrograde access. Retrograde access was attempted in 1 patient in whom the proper positioning of the right disc could not fully achieved. Finally, closure was successfully completed from the right ventricle, but with longer x-ray image and procedural times. The median x-ray image time was 27 minutes [IQR, 22-50].

There were no immediate complications in any of the cases reported except for 1 embolization in a small VSD with aneurysmal tissue (case #5) where the size of the VSD measured on the TEE and the angiography did not properly correlate. The device embolized to the left pulmonary artery and was retrieved percutaneously through a bailout procedure. The patient was treated with VSD elective surgery a few months later. No hemolysis or vascular complications were reported in the series with a maximum follow-up time of 17 months (median follow-up, 1.2 months; IQR, 0.9-15.5).

Immediate residual shunt was seen in 5 out of the 6 successfully closed VSDs. Two of the patients showed mild intradevice shunt that closed spontaneously within the first 24 hours; in another 2 patients the shunt disappeared 1 month after the procedure, and in the fifth case moderate residual shunt persisted 1 month after the procedure.

All patients were discharged from the hospital within the first 48 hours after the procedure. Three out of the 7 patients were already on acetylsalicylic acid due to their underlying condition while in the remaining 3 with successful closures, treatment with acetylsalicylic acid was started before discharge. Antibiotic prophylaxis was advised for 6 months after closing the residual shunt.

Regarding the clinical course, in 5 out of the 6 patients with successful device implantation and without previous ECG alterations, no conduction abnormalities were seen after closing the VSD. However, 1 case of progression into long-term preexisting postoperative AVB was reported that required pacemaker implantation. This was the case of a patient with repaired tetralogy of Fallot (case #3) who—before the percutaneous closure of the VSD—had advanced AVB of several years of evolution without an indication for pacemaker implantation. Fourteen months after the procedure, the patient required percutaneous pacemaker implantation because data on atrioventricular conduction worsened in Holter, ergometry, and electrophysiological studies.

DISCUSSION

This is a small and heterogeneous series of occluded VSDs with the KONAR-MF device with a short follow-up too. However, we wanted to share our case since this was the first experience in our country using a device that has joined the therapeutic arsenal of occluder devices available for the percutaneous treatment of VSD. Using this device was technically easy and reproducible from the interventional cardiology standpoint. Also, the echocardiographic visualization of the device was rather good from the imaging standpoint (figure 2).

The percutaneous occlusion of VSD with the KONAR-MF device is feasible and effective with complete closure of VSD rates 1 month after implantation of up to 98%,[9-12] which has been associated with the possibility of oversizing the device vs the VSD without damaging any adjacent structures given its flexibility.[9-12] In our series of a single patient with residual shunt vs 5 patients without it, the rate of occlusion was 83% 1 month after implantation.

Compared to other devices, the advantages attributed to this device are its flexibility and adaptability to the patient's anatomy, both favorable to minimize complications and increase the efficacy of occlusion. Also, other advantages are the possibility of implanting this device from the aortic side shortening procedural time.

Although, to this date, literature is scarce and only limited to early series of cases, the experience is growing, particularly in Asia.[9-14] It has been used in a wide array of clinical scenarios and patients including breastfed babies[13] proving effective and safe overall. However, as it occurs with all invasive procedures, it is not stranger to major complications being embolization the most common of all.[10,11]

The rates of success and major complications (embolization, AVB, and hemolysis) reported with this device are similar—or somehow lower—compared to those reported with other VSD closure devices.[11,15] However, the rates of immediate closure are higher compared to those reported with other devices, which would—theoretically speaking—minimize the risk of complications like hemolysis or endocarditis.[11,15]

Our results are consistent with the series published to this date without cases of hemolysis being reported. The serious complications reported were 1 embolization, and 1 AVB at the follow-up. In our series, embolization was attributed to the fact that a small device was selected as a consequence of the mismatch reported between the VSD size measured on the TEE and on the angiography. The presence of aneurysmal tissue when trying to measure the defect properly was seen as a setback. Future cases should examine the TEE-angiography correlation when measuring the size of VSD.

The medical literature reports 2 cases of permanent AVB (another transient AVB was reported during the procedure contraindicating implantation[13]): 1 early AVB in the series of Tanidir et al.[10] of 98 patients—a rate of AVB of 1%—plus another case deferred for a week[14] that made Leong et al.[14] review the rate of AVB described in the medical literature with what they referred to as «new» devices. In our sample no cases of rhythm disorders were reported after the procedure was performed in 5 out of 6 cases. However, it is relevant that in a patient with previous advanced AVB, disease progression was reported, which led to pacemaker implantation after closing the defect. Since this patient had tetralogy of Fallot, the device was implanted in a patch without prior direct compression on the cardiac conduction system. Also, this patient had a hemodynamic disorder with right ventricular overload due to acute respiratory failure, and significant stenosis of pulmonary arteries. Given this baseline situation, the worsening AVB cannot be fully attributed to the device although it cannot be discarded either. In any case, the previous presence of conduction abnormalities should be a warning of possible worsening after percutaneous closure of a VSD.

The results of our series should be interpreted in the context of its own limitations (small number of patients and short follow-up period). Although both the versatility of the device and the successful outcomes are encouraging, the presence of serious complications requires a careful approach. Therefore, larger studies with more cases and longer mid-term follow-ups are required to confirm the device safety profile.

CONCLUSIONS

The percutaneous closure of the VSD with the KONAR-MF device emerges as a proper alternative to occlusion with other devices. Also,

it is a feasible alternative to surgery for some patients. Also, it stands as an effective occlusion technique in selected defects being the right anatomical assessment of the VSD one of the keys for success. The rates of complete closure and complications of this early sample should improve with more cases, experience, and longer follow-ups. As it occurs with other devices, implanting this device is associated with complications like AVB, and embolization.

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None whatsoever.

AUTHORS' CONTRIBUTIONS

M. Álvarez-Fuente collected the patients' data and drafted the manuscript. J.I. Carrasco collected the patients' data and was involved in the review process of the manuscript. B. Insa drafted the manuscript. M. Toledano was involved in the review process of manuscript. E. Peiró participated in the review process of the manuscript. J.P. Sandoval participated as an advisor in the process of drafting the manuscript, as well as the manuscript final review process. M.J. del Cerro drafted the manuscript.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- Currently, the percutaneous closure of VSD is starting to become routine in PCI-capable centers specialized in congenital heart disease. However, this technique still cannot be compared to or even replace surgery. Numerous devices for the closure of VSD have been developed. However, not a single one has been found to perform this procedure with enough efficacy and safety.

WHAT DOES THIS STUDY ADD?

- This is the early experience using a new device to close VSDs with results that are promising enough to think that the interventional procedures performed with it are a reliable alternative to the surgical closure of VSD.

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Original article

Incidence, morbidity and mortality, and management of acute coronary syndrome during the time of COVID-19 lockdown

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ABSTRACT

***Introduction and objectives*:** During the lockdown due to the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a decrease in the number of admissions due to acute coronary syndrome (ACS) was observed. The objective of our study was to evaluate the impact lockdown had on the incidence, morbidity and mortality, and management of ACS.
***Methods*:** A retrospective and multicenter study was conducted including patients admitted due to ACS from February 14 through June 24, 2020. Patients with acute myocardial infarction and coronary arteries without significant lesions were excluded. The following groups were established based on the period of admission: *a)* 1 month before lockdown; *b)* during lockdown; and *c)* 1 month after lockdown. The differences in mortality seen among the 3 groups were evaluated, as well as the temporal differences reported between symptom onset and the first medical contact (FMC).
***Results*:** a total of 634 patients were included (group a, 205; group b, 303, and group c, 126). A 41% decrease in the number of admissions due to ACS was observed during the first month of lockdown compared to the previous month, as well as diagnostic delay during this same period (group a, 66 minutes (45-180), group b, 120 minutes (60-240), and group c, 120 minutes (60-240), $P = .007$). However, a higher mortality rate during confinement was not reported (RR, 1.26; 95%CI, 0.53-2.97; $P = .60$).
***Conclusions*:** During lockdown, a remarkable decrease in the number of admissions due to ACS was observed, and although there was an increase in the time elapsed from symptom onset to the FCM in this period in patients with STEMI, the mortality rate was similar in the 3 groups studied.

Keywords: COVID-19. SARS-CoV-2. Acute coronary syndrome. Pandemic. Revascularization. Lockdown.

Incidencia, morbimortalidad y tratamiento del síndrome coronario agudo durante el confinamiento por COVID-19

RESUMEN

Introducción y objetivos: Durante el confinamiento por la pandemia provocada por el coronavirus del síndrome respiratorio agudo grave de tipo 2 (SARS-CoV-2) se observó un descenso en los ingresos por síndrome coronario agudo (SCA). El objetivo de este estudio fue evaluar el impacto del confinamiento en la incidencia, la morbimortalidad y el tratamiento del SCA.
Métodos: Estudio retrospectivo y multicéntrico, en el que se incluyeron los pacientes ingresados por SCA entre el 14 de febrero y el 24 de junio de 2020. Se excluyeron los pacientes con infarto agudo de miocardio y coronarias sin lesiones significativas. Se establecieron 3 grupos en función del periodo de ingreso: a) 1 mes antes del confinamiento; b) durante el confinamiento; y c) 1 mes después del confinamiento. Se evaluaron las diferencias en la mortalidad entre los 3 grupos, así como las diferencias temporales entre el inicio de los síntomas y el primer contacto médico.

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Resultados: Se incluyeron 634 pacientes (grupo A: 205; grupo B: 303; grupo C: 126). Se observó un descenso del 41% en los ingresos por SCA durante el primer mes del confinamiento respecto al mes previo, así como un retraso en el diagnóstico durante este mismo periodo: grupo A, 66 minutos (45-180); grupo B, 120 minutos (60-240); grupo C, 120 minutos (60-240) (p = 0,007). Sin embargo, no hubo mayor mortalidad durante el confinamiento (riesgo relativo, 1.26; intervalo de confianza del 95%, 0.53-2.97; p = 0,60).
Conclusiones: Durante el confinamiento se produjo un marcado descenso en los ingresos por SCA y, a pesar de que se dilató el tiempo desde el inicio de los síntomas hasta el primer contacto médico en este periodo en los pacientes con SCA con elevación del segmento ST, la mortalidad fue similar en los 3 grupos estudiados.

Palabras clave: COVID-19. SARS-CoV-2. Síndrome coronario agudo. Pandemia. Revascularización. Confinamiento.

Abbreviations

ACS: acute coronary syndrome. **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

By the end of December 2019, The People's Republic of China reported the World Health Organization on the first cases detected of an unknown pneumonia caused by a new type of coronavirus in the City of Wuhan, China.[1,2] Since then, the disease caused by this virus has spread rapidly bringing the healthcare systems of several countries to the point of collapse ultimately triggering dramatic preventive measures by the health authorities.

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a tremendous social, economic, and health impact across the world. Again and again, the healthcare setting has sustained several organizational and care changes that have triggered significant variations in the management therapeutic approach of the remaining diseases.[3-5] Some studies have reported a lower number of admissions due to cardiovascular diseases, which has had a significant impact on morbidity and mortality alike.[6-8]

Pressure to the healthcare system due to COVID-19, the lockdown, and the lower demand for assistance are some of the reasons that may account for these changes. The objective of this study is to assess the rate of acute coronary syndrome (ACS) across the different stages of the pandemic in Spain, as well as the impact it has had on morbidity, mortality, and therapeutic management.

METHODS

Retrospective, observational, and multicenter study including data from patients admitted to 4 tertiary care centers of our country from 3 autonomous communities due to ACS from February 14, 2020 through June 24, 2020. Patients with ST-segment elevation acute coronary syndrome (STEACS), and non-ST-segment elevation acute coronary syndrome and were included. Patients with acute myocardial infarction and without significant lesions in coronary arteries were excluded. Patients were categorized into 3 groups based on the length of hospital stay: group A, from February 14 through March 14, 2020 (1 month before the lockdown); group B, from March 15 through May 24, 2020 (during the lockdown), and group C, from May 25 through June 24, 2020 (1 month after the stay-at-home lockdown). The patients' baseline characteristics, acute complications, and cardiovascular events reported at the follow-up like all-cause mortality, cardiac death, stroke, reinfarction, stent thrombosis, and need for rehospitalization were recorded.

In patients with STEACS the times elapsed between symptom onset and the first medical contact (FMC), and between electrocardiographic diagnosis until reperfusion were recorded. Clinical follow-up was completed back in July 25, 2020. Data curation was approved by the local ethics committee of each participant center.

The study primary endpoint was to assess the differences reported in all-cause mortality after 30 days since the onset of the acute coronary event among the 3 study groups. The study secondary endpoint was to analyze the differences reported in a composite of cardiac death, stroke, admission due to new ACS, stent thrombosis, and need for new revascularization. Complications reported after infarction at the follow-up, a high left ventricular ejection fraction, and revascularization times (from symptom onset until the first medical contact, and from diagnosis until reperfusion) were also studied in a secondary analysis and compared among the 3 groups.

Statistical analysis

Categorical variables were expressed as number and percentage using brackets and compared using the chi-square test or Fisher's exact test, when appropriate. Continuous variables were expressed as mean and standard deviation or median and interquartile range in cases without a normal distribution. The Shapiro-Wilk test was used to assess the normal distribution of continuous variables that were compared using the analysis of variance (ANOVA) for independent samples or Kruskall-Wallis H test based on their normal distribution looking for differences among the 3 groups. Survival was studied using the Kaplan-Meier curves, and differences were assessed using the log-rank test. Cox proportional hazards regression analysis was used to assess the impact of group B (lockdown period) in the overall mortality of the patients. All estimates were performed using the statistical software package STATA version 15.1. P values $< .05$ were considered statistically significant.

RESULTS

A total of 634 patients were included from February 14, 2020 through June 24, 2020. Of these, 205 were patients from group A, 303 from group B, and 126 from group C with a median follow-up of 98 days (63-137 days). The number of admissions due to ACS was 120, 138, and 151 within the first, second, and third months since the state of alarm declared. This lowered the rate of admissions due to ACS by 41%, 33%, and 26%, respectively compared

Table 1. Baseline characteristics, diagnosis at admission, and treatment

Variable	Total (N = 634)	Group A (N = 205)	Group B (N = 303)	Group C (N = 126)	*P*
Age	66.3 ± 12.6	67.4 ± 11.6	64.8 ± 12.7	68.2 ± 13.6	.012
Sex, male	494 (77.9)	158 (77.1)	241 (79.5)	95 (75.4)	.603
AHT	400 (63.1)	143 (69.8)	176 (58.1)	81 (64.3)	.027
DM	191 (30.1)	71 (35.1)	89 (29.4)	30 (23.8)	.086
DL	368 (58.0)	137 (66.8)	164 (54.1)	67 (53.2)	.008
Smoking	364 (57.4)	124 (60.5)	182 (60.1)	58 (46.0)	.015
PVD	36 (5.7)	15 (7.3)	16 (5.3)	5 (4.0)	.405
Stroke	37 (5.8)	11 (5.4)	16 (5.3)	110 (7.9)	.531
CKD (GF < 60)	30 (4.7)	18 (8.8)	7 (2.3)	5 (4.0)	.003
COPD	45 (7.1)	14 (6.8)	22 (7.3)	9 (7.1)	.981
AF	40 (6.3)	16 (7.8)	16 (5.3)	8 (6.4)	.517
IHD	150 (23.7)	79 (38.5)	46 (15.2)	25 (19.8)	< .001
AMI	103 (16.3)	52 (25.4)	31 (10.2)	20 (15.9)	< .001
PCI	117 (18.5)	60 (29.3)	36 (11.9)	21 (16.7)	< .001
CABG	23 (3.6)	12 (5.9)	7 (2.3)	4 (3.2)	.112
Diagnoses					
UA	83 (13.1)	36 (17.6)	27 (8.9)	20 (15.9)	.003
NSTEMI	195 (30.8)	67 (32.7)	83 (27.4)	45 (35.7)	.003
STEACS	356 (56.2)	102 (49.8)	193 (63.7)	61 (48.4)	.003
GRACE	120.1 ± 35.6	118.4 ± 35.4	119.1 ± 34.6	124.8 ± 38.3	.264
CRUSADE	31.4 ± 13.8	34.1 ± 15.2	30.4 ± 13.3	29.7 ± 11.8	.001
Cardiac catheterization	616 (97.5)	198 (96.6)	295 (97.7)	123 (98.4)	.565
Emergency	375 (59.5)	112 (54.9)	190 (63.1)	73 (58.4)	.447
Deferred	242 (38.4)	87 (42.7)	105 (34.9)	50 (40.0)	.447
Fibrinolysis	29 (5.1)	10 (5.7)	13 (4.5)	6 (6.1)	.652
PCI	534 (94.3)	165 (93.2)	276 (95.2)	93 (94.0)	.652
CABG	29 (4.6)	11 (5.4)	8 (2.7)	10 (8.1)	.045
LMCA or 3-vessel disease	136 (21.5)	52 (25.4)	55 (18.6)	29 (23.0)	.135
CABG (LMCA or 3-vessels)	22 (16.3)	9 (17.7)	3 (5.5)	10 (34.5)	.003
Conservative treatment	3 (0.5)	2 (1.1)	1 (0.3)	0 (0)	.652
Complete revascularization	456 (75.6)	138 (74.6)	223 (76.1)	95 (76.0)	.926
LVEF at discharge	49.2 ± 11.1	49.7 ± 11.6	48.6 ± 11.2	49.9 ± 10.0	.421

AF, atrial fibrillation; AHT, arterial hypertension; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DL, dyslipidemia; DM, diabetes mellitus; GF, glomerular filtration; HT, arterial hypertension; IHD, ischemic heart disease; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEACS, ST-segment elevation acute coronary syndrome; UA, unstable angina.
Data are expressed as no. (%) or mean ± standard deviation.

to the rates reported 1 month before the lockdown for the same 30-day period (figure 1).

A total of 356 (56.2%) from the overall number of patients were admitted due to STEACS, and 278 (43.8%) due to non-ST-segment elevation acute coronary syndrome. The cohort baseline characteristics are shown on table 1. Patients admitted during the lockdown (group B) were younger (P = .012) and had lower levels of hypertension and dyslipidemia. On the other hand, these patients' past medical history showed less ischemic heart disease, and coronary revascularization (P < .001).

A diagnostic coronary angiography was performed on 97.1% of the cohort without any differences being reported regarding

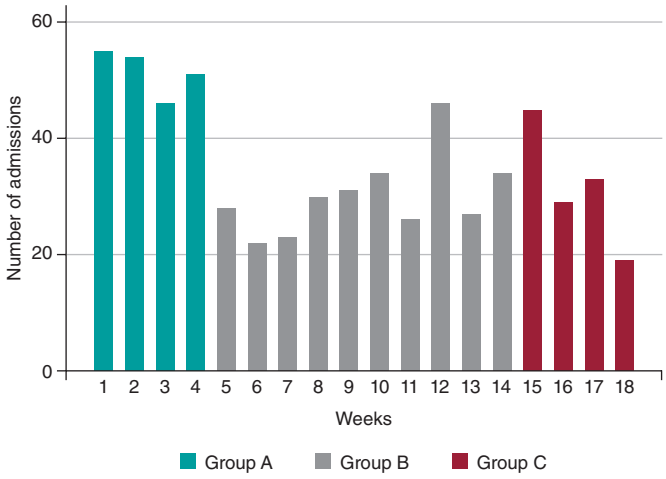

Figure 1. Absolute number of patients admitted due to acute coronary syndrome, expressed in weeks and categorized into group A, B, and C.

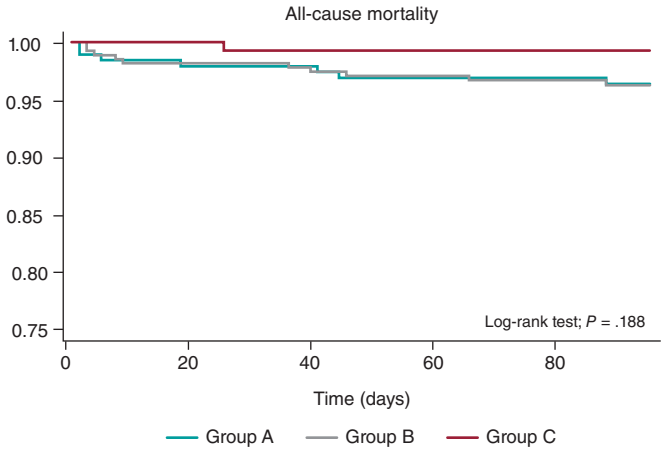

Figure 2. Kaplan-Meier survival curves for all-cause mortality in groups A (February 14-March 14), B (March 15-May 24), and C (May 25-June 24).

percutaneous coronary intervention throughout the different periods studied (P = .652); however, a significant reduction in the number of surgical coronary revascularizations performed during the lockdown was reported (group A, 5.4%; group B, 2.7%; group C, 8.1%; P = .045) including the subgroup of patients with left main coronary artery disease or 3-vessel disease (P = .003) (table 1).

A total of 36 deaths were reported, 22 of which were due to cardiovascular causes. No statistically significant differences were reported in the all-cause mortality rate after 30 days among the 3 groups (P = .327). According to a Cox regression analysis, being in the lockdown group (group B) was not associated with a higher all-cause mortality rate (P = .60). No survival differences were reported either among the 3 groups (figure 2).

No significant differences were reported at the follow-up in a composite of cardiac death, stroke, readmission due to new ACS, stent thrombosis, and new revascularization (P = .120). The remaining clinical events at the follow-up are shown on table 2 and the in-hospital events on table 3.

Regarding delay times, significant differences were reported among the different groups with longer times elapsed between symptom onset and the first medical contact during (group B) and after lockdown (group C) compared to the previous period (group A): group A, 66 min (45-180), group B, 120 min (60-240), group C, 120 min (60-240); P = .007). The time elapsed between symptom onset until the first medical contact was similar in groups B and C (P = .7102). Finally, the time elapsed between diagnosis and reperfusion was shorter in patients from group C (P = .025) compared to the remaining cohort (table 4).

DISCUSSION

The main findings from this study were a lower number of admissions due to ACS within the first few months of lockdown, and longer periods of time elapsed between symptom onset and the first medical contact in patients with STEACS that did not translate into higher morbidity and mortality rates.

Lower rate of acute coronary syndrome

Former studies have reported less activity at the cath lab due to fewer admissions due to ACS during the pandemic, especially in the STEACS setting.[7,9-11] Our findings confirm this trend with a significant 41% drop within the first 30 days compared to the previous month. This reduction was kept in the remaining time during and after lockdown; however, as the isolation measures were being lifted and the rate of cases of COVID-19 dropped, a gradual increase in the number of admissions due to ACS was confirmed. One of the contributing factors may have been the intense pressure put to the healthcare system within the first few months of lockdown with the corresponding underdiagnosis of ACS and fewer admissions reported.[12] Another hypothesis that may justified the lower rate of ACS during this time is the higher number of out-of-hospital sudden deaths reported. Although reported by other authors in the past, this was not cause for analysis in our study.[13-16]

Times elapsed among symptom onset, the first medical contact, and revascularization in patients with ST-segment elevation myocardial infarction, and association with adverse events

During the lockdown (group B) patients with STEACS were admitted more often (P = .003). The time elapsed between symptom onset and the first medical contact was significantly longer during this time compared to other times, which is consistent with the peak number of cases reported (similar findings to those reported by former studies);[17] however, this delay did not increase the rates of mechanical complications or mortality. This can be explained because patients admitted during the lockdown (group B) were younger and had fewer comorbidities.[18,19] Data suggests that elderly patients with more serious past medical histories and associated comorbidities may have delayed or even postponed indefinitely their access to the healthcare system over fears of getting infected.[20,21]

Rodríguez-Leor et al.[22] reported time delays between symptom onset and the first medical contact, and similar times between diagnosis and reperfusion. This delay was associated with a higher mortality rate during the pandemic (7.5% vs 5.1%), which contradicts our findings. The lack of a direct association between time delays until diagnosis and the appearance of adverse events is not easy to explain. However, a plausible hypothesis can be the higher number of out-of-hospital sudden deaths reported due to mechanical complications or malignant arrhythmias followed by the corresponding selection bias since this study included hospitalized patients only.

Table 2. Clinical events at the follow-up

Variable	Total (N = 634)	Group A (N = 205)	Group B (N = 303)	Group C (N = 126)	*P*
All-cause mortality	36 (5.7)	15 (7.3)	13 (4.3)	8 (6.4)	.327
Cardiac death	22 (64.7)	7 (50)	9 (75)	6 (75)	.427
Stroke	20 (3.2)	9 (4.4)	8 (2.6)	3 (2.4)	.551
Re-AMI	4 (0.7)	1 (0.5)	2 (0.7)	1 (0.8)	1.000
Stent thrombosis	12 (2.0)	8 (4.1)	1 (0.3)	3 (2.4)	.006
New revascularization	6 (1.0)	4 (2.0)	2 (0.7)	0 (0)	.259
CV death + stroke + Re-AMI + stent thrombosis + new revascularization	57 (9.0)	24 (11.7)	20 (6.6)	13 (10.3)	.120

CV, cardiovascular; Re-AMI, new acute myocardial infarction.
Data are expressed as no. (%).

Table 3. In-hospital events

Variable	Total (N = 634)	Group A (N = 205)	Group B (N = 303)	Group C (N = 126)	*P*
Inotropic agents	53 (8.5)	17 (8.4)	27 (9.0)	9 (7.2)	.836
PM at admission	12 (1.9)	4 (2.0)	8 (2.7)	0 (0)	.188
IABP	11 (1.7)	7 (3.4)	4 (1.3)	0 (0)	.048
OTI	41 (6.5)	15 (7.3)	21 (7.0)	5 (4.0)	.444
NIMV	18 (2.9)	6 (2.9)	7 (2.3)	5 (4.0)	.604
RRT	10 (1.6)	6 (3)	3 (1.0)	1 (0.8)	.192
AVB	20 (3.2)	7 (3.4)	12 (4.0)	1 (0.8)	.227
SMVT	18 (2.9)	6 (2.9)	9 (3.0)	3 (2.4)	1.000
VF	29 (4.6)	12 (5.9)	12 (4.0)	5 (4.0)	.582
AF at admission	42 (6.7)	11 (5.4)	23 (7.6)	8 (6.4)	.597
BARC bleeding type > 3	16 (2.5)	2 (1.0)	9 (3.0)	5 (4.0)	.161
Infection	57 (9.0)	12 (6.0)	28 (10.1)	17 (11.0)	.184
ARDS	12 (1.9)	1 (0.5)	7 (2.5)	4 (2.6)	.208
Mechanical complications	10 (1.6)	3 (1.5)	6 (2.0)	1 (0.8)	.774
Killip III or IV	62 (9.8)	20 (9.8)	31 (10.3)	11 (8.8)	.898

AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; AVB, atrioventricular block; BARC, Bleeding Academic Research Consortium; IABP, intra-aortic balloon pump; NIMV, non-invasive mechanical ventilation; OTI, orotracheal intubation; PM, pacemaker; RRT, renal replacement therapy; SMVT, sustained monomorphic ventricular tachycardia; VF, ventricular fibrillation.
Data are expressed as no. (%).

Table 4. Times between symptom onset and the first medical contact, and between electrocardiographic diagnosis and reperfusion (guidewire passage), in minutes, in the cohort of patients with ST-segment elevation acute coronary syndrome

Variable	Total	Grupo A	Grupo B	Grupo C	p
Symptom onset-first medical contact (N = 332)	120 [60-240]	66 [45-180] (N = 97)	120 [60-240] (N = 180)	120 [60-240] (N = 55)	.007
Diagnosis-reperfusion (N = 322)	120 [60-180]	120 [60-186] (N = 93)	120 [60-225] (N = 176)	60 [60-120] (N = 53)	.025

Data are expressed as median [interquartile range].

Therapeutic strategies: percutaneous coronary intervention and surgical revascularization

No differences were found regarding the percutaneous invasive management of patients with ACS before, during or after lockdown. This data is consistent with most studies published on the management of ACS during the pandemic.[12,22]

However, we should mention the significant decrease of myocardial revascularization procedures despite the non-negligible number of patients with left main coronary artery disease or 3-vessel disease. A total of 17.7% of these patients were treated with myocardial revascularization 1 month before the lockdown, only 5.5% during the lockdown, and 34.5% the following month. Although some registries confirm the lower number of coronary artery bypass grafts performed,[23] this tendency has not been confirmed in other studies.[18,23]

The fact that fewer myocardial revascularization procedures were performed during the lockdown can be explained by the overall tendency to delay any surgical acts as much as possible during these months, something already hypothesized in other studies.[24]

Limitations

This study has some limitations associated with the analysis of multicenter and observational data. Also, the study short follow-up period may have prevented the finding of potential consequences or differential events among the study groups. The lack of information on cases of ACS treated during the pandemic that never really made it to tertiary care centers also casts a shadow over the conclusions that can be drawn.

CONCLUSIONS

Significantly fewer admissions due to ACS were reported during the lockdown. Also, although time between symptom onset and the first medical contact was longer during this period in patients with STEACS, the mortality rate was similar among the 3 study groups.

FUNDING

None reported.

AUTHORS' CONTRIBUTIONS

J. Echarte-Morales: clinical data mining, manuscript drafting, project design, and management of the study. C. Minguito-Carazo: data analysis, manuscript drafting and revision process. PL Cepas-Guillén, V. Vallejo García, ID. Poveda Pinedo, A. Salazar Rodríguez, E. Arbas Redondo, J. Guzmán Bofarull, and D. Tebar Márquez: data mining and manuscript revision process. E. Sánchez Muñoz: data mining. E. Martínez Gómez: data mining, manuscript drafting and revision process. T. Benito-González: statistical counselling, and manuscript revision process. M. López Benito, A. Viana Tejedor, I. Cruz-González, PL Sánchez Fernández, M. Sabaté, and F. Fernández-Vázquez: project organization. Authors submitting this manuscript accept full responsibility for its content as defined by the International Committee of Medical Journal Editors (ICMJE).

CONFLICTS OF INTEREST

None whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Admissions due to STEACS decreased during the lockdown.
- More mechanical complications were reported during the pandemic due to delayed treatments.

WHAT DOES THIS STUDY ADD?

- Unlike former studies that mainly focused on patients with STEACS, this study includes patients admitted before, during, and 1 month after lockdown with a diagnosis of ACS (including STEACS and non-ST-segment elevation acute coronary syndrome).
- Fewer myocardial revascularization procedures were performed during the lockdown despite the growing number of patients with left main coronary artery disease or 3-vessel disease.
- Although time between symptom onset and the first medical contact was longer in the group of patients with STEACS, the mortality rate was similar before, during, and after lockdown, as it happened with mechanical complications.

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Original article

Rationale and study design on the effectiveness of vasodilators and topical local anesthetics to prevent radial spasm. The E-RADIAL trial

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ABSTRACT

Introduction and objectives: When using radial access established as the approach of choice to perform coronary angiographies it is important to avoid radial spasm as it is the leading cause of access failure. This study aims to determine whether a topical anesthetic cream reduces the rate of radial spasm, as well as the increased gain with the use of different vasodilators.
Methods: Randomized, double-blind, and single-center clinical trial. Patients will be randomized to receive the anesthetic cream vs placebo, and 4 types of different vasodilator cocktails will be used in each group. The presence—or not—of radial spam and caliper gain will be analyzed.
Conclusions: Demonstrating the efficacy of the anesthetic cream, and different vasodilators to reduce radial spam would have a significant clinical impact, and justify its systematic use when performing coronary angiographies.
Registered at The Spanish Agency of Medicines and Medical Devices (AEMPS) EudraCT number: 2017-000321-12.

Keywords: Radial spasm. Anesthetic cream. Vasodilators. Coronary angiography. Luminal diameter.

Justificación y diseño del estudio sobre efectividad en prevención del espasmo radial de vasodilatadores y anestesia local tópica. Ensayo E-RADIAL

RESUMEN

Introducción y objetivos: Con el abordaje radial establecido como técnica de elección para la coronariografía, es importante evitar el espasmo radial como principal causa de fallo en el acceso intravascular. En este estudio se pretende demostrar si la anestesia tópica en crema disminuye la incidencia de espasmo radial, así como conocer la ganancia de calibre con el uso de diferentes vasodilatadores.
Métodos: Ensayo clínico aleatorizado doble ciego en un solo centro. Los pacientes se aleatorizarán para recibir crema anestésica o placebo, y se utilizarán 4 tipos de cócteles vasodilatadores en cada grupo. Se analizará la presencia o no de espasmo radial y la ganancia de calibre como objetivos primarios.
Conclusiones: La demostración de la eficacia de la crema anestésica y de los diferentes vasodilatadores en la disminución del espasmo radial tendría un impacto clínico importante y justificaría su uso sistemático en la coronariografía.
Registrado en la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) con n.º EudraCT: 2017-000321-12.

Palabras clave: Espasmo radial. Crema anestésica. Vasodilatadores. Coronariografía. Diámetro luminal.

Abbreviations

MLD: mean luminal diameter. **RS:** radial spasm. **TA:** topical anesthesia.

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INTRODUCTION

Radial approach for cardiac catheterizations has become the most widely used across the world. In Spain it represents up to 75% of all the procedures performed and, in some centers, up to 91.1%.[1] Compared to traditional femoral approach, this access has clearly proven its superiority from the safety standpoint of the procedures.[2]

Arterial canalization failure is often due to radial spasm (RS), and it can occur in up to 10% of all attempts. Also, it is associated with feminine sex, young age, low weight[3] or deficits of certain enzymes that act on the endothelium.[4] The special histological characteristics of this artery—with a high density of alpha-adrenergic receptors and smooth muscle cells—make it more prone to spasm.[5]

On the other hand, pain during lumbar puncture contributes to arterial canalization failure due to a higher frequency of appearance of spasm, vasovagal reaction with hypotension and discomfort for patient and operator, and the patient's possible hemodynamic instability. Similarly, several patients complain of discomfort. As a matter of fact, the arterial puncture is described by many patients as the main moment of discomfort.[5]

Former studies have reported on the greater success achieved with isolated punctures for arterial gas analysis in the radial artery with the use of anesthesia injected around the puncture site. Also, more comfort and less pain have been reported by the patients.[6] However, for many professionals injected anesthesia is ill-advised due to the pain caused by the injection. Also, because there are times that pain leads discomfort, and eventually RS.[7] Despite of all this, the use of injected anesthesia is a common thing in procedures performed via radial access.

On the other hand, in the pediatric population as well as in different anatomical locations or in skin surgery, the use of topical anesthesia (TA) in the form of gel, cream or ointment has proven to minimize the pain associated with venous or arterial punctures, and some procedures too.[8] The use of this type of anesthetic agents has not been properly studied in the cardiac catheterization setting. However, it could minimize the rate of RS, reduce pain when using this access, and improve the patient's perception.

Together with TA, the use of different vasodilator drug combinations with unfractionated heparin (the so-called «radial cocktail»)—after successful arterial access—has proven to reduce the rates or arterial spasm and radial occlusion after the procedure.[9-12] In particular drugs like verapamil, nitroglycerin, nitroprusside, nicorandil, isosorbide dinitrate or phentolamine in different doses have been compared with one another and also with placebo with heterogeneous results with arterial spams having been reported in 4% to 12% of the cases. Verapamil in doses of 5 mg and nitroglycerin 200 µg have yielded the best results so far. However, to this date, no comparison studies between the 2 drugs at these doses have ever been drawn or randomized for this matter.[13] Therefore, it has not been fully established which is the best drug combination to prevent spasm and radial occlusion.

At our center, the current radial puncture procedure includes the use of injected anesthesia around the puncture site plus a cocktail of 5000 IU of unfractionated heparin, and 2.5 mg of verapamil. The rate of RS in our cath lab is around 10% of all punctures performed. In some patients, other drugs commonly available in our setting are often used—at the operator's criterion—like nitroprusside, nitroglycerin or high doses of verapamil.

The objective of this study is to demonstrate whether the administration of topical anesthesia reduces the rate of RS and improves the patient's perception regardless of the vasodilator used. Also, to compare arterial caliber gain with different vasodilators.

Table 1. Inclusion and exclusion criteria of the E-RADIAL study

Composition of the radial cocktail	Type of dilution
Cocktail #1 (verapamil 2.5 mg):	12.5 mg of verapamil are diluted in 95 mL of FSS at 0.9%. A total of 20 mL are loaded in the syringe and fully administered.
Cocktail #2 (verapamil 5 mg):	25 mg of verapamil are diluted in 90 mL of FSS at 0.9%. A total of 20 mL are loaded in the syringe and fully administered.
Cocktail #3 (nitroglycerin 0.2 mg):	5 mg of nitroglycerin are diluted in 95 mL of FSS at 0.9%. A total of 4 mL of this solution are loaded in a 20 mL-syringe that is completed with FSS at 0.9%. The entire load of the syringe is administered.
Cocktail #4 (nitroprusside 0.150 mg):	50 mg are diluted in 10 mL of FSS at 0.9% followed by the extraction of 1 mL of this solution that is diluted again in 100 mL of FSS at 0.9%. A total of 3 mL of the latter solution are loaded in a 20 mL-syringe that is completed with FSS at 0.9%. The entire load of the syringe is administered.

FSS, physiological saline solution.

Table 2. Inclusion and exclusion criteria of the E-RADIAL study

Inclusion criteria	Exclusion criteria
Age > 18 years	Allergy or intolerance to any of the drugs used in the study.
Informed consent signing	Baseline systolic arterial blood pressure < 90 mmHg.
Elective diagnostic cardiac catheterization with intended radial access	Impossibility to understand the study or give the corresponding informed consent.
Introductor 5 French	

METHODS

Study design

Double-blind randomized clinical trial conducted at a single center to analyze the rate of RS in patients treated with TA in cream with lidocaine 25 mg/g + prilocaine 25 mg/g (Emla) in topical solution compared to placebo, as well as the effect of vasodilators (table 1) (verapamil 2.5 mg or 5 mg, nitroglycerin 200 µg, nitroprusside 150 µg) in the arterial caliber while attempting vascular access to perform diagnostic transradial cardiac catheterization.

Study population

The study will be conducted entirely at Unidad de Hemodinámica y Cardiología Intervencionista of Complejo Hospitalario Universitario de Albacete, Spain. All consecutive patients treated with diagnostic cardiac catheterization via radial access from November 2020 until completing the sample estimated will be included. Patients will need to meet the inclusion criteria and none of the exclusion ones (table 2).

Ethical aspects

The study has been approved by the center ethics committee, and a favorable resolution was obtained. The study has been registered

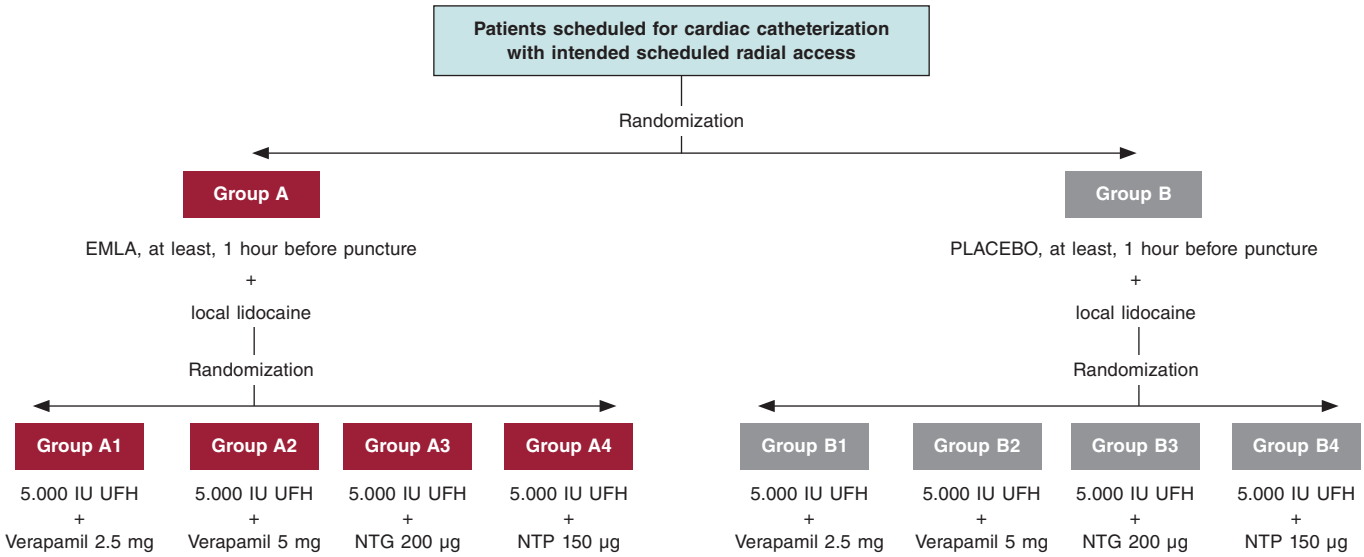

Figure 1. Flowchart of patients from the E-RADIAL study. NTG, nitroglycerin; NTP, nitroprusside; UFH, unfractionated heparin.

by *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)* with registration No. EudraCT: 2017-000321-12. The study will observe the principles established in the Declaration of Helsinki. Also, written informed consent will be obtained from all the patients before joining the study.

Study endpoints

Primary endpoints

- Study the rate of RS using a topical anesthetic cream before radial puncture.
- Study radial artery caliber gain using different vasodilators.

Secondary endpoints

- Study the rate of radial-radial, and radial-femoral crossing with each strategy.
- Study the rate of vasovagal reactions requiring treatment in each group.
- Study parameters associated with pain during radial artery canalization using pain assessment analogue scales.
- Subjective assessment of pain and comfort by the patient using pain assessment analogue scales, and dedicated tests.
- Subjective assessment of the difficulty involved in the puncture and perception of RS by the operator using dedicated tests.

Study development

The administration of TA/placebo plus cocktail (table 1) will be fully randomized (figure 1). Both the patient and the treating interventional cardiology will be blind to the group they'll be assigned to. If certain circumstances or complications occur, and if deemed necessary, the chain of secrecy can be broken only if investigators abide, and only under strict clinical judgement.

Placebo with cream of similar color, consistency, and characteristics to Emla will be prepared, and they both will be marked with letters A (Emla) and B (placebo). Both placebo and the TA will be prepared by personnel from the hospital pharmacy unit. The nursing team in charge of the patients while waiting for cardiac catheterization at the cath lab will randomize each patient, and the only blind element of the study. TA or placebo will be administered in both wrists and, at least, 1 hour before the procedure.

Prior to puncture, 25 mg of subcutaneous local anesthesia will be injected into the puncture area (mepivacaine at 2%). Another 1-2 minutes will need to pass before it starts to work.

Different cocktails (table 1) will be prepared at the dilution often used at Complejo Hospitalario Universitario de Albacete cath lab in 100 mL-jars of physiological saline solution (NaCl at 0.9%). Each jar will be marked with an alphanumeric code and its content will remain blind to everyone but the nursing team in charge of randomization.

Variable quantification during puncture

After monitoring the patient, arterial blood pressure will be determined invasively, as well as the baseline heart rate before administering the cocktail that will be used just after the introduction of hydrophilic guidewire (Radiofocus 5-Fr, Terumo, Japan). Similarly, arterial blood pressure will be recorded 2 minutes after the cocktail administration, as well as the maximum heart rate during puncture.

All vagal data that can occur and any other complications associated with access will be written down. The crossing rate to other accesses will also be studied prioritizing homolateral (cubital, distal radial) or contralateral access. Unless the operator specifies otherwise, femoral access will be set aside as the third go-to option.

Radial spasm determination and caliber gain quantification

RS will be defined as yes/no—both qualitative and dichotomically—and considered as sudden, transient, and abrupt narrowing of the radial artery during puncture. It will be clinically determined by, at least, 1 of the following events: loss of pulse during puncture,

pain in the upper limb during catheter manipulation or entrapment. Its presence can also be determined through the angiography if spasm is seen during contrast injection.

Caliber gain will be determined through quantitative analysis of the radial artery luminogram. Therefore, an angiography will be immediately performed after the insertion of the introducer sheath plus another one 2 minutes after the injection of the antispasmodic cocktail. The radial artery caliber will be measured in the segment located between the tip of the arterial introducer sheath—2 cm away from it—and the location where it meets the humeral artery. Measurements will be acquired through computerized quantitative analysis (Xcelera, Philips, United States) after previous calibration of the arterial introducer sheath in the same segment before and after the cocktail injection to determine the mean luminal diameter (MLD).

Caliber gain will be estimated in percentage according to the following formula:

$$\text{Caliber gain} = \frac{([\text{MLD post-cocktail} - \text{MLD pre-cocktail}]}{\text{MLD pre-cocktail})} \times 100$$

Postoperative patient assessment

The patient will be asked to give his opinion on the radial puncture through the pain qualitative analogue scale, and the comfort scale consisting of 4 questions (annex of the supplementary data).

Similarly, the interventional cardiologist will give his evaluation through a survey including 2 questions (annex of the supplementary data), the difficulties found while performing the puncture, and how the procedure was accomplished via the access used.

Statistical analysis

The analysis will be conducted using the SPSS statistical software package for Windows v 21.0.

In descriptive statistics frequencies and percentages will be used to express discrete variables while mean, median, mode, standard deviation, and ranges will be used to express continuous variables. The rate of spams and other study components will be described through frequencies and percentages. The statistical analysis of the main variables will be conducted by intention-to-treat analysis. The chi-square test will be used to study differences among proportions while the continuous variables will be analyzed using the Student *t* test if normally distributed or else non-parametric tests if not normally distributed. In the presence of non-homogeneous distribution of confounding variables between the groups that will be analyzed, a logistic regression analysis will be conducted that should collect those clinically significant and non-homogeneously distributed parameters.

It is our will to conduct an intermediate analysis after which the study will move on or not (existence of a significant difference in the primary endpoint of RS > 7,5% between both groups).

Estimate of the sample size

According to former studies, it is estimated that the proportion of patients who will have RS in the control group will be 10%[3,5] being the criterion of clinical effectiveness the reduction of this percentage off by 50%, which is why it will be necessary to have a minimum sample of 668 patients.

This volume of patients will allow us to confirm the statistical significance of the variations described in radial artery vasodilation with different types of vasodilators.

DISCUSSION

Currently, the arterial approach via radial access is used in 91.1%[1] of all diagnostic and therapeutic coronary angiographies performed. In particular, the rates of bleeding complications have dropped thus contributing to the patients' comfort. This access has facilitated the implementation of safe coronary angiography and outpatient angioplasty programs even in complex settings.[14-16]

Hand in hand with this and assuming pain hypothesis and adrenergic discharge are caused by puncture and risk factors for RS, different strategies have come up to contribute to the proper administration of anesthesia promoting patients' comfort, and looking to reduce the rate of RS. As it happens in other places, at our center the use of subcutaneously injected anesthesia is the common practice since the direct correlation between less RS and proper anesthetic release in the punction area has already been confirmed.[5] This study paves the way for a possible change in the routine clinical practice that could be associated—or not—with TA in cream pharmaceutical form. The medical literature includes different and very heterogeneous studies that, whether randomized or not, have tried to assess the utility of this type of creams. However, all of them include small samples (usually less than 100 patients), which makes it difficult to extrapolate the results.

We have a few examples of injected anesthesia vs a composite of TA plus injected anesthesia with favorable results from the latter.[17,18] As far as we know, the heterogeneity of designs, and the small sample sizes make us question studies like these.

Although subcutaneous anesthesia—often with lidocaine—has proven to improve pain at the puncture site and reduce the rate of RS compared to TA there is a huge controversy regarding the active principles and drug combination that should be used, the specific action times of these drugs or which are the best pharmaceutical forms. However, it seems that the cream/ointment formulation, and the lidocaine/prilocaine combination (Emla type) yield the best results of all.[18]

Assuming that this type of formulation is the most widely studied and looking to achieve an adequate design with a representative sample, the E-RADIAL trial (Effectiveness in preventing radial spasm of different vasodilators and topic local anesthesia during transradial cardiac catheterization) has just been started. Although it is not the first trial to propose this hypothesis, it is the first one indeed to confirm it on a double-blind randomized clinical trial and compare it to different radial cocktails and a wide sample size.

This vasolidator comparison is a particularly new approach of our trial. There is some controversy on the use, or not, of such drugs: although some centers in our country do not use vasodilators on a routine basis, it seems to be proven that, overall, its use promotes arterial dilatation and, therefore, the navigability of catheters with lower rates of spasm.[9,13] Currently, no such thing as head-on comparisons of cocktails have been drawn in trials to assess their efficacy and safety profile.[19] Therefore, we designed our study taking into consideration that a comparison can be drawn among these different drugs in quantitative terms using MLD gain.

Although not part of our study primary endpoints we assume that—with radial access clearly established in the routine clinical practice of cath labs—the operator's experience, his learning curve or even the rotating fellow/resident's learning curve can have an

impact on the rate of success of puncture, RS, as well as on other complications. This can be an interesting aspect we could discuss. As far as we know both in the current medical literature and good practice recommendations regarding the radial access[20]—although with limitations depending on the study analyzed—it seems reasonable to assume that the threshold to overtake the learning curve would be at around 30-50[21] cases for conventional diagnostic coronary angiography, and > 100-200 cases for complex coronary anatomies[22,23] or even in the ST-segment elevation acute coronary syndrome setting. In the E-RADIAL study, all operators widely exceed the number of cases recommended for this curve in diagnostic coronary angiography. Even so, while collecting data for the E-RADIAL we'll have the possibility to know the identity of the operator who will perform the puncture, his years of experience using radial access, and whether a resident or a novel interventional cardiology (< 2 years of experience) was involved. Also, we will try to know descriptively the rate of puncture success, and whether any RS differences or other complications occurred.

The design of this clinical trial used 4 types of radial cocktail (table 1) from the ones most widely used ones in today's clinical practice. However, this is also a controversial issue. On the one hand, some centers don't use vasodilators systematically after radial puncture. On the other hand, choosing one over the other at the cath labs where they're used is often based on the good clinical results obtained empirically in the routine clinical practice. Unlike the use of heparin to prevent radial occlusion, evidence is scarce regarding benefits from vasodilators, and no homogeneous head-on comparisons have been drawn among different drug cocktails. Verapamil in doses of 5 mg, and nitroglycerin in doses of 200 µg have yielded the best results so far. However, to this date, they have never been compared to one another at these doses or in a randomized way.[13] Certain clinical features of the patients can turn the use of these cocktails into a controversial issue. As an example of this, in patients with very severe left ventricular dysfunction or severe aortic stenosis the use of these drugs can trigger significant adverse reactions, mainly hypotension or significant hemodynamic changes. Although, in theory, overall, these drugs are contraindicated in these clinical settings, the dose used, slow infusion, and other factors like the patients' clinical stability, the existence—or not—of associated heart failure or different comorbidities can turn the use of these drugs into a safe practice. In its design the E-RADIAL study includes a head-on comparison of cocktails and some of the aforementioned drugs and doses. Therefore, it is an opportunity to know what the clinical implication of these drugs really is regarding adverse events.

One of the possible weaknesses or aspects that should be discussed in this trial is pain assessment and quantification. A reproducible design was attempted while assuming the difficulties posed by individual subjectivity. Therefore, following in the footsteps of former studies and registries, we decided to use the most standardized method available to this date in the medical literature: analogue scales.

Another possible weakness or cofounding factor in the study design is the systematic use of sodium heparin via arterial access as standard prevention against radial occlusion.[20] According to the drug label[24] the heparin-induced cardiac tamponade solution is often an acid solution with a pH between 5.0 and 7.5. The mean arterial pH is between the traditional values of 7.35 and 7.45, and could be partially altered when in contact with heparin solutions thus favoring, through different mechanisms, the development of RS, something not clearly established to this date. To solve this possible bias, the IV—not intraarterial use—of heparin was selected. Although evidence is certainly scarce and heterogeneous the IV use of heparin does not seem to increase the rate of radial occlusion, which is more associated with the heparin dose used and factors like compression time, type of material or size of the radial introducer sheath used that are well established as predictors of radial occlusion.[25,26]

CONCLUSIONS

The E-RADIAL study is the first randomized clinical trial to assess, on the one hand, the implications of less RS due to topical anesthesia and, on the other, arterial caliber gain with the use of different vasodilators.

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None whatsoever.

AUTHORS' CONTRIBUTIONS

J. J. Portero-Portaz: idea, methodology, validation, formal analysis, drafting of the original project; J. G. Córdoba-Soriano: idea, methodology, review and edition of the manuscript; A. Gutiérrez-Díez: idea, methodology, validation, formal analysis, review and edition of the manuscript; A. Gallardo-López, and D. Melehi El-Assali: idea, methodology, review and edition of the manuscript; L. Expósito-Calamardo, and A. Prieto-Lobato: research, review, and edition of the manuscript; E. García-Martínez, S. Ruiz-Sánchez, M. R. Ortiz Navarro, and E. Riquelme-Bravo: methodology, review, and edition of the manuscript; J. Jiménez-Mazuecos: idea, methodology, review and edition of the manuscript.

CONFLICTS OF INTEREST

Authors declared having no affiliation or participation in any organization or entity with any financial or non-financial interest in the topic at stake or in the materials discussed in this manuscript.

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WHAT IS KNOWN ABOUT THE TOPIC?

- RS is the leading cause of access failure in diagnostic or therapeutic coronary angiographies.
- The use of injected local anesthesia is standardized and reduces the rate of RS.
- There is no consensus on the use or non-use of vasodilators, which depends on the characteristics and routine clinical practice of each center.

WHAT DOES THIS STUDY ADD?

- The E-RADIAL study can pave the way to systematization in the use of other type of anesthesia.
- It will provide relevant information on the effectiveness of different vasodilators through head-on comparisons of the most widely used agents.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000279.

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Original article

Descriptive analysis of different reperfusion therapies in acute pulmonary embolism

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ABSTRACT

Introduction and objectives: Hemodynamically unstable patients with acute pulmonary embolism (PE) are eligible for systemic thrombolysis (ST). However, catheter-directed therapy (CDT) and surgical thrombectomy (SUT) can also be considered with less clinical evidence. Limited information exists regarding the best reperfusion therapy in this setting. Our objective was to perform a descriptive analysis of different reperfusion therapies in acute pulmonary embolism and determine their safety and efficacy profile.
Methods: Retrospective analysis from a prospective single-centre registry of patients admitted with a diagnosis of PE from 2006 through 2021 who required reperfusion therapy. We analyzed the in-hospital outcomes and at 14-day follow up.
Results: A total of 50 out of 399 patients admitted with a diagnosis of PE received reperfusion therapies and were included in our analysis. Mean age, 64.5 (53-72), 46% female. This was the reperfusion strategy applied: ST (44%), CDT (42%) and SUT (14%). All patients had right ventricular dilatation and high troponin levels. The overall in-hospital mortality was 18%. Major and minor bleeding rates among the different reperfusion methods were 9.0% vs 4.7% vs 57.4%; P = .001), and 18.1% vs 9.5% vs 14.2%; P = NS), respectively. The 14-day follow-up showed that only CDT and SUT reduced the pulmonary artery systolic pressure while ST and CDT were associated with a reduced right ventricular diameter and an improved right ventricular function.
Conclusions: High mortality rates were found in this population with acute PE. No differences were seen regarding effectiveness seen among the different reperfusion strategies used. CDT and SUT may be considered as alternative reperfusion methods especially if ST is contraindicated.

Keywords: Pulmonary embolism. Systemic thrombolysis. Catheter-directed therapy. Reperfusion therapy. Surgical thrombectomy.

Análisis descriptivo de diferentes tratamientos de reperfusión en la tromboembolia pulmonar aguda

RESUMEN

Introducción y objetivos: Los pacientes con tromboembolia pulmonar (TEP) aguda hemodinámicamente inestables son candidatos para recibir trombolisis sistémica (TS); sin embargo, el tratamiento guiado por catéter (TGC) y la trombectomía quirúrgica (TQ) también se pueden considerar, aunque con menor nivel de evidencia. Existe información limitada respecto a cuál es el mejor método de reperfusión en esta población. El objetivo es realizar un análisis descriptivo de las distintas terapias de reperfusión en la TEP aguda y determinar su efectividad y seguridad
Métodos: Análisis retrospectivo de un registro prospectivo unicéntrico de pacientes ingresados con TEP aguda entre los años 2006 y 2021, que requirieron tratamiento de reperfusión. Analizamos la evolución intrahospitalaria y en el seguimiento a 14 días.
Resultados: De 399 pacientes con TEP, 50 recibieron tratamiento de reperfusión y fueron incluidos en el análisis. La edad media era de 64,5 años (rango: 53-72) y el 46% eran mujeres. Los métodos de reperfusión fueron TS en el 44%, TGC en el 42% y TQ en el 14%. Todos presentaron dilatación del ventrículo derecho y elevación de las troponinas. La mortalidad intrahospitalaria fue del 18%. Las tasas de sangrado mayor en los grupos de TS, TGC y TQ fueron del 9,0%, el 4,7% y el 57,4% (p = 0,001), y las de sangrado menor fueron del 18,1%, el 9,5% y el 14,2% (p no significativa), respectivamente. Durante el seguimiento a 14 días, solo el TGC y la TQ lograron una reducción de la presión sistólica en la arteria pulmonar, y con la TS y la TGC hubo una reducción de los diámetros del ventrículo derecho y una mejoría de su función.

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Conclusiones: En esta población de pacientes con TEP aguda encontramos altas tasas de mortalidad intrahospitalaria. No se observaron diferencias en términos de efectividad entre los distintos tratamientos de reperfusión. El TGC y la TQ podrían considerarse métodos de reperfusión alternativos, en especial cuando la TS está contraindicada.

Palabras clave: Tromboembolia pulmonar. Tratamiento de reperfusión. Tratamiento guiado por catéter. Trombolisis sistémica. Trombectomía quirúrgica.

Abbreviations

CGT: catheter-guided therapy. **PASP:** pulmonary artery systolic pressure. **PTE:** pulmonary thromboembolism. **RV:** right ventricle. **ST:** systemic thrombolysis. **SUT:** surgical thrombectomy.

INTRODUCTION

Acute pulmonary thromboembolism (PTE) is the third leading cause of cardiovascular mortality, and most deaths are due to acute right heart failure following the obstruction of flow into the pulmonary arteries. The in-hospital mortality rate in patients whose first sign at presentation is hemodynamic instability is 30%. However, it can be as high as 50% in some registries, and 10 times higher compared to stable patients.[1]

In the registries of patients with PTE there is a group of intermediate risk patients with a higher mortality rate compared to that recorded in clinical trials involving a wide spectrum of individuals including a subgroup with a high mortality rate and similar to that of patients with high-risk PTE. Identifying this high-risk population and selecting those patients who may benefit from some reperfusion method is tremendously challenging for the treating heart team.[2-4] Similarly, PTE is associated with other complications at the follow-up like risk of recurrence of thromboembolic events and those associated with a reduced functional capacity or the eventual development of chronic thromboembolic pulmonary hypertension.[5,6]

There is consensus on the management of reperfusion in patients with high-risk PTE while in intermediate-risk patients, treatment is controversial and could only be indicated in patients with hemodynamic impairment on anticoagulant therapy.[7-9] Currently, the reperfusion strategy recommended as the first option in this group of patients is systemic thrombolysis (ST) despite the risk of bleeding involved.[7]

Although evidence is scarce on this regard, in selected cases, catheter-guided therapy (CGT), and surgical thrombectomy (SUT) could be associated with a lower rate of hemorrhagic complications with similar efficacy.[10-13]

To this date, no studies have been conducted comparing such reperfusion strategies, so it is unknown which one of them is safer and more effective. The objective of this study is to conduct a descriptive analysis on the different reperfusion mechanisms in acute PTE and determine their effectiveness and safety profiles.

METHODS

A single-center, retrospective, observational cohort study was conducted with patients admitted with PTE who required reperfusion treatment. Data were collected from the prospective registry of a teaching hospital between 2006 and 2021. Reperfusion methods studied were ST, CGT, and SUT.

Patients received reperfusion treatment based on the heart team criterion, evidence, and national and international recommendations available at that time. Patients with overt shock due to right ventricular (RV) failure, and patients without shock with RV dilatation, myocardial damage, and clinical signs indicative of early instability despite parenteral anticoagulant treatment in therapeutic doses were considered eligible to receive reperfusion treatment. Added to this, to be considered eligible for reperfusion treatment, patients should also present with, at least, 2 of the following: persistent tachycardia with a heart rate > 110 bpm or < 60 bpm, systolic arterial pressure < 100 mmHg, elevated lactic acid levels, oxygen saturation < 90%, shock index (heart rate/systolic arterial pressure) > 1 or high thrombotic load (modified Miller score > 22). We should mention that patients with moderate-to-severe RV dysfunction or thrombus in transit were considered eligible for reperfusion treatment on an emergency basis.

ST was preferred in young patients with low risk of bleeding and without absolute or relative contraindications for the use of fibrinolytic agents. In patients with higher risk of bleeding (old age, malignant neoplasm, elevated RIETE or HAS-BLED scores), absolute or relative contraindications for systemic thrombolytic therapy or presence of central thrombi, CGT was considered more suitable. SUT was preferred for patients with suspected subacute PTE (symptoms of >15-day evolution, pulmonary artery systolic pressure [PASP] > 60 mmHg or RV hypertrophy), severe RV dysfunction requiring circulatory support or thrombus in transit.

Streptokinase was the fibrinolytic agent used between 2006 and 2010, and only alteplase has been used ever since. From 2008 CGT started being used as an alternative reperfusion method. Regarding the devices used for CGT, from 2008 through 2017, pigtail-type catheters for thrombus fragmentation and multipurpose catheters for manual thrombus aspiration were being used; the Penumbra System (Penumbra, United States) has been used since 2017, and since 2020 the Angio-Jet device (Boston Scientific, United States) has been available as well.

Data was collected from each patient's baseline characteristics (age, sex, cardiovascular risk factors, past medical history, comorbidities), clinical status when acute PTE was diagnosed (arterial pressure, heart rate, hemodynamic stability, PESI score, thrombotic load), bleeding risk scores (HAS-BLED, RIETE), lab test parameters (ultra-sensitive cardiac T troponin, and lactic acid), and echocardiographic data on the RV size and function and PASP.

RV dilatation was assessed as a dichotomic variable and defined as normal with diastolic diameters < 41 mm, and dilated if ≥ 41 mm or else a RV/LV ratio > 0.9 as seen on the echocardiography or coronary computed tomography angiography.

RV function was also assessed as a dichotomic variable and defined as normal if the tricuspid annular plane systolic excursion was ≥ 16 mm and reduced if < 16 mm or in the presence of hypokinesia of the RV free wall as seen on the echocardiography.

PASP was assessed quantitatively by measuring the trans-tricuspid pressure gradient, and pressure to the right atrium derived from the inferior vena cava or its collapsibility as seen on the echocardiography.

Physician-investigators obtained this data from the patients' electronic health records and stored it in an encrypted database authorized by the center research ethics committee.

The privacy of patients in the registry was guaranteed because names or initials were not stored in the database, and access to it was limited to the lead investigator only.

The study of the patients' clinical progression while hospitalized included in-hospital mortality, the need for mechanical ventilation, major and minor bleeding according to the categorization established by the Bleeding Academic Research Consortium,[14] and a composite of in-hospital mortality and major bleeding. The echocardiographic parameters studied before reperfusion and at 14 days were the RV function, the presence of RV dilatation, and the value of PASP.

The informed consent forms of all the patients were collected for the use of data with academic, statistical, and scientific purposes in the healthcare setting. The protocol was assessed and approved by our hospital Bioethics Research Committee (resolution no. 19-041).

Statistical analysis

This was a single-center, retrospective, observational, cohort study. For quantitative variable description, the mean ± standard deviation or median and interquartile range (IQR) 25-75 were used based on their distribution. Qualitative variables were expressed as frequency and percentage. Regarding the bivariate analysis of the 3 strategies the ANOVA technique with Bonferroni correction was used for continuous variables with equal variances while the Kruskal Wallis test was used for different variances. The chi-square test was used for dichotomic variables. Student *t* test and the Kruskal Wallis test were used for paired sample analysis based on distribution while the dichotomic variables were studied using McNemar test. *P* values < .05 were considered statistically significant. Analysis was conducted using the Stata/SE v13.0 statistical software package (StataCorp, United States).

RESULTS

A total of 50 patients out of the 399 with PTE received reperfusion treatment and were included in our analysis. No patient was excluded. The patients' mean age was 64.5 years [53-72], and 46% were women. ST was indicated in 44% of the patients while CGT in 42%, and SUT in 14%. Three patients from the ST group required bailout CGT. The ST group (mean age, 53.5 years [50-68]) was younger compared to the CGT and SUT groups (69 [59-72] and 71 years [60-79]), respectively; *P* = .02. The remaining baseline characteristics were similar (table 1).

All patients had RV dilatation and elevated cardiac T troponin levels (mean, 48.5 pg/mL). The group that received ST had higher mean troponin levels around 31 pg/mL [24-48], which was not as high compared to the CGT and SUT groups with 64pg/mL [33-196], and 88 pg/mL [36-153], respectively (*P* = .02). A total of 88% of the patients had RV dysfunction (ST, 77.2%; CGT, 95.2%; ST, 100%; non-significant *P* value). A total of 14% had high-risk PTE according to the ESC classification from 2019 (ST, 13.6%; CGT, 19%; SUT,

Table 1. Baseline characteristics of the population

Variable	Overall (N = 50)	ST (N = 22)	CGT (N = 21)	SUT (N = 7)	*P*
Clinical characteristics					
Masculine sex, %	54 (27)	50 (11)	61.9 (13)	42.8 (3)	.61
Age, years (range)	64.5 (53-72)	53.5 (50-68)	69 (59-72)	71 (60-79)	.022
Dyslipidemia, %	36 (18)	36.6 (8)	42.8 (9)	14.2 (1)	.4
Current smoking, %	38 (19)	22.7 (5)	52.3 (11)	42.8 (3)	.13
Arterial hypertension, %	54 (27)	45.4 (10)	57.1 (12)	71.4 (5)	.46
Diabetes mellitus	18 (9)	22.7 (5)	19.5 (4)	0 (0)	.40
Ischemic heart disease, %	10 (5)	4.5 (1)	9.5 (2)	28.5 (2)	.18
Heart failure, %	4 (2)	0 (0)	4.7 (1)	14.2 (1)	.24
COPD, %	2 (1)	0 (0)	4.7 (1)	0 (0)	.51
Malignant neoplasm, %	26 (13)	18.1 (4)	38.1 (8)	14.2 (1)	.25
HAS BLEED > 4, %	10 (5)	9.0 (2)	4.76 (1)	28.5 (2)	.19
RIETE	1.5 (0-3)	0 (0-1.5)	1.5 (1-4)	3 (1-5)	.08
High risk ESC, %	14 (7)	13.6 (3)	19.0 (4)	0 (0)	.46

(Continues)

Table 1. Baseline characteristics of the population *(continued)*

Variable	Overall (N = 50)	ST (N = 22)	CGT (N = 21)	SUT (N = 7)	*P*
SAP, mmHg	120.5 (110-140)	121 (111-140)	118 (100-130)	135 (111-143)	.94
DAP, mmHg	78 (65-87)	80.5 (60-100)	76 (65-80)	91 (75-101)	.60
HR, bpm	110 (99-116)	110 (100-128)	110 (100-111)	105 (85-130)	.44
Absolute contraindication for ST, %			19 (4)	0 (0)	
Relative contraindication for ST, %			28 (6)	15 (1)	
PESI					
Very high, %	28 (14)	13.6 (3)	52.3 (11)	0 (0)	
High, %	30 (15)	31.8 (7)	23.8 (5)	42.8 (3)	
Intermediate, %	22 (11)	18.1 (4)	19.0 (4)	42.8 (3)	
Low, %	16 (8)	31.8 (7)	0 (0)	14.2 (1)	
Very low, %	4 (2)	4.5 (1)	4.7 (1)	0 (0)	
Echocardiographic parameters					
RV dysfunction, %	88.0 (44)	77.2 (17)	95.2 (20)	100 (7)	.11
RV dilatation, %	100 (50)	100 (22)	100 (21)	100 (7)	NS
PASP	55 (45-61.5)	45 (45-58)	56.5 (49-67.5)	60 (51-60)	.17
PTE location					
Multiple-subsegmental, %	1.3 (5)	13.6 (3)	10 (2)	0 (0)	
Pulmonary artery trunk, %	14.2 (7)	9.0 (2)	5 (1)	57.1 (4)	
Both branches, %	57.1 (28)	59.0 (13)	65 (13)	28.5 (2)	
1 branch only, %	18.3 (9)	18.1 (4)	20 (4)	14.2 (1)	
Laboratory parameters					
high sensitivity cardiac troponin T, pg/mL	48.5 (27.5-142)	31 (24-88)	64 (33-196)	88 (36-153)	.02
Lactic acid, mEq/L	2.1 (1.5-3)	2 (1.1-2.5)			.63
Procedural data					
Procedural time, m			97.7	209.1	
Thrombus aspiration, %			95 (20)		
Thrombus fragmentation, %			52 (11)		
Local thrombolytic agents, %			38 (8)		
Doses of thrombolytic agents					
Alteplase		100 mg (60%)	31.1 +- 11.9		
Streptokinase		2 000 000 (40%)			

bpm, beats per minute; CGT, catheter-guided therapy; COPD, chronic obstructive pulmonary disease; DAP, diastolic arterial pressure; ESC, European Society of Cardiology; HR, heart rate; NS, non-significant; PASP, pulmonary artery systolic pressure: PTE, pulmonary thromboembolism; RV, right ventricle; SAP, systolic arterial pressure; ST, systemic thrombolysis; SUT, surgical thrombectomy.
Data are expressed as percentage or interquartile range 25-75.

0%; non-significant *P* value). In 14.2% of the patients the pulmonary artery was compromised while in 75.4% of the patients 1 or the 2 main branches were compromised. The mean systolic arterial pressure was 120.5 mmHg, and the average heart rate 110 bpm with no inter-group differences being reported. A total of 58% of the population had high or very high PESI scores. PASP was high in all the patients for an average 55 mmHg [45-61.5] with no inter-group differences being reported (ST, 45 mmHg [45-58]; CGT, 56.5 mmHg [49-67,5]; SUT, 60mmHg [51-60]). Lactic acid levels were 2.1 mmol/L on average with no inter-group differences being reported (ST, 2 mmol/L [1.1-2.5]; CGT, 2.5 mmol/L [1.5-7.0]; SUT, 2.1 mmol/L [2-2.5]).

Alteplase was used in 60% of the patients from the ST group (mean dose, 100 mg) while streptokinase was used in the remaining 40% (mean dose, 2.0 million IU).

Table 2. In-hospital clinical outcomes

Variables	Overall (N = 50)	ST (N = 22)	CGT (N = 21)	SUT (N = 7)	*P*
Length of stay, days (range)	10 (7-18)	8.5 (7-15)	10 (6.5-15)	22 (15-34)	.02
Ventilatory support, %	40 (20)	18.1 (4)	42.8 (9)	100 (7)	.0002
Minor bleeding (BARC < 3), %	14 (7)	18.1 (4)	9.5 (2)	14.2 (1)	.72
Major bleeding (BARC ≥ 3), %	14.0 (7)	9 (2)	4.7 (1)	57.4 (4)	.001
In-hospital mortality, %	18 (9)	9.0 (2)	28.5 (6)	14.2 (1)	.25
Composite of in-hospital mortality and major bleeding, %	28.0 (14)	13.6 (3)	33.3 (7)	57.1 (4)	.064

BARC, Bleeding Academic Research Consortium; CGT, catheter-guided therapy; ST, systemic thrombolysis; SUT, surgical thrombectomy.
Data are expressed as percentages or interquartile range 25-75.

Within the CGT group, thrombus aspiration was performed in 95% of the patients, thrombus fragmentation in 52%, and local thrombolytic agents were used in 38%. Regarding the type of catheter used for CGT, we should mention that between 2008 and 2016 pigtail-type catheters were used for thrombus fragmentation and multipurpose catheters for thrombus aspiration in 10 patients; between 2017 and 2020 Penumbra catheters were used in 10 patients, and from 2020 to 2021 the Angio-jet catheters was used in 1 patient. Mean procedural time was 97.7 minutes and the fibrinolytic agent used in CGT was alteplase in 100% (mean dose, 31.1 mg ± 11.9 mg).

A total of 47% of the patients from the CGT group had absolute or relative contraindications to receive ST vs 15% of the patients from the SUT group. Similarly, the SUT mean procedural time was 209.1 minutes.

The mean length of stay was 10 days [7-18], which was longer for SUT (22 days [15-34]) compared to the other 2 groups (ST, 8.5 [7-15]; CGT, 10 days [6.5-15]; *P* = .02).

A total of 40% of the population required mechanical ventilation that was more widely used in the SUT group (100%) compared to the other 2 groups (ST, 18.1%; CGT, 42.8%; *P* = .0002).

Minor bleeding occurred in 14% of the population with no intergroup differences being reported while major bleeding occurred in 14% of the population, more often in the SUT group (57.4%) compared to the other 2 groups (ST, 9%,; CGT, 4,7%; *P* = .001). The only intracranial bleeding even reported occurred in 1 patient who received ST; the major bleeding events occurred in the SUT group were due to transfusion need and low hemoglobin count without need for reintervention. The only major bleeding event occurred in the CGT group was due to transfusion need after the intervention.

The in-hospital mortality rate was 18% (ST, 9%; CGT, 28.5%; SUT, 14.2%; non-significant *P* value), and except for 1 death due to cancer occurred in the CGT group, all deaths reported were due to cardiogenic shock following right ventricular failure. The rate of occurrence of the composite "in-hospital mortality and major bleeding" (table 2) was 28% (ST, 13.6%; CGT, 33.3%%; SUT, 57.4%; non-significant *P* value).

A total of 42% of the patients were lost to follow-up after 14 days, which limits the validity of the findings reported after hospital discharge. In the population that was able to complete the study, normal RV diameters were reported in 70% of the patients from the ST group (*P* = .002), 75% of the patients from the CGT group (*P* = .002) and 40% of the patients from the SUT group (non-significant *P* value). Also, normal RVs were reported in 92% of the patients from the ST group (*P* = .004), 92% of the patients from the CGT group (*P* = .001), and 20% of the patients from the SUT group (non-significant *P*) as shown on figure 1.

A significant reduction of PASP was reported after reperfusion therapy both in the CGT group and in the SUT group (table 3).

DISCUSSION

Our registry included a population of patients with acute PTE who required reperfusion treatment and whose in-hospital mortality rate was 18%, which is indicative that it was a population with high morbidity and mortality rates compared to the one seen in randomized clinical trials.[15-20] One of the reasons that explains this phenomenon is that, unlike registries, randomized clinical trials often include younger, less severe, and less complex patients with fewer comorbidities.

Although the current clinical guidelines recommend ST as the first reperfusion treatment, in our population, only 44% of the patients received ST, the remaining 42% received CGT, and 14% SUT. The high rate of reperfusion with CGT reported in our registry is consistent with that reported by other high-volume centers in the United States where it is used in nearly 11% to 29% of intermediate-high or very high-risk PTEs. In such registries there is a clear tendency towards a wider use of CGT replacing ST that was used in 5.6% of the patients only.[21-23] This phenomenon occurs in the context of low compliance to the ST recommendations made in this population. An example of this is the CONAREC XX registry where almost half of the patients with hemodynamic instability did not receive ST although it was the first option recommended by the clinical practice guidelines.[24] The reasons behind this are still unclear. However, the risk of major bleeding reported, including intracranial bleeding, associated with the use of systemic thrombolytic agents could partially explain it. It is well known that registries include patients who are often left out of the clinical trials like the elderly, patients with active cancers, postoperative patients, and critically ill patients who often have a higher risk of bleeding, and contraindications for the use of fibrinolytic agents as our study confirmed where almost half of the patients from the CGT group had some contraindication for the use fibrinolytic agents.

One of the theoretical benefits of CGT or SUT over ST is the possible lower rate of severe or fatal bleeding. In a meta-analysis that only included prospective studies of a total of 566 patients treated with CGT, the rate of major bleeding was 5.8% (33 patients),

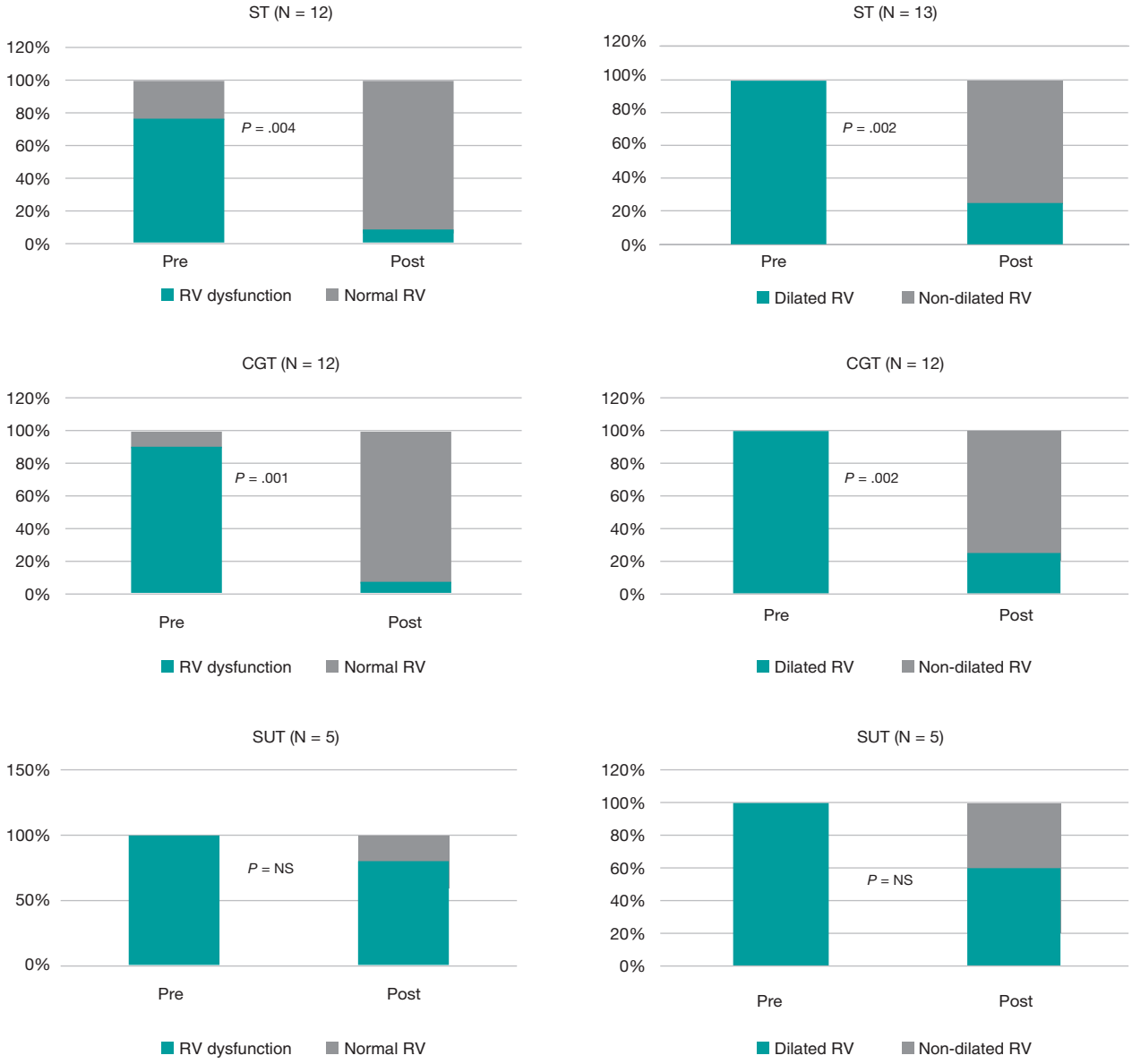

Figure 1. Presence of RV dilatation and dysfunction after reperfusion. CGT, catheter-guided therapy; NS, non-significant; RV, right ventricle; ST, systemic thrombolysis; SUT, surgical thrombectomy.

Table 3. Values of pulmonary artery systolic pressure at admission and at 14 days

Strategy	PASP at admission (mmHg)	PASP at 14 days (mmHg)	Difference (mmHg)	*P*
ST (N = 11)	46.8 ±18.7	36.7 ± 23.7	10.0 ± 15.1	.051
CGT (N = 12)	58.83 ± 12.6	31.3 ± 10.89	27.5 ± 15.2	.0001
SUT (N = 5)	56.2 ±-9.47	35 ± 7.9	21.2 ± 15.3	.036

CGT, catheter-guided therapy; PASP, pulmonary artery systolic pressure; ST, systemic thrombolysis; SUT, surgical thrombectomy.
Interquartile range 25-75.

similar to that of our registry.[25] Although these rates are lower compared to those seen on trials on ST (rate of major bleeding, 11.5%; intracranial hemorrhage, 2% to 3%), no studies have been published to this date comparing CGT and ST.[26-28]

Although in our registry no statistically significant differences were seen regarding the rates of major bleeding between CGT and ST, we should mention that the population of patients treated with CGT was 10 years older, and almost half of them had contraindications for systemic fibrinolytic agents. This suggests that the population with the highest risk of bleeding could benefit from this reperfusion strategy. Also, no intracranial bleeding was reported in patients who received CGT. Although SUT was not associated with more major bleeding events, these were due to transfusion needs and a low hemoglobin count without further need for a new intervention; also, the low number of cases reported in this group does not allow us to draw any definitive conclusions on this matter.

Currently, there is no solid evidence demonstrating the benefit of CGT in the in-hospital "hard" clinical endpoints like in-hospital mortality and hemodynamic instability or in long-term results like PTE recurrence, development of chronic thromboembolic pulmonary hypertension, and improved quality of life.

When in-hospital mortality was compared among the different reperfusion treatments, no statistically significant differences were seen (ST, 9%; CGT, 28.5%; SUT, 14.2%; non-significant *P* value). However, patients from the CGT and SUT groups were older, had a higher risk of bleeding, and elevated troponin levels, which means that they were higher-risk patients. This is indicative that these strategies could be particularly beneficial in this population. We should mention that comparisons between groups and conclusions have a limited value, mainly because of the usual selection bias found in the registries, and the small number of patients and events included (possible beta error).

To this date, the evidence on the efficacy of CGT to treat acute PTE is based on surrogate endpoints like the RV/LV ratio, PASP, and the thrombotic load using Miller score.[16-19] The use of CGT in patients with PTE would revert RV dilatation more rapidly compared to anticoagulation alone.[23] Based on the scientific evidence available, we can see that both ST and CGT reduced the RV size and function significantly, an essential endpoint since the leading cause of death in patients with acute PTE is shock due to RV failure. Also, reperfusion treatments could be useful to reduce PASP at the follow-up, and eventually reduce the risk of chronic thromboembolic pulmonary hypertension. Still, no definitive conclusions can be drawn because of the patients lost, and the lack of long-term follow-up. More multicenter, prospective registries with long follow-ups are needed to strengthen the evidence available and determine whether reperfusion in the management of patients with acute PTE could have implications in the rate of chronic thromboembolic pulmonary hypertension, which sits at around 4% in most registries.

In our own opinion and considering the current evidence available, ST is still the first option in patients with acute PTE who require reperfusion treatment while CGT and SUT should be indicated in the presence of contraindications for systemic thrombolytic agents. It is essential to define whether invasive strategies could be an alternative to ST in patients with high risk of bleeding. It seems obvious that randomized clinical trials with control groups are needed to compare the different reperfusion strategies available to treat acute PTE that should include "hard" endpoints within their efficacy and safety endpoints always bearing in mind that these results don't look anything like the real world.

However, there are numerous limitations that should be dealt with when facing this type of studies in the real world. That's why the evidence collected from ideally multicenter prospective registries with clear inclusion and exclusion criteria and standard and reproducible reperfusion techniques would be highly valuable.[29]

Limitations

As it occurs in other registries, our study was observational and the indication for reperfusion and the method used were left to the heart team and were backed by the international recommendations effective at the time. The significant selection and inclusion bias and the low number of patients included in our study limits group comparison. Also, there was a considerable number of patients who were lost to follow-up, which limits even more the conclusions of the elements studied after hospital discharge.

Similarly, we should mention that the extended period of patient recruitment of the registry is associated with significant changes within the same reperfusion strategy (type and dose of fibrinolytic agents administered, catheters used, and coadjuvant therapy). The results obtained may not be generalized to other less complex centers, use of other fibrinolytic agents or less experience in the use of CGT, and SUT.

CONCLUSIONS

In this population of patients with acute PTE we found high rates of in-hospital mortality. Although the study has several limitations and biases regarding patient selection, no differences were seen regarding effectiveness among the different reperfusion treatments used. Both ST and CGT reduced the RV diameter significantly and improved the RV function after reperfusion with similar rates of bleeding. CGT and SUT could be considered alternative reperfusion methods in selected cases, and especially when ST is contraindicated or there is a high risk of bleeding.

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AUTHORS' CONTRIBUTIONS

M. Iwanowski, J. A. Bilbao, and J. M. Bononino: study design, data curation, analysis and interpretation of data, draft of the manuscript, and final approval of the latest version of the manuscript. H. E. Fernandez, and S. J. Baratta: study design, critical review of the manuscript, final approval of the latest version of the manuscript. R. E. Melchiori: study design, analysis and interpretation of data, draft of the manuscript, final approval of the latest version of the manuscript. N. A. Torres: study design, data curation, draft of the manuscript. R. A. Costantini, J. C. Santucci, and G. N. Vaccarino: critical review of the manuscript, and final approval of the latest version of the manuscript. S. N. Márquez Herrero, P. M. Rubio, E. M. Spaini, G. M. García Juárez, and M. Bivort Haiek: data curation, analysis and interpretation of data, and draft of the manuscript.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- Patients with acute PTE and hemodynamic instability require reperfusion treatment because they are associated with high mortality and morbidity rates.
- CGT is associated with significant improvements in surrogate endpoints. However no significant reductions have been reported regarding the mortality rate.
- No randomized clinical trials have been conducted comparing ST, CGT, and SUT

WHAT DOES THIS STUDY ADD?

- Real-world patients who require reperfusion treatment have high mortality and morbidity rates that are higher compared to those seen in randomized clinical trials.
- No significant differences were found regarding the effectiveness of the different reperfusion treatments studied. Both CGT and ST reduce the RV size significantly and improve the RV function after reperfusion.
- Our study provides information on the feasibility, effectiveness, and safety of the different reperfusion methods available in an Argentinian teaching hospital where evidence is even more limited.

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Special article

A brief look into Bayesian statistics in cardiology data analysis

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ABSTRACT

Bayesian statistics assesses probabilistically all sources of uncertainty involved in a statistical study and uses Bayes' theorem to sequentially update the information generated in the different phases of the study. The characteristics of Bayesian inference make it particularly useful for the treatment of cardiological data from experimental or observational studies including different sources of variability, and complexity. This paper presents the basic concepts of Bayesian statistics associated with the estimation of parameters and derived quantities, new data prediction, and hypothesis testing. The latter in the context of model or theory selection.

Keywords: Posterior distribution. Prior distribution. Predictive distribution. Bayesian probability. Bayes' theorem.

Una pequeña mirada a la estadística bayesiana en el análisis de datos cardiológicos

RESUMEN

La estadística bayesiana valora de forma probabilística cualquier fuente de incertidumbre asociada a un estudio estadístico y utiliza el teorema de Bayes para actualizar, de manera secuencial, la información generada en las diferentes fases del estudio. Las características de la inferencia bayesiana la hacen especialmente útil para el tratamiento de datos cardiológicos procedentes de estudios experimentales u observacionales que contienen diferentes fuentes de variabilidad y complejidad. En este trabajo se presentan los conceptos básicos de la estadística bayesiana relativos a la estimación de parámetros y cantidades derivadas, predicción de nuevos datos y contrastes de hipótesis; estos últimos en el contexto de la selección de modelos o teorías.

Palabras clave: Distribución *a posteriori*. Distribución previa. Distribución predictiva. Probabilidad bayesiana. Teorema de Bayes.

INTRODUCTION: MATHETMATICS, PROBABILITY, AND STATISTICS

In the words of world famous astrophysicist Stephen Hawking, the goal of science is «nothing less than a complete description of the universe we live in».[1] Male and female scientists alike pursue this objective by building theories and assessing their predictions. It is the very essence of the scientific method.

Statistics is a scientific discipline that designs experiments and learns from data. It formalizes the process of learning through observations and guides the use the knowledge accumulated in decision-making processes. Concepts like chance, uncertainty, and luck are almost as old as mankind, and reducing uncertainty has always been a common goal for most human civilizations. Probability is the mathematical language used to quantify uncertainty and is at the core of statistical learning that represents—in probabilistic terms—both the study populations and the random samples that come from such populations.

There is not such a thing as a single statistical methodology. The most widely known and used ones are, by far, frequentist statistics, and Bayesian statistics. Both share common goals and use probability as the language of statistical learning. However, both understand the concept probability different. As a matter of fact, it is the element on which they largely disagree. According to the frequentist concept,

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it is only legitimate to assign probabilities to random phenomena that can be defined through experiments that can be repeated multiple times, and only under identical and independent conditions.

The Bayesian concept of probability is a much wider idea because it allows us to assign probabilities to all elements with uncertainty regardless of their nature. Bayesian probability applies to the occurrence of random events, both those that can be repeated under the conditions required by frequentist probability and those that don't (chances that Arnau, a 60-year-old male who lives alone will recover from a heart attack). The differences between both methodologies grow even larger because Bayesian probability assigns probabilities to different parameters (like the prevalence of people between the ages of 45 and 65 who have suffered a heart attack), statistical hypotheses (the efficacy of a new treatment for diabetic patients with heart failure is greater compared to conventional treatment), probabilistic models or even to missing data generated by non-randomized losses to follow-up (eg, ignoring the information of patients with losses to follow-up in a survival study on a given end-stage process would introduce biased information to the study).

The second distinctive element between both statistical methodologies is the use of Bayes' theorem. For Bayesian statistics it is an essential tool to sequentially update the relevant information that comes from a study. Therefore, after an initial analytical phase, the knowledge generated will be used to start a new process of learning that will be providing new information on the problem at stake.

Both the frequentist and Bayesian concepts of probability share the same axiomatic system, and the same probabilistic properties. This common niche makes them share a common mathematical language too.

The map of basic Bayesian concepts and their different associations is not easy to explain without falling into a plethora of technicalities. And this is even more evident in real-world studies in the cardiovascular research setting. Therefore, in this article we will be working on very clear cases we believe are powerful examples regarding conceptual terms that are, nonetheless, simple, and devoid of technical complexities.

This article includes 6 different sections. The first one, this introduction, refers to the general wisdom regarding Bayesian statistics and its association with mathematics, probability, and statistics. The second section includes brief historical references on Bayesian methodology. The next section is about Bayes' theorem in its most innocent version regarding the occurrence of random events. Afterwards, we'll be dealing with the concepts and basic protocol of Bayesian statistics: previous distribution, function of verisimilitude, posterior distribution, and predictive distribution to predict experimental results. Also, we'll include a brief explanation on the computational problems associated with the practical application of Bayesian methods and their power to generate inferences on relevant derived quantities. Hypothesis testing—the *P* value in particular—will also be dealt with later on as well as the Bayesian hypothesis testing proposal. The article will end with a small comment on the use of prior distributions.

IT ALL STARTED WITH BAYES, PRICE, AND LAPLACE

Knowing a little bit of Bayesian history is important because it allows us to put it into a temporal and social perspective that illuminates and boosts its learning. We'll give a few relevant hints on this history now. McGrayne[2] gives us an easy-to-understand and rigorous big picture on Bayesian history.

The very first time anybody heard of Bayes' theorem was in Great Britain halfway into the 18th century through Reverend Thomas Bayes while trying to prove the existence of God through mathematics. He would never dare to publish his findings. Prior to his death, he bequeathed all his savings to his friend Richard Price who—if okay with it—was supposed to spend this money to publish the findings, which is something he eventually did. However, these results went totally unnoticed.

We're still in the 18th century, but now we'll have to travel to France to meet Pierre-Simon Laplace, one of the most prominent mathematicians in history. He discovered, independently of Bayes and Price, Bayes' theorem in the format that we know today. Also, he developed the Bayesian concept of probability. After his death, his work fell into oblivion, under attack too because it was not in tune with the ruling idea of objectivity so embedded in the scientific world at the time.

Back to Great Britain now. Bletchley Park was a 19th century mansion in Northern London turned into a working center to break the secret messages of the German army during the Second World War (1939-1945). Here Alan Turing and his team—that included the Bayesian statistician Jack Godd—played a key role in the history of Bayesian statistics: Bayes' theorem was tremendously useful to decipher the code of the Enigma machines the Germans were using to code and decode messages. After the war, the British government classified all the information that had anything to do with Turing, mathematics, statistics, and decoding as top secret. Bayes' theorem became a useful tool for just a handful of scientists, and an anathema (or worse) for most of them. As a truly revealing anecdote, McGrayne[2] tells the story when Good presented the details of the method that Turing and his team had used to decipher the Nazi codes to members of Britain's Royal Statistical Society. This is what the next speaker had to say about the whole thing: «After that nonsense [...]».

During the second half of the 20th century, the future of Bayesian statistics looked grim: support from the English-speaking academic world grew thin, and the rest of the scientific community knew very little about Bayesian statistics. Also, there were many computational difficulties to implement it to real-world studies with data. But what seemed to be destined to happened never did. We're now back to the Second World War to Los Alamos National Laboratory in the state of New Mexico, United States. This center was created with absolute secrecy during Second World War to investigate the construction of nuclear weapons under the umbrella of the so-called Manhattan Project, led by the United States with the participation of Great Britain and Canada. It is in this context where the early Monte Carlo simulation methods were discovered back in 1946 by Polish mathematician Stanislaw Ulam while playing solitaire. Also, at that time, Metropolis et al.[3] publish the first Markov chain Monte Carlo (MCMC) simulation algorithm while conducting his investigations on the H-bomb.

Several years go by without any direct links whatsoever between Bayesian statistics and MCMC methods. However, some studies are published—especially on image recognition—combining both elements.[4] Encouraged by the technological advances made, especially in computing, Alan Gelfand, an American, and Adrian Smith, a British, collect former studies on MCMC methods and make a direct connection with Bayesian statistics.[5] This will mark the beginning of the great Bayesian revolution that starts in the field of applications to, little by little, move on to the academic world. Bayesian inference is now recognized, accepted, and validated by the scientific community as a useful statistical methodology for scientific and social development.

BAYES' THEOREM

The most widely known format of Bayes' theorem is presented for the occurrence of random events. If *A* and *B* are random events, then

$$p(A|B) = \frac{p(B|A)\ p(A)}{p(B)},$$

being $p(A)$ the probability of event A, $p(A|B)$ the associated probability A conditioned by the information that B occurred, and comparably $p(B) > 0$ and $p(B|A)$. It is important to distinguish between probabilities $p(A)$ and $p(A|B)$. Both quantify the occurrence of A, but $p(A)$ does so in absolute terms while $p(B|A)$ does so in relative terms and conditioned by the information picked up in B. For example, nobody would question that the chances that a person may suffer from angina pectoris are higher if this person is hypertensive as opposed to not having that information available, p (Angina pectoris|Hypertension) > p (Angina pectoris).

Example I: Infections and tests

The prevalence that a certain infection affects any given population is .004. There is a test to detect its presence with a 94% sensitivity and a 97% specificity. We want to assess the chances that a person from such population is really infected if he tested positive for an infection.

We will use V and V^c to define a success that describes whether a person is infected or not, respectively. Therefore, $p(V) = .004$ and $p(V^c) = .996$. We'll use (+) and (–) to describe a positive and negative test result for infection, respectively. In probabilistic terms, if a person is infected, he will test positive with a .94 probability, and negative with a .06 probability, $p(+|V) = .94$ and $p(-|V) = .06$ (false negative). If not infected, the person will test negative with a .97 probability and positive with a .03 probability, $p(-|V^c) = .97$ and $p(+|V^c) = .03$ (false positive).

According to Bayes' theorem, the chances that a person is infected with a positive test result are

$$p(V|+) = \frac{p(+|V)\ p(V)}{p(+)} = \frac{.94 \times .004}{.0336} = .112,$$

being $p(+) = p(+|V)\ p(V) + p(+|V^c)\ p(V^c) = .0336$ after implementing the total probability theorem (figure 1).

In principle, it is disconcerting that such a reliable test and with a positive test result for infection generates a small posterior probability, .112 favorable to the infection. However, if we take into consideration that the initial probability of being infected is $p(V) = .004$ and that, after the positive test result, probability is $p(V|+) = .112$, we'll see that it has gone up from 4 to 112 by a thousand—has multiplied by a factor of 28—and we believe that the influence of the test result in such posterior probability is more relevant. Anyways, we would, at least, need a second test to increase the evidence for or against the infection.

Figure 2 shows 2 charts. The upper curve is the posterior probability of infection when the test is positive, $p(V|+)$. The lower curve is the probability of infection too, but with a negative test result, $p(V|-)$. In both cases, such posterior probabilities are represented in terms of prior probability, $p(V)$, of being infected. When $p(V)$ is close to 0, as it is the case with this example, the probability $p(V|+)$ goes up a lot although, in absolute terms, it remains very low. On the contrary, when $p(V)$ is close to 1, the probability $p(V|-)$ will still be high despite evidence against a very reliable negative test result. The main element to understand this situation is that posterior probability, $p(V|+) = .112$, combines a very small probability of having an infection with a very high probability of testing positive when infected.

We'll move on now to assess our results. The prevalence of infection, $p(V) = .004$ indicates that in a population of 100 000 people we should be expecting around 400 people infected and, approximately, 99 600 people not infected (figure 2). If the entire population were tested, we would expect to see that around 376 of the 400 people infected would test positive (true positives), as opposed to 24 (false negatives). In the group of healthy people, around 96 612 people would test negative (true negatives), but nearly 2988 people would test positive (false positives). If we looked at the number of people who tested positive, we'd have around 376 true positives, and 2988 false positives. Therefore, most people with a positive test (nearly 89%) would not actually be infected.

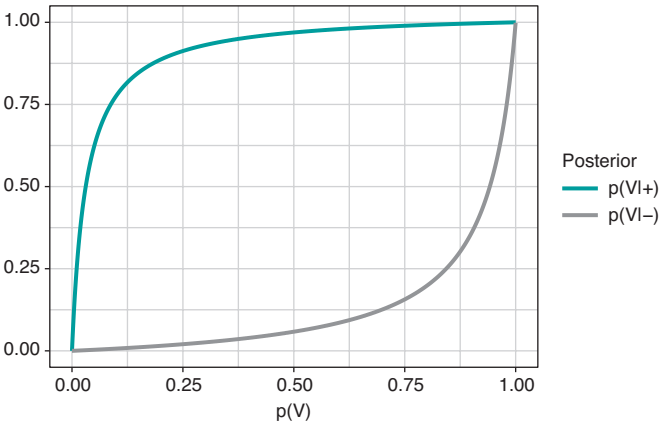

Figure 1. Posterior probability of infection with a positive test result $p(V|+)$ (upper chart) and a negative test result $p(V|–)$ (upper chart) in relation to the prior probability, $p(V)$, of infection.

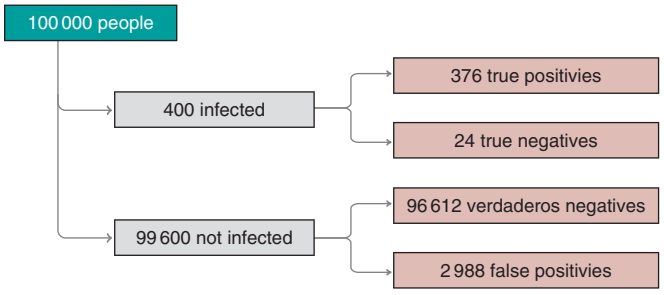

Figure 2. Approximate number of people infected, not infected, true positives, true negatives, false positives, and false negatives in a population of 100 000 inhabitants with an early prevalence for infection of .004 and a 94% sensitivity test and a 97% specificity test.

A second test with a positive result too would provide further evidence favorable to the infection. Its probability should be updated including the positive result of the second test as new information. If now (+1) and (+2) represent a positive test result for the first and second tests, the relevant probability would be $p(V|+1,+2)$. The sequential use of Bayes' theorem allows us to estimate such probability considering $p(V|+1) = .112$ as prior probability. The result obtained, $p(V|+1,+2) = .798$, is meaningful evidence favorable to an infection after 2 positive test results.

PARAMETER ESTIMATE

The true protagonists of basic Bayesian studies are probabilistic models governed by unknown parameters. These are at the core of Bayesian inferential machinery. We should mention that a parameter is a characteristic of a statistical population under study.

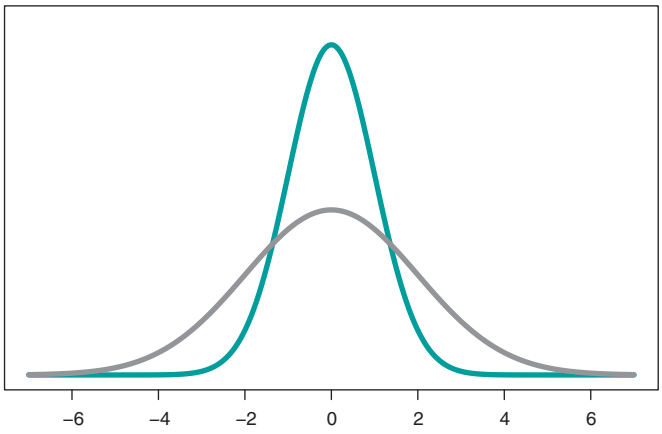

Figure 3. Chart of normal density with mean of 0, and standard deviation of 1 (green color), and normal density with mean of 0, and standard deviation of 2 (gray color).

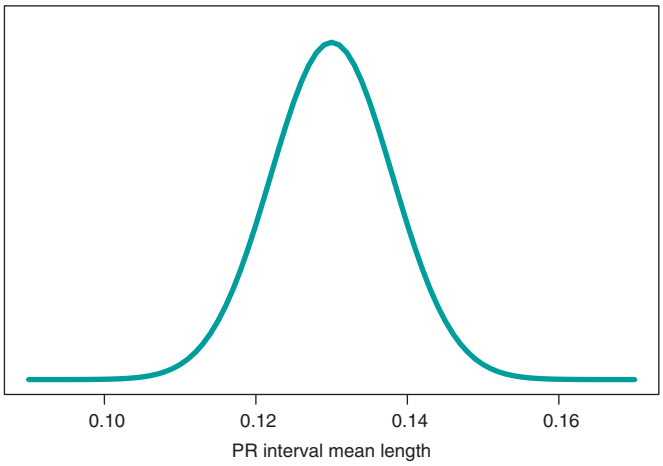

Figure 4. Posterior distribution of the PR interval mean length in children with spinal muscular atrophy type 2.

Examples of parameters are the percentage of effectiveness of any given drug, the 5-year survival rate of soft tissue sarcoma, the basic reproduction factor R_0 of an infection, etc. Parameters are estimated using partial information of the study population from data samples obtained through random procedures that guarantee their representativity and small population condition.

The most widely known probabilistic model is normal distribution with a dome-shaped symmetrical density function and defined by 2 different parameters, mean, μ, and standard deviation (σ). Mean is the center of gravity of distribution and corresponds to the peak of the dome. Standard deviation is a dispersion measurement that determines the width of the dome: in all normal distributions, the interval $(\mu - 3\sigma, \mu + 3\sigma)$ includes 99.7% of the values of distribution. Therefore, the interval-related probability $(-3, 3)$ in a normal distribution with mean = 0 and standard deviation = 1 would be the same as the one associated with the interval $(-6, +6)$ of a normal distribution with mean = 0 and standard deviation = 2 (figure 3).

Mean and standard deviation are unknown parameters in most studies based on normal data. In our case, and to avoid any technical complications, we'll assume that the standard deviation is known. Therefore, the statistical process will only have eyes from the mean μ. Bayes' theorem adapts itself to the territory of probability distributions with focus on the population mean symbol μ as parameter of interest according to the following formula

$$p(\mu \mid data) = \frac{p(data \mid \mu)\ p(\mu)}{p\ (data)},$$

being $p(\mu)$ the previous distribution (or prior distribution) of μ that quantifies, in probabilistic terms, the initial information available on μ and $p(\mu \mid data)$, the posterior distribution of μ that contains the information on μ available when the initial information is added to data. The term $p(data \mid \mu)$ is the verisimilitude function of μ, a measurement that assesses the compatibility of data with the possible μ values. The element $p(data)$ is the previous predictive distribution (also evidence in the automatic and machine learning setting), and assesses the plausibility of the data obtained.

Example II: the heart of boys and girls with spinal muscular atrophy

Falsaperla et al.[6] present the results of an observational study on the heart electrical conduction system disorder that causes bradycardia or electrocardiographic abnormalities in boys and girls with spinal muscular atrophy type 1 and 2 (SMA1, and SMA2, respectively). We gained our inspiration from this study to build a simulated database. Therefore, the results from this example do not come from Falsaperla et al.[6] and should not be compared to those from the original study.

We simulated the data on the PR interval length that extends from the origin of atrial depolarization until the origin of ventricular depolarization from 14 children with SMA2. We assumed a normal model with unknown measurement and known standard deviation. Out statistical goal was to estimate the mean.

We'll go on now with the Bayesian protocol. First, we need a previous distribution $p(\mu)$ to express our information of such parameter. Afterwards, we consider a scenario without new information on μ except for the information provided by data and use Jeffreys Prior to treat all possible μ values the same way.[7] The posterior distribution of μ, $p(\mu \mid data)$, is a normal distribution with a mean of .13, and a standard deviation of $.03/\sqrt{14}$ seconds that we can graphically see on figure 4. We estimate that μ is .13 seconds, and directly assess the accuracy of such estimate through a credibility interval that tells us that the posterior probability of μ will be taking values between .114 and .146 seconds is .95. We give it a very low probability of .05 that μ will be $> .146$ or $< .114$.

A frequentist analysis of this data would never allow direct probabilistic assessments of μ. A frequentist 95% confidence interval for μ would provide the same numerical results compared to the Bayesian interval. However, it should be interpreted in a completely different way. The frequentist 95% confidence interval is on the capacity of the interval to include μ true value, and not on the possible μ values. The interval built, (.114, .146), has a .95 probability of capturing μ true value, but also a .05 probability of not doing so. We should remember that the frequentist concept of probability prevents allocating probabilities to parameters and establishing direct probabilistic assessments of μ.

PREDICTING NEW OBSERVATIONS

Prediction and estimation are fundamental statistical concepts. We estimate parameters, but we predict data and experimental results always through distributions of probability.

The posterior predictive distribution of the results of a future experiment is built by combining the probabilistic model that

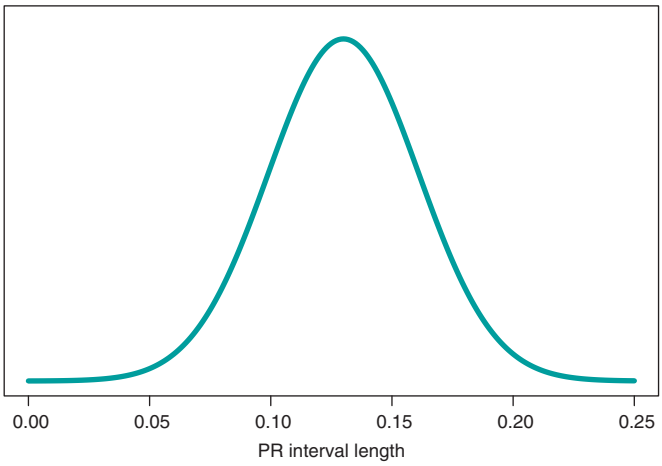

Figure 5. Posterior predictive distribution of the PR interval length of a new child with spinal muscular atrophy type 2.

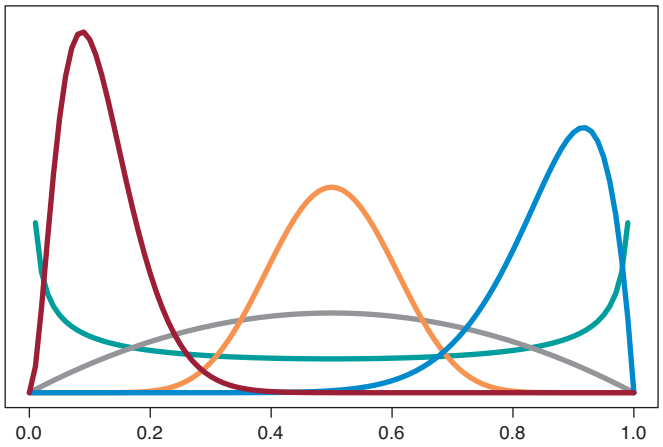

Figure 6. Chart of β densities: Be(.5, .5) in green color, Be(2, 2) in gray color, Be(3, 22) in maroon color, Be(12, 2) in blue color, and Be(12, 12) in pumpkin color.

correlates future data and parameters with posterior distribution. A significant aspect of predictive process regarding estimation is its greater uncertainty. Overall, the precision of estimations improves with larger samples, which means that in the hypothetical case of having all the data available, our estimation would be accurate. The process of prediction does not have such a feature. Although the precision of predictions increases parallel to the size of the sample, in the hypothetical case of having access to all the information from a population, error-free predictions would still be impossible.

Example II: the heart of boys and girls with muscular atrophy (continues)

In the estimation stage we studied the PR interval mean length in girls and boys with SMA2, learning based on a sample of 14 simulated data. Now we'll be dealing with totally different situation. We have a kid with SMA2 who did not participate in the study. Our objective is to predict his PR interval length. The goal now is not to estimate population means with SMA2, but to predict the value of the PR interval length in a particular kid.

Figure 5 shows the posterior predictive distribution of the PR interval length of a new boy with SMA2. Although this prediction is based on information from 14 children from the sample, it is about a new boy with SMA2. The anticipated value of this new child's PR interval length is .13 seconds. The accuracy of prediction is quantified through prediction intervals. In this case with a .95 probability, the anticipated value will be between .069 and .191 seconds.

SIMULATION AND GROUP COMPARISON

The Bayesian protocol with the 3 basic elements, previous distribution, verisimilitude function, and posterior distribution is common to almost all kinds of settings, both the basic ones including some parameters, as well as the complex ones with many sources of uncertainty with complex hierarchical structures. It is a robust and easy-to-use protocol, and a powerful and appealing idea.

Difficulties appear if we want to extrapolate this protocol to real studies of certain complexity. It is in just a couple of these cases that an analytical expression for the posterior distribution of parameters can be achieved. Impossible, nonetheless, for posterior distributions associated with derived quantities of interest. In most studies, mathematics becomes complicated, and posterior distributions are difficult to obtain. In these cases, the MCMC methods come to the rescue of Bayesian analysis. They can simulate our estimates of the relevant posterior distribution and from them generate the inferences or predictions required by the study.

In the following example we'll be showing the most basic situation we have discussed: starting with a target posterior (analytical) distribution we'll be simulating posterior distributions of relevant, non-analytical quantities of interest.

Example III: acute myocardial infarction and stents

The following example has been inspired by Iglesias et al.[8]. This is a study of 1300 patients with acute myocardial infarction treated with percutaneous coronary intervention. Each patient was randomized to sirolimus-eluting stent implantation with degradable polymer (group *S*) or everolimus-eluting stent implantation with durable polymer (group *E*).

We compared both treatments in relation to the rate of deaths 12 months after treatment. A total of 35 out of the 649 patients from group *S* stopped treatment or were lost within first year of follow-up, and 24 died. In group *E*, initially with 651 patients, 25 were lost or stopped treatment, and 22 died. The presence of missing data due to losses to follow-up is an important issue that should be dealt with carefully. In this case we'll omit it because our goal is to illustrate Bayesian procedures using the least possible technicalities.

We'll start by analyzing the risk of death θ_s and θ_E in groups *S* and *E*, respectively 1 year into treatment. Since anybody from either one of the 2 groups can die, or not, within the first year of treatment, in each group, the probabilistic model is binomial distribution that will be describing the number of deaths reported. The risk of death from each group is a rate with values that range between 0 and 1. For each rate we'll be selecting beta distribution because it's the proper probabilistic model to use with rates and doesn't pose any estimate difficulties. β distribution (that we'll representi as Be(α, β)) has 2 different parameters, $\alpha > 0$ and $\beta > 0$, that determine the way of the distribution as well as its mean and variance. It is a flexible distribution that can be symmetrical or asymmetrical, positive or negative (figure 6).

The prior β distribution that best describes the lack of information is Be(.5, .5). Its justification only responds to theoretical criteria. In each group, the posterior distribution of the risk of death will also

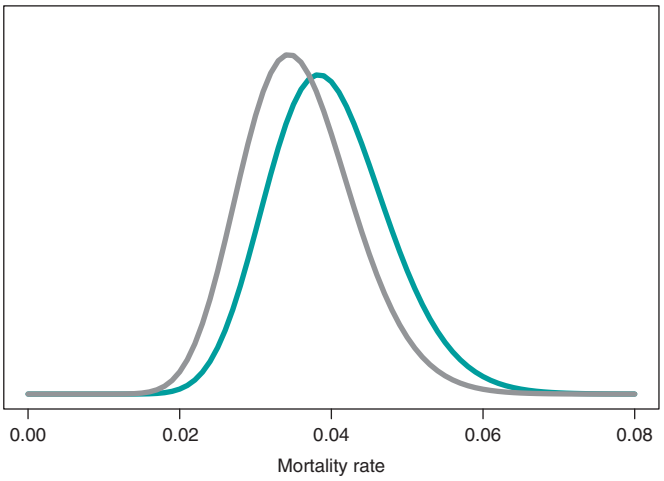

Figure 7. Posterior distribution of the mortality rate reported in patients from group *S* (green color) and group *E* (gray color).

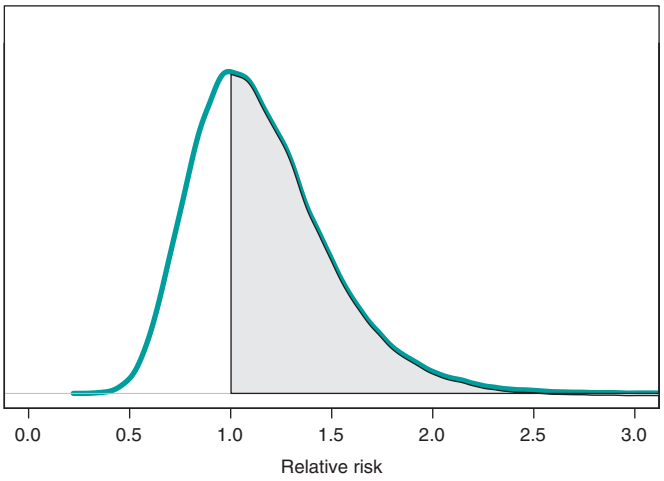

Figure 8. Posterior distribution of the relative risk of mortality at 1 year in patients with *S*-type stents vs patients with *E*-type stents. The shadow region is the probability, .641, that the mortality rate of group *S* is higher compared to group *E*.

be β whose updated parameters can be obtained by adding the number of deaths and the number of people alive in the study to the 2 values 0.5 and 0.5 of the prior beta distribution:

$$p(\theta_s) = \text{Be}(.5, .5);\ p(\theta_s \mid data) = \text{Be}(24.5, 590.5),$$
$$p(\theta_E) = \text{Be}(.5, .5);\ p(\theta_E \mid data) = \text{Be}(22.5, 604.5).$$

The estimation of the risk of death in patients from groups *S* and *E* is the mean of its posterior distribution, .040 and .036, respectively. Also, with a .95 probability the risk of death of group *S* is between .026 and .057, and between .023 and .052 in group *E*. These results indicate that the rate of death from both groups is small, although slightly higher in group *S*. The 95% credibility interval—both of θ_s and $\theta_E$is very informative (figure 7).

We assume that our goal is to compare the 1-year mortality risk in both groups. Although the tool we could think of first is hypothesis testing (that we'll introduce later on), the epidemiological and statistical literature on this regard is abundant, and 2 groups are often compared through relative risk (RR) or absolute risk (AR).[9] The 1-year RR of mortality in patients with type *S* stents vs patients with type *E* stents is $RR = \theta_s/\theta_E$, a ratio between 2 rates. RR values < 1 are indicative that the mortality rate from group *S* is lower compared to group *E* while values > 1 are indicative of precisely the opposite. Since RR is defined through θ_s and θ_E, the information from both rates, expressed through its posterior distribution, can propagate to RR as a posterior probability distribution, $p(RR \mid data)$ (figure 8). This distribution is not analytical, but it can come close to it through a Monte Carlo simulation from the 2 posterior distributions $p(\theta_s \mid data)$ and $p(\theta_E \mid data)$. Using this approximation, the posterior RR mean is 1.160, its standard deviation, .346, and the posterior probability of RR being >1 is .641. An analogue frequentist analysis would be more complicated from the mathematical standpoint and would not provide a direct probabilistic assessment of RR.

If we compare both groups through the AR of mortality at 1 year, our goal would be $AR = \theta_s - \theta_E$. This is a difference between 2 rates that could take values between -1 and 1. Negative values will be indicative that the mortality rate of group *E* is higher compared to groups *S* while positive values will indicate just the opposite. Figure 9 shows the AR posterior distribution.

The posterior AR mean is .004, its standard deviation, .011, and with a .641 probability, the AR will be > 0.

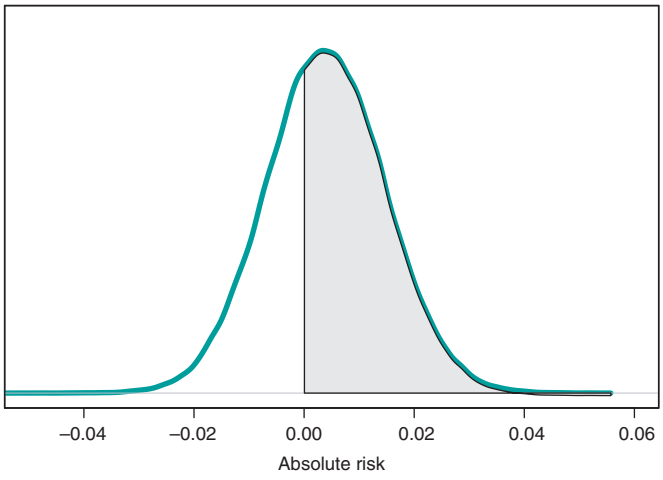

Figure 9. Posterior distribution of the absolute risk of mortality at 1 year in patients with *S*-type stents vs patients with *E*-type stents. The shadow region is the probability, .641, that the mortality rate of group *S* is higher compared to group *E*.

HYPOTHESIS TESTING: FREQUENTIST P VALUES

Hypothesis testing is the topic that generates the most irreconcilable differences between the Bayesian and the frequentist scientific communities because it is here where the consequences of their different concepts of probability become more evident. Testing hypothesis means testing new theories. Most of the latest theories have a quiet appearance among the scientific community, but little by little they start accumulating evidence in their favor until the sitting evidence is debunked.

The most widely known and used concept in frequentist statistics is the *P* value, as well as its .05 value that in some studies appears as the magical number used to reject or accept hypotheses or scientific theories. *P* value is another tool in the frequentist inference armamentarium that simply does not exist in the Bayesian one regarding the testing of 2 different hypotheses: the null hypothesis H_0 (that often represents the sitting scientific theory), and the alternative hypothesis H_1 (the new theory). *P* values are always

associated with data because without the latter there are no *P* values. Under these conditions, *P* value is the probability that a certain theoretical summary of data will be equal to the one observed or more incompatible with the null hypothesis supposing that such hypothesis holds true. Such compatibility is often represented by the $P = .05$ threshold. *P* values $\geq .05$ keep confidence in the null hypothesis; *P* values $< .05$, however, are favorable to the alternative one.

The excessive, and sometimes, inappropriate use of *P* values in scientific studies is still under discussion in the statistical community. It started in small scientific circles, but the use of the *P* value soon became a somehow «magical» element rather than a scientific tool. Back in 2014, the American Statistical Association, one of the world's leading statistical societies, approached this issue and drafted a document that has become the go-to guideline on this topic.[10] The following ones are some of the conclusions on significant *P* values for the management of biometrical data:

1. They are a probabilistic measurement of the compatibility of data with the null hypothesis. Smaller *P* values are associated with more data incompatibility with such hypothesis.

2. Do not assess the probability that a hypothesis will hold true or not.

3. The conclusions of a study should not only be based on whether a given *P* value exceeds this or that threshold. The use of the expression «statistically significant» ($P < .05$) to establish conclusions distorts all scientific procedures.

4. Do not measure the size of an effect or the significance of a given result. All small effects can produce small *P* values when the size of the sample or the accuracy of measurements is big, and all big effects can generate big *P* values with small samples or imprecise observations.

The *P* value has been given an unfair treatment because it has been attributed fantastical and surreal properties that have turned against it. Controversy has shattered the scientific debate and encouraged criticism in scientific disciplines that use data to generate knowledge. The huge interest in today's scientific reproducibility topics owes volumes to this debate.[11-15]

ACCUMULATING EVIDENCE FOR THE PROBABILISTIC ASSESSMENT OF NEW THEORIES

The Bayesian concept of probability is the key element to put hypotheses and theories to the test because it allows us to assign direct probabilities to both hypotheses and theories, both prior, *p*(theory holds true) and posterior, p(theory holds true|data).[16]

Frequentist statistics is based on hypothesis testing using *p*-type probabilities (data|theory holds true) while Bayesian statistics is based on *p*-type probabilities (theory holds true|data). The *p*-type(-data|theory holds true) frequentist probability assumes that the theory tested holds true, and based on that assumption assesses the concordance of data with such hypothesis. The *p*-type(theory holds true|data) Bayesian probability probabilistically assesses the certainty of the theory being tested in association with the data obtained.

The fundamental tool of Bayesian statistics to choose between hypotheses

H_0: theory #1 holds true,
H_1: theory #2 holds true,

based on a dataset is Bayes factor,[17] the ratio between the probabilities associated with data according to both theories. It can also be expressed as the ratio between *posterior odds (p*(theory #1 holds true|*data*)/*p*(theory #2 holds true|*data*)) favorable to the certainty of theory #1 compared to theory #2 and the corresponding *prior odds* (*p*(theory #1 holds true)/*p*(theory #2 holds true). Like this:

$$\text{Bayes factor, } B = \frac{\text{p(data}\,|\,\text{theory \#1 holds true)}}{\text{p(data}\,|\,\text{theory \#2 holds true)}} = \frac{\textit{posterior odds}}{\textit{prior odds}}$$

Bayes factor (B) holds evidence favorable to the certainty of theory #1 (compared to theory #2) provided by data: it turns prior probabilities into posterior probabilities. In logarithmic scale, log (*B*), the Bayes factor is also known as «weight of evidence», a term coined by Turing back in Bletchley Park during Second World War. Small Bayes factor values give little support to H_0 vs H_1; however, big Bayes factor values provide extensive support to H_0.

Example I: Infections and tests (continues)

Let's go back to the data from example I: Vallivana needs to be diagnosed on an infection with 2 positive test results. This problem can be faced as 2 hypotheses being tested:

H_0: Vallibana has an infection
H_1: Vallibana doesn't have an infection

We assume that Vallibana does not have any particular characteristics that give her a probability of infection different from the remainder of the population. Therefore, we know that *p*(Vallibana has an infection) = .004, and *p*(Vallibana doesn't have an infection) = .996. Vallibana's prior odds favorrable to the infection compared to non-infection are:

$$\frac{\text{p(Vallibana has an infection)}}{\text{p(Vallibana doesn't have an infection)}} = \frac{.004}{.996} = .004$$

Vallibana takes the test, and it turns out positive ($+_1$). She decides to retake it and tests positive again ($+_2$.). Vallibana's posterior odds favorable to the infection compared to non-infection are:

$$\frac{\text{p(Vallibana has an infection}\,|+_1,\ +_2)}{\text{p(Vallibana doesn't have an infection}\,|+_1,\ +_2)} = \frac{.789}{.202} = 3.951$$

The Bayes factor in favor of Vallibana being infected, that is, the ratio between the posterior odds and the prior odds is 987.75. Indeed, this value provides strong evidence in favor of Vallibana being infected (+).

Example II: the heart of boys and girls with spinal muscular atrophy (continues)

Now let's go back to the study conducted by Falsaperla et al.[6] from example II that aimed to compare the PR interval mean length in girls and boys with SMA1 and SMA2—that we'll refer to as μ_1 and μ_2, respectively—through hypothesis testing:

H_0: $\mu_2 \leq \mu_1$
H_1: $\mu_2 > \mu_1$

where the null hypothesis, H_0, claims that the PR interval mean length in girls and boys with SMA2 is shorter or equal to that reported in children with SMA1. The alternative hypothesis H_1 says otherwise. Here we'll be working with simulated normal data in both groups: $n_1 = 14$ observations in the SMA1 group with sample

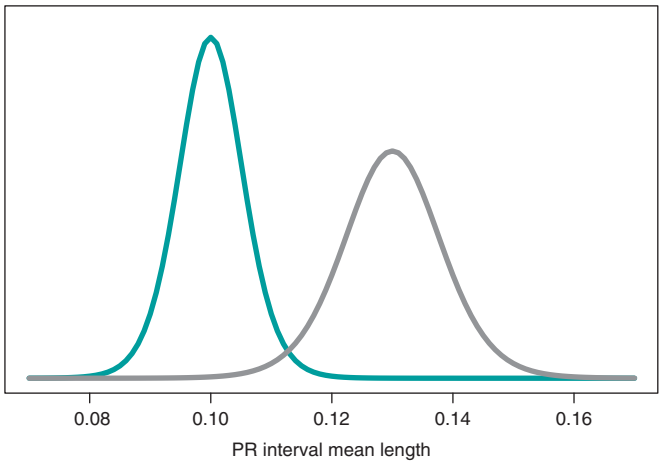

Figure 10. Posterior distribution of the PR interval mean length in girls and boys with spinal muscular atrophy type 1 (green color), and type 2 (gray color).

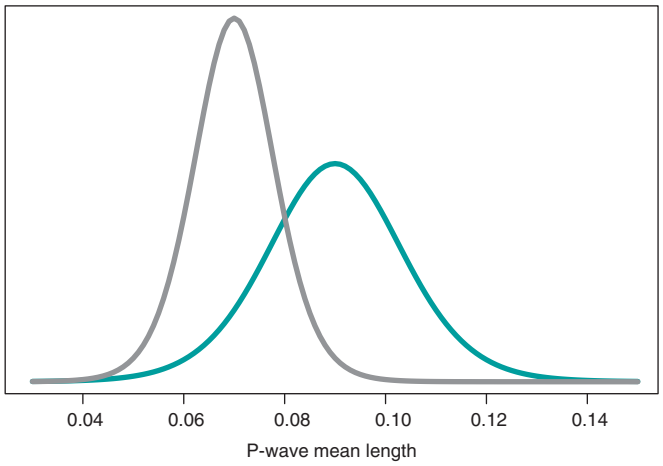

Figure 11. Posterior distribution of the P-wave mean length in girls and boys with spinal muscular atrophy type 1 (green color), and type 2 (gray color).

mean and standard deviation values of .10 and .02 seconds, respectively, and $n_2 = 14$ observations in the SMA2 group with sample mean and standard deviation values of.13 and .03 seconds, respectively.

What we´ll do is build an inferential process for the mean of each group separately. In both cases, we'll be considering a neutral previous distribution that gives all prominence to data. Figure 10 shows the posterior distribution of the mean of each group. Both distributions are rather separate from one another, which means that the posterior probabilities associated with each hypothesis will be very different as well: .002 for H_0, and .998 for H_1.

$$p(H_0|\text{data}) = p(\mu_2 \leq \mu_1|\text{data}) = .002$$
$$p(H_1|\text{data}) = p(\mu_2 > \mu_1|\text{data}) = .998$$

On a roughly basis, it is 500 times more likely that H_1 will hold true than not. In light of such an overwhelming piece of evidence the wise decision would be to choose H_1. The frequentist treatment of this testing is based on the *P* value. In our case, we'd obtain a *P* value of .002, which would imply rejecting the null hypothesis in favor of the alternative one. Both methodologies propose the same decision and provide the same numerical results: probabilities of .002. However, both probabilities are conceptually different. Bayesian probability tests the null hypothesis based on the data reported. Frequentist probability assesses the data observed with the assumption that the null hypothesis will hold true.

Still following in the footsteps of Falsaperla et al.[6] we wish to mention that our examples are not based on original cases. They are merely illustrative of Bayesian procedures. We'll now be working with the P-wave on the electrocardiogram. We wish to compare the P-wave mean length in children with SMA1 and SMA2. We'll be simulating 14 observations of the P-wave length in the group of children with SMA1 and compared it to children with SMAs. The sample mean and standard deviation is .09 and .05 seconds in group SMA1, respectively, and .07 and .03 seconds in group SMA2. We'll be comparing the means of both groups through hypothesis testing:

H_0: mean P-wave in SMA1 = mean P-wave in SMA2
H_1: mean P-wave in SMA1 > mean P-wave in SMA2

based on Bayesian inferential process like the one from the previous example. Figure 11 shows the posterior distribution of the P-wave mean length in both groups. There are fewer data from the group of girls and boys with SMA2 compared to the group with SMA1. The posterior probability associated with each hypothesis is:

$p(H_0 \mid \text{data})$ = p(mean P-wave in SMA1 ≤ mean P-wave in SMA2 | data)
$p(H_1 \mid \text{data})$ = p(mean P-wave in SMA1 > mean P-wave in SMA2 | data)

These results provide a significant piece of evidence favorable to the alternative hypothesis that is almost 8 times more likely than H_0. From the frequentist standpoint, the *P* value associated with data would be .107 (>.05), which is why we would conclude that data does not provide enough evidence to reject H_0. Bayesian decision could perfectly be the same. However, the Bayesian analysis provides a direct assessment on the certainty of both hypotheses. The findings from the Bayesian analysis could be used as previous information in future studies with more data. Therefore, the posterior distributions obtained (figure 11) would be prior distributions in this new study. Bayes' theorem allows us to generate knowledge sequentially searching for evidence for or against different hypothesis.

CARDIOLOGY POSES SOME OF DOUBTS ON THE IMPLEMENTATION OF METHODOLOGY IN CLINICAL TRIALS

One of the most controversial topics in Bayesian methodology is the selection of previous distributions. A Bayesian analysis will always allow us to avoid using any information on the amount of interest not provided by data. In this case, it works with previous distributions that play a neutral role in the learning process and that are useful only as the starting point of the Bayesian inferential protocol.

Previous informative distributions contain information that adds to the one provided by data like expert knowledge[18-20] or results from previous studies.[21,22] It is a highly valuable Bayesian characteristic in studies on which data is scarce like studies on rare diseases and orphan drugs. We should mention that inferential processes based on previous informative distributions should include sensitivity analyses of the results obtained regarding previously used distribution or distributions. Similarly, it has become popular to consider communities of previous distributions with diverse previous distributions—and a certain degree of skepticism or enthusiasm—with

the effect under test because they provide a scientific framework of reference.

On many occasions, in clinical trials, the use of previous informative distributions reduces the sizes of frequentist samples based on preassigned values of the test power, and previous parameter estimates.[22] An example of this situation is the BIOSTEMI trial.[8] The 1300 patient-sample was estimated using Bayesian methods through a previous robust distribution as a mixture that included—in equal proportion—historical information of 407 patients from the BIOSCIENCE trial,[23] and a practically non-informative distribution. The flexibility of Bayesian sequential learning is a key element of the so-called adaptative Bayesian designs[24] that allow us to include additional information in different phases of the trial without damaging the consistency and reliability of results.

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AUTHORS' CONTRIBUTIONS

C. Armero was involved in the structure, content, and drafting of this manuscript; P. Rodríguez, and J.M. de la Torre Hernández were actively involved in the review process of the manuscript final version.

CONFLICTS OF INTEREST

C. Armero, P. Rodríguez, and José M. de la Torre Hernández declared no conflicts of interest regarding the content, authorship, and publication of this manuscript. J.M. de la Torre Hernández is the editor-in-chief of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

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Review article

Calcified coronary artery disease: pathophysiology, intracoronary imaging assessment, and plaque modification techniques

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ABSTRACT

Calcified coronary artery disease poses a number of challenges to the interventional cardiologist when performing percutaneous coronary interventions, and patients with calcified coronary artery disease continue to have poorer outcomes at both the short and the long-term follow up. Stent underexpansion is the most feared outcome when performing percutaneous coronary interventions in these patients and is a strong predictor of stent failure. Therefore, intracoronary imaging to guide calcium modification is an important step in the treatment of this disease. The following review outlines a stepwise approach using intracoronary imaging in the assessment of coronary calcification, and in the selection of the appropriate calcium modification tool. Additionally, we describe current calcium modification techniques available, the evidence behind their use, their mechanism of action, and the typical results seen on intracoronary imaging.

Keywords: Coronary calcium. Calcium modification. Atherectomy. Lithotripsy. Optical coherence tomography. Intravascular ultrasound.

Enfermedad coronaria calcificada: fisiopatología, evaluación por imagen intracoronaria y técnicas de modificación de placa

RESUMEN

Las intervenciones coronarias percutáneas en enfermedad arterial coronaria calcificada representan un desafío para el cardiólogo intervencionista. Además, los pacientes con enfermedad arterial coronaria calcificada tienden a tener peores resultados en el seguimiento a corto y largo plazo. La infraexpansión del *stent* es el resultado más temido cuando se realiza una intervención coronaria percutánea en estos pacientes y es un gran predictor de falla del *stent*. Por lo tanto, la modificación del calcio guiada por imágenes intracoronarias, es un paso importante en el tratamiento de esta enfermedad. La siguiente revisión describe el uso «paso a paso» de imágenes intracoronarias en la evaluación de la calcificación coronaria y en la selección de una técnica de modificación de calcio adecuada. Además, se describen las técnicas actuales de modificación de calcio disponibles, la evidencia para su uso, su mecanismo de acción y los resultados típicos que se observan en las imágenes intracoronarias.

Palabras clave: Calcificación coronaria. Modificación de placa calcificada. Aterectomía. Litoplastia. Tomografía coherencia óptica. Ecografía intravascular.

Abbreviations

CAD: coronary artery disease. **IVI:** intravascular imaging. **IVL:** intravascular lithotripsy. **IVUS:** intravascular ultrasound. **OA:** orbital atherectomy. **OCT:** optical coherence tomography. **PCI:** percutaneous coronary intervention. **RA:** rotational atherectomy.

INTRODUCTION

Calcified coronary stenosis is a relatively common finding present in up to 30% of lesions planned for percutaneous coronary intervention (PCI).[1] Calcified atherosclerosis presents a number of difficulties when performing PCI especially stent underexpansion, a strong predictor of stent failure (thrombosis and restenosis).[2-4] It comes as no surprise, then, that worse clinical outcomes have been found following PCI in moderate-to-severe calcified disease compared to atherosclerotic plaques without calcium.[1] A number of plaque modification techniques are available although there is a paucity of head-to-head comparisons among the techniques making

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device selection difficult. Understanding calcium morphology can contribute to proper device or technique selection, and is best guided by intravascular imaging (IVI). In this review, we outline the assessment of coronary calcium using IVI, propose a simplified calcium modification algorithm we use at our center, and examine the mechanism of action and evidence behind the use of each of these techniques.

Pathophysiology and prognostic implications of coronary calcium

The pathophysiology of atherosclerosis is well documented and starts with injury to the vessel and accumulation of low density lipoprotein which undergoes oxidative changes that result in the release of proinflammatory cytokines. These attract monocytes that migrate towards the intima layer, mature into macrophages, and eventually form foam cells.[5] Further recruitment of smooth muscle cells from the media layer produce extracellular matrix that leads to intimal thickening and plaque progression. In time, and in the presence of risk factors including age, male sex, Caucasian race, hypertension, hyperlipidemia, diabetes, and chronic kidney disease, calcification of atherosclerotic plaques can occur and its pathogenesis has much in common with bone formation.[1,5-8] Transformation of vascular smooth muscle cells into an osteoblastic phenotype is thought to be the initiation factor prompted by exposure to bone morphogenetic protein-2 (BMP 2) produced by endothelial cells when exposed to stressors like hypoxia, high pressure, turbulent flow, and inflammation.[9] The result is the loss of expression of vascular smooth muscle specific markers, and the expression of genes typically found in bone generating cells.[10] Other pathways also play a role including apoptosis of vascular smooth muscle cells, and formation of calcifying matrix vesicles by macrophages.[6] The early result is the deposition of microcalcifications that eventually coalesce into larger calcium deposits that can be seen as "spotty calcification" on IVI. Further progression ultimately results in calcium sheets or plates which can extend across multiple quadrants of the vessel causing vessel stiffening and altering compliance.[11] Nodular calcification, an important morphological subtype which protrudes into the vessel lumen, forms when there is rupture of the calcium sheets.[6] Prognostically, the presence of calcified atherosclerosis is associated with poorer cardiovascular outcomes.[12,13] Initial spotty calcification represents an unstable period in the evolution of calcified coronary artery disease (CAD), and these lesions are more commonly associated with plaque rupture and acute coronary syndrome.[6,14] Conversely, lesions with a higher percentage calcified plaque volume as seen on computed tomography coronary angiography are more stable and present less frequently with acute cardiovascular events, yet more commonly with chronic coronary syndromes and multivessel disease.[6,15]

Percutaneous coronary intervention in calcified atherosclerosis

Calcific stenoses are found in up to 30% of all patients presenting for PCI.[1] The subsequent reduction of coronary artery compliance presents a number of procedural difficulties. Inadequate lesion dilation can potentially result in stent underexpansion,[16] one of the most important predictors of stent failure.[2-4] Other difficulties include a higher risk of dissection and perforation, difficulty passing equipment distally, damage to the stent polymer, altered drug elution kinetics from stents, and potentially stent deformation or loss.[1,17,18] Furthermore, patients with coronary artery calcification are less likely to undergo complete revascularization and more frequently experience adverse outcomes following PCI. In a pooled analysis of the HORIZONS-AMI and ACUITY studies, the presence of moderate or severe calcification (as assessed angiographically) was associated with poorer outcomes at 1 year for all endpoints including death, cardiac death, myocardial infarction, and overall major adverse cardiovascular events.[1] As a matter of fact, at 1 year, the risk of stent thrombosis increased by 62% and that of ischaemic target lesion revascularization (TLR) increased by 44% in calcified compared to non-calcified lesions. These findings have been replicated across numerous other studies at both short and long-term follow-up.[1,7,19-21] In a recent analysis of the SYNTAXES trial, heavily calcified lesions were associated with a higher all-cause mortality rate after 10 years regardless of the type of revascularization used (hazard ratio, 1.79; 95% confidence interval, 1.49-2.16; $P < .001$).[21] Optimizing the results of PCI is, therefore, of paramount importance with plaque preparation with calcium modification is an important step in this process.

Imaging for calcium detection

Detecting the presence of coronary calcium prior to PCI is important for procedural planning and a number of imaging techniques may be used as shown on table 1.[14,15,22-28]

Non-invasive imaging for coronary calcification

Coronary computed tomography angiography is highly sensitive and specific for the detection of calcium and is a non-invasive technique. Coronary computed tomography angiography can determine plaque morphology and percentage of calcified plaque volume, which has prognostic significance.[15] Its utility in procedural planning is increasingly seen in the planning of chronic total coronary occlusions, but it is less useful in the specifics of guiding intraprocedural strategy.

Invasive imaging for coronary calcification

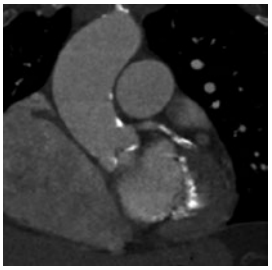
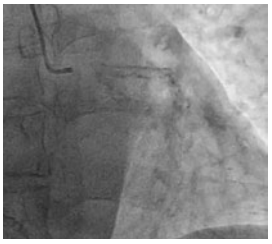
Invasive coronary angiography has long been known to have low sensitivity but high specificity for the detection of coronary calcium. Compared to intravascular ultrasound (IVUS), its overall sensitivity is ~48%, but it increase up to > 85% in the presence of severe (4 quadrant) calcification.[24,25] Nonetheless, an arc > 100° as seen on the IVI is required before calcium can be reliably detected on angiography, thus highlighting the potential for calcium to go undetected when the PCI is guided by angiography alone.[25] Calcification on angiography is typically classified as none/mild, moderate or severe (table 1). Although angiography provides valuable information to guide the procedure such as vessel tortuosity, angulation of bifurcations, etc, its limitations are well documented, and studies have consistently shown poorer outcomes when PCI is guided by angiography compared to IVI.[29-31]

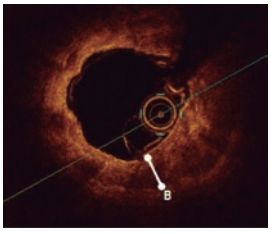
IVI overcomes much of the shortfalls of other imaging modalities. Both optical coherence tomography (OCT) and IVUS are more sensitive for the detection of calcium compared to coronary angiography.[25] Furthermore, both imaging modalities provide additional information to guide and optimize the procedure (table 1).[27] Co-registration with angiography is available for both modalities, and can reduce the learning curve significantly.[32] Although the advantages of IVI over angiography have been shown in a number of studies, no randomized studies have specifically examined its potential benefits regarding calcified CAD. Nonetheless, given the complexity of these lesions, performing IVI-guided PCIs seems reasonable.

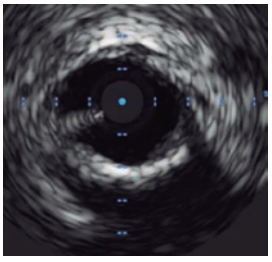
Intravascular ultrasound

IVUS has both high sensitivity and specificity (86.7% and 93.3%, respectively compared to histological samples) for the detection of dense calcification, although it is less sensitive for the detection

Table 1. Summary of available imaging techniques for the detection of coronary calcium

Imaging modality	Quantification	Sensitivity	Specificity	Advantages	Disadvantages
Computed tomography[14,15,22,23] 	• Calcium scoring on non-contrast images • Percentage calcified plaque	++++	++++	• Non-invasive • Calcium scoring provides prognostic information • Highlights the presence of calcium prior to undertaking an invasive procedure • Provides some information on the plaque morphology and composition (specific software available) • Percentage calcified plaque is a predictor of future events	• Blooming artifact can overestimate the degree of calcification • Circumferential arc difficult to assess • Radiation exposure • Contrast use • Does not provide intraprocedural guidance
Coronary angiography[23,24,25] 	• Mild: not visible • Moderate: radiopacities seen only with cardiac motion • Severe: radiopacities seen without cardiac motion, before contrast injection affecting both sides of the arterial wall (tram-track appearance)	++ +++ in the presence of severe calcification	+++	• Assessment of anatomical complexity, vessel tortuosity, side branch angulation	• Invasive • No information on calcium morphology (thickness, circumferential arc)

OCT[25,26,27] 	• Calcium thickness
	• Calcium circumferential arc
	• Calcium length
		++++	++++	• High resolution, 10 µm to 20 µm
				• Detailed calcium morphological assessment
				  ○ Distribution/arc
				  ○ Depth
				  ○ Volume
				  ○ Length
				  ○ Presence of calcium nodules
				• Procedural guidance
				  ○ Landing zones
				  ○ Vessel dimensions
				  ○ Lesion length
				  ○ Stent length
				  ○ Guide stent optimization
				  ○ Assess stent expansion
				  ○ Identify complications (dissection, under-expansion, malapposition, stent distortion)
				• Co-registration with angiography available
					• Invasive
					• Requires a blood-free environment for image acquisition
					• Contrast required for blood clearance
					• Limited assessment of ostial lesions
					• Difficult to advance the catheter distally in tortuous vessels

IVUS[25,27,28] 	• Calcium arc
	• Calcium length
		++++	++++	• Moderate-high resolution 100 µm to 150 µm (high-resolution IVUS 20 µm to 30 µm)
				• High penetration depth into non-calcific vessel wall ~10 mm
				• No specific imaging requirements
				• Can assess ostial lesions
				• Morphological assessment of calcium
				  ○ Distribution/arc
				  ○ Length
				  ○ Presence of calcium nodules
				• Procedural guidance
				  ○ Landing zones
				  ○ Vessel dimensions
				  ○ Lesion length
				  ○ Stent length
				  ○ Guide stent optimization
				  ○ Assess stent expansion
				  ○ Identify complications (dissection, underexpansion, malapposition, stent distortion)
				• Co-registration with angiography available
					• Invasive
					• Acoustic shadowing in severe calcification
					• Difficult to assess calcium thickness
					  ○ Use of surrogate markers of thickness (reverberations)

IVUS, intravascular ultrasound; OCT, optical computed tomography.

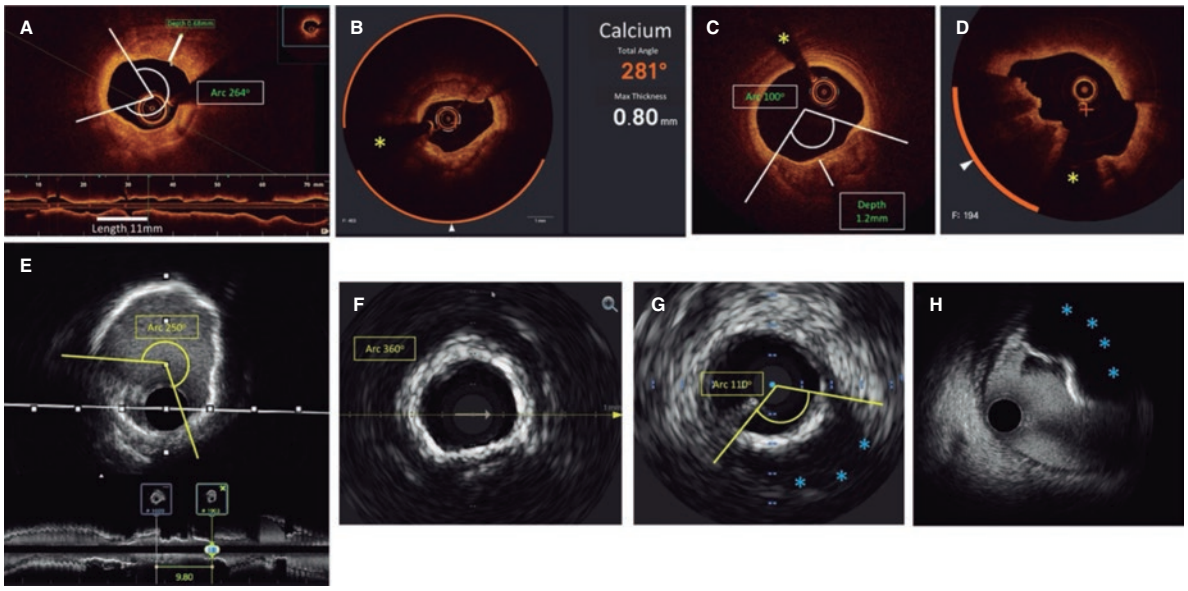


Figure 1. Calcium morphology and measurement using intracoronary imaging. **A:** concentric calcification on optical coherence tomography (OCT); calcium arc of 264°, depth of 0.68 mm, and length of 11 mm - high risk features by OCT for stent underexpansion and plaque preparation is advised. **B:** concentric calcification; arc 281°, and depth of 0.8 mm. Automatic calcium detection using Ultreon software; degrees of calcium detected outlined by the orange arc surrounding the OCT image. **C:** eccentric calcium on the OCT; arc < 180 degrees. Note the sharply demarcated borders of calcium that allow the assessment of calcium depth (1.2 mm) **D:** calcified nodule on the OCT. Significant posterior shadowing is caused by the nodule precluding the assessment of its posterior border. **E:** concentric calcification on IVUS with an arc of 250° and a length of 9.8 mm. Posterior shadowing and lack of reverberations suggests thick calcium (~1 mm). These features represent a high risk of stent underexpansion. **F:** concentric calcification on intravascular ultrasound (IVUS) with an arc of 360°. **G:** eccentric calcification on IVUS with an arc of < 180°. Significant posterior shadowing (blue asterisk). **H:** calcified nodule on IVUS protruding into the lumen and casting significant posterior acoustic shadowing (blue asterisk). The yellow asterisk (in all OCT images) denotes wire artefact.

of microcalcifications,[33] and in the presence of overlying fibrotic plaque.[34] Calcium reflects ultrasound resulting in a bright hyperechoic signal with significant posterior shadowing that often precludes the assessment of calcium thickness (figure 1).[35] Surrogate markers for calcium thickness can be used such as the presence of posterior reverberations (correlated with thinner calcium < 0.5 mm) while significant shadowing is suggestive of thicker calcification (> 1 mm).[25] Recently, an IVUS specific scoring system has been found to be useful in predicting stent underexpansion using 4 criteria: calcium arc > 270° for a length of ≥ 5 mm, presence of 360° calcium, presence of calcified nodules, and adjacent vessel diameter of < 3.5 mm. Scores ≥ 2 suggest that calcium modification should be undertaken and therefore operators should aim to measure each of these parameters on IVUS pullbacks.[36]

Optical coherence tomography

Although significantly more sensitive than angiography OCT is less sensitive compared to the IVUS at detecting coronary calcium. Wang et al. found that ∼6% of lesions with IVUS detectable calcium did not show visible calcium on OCT, which was mainly attributed to overlying fibrotic plaque.[25] On the OCT, calcium appears as a region of low signal intensity with sharply demarcated borders that facilitate the assessment of calcium depth.[26] Fujino et al. demonstrated that calcium arc > 180°, depth > 0.5 mm, and length > 5 mm on the OCT were associated with a higher risk of stent underexpansion and—similar to IVUS—operators should try to analyse each of these parameters.[37] Recently, artificial intelligence software has become available (Ultreon OCT system, Abbott, United States), which automatically identifies calcium arc and depth, as well as the external elastic lamina for vessel sizing further simplifying this analysis (figure 1).

In practical terms, therefore, it may be useful to assess the extent of coronary calcification on IVI by considering calcium arc, depth, length, and whether it is superficial or deep as shown on figure 1. Considering the circumferential arc, coronary calcium can be divided into 3 morphological subtypes (figure 1). Eccentric, extending across 2 or less quadrants with an arck < 180°, and concentric, with an arc > 180° and nodular calcification presenting as an eruptive-protrusion into the lumen. Calcium can also be divided into superficial (located at < 50% of the depth of the plaque plus media thickness) or deep (located at > 50% of the depth of the plaque plus media thickness).[28] Calcium length should be measured on the longitudinal projection on both IVUS and OCT.

Calcium modification

Although there is a lack of clinical trials comparing modification techniques in varying calcium morphologies, consensus in this regard suggests that balloon-based therapies may be effective in eccentric calcification, which is short in length. Ablative and lithotripsy-based therapies may be more useful in concentric calcification or long calcified lesions with lithotripsy being particularly useful in deeper calcium deposits. Nodular calcification presents the greatest challenge; however many advocate for the use of ablative techniques, and some recently presented data suggests lithotripsy may have a role.[38] Uncrossable and undilatable lesions may be treated with rotational atherectomy (RA) or excimer laser coronary angioplasty (ELCA). While acknowledging the paucity of data and the lack of head-to-head trials comparing the different techniques available, we have tried to summarize this practice, and the practice at our center, into a simplified calcium modification algorithm that can provide some guidance (figure 2). Table 2 summarizes the mechanism of action and specifications for these

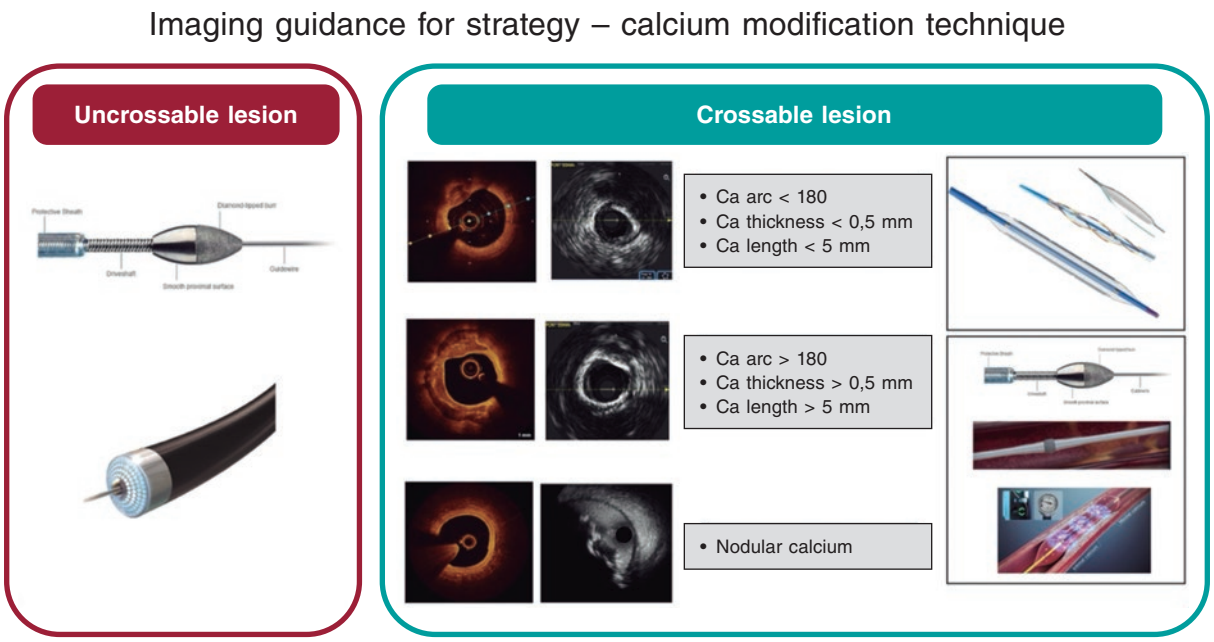


Figure 2. Calcium modification algorithm. Intravascular imaging (IVI) for lesion assessment is advised prior to undertaking plaque modification. Uncrossable lesions usually require rotational atherectomy or excimer laser coronary angioplasty (ELCA). Crossable lesions with eccentric calcification without high-risk features for stent underexpansion can be treated using noncompliant, cutting or scoring balloons. Concentric calcification or calcium with high-risk features for stent underexpansion can be treated with atherectomy techniques or intravascular lithotripsy (IVL). Nodular calcium can be modified using atherectomy techniques with emerging evidence that IVL may also be effective. Post plaque modification IVI is key for proper plaque modification assessment. Ca, calcium.

Table 2. Calcium modification tools: description, mechanism of action, and specifications

	Cutting balloons	Scoring balloons	High-pressure noncompliant NC balloons	Rotational atherectomy	Orbital atherectomy	Excimer LASER	Lithotripsy
Technology description	Balloon platform with a number of microblades	Several nitinol wires wrapped around a semi- or noncompliant balloon	Double layered noncompliant balloon	Diamond coated burr capable of atherectomy in a forward motion	Eccentrically mounted diamond coated crown capable of atherectomy in a forward and a backward motion	Concentric or eccentric array of laser fibers. Uses a mixture of rare gas and halogen to generate brief pulses of high-frequency, short wavelength UV light	Series of emitters encased within a balloon delivery system
Mechanism of action	Controlled incisions into calcium	Controlled incisions into calcium	Super high-pressure dilation with a rated burst pressure of 35 atm (often dilated at ~50 atm)	High speed burr rotation (140-160 000 rpm) results in differential atherectomy of fibrocalcific tissue Additional effect due to burr vibration (+)	Centrifugal force causes the crown to orbit at high speeds (80 or 120 000 rpm) resulting in calcium sanding Additional effect due to crown vibration (+++)	Disrupts plaque through 3 mechanisms Photochemical: by breaking carbon bonds between molecules Photothermal: by the production of thermal energy and vapour bubbles Photomechanical: by the expansion of vapour bubbles causing plaque disruption The light energy (fluence) used ranges between 30 mL/mm^2 and 80 mL/mm^2 Pulse repetition rate is between 25 Hz and 80 Hz	Emitters generate sparks creating a vapour bubble that expands and propagates an acoustic wave through the vessel wall. Causes compressive and decompressive forces when calcium is found resulting in fracture

(Continues)

Table 2. Calcium modification tools: description, mechanism of action, and specifications *(continued)*

	Cutting balloons	Scoring balloons	High-pressure noncompliant NC balloons	Rotational atherectomy	Orbital atherectomy	Excimer LASER	Lithotripsy
Sizes available	A number of brands available in sizes ranging from 2.0 mm to 4.0 mm	A number of brands available in sizes that range from 1.75 mm to 4.0 mm	1.5 mm to 4.5 mm balloons	1.25, 1.5, 1.75, 2.0, 2.15, 2.25, 2.38, 2.5 mm burr	1.25 mm crown	0.9 mm, 1.4 mm, 1.7 mm, and 2.0 mm	2.5 mm, 3.0 mm, 3.5 mm, and 4.0 mm diameters All sizes are 12 mm in length
Guide catheter compatibility	6-Fr	Some balloon sizes are compatible with 5-Fr and 6-Fr systems	6-Fr	6-Fr; 1.25 & 1.5 mm 7-Fr; 1.75 mm 8-Fr; 2.0, 2.15 mm 9-Fr; 2.25, 2.38 mm 10-Fr; 2.50 mm	6-Fr	6-Fr: 0.9 & 1.4 mm 7-Fr: 1.7 mm 8-Fr: 2.0 mm	6-Fr
Wire compatibility	Conventional 0.014 in guidewires	Conventional 0.014 in guidewires	Conventional 0.014 in guidewires	Specialized 0.009 or 0.014 in wire required	Specialized 0.012 or 0.014 in wire required Viper wire	Conventional 0.014 in guidewires	Conventional 0.014 in guidewires
Other caveats	1:1 balloon: vessel sizing Rotating the balloon followed by repeat inflation can increase the number of incisions	1:1 balloon: vessel sizing	1:1 balloon: vessel sizing	Burr-to-artery ratio of 0.5 to 0.6 Lubricant available but not mandatory and contraindicated in egg and olive oil allergies	Specific lubricant required which is contraindicated in egg and soy allergies	Catheter-to-artery ratio of 0.5 to 0.6 Requires continuous infusion of saline through the guide catheter Contrast infusion increases effectiveness but can also increase the risk of thermal damage	1:1 balloon: vessel sizing Rigorous balloon preparation to remove all air May require de-airing while being used
Advantages	Easy to use Compatible with conventional guidewires	Easy to use Compatible with conventional guidewires	Easy to use Compatible with conventional guidewires	Useful in undilatable lesions May be more useful for nodular calcium than other technologies	Useful in undilatable lesions May be more useful for nodular calcium than other technologies Can ablate in both a forward and a backward motion Produces smaller particles than rotational atherectomy	Easy to use Compatible with conventional guidewires	Easy to use Compatible with conventional guidewires Modifies superficial and deep calcification No particulate matter created so lower risk of slow flow or no-reflow
Disadvantages	May not be sufficient as monotherapy Bulky profile	May not be sufficient as monotherapy Bulky profile	Bulky profile	Specialized wire required Wire bias may result in differential atherectomy. Ablation in a forward motion only Cannot maintain a wire in a side branch during atherectomy. Produces larger particles compared to orbital atherectomy Distal embolization can result in slow flow or no-reflow	Specialized wire required Specialized lubrication infusion required Cannot maintain a wire in a side branch during atherectomy. Distal embolization can result in slow flow or no-reflow	Set up time Additional UV protection required	Bulky profile for lesion crossing 80 pulses per catheter may require the use of > 1 catheter to treat long lesions
Potential complications	Perforation Dissection Slow flow/no reflow	Perforation Dissection Slow flow/no reflow	Perforation Dissection Slow flow/no reflow	Perforation Dissection Burr entrapment Wire fracture Slow flow/no reflow Transient heart block	Perforation Dissection Crown entrapment Slow flow/no reflow	Perforation Dissection Thermal injury	Perforation Dissection

Fr, French; Hz, Hertz; in, inches; NC, noncompliant; rpm, revolutions per minute; UV, ultraviolet.

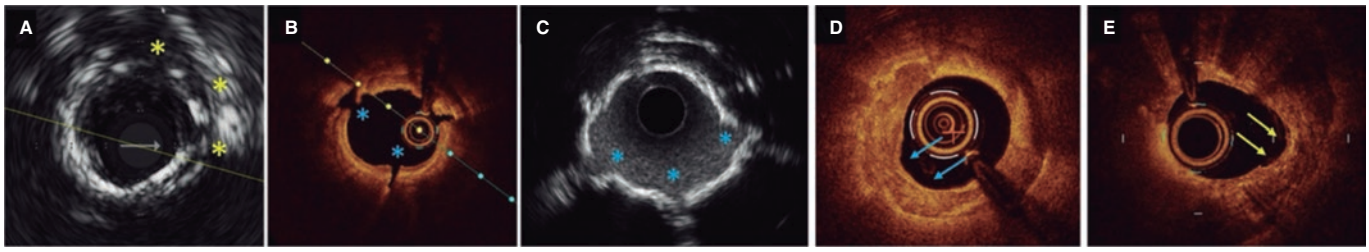


Figure 3. Calcium morphologies and results of different modification techniques on intravascular imaging. **A:** discrete calcium incisions and fracture following cutting balloon (yellow asterisk). **B, C:** calcium fractures following intravascular lithotripsy on optical coherence tomography and intravascular ultrasound (IVUS) (blue asterisk). Note how reverberations can be seen at fracture points (blue asterisk) on the IVUS due to acoustic waves now being able to pass through the fracture sites. **D:** results of calcium modification using rotational atherectomy in an uncrossable lesion. A "cored out" appearance can be seen with widening of the lumen and a semilunar appearance in some regions (blue arrow). **E:** results of calcium modification following orbital atherectomy. The semilunar shape of the orbital atherectomy crown can be seen at the yellow arrows.

techniques. The expected results following calcium modification are shown on figure 3.

Eccentric calcification therapies

Specialized balloon-based technologies

Specialized balloon-based technologies are most commonly used for eccentric calcification although they have some utility in concentric calcification in combination with other techniques. Cutting balloons consist of a number of microblades mounted on a balloon, while scoring balloons consist of a semi-compliant balloon around which several nitinol wires are wrapped. Both aim to make incisions into the calcium to facilitate vessel dilation. The advantage of these technologies is that they anchor to the calcium and are less likely to slip (watermelon seeding phenomenon) thus avoiding dissection of adjacent areas. Although sometimes used interchangeably, a study conducted by Matsukawa et al. using IVI demonstrated better calcium modification and increased luminal gain with cutting balloons vs scoring balloons.[39] However, regarding severe calcification, cutting balloons have lower rates of procedural success compared to RA.[40] Combining cutting balloons with other technologies may be useful. Observational studies have demonstrated increased luminal gain with cutting balloons following RA compared to conventional balloons or RA alone.[41,42]

Very high-pressure balloons may be effective to cause calcium fracture in both eccentric and concentric calcification. They are generally not first-line therapies and are most often used in undilatable lesions. They consist of a noncompliant twin-layered balloon with rated burst pressure of ∼35 atm. However, in practice they are often dilated at ∼50 atm. In a retrospective series of 326 consecutive undilatable lesions, Secco et al. reported angiographic success in > 90% using the OPN high-pressure balloon (OPN NC; SIS Medical AG, Switzerland).[43] Calcific lesions with calcium arcs > 270° were more likely to require pressures > 40 atm. More recently, the ISAR-CALC trial randomized lesions with residual stenosis > 30% following standard balloons to receive a scoring balloon or a super high-pressure balloon.[44] No differences on OCT defined stent expansion index between groups were found (0.72 vs 0.68; $P = .22$) nor were there differences in angiographic, procedural, or strategy success. Patients in the super high-pressure balloon group, however, less frequently required further dilation with NC balloons prior to stenting, had larger angiographically assessed minimal lumen diameters, and less residual stenosis compared to those in the scoring balloon cohort. Therefore, super high-pressure balloons play a role in the management of undilatable, but crossable lesions.

Concentric and nodular calcification

Lithotripsy

Intravascular lithotripsy (IVL) (SHOCKWAVE Medical inc, United States) is a recently introduced technique based on the use of acoustic energy. It consists of a balloon-based delivery system containing a number of emitters that generate short electric sparks. The sparks produce a vapour bubble in the fluid inside the balloon that is dilated to 4 atm. The vapour bubble expands creating an acoustic pressure wave that propagates through the vessel wall causing compression and decompression stress when calcium is encountered resulting in fracture.[45] Each short-lived pulse delivers an equivalent of ∼50 atm of pressure. Nonrandomized studies to date have demonstrated significant fissuring of both superficial and deep calcium on IVI (figure 3). A pooled analysis of the DISRUPT CAD series of studies has demonstrated procedural success (residual angiographic stenosis ≤ 30%) in > 90% of the lesions.[46] Although to date, IVL has been predominantly used in concentric calcium, analysis of angiographically defined eccentric vs concentric calcification suggests similar success in these 2 calcium morphologies.[47] Also, recently presented data suggests no differences in minimal stent area on OCT when IVL was used to treat eccentric, concentric, and nodular calcium.[38] Although still an off-label indication, a number of cases and series have reported on the use of IVL to treat stent underexpansion due to severe calcification, and calcified neoatherosclerosis.[48-51] The use of IVL in a newly deployed but underexpanded stent has not been widely reported and there are theoretical concerns regarding damage to the polymer. Our practice to date has been to use IVL predominantly in concentric calcification while further data is awaited. Figure 4 shows a case of plaque modification using OCT-guided IVL.

Rotational atherectomy

RA (Rotablator, Boston Scientific, United States) uses a diamond-tipped burr that rotates at 140-180 000 rpm Resulting in the differential ablation of calcified tissue while avoiding disruption of healthy elastic tissue. Ablation occurs only in a forward motion. A specialized wire (RotaWire Floppy or RotaWire Extra Support, Boston Scientific, United States) is required and the burr size should not exceed 0.5-0.6 times the size of the vessel. Previously, the infusion of nitroglycerin, verapamil or heparin were advocated to mitigate the effects of debris embolization while temporary pacing wire insertion or aminophylline infusion were used to combat bradycardia particularly when performing RA in the right coronary artery. However, changes to RA techniques have reduced these complications. Aggressive debulking with RA has been replaced by

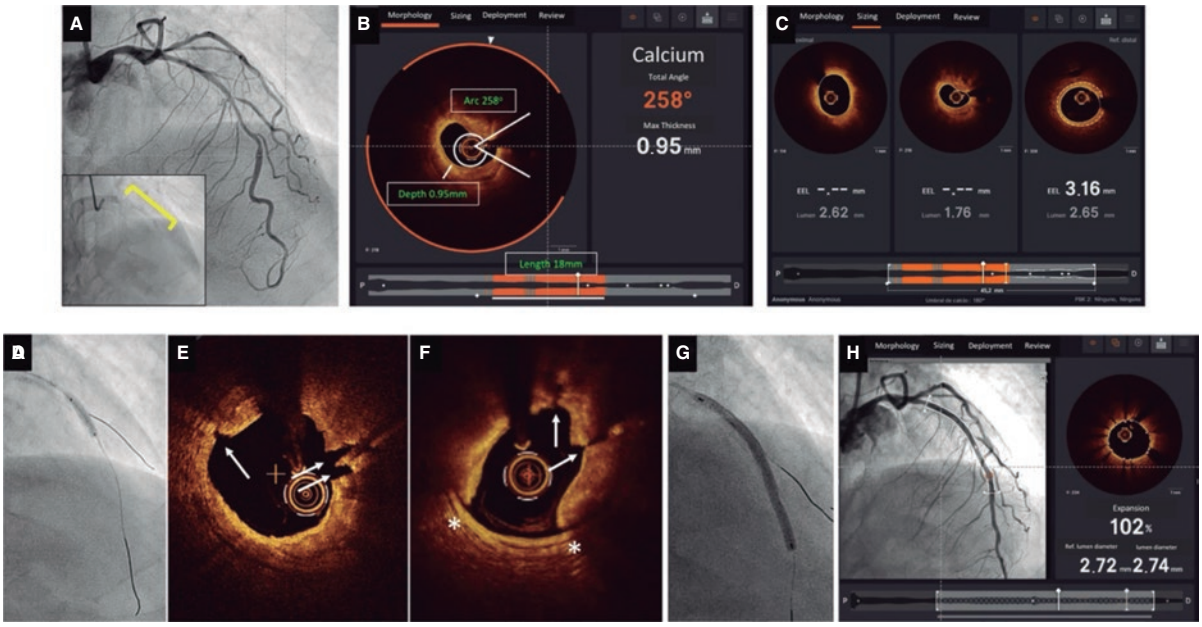


Figure 4. Case example demonstrating calcium modification using intravascular lithotripsy (IVL) guidance with co-registered optical coherence tomography (OCT) imaging using Ultreon software. **A:** severely calcified left anterior descending coronary artery stenosis with calcium visible on fluoroscopy (inset), **B:** OCT revealing concentric calcium; arc 258º and depth of 0.95 mm as identified automatically using the Ultreon software with a length of 18 mm. These parameters suggest a high risk of stent underexpansion. **C:** proximal and distal landing zones and length of stent required. The distal landing zone external elastic lamina to external elastic lamina (dashed white lines automatically detected by Ultreon system) measures 3.16 mm while, proximally, the external elastic lamina cannot be visualized, and lumen diameter is 2.62 mm. The predicted length of the stent required is 45 mm. **D:** 3.0 mm x 12 mm IVL balloon (1:1 sizing). Sixty pulses delivered along the calcified lesion. **E, F:** extensive calcium fracture seen on the OCT after IVL (white arrows). A dissection is also noted (white asterisk). **G:** stent implantation with a 3.0 mm x 48 mm drug-eluting stent according to the sizing by OCT. Optimized with a 3.0 mm x 12 mm noncompliant balloon. **F:** final OCT; optimal stent expansion (> 90%), no malapposition or complications (eg, dissection) at the proximal and distal landing sites.

the use of shorter runs (10-15 seconds), a pecking motion of the burr, smaller burr sizes, and resting periods to allow clearance of embolized particles. On IVI, a smoothing out of the calcium can be seen sometimes with a semilunar shape from where the burr has ablated (figure 3).

The ROTAXUS trial randomized 240 patients with calcified CAD to RA or conventional therapy prior to drug-eluting stenting.[52] Both procedural success and luminal gain (1.56 mm vs 1.44 mm, $P < .01$) were higher in the RA group at the index procedure. However, higher late luminal loss in the RA group was seen at 9 months (0.44 mm vs 0.31 mm, $P = .04$). Furthermore at 2-year follow-up no differences were seen between groups regarding major adverse cardiovascular events, myocardial infarction, target lesion revascularization or target vessel revascularization ($P > .05$ for all comparisons).[53] The PREPARE-CALC study examined RA vs modified balloons (cutting or scoring) in the treatment of severely calcified disease. Similar to the ROTAXUS trial, increased strategy success was seen in the RA arm vs the modified balloon arm (98% vs 81%, $P = .0001$) mainly attributed to a higher crossover rate in the modified balloon group (10% of modified balloon group).[40] However, improved strategy success in the RA arm did not translate into differences in clinical or angiographic outcomes at 9 months.[40] This may be partially explained by the fact that final stent expansion as seen on OCT was not different between groups (73.5% vs 73.1% for modified balloons vs RA respectively, $P = .85$).[54]

Combinations of complementary calcium modification therapies are increasingly being used. A study of 92 patients conducted by Tang et al. found greater decrease in percent stenosis (54.5% to 36.1% vs 55.7% to 46.9%, $P < .001$), and greater stent expansion (71.7% vs 54.5%) with RA followed by cutting balloon compared to RA alone.[41] Similarly, Amemiya et al. found greater calcium fracture and stent expansion (78.9% vs 66.7%, $P < .01$) on OCT with cutting balloon vs standard balloon angioplasty after RA.[42] Additionally, there have been numerous case reports regarding the use of IVL following RA with good effect.[55,56] Larger scale observational and randomized studies are required to determine if improved longer term outcomes can be achieved by these (and other) combinations. In practical terms and in our own clinical practice, RA plays a role in uncrossable and undilatable lesions, and severe concentric calcification (figure 2) often in combination with other techniques.

Orbital atherectomy

OA (DIAMONDBACK 360 orbital atherectomy system, Cardiovascular systems Inc., United States) consists of a diamond coated crown that uses centrifugal force to orbit resulting in preferential calcium sanding while flexing away from healthy elastic tissue. It requires a dedicated wire (ViperWire advance), and lubricant infusion (ViperSlide both Cardiovascular systems Inc., United States) during ablation. The 1.25 mm crown orbits at 1 of 2 speed settings (80 or 120 000 rpm), which results in widening or narrowing of the orbital arc. Unlike RA, the OA can ablate both in forward and backward motion, and requires slow smooth movements (~1mm/second). Atherectomy runs should be ≤ 30 seconds with resting periods to allow clearance of debris. IVI following OA demonstrates smoothed out calcium often with a visible arc or semilunar shape where sanding occurred (figure 3). The nonrandomized ORBIT I and II studies examined the safety and effectiveness of OA finding a reduction in percentage diameter stenosis to ≤ 50% in > 98% of the lesions.[57,58] Significant dissection occurred in 2.3% of the cases. However, the rate of other complications such as perforation, slow,

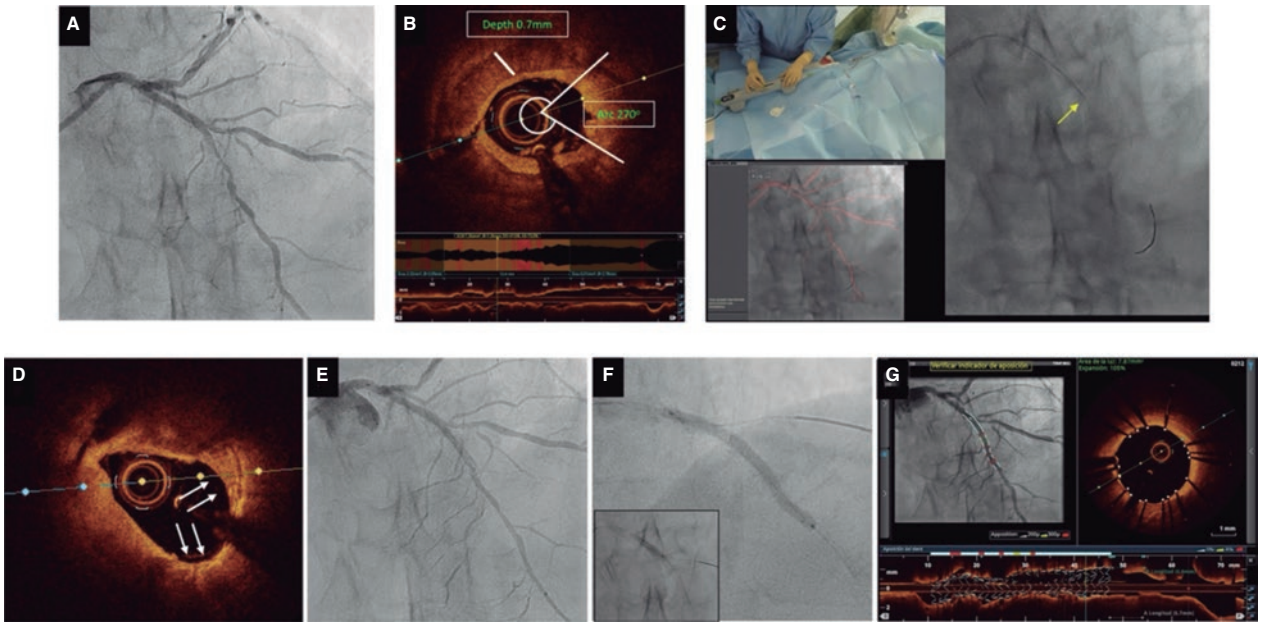


Figure 5. Calcium modification using orbital atherectomy guided by co-registered optical coherence tomography (OCT) imaging. **A:** severely calcified mid-left anterior descending coronary artery stenosis **B:** OCT showing severe circumferential calcification; arc of ~270°, depth of 0.7 mm, and length > 5 mm suggesting a high risk of stent underexpansion according to OCT criteria. Distal and proximal reference luminal diameters of 2.5 mm, and 3.25 mm, respectively, with a predicted stent length of 33 mm. **C:** orbital atherectomy (yellow arrow) using the DIAMONDBACK 360 orbital atherectomy system, and a 1.25 mm crown advanced at 1 mm/s. Sanding/atherectomy was performed in a forward and a backward motion. Dynamic road mapping was also used to guide the procedure (bottom left). **D:** smoothed out appearance–after orbital atherectomy. Image shows that calcium 'cap' has been greatly reduced by the sanding effect of orbital atherectomy (OA). A semilunar shape can be seen as an effect of the orbiting crown (white arrows). **E:** post-OA angiography demonstrating significantly reduced percent stenosis. **F:** implantation of a 2.5 mm x 36 mm drug-eluting stent with proximal optimization using a 3.5 mm x 10 mm noncompliant balloon (inset). **G:** final co-registered OCT post-OA, and stenting demonstrating adequate stent expansion and apposition without complications.

and no-reflow was low and < 1%.[58] The 3-year follow-up of the ORBIT II study demonstrated cumulative rates of major adverse cardiovascular events and target lesion revascularization of 23.5%, and 7.8%, respectively.[59] The single arm prospective COAST study examined a modified OA system with a distal microcrown to improve penetration with a reduction in percentage diameter stenosis to ≤ 50% in > 99% of the lesions.[60] There are currently no randomized trials comparing OA to other forms of calcium modification. However, a small OCT study suggested deeper calcium modification with OA vs RA,[61] and a meta-analysis of observational studies found no difference in procedural complications or 30-day events including death, myocardial infarction, and target vessel revascularization between OA and RA.[62] However, although more data is required, our practice is to use OA over RA in larger vessels with concentric or nodular calcium. Figure 5 demonstrates an example of OA plaque modification and table 3 summarizes the current data for both OA and RA.

Excimer laser coronary angioplasty

Excimer laser coronary angioplasty (ELCA) uses a mixture of rare gas and halogen to generate brief pulses of high-frequency ultraviolet light which disrupts atherosclerotic plaque through 3 mechanisms: photochemical by breaking down the carbon bonds between the molecules, photothermal due to the production of heat and vapour bubbles causing cell rupture, and photomechanical by the expansion of vapour bubbles causing the disruption of the plaque. Fluence (energy measured in mJ/mm^2), and pulse frequency can be altered to increase its effectiveness. Constant saline infusion is advised to avoid thermal injury. Also, the short wavelength (~308 nm) of ultraviolet light used reduces the depth of penetration, thus avoiding damage to healthy tissues. Evidence on the use of ELCA in calcified CAD is limited. A prospective multicentre study of 100 uncrossable/undilatable lesions demonstrated technical success in 92% of lesions[63] while a more recent prospective multicentre study of 126 uncrossable lesions demonstrated success in ~82% of cases.[64] However, severe calcification was significantly associated with ELCA failure. In the setting of in-stent restenosis, more calcium fracture on OCT was seen in the ELCA vs conventional treatment group.[65] Given the paucity of large-scale studies and considering the data available to date, ELCA has a relatively niche role predominantly for the management of uncrossable lesions although we prefer to use RA as the first-line ablative therapy in this circumstance.

CONCLUSIONS

Calcified CAD continues to present a barrier for successful PCI. Furthermore, our ageing population suggests that the proportion of patients with calcified CAD who will present for PCI is likely to increase. Its presence is associated not just with poorer acute outcomes, but also with more adverse events at long-term follow-up. Stent underexpansion is one of the most powerful predictors of stent failure, and often occurs in the presence of significant coronary calcification. Identifying the presence of coronary calcium is key in planning a PCI, and is more accurately done using IVI. A number of technologies with different mechanisms of action are now available to modify coronary calcium although head-to-head comparisons between these techniques are lacking. Nonetheless, we propose a simplified calcium modification algorithm based on IVI findings that is currently used at our center. Future studies should aim to compare techniques and elucidate the best technique combinations to ensure improved outcomes in these complex patients.

Table 3. Summary of the main prospective studies examining outcomes in RA and OA techniques

Technique	Study name	Design	Number of participants	Procedural outcomes	Short-to-medium term outcomes	Long-term outcomes
Rotational atherectomy	ROTAXUS study[52,53]	Randomized controlled trial	240 • 120 RA • 120 Standard therapy (Std Tx)	Strategy success • RA, 92.5% vs Std Tx, 83.3%, *P* = .03 Acute luminal gain • RA, 1.56mm vs Std Tx, 1.44, *P* < .01 Dissection • RA, 3.3% vs Std Tx, 3.3%, *P* = .99 Perforation • RA, 1.7% vs Std Tx, 0.8%, *P* = .56 Slow/no flow • RA, 0% vs Std Tx, 0.8%, *P* = .32	**9-month out comes** In-stent LLL • RA, 0.44mm vs Std Tx, 0.31, *P* = .04 Mortality • RA, 5.0% vs Std Tx, 5.8%, *P* = .78. MI • RA, 6.7% vs Std Tx, 5.8%, *P* = .79 TVR • RA, 16.7% vs Std Tx, 18.3%, *P* = .73 MACE • RA, 24.2% vs Std Tx, 28.3%, *P* = .46. TLR • RA, 11.7% vs Std Tx, 12.5%, *P* = .84	**2-year outcomes** MACE • RA, 29.4% vs Std Tx, 34.3%, *P* = .47 Death • RA, 8.3% vs Std Tx, 7.4%, *P* = 1.00) Myocardial infarction • RA, 8.3% vs Std Tx, 6.5%, *P* = .80), TLR • RA, 13.8% vs Std Tx, 16.7%, *P* = .58 TVR • RA, 19.3% vs Std Tx, 22.2%, *P* = .62)
	PREPARE-CALC[40]	Randomized controlled trial	200 • 100 RA • 100 MB	Strategy success • RA, 98% vs MB, 81%, *P* = .0001 Dissection • RA, 3% vs MB, 7%, *P* = .33 Perforation • RA, 4% vs MB, 2%, *P* = .68 Slow/no flow • RA, 2% vs MB, 0%, *P* = .49	**9 months** In-stent LLL • RA, 0.22 vs MB, 0.16mm, *P* = .21 Mortality • RA, 2% vs MB, 2%, *P* = 1.00 TVR • RA, 3% vs MB, 6%, *P* = .50 TLR • RA, 2% vs MB, 7%, *P* = .17 Definite/probable stent thrombosis • RA, 0% vs MB, 0%, *P* = 1.00 TVF • RA, 6% vs MB, 8%, *P* = .78	
Orbital atherectomy	ORBIT I[57]	Prospective non-randomized	50	• Device success, 98%, • Procedural success, 94% • Dissection, 12% • Perforation, 2% • In-hospital MACE, 4%	MACE • 30-days, 6% • 6 months, 8%	
	ORBIT II[58,59]	Prospective multicentre non-randomized	443	• Procedural success, 88.9% • Angiographic success, 91.4% • Severe dissection, 2.3% • Perforation, 0.9% • Slow/no flow, 0.2% • In-hospital MACE, 9.8%	MACE • 30-day, 10.4%	**3-years** • MACE, 23.5% • Cardiac death, 6.7% • MI, 11.2% • TVR, 10.2% • TLR, 7.8%
	COAST[60]	Prospective multicentre single-arm	100	• Procedural success, 85% • In-hospital MACE, 14% • Dissection, 2% • Perforation, 2% • Slow/no flow, 2%	MACE • 30-day, 15%	**1 year** • MACE, 22.2%

MACE, major adverse cardiovascular events; MB, modified balloons; MI, myocardial infarction; OA, orbital atherectomy; RA, rotational atherectomy; Std Tx, standard therapy, RS, residual stenosis; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

Definitions
- Strategy success: Successful stent delivery, < 20% in-stent RS, TIMI grade-3 flow without crossover or stent failure
- Device success: < 50% RS following OA without device malfunction
- Angiographic success: stent delivery with RS < 50%

ROTAXUS
- MACE: MI, TVR, and cardiac death

ORBIT I
- Procedural success: < 20% in-stent RS
- MACE: cardiac death, MI or TLR

ORBIT II
- Procedural success: stent delivery with a < 50% RS without in-hospital MACE.
- MACE: MI, TVR, and cardiac death

COAST
- MACE: cardiac death, MI or TVR

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AUTHORS' CONTRIBUTIONS

A. McInerney: concept, design, and drafting of the manuscript. J. Escaned: contributed clinical images, and was involved in the critical review of the manuscript. N. Gonzalo: concept, design, drafting, and critical review of the manuscript. Contributed clinical images.

CONFLICTS OF INTEREST

N. Gonzalo reports consultancy and speaker fees from Abbott and Boston Scientific. The remaining authors reported no conflicts of interest pertaining to the current publication.

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Review article

Intracoronary imaging: review and clinical use

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ABSTRACT

Invasive coronary angiography is the standard approach in the routine clinical practice. Intracoronary imaging modalities provide real-time images of intracoronary anatomy. On this basis, optical coherence tomography and intravascular ultrasound have a positive impact on diagnosis and percutaneous coronary intervention. This summary provides an insight on these imaging modalities for the interventional and clinical cardiologist with the currently available evidence.

Keywords: Intravascular ultrasound. Optical coherence tomography. Invasive coronary angiography.

Imagen intracoronaria: revisión y utilidad clínica

RESUMEN

La coronariografía es el método de elección para el estudio de la anatomía coronaria en la práctica clínica diaria. Las diferentes modalidades de imagen intracoronaria permiten valorar en tiempo real la anatomía de la pared arterial coronaria. Sobre esta base, la tomografía de coherencia óptica y la ecografía intravascular tienen un impacto positivo en el diagnóstico y en el intervencionismo percutáneo. La presente revisión proporciona un resumen de las técnicas de imagen intracoronaria basadas en la evidencia actual disponible.

Palabras clave: Ecografía intravascular. Tomografía de coherencia óptica. Coronariografía.

Abbreviations

CA: coronary angiography. **CTO**: chronic total coronary occlusion. **ICI**: intracoronary imaging. **IVUS**: intravascular ultrasound. **LMCAD**: left main coronary artery disease. **MACE**: major adverse cardiovascular events. **OCT**: optical coherence tomography. **PCI**: percutaneous coronary intervention.

INTRODUCTION

Coronary artery disease is still the leading cause of death across the world and can manifest through a wide range of presentations given its dynamic nature.[1] Coronary angiography (CA) is the gold standard approach to assess the presence and severity of coronary artery disease. However, it is limited by qualitative assessment although improvements have been made such as the development of quantitative coronary angiography.[2] New imaging modalities for coronary assessment have emerged over the last few decades to improve patient outcomes.[3]

Intracoronary imaging (ICI) modalities provide an in-depth understanding of the aspects that contribute to the pathogenesis of coronary artery disease, but also help us guide the decision-making process. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) produce real-time cross-sectional images of the coronary artery. Data from clinical studies have suggested improved outcomes during complex ICI-guided percutaneous coronary interventions (PCI).[4,5] Both the American and the European clinical guidelines on myocardial revascularization allocate a Class II recommendation—American College of Cardiology/American Heart Association: Class IIa[6] and European Society of Cardiology: Class

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Table 1. General characteristics of intracoronary imaging modalities

Intracoronary imaging modality	Source of image	Frequency (Mhz)	Wavelength (µm)	Minimal guide catheter (Fr)	Axial resolution (µm)	Lateral resolution (µm)	Tissue penetration (mm)	Pullback length (mm)	Pullback speed (mm/sec)
IVUS[a]	Ultrasound	20-60	40-50	5	20-170	50-260	3-8	100	0.5-10
OCT[b]	Infrared light	NA	1.3	5	15-20	20-40	1-3	75	10-40
Hybrid (OCT/IVUS)[c]	Ultrasound and Infrared light	40	1.3	5	200/15	200/30	3-8	100-150	0.5-40

IVUS, intravascular ultrasound; OCT, optical computed tomography; NA, not applicable.
[a] Includes OptiCross (Boston Scientific, United States), Volcano (Philips, United States), Infraredx (Burlington, United States), ACIST CVi (ACIST, United States), and Fastview (Terumo, Japan).
[b] Includes OPTIS (Abbott Vascular, United States), and Lunawave (Terumo, Japan).
[c] Includes Novasight Hybrid (Conavi Medical, Canada), and Dual Sensor (Terumo, Japan).

IIa—to IVUS–guided PCI,[7] being the OCT-guided PCI an alternative with the exception of ostial left main coronary artery disease.[6,7] However, its use is still uneven worldwide.

This review seeks to summarize the evidence available to portray all the potential advantages and downsides of these 2 catheter-based imaging modalities in the routine clinical practice.

IMAGING MODALITIES

IVUS

IVUS catheters are rapid exchange catheters that have a piezoelectric crystal that produces soundwaves through transducers when electrically excited. Soundwaves propagate through the different tissues reflecting on the surfaces according to the acoustic properties of the tissue. These returned soundwaves are formatted into a grayscale image with dynamic contrast resolution. This modality allows the interventional cardiologist to evaluate the integrity of the vessel wall, characterize tissue composition, and tackle PCI challenges (stent malapposition and underexpansion).[8]

The quality of the images depends on the soundwave, transducer, and tissue properties. The resulting image resolution is greater at shorter distances (near-field), but it appears less clear in the deep fields (far-field) due to beam scattering. Flow properties also make it more difficult to distinguish the lumen from the tissues. Mechanical or rotational catheters work at 40-60 MHz frequencies, as opposed to electronic ones that operate at 20 MHz frequencies and have greater axial and lateral resolution. Overall, the best images are obtained when the catheter is coaxial to the vessel, the beam is perpendicular to the lesion, and with clear lumens.[8,9]

IVUS image acquisition should be routinely performed with IV anticoagulation and intracoronary nitrates to prevent device-related complications.[5] Vessel interrogation can be performed with manual or automatic pullback starting, at least, 10 mm distal to the target lesion until the aorta or the guiding catheter can be seen. In the case of aorto-ostial lesions, the guiding catheter must be disengaged to unmask ostial lesions. Automatic pullbacks have the advantage of providing measurements of lesion length, which is estimated with the average time and pullback speed. Multiple lesions are considered when distance is > 5 mm within the same coronary segment. However, spatial orientation is a major limitation.[8,9] The main features of IVUS are shown on table 1 and table 2.

Efforts to explore the potential benefits of IVUS over CA have been reported over the years with promising results. In a recent meta-analysis of 27 610 patients that compared IVUS-guided PCI vs CA-guided PCI, IVUS was associated with less cardiac death (risk ratio [RR], 0.63; 95% confidence interval [95%CI], 0.54–0.73), and PCI-related complications. Similarly, the risk of myocardial infarction (RR, 0.71; 95%CI, 0.58–0.86), target lesion revascularization (RR, 0.81; 95%CI, 0.70–0.94), and stent thrombosis (RR, 0.57; 95%CI, 0.41–0.79) was lower with IVUS-guided PCI.[10]

Table 2. Main advantages and drawbacks of intracoronary imaging modalities

Intravascular ultrasound	Optical computed tomography
• More penetration capabilities, capable of assessing plaque volume and deeper plaques. • Better suited for CTO, aorto-ostial junction, LMCAD, and stent sizing assessment. • Does not require contrast.	• Higher resolution, fewer artifacts, and facilitates the identification of subtle details • More user friendly. • Capable of assessing calcium thickness. • Better suited for strut and thrombus evaluation.
• Lower resolution. • Requires anticoagulation and additional time. • Image interpretation requires experience and expertise. • Cannot penetrate calcium or adequately evaluate thrombi. • Expensive.	• Less penetration capabilities, cannot adequately evaluate ostial lesions. • Requires anticoagulation and additional time. • Image acquisition requires blood clearance through contrast or other means. • Image interpretation requires experience and expertise. • Expensive.

CTO, chronic total coronary occlusions; LMCAD, left main coronary artery disease.

Optical coherence tomography

OCT image generation is based on infrared light (1.3 µm wavelength). Compared to IVUS, this imaging modality provides greater axial resolution (10-20 µm vs 50-150 µm) with limited soft tissue penetration (1-2 mm vs 5-6 mm except for calcium evaluation).[3,4,11]

Current devices are 5-Fr compatible through a rapid exchange system that also allows automatic pullbacks with angiography co-registration and automatic lumen measurements and calcium detection. The quality of the images depends on the interaction of light with the surrounding tissues (echo-time delay). As such, light reflection, refraction, and attenuation (absorption) determine the final image resolution. Metal devices and fibrous plaques are considered strong reflectors while low reflectors are calcium and necrotic cores (lipid-rich). Red blood cells cause light scattering that requires contrast washout causing the

appearance of a "pseudo-thrombus" image with poor blood clearance.

OCT imaging is also routinely performed with IV anticoagulation and intracoronary nitrates to prevent complications. The study of the vessel begins 10 mm distal to the target lesion, the catheter is then purged with contrast, and an automatic pullback with co-registration (if available) is performed. The average pullback speed of 10-40 mm/s usually allows a single bolus injection of contrast to achieve a blood-free environment.[12] The general OCT features are shown on table 1 and table 2.

Compared to the CA-guided PCI, observational studies have suggested a potential benefit of OCT-guided PCI with lower rates of major adverse cardiovascular events (MACE) and stent-related complications.[13] Furthermore, the OCT provides more reliable and reproducible images with less inter-observer variability compared to the IVUS. In this regard, the OCT may be superior to assess stent and lumen diameters.[14,15]

SPECIFIC SCENARIOS

Acute coronary syndromes

Acute coronary syndromes are mostly caused by coronary thrombosis due to plaque rupture, plaque erosion or an eruptive calcified nodule.[16] Accurate diagnosis may have prognostic implications. The rupture of the plaque is associated with a greater rate of no-reflow and distal embolization. Plaque erosion can be conservatively managed in non-critical stenoses. Calcified nodules are associated with a higher rate of stent restenosis and thrombosis[17] (figure 1).

The OCT is often used for the perioperative identification of culprit lesions after careful evaluation of the morphological characteristics of the fibrous cap.[18] The plaque classification algorithm through OCT classifies plaques based on the state of fibrous caps, thereby showing an intact fibrous cap in plaque erosion, a disrupted cap as the hallmark of a ruptured plaque or a calcified nodule. The OCT can also determine thrombus burden, but is not necessary to ascertain the culprit lesion. However, a recent publication that compared near infrared spectroscopy combined with IVUS to OCT in 276 patients found that the former can accurately characterize culprit lesions after the characterization of calcium, plaque cavity, and the maximum lipid core burden index with 93% and 100% sensitivity and specificity, respectively.[19]

Moreover, data supports the preference of ICI-guided PCI to improve outcomes in the management of acute coronary syndrome. A meta-analysis of 26 610 patients reported a net benefit of IVUS regardless of the presence of acute coronary syndrome with a lower rate of MACE (RR, 0.57; 95%CI, 0.41-0.79) compared to the CA-guided PCI.[10] Similarly, an observational Korean registry of 11 731 patients treated with primary PCI reported a lower rate of cardiac death, target vessel reinfarction, and target lesion revascularization with either IVUS- or OCT-guidance.[20]

Bifurcated lesions

Coronary bifurcation lesions are found in 15% to 20% of all patients treated with PCI.[21] The main challenge when treating bifurcation lesions is selecting the right PCI strategy to avoid target lesion failure or side-branch occlusion. The importance of careful evaluation is evident with the distal left main coronary artery disease (LMCAD). The European Bifurcation Club recommends intracoronary imaging to treat bifurcated lesions.[22]

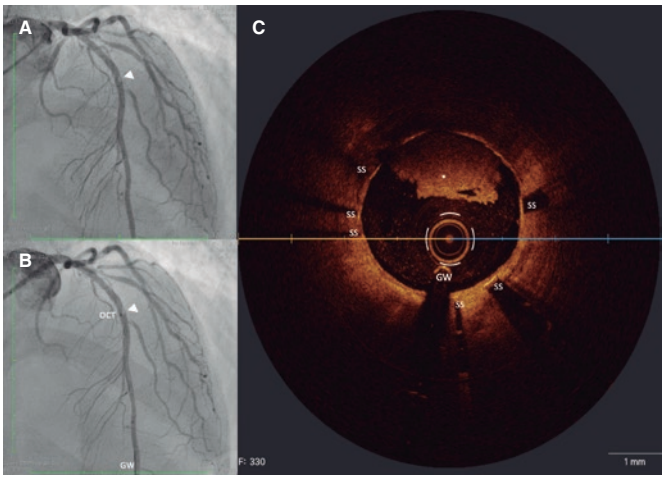

Figure 1. Stent thrombosis. **A:** filling defect (arrowhead) in the mid left anterior descending coronary artery on the right oblique anterior projection. **B:** co-registration of optical coherence tomography and angiography. **C:** OCT cross-sectional image showing non-occlusive stent thrombosis (white asterisk). GW, guidewire; OCT, optical coherence tomography; SS, stent struts.

The risk of side-branch compromise can be diminished with both the IVUS and the OCT by selecting the proper stent (type and size), landing zone, and evaluation of post-PCI results (stent expansion and apposition; distal dissection). Intracoronary imaging can identify a "spiky" carina in cases of distal LMCAD, which has been associated with restenosis due to carina shift. Also, some predictors of side-branch compromise with IVUS (minimum lumen area of side-branch and plaque burden)[19] and OCT (angle < 50º and branching point to carina tip length < 1.70 mm)[23] have been reported.

Also, both imaging modalities can be used for stent sizing in bifurcation lesions; however, areas with high plaque burden or lipid plaques where both imaging modalities are useful should be avoided as landing zones. Overall, ICIs are also useful to treat bifurcations with PCI since they evaluate side-branch wire entry, calcification, lesion length, and post-stent-related complications that may interfere with the clinical outcomes.[22] Two randomized control trials are currently evaluating the role of OCT in patients with bifurcated lesions (NCT03171311; NCT03507777).

Coronary artery calcification

Coronary artery calcification increases PCI complexity by impairing stent deployment, expansion, and apposition, which in turn increases the risk of stent thrombosis and restenosis.[24] CA can detect—with a low-to-moderate sensitivity—the presence of coronary artery calcification with severe cases being visible without cardiac motion and contrast injection.[25]

Calcified plaques appear as hyperechoic structures with a characteristic acoustic shadowing on the IVUS (figure 2).[8] The IVUS can assess coronary artery calcification quantitatively (angle and length), semiquantitatively (absent or quadrant distribution), and qualitatively (depth of acoustic shadowing based on plaque and medial thickness).[25] A study that compared IVUS to CA in 67 chronic total coronary occlusions (CTO) lesions found that IVUS was superior regarding the identification of calcium deposits (96% vs 61%).[26] However, IVUS cannot evaluate microcalcifications (> 5 µm), but it can estimate the depth or thickness of calcium deposits.[25]

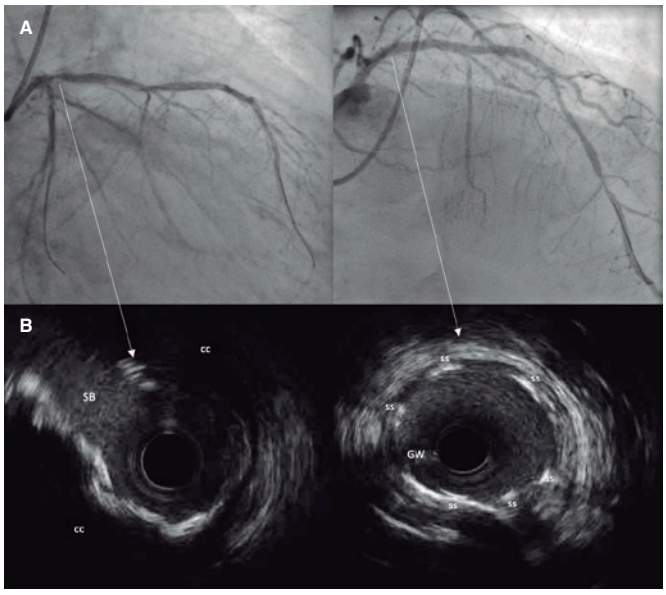

Figure 2. Coronary angiography (A) and intravascular ultrasound imaging (B) of ostial left anterior descending coronary artery showing severe concentric coronary calcification. Panels C, and D show the immediate outcomes after definitive stent implantation. CC, concentric calcification; GW, guidewire; SS, stent struts.

On the OCT, calcification appears as a heterogeneous structure with well-defined borders that can be used to offset some of the limitations of IVUS. Although the OCT has less depth penetration capabilities,[25] its evaluation of the calcium thickness, area, and volume is more precise and reliable.[27]

The ICI analysis of calcium features can provide some insights for efficient planning to prevent stent underexpansion or malapposition.[28,29] Therefore, calcium circumferences > 180°, thicknesses > 0.5 mm or lengths > 5 mm on the ICIs should involve adjunctive therapies to plaque modification.[30] The OCT analysis of 31 patients from the Disrupt CAD study showed that calcium fractures were the leading mechanism of action of coronary lithotripsy and a tendency towards more adequate stent expansion was observed.[31] Similar results were reported with rotational atherectomy where a study that evaluated 88 calcified lesions with both ICI modalities confirmed that OCT-guided rotational atherectomy was associated with better stent expansion (83% vs 72%; $P = .0004$), but with similar survival rates at the 1-year follow-up.[32] Nevertheless, the IVUS may help while performing a PCI on the left main artery disease,[33] where an early assessment can identify the optimal plaque modification technique to be used.[34]

Chronic total coronary occlusion lesions

The prevalence of CTO is 20% among patients with coronary artery disease. Performing a PCI on a CTO can improve the patients' symptoms, workout abilities, and quality of life.[35] The reported success rate for CTO procedures is estimated at 70% to 90%. With careful planning, better results can be achieved.[36,37]

IVUS provides an adequate and more efficient way to evaluate CTO features (cap ambiguity, lesion length, and calcification) allowing optimal re-entries into the true lumen with both antegrade and retrograde approaches.[38] Studies that compared IVUS vs CA in PCIs performed on CTOs have yielded conflicting results regarding the rate of MACE (table 3).[39-41] Furthermore, the IVUS has proven beneficial to predict restenosis in PCIs performed on CTOs where post-minimal luminal diameters of ≤ 2.4 mm and stent expansion rates of ≤ 70% were independent predictors of post-PCI restenosis at the mid-term follow-up, particularly in complex CTOs.[42] A major limitation of IVUS guided PCIs performed on CTOs is the artifact generated by calcium rendering, which complicates the interpretation of images.[38]

The main obstacle of the OCT in PCIs performed on CTOs is the need for contrast washout and the propagation of dissections due to the need for blood clearance, which is why it has been considered inadequate. However, this imaging modality could find its way into optimized PCIs performed on CTOs and follow-up monitorizations. A retrospective study reported a higher rate of stent malapposition and uncovered struts at 6-months after OCT examinations of patients with successful PCIs performed on CTOs.[43] The ALSTER-OCT-CTO registry reported similar results after evaluating 111 lesions with OCT and saw a higher rate of malapposed and uncovered stent struts in CTOs vs non-CTO lesions at the 12-month follow-up.[44]

Coronary artery aneurysms

Coronary artery aneurysms are often clinically silent and can be identified in approximately 5% of all the patients undergoing CA. The most common causes are atherosclerosis in adults and Kawasaki disease in children. Coronary artery aneurysm is defined as a focal dilation of at least > 1.5 times the adjacent normal coronary artery while diffuse dilation is considered as coronary artery ectasia. Morphologically, when looked at from their maximum diameter, saccular and fusiform aneurysms can be seen with the former greater transverse rather than longitudinal diameter.[45]

The optimal ICI modality remains controversial, but historically IVUS has been the preferred approach for the evaluation and follow-up of coronary artery aneurysm in Kawasaki disease. The deeper penetration capabilities of IVUS allows us to assess the diameter of the vessel. Besides, it can accurately differentiate false from true coronary aneurysms by identifying a single-layered bulging. IVUS-guided preoperative planning is advised as aneurysms often go undersized with CA.[45]

Dionne et al. conducted an analysis of coronary artery aneurysms using OCT in a pediatric population with a past medical history of Kawasaki disease. The OCT proved to be safe, and similar findings (intimal hyperplasia, fibrosis, and media disruption) were observed in aneurysmal lesions compared to former histopathological studies. Nonetheless, these findings were also seen in non-aneurysmal coronary segments, which could drive the higher risk of ischemia in patients with a past medical history of Kawasaki disease.[46]

Left main coronary artery disease

The prevalence of LMCAD is 4% and, traditionally, coronary artery bypass graft has been the standard treatment with growing evidence to this date supporting PCI.[47] Selecting the right imaging modality is important to determine accurately the clinical significance of LMCAD. CA remains the standard evaluation of choice, but it is subject to a high inter and intra-observer variability in the detection of intermediate lesions (30% to 70%).[48] Consequently, intracoronary imaging can improve the assessment of LMCAD, and the long-term outcomes.

The importance of IVUS assessing the anatomy of LMCAD is evident given its more consistent tissue penetration capabilities that allows proper plaque evaluations. Former studies (table 4) described

Table 3. Invasive coronary angiography vs intracoronary imaging for percutaneous coronary interventions on chronic total coronary occlusions

Reference	Type of study	IVUS vs CA (n)	Primary endpoint	Study outcomes
Tian et al.[39]	Prospective RCT	130 vs 130	In-stent late lumen loss	• Rate of stent restenosis (3.9% vs 13.7%; P = .021) • Adverse event rate after 2 years (21.7% vs 25.2%; P = .641)
Hong et al.[40]	Retrospective	206 vs 328	Stent thrombosis	• Similar rate of MACE in the matched cohort • Lower stent thrombosis in IVUS-guided PCI (0% vs 3%; P = .015)
Kim et al.[41]	RCT	201 vs 201	Cardiac death	• Less MACE (HR, 0.35; 95%CI, 0.13–0.97) and stent thrombosis (0% vs 1.5%; P = .11) in IVUS-guided PCI

CA, coronary angiography; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; OCT.

Table 4. Summary of the studies that evaluated invasive coronary imaging for the assessment of left main coronary artery disease

Reference	Type of study	ICI use	Follow-up time	Outcomes
De la Torre Hernandez et al.[33]	Prospective multicenter	IVUS	2 years	Defer PCI with MLA > 6 mm^2 is safe
Fassa et al.[49]	Prospective	IVUS	3 years	Defer PCI with MLA ≥ 7.5 mm^2 is safe
Jasti et al.[50]	Prospective	IVUS	3 years	MLA < 5.9 mm^2 is well correlated with a FFR < 0.75
Park et al.[51]	Prospective	IVUS	NA	FFR < 0.8 had a good correlation with MLA ≤ 4.5 mm^2 among Asians

ICI, intracoronary imaging; IVUS, intravascular ultrasound; MLA, minimum lumen area; PCI, percutaneous coronary intervention.

significant LMCAD with minimal lumen areas between 6 mm^2 and 9 mm^2 estimated using IVUS[33,49] with values < 6 mm^2 showing a good correlation with fractional flow reserve < 0.75.[50] However, smaller areas have been reported in the Asian population.[51] A multicenter prospective study that evaluated LMCAD with IVUS reported a similar rate of cardiac events after 2-years in patients undergoing revascularization with minimum lumen areas (MLA) < 6 mm^2 (5.5%), as well as in those with MLAs ≥ 6 mm^2 (2.3%) with revascularization deferral.[33] Therefore, an angiographically ambiguous LMCAD with an IVUS-derived MLA > 6 mm^2 can be considered non-ischemic whereas those with a MLA ≤ 4.5 mm^2 could be deemed as ischemia-generating LMCAD. However, for those with a MLAs from 4.5 mm^2 to 6 mm^2, additional invasive or non-invasive assessment tools are required to rule out the presence of ongoing ischemia.[52]

Former studies have demonstrated that plaque burdens > 60% in non-LMCAD is a predictor of MACE and can be recognised when assessing the risk of future events after PCI.[4] Through IVUS analysis, it was shown that the larger the plaque burden in the LMCAD, the greater the overall plaque burden in the coronary tree.[53] However, in the PROSPECT study a greater plaque burden was not associated with a higher rate of MACE as opposed to the overall plaque burden (hazard ratio, 1.06; 95%CI, 1.01–1.11; P = .02).[54] Therefore, the IVUS assessment of the LMCAD plaque burden can identify high-risk patients with coexisting non-LMCAD atherosclerotic disease.

The role of IVUS in LMCAD is not limited to diagnosis only (table 5).[55-59] A meta-analysis that compared IVUS-guided vs CA-guided PCI in LMCAD found that the former was associated with less cardiovascular mortality (RR, 0.47; 95%CI, 0.33–0.66; P < .001), new target lesion revascularization (RR, 0.43; 95%CI, 0.25–0.73; P = .002), and stent thrombosis (RR, 0.28; 95%CI, 0.12–0.67; P = .004).[60] Also, de la Torre Hernández et al. reported that IVUS-guided PCI was particularly useful in distal lesions with a lower event rate compared to non-IVUS guided PCI (hazard ratio, 0.54; 95%CI, 0.34–0.90).[56] Other studies have proposed a role for IVUS in the optimization of LMCAD after stent deployment where minimum lumen areas were associated with stent underexpansion and could predict in-stent restenosis with different thresholds regarding the assessed segment (8 mm^2 for the proximal left main coronary artery, 6 mm^2 for the ostium of the left anterior descending coronary artery, and 5 mm^2 for the ostium of the left circumflex artery).[61]

On the contrary, the OCT has limited utility in the assessment of LMCAD given its average diameter (3 mm to 5 mm) and inability to evaluate aorto-ostial lesions where blood-free fields are difficult to achieve.[48] A multicenter retrospective study (ROCK cohort II) recently reported a lower 1-year rate of target lesion failure in intravascular imaging guided vs angiographically guided distal PCIs on the LMCA (12.7% vs 21.2%; P = .039) with similar outcomes between the OCT and the IVUS (P = .26).[62] However, future prospective data supporting OCT-guided PCI is expected to better define the optimal clinical management of patients with LMCAD (NCT04248777, NCT04391413, NCT03474432, NCT03820492, and NCT04531007).

Spontaneous coronary artery dissections

Spontaneous coronary artery dissection is a classically misdiagnosed life-threatening condition that can occur in otherwise healthy individuals. Coronary flow is compromised after the development of a false lumen through an "inside-out" or "outside-in" mechanism. The Yip-Saw coronary classification has revealed the limitations of coronary angiography. Diagnosis is particularly challenging with type 2 (diffuse smooth stenosis) and type 3 (mimic atherosclerotic stenosis) spontaneous coronary artery dissections.[63,64]

The benefits of implementing ICIs (table 6) for diagnostic purposes or even to guide coronary intervention in spontaneous coronary artery dissections are their higher resolution.[65,66] IVUS has a deeper power of penetration to visualize the vessel wall and intramural hematoma, consequently, it is also recommended for proximal dissections[8]. It can also differentiate between true and false lumens once fused with color interpolation. However, the OCT is more sensitive regarding the

Table 5. Summary of the studies that compared IVUS-guided vs coronary angiography-guided percutaneous coronary interventions on left main coronary artery disease

Reference	Endpoints	Outcomes
Park et al.[55]	• Primary endpoint was all-cause mortality • Secondary endpoints were MI, TVR, and the composite endpoint	• IVUS-guided PCI was associated with a lower rate of overall mortality (HR, 0.31; 95%CI, 0.19–0.51), and MI (HR, 0.470; 95%CI, 0.33-0.67). • The risk of TVR (HR, 0.47; 95%CI, 0.33-0.67) did not decrease with IVUS guidance
De la Torre Hernandez et al.[56]	• Primary endpoint was MACE (cardiac death, MI, TLR) • Secondary endpoints were all-cause mortality, cardiac death, infarction-free survival, TLR-free survival, and the rate of ST	• The 3-year rate of all-cause mortality was lower with IVUS-guided PCI (4.7% vs 16%; *P* = .048) • Lower rate of ST with IVUS-guided PCI (0.6% vs 2.2%; *P* = .04) • IVUS-guided PCI of LMCAD was associated with minor adverse events in distal lesions (HR, 0.34; 95%CI, 0.34-0.90), and in the overall population (HR, 0.70; 95%CI, 0.52-0.99)
Gao et al.[57]	• Primary endpoint was the 1-year rate of MACE (cardiac death, MI, TVR) • Safety outcome was ST	• The 1-year rate of MACE in the IVUS-guided group was lower (14.8% vs 27.7%) • Coronary angiography-guided PCI was associated with a higher rate of ST (2.7% vs 0.6%; *P* = .026)
Tan et al.[58]	• 2-year rate of MACE (death, MI or TLR)	• Similar event rate regarding SR (3.28% vs 8.15%; *P* = .11), and ST (1.6% vs 3.2%; *P* = .568) • The IVUS-guided PCI was associated with a lower rate of MACE (OR, 0.414; 95%CI, 0.129-0.867), and TLR (8.2% vs 19%; *P* = .045)
Andell et al.[59]	• Primary endpoint was a composite endpoint of all-cause mortality, SR, and ST) • Secondary endpoints were all-cause mortality, SR, ST, and unexplained death within 30-days	• The IVUS group was associated with fewer composite endpoints (HR, 0.65; 95%CI, 0.50–0.84) and a lower all-cause mortality rate (HR, 0.62; 95%CI, 0.47–0.82) • Not differences were seen in the rate of ST and SR

95%CI, 95% confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; LMCAD, left main coronary artery disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SR, stent restenosis; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization.

Table 6. Benefits of intravascular imaging modalities in spontaneous coronary artery dissection

IVUS	OCT
Intramural hematoma (complete visualization of the vessel wall)	Detail characterization of the intimal flap (intimal-medial disruption)
True and false lumen (with IVUS and ChromaFlo*)	Connection between true-false lumen (entry tear)
Thrombosis of the false lumen	Involvement of side branches and/or thrombus
Guidewire position	Guidewire position

IVUS, intravascular ultrasound; OCT, optical computed tomography.
* Chromaflo Volcano (Philips, United States).

identification of subtle signs such as an intimal tear (entry site to the false lumen), and Ribero et al. used it for establishing the mechanism behind coronary dissection.[67]

If the ICI is deemed necessary during the management of spontaneous coronary dissection, it is important to acknowledge that there is a risk of procedural complications (eg, dissections with contrast injection during the OCT, especially in type I spontaneous dissections or lead to vessel occlusion). A study of 28 patients with spontaneous coronary artery dissections found that intracoronary imaging assessment was associated with iatrogenic wire (3.5%) and guide catheter dissections (3.5%), but also with propagation with wiring (10.7%) or advancement of the OCT catheter (3.5%).[68] Therefore, the benefit may be greater in cases of diagnostic uncertainty or with complex dissections requiring PCI.

Heart transplant vasculopathy

The clinical presentation of cardiac allograft vasculopathy is often silent. Still, it is characterized by aggressive and concentric diffuse fibromuscular dysplasia. The International Society for Heart and Lung Transplantation classifies allograft vasculopathy into 4 categories based on graft function and angiographic findings having CAV2 and CAV3 the worst prognosis of all.[69] CAV is considered the gold standard technique for routine screening and definitive diagnosis.

Heart transplant patients may present with an intimal thickening identifiable through IVUS only. Former studies have reported that an intimal thickening > 0.5 mm from baseline is associated with a higher rate of adverse events within the first year after the heart transplant.[70,71] Consistent with these findings, volumetric studies with IVUS have shown that the combination of intimal thickening plus negative remodelling of the proximal left anterior descending coronary artery were associated with acute rejection and major adverse events within the first year.[72] However, the OCT can identify early stages of intimal thickening in the form of intimal hyperplasia (thickness > 100 µm), and improve the clinical outcomes.[73]

Post-stent findings

Both imaging modalities have been used to identify stent underexpansion, incomplete apposition, and edge dissection as potential causal mechanisms of stent failure.

In this regard, minimal stent area (MSA) is associated with both restenosis and stent thrombosis. IVUS studies reported MSAs between 5.3 mm^2 and 5.7 mm^2 with smaller areas identified in patients with definitive stent restenosis at the short-term follow-up after stent implantation.[74,75] Similarly, 2 studies reported that MSAs < 5 mm^2 as seen on the OCT were associated with a higher rate of target lesion revascularization and stent thrombosis with drug-eluting stents.[76,77] On the contrary, stent patency assessed through the OCT suggested that values > 4.5 mm^2 had a lower rate of MACE,[76] but higher cut-off values for proximal (> 8 mm^2) and distal (> 7 mm^2) LMCA with IVUS assessment. Therefore, clinical guidelines recommend a post-PCI MSA/mean reference lumen of > 80%.

A series of OCT registries observed that a common leading mechanism responsible for early (1 to 30 days), late (1 to < 12 months), and very late (> 1 year) thrombus formation is the malapposition (axial distance > 0.4 mm with a longitudinal extension > 1 mm) of stented

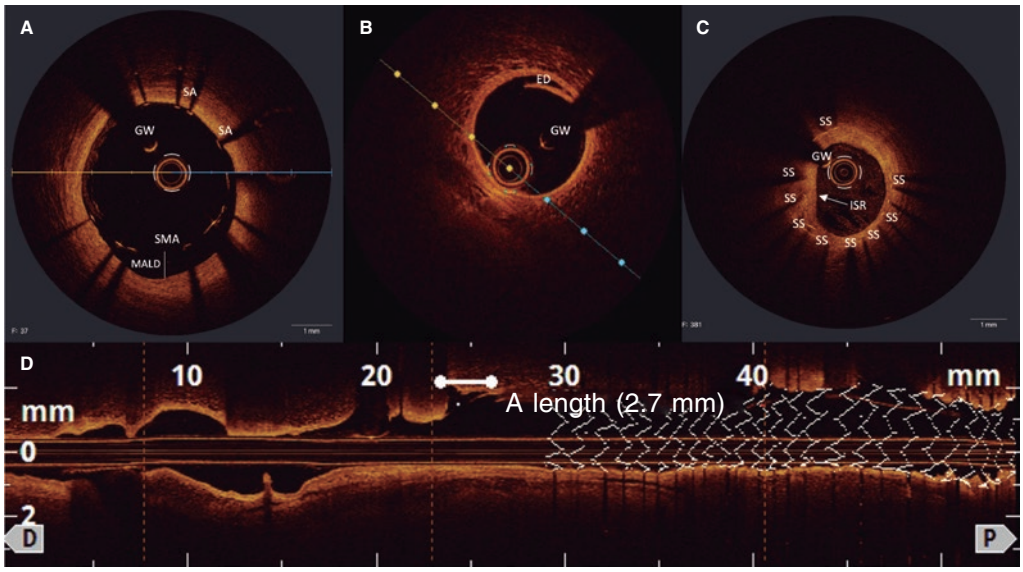

Figure 3. Post-stent findings with optical coherence tomography: **A:** stent malapposition from the 16 o'clock to the 19 o'clock position; **B** and **D:** edge dissection with flap (white asterisk) distal to an implanted drug-eluting stent; **C:** stent restenosis (white arrow) due to concentric neointimal proliferation; the stent struts are visible under the homogenous bright layer. ED, edge dissection; GW, guidewire; ISR, in-stent restenosis; MALD, malapposed distance; SA, strut apposition; SMA, strut malapposition; SS, stent struts.

Table 7. Summary of studies comparing IVUS vs OCT and/or CA for PCI guidance

Reference	Type of study	ICI modality	Outcomes
Ali et al.[89]	Multicenter RCT	OCT vs IVUS vs CA	No differences in procedural MACE[a] were reported between OCT (3%) and IVUS (1%; *P* = .37) and CA (1%; *P* = .37) Similar rate of procedural complication
Habara et al.[90]	Prospective RCT	OCT vs IVUS	Similar rate of procedural time (40 ± 16.4 min vs 47 ± 17.6 min; *P* = .09), and fluoroscopy time (20.4 ± 8.4 min vs 24.8 ± 10.4 min; *P* = .05) Similar rate of complications, no deaths reported (*P* > .99)
Kubo et al.[91]	Prospective multicenter RCT	OCT vs IVUS	Similar rates of cardiac death (0% vs 0.2%; *P* = .99) and MACE[b] (2.9% vs 3.5%; *P* = .81) No contrast-induced nephropathy reported with a similar rate of complications between the groups
Van der Sijde et al.[92]	Single-center Prospective	OCT vs IVUS	Similar rate of procedural cardiac events (< 1%) No predictors of adverse events were identified

CA, coronary angiography; ICI, intracoronary imaging; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular event; OCT, optical computed tomography; RCT, randomized controlled trial.
[a] Defined as procedural complications (angiographic dissection, perforation, thrombus, or acute closure), and active procedures (balloon inflations, additional stent implantations or pericardiocentesis).
[b] Defined as a composite of cardiac death, myocardial infarction or ischemia-driven target lesion revascularization.

segments.[78-80] Consistent with this, stent edge dissection is also associated with adverse events as seen on the CLI-OPCI II study, where distal stent edge dissections > 200 µm had a higher rate of MACE.[76]

SAFETY

The development of ICI techniques has resulted in significant clinical improvements, but they are not free from procedural complications (figure 3).

Safety trials on IVUS have reported an estimated rate of complications between 1% to 3%, mostly associated with the size of the catheter. The setback of CA is the use of contrast materials to enhance image quality with the inherent risk of contrast-induced nephropathy.[81] On this regard, a small retrospective study of 37 patients with advanced kidney disease evaluated the safety of IVUS-guided zero contrast PCI without a higher rate of renal replacement therapy or MACE being reported.[82] Similar findings were described in a prospective and multicenter study,[83] and a randomized control trial.[84] Safety and feasibility have also been assessed on the OCT without a higher rate of MACE,[85] procedural complications or acute kidney injury being reported.[86] Additionally, data from 2 prospective studies suggests that contrast-less OCT would be a feasible imaging modality.[87,88]

In former studies that compared ICI modalities (table 7), similar complication rates were reported.[89-91] Van der Sijde et al. used a prospective study to compare the procedural complications of both ICIs and did not observe a higher event rate during image acquisition. Also, they did not identify any potential risk factors regarding major adverse events suggesting that both the safety and feasibility of ICIs are greater than expected and unrelated to the operator's experience.[92]

CONCLUSIONS

Beyond the limitations of coronary angiography, coronary assessment remains complex given the different forms of presentation. Therefore, the ideal imaging modality would be one that is easy to use, interpret, and safe. Intracoronary imaging guidance is widely recognized for diagnosis, PCI planning, and to guide post-PCI treatment. However, there is still room for improvement, and future randomized studies will contribute to the wider adoption of these imaging modalities in all cath labs.

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CONFLICTS OF INTEREST

None reported.

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Debate: Pharmacological or invasive therapy in acute pulmonary embolism. The clinician perspective

A debate: Terapia farmacológica o invasiva en la tromboembolia pulmonar aguda. Perspectiva del clínico

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Question: In the current management of acute pulmonary thromboembolism (PTE) to what extent is thrombolytic therapy used? and what about invasive therapy?

Answer: During the early management of PTE, we're going after the clinical stabilization of the patient and the alleviation of symptoms, the resolution of vascular obstruction, and the prevention of thrombotic recurrences. The priority of these goals depends on the severity of the patient. Most times (over 90%) these goals can be achieved using conventional anticoagulant treatment to stop the progression of the thrombus while the patient's endogenous fibrinolytic system resolves the vascular obstruction developing collateral circulation. In a minority of the patients (5% to 10%)—often those with hemodynamic instability (high-risk PTE)—aggressive therapies (of reperfusion) can be used to resuscitate the patient or accelerate the lysis of the blood clot.

When reperfusion therapy is advised for a patient with symptomatic acute PTE, the clinical practice guidelines recommend the use of full-dose systemic fibrinolysis as long as it has not been contraindicated.[1] Some of the reasons behind this recommendation are:

a) Numerous clinical trials (with over 2000 patients included) have assessed the efficacy and safety profile of systemic fibrinolysis (compared to anticoagulation) demonstrating a statistically significant drop of the mortality rate. On the other hand, to this date, only 1 clinical trial has been published assessing the efficacy and safety profile of a catheter-directed treatment (ultrasound enhancement fibrinolysis) in 59 patients with acute PTE and echocardiographic dilatation of the right ventricle.[2] The trial used an event of echocardiographic result and was not statistically powered to detect any differences regarding clinical events (mortality, thrombotic recurrences or bleeding).

b) Percutaneous (local fibrinolysis, embolectomy or a combination of different techniques) and surgical (embolectomy) therapies require infrastructure and experience before they can be applied, and most centers and clinicians who often treat these patients just don't have what it takes.

Q: Regarding invasive therapy, to what extent is it surgical or percutaneous nowadays?

A: RIETE[3] is a real-world, multicenter, and international registry—led by Dr. Manuel Monreal Bosch—of consecutive patients diagnosed with deep venous thrombosis or symptomatic acute PTE. Recent analyses indicate that only 20% of hemodynamically unstable patients with PTE receive reperfusion treatment. Most of these patients (87%) receive systemic fibrinolysis, 10% surgical embolectomy, and 3% percutaneous treatments.

Q: On cardiac catheterization, which is the clinical evidence available regarding intravascular thrombolysis? and regarding thrombus aspiration therapies?

A: The evidence available on the use of percutaneous treatments is still very weak. As I said only 1 clinical trial has been published to this date on the efficacy and safety profile of a catheter-directed therapy (ultrasound enhancement fibrinolysis) in 59 patients with acute PTE and echocardiographic dilatation of the right ventricle (see answer #1).[2] Recently, the findings of the prospective FLASH registry have been published including 250 patients treated with percutaneous thrombectomy through the FlowTriever system.[4] A total of 3 serious adverse events occurred (1.2%)—all of the severe hemorrhages—that resolved uneventfully. The 30-day all-cause mortality rate was 0.2% (1 death unrelated to PTE). Although the results of clinical registries—that are hypothesis-generating—provide useful medical information, they are no stranger to several biases

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and confounding factors, which is why they should not be used on a routine basis to assess the efficacy and safety profile of medical procedures. Currently, intermediate-high risk patients are being recruited (sample size, 406-544) with intermediate-high risk PTE for the HI-PEITHO clinical trial. These patients are being randomized to receive conventional anticoagulation or anticoagulation plus ultrasound enhancement local fibrinolysis. The efficacy primary endpoint is assessed by an independent committee 1 week after randomization includes PTE-related death, thrombotic recurrence or hemodynamic collapse.

Q: What are today's indications for invasive treatment, and how does your center work in this sense? how important is bleeding risk in the decision-making process?

A: At our center we have a PTE code for making decisions on the management of patients with severe PTE (especially high and intermediate-high risk patients). Overall, we follow the recommendations from the Spanish multidisciplinary consensus recently published in *Archivos de Bronconeumología*.[5] We use full-dose systemic fibrinolysis in patients with an indication for reperfusion and without contraindications for use. In patients with an indication for reperfusion and relative contraindications—minor—for full-dose systemic fibrinolysis we use catheter-directed percutaneous treatment (percutaneous thrombectomy, local fibrinolysis or both) or low-dose systemic fibrinolysis. In patients with symptomatic acute PTE, an indication for reperfusion treatment and absolute contraindication for full-dose systemic fibrinolysis we use surgical embolectomy or catheter-directed percutaneous treatment (percutaneous thrombectomy).

From this we can deduce that assessing the bleeding risk is key regarding decision making with reperfusion therapies. In our clinical practice we use the BACS (Bleeding, Age, Cancer, Syncope) scale to identify patients with very low risk of bleeding after the administration of full-dose systemic fibrinolysis.

Q: Can you tell us something on what's coming in this field, in particular any ongoing studies you think are relevant?

A: As I already mentioned, the HI-PEITHO clinical trial is studying the efficacy and safety profile of ultrasound enhancement local fibrinolysis in intermediate-high risk patients with PTE. Additionally, the PEITHO III clinical trial is currently randomizing intermediate-high risk patients with PTE to receive low-dose systemic fibrinolysis (r-TPA at doses of 0.6 mg/kg up to a maximum of 50 mg) or placebo plus conventional anticoagulation; the efficacy primary endpoint is the same as in the HI-PEITHO trial.

Also, clinical trials are being conducted to assess the efficacy and safety profile of other procedures (non-reperfusion therapies) in patients with severe PTE. In the DiPER clinical trial, a total of 276 patients were recruited to assess the efficacy and safety profile of diuretic therapy to treat PTE with right ventricular dysfunction.[6] The administration of a bolus of furosemide improved diuresis and did not make renal function worse. The AIR clinical trial (ClinicalTrials.gov identifier: NCT04003116) is currently studying the efficacy and safety profile of the administration of oxygen to patients with PTE and right ventricular dysfunction.

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CONFLICTS OF INTEREST

None reported.

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Debate: Pharmacological or invasive therapy in acute pulmonary embolism. The interventional cardiologist perspective

A debate: Terapia farmacológica o invasiva en la tromboembolia pulmonar aguda. Perspectiva del intervencionista

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Question: What types of catheter-based invasive approaches are available today to treat acute pulmonary thromboembolism? Please give us a brief description of the techniques used.

Answer: Catheter-directed therapy (CDT) to treat pulmonary thromboembolism falls into 3 different categories: mechanical thrombectomy, local thrombolysis, and a combination of both.

Mechanical thrombectomy (MT) consists of thrombus fragmentation, aspiration or removal. Fragmentation consists of using CDT nonspecific devices such as pig-tail catheters (forced rotation inside the thrombus) or dilatation balloons to break down and fenestrate the thrombotic occlusion to improve flow towards completely occluded regions. This technique is not very precise or reproducible so as new specific devices appear it will probably fall into oblivion. It is often used as an early facilitator of aspiration or penetration of the thrombolytic drug. Thrombus aspiration or removal consists of using hollow catheters of different calibers to aspirate the thrombus. This technique is highly dependent on the age the thrombus (more effective the more acute the case is) and the caliber of the aspiration catheter. Nonspecific material for coronary interventions (guide catheters of up to 8-Fr) or structural or peripheral heart procedures can be used (long introducers or sheaths > 8 Fr), with the advantage of its wide availability and low prices; the setback, however, is that the catheter usually becomes occluded, which is why it is often used in double 'mother-and-child' systems.

Also, there are 2 aspiration devices that have been specifically approved to treat PTE: the Indigo system (Penumbra, United States), a 115 cm 8-Fr angled tipped catheter with an olive-shaped burr to facilitate the entry and advancement of the thrombus, which will soon will be available in 12-Fr,[1] and the FlowTriever system (Inari Medical, United States), specifically designed for PTE aspiration, and including a 24-Fr catheter, a 16-Fr guide catheter extension system, and a nitinol disc-shaped thrombus retriever. Its main advantage is that its outside connections are oversized at larger diameters compared to the Luer medical device standard.[2] The Nautilus—a 10-Fr catheter system from iVascular, Spain—is currently in the pipeline. Other peripheral thrombectomy non-specific PTE devices like AngioVac (Angiodynamics, United States) or AngioJet (Boston Scientific, United States) are less common since more complications have been reported.

Compared to local thrombolysis, the advantages of MT by strong aspiration are that it can facilitate the patients' rapid hemodynamic improvement, also ending in a single procedure that can prevent the use of fibrinolytic agents when used as monotherapy.

Local thrombolysis (LT) consists of introducing 1 or 2 usually multiperforated catheters into the pulmonary artery and in the intra-thrombus position through which 1 variable dose (around 25% of the systemic dose) of a fibrinolytic agent (often rt-PA) is introduced for a certain time (6 h to 24 h) with or without an initial bolus. Its main advantages are that it is easy to use, the possibility of using peripheral vascular access (antecubital vein or veins), and its low cost (a pig-tail catheter can be used). There is an ultrasound-facilitated LT (UFLT) device manufactured by EKOS (Boston Scientific, United States) that comes with a catheter with multiple ultrasound pulse generators to facilitate the fragmentation the fibrin threads while improving drug penetration into the thrombus.

Finally, the combination of MT[1] plus LT is based on the principle that MT can act upon the most proximal segments of pulmonary and lobar branches while LT can later act upon lower caliber branches in the entire pulmonary tree.

Q.: What is the clinical evidence available on intravascular thrombolysis and thrombus aspiration therapies?

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A.: Most historic evidence on CDT comes from registries and case series. However, over the last few years, the development of specific devices has produced new and high-quality pieces of evidence. There are still gaps of knowledge on the use of CDT to treat high-risk PTE (scarce and heterogeneous data), and comparative data on the different CDT techniques available.

Several registries prior to the development of specific devices like the PERFECT showed, for the very first time, better clinical outcomes with low rates of bleeding too. A meta-analysis of multiple trials on CDT conducted over the last decade provides aggregate data of 1168 patients showing overall rates of procedural success (95% confidence interval [95%CI], 72.5-89.1%), 30-day mortality (95%CI, 3.2-14.0%), and major bleeding (95%CI, 1.0-15.3%) of 81.3%, 8.0%, and 6.7%, respectively, in high-risk PTE. In intermediate-risk PTE, the rates of procedural success (95%CI, 95.3-99.1%), 30-day mortality (95%CI, 0%-0.5%), and major bleeding (95%CI, 0.3-2.8%) were 97.5%, 0% and > 1.4%, respectively.[4]

MT (aspiration) with the Indigo device was included in the single arm EXTRACT-PE clinical trial[5] of 119 patients with intermediate-risk PTE. The efficacy (a 0.43 reduction in the right ventricle/left ventricle (RV/LV) ratio at 48 hours) and safety profile (rates of major bleeding, and intracranial hemorrhage of 1.7%, and 0%, respectively) was confirmed in a protocol with almost non-use of LT (98.3%). The FlowTriever device was used to conduct the FLARE trial[6] of 106 intermediate-risk patients treated without thrombolytic drugs. The device proved its efficacy (a reduction of 0.38 in the RV/LV ratio at 48 hours) and safety profile (rates of major adverse events, major bleeding, and intracranial hemorrhage of 3.8%, 1%, and 0%, respectively). These results were confirmed in the first 250 patients of the FLASH registry[7] with a rate of major adverse events of 1.2% (3 hemorrhages, none of them intracranial).

The EKOS device was studied in the ULTIMA randomized clinical trial[8] of 59 patients with acute intermediate-risk PTE and a RV/LV ratio > 1 who were randomized to receive fixed doses of rt-PA (10 mg or 20 mg in bilaterals) in UFLT. It confirmed further reductions of the RV/LV ratio at 24 hours compared to standard therapy with heparin (mean reduction of 0.30 ± 0.20 vs 0.03 ± 0.16 (P < .001). The SEATTLE II registry[9] of 150 patients most of them with submassive PTE demonstrated a similar efficacy profile with reasonable safety data (rates of 30-day major bleeding and intracranial hemorrhage of 10% and 0%, respectively).

The only comparative randomized clinical trial published to this date of 2 CDT strategies is the SUNSET sPE[10] that found no differences in the radiologic thrombus load reduction with UFLT or simple LT with similar doses of thrombolytic drugs.

Q.: What are today's indications for invasive treatment and how does the routine clinical practice at your center look like?

A.: In the clinical practice guidelines published by the European Society of Cardiology in 2019, CDT is given an indication IIa, level of evidence C, for patients with high-risk PTE in whom systemic thrombolysis (ST) is contraindicated or in cases when it has failed. Also, these guidelines rank CDT as an alternative to ST as a bailout therapy in patients initially treated with anticoagulation (often intermediate-high-risk PTE) with hemodynamic impairment (indication IIa, level of evidence C).

The alternative to CDT with a similar indication but a higher level of recommendation (indication I – level of evidence C) is surgical embolectomy. However, the availability of surgical teams ready to operate on these patients is very limited, as well as evidence compared to CDT.

In some centers with PTE response teams, CDT is used to treat intermediate-risk PTE (often intermediate-high-risk PTE) as coadjuvant therapy to anticoagulation. Still, there is not such a thing as a formal indication for ST. This strategy is based on studies that show that surrogate parameters like right ventricular function improve faster. However, there is no solid evidence regarding improved clinical parameters compared to anticoagulation therapy only.

Added to the indications approved in the European clinical guidelines, at our center, CDT is used in patients with an indication for LT and high risk of bleeding. Evidence shows that 30% to 50% of the patients with an indication for ST won't receive this therapy afraid that complications will arise (basically severe or intracranial hemorrhages). Factors associated with high risk of bleeding in ST studies are active neoplasms, age ≥ 75 years, low weight (< 50 kg), acute kidney injury (glomerular filtration rate < 30) or active anticoagulation. These patients can benefit from CDT thanks to their lower risk of bleeding—particularly intracranial—based on data of indirect comparisons with ST.

Q.: Please tell us which trials are currently in the pipeline assessing these invasive strategies.

A.: Scientific societies have been developing European multicenter registries like EuroPE-CDT and NCT04037423 and, at national level, the TROMPA registry that is backed by the Interventional Cardiology Association of the Spanish Society of Cardiology.[11]

Several studies have already been started by device manufactures and are currently in the pipeline. Regarding the MT strategy, the Indigo device is being studied to collect efficacy, safety, and functional recovery data from 600 patients selected in the already started STRIKE-PE registry (NCT04798261). There is also an active registry currently recruiting patients to test the FlowTriever device that will include 1300 participants (FLASH, NCT03761173). Also, the upcoming PEERLESS clinical trial (NCT05111613) will recruit 550 patients with PTE and intermediate-high risk who will be randomized to receive the FlowTriever aspiration system or CDT based on the local routine clinical practice with other devices available in the market. The study primary endpoint will be death, intracranial hemorrhage, major bleeding, clinical impairment or length of stay at an intensive care unit.

The most relevant studies that are being conducted on the EKOS device are the KNOCOUT PE registry (NCT03426124)—in a phase of active recruitment—that will include up to 1500 patients, and the HI-PEITHO trial (NCT04790370). The latter is an international, prospective, multicenter clinical trial that will be comparing anticoagulation vs anticoagulation plus UFLT. The study primary endpoint is a composite of PTE-related mortality, cardiorespiratory decompensation or nonfatal PTE recurrence at 7 days. We should also mention the NCT03581877 trial (Peripheral systemic thrombolysis vs catheter-directed thrombolysis for submassive PE) that is comparing UFLT vs the same dose (24 mg) of rt-PA administered via peripheral vein for 12 hours.

Today's challenges regarding research are to define procedural success, standardize the endpoints of clinical trials, and establish what intermediate-risk patients with PTE may benefit the most from CDT compared to standard therapy.

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CONFLICTS OF INTEREST

None reported.

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Technological advances in the management of cardiovascular diseases: perspective of physicians and administrators

Avances tecnológicos en el tratamiento de las enfermedades cardiovasculares: perspectiva de médicos y administradores

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To the Editor,

New technologies have improved the effectiveness of treatments for cardiovascular diseases, yet these technologies pose poorly explored challenges. Therefore, a study was conducted in Spain to find out about the perspective of doctors and administrators on the implications of technology in the management of coronary artery disease and peripheral arterial disease.

The insights and perspectives of doctors and administrators were obtained using the Delphi method following the RAND/UCLA Appropriateness Method (RUAM).[1] A scientific committee including 6 cardiologists, 1 vascular surgeon, and 1 interventional radiologist selected the panel of doctors (16 cardiologists, 3 endocrinologists, 3 vascular surgeons, 1 internist, and 1 surgeon specialized in diabetic foot disease), and administrators (12 administrators from both the public and private sectors) (annex 1 of the supplementary data). The doctors' questionnaire had 112 items and the administrators' one 79 (74 items were common to both panels). The panelists scored the relevance of each item on a scale from 1 (irrelevant) to 9 (maximum relevance). «Agreement» was defined as less than a third of the panelists giving scores from 1 to 3 to a given item, and less than a third gave scores from 7 to 9. «Low relevance» items were those whose median scores were < 4, «high relevance» items with median scores ≥ 7, and «medium relevance» items with median scores ≥ 4 and < 7.[1] Concordance between doctors and administrators in the 74 items studied was measured using the kappa index (κ).[2] Figure 1 shows the study diagram.

Some of the «high relevance» items scored by doctors and administrators had to do with technology improving patient care, the identification of risk factors, the ability to treat patients from the start with the corresponding reduction of readmissions and costs, and with the ability to achieve more accurate diagnoses. Doctors believe that the best measure to identify patients at risk is to improve relations with primary care. Reduced time spent with each patient, the scarcity of resources to make patients change their lifestyles, and the lack of facilities available for rehabilitation purposes are significant limitations for doctors. Doctors and administrators believe that within the next few years better solutions will come along for the diagnosis and treatment of cardiovascular diseases. However, some of the barriers they refer to are the difficulties referring patients for early interventional procedures or the scarcity of personnel for the early management of patients (tables 1-23 of the supplementary data).

Compared to administrators, doctors insist that technology requires training, which requires time they don't have (figure 2A). Administrators, however, insist that technology allows the proper sizing of the healthcare personnel (figure 2B; tables 24-32 of the supplementary data). The differences found are indicative of a moderate level of agreement between doctors and administrators ($\kappa = 0.408$)[2] (table 1).

These findings suggest that both doctors and administrators believe that technological advances have improved patient care. However, they also identify certain barriers. The moderate level of agreement between doctors and administrators is understandable, but the success of each center largely depends on this level of agreement between the two. For these reasons, different strategies have been proposed for doctors and administrators to come closer in a coherent and collaborative way.[3]

These strategies and those aimed at eliminating the barriers and limitations found are particularly relevant in interventional cardiology. Recommendations on requirements and equipment in interventional cardiology recently published in Spain are some of these strategies.[4] These recommendations establish the structural and functional requirements of each center regarding human resources, training, competences, and material resources. Also, they develop

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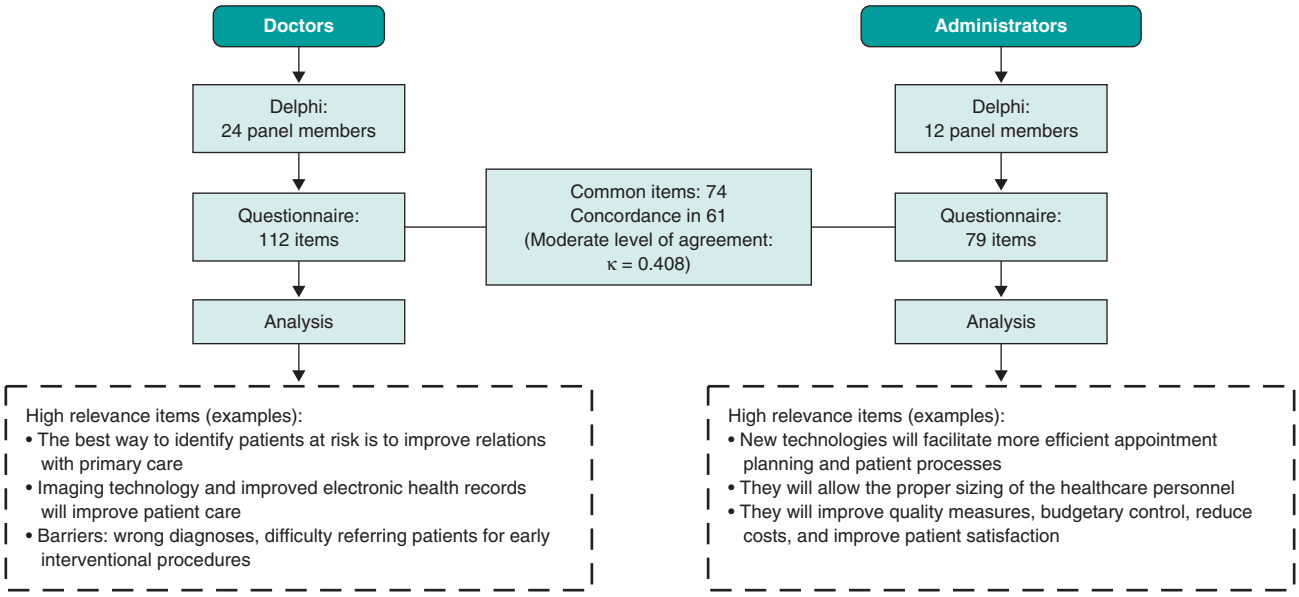

Figure 1. Summary of the study diagram.

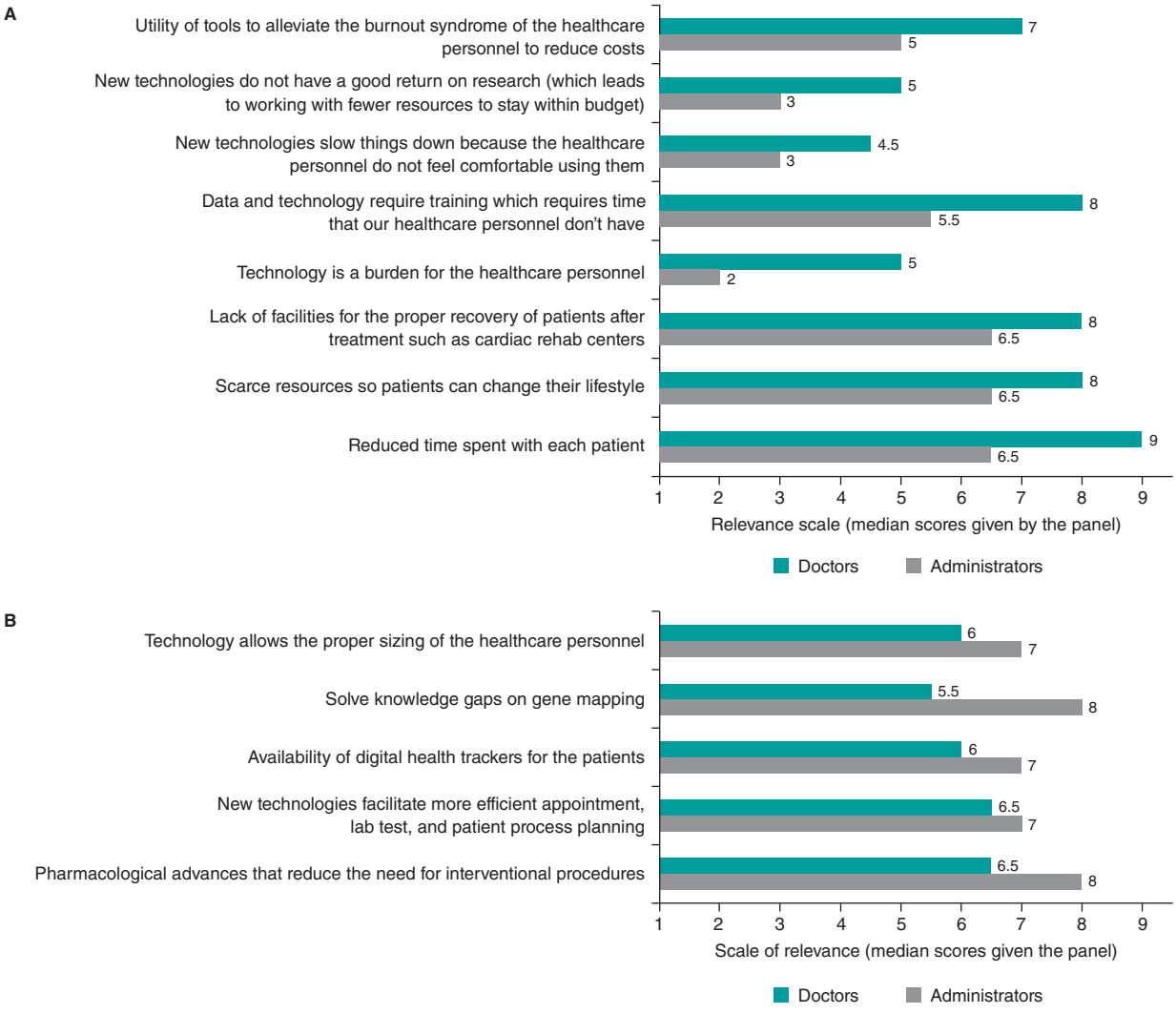

Figure 2. **A:** items scored with the highest category of relevance by doctors vs administrators. **B:** items scored with the highest category of relevance by administrators vs doctors.

Table 1. Concordance in the category of relevance between the panel of doctors and the panel of administrators

			Panel of administrators			
			Number of items scored with relevance			
		Relevance	High	Medium	Low	Overall
Panel of doctors	Number of items scored with relevance	High	56	5	0	61
		Medium	5	5	3	13
		Low	0	0	0	0
		Overall	61	10	3	74

κ index, 0.408 (moderate level of agreement).

the model of satellite or supervised cath labs as an efficient alternative for lower level hospitals.[4] The implementation of these strategies can improve the quality, efficiency, and equal access to interventional cardiology in Spain.

Evidence on the validity and reproducibility of the Delphi format used in our study (RUAM)[5] plus the fact that it is the method used to develop appropriate use criteria for coronary revascularization[6] suggests that the findings of this study represent reasonably well the perspectives of doctors and administrators on the implications of technology in the management of cardiovascular diseases, and specifically interventional cardiology in Spain.

FUNDING

This study was funded by Abbott Vascular that did not participate in the design of the study or in the processes of data mining, handling, analysis or interpretation.

AUTHORS' CONTRIBUTIONS

All authors contributed to the drafting of this manuscript.

CONFLICTS OF INTEREST

None whatsoever.

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Also, the authors wish to thank the members from the panels of expert doctors and administrators for their kind participation in the Delphi method, and collaboration in the study since their answers to the questionnaires allowed us to conduct this project. The list of members from each panel of experts is shown in annex 2 of the supplementary data.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000271.

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Multi-state models for survival analysis in cardiology: an alternative to composite endpoints

Modelos multiestado para análisis de supervivencia en cardiología: una alternativa a los composite endpoints

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To the Editor,

The main objective of longitudinal studies conducted in cardiology is often time-to-adverse events (AE) to identify possible risk factors or the efficacy of treatment. Traditionally, composite endpoints have been used, often major adverse cardiovascular events (MACE) in their different versions. Their great advantage is to increase the statistical power of the studies and simplify analysis. However, they complicate the interpretation of results[1] and have other limitations like giving the same weight to every event or using the information of the index event only. Therefore, over the last few years, concern has been growing on whether these methods should be updated.[2]

The problem with data analysis in longitudinal studies with several AE of interest can be approached using multi-state models in a natural way since they create models with a complex structure of relations during the appearance of different events and account for all the data available from every patient. Also, they provide information on time expected and probability of appearance of each AE, and establish their interdependence with risk factors or with the characteristics of treatment.[3] The main advantages of multi-state models compared to other models commonly used are shown on table 1.

We propose a multi-state model as an alternative to MACE to conduct longitudinal studies in interventional cardiology. To demonstrate the utility of the model, data from the SYNERGY ACS trial[4] of 1008 patients with acute coronary syndrome treated with percutaneous coronary intervention between 2013 and 2019 were analyzed. The study was approved by the local ethics committee. Since it was a retrospective study with data anonymization, no informed consent was required from the patients. As an alternative to MACE, we propose a multi-state model called disability model. In this model, patients are recruited while on treatment (state 1), when they have an infarction or receive a new revascularization (state 2) o when they die (state 3) (figure 1). In this model different factors for each transition among the 3 states can be included, as well as the risk of death before and after the occurrence of AE after treatment. A nonparametric survival model was considered for each

Table 1. Comparison between the most commonly used models regarding survival data in interventional cardiology and the multi-state model proposed

	Composite endpoint (non-longitudinal)[a]	Composite endpoint (longitudinal)[b]	Competitive risks[c]	Multi-state
Use of index event	Yes	Yes	Yes	Yes
Use of time-to event	No	Yes	Yes	Yes
Includes all the events	No	No	Yes	Yes
It can include covariates (explanatory)	No	Yes	Yes	Yes
Different risk factors for every (type of) event	No	No	Yes	Yes
Based on the sequential history of events	No	No	No	Yes
Assumes proportional risks	No	Yes	Yes	No
Nonparametric model	Yes	No	No	Yes

[a] Comparison of the number of MACE between the groups.
[b] Study of the risk of MACE, often using Cox proportional hazard model.
[c] Risk analysis of an event in the presence of other events often the Fine & Grey model.

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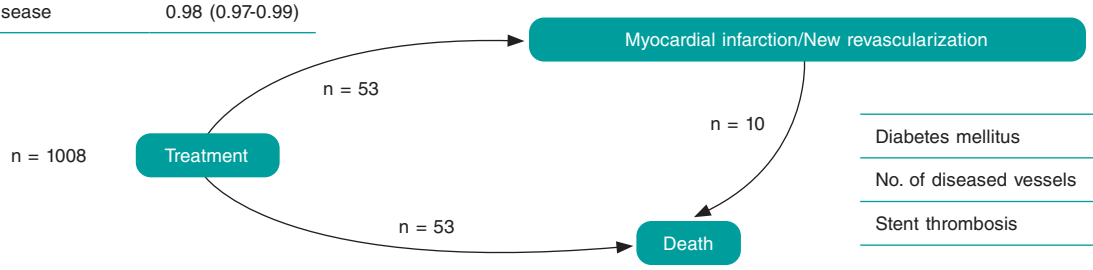
	HR (95%CI)
Diabetes mellitus	1.67 (1.11-2.48)
No. of diseased vessels	1.65 (1.32-2.09)
Kidney disease	0.98 (0.97-0.99)



	HR (95%CI)
Diabetes mellitus	1.67 (1.11-2.48)
No. of diseased vessels	1.65 (1.32-2.09)
Stent thrombosis	31.4 (16.6-59.5)

	HR (95%CI)
Age	1.04 (1.02-1.06)
Left ventricular ejection fraction	0.97 (0.95-0.98)
Previous percutaneous coronary intervention	2.11 (1.37-3.24)

Figure 1. Structure of the states of the model proposed. The numbers shown by the transitions represent the number of patients who suffered the corresponding adverse event starting at 1008 patients. Tables show the covariates selected for the survival model of each transition among the 3 states with their corresponding hazard ratios (HR), and the associated 95% confidence interval (95%CI).

Type of patients	Diabetes mellitus	Age (mean)	Stent thrombosis	Left ventricular ejection fraction	Previous percutaneous coronary intervention	No. of diseased vessels	Glomerular filtration rate (mean)
Low risk	No	54	No	65	No	1	100
High risk	Yes	79	Yes	45	Yes	3	55

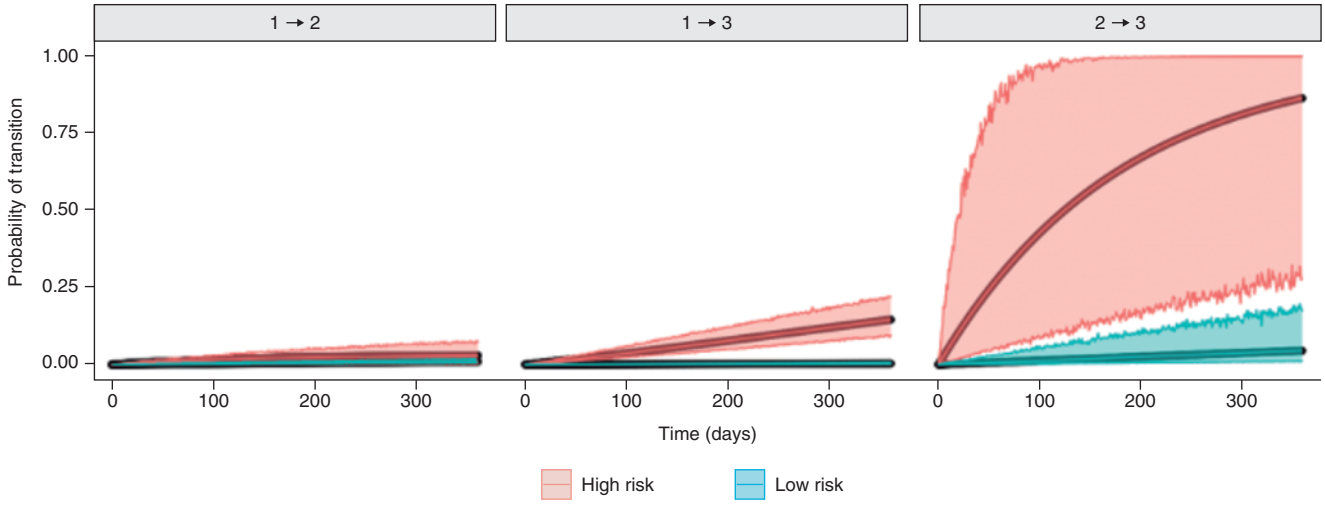


Figure 2. The table shows patients' characteristics (defined as high- and low-risk patients). Figures show the probability of occurrence of a single adverse event associated with each transition within the first year after percutaneous coronary intervention for low-risk (green) and high-risk (red) patients. The shadow region represents uncertainty in the estimate. In this graph we can see that the prognosis of high-risk patients is worse compared to low-risk patients, as well as the uncertainty associated with fewer data in the transition from state 2 to state 3 (from infarction/revascularization to death). This type of prognosis could be made for the specific characteristics of every patient.

transition among states using the Akaike information criterion, and clinical assessment for covariate selection. The model was adjusted using the MM spackage of R.[5]

The median follow-up was 856.52 days (Q_1 = 546, Q_3 = 1115). The most common AE is death (6.25%), revascularization (4.76%) followed by infarction (3.08%). The adjusted model shows that the factors associated with infarction or revascularization are diabetes, kidney disease, and the number of diseased vessels. On the other hand, age, the left ventricular ejection fraction, and previous percutaneous coronary intervention are associated with death (figure 1). To illustrate the utility of the model we defined 2 types of patients

(high and low risk) including the chances of moving from one state to the next within the first year after treatment (figure 2).

Results show a great potential of multi-state models in the analysis of longitudinal studies in interventional cardiology. This method allows us to use information on all AE occurred in all the patients while separating the contribution of risk factors for each type of AE. Also, a model of survival can be drawn after the occurrence of a single AE after treatment. This model is predictive regarding the probability and time expected until the occurrence of an AE in every patient (including the associated uncertainty as well) based on his characteristics, treatment, and disease progression, and provides individual estimates.

Finally, the multi-state model proposed has been successfully used in other fields of medicine. However, it has some limitations. In the first place, we need to see if it satisfies the «Markov property», that is, that the probability of moving from state 2 to state 3 do not depend on the time elapsed until reaching state 2 to assume such probability. If this property is not satisfied, the implementation of the model becomes more complicated. Secondly, although there is software available to implement it, it is not easy to use. In the third place, the model has all the limitations of nonparametric models. Future versions of this model will include Bayesian inference with parametric models and more sophisticated state structures.[6]

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AUTHORS' CONTRIBUTIONS

All the authors contributed to the design of the multi-state model. J. M. de la Torre-Hernández provided data. N. Montoya, and A. Quirós analyzed data and implemented the model. N. Montoya, A. Quirós, and A. Pérez de Prado drafted this manuscript, and all the authors contributed substantially to the manuscript process of revision.

CONFLICTS OF INTEREST

J. M. de la Torre-Hernández is editor-in-chief, and A. Pérez de Prado is associate editor of *REC: Interventional Cardiology;* the journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

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Drug-eluting balloon angioplasty improves the distal run-off in retrograde chronic total occlusion revascularization

La angioplastia con balón liberador de fármaco mejora el flujo distal en la revascularización de oclusiones crónicas por vía retrógrada

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To the Editor,

This is the case of a 72-year-old male examined due to exertional angina, and severe inferior wall ischemia through a single-photon emission computed tomography with Tc-99. After obtaining the patient's written informed consent he was referred for a coronary angiography that confirmed the chronic total coronary occlusion (CTO) of the proximal right coronary artery (RCA) (figure 1A) with a J-CTO score of 3 (blunt entry shape, lesion > 20 mm, and calcification), and the presence of septal collaterals from the left anterior descending coronary artery (figure 1B, video 1 of the supplementary data). Initial antegrade approach was planned that quickly had to be changed for the retrograde approach due to the unfavorable characteristics of the lesion.

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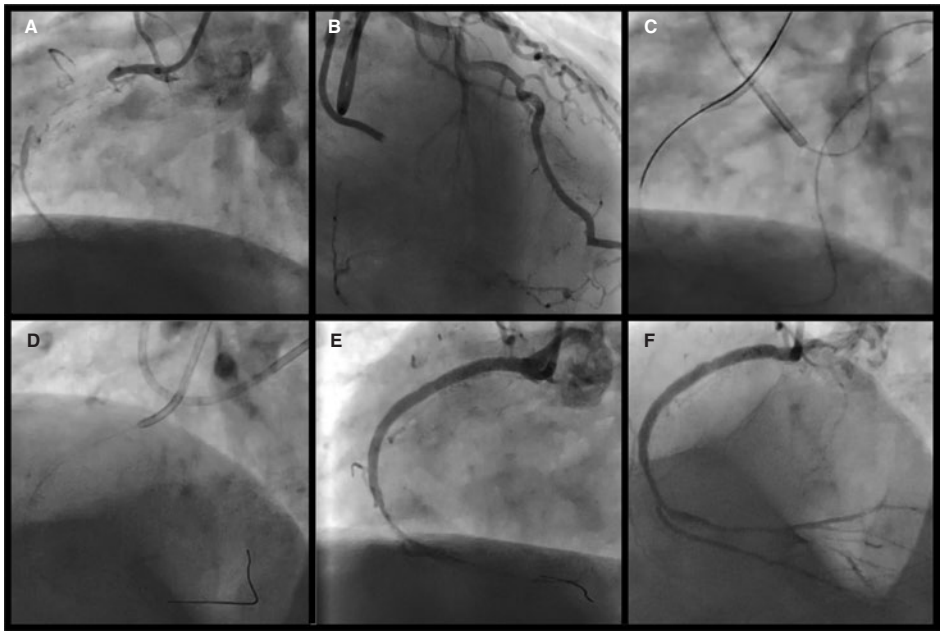

Figure 1. **A:** total occlusion of proximal RCA. **B:** septal collaterals from the left anterior descending coronary artery. **C:** externalized retrograde wire from the septal collateral crossing the right coronary artery occlusion. **D:** antegrade wiring with the help of a microcatheter placed in the distal right coronary artery. **E:** angiographic result after occlusion predilatation and stenting with TIMI grade-1 flow. **F:** after drug-eluting balloon, TIMI grade-3 flow is achieved with a diseased distal vessel.

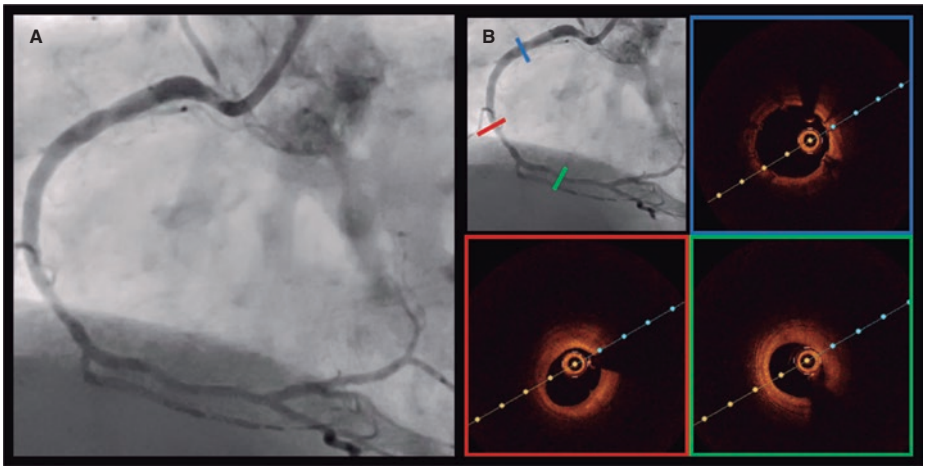

Figure 2. **A:** excellent angiographic evolution of right coronary artery at the 6-month follow-up. **B:** excellent stent apposition and distal vessel improvement according to the optical coherence tomography.

After surfing across the septal collateral channels, the distal cap of the occlusion was crossed using a Corsair Pro XS microcatheter (Asahi Intecc, Japan) loaded with a Gaia Third wire (Asahi Intecc, Japan). A RG3 wire (figure 1C) was externalized followed by the antegrade advancement of the microcatheter (figure 1D). Finally, predilatation of the mid and proximal segments of the RCA plus 3 SYNERGY drug-eluting stents (DES) (Boston Scientific, United States) were deployed (figure 1D). The severe and diffuse stenosis of the distal RCA provided a poor run-off with a Thrombolysis in Myocardial Infarction (TIMI) grade-1 flow (figure 1E).

The vessel characteristics ruled out further DES implantation to avoid perforation, and minimize the risk of stent thrombosis. For this reason, a decision was made to treat the distal bed with prolonged inflations of drug-eluting balloons (DEB) (SeQuent Please NEO 2.5 mm × 30 mm, and 2 mm × 30 mm, Braun Melsungen, AG Vascular Systems, Germany) to improve the run-off. TIMI grade-3 flow was confirmed at the end of the procedure (figure 1F, video 2 of the supplementary data).

The patient was scheduled for a deferred coronary angiography to see the evolution of the distal bed. After 6 months, the study shows the patency of the stents, and a significant improvement of the distal vessel with TIMI grade-3 flow (figure 2A, video 3 of the supplementary data). An optical coherence tomography (Abbott, United States) confirmed the excellent results of the distal RCA, and the correct apposition and expansion of the DES (figure 2B, video 4 of the supplementary data).

Only a few studies and case reports have analyzed DEBs in the CTO and complex PCI setting as an alternative to stent implantation.[1-3] Köln et al. used a DEB as the only strategy after successful CTO recanalization with rates of procedural success and re-occlusion of 79.4% and 7.4%, respectively, at the follow-up.[1] Our case emphasizes the feasibility of a hybrid approach by treating the occlusion zone with a DES, and the distal bed with a DEB to avoid further stenting. With this approach, the operator can reduce small caliber, and total stent length both associated with restenosis and worse clinical outcomes. The BASKET-SMALL 2 randomized trial showed that the DEB was non-inferior to the DES regarding major adverse cardiovascular events in small-vessel native coronary artery disease. In addition, the PICCOLETO II randomized trial showed lower in-lesion late lumen loss using a novel DEB.[4,5]

We should mention that in the CTO setting, the distal bed can increase its size just by reestablishing blood flow. Yet, this is another reason to refrain from DES implantation to avoid malapposition by selecting inadequate diameters.

This case confirms the feasibility of treating small-vessel native coronary artery disease in CTO cases with DEBs to improve the distal bed, avoid unnecessary stenting, and minimize the risk of stent thrombosis/restenosis.

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AUTHORS' CONTRIBUTIONS

Conceptualization: I. Pascual, and M. Almendarez. Writing: M. Almendarez, and I. Pascual. Image and video editing: A. Alperi, and R. Álvarez-Velasco. Revision and editing of the final draft: C. Moris, P. Avanzas. I. Pascual, and M. Almendarez contributed equally to the first authorship.

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000280.

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Clinical case

Percutaneous closure of left ventricular pseudoaneurysm

Cierre percutáneo de seudoaneurisma ventricular izquierdo

Lola Gutiérrez Alonso,[a,*] Dabit Arzamendi Aizpurua,[a] Xavier Millán Álvarez,[a] Lluis Asmarats Serra,[a] Mario Torres Sanabria,[a] and Chi Hion Li[b]

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CASE PRESENTATION

This is the case of a 72-year-old woman with a past medical history of permanent atrial fibrillation treated with acenocoumarol, and rheumatic valvular heart disease that appears as a double severe mitral lesion and severe tricuspid regurgitation due to annular dilatation with dyspnea-like symptoms. The cardiologic examination completed before planning valve replacement surgery discarded the presence of coronary lesions. The case was presented to the medical-surgical committee and approved for mitral valve replacement, and tricuspid annuloplasty.

Procedure was performed electively with a 25 mm On-X 25 prosthetic mechanical mitral valve (Life Technologies, GA, United States) followed by tricuspid annuloplasty with annular prosthesis. After weaning from extracorporeal support and circulation machine, a hemorrhage was revealed due to the rupture of the atrioventricular groove in the vicinity of left atrial appendage that was repaired with suture reinforcement on the pericardium and Teflon until achieving hemostasis. In this context, the patient showed hemodynamic impairment, and ventricular function deterioration that required escalating the inotropic support, and intra-aortic balloon pump implantation.

The postoperative period at the critical care unit was torpid. Five days after surgery, the patient broke a fever in the context of ventilator-associated pneumonia. That is why a thoracic computed tomography scan was performed that revealed the presence of a tear—7 mm of maximum diameter—in the left ventricular lateral wall with formation of a large intrapericardial pseudoaneurysm of 8 cm of maximum diameter (figure 1) (video 1 from the supplementary data).

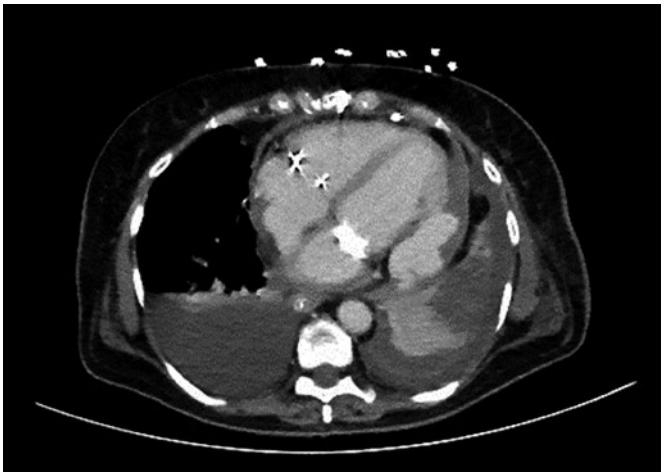

Figure 1. Changes after heart surgery: mitral valve replacement and tricuspid annuloplasty. Tear of 7 mm of maximum diameter in the left ventricular lateral wall with formation of a large cavity/intrapericardial pseudoaneurysm (asterisk) of 8 cm of maximum diameter associated with hemopericardium.

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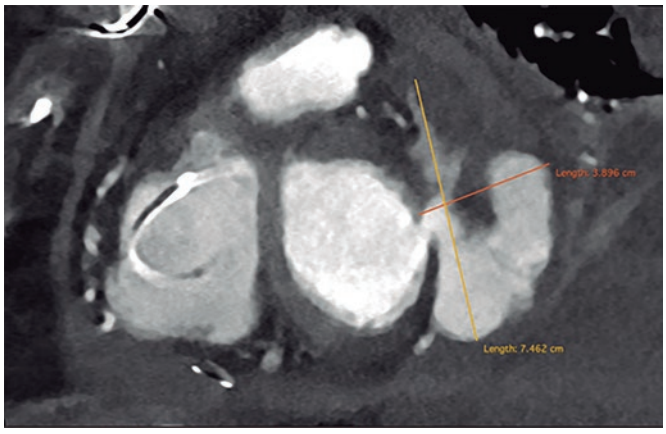

Figure 2. Cardiac computed tomography. Details of the defect. Maximum (yellow) and minimum (orange) diameters of the pseudoaneurysm.

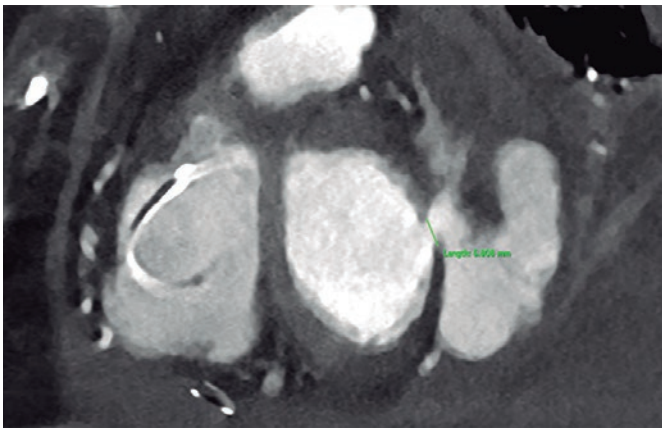

Figure 3. Cardiac computed tomography. Detail of the entry orifice of the defect and its diameter.

The cardiac computed tomography confirmed the existence of a large defect with a maximum diameter of 7.46 cm, and a minimum diameter of 3.89 cm (figure 2). The entry orifice of the defect—of almost circular morphology—had a maximum diameter of 7.45 mm and a minimum diameter of 6.8 mm (figure 3). The defect was found in the left ventricular lateral wall underneath the mitral valvular projection (video 2 from the supplementary data).

The patient's written and verbal informed consents were obtained before publishing this case report.

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AUTHORS' CONTRIBUTIONS

L. Gutiérrez Alonso drafted the manuscript and was directly involved in patient care. D. Arzamendi, X. Millán, L. Asmarats, and M. Torres were directly involved in patient care. D. Arzamendi supervised the draft of the manuscript. Chi Hion Li was directly involved in the case and provided the images.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

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Percutaneous closure of left ventricular pseudoaneurysm. How would I approach it?

Cierre percutáneo de seudoaneurisma ventricular izquierdo. ¿Cómo lo haría?

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HOW WOULD I APPROACH IT?

Authors present an exceptional case of early formation of 1 ventricular pseudoaneurysm after surgical mitral valve replacement complicated with the rupture of the atrioventricular groove that was repaired surgically. The excellent images provided by the computed tomography scan reveal a large multilobulated irregular pseudoaneurysm with an anatomy eligible for percutaneous treatment.

For quite a few years, the closure of pseudoaneurysms has been described in the medical literature as case reports and case series with satisfactory results,[1] which is why it is currently considered a therapeutic alternative to surgery.

In this case, surgery does not seem like a good option due to the patient's critical condition, and the technical complexity involved in the repair, which is suggestive of percutaneous closure through occluder device implantation. The images provided reveal characteristics associated with location and morphology favorable to the use of percutaneous treatment: saccular morphology of the pseudoaneurysm, circular neck, and relatively small size (< 10 mm), apparently demarcated borders (muscular) in the defect, and distance from mitral annulus without the possibility of a compromised prosthetic function.

The excellent images provided by the computed tomography scan allow us to plan the procedure and select the type and size of the device that should be used. Since the transesophageal echocardiogram can lose quality due to the interference from the mechanical mitral valve and in an attempt to prevent the morbidity associated with anesthesia, I would perform the procedure guided by angiography and transthoracic echocardiography only.

Theoretically speaking, the closure of a left ventricular pseudoaneurysm can be performed through 3 different accesses: transseptal, transapical, and aortic retrograde. In this case, transseptal access is not viable due to the presence of a mechanical mitral valve. Transapical access offers the advantages of an easy access to the defect thanks to its proximity and the possibility of using large caliber introducer sheaths when performed surgically. However, it is a more traumatic access that I would spare for cases with mechanical aortic valves involved or when other accesses have already failed. Aortic retrograde access—often via femoral artery but equally feasible from a different arterial access—seems, in my opinion, like the most appealing of all as first-line therapy considering the patient's status and the location of the defect, which anticipates proper coaxiality in the delivery system. One additional access that has been described is to directly puncture the pseudoaneurysm. But, in this case, it was not a viable option either given the location of the pseudoaneurysm.

Via retrograde access, one of the sensitive parts of the procedure is accessing the cavity and introducing a delivery catheter of the caliber required. Although multipurpose catheters have traditionally been used, in this case, to access the cavity, the use of coronary catheters with JL, AL or extra-backup L tips can help in our way towards the lateral wall. Guide catheter extension systems are also useful. Although the ideal thing to do would be to place a high-support guidewire once inside the defect, there is this risk of neck laceration and rupture of the pseudoaneurysm. Although the use of a 0.35 in standard Teflon-coated guidewire is feasible, I believe that the use of a 260 cm 0.35 in hydrophilic guidewire could provide greater support because given the size of the aneurysm several loops inside of it would be possible. Afterwards, I would carefully advance the delivery system until it reaches the cavity. If it were a straight introducer, I would pre-form the tip with a Mullins-type curve. Given the deep location of the defect, and depending on the size of the patient, the usual delivery catheters via femoral access can sometimes be a little small. We should make sure we have longer introducer systems (≥ 90 cm) of a caliber that matches the device we're going to use. For the lack of it, an alternative is to use brachial access to gain over 20 cm of catheter length.

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On the occluder device that should be used there are different options available, but specific designs for ventricular septal defects (VSD) and interatrial shunts (IAS) seem like the most suitable ones. The standard device used to close the ductus arteriosus does not have a double retention disc, which does not seem like a good option. «Vascular plug» devices provide good occlusion capabilities, but they require significant oversizing to have enough radial strength. Both VSD and IAS devices provide proper and balanced radial strength, and anatomic conformability of the self-centering waist. Also, the retention discs are large too. I would personally use a muscular VSD occluder device because it comes with symmetrical retention discs and provides great radial strength, particularly in small and intermediate sizes. Regarding size I would choose a slightly oversized device (≈20%), which is why a muscular VSD device of 10 mm or 12 mm would be enough and compatible with 7-Fr or 8-Fr introducer sheaths.

FUNDING

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CONFLICTS OF INTEREST

None reported.

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Percutaneous closure of left ventricular pseudoaneurysm. Case resolution

Cierre percutáneo de seudoaneurisma ventricular Izquierdo. Resolución

Lola Gutiérrez Alonso,[a,*] Dabit Arzamendi Aizpurua,[a] Xavier Millán Álvarez,[a] Lluis Asmarats Serra,[a] Mario Torres Sanabria,[a] and Chi Hion Li[b]

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CASE RESOLUTION

The case was presented in the medical-surgical session and given the high risk involved the percutaneous closure of the pseudoaneurysm was decided.[1,2]

The procedure was performed under general anesthesia and guided by transesophageal echocardiography and fluoroscopic fusion imaging.

Since the patient carried a prosthetic mitral valve, a retrograde approach strategy was decided via right femoral arterial access (6-Fr).

With help from an AL 1 catheter (Cordis Corporation, FL, United States) and a Terumo straight guidewire (Terumo Medical Corporation, NJ, United States), the native aortic valve was crossed, and the AL 1 catheter was advanced towards the left ventricle. A Pigtail catheter was used to perform a left ventriculography (Cordis Corporation, FL, United States) that revealed a cavity in relation to the left ventricle

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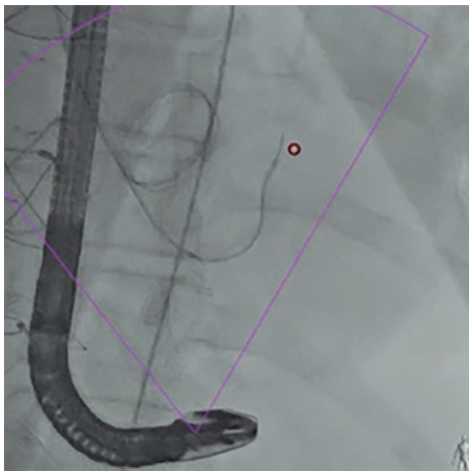

Figure 1. Location of the origin of pseudoaneurysm through fluoroscopic fusion imaging (red circumference).

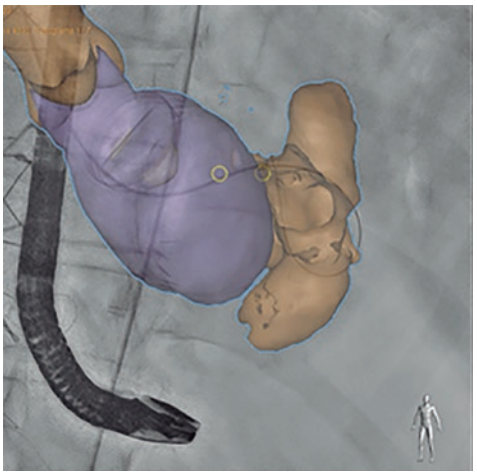

Figure 2. Fusion imaging (fluoroscopy, transesophageal echocardiography, and computed tomography) facilitating the location of the origin of the defect (yellow circumference).

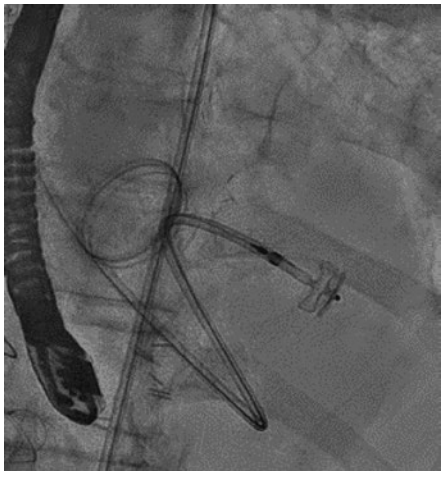

Figure 3. Delivery sheath. The Amplazter device can be seen in the distal border.

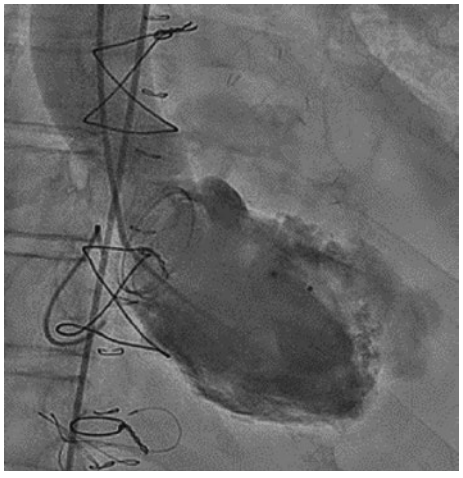

Figure 4. Left ventriculography showing the Amplatzer device in the left ventricular lateral wall with little passage of contrast towards the pseudoaneurysm (video 4 of the supplementary data).

with the passing of contrast towards such cavity (video 1 of the supplementary data). After several attempts trying to place the catheter at the origin of the defect, the pseudoaneurysm cavity was finally crossed using a curved Terumo guidewire. At this point, the information provided by fluoroscopic fusion imaging was crucial because it revealed the origin of the defect and facilitated guidewire crossing towards the cavity (figure 1 and figure 2).

The AL 1 catheter was exchanged for a 4-Fr straight tip catheter (Teleflex interventional, United States), and then for a XtraStiff guidewire (Cook Medical IN, United States) on which a 6-Fr delivery sheath was advanced (figure 3).

Selecting the right device was key for the procedure. Considering the anatomical characteristics of the defect and the risk of interference from the devices commonly used (Amplatzer Vascular Plug III or Amplatzer perimembranous ventricular septal defect occluder, AGA Medical Corporation, MN, United States) associated with the closure of this type of defects with the discs of the prosthetic mitral valve (due to the proximity of the defect to the prosthetic valve) a 12 mm Amplatzer Vascular Plug II device (AGA Medical Corporation, MN, United States) was used. Its proper positioning was confirmed with the distal disc of the device body inside the cavity while the proximal disc seals off the defect entry on the left ventricular lateral wall.[2]

After confirmation of proper stability, the device was released (figure 3). Control venticulography showed little passage of contrast towards the pseudoaneurysm cavity with significant reduction compared to the baseline ventriculography, and appearance of spontaneous echocardiographic contrast inside the cavity (figure 4) (video 2 of the supplementary data).

The control transesophageal echocardiography revealed the presence of residual cranial leak with less systolic-diastolic flow compared to baseline levels, and appearance of spontaneous echocardiographic contrast inside the cavity (videos 3 and 4 of the supplementary data).

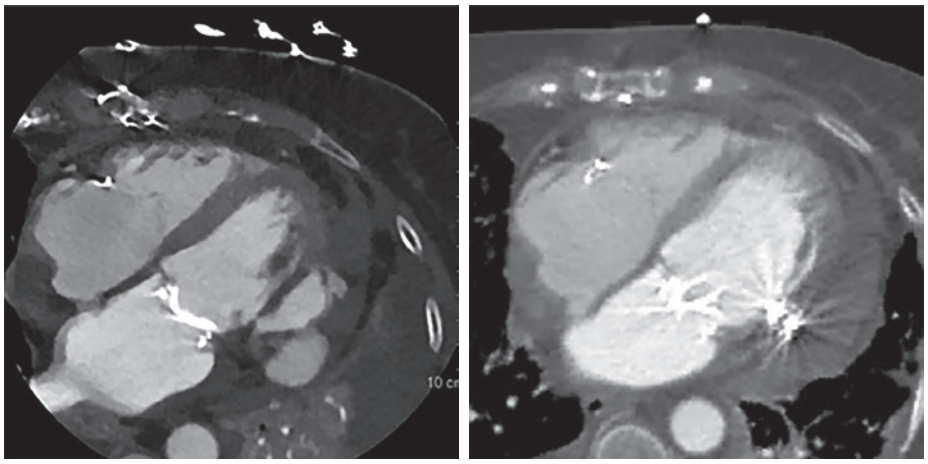

Figure 5. Left: image before the procedure (unsealed defect). Right: computed tomography imaging after Amplatzer device implantation.

After the procedure, a control cardiac computed tomography confirmed that the Amplatzer device had been perfectly anchored to the left ventricular lateral wall and properly sealed off without any passage of contrast through it or cavity filling (figure 5).[1]

However, 10 days after the percutaneous procedure, the patient died of multiorgan failure in a context of a septic shock.

The percutaneous closure of ventricular pseudoaneurysm can be a therapeutic option for patients ineligible for surgical correction.[3] Fluoroscopic fusion imaging, and the 3D reconstruction of the defect were key to plan the procedure and select the most appropriate occluder device.

The patient's written and verbal informed consents were obtained before publishing this case report.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

L. Gutiérrez Alonso drafted the manuscript and was directly involved in patient care. D. Arzamendi, X. Millán, L. Asmarats, and M. Torres were directly involved in patient care. D. Arzamendi supervised the draft of the manuscript. Chi Hion Li was directly involved in the case and provided the images.

CONFLICTS OF INTEREST

None whatsoever.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M22000285.

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Giant coronary aneurysms in incomplete Kawasaki disease

Aneurismas coronarios gigantes en la enfermedad de Kawasaki incompleta

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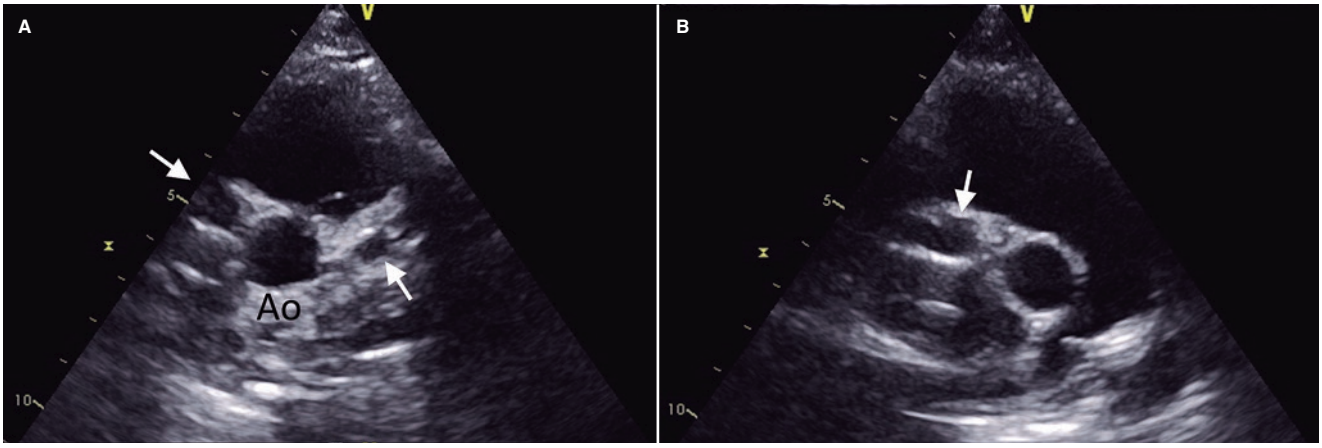

Figure 1.

The association of Kawasaki disease with the formation of aneurysms and coronary stenoses is well established, especially in gammaglobulin-naïve patients. This is the case of a female patient monitored due to patent ductus arteriosus. The control echocardiography performed at the age of 2 years revealed the presence of giant coronary aneurysms in both coronary arteries. The coronary computed tomography angiography (CCTA) and following cardiac catheterization performed confirmed this finding. The patient's past medical history revealed she had been admitted at the age of 9 months due to fever compatible with pyelonephritis with good response to antibiotic therapy that could have been consistent with incomplete Kawasaki disease due to fever and further desquamation. Antiplatelet and anticoagulant therapies were administered that, to this date, have been maintained indefinitely.

When the patient was 6 years old, another echocardiography (figure 1: short axis, Ao, aorta, 1A: right arrow: left coronary aneurysm; left arrow: right coronary aneurysm; arrow 1B: right coronary aneurysm), CCTA (figure 2, right arrows: left coronary aneurysm; left arrows: right coronary aneurysm), and cardiac catheterization were performed that revealed the presence of 2 17 mm x 8.8 mm and 7.3 mm × 5.3 mm calcified aneurysms in the right coronary artery (figure 3A,B and videos 1 and 2 of the supplementary data) plus another 8.3 mm × 6.7 mm aneurysm in the left anterior descending coronary artery (figure 3C,D and videos 3 and 4 of the supplementary data) with mild stenosis in the posterior descending artery (figure 3A,B, asterisk). The clinical course revealed no significant size changes compared to diagnosis or complications.

Since the patient had a high cardiovascular risk, after the last cardiac catheterization, treatment with statins was added according to the clinical practice guidelines on the management of Kawasaki disease published by the American Heart Association

To this date, the patient remains asymptomatic, and no complications associated with her disease or treatment have been reported.

The patient's mother gave her written informed consent to be able to publish this case.

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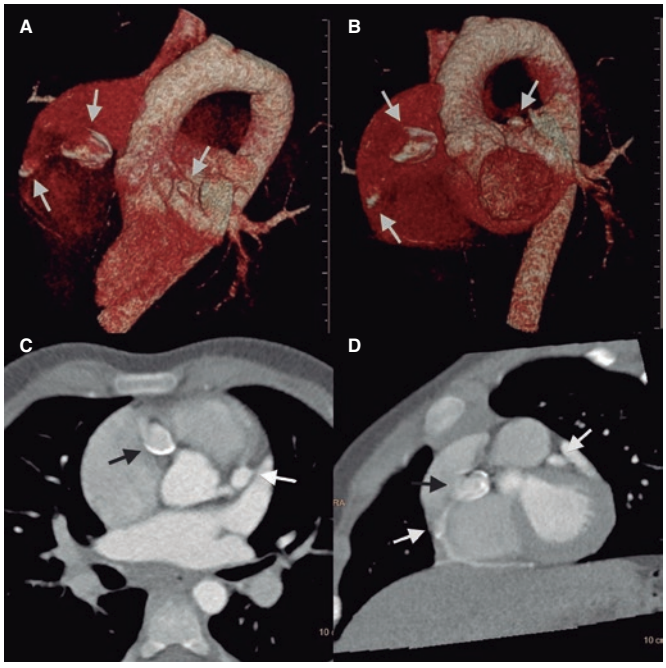

Figure 2.

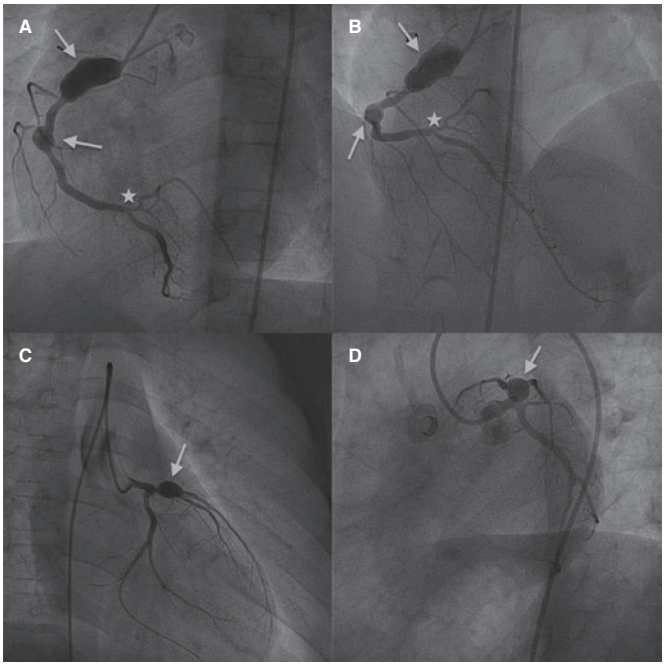

Figure 3.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

All authors participated in the drafting of this manuscript, read, and approved its final version.

CONFLICTS OF INTEREST

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Coronary fistula embolization with neurovascular microcoils

Embolización de fístula coronaria con microcoils neurovasculares

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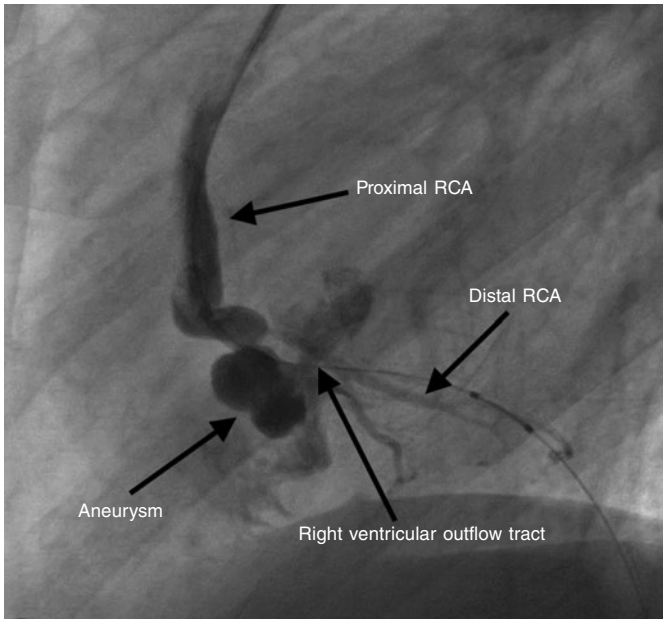

Figure 1.

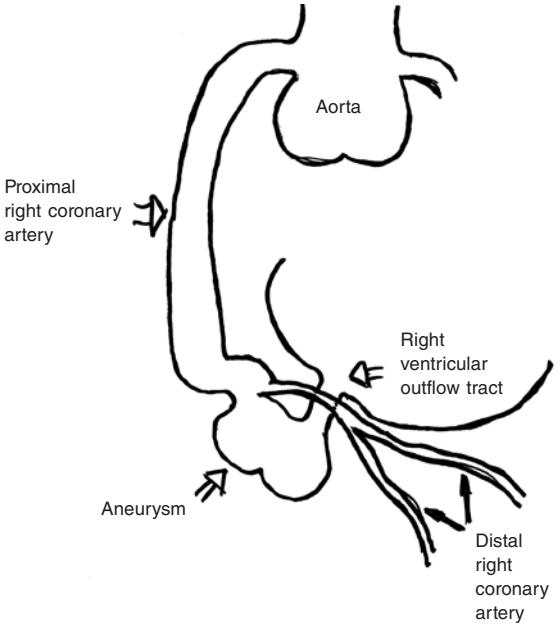

Figure 2.

This is the case of a 55-pound 6-year-old male diagnosed with right coronary artery (RCA) fistula draining into the right ventricle (RV). Due to progressive dilatation of the RCA, percutaneous closure was decided.

The femoral artery and veins were canalized using 5-Fr and 6-Fr introducer sheaths, respectively. A right coronary angiography revealed the presence of a RCA proximal to the 7.1 mm fistula—a fistula with a 11.2 mm × 7.2 mm bilobulated aneurysm with a 2.1 mm right ventricular outflow tract—and a coronary artery distal to the fistula of normal diameter (figure 1, figure 2, and video 1 of the supplementary data).

The fistula was catheterized with a coronary guidewire that was advanced towards the pulmonary artery where it was captured with a snare creating an arteriouvenous loop. From the venous side of this loop a 4 mm × 8 mm Apex Monorail balloon catheter (Boston Scientific, United States) was advanced and then inflated in the ostium of the fistula in the RV for 10 minutes without any signs of ischemia.

Considering the risk of progressive aneurysmal dilatation if the fistula was closed in its distal edge and given the lack of space to fit a device in its proximal edge, it was decided to embolize the aneurysm using microcoils. Using a 5-Fr JR4 guide catheter allocated in the RCA an Excelsior SL microcatheter (Stryker Neurovascular, United States) was advanced. The aneurysm was embolized with 6 Barricade microcoils (Invine, United States) that were released after confirming their stable position inside the aneurysm and lack of residual shunt (figure 3 and video 2 of the supplementary data). No complications were reported after cardiac catheterization. The patient's father gave his consent to publish the case.

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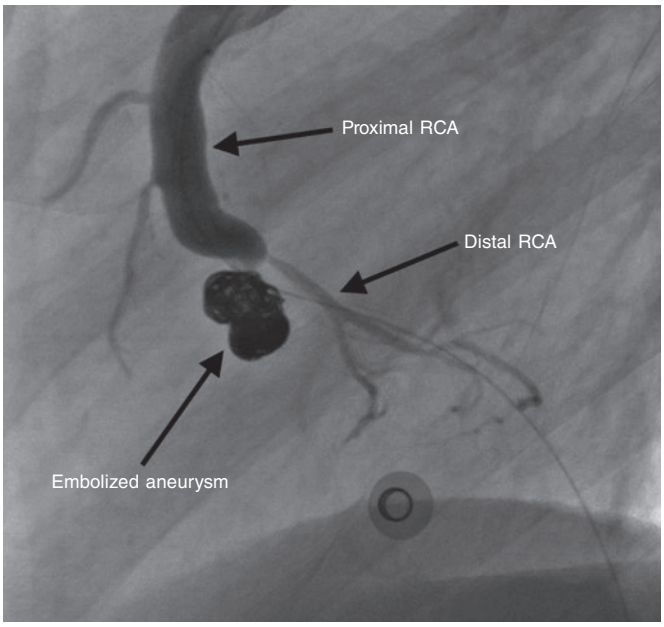

Figure 3.

FUNDING

None whasoever.

AUTHORS' CONTRIBUTIONS

A. Mendoza drafted the manuscript. D. Herrera, M. Flores, J. Campollo, and F. Ballenilla participated in case resolution, and in the revision, and final approval of this manuscript.

CONFLICTS OF INTEREST

None reported.

SUPPLEMENTARY DATA

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