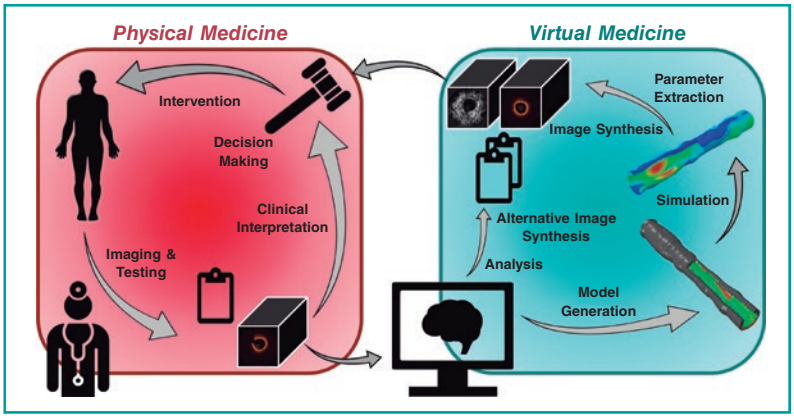
REVISTA ESPAÑOLA DE CARDIOLOGÍA

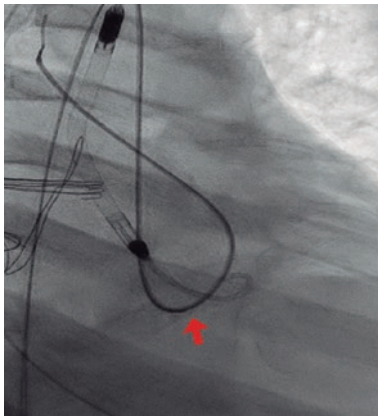
REC: INTERVENTIONAL CARDIOLOGY

Included in: DOAJ, Latindex, and Dialnet

Volume 3, Issue 3 | July-September 2021

ISSN: 2604-7314; e-ISSN:2604-7322





SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Asociación de Cardiología Intervencionista

www.recintervcardiol.org

REC publications

REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

CONTENTS

VOLUME 3, ISSUE 3, JULY-SEPTEMBER 2021

REC Interv Cardiol. 2021;3(3):157-160
https://doi.org/10.24875/RECICE.M21000205

Editorial

Registry-based randomized clinical trials in cardiology: opportunities and challenges

Ensayos clínicos basados en registros en cardiología: oportunidades y retos

David Erlinge*

Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden

INTRODUCTION

The randomized clinical trial (RCT) has become the gold standard for evaluating clinical treatments thanks to its low selection bias and unknown confounders. However, good clinical practice guidelines and demands from regulatory agencies have become so elaborate over time that, basically, only big pharmaceutical companies have the resources to conduct large RCTs. Therefore, important questions raised by academic scientists could be impossible to test in clinical trials.

One way to circumvent these problems is to use the registry-based randomized clinical trial (RRCT) design. A RRCT uses the platform of an already-existing high-quality observational health registry as a case-report form for randomization and follow-up purposes. This design facilitates the randomization of a large number of patients over a short period of time, reduces costs to a fraction of the cost of conventional randomized clinical trials, and facilitates the follow-up of all eligible patients not enrolled in the study (table 1).[1-4]

Table 1. Major functions for trial conduction provided by the registry

Major functions for trial conduction provided by the registry
Identification of eligible patients
Alert investigator of an eligible patient
Link to randomization module
Randomization
Collection of baseline and procedural characteristics from a registry (eCRF)
Presentation of additional trial-specific questions for eCRF
Identification of clinical endpoints (endpoint detection)
Clinical outcomes reporting
Reporting of characteristics of enrolled and non-enrolled patients from the overall population

eCRF, electronic case report form.

RRCT-SUITABLE REGISTRIES

Nearly all healthcare data are stored digitally today, which poses an excellent opportunity to use these data in a RRCT. However, healthcare records are often not structured in a way that allows useful data extraction. Today, disease-specific quality registries with full nationwide coverage are the most suitable ones as the basis for RRCTs, but this may change in the future. Our experience comes from using the Swedish Web-system for the Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) and its Swedish Coronary Angiography and Angioplasty Registry (SCAAR)[5] through which a large number of RRCTs have been conducted or are in ongoing phases (table 2).[6-10] The validation of registry data vs health records has an overall percent agreement of 96%.[11] The first pure RRCT was the TASTE trial where thrombus aspiration in patients with ST-segment elevation myocardial infarction (STEMI) was studied with mortality as the primary endpoint.[1] A large number of patients were rapidly included and with a limited budget by only using registries of baseline demographics, randomization, and endpoint collection in a prospective and randomized fashion. In this trial of a simple device intervention and a solid endpoint, the SWEDEHEART registry provided all the necessary steps to conduct a RCT (table 1). First, identify eligible patients and "flag" them with a pop-up window to the investigator appointed prior to the procedure. Secondly, open up a randomization window with 2 questions: Have the inclusion/exclusion criteria been met? Has the patient given his consent to enter the study? If the answers to both these questions were positive, the patient was randomized and the result shown on the screen momentarily. Thirdly, both the baseline characteristics and the follow-up endpoints were collected from the registry. Furthermore, data on all of the unrecruited patients with complete baseline characteristics are collected. It is interesting to compare the TASTE to the TOTAL trial that examined thrombus aspiration using the traditional RCT design.[12] While the cost of the TOTAL trial was approximately €15 000 000 with 87 centers enrolling patients for 48 months on a 6-month follow-up, the cost of the TASTE trial was €500 000 (3%!) with 30 centers enrolling patients for 33 months on a 42-month follow-up being the results nearly identical. In these circumstances of low complexity in both treatment and endpoints an RRCT is superior, in almost every aspect, to a traditional RCT.

ADVANTAGES AND LIMITATIONS OF PURE RRCTS COMPARED TO TRADITIONAL RCTS

The major advantages of the RRCT design are: *a)* a broader and more representative population to clinical reality; in the TASTE and VALIDATE-SWEDEHEART trials 70% of all eligible patients were

* **Corresponding author:** Department of Cardiology, Lund University, Skane University Hospital, S-221 85 Lund, Sweden.
E-mail address: david.erlinge@med.lu.se (D. Erlinge).

Online: 03-16-2021.

Table 2. Registry-based randomized clinical trials in the SWEDEHEART registry: completed, ongoing or in the pipeline

RRCT	Patients, N	Question	Dates
TASTE, Fröbert et al.[1] (2013)	7200	Thrombus aspiration in primary PCI	2013 + 2014
IFR-SWEDEHEART, Gotberg et al.[6] (2017)	2018	iFR vs FFR in stable angina or ACS	2017
VALIDATE-SWEDEHEART Erlinge et al.[7] (2017)	6006	Bivalirudin vs UFH for PCI in ACS	2017
DETO2X-AMI, Hofmann et al.[8] (2017)	6629	Oxygen therapy in MI	2017
FULL-REVASC, NCT02862119	4052	FFR-guidance in MI	Enrollment stopped after 1545 patients
PROSPECT-II, NCT02171065	900	Near-infrared spectroscopy in PCI	Presented, TCT 2020
IAMI, Fröbert ret al.[9] (2017)	4400	Influenza vaccination after MI	Completed enrollment
SPIRRIT, NCT02901184	3200	Spironolactone for HFpEF	Ongoing
REDUCE, NCT03278509	6600	Beta-blocker post MI in patients with ejection fraction > 50%	Ongoing
ABC-AF, NCT03753490	6500	Biomarker score-based treatment vs standard care	Ongoing
MINOCA-BAT, NCT03686696	2048	ACEi/beta-blockers after MI with non-obstructive CAD	Ongoing
TACSI, NCT03560310	2200	Post-CABG ACS, ticagrelor	Ongoing
SWEDEGRAFT, NCT03501303	902	CABG grafting	Completed enrollment
Infinity-Swedeheart, NCT04562805	2400	Disengaging DES vs DES	Ongoing
DAPA-MI, NCT04564742	6400	SGLT2 inhibitor post-AMI	Ongoing
HELP-SWEDEHEART[a]	20 000	*Helicobacter pylori* screening after AMI to prevent upper gastrointestinal bleeding (cluster-randomization)	Q2, 2021
SWITCH[b]	20 000	Prasugrel or ticagrelor post-MI (cluster-randomization)	In the pipeline
BROKEN-Swedeheart, NCT04666454	1000	Optimal medical treatment for Tako-tsubo syndrome	In the pipeline

[a] Still unregistered; pilot study: NCT04289012.
[b] Still unregistered.
ACEi, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ACS, acute coronary syndromes; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; FFR, fractional flow reserve; HFpEF, heart failure with preserved ejection fraction; iFR, instantaneous wave-free ratio; MI, myocardial infarction; EFPCI cabg SGLT2, sodium-glucose cotransporter-2; PCI percutaneous coronary intervention; TCT, Transcatheter Cardiovascular Therapeutics conference; UFH, unfractionated heparin.

included[1,7]; *b)* clinically significant endpoints were included, and not multiple composite weak or surrogate endpoints; *c)* long-term follow-up periods, actually life-long follow-ups, if applicable; *d)* thanks to random selection, bias and confounding factors are reduced to a minimum; *e)* significantly lower costs; *f)* rapid inclusion of a large number of patients; and *g)* initiated and conducted by independent academic researchers with no links to the industry.

The limitations are: *a)* open label design with a risk of biased endpoint reporting; *b)* rare, unexpected events may be missing, and serious adverse event reporting may be difficult; *c)* events are, for the most part, not adjudicated, which may result in variable data quality; *d)* difficulties having central chemical analysis and biobanking; *e)* long-term oral drugs can be difficult to distribute and follow; and *f)* lack of or limited site monitoring (figure 1).

Depending on the limitations of the registry used, need for treatment escalation or endpoint complexity the RRCT can be complemented with different traditional trial elements resulting in a hybrid RRCT (figure 2).

DEVELOPMENT OF RRCTS

In the SORT OUT series of coronary stent trials, baseline demographics and endpoint screening were conducted using a registry approach. However, randomization took place using different approaches (telephone allocation service, internet-based randomization systems), and endpoints were centrally adjudicated.[13] In the SAFE-PCI study, randomization was performed outside the registry obtaining additional clinical information and adjudication to the registry data.[14]

In the VALIDATE-SWEDEHEART trial, 2 short-acting IV antithrombotic agents (bivalirudin and heparin) were assessed using the RRCT approach. As far as we know, this was the first pharmaceutical RRCT ever conducted.[7] In a pharmaceutical trial the requirements from the medical regulatory authorities are more demanding even if the drugs have been approved and used for decades. Furthermore, we realized that our registry did not capture bleeding complications satisfactorily. Therefore, we added phone calls after 7 to 180 days followed by the central adjudication of bleeding complications and MI, limited serious event reporting, and data on the entire index hospitalization. Thanks to the simplicity of the trial, 25 centers were able to enroll over 6000 patients with MI over 2 years. Some large centers enrolled more than 1000 patients (figure 2, table 2).

In the IFR-SWEDEHEART trial the instantaneous wave-free ratio diagnostic modality was evaluated. The complexity of the intervention was low, but the composite endpoint included MI and unplanned revascularization.[6] Although the endpoints were found in the registries, data were collected from medical records from the centers and adjudicated by a central committee.

Classic RCT	RRCT	Observational Registry
Randomized	Randomized	Non-randomized
Causality	Causality	Hypothesis generating
Cumbersome screening	Registry screening and alert to local investigator	Registration of eligible patients
Narrow selection (5%)	Broad selection (50%-70%)	All-comers
Endpoint adjudication	Registry endpoints ± adjudication	Registry endpoints
Expensive	Low cost	Minimal cost
Blinded	Open label/single blinded	Open label
Extensive on-site monitoring	Selected monitoring	Registry monitoring
SAE reporting	Selected SAE reporting	None
Cumbersome screening failed reporting	Report of all unrecruited eligible patients	Registry of an entire disease population
Limited generalizability	High degree of generalizability	Real-world patients
Slow recruitment	Rapid recruitment	Continuous recruitment

Figure 1. Comparison of traditional randomized clinical trials (RCTs), registry studies, and registry-based randomized clinical trials (RRCT). Classical RCTs are the gold standard of clinical research, but they have limitations because they are very expensive, selective, and a cumbersome process. Retrospective registry studies can be conducted much cheaper, and may be more representative of the real world, yet they are always hampered by unknown confounders. An RRCT can profit from the best parts of these modalities. SAE, serious adverse event.

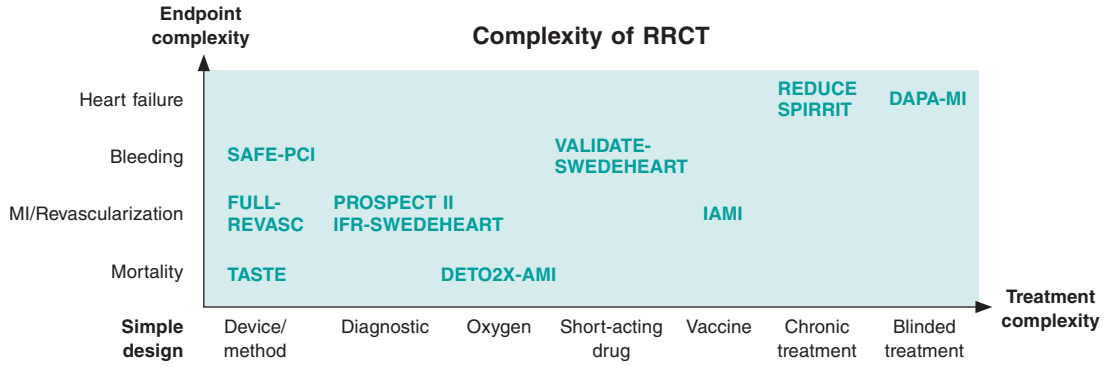


Figure 2. Simple versus complex registry-based randomized clinical trials (RRCT). The purest RRCT examines a simple therapy like a thrombus aspiration device and has a robust endpoint like mortality. When the complexity increases for either treatment or endpoint, then additions to the RRCT design have to be made. These additions could be phone calls, central adjudication, or even blinded treatment with placebo. This increases complexity and costs, but the registry may still be the basis for the trial and facilitate performance. MI, myocardial infarction.

In the DETO2X-AMI trial the endpoint was mortality, which does not need adjudication; however, the oxygen of the procedure had to be administered to the patient in a single blinded fashion adding some extra complexity to the study[8] (figure 2, table 2). Similarly, the influenza vaccine study conducted post-MI (IAMI trial) needed blinded treatment.[9] Furthermore, other countries without the SWEDEHEART registry structure were needed to get a sufficient number of patients, which resulted in a parallel randomization module and electronic case report forms (figure 2, table 2).[9]

There are 2 ongoing RRCTs with chronic oral treatment and a composite endpoint of death and hospitalizations due to heart failure: the REDUCE (beta-blocker post-MI, NCT03278509) and the SPIRRIT (Spironolactone for Heart Failure with Preserved Ejection Fraction, NCT02901184). However, despite the complex treatment and endpoint of both of them, they rely nearly only on registries. The treatment is randomized in the registry, prescribed, and then followed by the Swedish Prescribed Drug Register. Hospitalizations due to heart failure are collected from the National Patient Register where this diagnosis has proven to have a high validity in previous studies.

FUTURE POSSIBILITIES OF THE RRCT CONCEPT

So far, the RRCT technology has mostly been used for the assessment of devices or generic drugs that have been used for decades often with results that the treatment examined has been redundant, as it has been the case with the TASTE and VALIDATE-SWEDEHEART trials. Sometimes, as it occurred with the IFR-SWEDEHEART study, a new diagnostic procedure proves to be non-inferior to the current standard.[6] This resulted in an IA recommendation for the instantaneous wave-free ratio in the clinical practice guidelines. In general, RRCTs have been deemed unsuitable by the medical regulatory authorities for first approval, but this is about to change. The INFINITY trial (NCT04562805) is examining a new type of stent capable of disengaging its metal struts after half a year. This is a currently ongoing RRCT whose objective is to support an approval given by the US Food and Drug Administration (FDA). Demographics, randomization, and endpoint follow-up are already taken care of by the SWEDEHEART registry, still a phone call at 1 month and 1 year combined with central adjudication was added.

The first study, that has been analyzing an expanded use for an oral drug, is the DAPA-MI study (NCT04564742) where dapagliflozin is being tested for post-MI patients with reduced ejection fraction but without diabetes. The registry is the basis of the study, yet visits have been added to dispense the blinded medication. The study is sponsored by AstraZeneca and intends to develop new more cost-efficient ways to conduct phase III trials. The study profits from 2 countries with nationwide MI registries, the UK and Sweden, with their MINAP[16] and SWEDEHEART[5] registries, respectively.

In Europe, the European Society of Cardiology has mostly relied on surveys to register different heart conditions. These are valuable, but they only give us a snapshot of a short timeframe and the selection of patients is unclear and may not be representative of the real world. However, a new initiative called EuroHeart[17] has been trying to establish a common basic structure for continuous cardiac registries that could be used by any countries. One of its objectives is to facilitate conducting RRCTs in several European countries making the results more representative and allowing larger studies being conducted more rapidly.

CLUSTER-RANDOMIZED RRCTS

Cluster randomization design simplifies enrollment and does not often require signed informed consent forms, only general information about the ongoing study. It facilitates the recruitment of nearly all patients from a region during a certain period of time and it basicaly uses a cross-over design. In the HELP-SWEDEHEART trial—still not registered—20 000 patients diagnosed with MI in the SWEDEHEART registry will, based on hospital data, be cluster-randomized in a crossover design to receive *Helicobacter pylori* screening and, if they test positive, be recommended eradication therapy. The primary endpoint is upper gastrointestinal bleeding, which is collected from the National Patient Register. The still unregistered SWITCH trial is planning to investigate prasugrel compared to ticagrelor for the treatment of patients hospitalized due to MI with the composite endpoint of death, MI or stroke collected from the National Patient Register and the National Cause of Death Registry. A total of 4 Swedish regions will be randomized in blocks to standard use of either prasugrel or ticagrelor over 2 years.

In conclusion, RRCTs combine some of the best parts of the classical RCT design and traditional registries when conducting large, randomized, real-world, representative, and cost-effective clinical studies. They give academic researchers an opportunity to obtain important clinical answers that would have never been funded by industry.

FUNDING

The study is supported by the Swedish Heart and Lung Foundation, the Swedish Scientific Research Council, and the Knut and Alice Wallenberg Foundation. The author is solely responsible for the content of this manuscript.

CONFLICTS OF INTEREST

D. Erlinge declares having received speaker or advisory board fees from AstraZeneca, Bayer, Sanofi, and Chiesi.

REFERENCES

1. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587-1597.
2. James S, Frobert O, Lagerqvist B. Cardiovascular registries: a novel platform for randomised clinical trials. *Heart*. 2012;98:1329-1331.
3. Yndigegn T, Hofmann R, Jernberg T, Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. *Heart*. 2018;104:1562-1567.
4. Lauer MS, D'Agostino RB, Sr. The randomized registry trial--the next disruptive technology in clinical research? *N Engl J Med*. 2013;369:1579-1581.
5. Start - SWEDEHEART (uu.se). Available at: https://www.ucr.uu.se/swedeheart/start-scaar. Accessed 8 Feb 2021.
6. Gotberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376:1813-1823.
7. Erlinge D, Omerovic E, Frobert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. *N Engl J Med*. 2017;377:1132-1142.
8. Hofmann R, James SK, Jernberg T, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med*. 2017;377:1240-1249.
9. Fröbert O, Gotberg M, Angeras O, et al. Design and rationale for the Influenza vaccination After Myocardial Infarction (IAMI) trial. A registry-based randomized clinical trial. *Am Heart J*. 2017;189:94-102.
10. Hambraeus K, Held C, Johansson P, et al. SWEDEHEART Annual report 2012. *Scan Cardiovasc J*. 2014;48(Suppl 63):2-133.
11. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart*. 2010;96:1617-1621.
12. Jolly SS, Cairns JA, Dzavik V. Primary PCI with or without Thrombectomy. *N Engl J Med*. 2015;373:682-683.
13. Raungaard B, Jensen LO, Tilsted HH, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. *Lancet*. 2015;385:1527-1535.
14. Rao SV, Hess CN, Barham B, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. *JACC Cardiovasc Interv*. 2014;7:857-867.
15. Neumann FJ, Sousa-Uva M, Ahlsson A, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
16. NICOR. Myocardial Ischaemia/MINAP (Heart Attack audit). Available at: https://www.nicor.org.uk/national-cardiac-audit-programme/myocardial-ischaemia-minap-heart-attack-audit/. Accessed 8 Feb 2021.
17. European Society of Cardiology. EuroHeart. Available at: https://www.escardio.org/Research/euroheart. Accessed 8 Feb 2021.

REC Interv Cardiol. 2021;3(3):161-163
https://doi.org/10.24875/RECICE.M21000202

Editorial

The coming convergence of intravascular imaging with computational processing and modeling

La convergencia de la imagen intravascular con el procesamiento y el modelado computacionales

Max L. Olender[a,b,*] and Elazer R. Edelman[a,c]

[a] *Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States*
[b] *Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States*
[c] *Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, United States*

Medicine and technology have long advanced hand-in-hand. Clinicians push boundaries, expertly yielding the tools at their disposal. Scientists and engineers, in turn, respond to the demands and needs of clinicians by developing the next generation of tools, thereby expanding the space in which clinicians can operate and explore. This boundary-pushing partnership is particularly prevalent in the field of interventional cardiology, which has enthusiastically and effectively embraced advancements in percutaneous and imaging technologies to revolutionize cardiovascular medicine. Continuing this tradition, several developments in computational processing and modeling promise to enhance the utility and efficacy of arterial imaging, with some tools having already entered the clinical setting. For example, a tool that uses computational models built from computed tomography angiography to assess the fractional flow reserve has improved the clinical decision-making process and lowered the rates of unnecessary invasive procedures.[1] Additional tools will further unify the physical and virtual realms of medicine through the bridge provided by imaging, offering both simple tools to label and quantify individual images and advanced tools to simulate and profile entire lesions. The future of the cooperative alliance between medicine and technology must be continuously nurtured and will continue to thrive with the enthusiastic and critical contributions of well-informed interventional cardiologists.

WHAT IS COMPUTATIONAL PROCESSING AND MODELING?

Computational processing is the application of algorithms and software to perform specified and encoded procedures. Computational processing can be applied to intravascular images to enhance, characterize or detect and quantify features depicted in the images. One application of such processing is to extract physiological features used to generate computational models of the imaged vessel region. Computational modeling is the creation and use of virtual representations of physical systems. Such representations can be programmed with sets of rules that prescribe how they should behave and respond under different conditions, and in that way the models can be used to simulate the behavior of the physical system under various hypothetical scenarios.

UNMET NEEDS IN INTERVENTIONAL CARDIOLOGY

In moving towards a more personalized and precise provision of medical care, the convergence of intravascular imaging with computational processing and modeling will be a pivotal step to empower interventional cardiologists. The role and need for this convergence (figure 1), part of a wider vision of computational cardiology,[2] is highlighted by several key challenges faced by the current interventional cardiology practice.

Standard assessments with less interventional workload

Among the most critical and urgent roles of computational processing is integrating and augmenting—*not* displacing—the role played by interventional cardiologists. Computational methods can remove the inter- and intra-observer variability, time consumption, and monotony associated with extensive manual measurements of intravascular images. Such analysis can be performed in the background and continuously without the constraints of busy clinical schedules. Support from processing technologies can also assist physicians with limited training, experience or expertise who may otherwise be unable to identify important features in intravascular images. Additionally, modeling offers relevant quantitative metrics of the vascular state that simply cannot be directly measured, such as estimates of stress along and within the vessel walls.

Patient profiling and stratification

The core premise of precision medicine is that patient populations can be segmented into narrow classes that respond differently to interventions. The cardiology community has proposed broad classifications to divide atherosclerotic plaques, typically driven by the prevailing tissue type and presumed degree of progression.[3] Despite or in deference to its simplicity, there have been few significant updates to this classification in recent decades, even as intravascular imaging offers more and richer information on lesion geometry and morphology and as treatment of the disease has evolved. Computational processing and modeling may offer improved

*** Corresponding author:** 77 Massachusetts Avenue, Cambridge, MA 02139, United States.
E-mail address: molender@mit.edu (M. Olender).

Online: 02-04-2021.

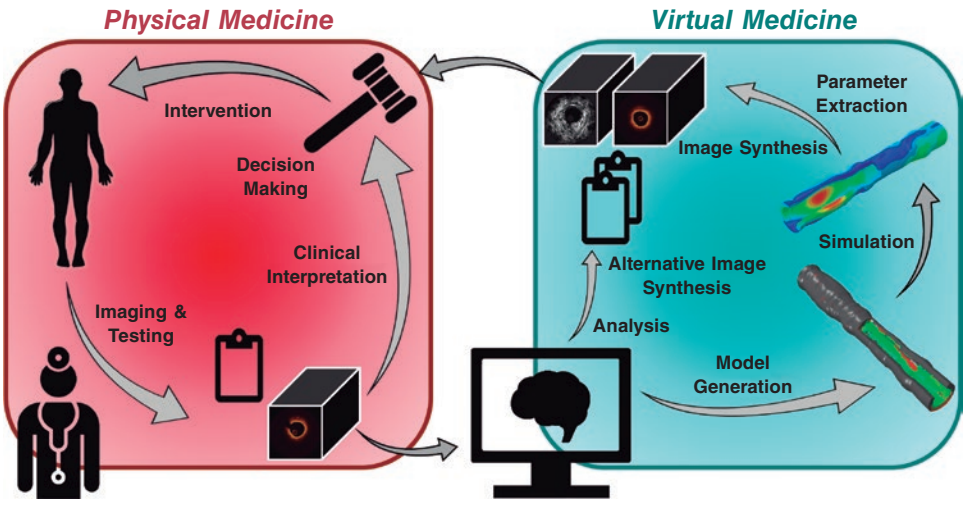


Figure 1. Our vision for the future of cardiovascular medicine is one in which physical and virtual medicine forms a continuum. Clinicians collect data including images and other test results from a patient. Anatomical and morphological information will be automatically extracted by algorithmic processing routines, distilled into reported quantitative metrics, and used to generate patient-specific computational models. Various simulated tests and procedures will be performed on the virtual patient. Results of the analyses and simulations will be transformed back into clinical data to enable a seamless integration and assessment by the heart team; the outcomes could inform the decision-making process and guide the patient's procedure.

profiling of individual patients on the basis of clinical presentation, disease state, detailed lesion phenotype, and even mechanical condition. By computing series of quantitative measures to describe patient and lesion, the possibility of building a more robust patient profile becomes real. Such granular profiling could enable stratification to better assess who benefits the most from which interventions, thus guiding the therapeutic decisions.[4]

Prediction and risk assessments for clinical decision support

In addition to improved patient profiling and stratification, modeling offers the ability to engage in truly personalized risk assessment and prediction of disease progression under various treatment regimens. Because much of the interpretation of intravascular images is currently qualitative, decision-making during patient care can be an exquisite art and formulaic science alike and depend on each cardiologist's personal experiences (and biases), training, and institutional practices. Advancing beyond personal clinician experience and intuition, computer processing and modeling offer repeatable, standardized quantification to inform the decision-making process. For example, simulations of detailed patient- and lesion-specific models, or "Digital Twins",[5] could facilitate various virtual interventions or intervention parameters to be tested before selecting an optimal strategy to minimize risk. Alternatively, disease progression and plaque growth models may help to predict which vessels and mild lesions may progress dangerously—suggesting the need for prophylactic action—and which are likely to remain benign and inconsequential over time.

TECHNOLOGICAL TOOLS IN DEVELOPMENT

To fulfill the needs of computational processing and modeling in interventional cardiology, various new technologies are being developed that leverage the rich data available from intravascular imaging. The detection and measurement of geometric features is already available in limited cases, and it is likely to expand. The automated delineation of the lumen and external elastic lamina is incorporated in some intravascular ultrasound systems, and developments in computational processing have recently yielded promising results to identify these, as well as the internal elastic lamina, in optical coherence tomography images. Facilitated by automated detection of inner and outer vessel borders, automatic measurements from pullbacks such as lumen area, plaque burden, eccentricity, and remodeling index will reduce the need for manual identification and annotation of the most critical frames and will enable better visualization of diseased vessels. This information may also be used, for example, in the proper sizing of balloons and stents.

Advances in image processing also offer improved availability of information on lesion morphology. While experts are generally adept at determining the composition and distribution of plaque from cross-sectional images, doing so is a slow process that requires extensive expertise. Increased availability of automated virtual histology will improve the characterization, profiling, and stratification of lesion phenotypes. New image-based methods to characterize the stiffness of diseased tissue also promise greater insight into the mechanical profile of a lesion. Altogether, this information on plaque distribution and properties will help cardiologists to plan and guide interventions (eg, by informing the need for lesion preparation or modification prior to ballooning or stenting).

Computational modeling is a central focus of ongoing technological research and development. The ability to simulate disease progression and interventions is an enticing challenge that has been drawing the attention of multidisciplinary teams. Among these efforts, major collaborative, international European projects have sought to develop and refine advanced predictive models of atherosclerotic plaque processes and angioplasty by integrating patient risk factors, blood panel results, and imaging data.[6] Robust longitudinal validation of such models remains an obstacle.

Computational processing offers another little-explored function to synthesize and enhance images. As intravascular imaging is the cornerstone of interventional cardiology, these generative abilities could be used with great effect to improve diagnostic image quality and efficacy, convey information generated from computational models, and facilitate education and training for reading and interpreting images.

Several technologies in development may require changes to future clinical practice. For example, some methods require multiple image pullbacks or simultaneous measurement of pressure and matched image acquisition. Changes will be limited by the corresponding progress in hardware development and adoption, demonstrated cost-benefit tradeoffs for patients, and receptiveness of the interventional cardiology field.

THE INDISPENSIBLE ROLE OF INTERVENTIONAL CARDIOLOGISTS

Interventional cardiologists will not only have a pivotal role in the future adoption of computational processing and modeling technologies but also an important present role in defining and achieving that future. Those experienced in managing and treating patients are needed to direct, develop, and shepherd new technologies—their deep knowledge of the demands and practical limitations of clinical care are indispensable to scientists and engineers. There is also ongoing profound need for data with which to train and validate new methods and models. Here, too, the involvement, expertise, and contributions of collaborative cardiologists are essential.

The increasing integration of more complex technologies also introduces a growing imperative for cardiologists to further cultivate their technical literacy. While medical and health sciences must remain a priority in the training of interventional cardiologists, broader training is an important prerequisite to critically assess new claims and make informed decisions on the applicability and reliability of new techniques as they enter the medical arena. Clinicians will need to understand the assumptions, uncertainties, and conditions under which these tools should be beneficially applied to treat their patients. Interventional cardiologists and other medical professionals are already well-equipped for many of these tasks. Looking beyond the novelty and flair of the methods, familiar and fundamental concepts considered for other diagnostic tests, such as sensitivity and specificity, should be equally applied to scrutinize advanced new software tools.

As computational processing and modeling converge with intravascular imaging in the coming years, interventional cardiologists will be empowered to deliver more personalized and precise medical care. Those in the field should expect to play an active role in the development, assessment, and adoption of new technologies, and equip themselves with the evolving knowledge and skills necessary to make the most of these tools in the management of their patients.

FUNDING

This work was supported by the U.S. National Institutes of Health (Bethesda, MD, United States; grant number 5R01GM049039-24) and the Massachusetts Institute of Technology (Cambridge, MA, United States; MathWorks Engineering Fellowship).

CONFLICTS OF INTEREST

M. Olender and E.R. Edelman have the patent "Arterial Wall Characterization in Optical Coherence Tomography Imaging" (16/415,430) pending, and the patent "Systems and Methods for Utilizing Synthetic Medical Images Generated Using a Neural Network" (62/962,641) pending. In addition M. Olender reports grants from MathWorks while conducting the study; and E.R. Edelman reports grants from the U.S. National Institutes of Health while conducting the study; grants from Abiomed, grants from Edwards LifeSciences, grants from Boston Scientific, grants from Medtronic, grants from Autus Medical, other from Biodevek, other from Panther Therapeutics, personal fees from Abbvie, outside the submitted work.

REFERENCES

1. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: The prospective longitudinal trial of FFRCT: Outcome and resource impacts stud. *Eur Heart J*. 2015;36:3359-3367.
2. Athanasiou LS, Nezami FR, Edelman ER. Computational Cardiology. *IEEE J Biomed Health Inform*. 2019;23:4-11.
3. Stary HC, Chandler AB, Dinsmore RE, et al. A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis. *Circulation*. 1995;92:1355-1374.
4. Gray RA, Pathmanathan P. Patient-Specific Cardiovascular Computational Modeling: Diversity of Personalization and Challenges. *J Cardiovasc Transl Res*. 2018;11:80-88.
5. Corral-Acero J, Margara F, Marciniak M, et al. The 'Digital Twin' to enable the vision of precision cardiology. *Eur Heart J*. 2020;41:4556-4564.
6. Sakellarios AI, Pelosi G, Fotiadis DI, et al. Predictive Models of Coronary Artery Disease Based on Computational Modeling: The SMARTool System. *Annu Int Conf IEEE Eng Med Biol Soc*. 2019;2019:7002-7005.

REC Interv Cardiol. 2021;3(3):164-165
https://doi.org/10.24875/RECICE.M21000208

Editorial

Colchicine: an emerging treatment for coronary artery disease

Colchicina: una terapia emergente para el tratamiento de la enfermedad coronaria

Waseem Hijazi,[a] and Sanjit S. Jolly[b,*]

[a] *Department of Medicine, McMaster University, Hamilton, Canada*
[b] *McMaster University and Population Health Research Institute, Hamilton Health Sciences, Hamilton, Canada*

Coronary artery disease (CAD) is one of the leading causes of death worldwide. These rates are only likely to be buoyed in the future by the rising prevalence of obesity, diabetes, and metabolic syndrome.

The pathogenesis of atherosclerosis, the main cause of CAD, has been a topic of great interest.[1] As a brief review, dyslipidemia plays a key role. Beginning with the incorporation of serum low-density lipoprotein into the endothelium tunica intima, chemokines and endothelial adhesion molecules attract macrophages into the arterial wall. Eventually, cholesterol droplets are incorporated into the macrophage cytosol, become oxidized, and form the so-called 'foam cell'. In a reciprocal exchange, inflammatory mediators released by foam cells trigger ongoing endothelial damage, fibrosis, and intimal hyperplasia. Eventually, coronary artery stenosis occurs; a condition at the basis of CAD and for which inflammation is a key component.

Inflammation is likely to play a role in both stable and unstable CAD. Many patients may present small atheromas, but still suffer from acute coronary thromboses–the acute coronary syndrome. Pathological studies have shown that T-cells, macrophages, and mast cells congregate to plaque rupture sites where they upregulate matrix metalloproteases, degrade collagen, and weaken the fibrous cap that supports the plaques. Additionally, once the endothelium is exposed to the plaque following a rupture, these inflammatory cells facilitate thrombosis, and platelet plug formation. As clues to their damage, such patients show high levels of interleukin-6, and C-reactive protein in their blood.[1]

ANTI-INFLAMMATORY THERAPIES FOR CAD

The centerpiece role of inflammation in CAD led to descriptions of atherosclerosis as a "chronic inflammation of the arteries," a fact borne out by science as early as the 1980s.[2] Yet, decades later no routinely used CAD therapies target any inflammatory pathways (figure 1). Many extant anti-inflammatory therapies have tried so but have proven unsuccessful. For instance, corticosteroids exhibit a broad range of anti-inflammatory properties, but their promotion of dyslipidemia and hypertension ultimately cause atherogenesis. Non-steroidal anti-inflammatory drugs other than aspirin inhibit prostacyclin, which increases vascular tone and platelet aggregation in the coronary arteries. Interest in methotrexate arose from observational studies that showed cardioprotective properties in patients with rheumatoid arthritis. However, a randomized clinical trial that analyzed its effect in patients with atherosclerosis showed that it does not lower the serum inflammatory markers or prevent myocardial infarction.[3]

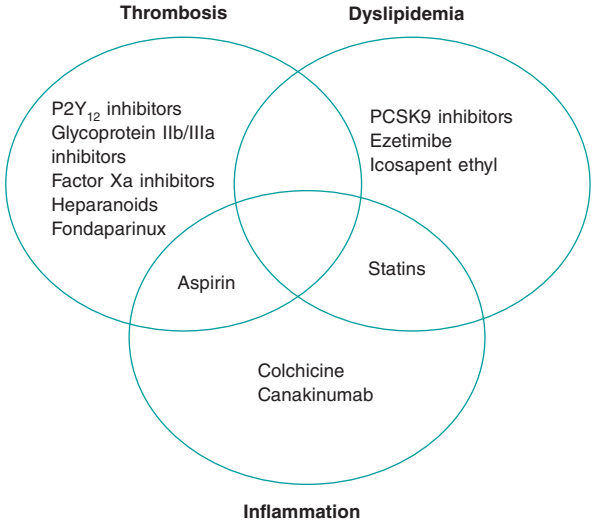


Figure 1. Therapeutic foundations for the management of coronary artery disease. The figure shows agents with proven mortality benefits in the management of coronary artery disease. Although thrombosis, dyslipidemia, and inflammation are all key in the pathogenesis of coronary artery disease, the scarcity of effective anti-inflammatory agents is evident.

An interleukin-1b inhibitor, canakinumab, was the first agent to successfully prevent cardiovascular events in patients with a recent myocardial infarction. In the CANTOS trial, canakinumab

* **Corresponding author:** Room C3-118, DBCVSRI Building, Hamilton General Hospital, 237 Barton St East, Hamilton, ON L8L 2X2, Canada.
E-mail address: sanjit.jolly@phri.ca (S.S. Jolly).

Online: 07-04-2021.

150 mg once daily lowered the rates of nonfatal myocardial infarction, stroke, and death (hazard ratio [HR], 0.85; 95% confidence interval [95%CI], 0.74-0.98) at the cost of increasing the rate of fatal sepsis, and infection (0.31 vs 0.18 per 100 person-years; P = .02). This trial was an important scientific breakthrough that showed that the inflammatory hypothesis is a therapeutic option for CAD. However, the costs of therapy and a modest effect size have both limited its use.[4]

Like methotrexate, interest in colchicine was borne out by observational data. In patients suffering gout flares, the use of colchicine was associated with fewer cardiovascular events compared to non-use.[5] These observations led to a non-blinded randomized analysis of colchicine (the Low-dose colchicine for secondary prevention of cardiovascular disease [LoDoCo] trial) that proved a reduction in cardiovascular events in patients with stable CAD.[6] Although there were some methodological limitations, the trial served as the niche for more upcoming robust clinical data on colchicine.

Colchicine is an inhibitor of microtubules and may prevent leukocyte migration into sites of plaque formation and rupture. Moreover, colchicine helps inhibit the formation of the NLRP3 inflammasome –a structure recently involved in cytokine mediated cell death. These pro-inflammatory protein complexes are activated by cholesterol crystals in macrophages and secrete interleukin (IL)-1b, the cytokine target of canakinumab. Colchicine has also been shown to reduce C-reactive protein, IL-1, and IL-6.[7]

A larger follow up trial to the initial LoDoCo trial, the LoDoCo2, enrolled 5522 patients with chronic CAD, and randomized them to receive colchicine or placebo for a median of 28.6 months after an open label run-in period to ensure colchicine tolerability. Colchicine was associated with a 31% reduction (HR, 0.69; 95%CI, 0.57-0.83; P < .001) of cardiovascular death, infarction, ischemic stroke, and revascularization. Adversely, patients who received colchicine showed higher rates of non-cardiovascular death, although the rate of events was low (HR, 1.51; 95%CI, 0.99-2.31; P = .06).[8] Other adverse occurrences and intolerances were rare.

COLCHICINE IN ACS

Another 2 trials examined colchicine in a recent myocardial infarction setting: the COLCOT trial (efficacy and safety profile of low doses of colchicine after myocardial infarction), and the COPS trial (colchicine in patients with acute coronary syndrome). The first and larger of the two, the COLCOT trial, randomized 4745 patients who had a myocardial infarction within 30 days into colchicine therapy or placebo and followed them for a median of 22.6 months. The patients who received colchicine enjoyed a 23% reduction (HR, 0.77; 95%CI, 0.61-0.97; P = .02) in the composite endpoint of cardiovascular death, cardiac arrest, ischemic stroke, infarction, and angina requiring urgent revascularization. Though a positive outcome, it was driven primary by fewer revascularizations in the colchicine arm. Additionally, patients randomized to colchicine experienced more pneumonia (0.9% vs 0.4%; P = .03) compared to placebo.[9] An early administration of colchicine was associated with greater benefits (within 3 days) in the COLCOT trial (HR, 0.52; 95%CI, 0.32-0.84 for initiation within 3 days vs HR, 0.98; 95%CI, 0.53-1.75 for initiation between days 4 and 7).[10]

The COPS trial enrolled 795 patients and randomized them to receive colchicine or placebo for 12 months. At the 1-year follow-up, no statistical differences were seen in the composite endpoint of cardiovascular death, infarction, ischemic stroke, and cardiac arrest with colchicine compared to placebo (HR, 0.65; 95%CI, 0.38-1.09; P = .10), likely due to a lower rate of events from a shorter follow-up period, and a smaller sample size. Moreover, 8 patients from the colchicine arm and 1 from the placebo group died, an effect that reached statistical significance and was driven by non-cardiovascular mortality (P = .047).[11] Although this trial enrolled relatively few patients, it reproduced a signal towards mortality as seen on the larger LoDoCo2 trial.

The largest trial of colchicine post-myocardial infarction, the Colchicine and spironolactone in acute MI (CLEAR SYNGERY, NCT03048825), is underway. It will randomize 7000 patients and help solve the issue of whether colchicine increases non-cardiovascular mortality. The findings of the COPS and LoDoCo2 trials may be spurious findings, similar to what was found in earlier statin trials, and eventually disproved. On the other hand, there could be an important impact of colchicine due to a reduction of host defenses that went previously unnoticed.

Colchicine may be the first widely available, inexpensive anti-inflammatory therapy for the management of CAD. However, the issue of non-cardiovascular mortality should be resolved before it is widely adopted.

FUNDING

The authors received no specific funding for this work.

CONFLICTS OF INTEREST

S.S. Jolly reports grant support from Boston Scientific and the Canadian Institutes of Health Research. W. Hijazi declared no conflicts of interest.

REFERENCES

1. Bouabdallaoui N, Tardif JC, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *Eur Heart J*. 2020;41:4092-4099.
2. Butt AK, Cave B, Maturana M, Towers WF, Khouzam RN. The Role of Colchicine in Coronary Artery Disease. *Curr Probl Cardiol*. 2021;46:100690.
3. Hansson GK. Inflammation, Atherosclerosis, and Coronary Artery Disease. *N Engl J Med*. 2005;352:1685-1695.
4. Nabel EG, Braunwald E., 2012. A Tale of Coronary Artery Disease and Myocardial Infarction. *N Engl J Med*. 2012;366:54-63.
5. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease. *J Am Coll Cardiol*. 2013;61:404-410.
6. Nidorf SM, Fiolet ATL, Mosterd A, et al.; LoDoCo2 Trial Investigators. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. 2020; 383:1838-1847.
7. Ridker PM, Everett BM, Pradhan A, et al.; CIRT Investigators. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N Engl J Med*. 2019;380:752-762.
8. Ridker PM, Everett BM, Thuren T, et al.; CANTOS Trial Group Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med*. 2017;377:1119-1131.
9. Solomon D, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. *Ann Rheum Dis*. 2016;75:1674-1679.
10. Tardif JC, Kouz S, Waters DD, et al. 2019. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*. 2019;381:2497-2505.
11. Tong DC, Quinn S, Nasis A, et al. 2020. Colchicine in Patients With Acute Coronary Syndrome. *Circulation*. 2020;142:1890-1900.

REC Interv Cardiol. 2021;3(3):166-174
https://doi.org/10.24875/RECICE.M21000203

Original article

Outcomes of emergency compared to elective TAVI: a meta-analysis

Álvaro Aparisi,[a] Sandra Santos-Martínez,[a] José Raúl Delgado-Arana,[a] Tania Rodríguez-Gabella,[a] Alfredo Redondo,[a] Hipólito Gutiérrez,[a] Gema Pastor,[a] Carlos Veras,[a] Mario García Gómez,[a] Carlos Baladrón,[b] Manuel Carrasco-Moraleja,[b] José Alberto San Román,[a,b] and Ignacio J. Amat-Santos,[a,b,*]

[a] *Servicio de Cardiología, Hospital Clínico Universitario de Valladolid, Instituto de Ciencias del Corazón (ICICOR), Valladolid, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

ABSTRACT

Introduction and objectives: Transcatheter aortic valve implantation (TAVI) has proven safe and effective in low-to-high risk patients, but emergency procedures have been excluded from the landmark trials. We aimed to assess the current outcomes and main factors conditioning the prognosis during emergency TAVI.
Methods: A systematic search in PubMed and Google Scholar was conducted for all studies comparing elective vs emergency TAVI. Searched terms were "emergency" and/or "urgent", "elective", and "transcatheter valve replacement" and/or "heart failure" and/or "cardiogenic shock". Emergency TAVI was considered as any unscheduled TAVI performed to treat refractory heart failure or cardiogenic shock. A random-effects model was used.
Results: A total of 7 studies with 84 427 TAVI patients were included (14 241 emergency procedures; 70 186 elective TAVIs). Emergency cases presented higher risk scores (logistic EuroSCORE 65.9% ± 21% vs 29.4% ± 18%, $P < .001$; Society of Thoracic Surgeons Risk Score 29.4% ± 27.4% vs 13.7% ± 11.6%, $P < .001$). More advanced heart disease was observed with deterioration of left ventricular (LV) function (39.5% ± 17.8% vs 52.5% ± 12.8%; $P < .001$) and larger LV end-diastolic diameters (55 ± 9 mm vs 48 ± 7 mm; $P < .001$) despite similar aortic valve areas and gradients. Elective TAVIs presented a greater success rate (93.6% vs 92.5%; odds ratio [OR] = 0.84; 95%CI, 0.74-0.95; $P = .005$), less acute kidney injury, and a lower need for dialysis and mechanical circulatory support. Overall, non-emergency cases had lower in-hospital (3.3% vs 5.7%; $P < .001$), 30-day (4.4% vs 8.8%; $P < .001$) and 1-year mortality rates (19.7% vs 34.75%; $P = .0001$). The main determinants of mortality were need for new dialysis (OR = 2.26; 95%CI, 1.84-2.76; $P < .001$) or mechanical circulatory support (OR = 2.55; 95%CI, 1.14-5.67; $P < .001$).
Conclusions: Emergency TAVI recipients presented worse baseline risk and more advanced cardiac disease that determined greater in-hospital, 30-day, and 1-year mortality rates. The early identification of patients at risk for requiring mechanical circulatory support or dialysis may contribute to a better indication of TAVI in emergency scenarios.

Keywords: Cardiogenic shock. Heart failure. Transcatheter aortic valve replacement. Aortic stenosis.

Resultados del TAVI emergente comparado con el procedimiento electivo: metanálisis

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica (TAVI) ha demostrado ser seguro y eficaz en pacientes tanto de bajo como de alto riesgo, pero los procedimientos emergentes se han excluido en los principales estudios. El objetivo fue determinar los resultados actuales y los condicionantes del pronóstico durante el TAVI emergente.
Métodos: Se realizó una búsqueda sistemática en PubMed y Google Scholar de cualquier estudio que comparara el TAVI electivo frente al emergente. Los términos empleados fueron «emergent» y/o «urgent», «elective», y «transcatheter valve replacement» y/o «heart failure» y/o «cardiogenic shock». Se consideró TAVI emergente todo procedimiento no programado realizado para tratar la insuficiencia cardiaca refractaria o el *shock* cardiogénico. Se utilizó un modelo de efectos aleatorios.
Resultados: Se incluyeron 7 estudios (84.427 pacientes) tratados con TAVI (14.241 emergentes y 70.186 electivos). Los casos electivos presentaron una mayor puntuación de riesgo (EuroSCORE logístico 65,9 ± 21 frente a 29,4 ± 18%, p < 0,001; *Society of Thoracic Surgeons Risk Score* 29,4 ± 27,4 frente a 13,7 ± 11,6%, p < 0,001). Presentaron una enfermedad cardiaca más avanzada, con peor

*** Corresponding author:** Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario de Valladolid, Ramón y Cajal 3, 47005 Valladolid, Spain.
E-mail address: ijamat@gmail.com (I. J. Amat-Santos)

Received 6 October 2020. Accepted 19 January 2021. Online: 24-02-2021.

función ventricular izquierda (39,5 ± 17,8 frente a 52,5 ± 12,8%; p < 0,001) y mayor diámetro telediastólico del ventrículo izquierdo (55 ± 9 frente a 48 ± 7 mm; p < 0,001), pese a tener similar área valvular aórtica y gradientes. El TAVI electivo tuvo mayor tasa de éxito (93,6 frente a 92,5%; *odds ratio* [OR] = 0,84; IC95%, 0,74-0,95; p = 0,005), con menor tasa de fallo renal agudo y menos necesidad de diálisis y de soporte circulatorio mecánico. En conjunto, los casos no emergentes tuvieron menor mortalidad intrahospitalaria (3,3 frente a 5,7%; p < 0,001), a 30 días (4,4 frente a 8,8%; p < 0,001) y a 1 año (19,7 frente a 34,75%; p = 0,0001). Los principales determinantes de mortalidad fueron la nueva necesidad de diálisis (OR = 2.26; IC95%, 1,84-2,76; p < 0,001) o requerir soporte circulatorio mecánico (OR = 2,55; IC95%, 1,14-5,67; p < 0,001).
Conclusiones: Los receptores de TAVI emergente presentaron peor riesgo basal y enfermedad cardiaca más avanzada, que determinaron una mayor mortalidad intrahospitalaria, a 30 días y a 1 año. La identificación precoz del riesgo de precisar soporte circulatorio mecánico o diálisis podría ayudar a una optimización de la indicación de TAVI emergente.

Palabras clave: *Shock* cardiogénico. Insuficiencia cardiaca. Implante percutáneo de válvula aórtica. Estenosis aórtica.

Abbreviations

AS: aortic stenosis. **CKD:** chronic kidney disease. **CS:** cardiogenic shock. **HF:** heart failure. **SAVR:** surgical aortic valve replacement. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Aortic stenosis (AS) is the most commonly treated valvular heart disease in Western countries.[1] In a relatively small but growing proportion of patients (from 3.5% to 12%), AS may present as cardiogenic shock (CS) with an estimated short-term mortality as high as 70% if definitive surgical or percutaneous treatment is not provided.[2] CS is characterized by an inadequate tissue perfusion as a result of a decompensated cardiac disease that translates into a low-output state. Early management is directed toward keeping a steady hemodynamic profile and ensuring tissue oxygenation through medication or advanced support.[3] However, specific therapies are required to ensure a complete resolution, yet conventional surgical aortic valve replacement (SAVR) is often associated with a very high risk of mortality.[2]

Several trials have shown that transcatheter valve implantation (TAVI) is a safe alternative to SAVR in low-to-high risk patients in stable situations and it is currently considered the preferred alternative in those of high prohibitive surgical risk.[4-7] Nevertheless, the risk scores for the main studies that settled the evidence for TAVI procedures were estimated after excluding patients with CS. As a consequence, the main outcomes in this challenging scenario have not been randomly compared to surgery. Actually, such a comparison is unlikely to be performed due to the highly variable baseline profile and differential availability of resources such as mechanic circulatory assist devices. In addition, the different outcomes in emergency TAVIs and planned interventions have been scarcely researched; still, they are key to improve results in what stands as the worst possible clinical scenario. We aimed to assess the current outcomes of emergency/urgent TAVI and the main factors conditioning its prognosis through a systematic review and meta-analysis.

METHODS

Literature search strategy

A systematic review of all published articles in PubMed and Google Scholar databases between January 2014 and January 2020 regarding emergency/urgent versus elective TAVI in severe AS was independently performed by 2 of the authors (A. Aparisi and M. Carrasco-Moraleja). Searched terms were "emergency" and/or "urgent", "elective", AND "transcatheter valve replacement" or "TAVR" (transcatheter aortic valve replacement) or "heart failure" and/or "cardiogenic shock". Definition of emergency/urgent procedures was variable, but the consensus reached for this article was to include patients who required an unscheduled TAVI procedure to treat their refractory heart failure or CS to correct this condition within the next 72 hours after admission. A total of 7 studies[8-14] were chosen, and the inclusion criteria established by our group were: *a)* the study population included patients with aortic stenosis who underwent TAVI; *b)* only cohort studies that compared emergency or urgent to elective TAVI were included; *c)* only full English peer-reviewed papers with enough data of outcomes were chosen. The selected exclusion criteria were: *a)* abstracts; *b)* case reports; c) editorials; *d)* experts' opinions; and *e)* repetitive studies. Discrepancies between reviewers were resolved through discussion, and consensus was reached. Flowchart is shown on figure 1 and the main features of the studies included are shown on table 1 of the supplementary data.

Primary endpoints

Primary endpoints were short-term mortality and procedural success. Secondary outcomes were perioperative complications. Complications were mostly reported by using the definitions established by the Valve Academic Research Consortium-2.[15]

Statistical analysis

Qualitative variables were expressed as absolute frequency and percentage. Continuous variables were expressed as mean ± standard deviation unless specified otherwise. To compare the demographic variables and the risk factors between thew groups, the chi-square test or Fisher's exact test were used for the categorical variables. The Student *t* test was used for the continuous variables, when applicable.

As a measure of the combined effect, the studies included the odds ratio (OR), a 95% confidence interval, and statistical significance. The homogeneity among the studies was compared using the QH statistic. With regard to the low sensitivity of this test, *P* values < .10

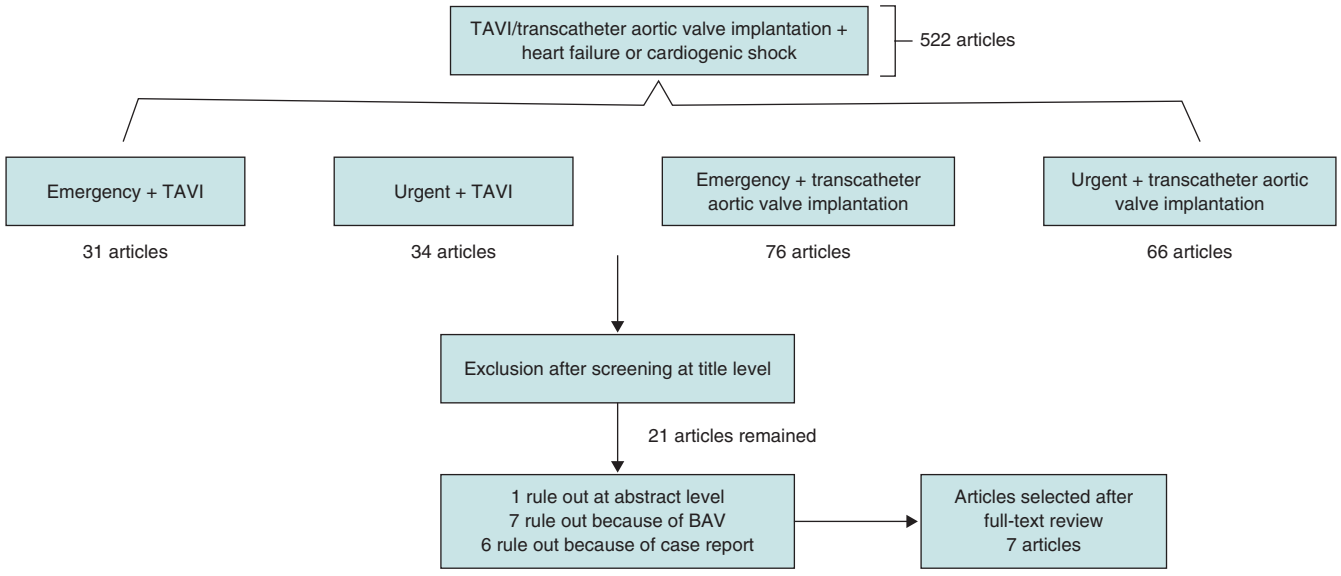


Figure 1. Flowchart showing search results and selection of the studies included in the meta-analysis.

were considered significant. To somehow overcome this limitation, the I^2 statistic was estimated as well, which measures the percentage of the overall variation of the studies explained by the heterogeneity and its 95%CI. A random effects model was used for cases in which the I^2 statistic was > 50% and a fixed effects model was used for the opposite cases. The potential publication bias was assessed using a funnel plot, Egger's test, and Begg and Mazumdar rank correlation test. In the presence of publication bias, the trim-and-fill method was used to reassess the pooled OR. Sensitivity analyses sequentially eliminating dissimilar studies were also conducted.

All *P* values were 2-tailed. Statistical analyses were conducted using the R software, version 3.6.1 (R Project for Statistical Computing) and Review Manager 5.3.

RESULTS

Patient distribution and baseline characteristics

Seven studies were selected including a total of 84 427 patients who underwent TAVIs, with 70 186 elective procedures (83.1%) and 14 241 emergency ones (16.9%). The main baseline characteristics according to the elective or emergency character of the intervention are shown on table 1 and sensitivity and asymmetry analyses are shown on table 2 of the supplementary data and figure 1 of the supplementary data. Asymmetry was detected for acute kidney injury and, therefore, the trim-and-fill method had to be used to reassess the odds ratio. The percentage of men who underwent elective procedures (52.1%) was higher compared to emergency interventions (50.27%, $P < .001$). Overall, patients treated urgently showed more comorbidities as summarized by the logistic EuroSCORE (65.9% ± 21% vs 29.4% ± 18%, $P < .001$) and the Society of Thoracic Surgeons Risk Score (STS) (29.4 ± 27.4 vs 13.7 ± 11.6, $P < .001$). However, the classical cardiovascular risk factors did not differ among groups (hypertension and diabetes mellitus) and the rates of myocardial infarction and percutaneous coronary intervention were similar. On the contrary, those treated urgently more often had undergone a previous aortic valve replacement. Regarding the main echocardiographic characteristics, emergency procedures were performed in patients with left ventricular (LV) function deterioration (39.5% ± 17.8% vs 52.5% ± 12.8%; $P < .001$), larger LV end-diastolic diameters (55 ± 9 vs 48 ± 7; $P < .001$), but similar aortic valve areas (0.66 ± 0.21 vs 0.70 ± 0.23; $P = .308$), and transaortic mean gradients (40.3 ± 18.3 vs 43.9 ± 16.3; $P = .061$).

Perioperative characteristics

Procedural results from the studies included are shown on table 2. Transfemoral access (79.3% vs 76.8%; $P = .177$) and use of general anesthesia (84.5% vs 85.4%; $P = .17$) were the preferred approaches in both groups. Elective TAVIs showed a higher procedural success rate (93.6% vs 92.5%; $P = .007$) and a lower need for mechanical circulatory support (1.96% vs 3.56 %; $P < .001$). Other procedural outcomes were comparable between both cohorts.

Postoperative outcomes

The main postoperative outcomes are shown on table 3 and figure 2. The ORs for perioperative myocardial infarction, life-threatening bleedings, need for permanent pacemaker implantation, and stroke were similar regardless of the planned or emergency setting. On the contrary, the elective cohort showed a smaller rate of acute kidney injury (9.6% vs 22.4%; OR = 2.26; 95%CI, 1.84-2.76; $P < .001$), and need for dialysis (1.1% vs 2.8%; OR = 2.37; 95%CI, 2.09-2.68; $P < .001$). Overall, this translated into shorter hospital stays for elective cases, lower in-hospital (3.3% vs 5.75%; OR = 1.32; 95%CI, 1.32-2.83; $P < .001$), 30-day (4.43% vs 8.84%; OR = 3.13; 95%CI, 1.68-5.80; $P < .001$), and 1-year mortality rates (19.7% vs 34.47%; OR = 2.87; 95%CI, 1.67-4.94; $P = .0001$) for elective TAVI (figure 3).

DISCUSSION

When patients with AS present with severe acute heart failure (HF) or CS the 5-year all-cause mortality is above 60% despite the implementation of therapies to treat valvular heart disease, which poorly compares to this rate in patients free of HF (~20%) or with chronic HF symptoms (~30%) in this setting (16). Determining the factors that condition such a high mortality rate is the key to

Table 1. Baseline clinical and echocardiographic characteristics of patients undergoing elective or emergency TAVIs

Variable	No. of patients	Overall TAVI population N = 84 427	Elective TAVI N = 70 186 (83.1%)	Emergency/urgent TAVI N = 14 241 (16.9%)	*P*
Clinical characteristics					
Sex (male) (%)	84 427	43 735/84 427 (51.8%)	36 576/70 186 (52.11%)	7 159/14 241 (50.27%)	< .001
Age (years)	44 385	81.12 ± 8.47	81.16 ± 8.27	80.96 ± 9.08	.041
EuroSCORE (%)	1387	31.24 ± 18.15	29.42 ± 17.99	68.88 ± 20.97	< .001
STS score (%)	985	14.76 ± 13.34	13.66 ± 11.61	29.39 ± 27.39	< .001
Anemia (%)	42 524	11 415/42 524 (26.84%)	8004/32 382 (24.71%)	3411/10 142 (33.63%)	< .001
Atrial fibrillation (%)	41 185	17 373/41 885 (41.47%)	15 304/37 780 (40.51%)	2069/4105 (50.40%)	< .001
CAD (%)	41 329	25 723/41 329 (62.24%)	23 178/37 308 (62.13%)	2545/4021 (63.29%)	.147
CKD (%)	83 308	17 948 /83 308 (21.54%)	13 368/69 187 (19.32%)	4580/14 121 (32.43%)	< .001
COPD (%)	84 398	25 081/84 398 (29.72%)	20 315/70 157 (28.96%)	4766/14 241 (33.47%)	< .001
Diabetes (%)	84 040	29 670/84 040 (35.30%)	24 571/69 820 (35.19%)	5099/14 220 (35.86%)	.130
Hypertension (%)	83 308	70 608/83 308 (84.75%)	59 117/69 187 (85.44%)	11 491/14 121 (81.38%)	< .001
NYHA III-IV (%)	41 143	33 056/41 143 (80.34%)	29 297/37 065 (79.04%)	3759/4078 (92.17%)	< .001
PAD (%)	84 069	25 236/84 069 (30.02%)	20 933/69 849 (29.96%)	4303/14 220 (30.26%)	.490
Porcelain aorta (%)	40 669	2158/40 669 (5.3%)	1914/36 669 (5.22%)	244/4000 (6.1%)	.018
Previous AVR (%)	40 658	1599/40 658 (3.93%)	1292/36 664 (3.53%)	307/3994 (7.69%)	< .001
Previous CABG (%)	83 656	20 924/83 656 (25.01%)	18 000/69 442 (25.92%)	2924/14 214 (20.57%)	< .001
Previous MI (%)	83 040	15 173/83 040 (18.27%)	12 597/68 868 (18.29%)	2576/14 172 (18.18%)	.747
Previous PCI (%)	83 029	22 118/83 029 (26.64%)	18 979/68 863 (27.56%)	3139/14 166 (22.16%)	< .001
Previous PM/ICD	40 774	8304/40 774 (20.36%)	7401/36 723 (20.15%)	903/4051 (22.29%)	.001
Previous stroke/TIA (%)	42 244	8815/42 244 (20.87%)	7884/38 118 (20.68%)	931/4126 (22.57%)	.005
Ecocardiographic characteristics					
Aortic valve area (cm²)	2 230	0.7 ± 0.23	0.7 ± 0.23	0.66 ± 0.21	.308
LVEDD (mm)	616	48.98 ± 7.34	48.53 ± 7.20	55.05 ± 9.03	< .001
LVEF (%)	1861	51.51 ± 13.24	52.23 ± 12.71	29.58 ± 14.89	< .001
Mean gradient (mmHg)	1398	43.71 ± 16.42	43.91 ± 16.31	40.26 ± 18.29	.061
AR III-IV (%)	41 032	8156/41 032 (19.88%)	7159/37 033 (19.33%)	997/3999 (24.93%)	< .001
PHT (%)	43 251	2003/43 251 (4.63%)	1536/33 088 (4.64%)	467/10 163 (4.6%)	.843

AR, aortic regurgitation; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA; New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PHT; pulmonary hypertension; PM, pacemaker; STS, Society of Thoracic Surgeons score; TIA, transient ischemic attack; TAVI, transcatheter aortic valve implantation.

improve the management of this growing group of patients. The main findings of this study are: *a)* patients who required emergency TAVIs had a higher baseline risk compared to planned procedures, not only due to the emergency setting, but also to a high burden of comorbidities and deterioration of LV function; *b)* although procedural success rate was significantly higher in planned cases, this difference was small (93.6% vs 92.5%; $P = .007$) suggestive that the higher short- and mid-term mortality rates seen in emergency cases were mainly due to postoperative complications, not to the intervention *per se*; *c)* need for mechanical circulatory support and dialysis was higher after emergency cases. The early identification of patients at risk who may require these therapies might be useful for a better indication of TAVI in emergency settings.

Baseline characteristics and predicted mortality

In our study, emergency/urgent TAVI patients had a more significant number of comorbid conditions compared to those who underwent elective procedures. We should mention that the Society of Thoracic Surgeons (STS) score has been widely used to assess mortality risk in SAVR patients.[17] Nevertheless, the score developed

Table 2. Procedural characteristics of patients undergoing elective or emergency/urgent TAVIs

Variable	No. of patients	Overall TAVI population	Elective TAVI	Emergency/urgent TAVI	*P*
Success rate (%)	41 140	38 765/41 440 (93.54%)	35 038/37 413 (93.65%)	3727/4027 (92.55%)	.007
Device migration (%)	40 042	105/40 042 (0.26%)	90/36 090 (0.25%)	15/3952 (0.38%)	.129
General anesthesia (%)	40 669	34 419/40 669 (84.6%)	31 004/36 669 (84.55%)	3415/4000 (85.37%)	.170
Transapical (%)	83 953	14 742/83 953 (17.56%)	12 194/69 790 (17.47%)	2548/14 163 (18%)	.139
Transfemoral (%)	83 811	66 526/83 811 (79.38%)	55 196/69 612 (79.29%)	11 330/14 199 (79.79%)	.177
Transsubclavian (%)	40 813	643/40 813 (1.57%)	573/36 834 (1.55%)	70/3979 (1.76%)	.327
Mechanical circulatory support (%)	83 326	1858/83 326 (2.29%)	1355/69 211 (1.96%)	503/14 115 (3.56%)	< .001

TAVI, transcatheter aortic valve implantation.

Table 3. Main postoperative outcomes of patients undergoing elective or emergency/urgent TAVIs

Variable	No. of patients	Overall TAVI population	Elective TAVI	Emergency/urgent TAVI	*P*
Clinical outcomes					
Life-threatening bleeding (%)	83 811	13 170/83 811 (15.71%)	9903/69 612 (14.22%)	3267/14 199 (23.01%)	< .001
Major bleeding (%)	43 400	14 725/43 400 (33.93%)	11 065/33 180 (33.35%)	3660/10 220 (35.81%)	< .001
Major vascular complications (%)	41 656	513/41 656 (1.23%)	460/37 572 (1.22%)	53/4084 (1.29%)	.686
Myocardial infarction (%)	82 671	1299/82 671 (1.57%)	557/68 526 (0.81%)	742/14 145 (5.24%)	< .001
Acute kidney injury (%)	83 811	9856/83 811 (11.75%)	6678/69 612 (9.59%)	3178/14 199 (22.38%)	< .001
Need for dialysis (%)	82 197	1178/82 197 (1.43%)	782/68 130 (1.15%)	396/14 067 (2.81%)	< .001
PPMI (%)	84 069	8786/84 069 (10.45%)	7188/69 849 (10.29%)	1598/14 220 (11.24%)	< .001
Stroke (%)	83 442	2242/83 442 (2.69%)	1824/69 270 (2.63%)	418/14 172 (2.94%)	.034
In-hospital mortality rate	83 427	3099/83 427 (3.71%)	2284/69 255 (3.3%)	815/14 172 (5.75%)	< .001
30-day mortality rate	46 228	2268/46 228 (4.9%)	1830/41 274 (4.43%)	430/4954 (8.84%)	< .001
1-year mortality rate	41 156	8706/41 156 (21 15%)	7327/37 156 (19.72%)	1379/4000 (34.75%)	< .001
Echocardiographic outcomes					
Mean gradient (mmHg)	369	7.75 ± 4.15	7.82 ± 4.22	6.9 ± 3.2	.269
AR III-IV (%)	17 977	1465/17 977 (8.15%)	1299/16 125 (8.05%)	166/1852 (8.96%)	.176

AR, aortic regurgitation; PPMI, permanent pacemaker implantation; TAVI, transcatheter aortic valve implantation.

by the Transcatheter Valve Therapy (TVT) group to evaluate in-hospital and 30-day mortality rates[18] may be more accurate. According to that score, the prognosis is strongly influenced by the presence of chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and need for emergency TAVI. Of note, AS with concomitant CKD has been linked to higher all-cause and cardiovascular mortality rates compared to patients with AS and without this condition; indeed, the increase of all-cause mortality exponentially correlates with a decline in the glomerular filtration rate.[19] In addition, the higher rate of anemia[20] and increased bleeding risk in CKD patients is well-known, which conditions a higher need for red blood cell transfusion[21] parallel to a deterioration of renal function and survival rate.

The LV function is a well-known prognostic factor of valvular heart disease and its deterioration conditions surgical or transcatheter aortic valve treatment even in asymptomatic patients.[22] We should mention that the similar transaortic gradient, despite a reduced LV function in the emerging baseline cases, suggests a more severe valve disease, probable more calcified and degenerated native valves, as also suggested by the higher rate of aortic regurgitation of this cohort. Therefore, the multidisciplinary and multi-imaging approach might be particularly useful for procedural planning and outcome improvement.[23]

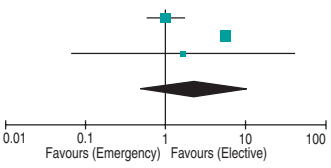
Procedural complications and mortality

Most procedural complications were similar in elective and emergency TAVIs. Although this may be partially explained by the growing operators' experience worldwide and the lack of differences in the rate of transfemoral approach,[24] the greater use of mechanical circulatory support devices may have been particularly relevant in emergency/urgent cohorts. Indeed, the more limited LV contractile reserve of this group of patients can lead to rapid deterioration in the presence of complications like periannular shunts, severe aortic

Myocardial infarction

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
D. Kolte. JACC. 2018	15	3952	137	36090	41.3%	1.00 (0.59-1.71)
Elbadawi. Catheter Cardiovasc Interv. 2019	727	10115	419	32040	43.3%	5.84 (5.17-6.61)
Ichibori Y. J Invasive Cardiol. 2019	0	78	1	396	15.3%	1.68 (0.07-41.60)
Total (95%CI)		**14145**		**68526**	**100.0%**	**2.33 (0.49-11.08)**
Total events	742		557			

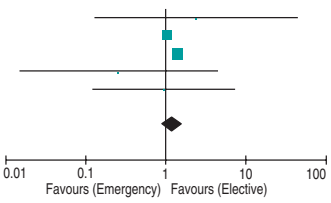
Heterogeneity: Tau² = 1.46; χ² = 40.39, df = 2 (*P* < .00001); I² = 95%
Test for overall effect: Z = 1.06 (*P* = .29)



Life-threatening bleeding

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
C. Frerker. Eurointervention. 2016	0	27	5	744	1.0%	2.44 (0.13-45.33)
D. Kolte. JACC. 2018	324	3952	2809	36090	46.4%	1.06 (0.94-1.19)
Elbadawi. Catheter Cardiovasc Interv. 2019	2942	10115	7067	32040	49.7%	1.45 (1.38-1.52)
Ichibori Y. J Invasive Cardiol. 2019	0	78	9	396	1.0%	0.26 (0.01-4.51)
U. Landes. Canandian J of Cardiology. 2015	1	27	13	342	1.9%	0.97 (0.12-7.74)
Total (95%CI)		**14199**		**69612**	**100.0%**	**1.23 (0.92-1.64)**
Total events	3267		9903			

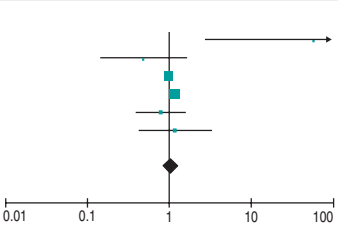
Heterogeneity: Tau² = 0.04; χ² = 24.03, df = 4 (*P* < .00001); I² = 83%
Test for overall effect: Z = 1.38 (*P* = .17)



Permanent pacemaker implantation

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
A. Unbehaun. Acquired Cardiovascular D. 2012	2	21	0	237	.5%	60.90 (2.82-1313.51)
C. Frerker. Eurointervention. 2016	3	27	153	744	2.8%	0.48 (0.14-1.62)
D. Kolte. JACC. 2018	416	3952	3789	36090	41.3%	1.00 (0.90-1.12)
Elbadawi. Catheter Cardiovasc Interv. 2019	1161	10115	3123	32040	43.9%	1.20 (1.12-1.29)
Ichibori Y. J Invasive Cardiol. 2019	11	78	68	396	7.7%	0.79 (0.40-1.58)
U. Landes. Canandian J of Cardiology. 2015	5	27	55	342	3.9%	1.19 (0.43-3.27)
Total (95%CI)		**14220**		**69849**	**100.0%**	**1.07 (0.87-1.32)**
Total events	1598		7188			

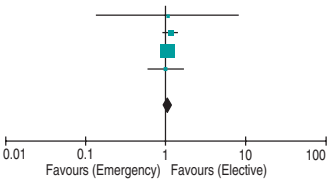
Heterogeneity: Tau² = 0.02; χ² = 16.92, df = 5 (*P* = .005); I² = 70%
Test for overall effect: Z = 0.65 (*P* = .52)



Stroke

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio M-H Fixed, 95%CI
C. Frerker. Eurointervention. 2016	1	27	26	744	.3%	1.06 (0.14-8.13)
D. Kolte. JACC. 2018	91	3952	713	36090	24.9%	1.17 (0.94-1.46)
Elbadawi. Catheter Cardiovasc Interv. 2019	274	10115	823	32040	69.6%	1.06 (0.92-1.21)
Ichibori Y. J Invasive Cardiol. 2019	52	78	262	396	5.2%	1.02 (0.61-1.71)
Total (95%CI)		**14172**		**69270**	**100.0%**	**1.08 (0.97-1.21)**
Total events	418		1824			

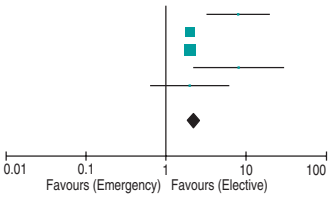
Heterogeneity: χ² = 0.64, df = 3 (*P* = .89); I² = 0%
Test for overall effect: Z = 1.36 (*P* = .17)



Acute Kidney injury

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
C. Frerker. Eurointervention. 2016	8	27	37	744	4.7%	8.05 (3.30-19.59)
D. Kolte. JACC. 2018	323	3952	1511	36090	41.8%	2.04 (1.80-2.31)
Elbadawi. Catheter Cardiovasc Interv. 2019	2837	10115	5099	32040	48.1%	2.06 (1.95-2.17)
Ichibori Y. J Invasive Cardiol. 2019	6	78	4	396	2.4%	8.17 (2.25-29.66)
U. Landes. Canandian J of Cardiology. 2015	4	27	27	342	3.0%	2.03 (0.65-6.29)
Total (95%CI)		**14199**		**69612**	**100.0%**	**2.26 (1.84-2.76)**
Total events						

Heterogeneity: Tau² = 0.02; χ² = 13.39, df = 4 (*P* < .010); I² = 70%
Test for overall effect: Z = 7.86 (*P* < .00001)



New dialysis

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio M-H Fixed, 95%CI
D. Kolte. JACC. 2018	94	3952	373	36090	27.4%	2.33 (1.86-2.93)
Elbadawi 2019	302	10115	409	32040	72.6%	2.38 (2.05-2.77)
Total (95%CI)		**14067**		**68130**	**100.0%**	**2.37 (2.09-2.68)**
Total events	396		782			

Heterogeneity: χ² = 0.02, df = 1 (*P* = .89); I² = 0%
Test for overall effect: Z = 13.42 (*P* < .00001)

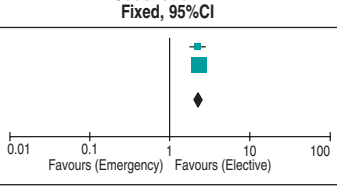
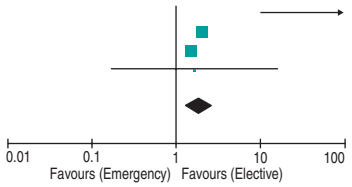


Figure 2. Forest plot showing the main postoperative complications of patients included in the meta-analysis.*
* Vertical line represents "no difference" point between the emergency and the elective TAVI groups. Horizontal lines represent the 95%CI. Squares represent the OR for each study (the size of each square shows the amount of information given by each study). Diamonds represent pooled OR from all studies.

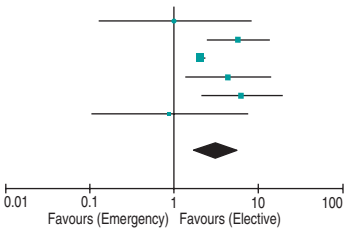
In-hospital global mortality

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
C. Frerker. Eurointervention. 2016	3	27	0	729	1.6%	208.43 (10.48-4146.43)
D. Kolte. JACC. 2018	241	3952	1083	36090	47.1%	2.10 (1.82-2.42)
Elbadawi. Catheter Cardiovasc Interv. 2019	570	10115	1198	32040	48.7%	1.54 (1.39-1.70)
Ichibori Y. J Invasive Cardiol. 2019	1	78	3	396	2.7%	1.70 (0.17-16.57)
Total (95%CI)		**14172**		**69255**	**100.0%**	**1.93 (1.32-2.83)**
Total events	815		2284			
Heterogeneity: Tau² = 0.08; χ² = 21.89, df = 3 (*P* < .00001); I² = 86%						
Test for overall effect: Z = 3.36 (*P* = .0008)						



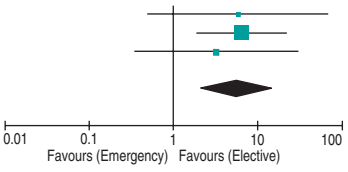
30-day global mortality

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
A. Unbehaun. Acquired Cardiovascular D. 2012	1	21	11	237	6.9%	1.03 (0.13-8.37)
C. Frerker. Eurointervention. 2016	9	27	56	729	20.9%	6.01 (2.58-13.99)
D. Kolte. JACC. 2018	416	4780	1726	39233	33.9%	2.07 (1.85-2.32)
G. D'Ancona. Interactive CardioVascular. 2014	4	21	17	337	15.1%	4.43 (1.34-14.61)
Ichibori Y. J Invasive Cardiol. 2019	7	78	6	396	16.1%	6.41 (2.09-19.63)
U. Landes. Canandian J of Cardiology. 2015	1	27	14	342	7.1%	0.90 (0.11-7.12)
Total (95%CI)		**4954**		**41274**	**100.0%**	**3.13 (1.68-5.80)**
Total events	438		1830			
Heterogeneity: Tau² = 0.29; χ² = 12.31, df = 5 (*P* = .03); I² = 59%						
Test for overall effect: Z = 3.61 (*P* = .0003)						



30-day cardiovascular mortality

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
A. Unbehaun. Acquired Cardiovascular D. 2012	1	21	2	237	13.0%	5.88 (0.51-67.64)
Ichibori Y. J Invasive Cardiol. 2019	6	78	5	396	63.5%	6.52 (1.94-21.92)
U. Landes. Canandian J of Cardiology. 2015	1	27	4	342	23.6%	3.25 (0.35-30.14)
Total (95%CI)		**126**		**975**	**100.0%**	**5.66 (2.16-14.85)**
Total events	8		11			
Heterogeneity: χ² = 0.29, df = 2 (*P* < .86); I² = 0%						
Test for overall effect: Z = 3.52 (*P* = .0004)						



1-year global mortality

Study or subgroup	Emergency Events	Emergency Total	Elective Events	Elective Total	Weight	Odds ratio IV Random, 95%CI
C. Frerker. Eurointervention. 2016	11	27	13	744	32.1%	38.66 (15.05-99.31)
D. Kolte. JACC. 2018	1357	3952	7140	36090	35.6%	2.12 (1.98-2.28)
G. D'Ancona. Interactive CardioVascular. 2014	11	21	57	337	32.4%	5.40 (2.19-13.32)
Total (95%CI)		**4000**		**37171**	**100.0%**	**7.28 (1.32-40.12)**
Total events	1379		7210			
Heterogeneity: Tau² = 2.13; χ² = 40.14, df = 2 (*P* < .00001); I² = 95%						
Test for overall effect: Z = 2.28 (*P* = .02)						

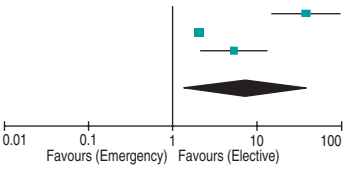


Figure 3. Forest plot showing the in-hospital to 1-year mortality rates of patients included in the meta-analysis.*
* Vertical line represents "no difference" point between the emergency and the elective TAVI groups. Horizontal lines represent the 95%CI. Squares represent OR for each study (the size of each square shows the amount of information given by each study). Diamonds represent pooled OR from all studies.

regurgitation or coronary obstruction. Therefore, the presence of risk factors for these complications may suggest the need for circulatory support devices in certain cases before valve implantation as a potential strategy to avoid dreadful prognoses if they occur in the emergency setting.[25-27] Prior experience with the Impella device and extracorporeal membrane oxygenation is shown on table 3 of the supplementary data; however, whether there are mortality differences between those with and without mechanical support requires further research. Since procedural success was similar to that of the standard setting, the clinical translation of this is that, even if these cases can be performed successfully in all centers by implanting TAVI, this profile of patients should only be treated in centers with mechanical circulatory support devices available (particularly ECMO), which would exclude low volume or non-surgical centers.

In the present meta-analysis, the cases treated with isolated balloon aortic valvuloplasty were not included. This strategy bears a class IIb-C level of evidence in the last iteration of the guidelines, but it is often used as a bridging therapy to definitive TAVI in hemodynamically unstable patients.[28,29] A single-center retrospective study found that TAVI may be superior to a stand-alone balloon aortic valvuloplasty and medical therapy in patients with severe AS and CS, since the isolated balloon aortic valvuloplasty is not free of complications (~25%) and has higher mortality rates.[30] Despite of this, large randomized controlled trials exploring this scenario with TAVI are lacking.

Postoperative complications associated with a higher mortality rate

In this systematic review and meta-analysis, we found that emergency/urgent TAVIs had a significantly higher rate of AKI, hemodialysis, and mortality. This is consistent with previous reports that found that patients with post-TAVI AKI were more likely to die. Besides, AKI is a predictor of sepsis, which is also an independent predictor of mortality. The main factors increasing the risk of AKI include CKD, peripheral artery disease, diabetes mellitus, and deterioration of LV function.[31,32] A prophylactic strategy may vary from

simple hydration with a normal saline solution to forced diuresis with early supportive measures;[33] indeed, the use of prophylactic dialysis has been explored in TAVI patients with a high risk of AKI and may be particularly useful in the emergency setting.

Study limitations

There are several limitations related to this systematic review and meta-analysis. First, the studies included were observational since no multicenter randomized studies specifically addressing this topic could be found. Secondly, the definition of emergency/urgent procedures was variable in the studies although an inclusive definition was reached by the study team. Finally, the results may not be generalizable and should be interpreted with caution due to the high heterogenicity reported, which may relate to variability in the study samples and designs.

CONCLUSIONS

In conclusion, the association between emergency/urgent TAVIs and a higher short-to-mid-term mortality rate is mainly due to a high-risk baseline profile, advanced stage of the cardiac disease, and higher rate of acute renal failure. The early identification and referral of patients at high risk for circulatory collapse or AKI need to be properly identified to reduce the TAVI related mortality rate. Further research is needed to elucidate the role of TAVI in emergency or urgent scenarios.

FUNDING

No funding to declare.

CONFLICTS OF INTEREST

I. J. Amat-Santos is a proctor for Boston Scientific.

WHAT IS KNOWN ABOUT THE TOPIC?

– TAVI is performed mainly in hemodynamically stable patients, otherwise aortic balloon valvuloplasty is empirically preferred as a bridging therapy to TAVI. However, few studies have addressed TAVI in life-threatening scenarios and multicenter randomized controlled trials are still lacking.

WHAT DOES THIS STUDY ADD?

– In this large pooled meta-analysis (n = 84 427) emergency TAVI was not rare but associated with higher in-hospital, 30-day, and 1-year mortality rates compared to elective procedures. The need for dialysis or mechanical circulatory support conditioned the mortality rate following emergency TAVIs. The early identification of patients at risk of circulatory collapse or acute kidney injury may help to determine if TAVI is futile in this setting.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000203.

REFERENCES

1. Thaden JJ., Nkomo VT., Enriquez-Sarano M. The Global Burden of Aortic Stenosis. *Prog Cardiovasc Dis.* 2014;56:565-571.
2. Akodad M., Schurtz G., Adda J., Leclercq F., Roubille F. Management of valvulopathies with acute severe heart failure and cardiogenic shock. *Arch Cardiovasc Dis*. 2019;112:773-780.
3. Castrodeza J, Serrador Frutos AM, Amat-Santos IJ, et al. Prophylactic percutaneous circulatory support in high risk transcatheter aortic valve implantation. *Cardiol J*. 2019; 26:424-426.
4. Smith CR., Leon MB., Mack MJ., et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *New Engl J Med*. 2011; 364:2187-2198.
5. Leon MB., Smith CR., Mack MJ., et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *New Engl J Medicine.* 2016;374:1609-1620.
6. Reardon MJ., Mieghem NMV., Popma JJ., et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. New Engl J Medicine 2017;376:1321-1331.
7. Waksman R., Rogers T., Torguson R., et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Aortic Stenosis. *J Am Coll Cardiol*. 2018;72:2095-2105.
8. D'Ancona G., Pasic M., Buz S., et al. Transapical transcatheter aortic valve replacement in patients with cardiogenic shock. *Interact Cardiov Th*. 2012; 14:426-430.
9. Unbehaun A., Pasic M., Buz S., et al. Transapical aortic valve implantation in patients with severely depressed left ventricular function. *J Thorac Cardiovasc Surg*. 2012;143:1356-1363.
10. Landes U., Orvin K., Codner P., et al. Urgent Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis and Acute Heart Failure: Procedural and 30-Day Outcomes. *Can J Cardiol*. 2016;32:726-31.
11. Frerker C., Schewel J., Schlüter M., et al. Emergency transcatheter aortic valve replacement in patients with cardiogenic shock due to acutely decompensated aortic stenosis. *Eurointervention*. 2016;11:1530-1536.
12. Kolte D., Khera S., Vemulapalli S., et al. Outcomes Following Urgent/Emergency Transcatheter Aortic Valve Replacement: Insights from the STS/ACC TVT Registry. Jacc Cardiovasc Interventions 2018;11:1175-1185.
13. Elbadawi A., Elgendy IY., Mentias A., et al. Outcomes of urgent versus nonurgent transcatheter aortic valve replacement. *Catheter Cardiovasc Interv.* 2020 Jul;96:189-195.
14. Ichibori Y., Li J., Patel T., et al. Short-Term and Long-Term Outcomes of Patients Undergoing Urgent Transcatheter Aortic Valve Replacement Under a Minimalist Strategy. *J Invasive Cardiol.* 2019:E30-E36.
15. Kappetein AP., Head SJ., Généreux P., et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33:2403-2418.
16. Nagao K., Taniguchi T., Morimoto T., et al. Acute Heart Failure in Patients With Severe Aortic Stenosis- Insights From the CURRENT AS Registry. *Circ J*. 2018;82:874-885.
17. Yakubov SJ., Adams DH., Watson DR., et al. 2-Year Outcomes After Iliofemoral Self-Expanding Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis Deemed Extreme Risk for Surgery. *J Am Coll Cardiol*. 2015;66:1327-1334.
18. Arnold SV., O'Brien SM., Vemulapalli S., et al. Inclusion of Functional Status Measures in the Risk Adjustment of 30-Day Mortality After Transcatheter Aortic Valve Replacement A Report From the Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC Cardiovasc Interv*. 2018;11:581-589.
19. Patel KK., Shah SY., Arrigain S., et al. Characteristics and Outcomes of Patients With Aortic Stenosis and Chronic Kidney Disease. *J Am Heart Assoc*. 2019 Feb 5;8:e009980.
20. DeLarochellière H., Urena M., Amat-Santos IJ., et al. Effect on Outcomes and Exercise Performance of Anemia in Patients With Aortic Stenosis Who Underwent Transcatheter Aortic Valve Replacement. *Am J Cardiol*. 2015;115:472-479.
21. Kanjanahattakij N., Rattanawong P., Krishnamoorthy P., et al. Anaemia and mortality in patients with transcatheter aortic valve replacement: a systematic review and meta-analysis. *Acta Cardiol*. 2018;74:1-7.
22. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.
23. Fassa A-A., Himbert D., Vahanian A. Mechanisms and management of TAVR-related complications. *Nat Rev Cardiol*. 2013;10:685-695.
24. Terré JA., George I., Smith CR. Pros and cons of transcatheter aortic valve implantation (TAVI). *Ann Cardiothorac Surg*. 2017;6:444-452.
25. Chieffo A., Ancona MB., Burzotta F., et al. Observational multicentre registry of patients treated with IMPella mechanical circulatory support

device in ITaly: the IMP-IT registry. *EuroIntervention*. 2020 Feb 7;15: e1343-e1350.
26. Singh V., Damluji AA., Mendirichaga R., et al. Elective or Emergency Use of Mechanical Circulatory Support Devices During Transcatheter Aortic Valve Replacement. *J Interv Cardiol.* 2016;29:513-522.
27. Shreenivas SS., Lilly SM., Szeto WY., et al. Cardiopulmonary bypass and intra-aortic balloon pump use is associated with higher short and long term mortality after transcatheter aortic valve replacement: A PARTNER trial substudy. *Catheter Cardiovasc Interv*. 2015:316-322.
28. Singh V, Damluji AA, Mendirichaga R, et al. Elective or Emergency Use of Mechanical Circulatory Support Devices During Transcatheter Aortic Valve Replacement. *J Interv Cardiol.* 2016; 29:513-522.
29. Baumgartner H., Falk V., Bax JJ., et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.
30. Saia F., Marrozzini C., Ciuca C., et al. Emerging indications, in-hospital and long-term outcome of balloon aortic valvuloplasty in the transcatheter aortic valve implantation era. *Eurointervention*. 2013;8:1388-1397.
31. Ram P., Mezue K., Pressman G., Rangaswami J. Acute kidney injury post-transcatheter aortic valve replacement. *Clin Cardiol.* 2017;40:1357-1362.
32. Wang J., Yu W., Zhou Y., et al. Independent Risk Factors Contributing to Acute Kidney Injury According to Updated Valve Academic Research Consortium-2 Criteria After Transcatheter Aortic Valve Implantation: A Meta-analysis and Meta-regression of 13 Studies. *J Cardiothor Vasc An*. 2017;31:816-826.
33. Putzu A, Berto MB, Belletti A, et al. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: a systematic review and meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2017;10:355-363.

REC Interv Cardiol. 2021;3(3):175-181
https://doi.org/10.24875/RECICE.M21000210

Original article

Single or dual antiplatelet therapy after transcatheter aortic valve implantation. A meta-analysis of randomized controlled trials

Jorge Sanz-Sánchez,[a,b,c,◊] Carlo Andrea Pivato,[a,b,◊] Pier Pasquale Leone,[a,b,◊] Damiano Regazzoli,[b] Mauro Chiarito,[a,b] Gennaro Petriello,[b] Bernhard Reimers,[a,b] Gianluigi Condorelli,[a,b] and Giulio G. Stefanini[a,b,*]

[a] *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy*
[b] *Cardio Center, Humanitas Clinical and Research Center - IRCCS, Rozzano, Milan, Italy*
[c] *Servicio de Cardiología, Hospital Universitario y Politécnico La Fe, Valencia, Spain*

ABSTRACT

Introduction and objectives: Current expert consensus guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel as antithrombotic strategy after transcatheter aortic valve implantation (TAVI) in patients without an indication for long-term oral anticoagulation. However, these recommendations have not been developed based on the results of large randomized clinical trials**.** The objective of this study is to compare single antiplatelet therapy (SAPT) to DAPT in patients without an indication for long-term anticoagulation after TAVI.
Methods: The PubMed, Embase, and the main international conference proceedings were reviewed in the search for randomized controlled trials comparing SAPT to DAPT after TAVI. Data were pooled using a meta-analysis and a random-effects model. The primary endpoint was life-threatening or major bleeding.
Results: Four trials enrolling 1086 patients were included. Compared to patients treated with DAPT, those treated with SAPT showed a lower risk of life-threatening or major bleeding (OR, 0.44; 95%CI, 0.27-0.70), and any bleeding (OR, 0.51; 95%CI, 0.36-0.71). No differences were observed between patients treated with SAPT compared to those treated with DAPT regarding all-cause mortality (OR, 1.01; 95%CI, 0.61-1.68), myocardial infarction (OR, 0.50; 95%CI 0.17-1.41), and stroke (OR, 0.98; 95%CI, 0.54-1.77).
Conclusions: In patients without an indication for long-term anticoagulation undergoing TAVI, single antiplatelet therapy with aspirin compared to DAPT is associated with a lower risk of life-threatening or major bleeding and a comparable risk of all-cause mortality, myocardial infarction, and stroke.

Keywords: Antithrombotic therapy. TAVI. Antiplatelet therapy. Aspirin. Bleeding.

Tratamiento antiagregante plaquetario único o doble tras implante percutáneo de válvula aórtica. Metanálisis de ensayos clínicos aleatorizados

RESUMEN

Introducción y objetivos: Las guías de práctica clínica actuales recomiendan la terapia antiagregante plaquetaria doble con ácido acetilsalicílico y clopidogrel como estrategia antitrombótica tras el implante percutáneo de válvula aórtica (TAVI) en pacientes sin indicación de anticoagulación oral a largo plazo. Sin embargo, estas recomendaciones no se han desarrollado de acuerdo con los resultados de grandes ensayos aleatorizados. Por ello, el objetivo de esta investigación es comparar la terapia antiplaquetaria en monoterapia con el tratamiento antiagregante doble en pacientes sin indicación de anticoagulación a largo plazo después de un TAVI.
Métodos: Se realizaron búsquedas en PubMed, Embase y los principales congresos internacionales para encontrar ensayos clínicos aleatorizados que compararan el tratamiento antiagregante único con la doble terapia antiplaquetaria después de un TAVI. Los datos se agruparon en un metanálisis mediante un modelo de efectos aleatorios. El objetivo principal del estudio fue la hemorragia grave o potencialmente mortal.

◊ J. Sanz-Sánchez, C. A. Pivato and P. P. Leone contributed equally to this work.

*** Corresponding author:** Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele - Milan, Italy.
E-mail address: giulio.stefanini@gmail.com (G. G. Stefanini).

Received: 15 January 2021. Accepted: 4 March 2021. Online: 07-04-2021.

Resultados: Se incluyeron cuatro ensayos que en total reclutaron 1086 pacientes. Los pacientes bajo tratamiento antiagregante en monoterapia, en comparación con aquellos con doble terapia antiplaquetaria, tuvieron menor riesgo de hemorragia grave o potencialmente mortal (odds ratio [OR] = 0,44; intervalo de confianza del 95% [IC95%], 0,27-0,70) y de cualquier sangrado (OR = 0,51; IC95%, 0,36-0,71). No se observaron diferencias entre los pacientes tratados con monoterapia y los tratados con doble terapia antiagregante en cuanto a muerte por cualquier causa (OR = 1,01; IC95%, 0,61-1,68), infarto de miocardio (OR = 0,50; IC95%: 0,17-1,41) y accidente cerebrovascular (OR = 0,98; IC95%, 0,54-1,77).
Conclusiones: En los pacientes sin indicación de anticoagulación a largo plazo sometidos a TAVI, la monoterapia con ácido acetilsalicílico en comparación con la doble terapia antiagregante se asocia con un menor riesgo de hemorragia grave o potencialmente mortal y con un riesgo comparable de muerte por cualquier causa, infarto de miocardio y accidente cerebrovascular.

Palabras clave: Tratamiento antitrombótico. TAVI. Tratamiento antiagregante. Ácido acetilsalicílico. Sangrado.

Abbreviations

DAPT: dual antiplatelet therapy. **PCI:** percutaneous coronary intervention. **RCT:** randomized clinical trial. **SAPT:** single antiplatelet therapy. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Over the last 20 years, transcatheter aortic valve implantation (TAVI) has emerged as a successful therapeutic alternative strategy to surgery to treat aortic valve stenosis in patients of high, intermediate, and low surgical risk.[1-6]

Ischemic and bleeding complications are not rare after TAVI and can be life-threatening. Recently, the PARTNER 3 and Evolut Low Risk clinical trials have shown low, yet non-negligible, incidence rates of both stroke, and major bleeding within 30 days after TAVI.[5,6]

As of today, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is the most commonly used antithrombotic regimen after TAVI in patients without an indication for long-term oral anticoagulation enrolled in clinical studies. Indeed, the recommendations from different societal guidelines suggest 1 to 3, 3 to 6 or 6 months of therapy with clopidogrel plus low doses of aspirin. However, such recommendations have not been developed based on the results of large randomized clinical trials.[7-10] Indeed, reports on course duration over the last decade have suggested a neutral or beneficial effect of single antiplatelet therapy (SAPT) compared to early DAPT followed by SAPT regarding vascular complications and major or life-threatening bleeding and no higher risk for myocardial infarction, and stroke.[11-13] Recently, aspirin alone proved superior compared to a 3-month course of aspirin plus clopidogrel followed by aspirin in terms of bleeding alone and combined with thromboembolic complications at the 1-year follow-up.[14]

We conducted a meta-analysis of available randomized clinical studies to provide a comprehensive and quantitative assessment of the evidence available on the safety and efficacy profile of SAPT compared to DAPT after TAVI in patients with no indication for long-term oral anticoagulation.

METHODS

Search strategy and selection criteria

Randomized clinical trials (RCTs) including patients undergoing TAVI were evaluated to be included in this meta-analysis. Eligible studies had to meet the following prespecified inclusion criteria: *a)* RCTs comparing SAPT to DAPT after TAVI, and *b)* availability of clinical outcome data. The exclusion criteria were these: *a)* RCTs including patients requiring oral anticoagulation, *b)* lack of randomized design, *c)* lack of any clinical outcome data.

The search strategy, study selection, data extraction, and data analysis were performed based on The Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[15]

Back in August 31, 2020, we searched the PubMed and Embase databases. We also searched abstracts presented at relevant scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, EuroPCR, and Transcatheter Cardiovascular Therapeutics). We also used backward snowballing (ie, review of references from identified articles and pertinent reviews). The search strategy is available in the supplementary data.

Data extraction

Three investigators (J. Sanz-Sánchez, C. A. Pivato, and P. P. Leone) independently assessed studies with potential to be included. The senior investigator (G. G. Stefanini) resolved the discrepancies. Non-relevant articles were excluded based on title and abstract. The same investigators independently extracted data on the study design, measurements, patient characteristics, and outcomes, using a standardized data-extraction form. Data extraction conflicts were discussed and resolved with the senior investigator (G. G. Stefanini).

Data about the authors, year of publication, inclusion, and exclusion criteria, sample size, the patients' baseline characteristics, endpoint definitions, effect estimates, and follow-up time were collected.

Outcomes of interest

The prespecified primary endpoint was life-threatening or major bleeding. The secondary clinical endpoints were all-cause mortality, myocardial infarction, stroke, and any bleeding. Each endpoint was assessed according to the definitions reported in the original study protocols as shown on table 1 of the supplementary data.

Risk of bias

The risk of bias in each study was assessed using the revised Cochrane risk-of-bias tool (RoB 2.0).[16] Three investigators (J. Sanz-

Sánchez, C. A. Pivato, and P. P. Leone) independently assessed 5 domains of bias in the RCTs: 1) randomization process, 2) deviations from intended interventions, 3) missing outcome data, 4) outcome measurements, and 5) selection of reported results (table 2 of the supplementary data).

Statistical analysis

The odds ratios (OR) and the 95% confidence intervals (CI) were calculated using the DerSimonian and Laird random-effects model with the estimate of heterogeneity being taken from the Mantel-Haenszel method. The number needed to treat (NNT) to prevent 1 event was calculated from weighted estimates of pooled ORs using the random-effects meta-analytic model. The presence of heterogeneity among the studies was evaluated using Cochran Q test based on a chi-square distribution with P values ≤ .10 considered statistically significant, and the I^2 test to evaluate inconsistencies. A value of 0% indicates no observed heterogeneity, and values of ≤ 25%, ≤ 50%, > 50% are indicative of low, moderate, and high heterogeneity, respectively. The presence of publication bias was investigated by visual estimation through funnel plots. We conducted a leave-one-out sensitivity analysis for the primary endpoint by iteratively removing 1 study at a time to confirm that our findings were not driven by any single study. Further sensitivity analyses were conducted by calculating the ORs with a 95%CI using a fixed-effects model with the Mantel and Haenszel method and the risk ratios with a 95%CI using both fixed-effects and random-effects models. The statistical level of significance was 2-tailed P values < .05. Statistical analyses were performed using the Stata software version 13.1 (StataCorp LP, College Station, United States).

RESULTS

Search results

Figure 1 shows the PRISMA study search and selection process. A total of 4 RCTs were identified and included in this analysis. The main features of the studies included are shown on table 1.

A total of 541 patients treated with aspirin and 545 patients treated with DAPT after TAVI were included.

Baseline characteristics

The main baseline characteristics of the patients included are shown on table 2. Most patients underwent TAVI due to aortic stenosis. The Society of Thoracic Surgeons mean predicted risk of mortality was 4.4% and most of the procedures were performed via transfemoral access.

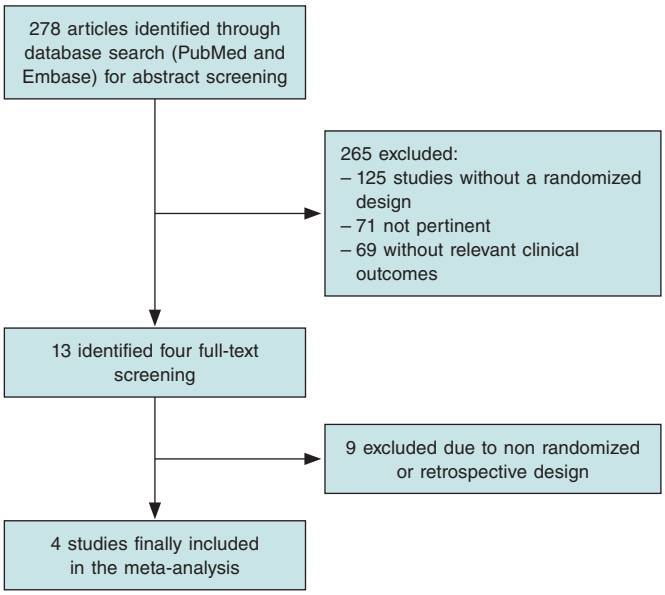


Figure 1. Flowchart of the study selection process.

Publication bias and asymmetry

The funnel-plot distributions of the prespecified outcomes are indicative of lack of publication bias for all the outcomes (figures 1-5 of the supplementary data).

Outcomes

Compared to patients treated with DAPT, those treated with SAPT had a lower risk of life-threatening or major bleeding (OR, 0.44; 95%CI, 0.27-0.70; I^2 = 0%), and any bleeding (OR, 0.51; 95%CI, 0.36-0.71; I^2 = 0%) (figure 2). No differences were seen between patients treated with SAPT compared to those treated with DAPT in terms of all-cause mortality (OR, 1.01; 95%CI, 0.61-1.68; I^2 = 0%), myocardial infarction (OR, 0.50; 95%CI, 0.17-1.41; I^2 = 0%), and stroke (OR, 0.98; 95%CI, 0.54-1.77; I^2 = 0%) (figure 3). The NNT to prevent 1 life-threatening or major bleeding was 17 patients and the NNT to prevent any bleeding was 11 patients.

Risk of bias assessment

Table 2 of the supplementary data shows the results of the risk of bias assessment using the RoB 2.0 tool. Two trials were considered at a low overall risk of bias[11,14] and 2 presented some concerns.[12,13]

Table 1. Key study features

Study	Year of publication	Study design	N of patients			Multicentre	Follow-up	DAPT duration
			Overall	DAPT	SAPT			
POPular TAVI[14]	2020	RCT	665	334	331	Yes	12 months	3 months
ARTE[11]	2017	RCT	222	111	111	Yes	3 months	3 months
SAT-TAVI[12]	2014	RCT	120	60	60	No	6 months	6 months
Ussia et al.[13]	2011	RCT	79	40	39	No	6 months	3 months

DAPT, dual antiplatelet therapy; RCT, randomized clinical trial; SAPT, single antiplatelet therapy.

Table 2. Baseline clinical characteristics of the patients included

Study	Age (years)	Male	Diabetes	Hypertension	Atrial fibrillation	NYHA ≥ III	LVEF	STS-PROM score	Previous stroke	Previous MI	Transfemoral access	Valve-in-valve	TAVI indication: aortic stenosis
POPular TAVI[14]	80	50	24	75	–	65	–	2.5	4	9	89	6	98
ARTE[11]	79	58	35	79	–	–	54	6.3	–	21	69	–	–
SAT-TAVI[12]	81	37	27	95	–	89	52	10	–	–	100	–	100
Ussia et al.[13]	81	46	27	84	13	62	52	7.3	8	14	97	0	100
Overall	80	50	27	79	–	68	53	4.4	–	12	87	–	98

LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons Predicted Risk Of Mortality; TAVI, transcatheter valve implantation.
Data are expressed as %.

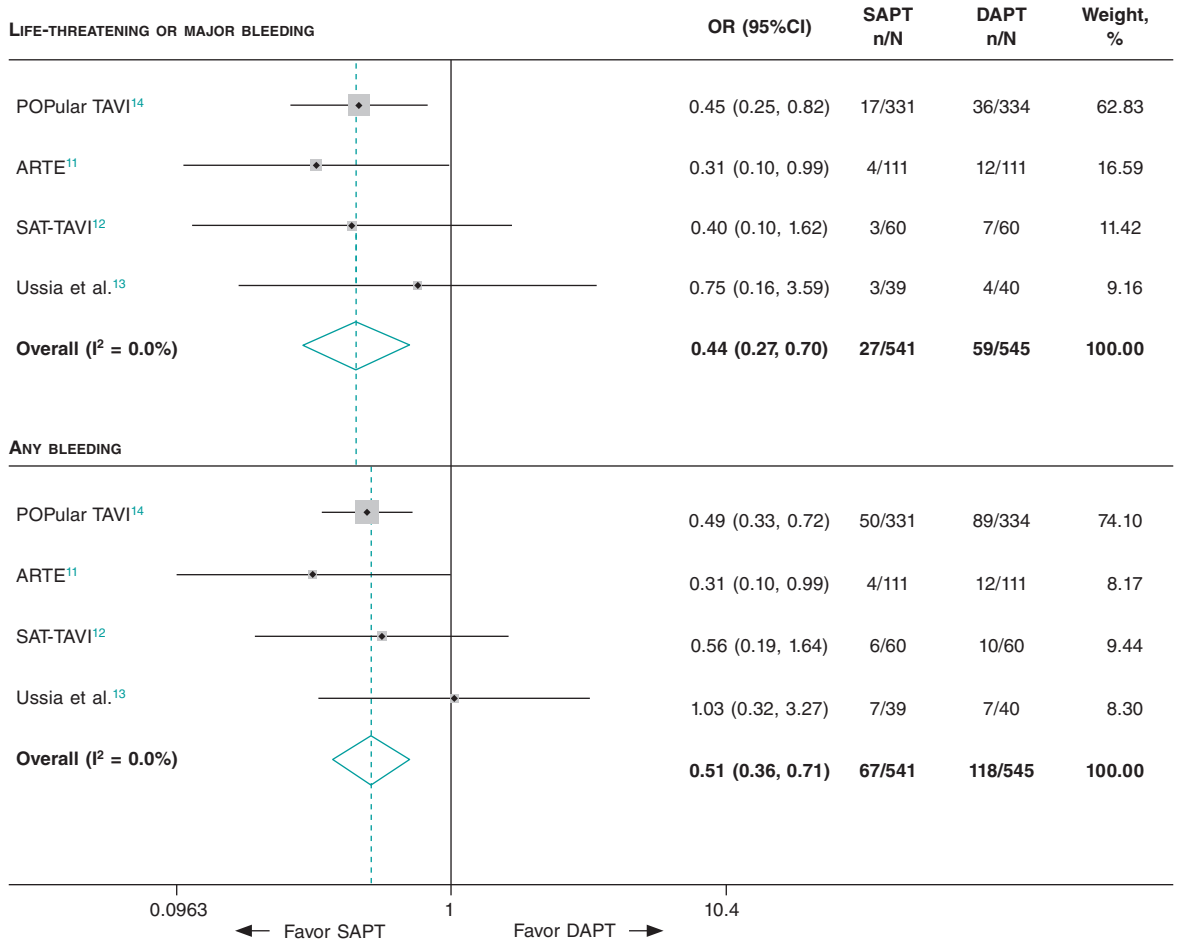


Figure 2. Bleeding outcomes in patients treated with SAPT compared to DAPT after TAVI. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation.

Sensitivity analyses

Findings remained consistent with the main analysis after calculating the ORs using a fixed effects model and risk ratios with both fixed and random-effects models (table 3 of the supplementary data).

The leave-one-out sensitivity analysis results remained consistent with the primary analysis (table 4 of the supplementary data).

DISCUSSION

The current meta-analysis evaluated available RCTs comparing SAPT with aspirin to DAPT in patients undergoing TAVI with no indication for long-term oral anticoagulation. The main findings were these:

1) The risk of life-threatening or major bleeding, and any bleeding is reduced in patients treated with SAPT compared to DAPT.

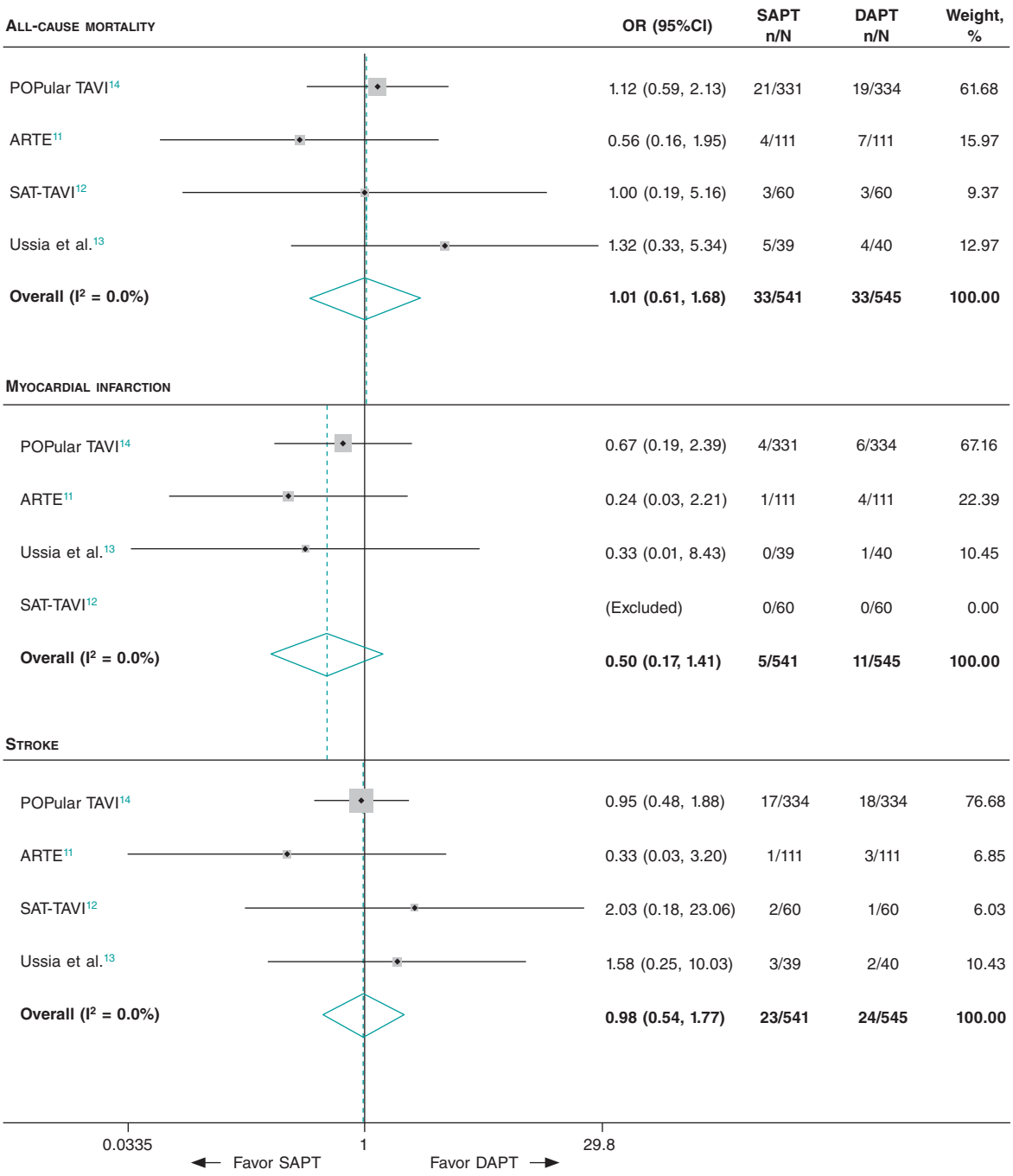


Figure 3. All-cause mortality and efficacy outcomes in patients treated with SAPT compared to DAPT after TAVI. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation.

2) The risk of all-cause mortality, myocardial infarction, and stroke did not differ between the 2 treatment strategies.

Currently, the clinical practice guidelines recommend DAPT for 1 to 6 months after TAVI in patients with no indication for long-term oral anticoagulation.[7-9] However, this regimen is not supported by actual evidence available. This practice is derived from the percutaneous coronary intervention field where the addition of a $P2Y_{12}$ inhibitor to aspirin compared to aspirin monotherapy proved to reduce the risk of ischemic complications especially stent thrombosis.[17] The addition of clopidogrel to aspirin after TAVI has the theorical rationale of reducing the rate of ischemic cerebrovascular events, myocardial infarction, and valve thrombosis.

Ischemic stroke is one of the worst complications after TAVI. Its highest incidence rate occurs within the first 24 hours after the procedure. It seems to be mainly associated with embolized tissue waste during TAVI due to dilation of the calcified valve or navigation through the aortic arch.[18-20] Instead, subacute stroke (between 1 to 30 days after the procedure)—representative of a quarter of the total number events at 2 years—[4,21] are often associated with new-onset atrial fibrillation,[22-24] against which DAPT is known to perform poorly.

Another motivation to prescribe DAPT after TAVI is to limit the rate of myocardial infarction. Nevertheless, the reported rate of myocardial infarction after TAVI is relatively low,[4,21] and

concomitant coronary artery disease is often treated percutaneously before TAVI. Therefore, the addition of a $P2Y_{12}$ inhibitor to aspirin after TAVI does not seem to offer any additional advantages compared to aspirin monotherapy regarding the reduction of the risk of myocardial infarction as our results showed.

Finally, while symptomatic valve thrombosis is a rare condition (< 1%), subclinical thrombosis has a higher incidence rate (from 10% to 40% according to different series).[25-27] The clinical impact of this phenomenon is still unknown: it could not only impact valve durability due to pannus formation, but it also has been associated with a higher rate of transient ischemic attack.[25,26] In this setting, the pathophysiology of thrombus formation after TAVI is also still under discussion as the relative weight of primary and secondary hemostasis is still to be established. On the one hand, the endothelial injury and high shear stress environment present all around the valve stent frame before re-endothelialization may favour platelet aggregation, thus leading to the formation of a platelet-rich thrombus. This is somehow similar to what happens during coronary stent thrombosis against which the most effective treatment has proven to be DAPT.[17] On the other hand, the bioprosthetic sinus of the valve leaflets could favour a condition of low shear stress and flow turbulence, thus predisposing to the development of a thrombin-rich thrombus. DAPT seems to offer no benefit over SAPT in terms of reducing bioprosthetic valve thrombosis while oral anticoagulants have proven to both prevent and resolve this complication.[25-27] However, so far the only trial to assess the role of anticoagulant therapy following TAVI in patients with no indication for long-term oral anticoagulation is the Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes (GALILEO). It was stopped following relevant safety issues seen on the interim analyses revealing higher rates of complications with low doses of rivaroxaban/aspirin compared to DAPT including hard endpoints like mortality (6.8% vs 3.3%).[28]

Overall, ischemic events post-TAVI seem to elude the antiplatelet action provided by thienopyridines added to aspirin. A current meta-analysis confirms that the addition of a $P2Y_{12}$ inhibitor does not reduce the risk of ischemic events (ie, myocardial infarction, and stroke), but most importantly predisposes patients to a higher risk of life-threatening or major bleeding. The bleeding risk reduction seen with SAPT compared to DAPT shown by this meta-analysis is of great clinical relevance, with a NNT of only 11 patients to prevent any bleeding and a NNT of 17 patients to prevent 1 life-threatening or major bleeding. Moreover, since most of the bleeding events occur within 30 days after the procedure, likely due to periprocedural antithrombotic therapy and access site bleeding complications,[1-4,29] even a short-term DAPT course raises safety issues in term of bleeding events.

Based on the evidence published so far and the results of this research, in patients with no indication for long-term anticoagulation undergoing TAVI, aspirin monotherapy should be preferred over DAPT. However, larger trials are still needed to determine whether antiplatelet strategies should be tailored and based on the valve implanted (balloon-expandable vs self-expandable) or on the particular valve-in-valve implantation setting; also, to elucidate the role of alternative antiplatelet regimens (ie, $P2Y_{12}$i monotherapy), and oral anticoagulants.

Limitations

The results of our study should be interpreted considering some limitations. First, this was a study-level meta-analysis that provided average treatment effects. Also, the lack of patient-level data from the studies included data prevents us from assessing the impact baseline clinical and procedural characteristics had on treatment effects. Secondly, minor differences in the definition used were present in the ischemic endpoints, thus limiting the reliability of the effect estimates. However, in terms of the bleeding endpoints, the VARC definition was used in all the studies included, which adds to the robustness of our findings. Finally, the limited number of studies and patients as well as the small event rate for certain endpoints such as myocardial infarction may have reduced the statistical power to detect any significant inter-group differences.

Additional evidence will be provided by ongoing randomized trials: the Antithrombotic strategy after trans-aortic valve implantation for aortic stenosis (ATLANTIS, NCT02664649) trial will evaluate the benefit of apixaban therapy (standard dose) vs standard of care; the Anticoagulant versus dual antiplatelet therapy for preventing leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement (ADAPT-TAVR, NCT03284827) trial will compare edoxaban (standard dose) vs DAPT. Finally, the Dual antiplatelet therapy versus oral anticoagulation for a short time to prevent cerebral embolism after TAVI (AUREA, NCT01642134) trial will study a strategy of vitamin K antagonist vs a 3-month course of DAPT.

CONCLUSIONS

In patients without an indication for long-term anticoagulation undergoing TAVI, monotherapy with aspirin compared to DAPT is associated with a lower risk of life-threatening or major bleeding, and a comparable risk of all-cause mortality, myocardial infarction, and stroke.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

J. Sanz-Sánchez, C. A. Pivato, P. P. Leone, and M. Chiarito contributed to the design, analysis, and writing of this manuscript. D. Regazzoli, and G. Petriello contributed to the design, and writing of this manuscript too. B. Reimers, G. Condorelli, and G. G. Stefanini contributed to the study design, writing, and supervision.

CONFLICTS OF INTEREST

G. G. Stefanini reported a research grant from Boston Scientific, and speaker/consulting fees from B. Braun, Biosensors, and Boston Scientific. D. Regazzoli reported speaker fees from Amgen, and Boehringer. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Ischemic and bleeding complications are not rare after TAVI and can be life-threatening. To reduce the rate of stroke, myocardial infarction, and valve thrombosis, the clinical practice guidelines recommend a 1 to 6 month DAPT course after TAVI in patients with no indication for long-term oral anticoagulation. However, this regimen is

not supported by the current evidence and overall, ischemic events post-TAVI seem to elude the antiplatelet action provided by thienopyridines added to aspirin. Indeed, reports on therapy duration over the last decade have suggested a neutral or beneficial effect of aspirin monotherapy compared to early DAPT followed by aspirin regarding vascular complications, and major or life-threatening bleedings.

WHAT DOES THIS STUDY ADD?

– The present study confirms that the addition of thienopyridines added to aspirin does not reduce the risk of ischemic events (namely myocardial infarction, and stroke). Instead it predisposes patients to an increased risk of life-threatening or major bleeding. The bleeding risk reduction with aspirin compared to DAPT is of great clinical relevance, with a NNT of only 11 patients to prevent any bleeding and a NNT of 17 patients to prevent 1 life-threatening or major bleeding. Based on the evidence published so far and the results of this study, in patients without an indication for long-term anticoagulation undergoing TAVI, aspirin monotherapy should be preferred over DAPT.

SUPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000210.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-2198.
3. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-1798.
4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2016;374:1609-1620.
5. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019:NEJMoa1816885.
6. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695-705.
7. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.
8. Webb J, Rodés-Cabau J, Fremes S, et al. Transcatheter Aortic Valve Implantation: A Canadian Cardiovascular Society Position Statement. *Can J Cardiol*. 2012;28:520-528.
9. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159-1195.
10. Mangieri A, Jabbour RJ, Montalto C, et al. Single-Antiplatelet Therapy in Patients with Contraindication to Dual-Antiplatelet Therapy After Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2017;119:1088-1093.
11. Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2017;10:1357-1365.
12. Stabile E, Pucciarelli A, Cota L, et al. SAT-TAVI (single antiplatelet therapy for TAVI) study: A pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. *Int J Cardiol*. 2014;174:624-627.
13. Ussia GP, Scarabelli M, Mul M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2011;108:1772-1776.
14. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. *N Engl J Med*. 2020:NEJMoa2017815–NEJMoa2017815.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ. 2009;339:b2700*.
16. Risk of bias tools - Current version of RoB 2 n.d. https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2. Accessed 23 June 2019.
17. Stefanini GG, Holmes DR. Drug-Eluting Coronary-Artery Stents. *N Engl J Med*. 2013;368:254-265.
18. Van Mieghem NM, El Faquir N, Rahhab Z, et al. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2015;8:718-724.
19. Schmidt T, Leon MB, Mehran R, et al. Debris Heterogeneity Across Different Valve Types Captured by a Cerebral Protection System During Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2018;11:1262-1273.
20. Kahlert P, Al-Rashid F, Döttger P, et al. Cerebral embolization during transcatheter aortic valve implantation: A transcranial doppler study. *Circulation*. 2012;126:1245-1255.
21. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321-1331.
22. Nombela-Franco L, Webb JG, De Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation*. 2012;126:3041-3053.
23. Siontis GCM, Praz F, Lanz J, et al. New-onset arrhythmias following transcatheter aortic valve implantation: A systematic review and meta-analysis. *Heart*. 2018;104:1208-1215.
24. Vora AN, Dai D, Matsuoka R, et al. Incidence, Management, and Associated Clinical Outcomes of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement: An Analysis From the STS/ACC TVT Registry. *JACC Cardiovasc Interv*. 2018;11:1746-1756.
25. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015-2024.
26. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383-2392.
27. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J*. 2016;37:2263-2271.
28. Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:120-129.
29. Piccolo R, Pilgrim T, Franzone A, et al. Frequency, Timing, and Impact of Access-Site and Non–Access-Site Bleeding on Mortality Among Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2017;10:1436-1446.

REC Interv Cardiol. 2021;3(3):182-189
https://doi.org/10.24875/RECICE.M21000206

Original article

Usefulness of physiological coronary assessment with iFR in daily practice and all-comer patients: immediate and follow-up results

Cristina Pericet-Rodríguez, Francisco José Hidalgo-Lesmes,* Rafael González-Manzanares, Soledad Ojeda-Pineda, Aurora Luque-Moreno, Javier Suárez de Lezo, Miguel Ángel Romero-Moreno, Francisco Mazuelos-Bellido, José María Segura Saint-Gerons, Ana Fernández-Ruiz, María Guisela Flores-Vergara, and Manuel Pan Álvarez-Ossorio

Servicio de Cardiología, Hospital Universitario Reina Sofía, Universidad de Córdoba, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain

ABSTRACT

Introduction and objectives: The objective of this study was to describe our experience with coronary physiology assessment using the instantaneous wave-free ratio (iFR) and/or a Syncvision-guided iFR-pullback study [Syncvision version 4.1.0.5, Philips Volcano, Belgium] in all-comer patients.
Methods: Consecutive patients undergoing coronary physiology assessment with the iFR (and/or a Syncvision-guided iFR-pullback study) at our center between January 2017 and December 2019 were included. The iFR cut-off value was 0.89. The primary endpoint was a composite of cardiac death, myocardial infarction, probable or definitive stent thrombosis, and target lesion revascularization.
***Results*:** A total of 277 patients with 433 lesions evaluated were included. The mean age was 65 ± 10 years and 74% were men. Personal history of diabetes mellitus was present in 41% of patients. Clinical presentation was stable angina in 160 patients (58%), and acute coronary syndrome in 117 patients (42%). iFRs > 0.89 were obtained in 266 lesions (61.4%) on which the PCI was postponed. The remaining lesions were revascularized. The Syncvision software was used to guide the iFR-pullback study in 155 lesions (36%) and the decision-making process, mainly in long, diffuse or sequential lesions (91 lesions, 58.7%), and intermediate lesions (52 lesions, 33.5%). After a median follow-up of 18 months, the primary endpoint occurred in 17 patients (6.1%) without differences regarding the baseline iFR (≤ 0.89 or > 0.89) (4.2% vs 3.8%; $P = .9$) or the clinical presentation (stable angina or acute coronary syndrome) (4.4% vs 8.5%; $P = .1$)
Conclusions: The use of coronary physiology assessment with the iFR and the Syncvision-guided iFR-pullback study in the routine daily practice and in all-comer patients seems safe with a low percentage of major adverse cardiovascular events at the mid-term follow-up.

Keywords: Physiological assessment. All-comer patients. Syncvision-guided iFR-pullback study.

Utilidad de la valoración fisiológica coronaria con iFR en la práctica diaria y en todo tipo de pacientes: resultados inmediatos y en el seguimiento

RESUMEN

Introducción y objetivos: El propósito del estudio fue describir nuestra experiencia con el uso del índice diastólico instantáneo sin ondas (iFR) para la evaluación fisiológica coronaria o el uso del *software* Syncvision/iFR (Syncvision versión 4.1.0.5, Philips Volcano, Bélgica) en todo tipo de pacientes.
Métodos: Se incluyeron todos los pacientes consecutivos a quienes, entre enero de 2017 y diciembre de 2019, se realizó en nuestro centro una evaluación fisiológica coronaria con iFR o con Syncvision/iFR. El valor de corte establecido para el iFR fue 0,89. El objetivo primario fue un compuesto de muerte cardiaca, infarto de miocardio, trombosis de *stent* probable o definitiva y nueva revascularización de la lesión evaluada.
Resultados: Se incluyeron 277 pacientes con 433 lesiones evaluadas. La edad media fue de 65 ± 10 años y el 74% eran varones. El 41% tenía antecedente de diabetes mellitus. La presentación clínica fue angina estable en 160 pacientes (58%) y síndrome

* **Corresponding author:** Servicio de Cardiología, Hospital Universitario Reina Sofía, Avda. Menéndez Pidal s/n, 14004 Córdoba, Spain.
E-mail address: fjhl.87@gmail.com (F. Hidalgo Lesmes).

Received 1 December 2020. Accepted 10 February 2021. Online: 06-04-2021.

coronario agudo en 117 pacientes (42%). Se obtuvo un iFR > 0,89 en 266 lesiones (61,4%), en las cuales la intervención coronaria percutánea fue diferida. Las lesiones restantes se revascularizaron. El *software* Syncvision/iFR se usó en 155 lesiones (36%) para guiar la toma de decisiones, principalmente lesiones largas, difusas o secuenciales (91 lesiones, 58,7%) y lesiones intermedias (52 lesiones, 33,5%). Tras un periodo de seguimiento de 18 meses, el objetivo primario se observó en 17 pacientes (6,1%), sin diferencias en función del iFR basal (≤ 0,89 o > 0,89) (4,2 frente a 3,8%; p = 0,9) ni de la presentación clínica (angina estable o síndrome coronario agudo) (4,4 frente a 8,5%; p = 0,1).
Conclusiones: La evaluación fisiológica coronaria con iFR y el *software* Syncvision/iFR en la práctica diaria y en todo tipo de pacientes parece ser segura, con un bajo porcentaje de eventos cardiacos adversos mayores a medio plazo.

Palabras clave: Evaluación fisiológica. Todo tipo de pacientes. Software Syncvision/iFR.

Abbreviations

iFR: instantaneous wave-free ratio. **PCI:** percutaneous coronary intervention. **MACE:** major adverse cardiovascular events.

INTRODUCTION

Physiological assessment using the fractional flow reserve (FFR) or the instantaneous wave-free ratio (iFR) is strongly recommended by the European guidelines to the guide percutaneous coronary intervention (PCI) decision-making process to treat intermediate coronary stenosis (indication I, level of evidence A) and multivessel disease (indication IIa, level of evidence B).[1-7]

The established cut-off values based on landmark trials to safely postpone treatment of a coronary lesion are FFRs > 0.80 and iFRs > 0.89.[2–7] Unlike the FFR, the new iFR resting index allows us to analyze the physiological significance of each segment in the presence of coronary arteries with several lesions. Syncvision is a new software that analyzes the specific contribution of each coronary segment allowing us to predict physiological improvement after percutaneous treatment.[8,9] It's not necessary to use any vasodilators either, thus reducing any potential side effects.[3,4]

However, the evidence supporting the use of coronary physiology assessment with both indices and the use of the Syncvision software in other type of lesions and other clinical scenarios is scarce.[8-10] For this reason, it is not quite clear whether the same cut-off value established in the landmark trials should be used; or if safety, utility, and efficacy will be the same.

The objective of this study is to describe our experience with coronary physiology assessment using the iFR (and/or the Syncvision-guided iFR-pullback study) in all-comer patients undergoing invasive coronary angiography.

METHODS

We performed a single-center retrospective study including all patients who underwent functional assessments (using the iFR) and/or the Syncvision software at our center between January 2017 and December 2019 on a PCI decision-making process. The cut-off value to consider the need for revascularization was the same one established by the landmark clinical trials (iFR ≤ 0.89).[3,4] The pressure guidewires used for the functional assessment were the Volcano Verrata, and the Volcano Verrata Plus (Philips Volcano, Belgium). The use of the Syncvision software to guide the iFR study as well as the lesions assessed were left to the operator's discretion.

All subjects included in the study gave their informed consent to undergo the procedure and for data analysis and publication. Additionally, the study received the proper ethical oversight and was approved by our center ethics committee.

Inclusion and exclusion criteria

Patients with the following criteria were included: *a)* consecutive patients in whom an invasive coronary angiography was performed due to stable or unstable symptoms or silent ischemia; *b)* presence of, at least, a lesion or vessel physiologically assessed with the iFR during the index procedure. The following exclusion criteria were stablished: *a)* impossibility to understand the informed consent during the index procedure; *b)* written informed consent to use data for research purposes not provided.

Lesion classification

The lesions physiologically assessed were classified based on their angiographic characteristics and/or clinical setting: *a)* intermediate lesions: lesions with a 40% to 80% angiographic stenosis as seen on the quantitative coronary angiography (QCA); *b)* sequential or diffuse coronary lesions: presence of, at least, 2 sequential lesions or a coronary segment with diffuse disease (coronary vessel with multiple plaques in most of the epicardial territory) with a total length of 25 mm; *c)* bifurcation lesions: presence of a coronary stenosis at bifurcation level with a side branch size large enough to be protected; *d)* in-stent restenosis: presence of focal or diffuse in-stent restenosis with a a 40% to 80% angiographic stenosis as seen on the QCA; *e)* coronary bypass lesion, defined as, at least, a lesion in the coronary artery bypass grafting or native vessel presenting with proximal total occlusion.

Endpoints

The primary endpoint of the study was the rate of major adverse cardiovascular events (MACE) at the follow-up. The MACE were defined as a composite of cardiac death, myocardial infarction (MI), definitive or probable stent thrombosis, and new target lesion revascularization (TLR). All deaths were considered cardiovascular unless unequivocal non-cardiac causes would be established. Myocardial infarction included spontaneous ST-segment elevation

MI or non-ST-segment elevation acute myocardial infarction. The TLR was defined as a new revascularization of a baseline physiologically negative lesion at the follow-up or as a repeat revascularization of a baseline physiologically positive lesion percutaneously treated during the index procedure.

The secondary endpoints established were: *a)* analysis of the primary endpoint components separately; *b)* rate of MACE based on the clinical setting (stable angina or acute coronary syndrome), non-ST-segment elevation acute myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI); *c)* rate of MACE based on the baseline iFR; *d)* to determine the type of lesions where the Syncvision software was used for the iFR-pullback study.

Follow-up

The patients' follow-up was performed through phone calls, hospital record reviews or outpatient visits.

Quantitative coronary measurements

Quantitative coronary measurements were performed using a validated system (CAAS system, Pied Medica Imaging, The Netherlands). These were the measurements analyzed: reference vessel diameter, minimum lumen diameter, percent diameter stenosis, and lesion length. All measurements were performed at baseline and after the PCI.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and the Student *t* test was used to establish comparisons. The categorical variables were expressed as frequency and percentage, and compared using the chi-square test. The univariate analysis was performed with the following covariates: age, male sex, current smoking status, dyslipidemia, left ventricular ejection fraction, acute coronary syndrome, multivessel disease, clopidogrel, ticagrelor, right coronary artery as the study vessel, other vessels analyzed, and baseline iFRs ≤ 0.89. Results were reported using odds ratios (OR), and two-sided 95% confidence intervals. In all the cases, *P* values < .05 were considered statistically significant. The statistical analysis was performed using the IBM-SPSS statistical software package (version 24.0 for Macintosh, SPSS Corp., United States).

RESULTS

The study flowchart is shown on figure 1. During the study period, a total of 2951 patients underwent coronary angiography at our center. The iFR-based physiological assessment was performed in 277 patients (9.4%) with 433 lesions. The baseline clinical data are shown on table 1. The mean age was 65 ± 10 years, and 74% of the patients (204) were men. The prevalence of comorbidities was high (diabetes mellitus, 41%; previous MI, 32%; peripheral arterial disease, 4%; cerebrovascular disease, 6%; chronic kidney disease, 13%). The clinical presentation included stable angina in 160 patients (58%), NSTEMI in 91 patients (33%), and STEMI in 26 patients (9%).

Angiographic and procedural data

Angiographic and procedural data are shown on table 2. Radial access was the access of choice in most of the cases (392 lesions, 91%). A total of 186 patients (67%) showed angiographic multivessel

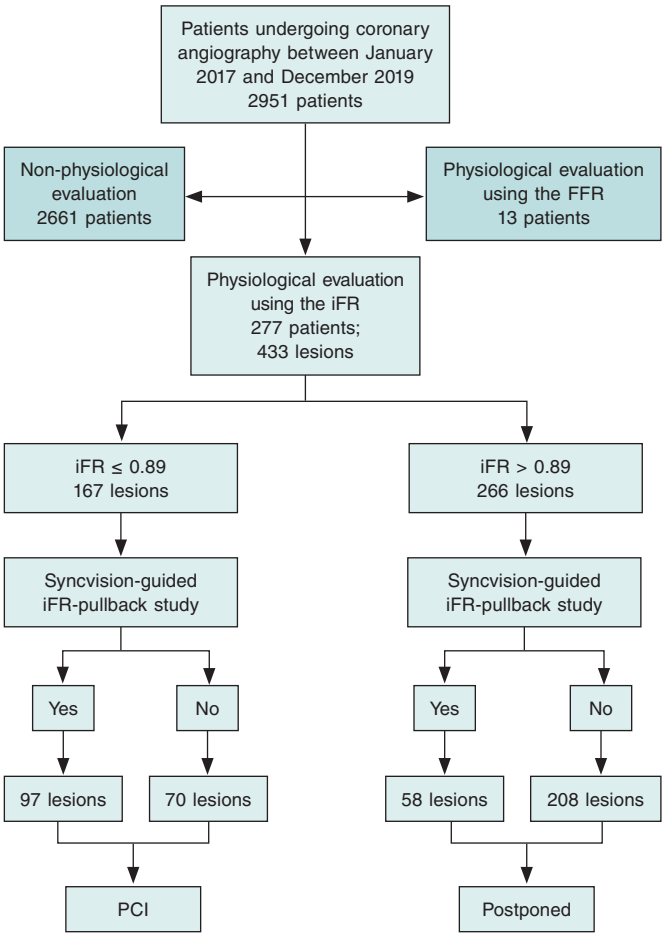


Figure 1. Flowchart of the study period.

disease. Regarding the angiographic Syntax I score, 232 patients (84%) had Syntax scores < 22, 41 patients (15%) between 22 and 32, and only 4 patients (1%) > 32 without any differences being reported between stable and unstable patients. The vessel most frequently analyzed was the left anterior descending coronary artery (180, 42%) followed by the right coronary artery (99, 23%). The left main coronary artery was evaluated in 23 patients (5%).

The mean reference diameter was 3.3 mm ± 3 mm with a mean vessel stenosis of 49% ± 16%, and a mean lesion length of 21 mm ± 12 mm. The mean diameter of the stent implanted was 2.8 ± 0.4. All the stents implanted were drug-eluting stents (100%). Intracoronary imaging was used in 14 patients (3%).

The instantaneous wave-free ratio was obtained in 433 lesions, with a baseline value of 0.89 ± 0.12. The physiological assessment results after the PCI were obtained in 129 lesions (29.8%) with a final iFR of 0.93 ± 0.04.

The lesions physiologically assessed are shown on table 2. The most common type of lesions undergoing physiological assessment were angiographically moderate lesions (244, 56.4%) followed by sequential and diffuse lesions (118, 27.3%). Physiological assessment was used in 51 bifurcation lesions (11.8%) basically to guide the intervention over the side branch while using a provisional stenting strategy.

The Syncvision software for the iFR-pullback study was used in 155 lesions to guide the decision-making process (35.8%).

Table 1. Baseline clinical data

Patients	Total (N = 277)	Stable angina (N = 160)	ACS (N = 117)	*P*
Age, years	65 ± 10	65 ± 10	64 ± 11	.071
Sex, male, N (%)	204 (74)	116 (72)	94 (80)	.112
Hypertension, N (%)	175 (63)	101 (63)	77 (66)	.645
Diabetes mellitus, N (%)	114 (41)	58 (36)	52 (44)	.169
Dyslipidemia, N (%)	157 (57)	101 (63)	58 (50)	.024
Current smoker, N (%)	72 (26)	29 (18)	42 (36)	.001
Previous myocardial infarction, N (%)	89 (32)	53 (33)	37 (32)	.792
Previous revascularization, N (%)	94 (34)	50 (31)	32 (27)	.518
Percutaneous, N (%)	80 (85)	50 (31)	30 (26)	.336
Surgical, N (%)	14 (15)	8 (16)	6 (19)	.095
Atrial fibrillation, N (%)	39 (14)	19 (12)	13 (11)	.844
Heart failure, N (%)	8 (3)	7 (4)	2 (2)	.216
Prior ACE, N (%)	17 (6)	11 (7)	9 (8)	.795
Peripheral arterial disease, N (%)	11 (4)	7 (4)	5 (4)	.967
Previous bleeding, N (%)	3 (1)	2 (1)	2 (2)	.752
Chronic kidney disease, N (%)	36 (13)	19 (12)	17 (15)	.486
Hemoglobin, g/dL	13.96 ± 1.7	13.87 ± 1.8	14.13 ± 1.8	.365
Creatinine, g/dL	0.98 ± 0.47	1 ± 0.63	1 ± 0.37	.584
Left fentricular ejection fraction, %	59 ± 15	57 ± 16	60 ± 13	.098

ACE, acute cerebrovascular event; ACS, acute coronary syndrome. Data are expressed as number (N) and percentage (%).

Sequential and diffuse coronary lesions were the most common lesions analyzed by the iFR-pullback study (91 vessels, 58.7%, figure 2) followed by angiographically moderate lesions (52 vessels, 33.5%). This software was used in 5 bifurcation lesions (3.2%) to establish a baseline physiological classification or confirm an optimal physiological result after the PCI in both branches. The remaining lesions assessed by the iFR-pullback study were 6 focal or diffuse in-stent restenoses (3.9%) and 1 saphenous vein bypass graft with diffuse disease (0.6%).

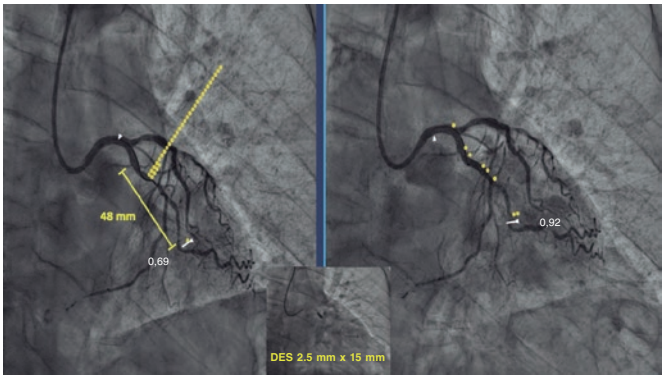


Figure 2. Images of iFR-coregistration with the Syncvision software from a left circumflex artery with diffuse disease in its middle segment (48 mm of lesion length). The baseline distal iFR was 0.69. The Syncvision-guided iFR-pullback study demonstrated physiological significance only in the proximal segment. Direct implantation of a 2.5 mm × 15 mm DES was performed with a final iFR of 0.92. The stent length reduction regarding the angiographic lesion was 33 mm.

Follow-up

Follow-up data were available for 274 out of 277 patients (99%). After a mean 18 ± 10-month follow-up, 17 patients (6.1 %) presented with a major adverse cardiovascular events (table 3), 7 patients (2.5 %) with TLR, 2 of them over a lesion treated during the index procedure (0.7%) and 5 (1.8%) due to disease progression of a baseline physiologically negative lesion; 6 patients (2.2 %) suffered from acute myocardial infarction (1 patient due to acute stent thrombosis, another to a new lesion not evaluated at the index procedure, another to a baseline physiologically non-significant lesion, and the remaining 3 patients due to failed previously revascularized lesions); also, 4 patients (1.4%) presented with unclear or cardiac death. There were no differences regarding MACE between baseline physiologically negative and positive lesions (table 3).

Based on their clinical signs, patients who presented with ACS had an increased rate of new myocardial infarction at the follow-up (5.3% vs 0.6%; $P < .05$), although no differences were found regarding unclear or cardiac death (0.9% vs 1.8%; $P = .9$) and the overall MACE (8.5% vs 4.4%; OR, 2.056, 0.759-5.572; $P = .156$ (table 3).

Finally, we performed a univariate analysis and found no risk or protective factors for MACE in this cohort of patients (table 4).

Table 2. Angiographic and procedural data

Patients	Total (N = 277)	Stable angina (N = 160)	ACS (N = 117)	*P*
Radial access, N (%)	251 (90)	147 (92)	104 (89)	.329
Multivessel disease, N (%)	165 (59)	84 (52)	81 (69)	.004
Syntax score	11 ± 8	10 ± 8	12 ± 8	.885
Low risk (< 22)	45 (16)	25 (16)	20 (17)	.184
Intermediate risk (22-32)	6 (2)	1 (1)	5 (4)	.066
High risk (> 32)	1 (1)	1 (1)	0	.331
Acetylsalicylic acid, N (%)	245 (88)	142 (88)	103 (88)	.740
P_2Y^{12} inhibitor, N (%)	195 (71)	98 (61)	97 (83)	
Clopidogrel	63 (23)	40 (25)	23 (20)	.011
Ticagrelor	127 (46)	56 (35)	71 (61)	.019
Prasugrel	65 (2)	2 (1)	3 (3)	.642
Vessel analyzed, N (%)				
LAD	121 (44)	66 (41)	55 (47)	.318
LCx	40 (14)	26 (16)	14 (12)	.327
RCA	75 (27)	50 (31)	25 (21)	.072
LMCA	15 (5)	8 (5)	7 (6)	.712
Other	27 (10)	11 (7)	16 (14)	.057
Reference vessel diameter (mm)	3.3 ± 3	3.3 ± 3	3.3 ± 3	.971
Vessel stenosis (%)	49 ± 16	49 ± 17	49 ± 16	.816
Vessel minimal lumen diameter (mm)	1.6 ± 0.6	1.5 ± 0.6	1.5 ± 0.5	.203
Vessel lesion length (mm)	21 ± 12	21 ± 13	20 ± 11	.174
Vessel stent diameter (mm)	2.8 ± 0.4	2.8 ± 0.4	2.8 ± 0.4	.581
Type of stent implanted (%)				
DES	100			
BMS	0			
Other	0			
Immediate angiographic optimal result (%)	100			
Contrast used (mL)	142 ± 91	151 ± 110	164 ± 72	.166
Intracoronary imaging, N (%)	6 (2)	6 (4)	0	.034
Procedural complications, N (%)	3 (1)	2 (1)	1 (1)	.754
Baseline iFR	0.88 ± 0.12	0.89 ± 0.12	0.86 ± 0.14	.097
Final iFR	0.93 ± 0.04	0.93 ± 0.04	0.93 ± 0.04	.951
Syncvision-guided iFR-pullback study, N (%)	155 lesions (36)	94 lesions (36)	61 lesions (35)	.4
Lesions evaluated	**Total (N = 433)**	**Stable angina (N = 258)**	**ACS (N = 175)**	***P***
Angiographically moderate lesions, N (%)	244 (56.4)	149 (58)	95 (54)	.475
Sequential/diffuse coronary lesions, N (%)	118 (27.3)	64 (25)	53 (30)	.208
Bifurcation lesions, N (%)	51 (11.8)	31 (12)	20 (11)	.853
In-stent restenosis, N (%)	15 (3.5)	11 (4.3)	4 (2.3)	.269
Coronary artery bypass grafting, N (%)	2 (0.5)	0 (0)	2 (1.1)	.085
Other lesions, N (%)	3 (0.75)	2 (0.8)	1 (0.6)	.802

ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; iFR, instantaneous wave-free ratio; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery. Data are expressed as number (N) and percentage (%).

Table 3. Rate of major adverse cardiovascular events at the follow-up based on the clinical presentation

	MACE (277 patients, 433 lesions)	iFR ≤ 0.89 (N = 167 lesions)	iFR > 0.89 (N = 266 lesions)	*P*	Stable angina (N = 160)	ACS (N = 117)	*P*
Overall, N (%)	17 (6.1)	7 (4.2)	10 (3.8)	.9	7 (4.4)	10 (8.5)	.1
Unclear or cardiac death, N (%)	4 (1.4)	2 (1.2)	2 (0.8)	.2	3 (1.9)	1 (0.8)	.9
Myocardial infarction, N (%)	6 (2.2)	1 (0.6)	5 (1.9)	.46	1 (0.6)	5 (4.3)	< .05
Target lesion revascularization, N (%)	7 (2.5)	4 (2.4)	3 (1.1)	.09	3 (1.9)	4 (3.4)	.2

ACS, acute coronary syndrome; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular events. Data are expressed as number (N) and percentage (%).

Table 4. Univariate analysis of the different variables with potential impact in the rate of major adverse cardiovascular events between groups

	Univariate analysis	
Variable	**OR (95%CI)**	***P***
Age	1.01 (0.97-1.06)	.608
Male	2.54 (0.57-11.40)	.224
Current smoker	1.23 (0.42-3.60)	.713
Dyslipidemia	1.39 (0.50-3.87)	.531
Left ventricular ejection fraction (%)	0.99 (0.95-1.04)	.684
Acute coronary syndrome	2.06 (0.76-5.57)	.156
Multivessel disease	0.90 (0.33-2.45)	.842
Clopidogrel	0.75 (0.23-2.44)	.623
Ticagrelor	1.52 (0.46-4.96)	.490
Right coronary artery as examined vessel	1.52 (0.54-4.26)	.428
Other vessel analyzed	1.26 (0.27-5.82)	.769
Baseline iFR ≤ 0.89	1.43 (0.88-2.32)	.152

95%CI, confidence interval; iFR, instantaneous wave-free ratio; OR, odds ratio.

DISCUSSION

This study tried to describe our experience using the physiological assessment and the Syncvision software in all-comer patients who underwent percutaneous coronary evaluations. The main findings of our study are: *a)* the use of the iFR in lesions of all-comer patients with the same cut-off values than established in the main trials showed a low percentage of MACE at the mid-term follow-up (6.1%); *b)* patients who presented with acute coronary syndrome showed an increased rate of myocardial infarction at the mid-term follow-up, and a trend towards a higher rate of MACE (OR, 2.056, 0.759-5.572; *P* = .156); *c)* The Syncvision-guided iFR-pullback study provided additional information to guide the PCI decision-making process, especially in complex lesions like sequential lesions and diffuse coronary artery disease.

The fractional flow reserve was the first physiological index that demonstrated its utility, safety, and efficacy guiding the revascularization decision-making process.[2,5-7] To obtain it, the use of a hyperemic agent to reduce vascular resistance is mandatory. Adenosine is the most commonly used drug, but it presents a series of side effects and contraindications.[3,4,11,12] The more recent resting index (the instantaneous wave-free ratio) has demonstrated similar utility, safety, and efficacy to the FFR.[3,4] Furthermore, it has 2 main advantages: first, it is not necessary to use vasodilators, thus reducing side effects, contraindications for use, and procedural time; secondly, it allows us to assess the contribution of each lesion when the vessel presents several lesions, with the specific Syncvision-guided iFR-pullback study.[8,9]

For these reasons, the coronary physiology assessment is already the routine practice at the cath lab for the assessment of intermediate lesions,[2-5] and multivessel disease.[6,7] The main clinical setting included in these studies was stable angina. Patients with NSTEMI could be included if the lesion evaluated was identified as a non-culprit lesion. However, patients with STEMI, left main coronary artery lesions, and coronary artery bypass grafting lesions were not represented in the trials; also, the percentage of bifurcation lesions and sequential or diffuse coronary lesions is tiny. The cut-off value for the FFR and the iFR is well defined in those trials, being safe to postpone a lesion with a FFR > 0.80 or an iFR > 0.89. However, information is scarce on the utility and efficacy of physiological assessment and the same cut-off values in other types of lesions and clinical presentations.[13] A multicenter registry that used the iFR to guide revascularization in patients with left main coronary artery stenosis has just been published. Using a cut-off value of 0.89, the authors conclude that postponing a left main coronary artery lesion with a iFR > 0.89 seems to be safe.[10]

Our study results suggest that the use of physiological assessment and the Syncvision software to guide the PCI decision-making process in all-comer patients with the same cut-off values as established by the landmark trials seems useful and safe regardless of the lesion and clinical presentation undergoing evaluation. Also, the MACE rates are similar to those reported by the landmark trials with selected lesions and patients.[3,4] The iFR was the index used more often. The reasons are the faster and more comfortable use,[3,4] and the possibility of lesion assessment with the Syncvision software.[8,9]

An important point of the study was to evaluate the rate of MACE based on the clinical presentation. Although no significant differences in the overall rate of MACE were found, patients who presented with acute coronary syndrome showed a significantly higher rate of MI at the follow-up, and a trend towards a higher rate of overall MACE. We think that this absence of statistical significance could be associated with a lack of statistical power.

A type of lesion included in the study was bifurcation lesions. Physiological assessment was used mainly to guide the side branch results during a provisional stenting strategy, thus keeping the pressure wire jailed as previously described.[14,15] However, another interesting use of the iFR-pullback study with the Syncvision software was to stablish the baseline physiological contribution of every segment included in the most accepted classification.[16]

Finally, the Syncvision-guided iFR-pullback study was used in 155 lesions (36%). The main type of lesions where this software was used were diffuse and tandem lesions. This software can predict the

physiological contribution of each lesion or coronary segment, which is why we believe that it is a very useful tool to avoid treating lesions without any physiological contribution and probably without clinical benefits. That is why this software seems to reduce the total stent length implanted regarding angiographically-guided revascularization with potential benefits at long-term follow-up.[17,18] A clinical trial is currently in the recruitment phase to demonstrate the efficacy of this software reducing the length of the stent implanted in this type of lesions without detriment to the adverse events.[19]

In our experience, the key aspects to properly perform this technique are: *a)* a perfect aortic pressure curve allows the accurate detection of diastole through the software; *b)* passing the pressure sensor as distally as possible; *c)* finding a projection where the artery can be seen completely and with the least foreshortening possible; *d)* withdrawing the pressure guidewire very slowly so that the software can perfectly recognize the length of each arterial segment; *e)* checking that there is not drift when the pressure guidewire reaches the coronary ostium (iFR different to 1 ± 0.02) to avoid erroneous results; *f)* performing the coronary angiography in the same position as the guidewire withdrawal without any modifications to the height of the table or the C-arm, and with a higher flow and volume of contrast to facilitate the software recognition of all the lesions. The main problem when using this technique is the presence of lesions with complicated wiring. The pressure wire has a hydrophilic non-polymeric coating that is useful in most lesions. However, it may be very challenging to reach the distal part of the artery in very complex lesions (calcified, angled lesions...), and our experience with previous normalization, wire disconnection, the microcatheter exchange technique, and reconnection is very limited, but still there is a significant level of drift.

Limitations

The study presents several limitations. It is a retrospective, single-center analysis with a low number of patients and lesions. Therefore, the results should be interpreted with caution, although it could be a hypothesis-generating study for future larger scale randomized clinical trials.

CONCLUSIONS

The use of coronary physiology assessment using the iFR and the Syncvision-guided iFR-pullback study in the routine daily practice and in all-comer patients seems safe with a low percentage of MACE at the mid-term follow-up. The Syncvision-guided iFR-pullback study provides additional information to guide the PCI decision-making process.

FUNDING

The study has not had funding.

AUTHORS' CONTRIBUTION

F.J. Hidalgo-Lesmes prepared the main draft of the manuscript. S. Ojeda-Pineda participated in the drafting of the manuscript. C. Pericet-Rodríguez, R. González-Manzanares, A. Fernández-Ruiz, and M.G. Flores-Vergara all contributed to the analysis and interpretation of data. A. Luque-Moreno, J. Suárez de Lezo, and F. Mazuelos-Bellido participated in the conception and design of the study. M.A. Romero-Moreno, and J.M. Segura Saint-Gerons revised the manuscript critically for important intellectual content. M. Pan Álvarez-Ossorio approved the final version of the manuscript.

CONFLICTS OF INTEREST

F.J. Hidalgo-Lesmes received minor fees from Philips Volcano Europe unrelated to the manuscript; S. Ojeda-Pineda received minor fees from Terumo and Philips Volcano Europe unrelated to the manuscript; M. Pan Álvarez-Ossorio received minor fees from Terumo, Abbott Vascular, and Philips Volcano Europe unrelated to the manuscript. The remaining authors declared no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Physiological assessments with the iFR are strongly recommended by the European guidelines on coronary revascularization to guide the PCI decision-making process in intermediate coronary stenosis.
- However, the evidence supporting the use of coronary physiology assessment, and the new Syncvision-iFR software in other type of lesions and clinical settings is scarce.

WHAT DOES THIS STUDY ADD?

- This study describes our experience with the iFR and the Syncvision-iFR software in all-comer patients and demonstrates an acceptable percentage of MACE at the mid-term follow-up.
- Furthermore, the study shows that the Syncvision-guided iFR-pullback study provides additional information to guide the PCI decision-making process, particularly in complex lesions like sequential lesions and diffuse coronary artery disease.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Pijls NHJ, van Schaardenburgh P, Manoharan G, et al. Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis. 5-Year Follow-Up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105-2111.
3. Davies JE, Sen S, Dehbi H-M, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
4. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376:1813-1823.
5. Pijls NHJ, de Bruyne B, Peels K, et al. Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses. *N Engl J Med*. 1996;334:1703-1708.
6. Tonino AL, Bruyne B De, Pijls NHJ, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention Pim. *N Engl J Med*. 2015:687-696.
7. Van Nunen LX, Zimmermann FM, Tonino PAL, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet*. 2015;386:1853-1860.
8. Nijjer SS, Sen S, Petraco R, Mayet J, Francis DP, Davies JER. The Instantaneous wave-Free Ratio (iFR) pullback: A novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. *Cardiovasc Revasc Med*. 2015;16:167-171.
9. Nijjer SS, Sen S, Petraco R, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. *JACC Cardiovasc Interv*. 2014;7:1386-1396.
10. Warisawa T, Cook CM, Rajkumar C, et al. Safety of Revascularization Deferral of Left Main Stenosis Based on Instantaneous Wave-Free Ratio Evaluation. *JACC Cardiovasc Interv*. 2020;13:1655-1664.
11. Gili S, Barbero U, Errigo D, et al. Intracoronary versus intravenous adenosine to assess fractional flow reserve: A systematic review and meta-analysis. *J Cardiovasc Med*. 2018;19:274-283.

12. Patel HR, Shah P, Bajaj S, Virk H, Bikkina M, Shamoon F. Intracoronary adenosine-induced ventricular arrhythmias during fractional flow reserve (FFR) measurement: case series and literature review. *Cardiovasc Interv Ther*. 2017;32:374-380.
13. Ihdayhid AR, Koh JS, Ramzy J, et al. The Role of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Measurements in Patients with Acute Coronary Syndrome. *Curr Cardiol Rep*. 2019;21.
14. Burzotta F, Lassen JF, Banning AP, et al. Percutaneous coronary intervention in left main coronary artery disease: The 13th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;14:112-120.
15. Hidalgo F, Pan M, Ojeda S, et al. Feasibility and Efficacy of the Jailed Pressure Wire Technique for Coronary Bifurcation Lesions. *JACC Cardiovasc Interv*. 2019;12:109-111.
16. Medina A, Suárez de Lezo J, Pan M. A New Classification of Coronary Bifurcation Lesions. *Rev Esp Cardiol*. 2006;59:183.
17. Mauri L, O'Malley AJ, Popma JJ, et al. Comparison of thrombosis and restenosis risk from stent length of sirolimus-eluting stents versus bare metal stents. *Am J Cardiol*. 2005;95:1140-1145.
18. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease: Primary Results of the International Multicenter iFR GRADIENT Registry. *JACC Cardiovasc Interv*. 2018;11:757-767.
19. Hidalgo F, Ojeda S, de Lezo JS, et al. Usefulness of a co-registration strategy with iFR in long and/or diffuse coronary lesions (iLARDI): study protocol. *REC Interv Cardiol*. 2021;3:190-195.

REC Interv Cardiol. 2021;3(3):190-195
https://doi.org/10.24875/RECICE.M20000143

Original article

Usefulness of a co-registration strategy with iFR in long and/or diffuse coronary lesions (iLARDI): study protocol

Francisco Hidalgo,[a,*] Soledad Ojeda,[a] Javier Suárez de Lezo,[a] Miguel Romero,[a] Adrián Lostalo,[b] Rafael González,[a] Cristina Pericet,[a] Nick Paredes,[a] Juan C. Elizalde,[a] Aurora Luque,[a] Francisco Mazuelos,[a] José Segura,[a] and Manuel Pan[a]

[a] *Servicio de Cardiología, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain*
[b] *Departamento de Cardiología Intervencionista, Hospital de México, San José, Costa Rica*

ABSTRACT

Introduction and objectives: patients with long, sequential and diffuse coronary lesions who undergo a percutaneous coronary intervention remain at a high risk of suffering cardiovascular events despite the improved safety and efficacy of the new drug-eluting stents. The objective of this study was to analyze the utility of SyncVision/iFR-guided revascularization (SyncVision version 4.1.0.5, Philips Volcano, Belgium) in this type of lesions.
Methods: Randomized, multicenter, controlled, and open-label trial designed to compare SyncVision/iFR-guided and angiography-guided revascularizations in patients with long, sequential or diffuse significant angiographic coronary stenosis (ClinicalTrials.gov identifier: NCT04283734). A total of 100 patients will be randomized (1:1, no stratification). The primary endpoint is the average length of the stent implanted. The secondary endpoint is a composite of cardiac death, myocardial infarction, definitive or probable stent thrombosis, new target lesion revascularization or new target lesion failure; and the presence of residual ischemia as seen on single-photon emission computed tomography at the 6-month follow-up. Patients will be followed for 12 months after the procedure.
Results: The trial is currently in the recruitment phase, and it has already recruited the first 7 patients. We expect to complete the recruitment phase by February 2021 and the follow-up by February 2022.
Conclusions: The iLARDI study is the first randomized trial to assess the potential utility of SyncVision-guided revascularization in long, sequential and diffuse coronary lesions.

Keywords: Diffuse coronary artery disease. Long coronary artery disease. Instantaneous wave-free ratio. SyncVision software.

Utilidad de la estrategia de corregistro con iFR en lesiones coronarias largas o difusas (iLARDI): protocolo del estudio

RESUMEN

Introducción y objetivos: Los pacientes con lesiones coronarias largas, secuenciales o difusas tratadas percutáneamente continúan presentando un riesgo alto de eventos cardiovasculares a pesar de la mejoría de la seguridad y de la eficacia de los nuevos *stents* liberadores de fármacos. El objetivo de este estudio es analizar la utilidad del *software* SyncVision/iFR (SyncVision versión 4.1.0.5, Philips Volcano, Bélgica) para guiar la revascularización en este tipo de lesiones.
Métodos: Estudio aleatorizado, multicéntrico, controlado y abierto para comparar la revascularización guiada por SyncVision/iFR respecto a la revascularización guiada por angiografía en pacientes con lesiones coronarias largas, secuenciales o difusas (identificador de ClinicalTrials.gov: NCT04283734). Se incluirá a 100 pacientes (aleatorización 1:1 no estratificada). El objetivo primario es la longitud total del *stent* implantado. Como objetivo secundario se ha establecido un combinado de muerte cardiaca, infarto de miocardio, trombosis definitiva o probable del *stent*, nueva revascularización de la lesión tratada en el procedimiento basal o nueva revascularización de la lesión analizada en el procedimiento basal, y la presencia de isquemia residual evaluada por tomografía computarizada por emisión de fotón simple a los 6 meses de seguimiento. El tiempo de seguimiento será de 12 meses tras el procedimiento índice.

*** Corresponding author:** Servicio de Cardiología, Hospital Universitario Reina Sofía, Avenida Menéndez Pidal 1, 14004 Cordoba, Spain.
E-mail address: fjhl.87@gmail.com (F. Hidalgo Lesmes).

Received 21 March 2020. Accepted 26 May 2020. Online: 06-07-2021.

Resultados: El estudio se encuentra actualmente en fase de reclutamiento, con los primeros 7 pacientes ya incluidos. Esperamos completar el reclutamiento en febrero de 2021 y el seguimiento en febrero de 2022.
Conclusiones: El estudio iLARDI es el primer estudio aleatorizado para la evaluación de la potencial utilidad de la revascularización guiada por SyncVision en lesiones coronarias largas, secuenciales y difusas.

Palabras clave: Lesiones coronarias difusas. Lesiones coronarias largas. Relación en el periodo instantáneo libre de ondas. *Software* SyncVision.

Abbreviations

PCI: percutaneous coronary intervention. **iFR:** instantaneous wave-free ratio. **MACE:** major adverse cardiovascular events.

INTRODUCTION

The physiological assessment of coronary lesions is a routine practice in contemporary cath labs and is strongly recommended by the European guidelines to guide the percutaneous coronary intervention (PCI) decision-making process.[1] Unlike fractional flow reserve, the new instantaneous wave-free ratio (iFR) index allows us to analyze the physiological significance of each lesion and each coronary segment.[2-5] This has led to the creation of the new and specific SyncVision software package (SyncVision version 4.1.0.5, Philips Volcano, Belgium), that shows the functional compromise of each lesion and predicts the expected iFR improvement after percutaneous treatment.[3,4]

Few observational studies published have analyzed the reduction in the length of the stent implanted compared to angiography-guided revascularization in long and diffuse coronary lesions.[4,5] However, this reduction could be detrimental to the complete coverage of the plaque in this type of lesions, which has proven to be a predictor of major adverse cardiovascular events at the follow-up.[6]

The objective of our study is to analyze the utility of the iFR and SyncVision software to guide the PCI decision-making process in long, sequential, and diffuse coronary lesions.

METHODS

We have designed a multicenter, randomized, controlled, and open-label trial to compare SyncVision/iFR-guided revascularization to angiography-guided revascularization in patients with long, sequential or diffuse significant angiographic coronary lesions (ClinicalTrials.gov identifier: NCT04283734). All the variables that will be analyzed during the study are shown on table 1. Additionally, the study has received the proper ethical oversight and has been approved by the Ethical Comitee of Córdoba.

Inclusion and exclusion criteria

Patients with the following criteria are being included: *a)* patients > 18 years old who require percutaneous coronary treatment due to ischemia (silent, stable angina or acute coronary syndrome); *b)* presence of a vessel with sequential lesions separated by < 10 mm from each other with a total lesion length > 25 mm and a percent diameter stenosis > 60% (as seen on the quantitative coronary angiography assessment) in, at least, 1 segment; or a coronary segment > 30 mm with diffuse disease, and a percent diameter stenosis > 60% (as seen on the quantitative coronary angiography assessment) in, at least, 1 region; *c)* baseline iFR ≤ 0.89 distal to a potentially randomizable lesion.

We have stablished the following exclusion criteria: *a)* patients with acute coronary syndrome with non-optimal results in the culprit vessel (final Thrombolysis in Myocardial Infarction (TIMI) flow grade < III, non-reflow phenomenon during treatment, residual coronary dissection, lost or compromise of a major side branch); *b)* patients with acute coronary syndrome and left ventricular ejection fraction < 45%; *c)* life expectancy < 12 months; d) patients with severe aortic stenosis; *e)* contraindication for dual antiplatelet therapy for at least 12 months; *f)* presence of significant thrombocytopenia (< 10 x 10^9/L); *g)* patients with an indication for bypass surgery according to the heart team; *h)* pregnancy; *i)* inability to understand the informed consent.

Endpoints

The study primary endpoint is the reduction of the average length of the stent implanted in the SyncVision-guided group measured in millimeters (mm) compared to the angiography-guided group. The study secondary endpoint is a composite of cardiac death, myocardial infarction, definitive or probable stent thrombosis, new target lesion revascularization or new target lesion failure (major adverse cardiovascular events [MACE]); and the assessment of residual ischemia through single-photon emission computed tomography at the 6-month follow-up.

Procedure

After the diagnostic phase, the use of intracoronary vasodilators is mandatory to exclude possible coronary spasms. Lesions will be assessed by 2 expert operators (prior to randomization) to determine the coronary segment to treat when the revascularization is angiography-guided based on current routine clinical practice. Afterwards, the iFR will be determined at baseline. If the obtained iFR is ≤ 0.89, patients will be randomized to the angiography-guided revascularization group (the control group) or to the iFR pullback-guided revascularization group using the SyncVision software (figure 1). Intracoronary imaging can be used in both groups based on the operator's criteria to optimize the angiographic result.

In the intervention group, a pressure wire (Verrata pressure guidewire, Philips Volcano, Belgium) will be inserted trough a guide catheter towards the vessel ostium to normalize the pressure

Table 1. Variables that will be analyzed during the study

Nº	Variable	Expressed as
	Personal medical history	
1	Sex (men/women)	no. (%)
2	Age (years)	no. ± SD
3	Hypertension	no. (%)
4	Diabetes mellitus	no. (%)
5	Dyslipidemia	no. (%)
6	Former smoker	no. (%)
7	Previous ischemic cardiomyopathy	no. (%)
8	Previous revascularization	no. (%)
9	Atrial fibrillation	no. (%)
10	Heart failure	no. (%)
11	Previous stroke	no. (%)
12	Peripheral artery disease	no. (%)
13	Previous significant bleeding	no. (%)
14	Basal hemoglobin levels (mg/dL)	no. ± SD
15	Basal creatinine levels (mg/dL)	no. ± SD
16	Left ventricular ejection fraction (%)	no. ± SD
17	Clinical presentation (stable angina/NSTEMI/STEMI)	no. (%)
18	Baseline ultra-sensitive troponin levels (ng/L)	no. ± SD
	Procedural data	
19	Arterial access (radial/femoral/other)	no. (%)
20	$P2Y_{12}$ inhibitor preload	no. (%)
21	IIb/IIIa inhibitor use during the procedure	no. (%)
22	Multivessel disease	no. (%)
23	Syntax score	no. ± SD
24	Randomized vessel (LAD/LCx/RCA/other)	no. (%)
25	Vessel lesion length (mm)	no. ± SD
26	Vessel reference diameter (mm)	no. ± SD
27	Vessel stenosis (%)	no. ± SD
28	Total stent length as seen on the angiography (mm)	no. ± SD
29	Total length of the stent implanted (mm)	no. ± SD
30	Differences between stent length estimated and implanted (mm)	no. ± SD
31	Stent diameter (mm)	no. ± SD
32	Optimal angiographic result (final TIMI III flow, absence of dissections and residual stenosis < 20%)	no. (%)
33	Contrast (milliliters)	no. ± SD
34	Use of intracoronary imaging	no. (%)
35	Use of rotablation	no. (%)
36	Procedural complications (no reflow/ dissection/acute vessel closure/perforation/other)	no. (%)
37	Baseline iFR in the intervention group	no. ± SD
38	Diffuse improvement of iFR by SyncVision	no. (%)
39	Estimated stent length to achieve an iFR > 0.89 (mm)	no. ± SD
40	Final iFR in the intervention group	no. ± SD
41	Need to implant an additional stent	no. (%)
	Hospitalization data	
42	Bleeding complications	no. (%)
43	Ultra-sensitive troponin peak levels (ng/L)	no. ± SD
44	Periprocedural myocardial infarction	no. (%)
45	In-hospital death	no. (%)
46	In-hospital stroke	no. (%)
47	In-hospital stent thrombosis	no. (%)
	Pharmacological treatment at discharge	
48	Aspirin	no. (%)
49	$P2Y_{12}$ Inhibitor (no/clopidogrel/ticagrelor/prasugrel)	no. (%)
50	Anticoagulation (no/acenocumarol/rivaroxaban/ dabigatran/apixaban/edoxaban)	no. (%)
51	Beta-blockers	no. (%)
52	ACEI/ARB/ARNI	no. (%)
53	Calcium antagonists	no. (%)
54	Other anti-ischemic drugs	no. (%)
	Follow-up visits (after 3, 6, and 12 months)	
55	Bleeding complications	no. (%)
56	Dual antiplatelet therapy	no. (%)
57	Anticoagulation (no/acenocumarol/rivaroxaban/ dabigatran/apixaban/edoxaban)	no. (%)
58	Probable or definitive stent thrombosis	no. (%)
59	Spontaneous myocardial infarction	no. (%)
60	New target lesion revascularization	no. (%)
61	New target vessel revascularization	no. (%)
62	Revascularization of other vessel	no. (%)
63	Death	no. (%)
64	Cause of death (cardiac/non cardiac)	no. (%)
65	Stroke	no. (%)
66	Beta-blockers	no. (%)
67	ACEI/ARB/ARNI	no. (%)
68	Calcium antagonists	no. (%)
69	Other anti-ischemic drugs	no. (%)
70	Residual angina (I/II/III/IV)	no. (%)
71	Withdrawal from the study	no. (%)
72	Lost to follow-up	no. (%)

ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor blocker and neprilysin inhibitor; LAD, left anterior descending coronary artery; LCx, left circunflex artery; RCA, right coronary artery; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

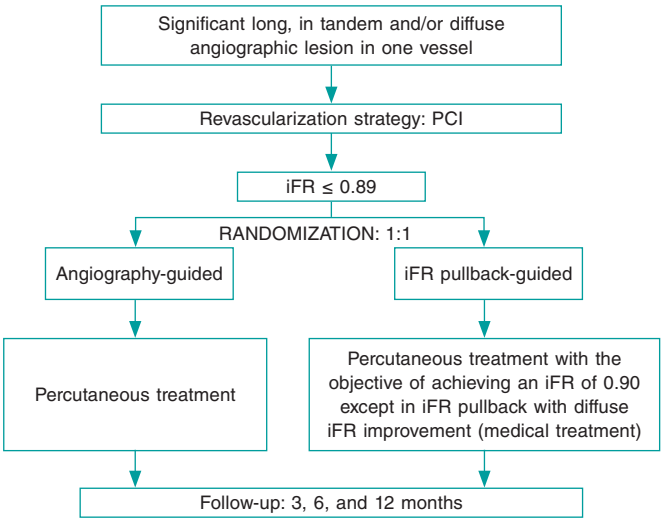


Figure 1. Summary of randomization, treatment targets, and follow-up of the iLARDI study. iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

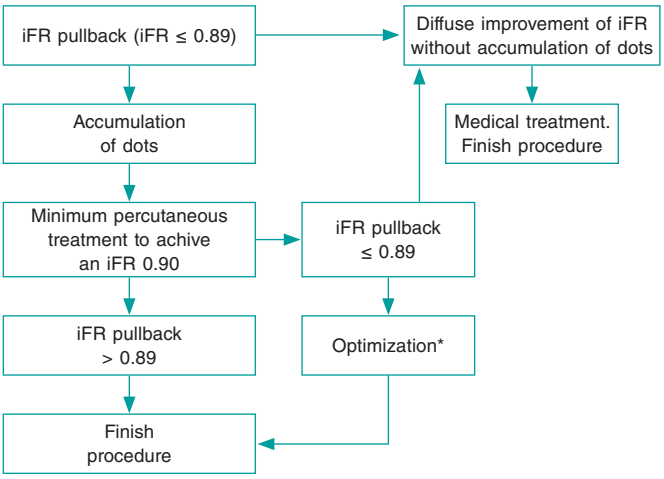


Figure 2. Flowchart of technical treatment details of patients randomized to the intervention group.
* We consider as optimization the postdilatation of the previous stented area if an in-stent accumulation of yellow dots is seen; or the percutaneous treatment of a new segment with physiological compromise not seen in the baseline iFR-pullback study. iFR, instantaneous wave-free ratio.

between the aortic and the vessel ostium. Secondly, the pressure wire will be advanced distally to the lesion. Under stable hemodynamic conditions (without the administration of vasodilators), we will determine the baseline iFR. Afterwards, the wire will be removed under continuous fluoroscopy, and in the same projection. If the iFR at the vessel ostium is 1 ± 0.02, the absence of drift will be confirmed and an angiogram in the same angiographic position will be performed. The SyncVision software can recognize the vessel analyzed and identify the physiological contribution of every lesion and every segment, predicting the improvement of the iFR after treatment. The iFR improvement is depicted as yellow dots. Each yellow dot represents an iFR improvement of 0.01 if that zone was percutaneously treated. The accumulation of many yellow dots suggests that the contribution of that lesion to physiological compromise is high. After performing the physiological assessment of each lesion, the operator would have to treat the minimum segment needed to achieve an iFR of 0.90. Cases without an accumulation of dots have been considered as physiological diffuse disease (defined as the presence of < 20% of the total number of dots) in the coronary segment physiologically assessed. Those cases will be medically treated due to the theoretical absence of benefit of the percutaneous treatment (figure 2 and figure 3).

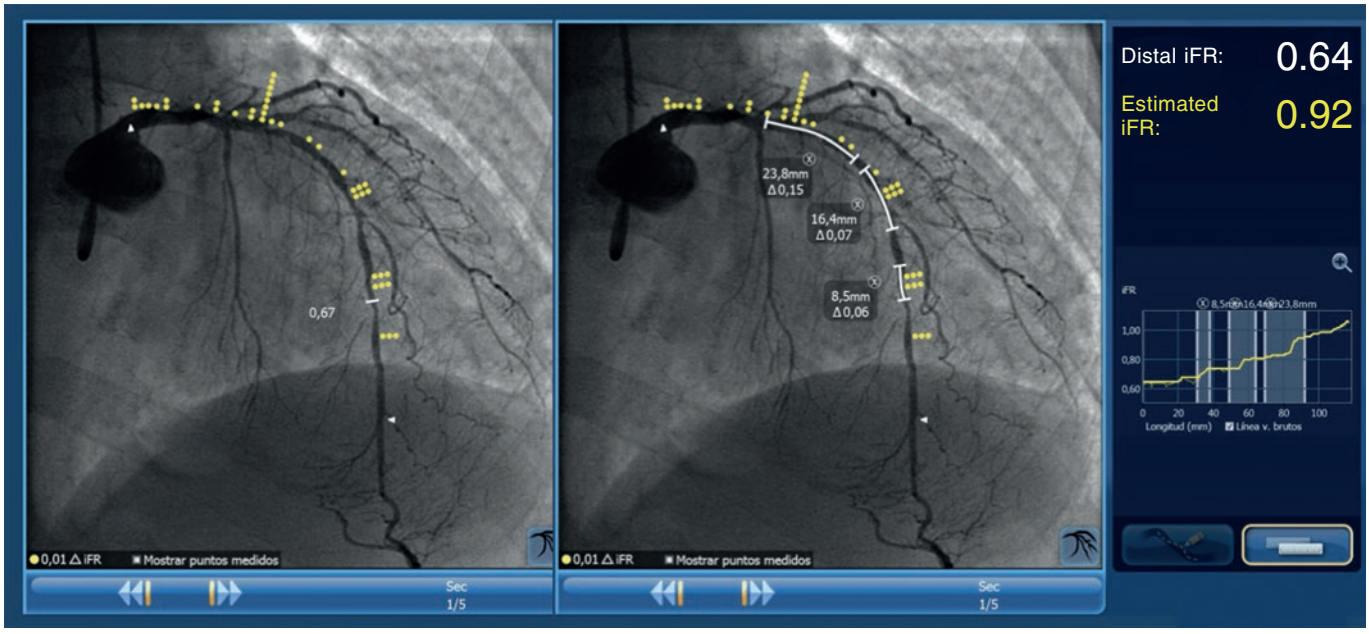


Figure 3. Image of iFR co-registration using the SyncVision software in a patient included in the study and randomized to the intervention group with a diffuse lesion in the left anterior descending coronary artery, and the physiological contribution of every segment. The estimated length of the stent to achieve an iFR > 0.89 is 50.6 mm.

Follow-up

Patients will be followed either through phone calls or physical examination at the 3, 6 and 12-month follow-up. At the 6-month follow-up a stress single-photon emission computed tomography (physiological or pharmacological) will be performed in all patients. The composite of cardiovascular death, definitive or probably stent thrombosis, new target lesion failure or new target lesion revascularization will be considered as MACE.

Quantitative coronary measurements

Quantitative coronary measurements will be performed using a validated system (CAAS system, Pie Medica Imaging, Netherlands). The measurements analyzed will be the vessel reference diameter, the vessel minimal lumen diameter, and the percentage of stenosis. All measurements will be taken at baseline and after the PCI.

Statistical analysis

Regarding the statistical analysis, quantitative variables will be expressed as mean ± standard deviation and qualitative variables as absolute numbers and percentages. To determine the relationship among quantitative variables, we will be using the paired Student *t* test for paired data. To determine the relationship among the qualitative ones, we will use the chi-squared test. In all cases, differences will be considered significant with P values < .05. We will be using the IBM SPSS Statistics software package (version 24.0 for Macintosh, SPSS Corp., United States). To calculate the sample size, we have performed a retrospective analysis of the last 20 patients who were treated at our centre and showed a sequential or diffuse lesion in the coronary vessel analyzed from the iFR-pullback study. The mean length of the stent implanted was 43 ± 9 mm and the reduction of stent length was 12 ± 8 mm on the angiographic analysis. With these data, we have stablished an expected length reduction of 15 mm. The calculated sample size to achieve the primary endpoint with an 80% confidence level and a 5% margin of error was 100 patients.

RESULTS

The recruitment of patients started back in February 2020. After 1 month, we have included the first 7 patients. We expect to complete the recruitment by February 2021 and the follow-up by February 2022.

DISCUSSION

To our knowledge, this randomized study is, the first one to assess the potential benefits of using the SyncVision software in long, sequential or diffuse coronary lesions. Currently, the study is in the recruitment phase and the first patients have already been recruited.

The iFR has proven to be useful in the PCI guide decision-making process.[7,8] However, the evidence supporting the use of SyncVision is scarce and controversial in long, sequential or diffuse lesions. On the one hand, the software allows us to know the coronary segments with the highest physiological compromise. This allows us to revascularize only those segments that immediately improve the physiological result with a potential reduction of the length of the stent implanted, which happens to be a predictor of MACE at the follow-up.[9] On the other hand, it's possible that even if we obtain a good immediate physiological result and a reduction of the stent length implanted we won't be fully covering the plaque in some lesions or coronary segments, which has also proven to be a predictor of MACE.[6]

A limitation of the study is the sample size, enough to achieve the primary endpoint, but probably inadequate to see differences in MACE. However, we think that it can provide an early insight on the utility of iFR pullback study to guide the PCI decision-making process in this type of lesion. Also, it can be a hypothesis-generator study for future larger-scale studies to show benefits in terms of clinical events reduction.

For these reasons, we believe that the iLARDI is an interesting study that will shows us the potential benefit of SyncVision to guide the PCI decision-making process in long, sequential or diffuse coronary lesions. We intend to complete the results by February 2022.

CONCLUSIONS

The iLARDI study is the first randomized trial to assess the potential utility of SyncVision-guided revascularization in long, sequential and diffuse coronary lesions.

FUNDING

Funds from the *Plan Andaluz de Investigación, Desarrollo e Innovación* (PAIDI) have been used to pay for the liability insurance associated with clinical research.

AUTHORS' CONTRIBUTION

All the authors have participated in the study and in the manuscript:

F. Hidalgo has participated has mainly drafted of the manuscript and has participated in the conception and design of the study. R. González has also participated in the conception and design of the study, and in the analysis and interpretation of data. S. Ojeda has mainly participated in the conception, design of the study and revision of the manuscript. C. Pericet has participated in the conception and design of the study. A. Lostalo has also collaborated in the analysis and interpretation of data. J. Segura has also revised it critically for important intellectual content. N. Paredes and J.C. Elizalde have also contributed in the analysis and interpretation of data. A. Luque has participated in the draft of the manuscript. F. Mazuelos has also contributed in the analysis and interpretation of data. J. Suárez de Lezo and M. Romero have revised it critically for important intellectual content. M. Pan has done the final approval of the manuscript submitted.

CONFLICTS OF INTEREST

F. Hidalgo, S. Ojeda, and J. Segura received personal fees from Philips Volcano. M. Pan received minor fees from Abbott, Philips Volcano, and Terumo. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

– The physiological assessment of coronary lesions is a routine practice in the cath lab. The iFR and the SyncVision software allow us to know what is the individual contribution of every coronary lesion and contribute in the PCI decision-making process. However, to our knowledge, no randomized studies have been published on the utility of their use in long, sequential and diffuse coronary lesions.

WHAT DOES THIS STUDY ADD?

– The iLARDI study will show the potential utility of SyncVision/iFR-guided revascularizations in this type of lesions (long, sequential and diffuse coronary lesions) regarding the reduction of the stent length and the potential reduction of major adverse cardiovascular events at the follow-up.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Kim H-L, Koo B-K, Nam C-W, et al. Clinical and physiological outcomes of fractional flow reserve guided percutaneous coronary intervention in patients with serial stenosis within one coronary artery. *JACC Cardiovasc Interv*. 2012;5:1013-1018.
3. Nijjer SS, Sen S, Petraco R et al. The Instantaneous Wave-Free Ratio (iFR) pullback: a novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. *Cardiovasc Revasc Med*. 2015;16:167-171.
4. Nijjer SS, Sen S, Petraco R et al. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Provides Virtual Intervention and Predicts Hemodynamic Outcome for Serial Lesions and Diffuse Coronary Artery Disease. *JACC Cardiovasc Interv*. 2014;7:1386-1396.
5. Kikuta Y, Cook CM, Sharp ASP et al. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease. Primary Results of the International Multicenter iFR GRADIENT Registry. *JACC Cardiovasc Interv*. 2018;11:757-767.
6. Costa MA, Angiolillo DJ, Tannenbaum M et al. Impact of Stent Deployment Procedural Factors on Long-Term Effectiveness and Safety of Sirolimus-Eluting Stents (Final Results of the Multicenter Prospective STLLR Trial). *Am J Cardiol*. 2008;101:1704-1711.
7. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS et al. Use of instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
8. Gotberg M, Crhistiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813-1823.
9. Coner A, Cicek D, Akinci S, et al. Mid-term clinical outcomes of new generation drug-eluting stents for treatment of diffuse coronary artery disease. *Turk Kardiyol Dern Ars*. 2018;46:659-666.

REC Interv Cardiol. 2021;3(3):196-203
https://doi.org/10.24875/RECICE.M21000207

Original article

Mortality with ECMO in critically ill patients with SARS-CoV-2 infection during the COVID-19 pandemic. A systematic review

Néstor Báez-Ferrer,[a,*] Alejandra Bompart-Cairós,[b] Dénis López-Rial,[b] Pedro Abreu-González,[c] Daniel Hernández-Vaquero,[d,e] and Alberto Domínguez-Rodríguez[a,b]

[a] *Servicio de Cardiología, Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain*
[b] *Facultad de Ciencias de la Salud, Universidad Europea de Canarias, La Orotava, Santa Cruz de Tenerife, Spain*
[c] *Departamento de Ciencias Médicas Básicas, Unidad de Fisiología, Universidad de La Laguna, La Laguna, Santa Cruz de Tenerife, Spain*
[d] *Servicio de Cirugía Cardiaca, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[e] *Instituto de Investigación Sanitaria del Principado de Asturias, Departamento de Fisiología, Universidad de Oviedo, Oviedo, Asturias, Spain*

ABSTRACT

Introduction and objectives: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an infectious disease that can present as adult respiratory distress syndrome (ARDS). Without an effective drug therapy, extracorporeal membrane oxygenation (ECMO) is essential when invasive mechanical ventilation fails in severe cases. Our study carried out a systematic review of the studies published in 2020 to analyze the mortality of patients with ARDS due to SARS-CoV-2 who required ECMO.
Methods: A systematic review was conducted on Medline combining keywords on SARS-CoV-2 and ECMO. All studies published during 2020 with positive cases of SARS-CoV-2 treated with ECMO were included, whether observational studies or case series. However, due to the heterogeneity in the methodology of the studies, a proper statistical analysis could not be carried out, which ended up limiting our findings.
Results: Our research identified 41 publications during this period including 2007 cases of patients with severe SARS-CoV-2 infection who required invasive support with ECMO. Among these, 985 (49%) improved clinically and were decannulated or discharged from the hospital, while 660 (32.8%) died despite invasive mechanical support. Only 357 patients (17.7%) still needed ventilation support with ECMO at the time of publication of these studies without describing the final clinical outcome.
Conclusions: ECMO therapy could be useful in patients with ARDS due to SARS-CoV-2 according to the recommendations established in the clinical guidelines and based on the availability of financial resources during the pandemic. Conducting a randomized clinical trial comparing the use of ECMO with conventional invasive ventilatory therapy would provide more evidence on this regard and, consequently, more data on the management of severe SARS-CoV-2 infection.

Keyword: COVID-19. ECMO. SARS-CoV-2. Extracorporeal membrane oxygenation. Mortality. ARDS.

Mortalidad con ECMO en pacientes críticos infectados por SARS-CoV-2 durante la pandemia de COVID-19. Una revisión sistemática

RESUMEN

Introducción y objetivos: El coronavirus del síndrome respiratorio agudo grave de tipo 2 (SARS-CoV-2) genera una enfermedad infecciosa que puede presentarse como síndrome de distrés respiratorio del adulto (SDRA). Sin un tratamiento farmacológico eficaz, el oxigenador extracorpóreo de membrana (ECMO) es fundamental cuando en los casos graves fracasa la ventilación mecánica invasiva. Presentamos una revisión sistemática de los trabajos publicados en el año 2020 para analizar la mortalidad de pacientes con SDRA por SARS-CoV-2 que precisaban ECMO.
Métodos: Se realizó una revisión sistemática en Medline combinando palabras clave sobre SARS-CoV-2 y ECMO. Se incluyeron todos los estudios publicados durante el año 2020 que registraran casos positivos de SARS-CoV-2 tratados con ECMO, ya fueran estudios observacionales o series de casos. Sin embargo, debido a la heterogeneidad en la metodología de los trabajos, no se pudo llevar a cabo un análisis estadístico adecuado, lo cual limita los hallazgos.

*** Corresponding author:** Servicio de Cardiología, Hospital Universitario de Canarias, Ofra s/n, La Cuesta, 38320, Tenerife, Spain.
E-mail address: nestor.baez@hotmail.com (N. Báez-Ferrer).

Received 18 December 2020. Accepted 15 February 2021. Online: 19-04-2021.

Resultados: La búsqueda identificó 41 publicaciones y se recogieron 2.007 casos de pacientes con infección grave por SARS-CoV 2 que precisaron soporte invasivo con ECMO. De estos, 985 (49%) mejoraron clínicamente y fueron descanulados o dados de alta del hospital, y 660 (32,8%) fallecieron a pesar del soporte invasivo. Solo 357 (17,7%) pacientes aún persistían con necesidad de asistencia ventilatoria con ECMO en el momento de la publicación de los estudios, sin que se describa la evolución clínica final.
Conclusiones: El tratamiento con ECMO podría ser útil en pacientes con SDRA por SARS-CoV-2, según las directrices de las guías clínicas y en función de la disponibilidad de los recursos económicos durante la pandemia. La realización de un ensayo clínico aleatorizado que compare el uso de ECMO con el tratamiento convencional ventilatorio invasivo arrojaría mayor evidencia, con el fin de aportar más datos sobre el tratamiento de la infección grave por SARS-CoV-2.

Palabras clave: COVID-19. ECMO. SARS-CoV-2. Oxigenador extracorpóreo de membrana. Mortalidad. SDRA.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2. **COVID-19:** coronavirus disease-2019. **ARDS:** acute respiratory distress syndrome. **ECMO:** extracorporeal membrane oxygenation.

INTRODUCTION

In 2020, the World Health Organization (WHO) declared a public health emergency of international concern on a new strain of coronavirus different from the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) with which it shares some similar characteristics.[1] This new strain known as severe acute respiratory syndrome type 2 (SARS-CoV-2) causes an infectious disease called COVID-19 (coronavirus disease-2019) by the WHO.[1] The first case ever reported occurred in Wuhan, China, in December 2019.[1] Since then, the number of contagions and deaths attributed to COVID-19 has been growing with unprecedented numbers. Until January 2021, a total of 91,492,398 and 2,252,164 cases of COVID-19 had been diagnosed worldwide and Spain, respectively.[2] A total of 1,979,507 deaths due to this virus have been confirmed across the world. In Spain 19 516 cases have required ICU admission, and 53 314 deaths have been reported.[2]

Clinical signs are varied and go from upper respiratory tract infections to severe respiratory distress. It is possible that the intensity of the clinical response is associated with the level of expression of proinflammatory cytokines.[3] As a matter of fact, the cases that end up in an intensive care unit show overexpression of cytokines, mainly IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), macrophage inflammatory protein-1 alpha (MIP-1α), and tumor necrosis factor alpha TNFα.[3] This mechanism contributes to the development of acute respiratory distress syndrome (ARDS). Patients who develop ARDS and survive have high chances of dying due to pulmonary fibrosis in the future.[4] An autopsy study of patients dead due to ARDS conducted in 2013 found that the prevalence of pulmonary fibrosis with a 1 to 3 weeks clinical course was 24%. However, when the duration of ARDS was > 3 weeks, prevalence went up to 63%.[5] As a matter of fact, ARDS survivors showed reticular patterns in the computed tomography scan in up to 85% of the cases.[4] This reticular pattern is often found on a CT scan in the acute phase of patients with COVD-19.[1]

Although the lung is the organ most commonly affected in severe cases, SARS-CoV-2 infections can damage other organs and progress to multiorgan failure. Several drugs have been used during this pandemic, but none has improved survival to this date.[6] The management of ARDS in severe cases of COVID-19 includes invasive mechanical ventilation, muscle relaxation, and prone positioning.[1] When these measures fail, and for the lack of an effective drug therapy, the Extracorporeal Life Support Organization guidelines suggest the use of extracorporeal membrane oxygenation (ECMO).[7]

The use of ECMO has proven beneficial to treat ARDS due to other viral infections. During the 2009 pandemic caused by the H1N1 influenza virus, mortality went down 21% in Australia and New Zealand in patients treated with ECMO after developing ARDS.[8] These data were similar to those obtained in the United Kingdom during this same pandemic (mortality rate dropped 23% in patients on ECMO vs 52% in patients without it).[9] Also, refractory respiratory distress due to MERS-CoV studied in 2014-2015 in Saudi confirmed a lower in-hospital mortality rate in the group of patients treated with ECMO.[10]

Therefore, the main objective of our study was to conduct a systematic review of mortality in patients with severe SARS-CoV-2 infection who required invasive support with ECMO after developing ARDS refractory to conventional therapy.

METHODS

A systematic review was conducted following the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] A combination of the following keywords was used in Medline: «COVID-19», «ECMO», «SARS-CoV-2», «extracorporeal membrane oxygenator/ extracorporeal membrane oxygenation», «mortality», and «ARDS». Inclusion criteria were studies from 2020, whether observational studies or case series, that analyzed the mortality of patients with ARDS and SARS-CoV-2 infection treated with ECMO. Exclusion criteria were publications on ECMO and COVID-19 that would not include additional patients eligible for this research, with the objective of focusing on ECMO related complications, that proved its benefits compared to other therapies, with authors reporting on isolated case reports including children, pregnant and postpartum women with COVID-19 who required ECMO. However, due to the heterogeneous methodology of the studies included a proper statistical analysis could not be conducted. The study was conducted in observance of the Declaration of Helsinki regarding ethical principles on medical research with human beings. This study was approved by the *Complejo Hospitalario Universitario* ethics committee of the Canary Islands, Spain.

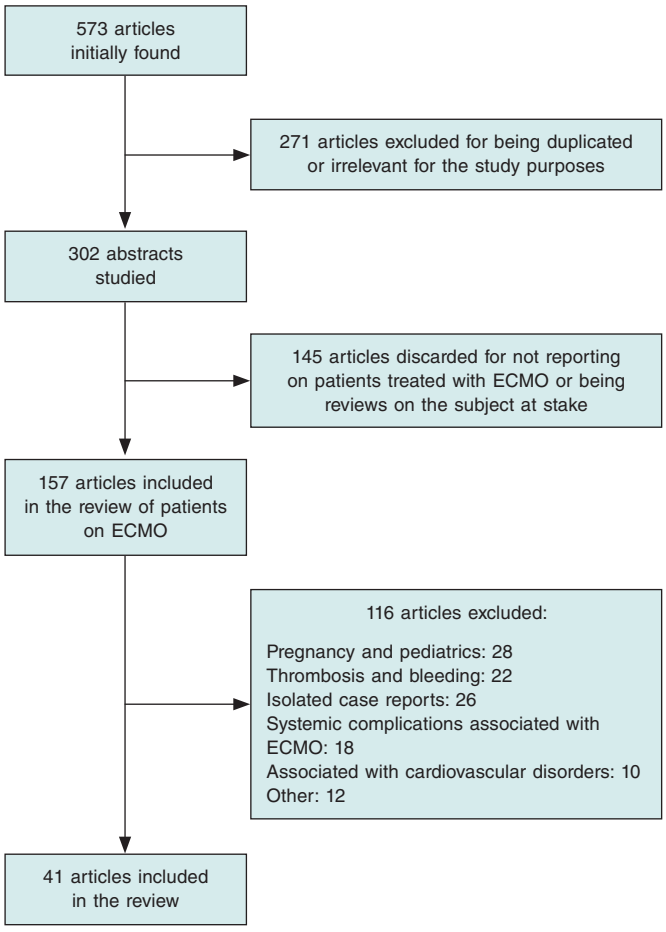


Figure 1. Flowchart depicting the search for articles on extracorporeal membrane oxygenation (ECMO) and COVID-19.

RESULTS

After combining the keywords, the search identified 573 publications. A total of 271 were ruled out for being duplicated or irrelevant. After reviewing the abstracts of the remaining 302 articles, 145 were excluded for not including any additional cases of patients who needed mechanical support or ECMO or for being reviews on ECMO and COVID-19. Out of the 157 studies that described cases with ECMO, 116 were discarded based on the exclusion criteria. Finally, a total of 41 publications were analyzed (figure 1) with a total of 2007 cases of patients with severe SARS-CoV-2 infections who required ECMO support with a mean age of 54 years (72% of whom were predominantly men) (table 1). Venovenous or veno-venovenous ECMO (VV-ECMO or VVV-ECMO) was administered to 1545 patients due to refractory hypoxemia yet despite prone positioning or ARDS. Venoarterial or veno-arteriovenous ECMO (VA-ECMO or VAV-ECMO) was administered to 84 patients due to cardiogenic shock. Of these, 985 (49%) patients improved clinically and were ECMO decannulated or released from the hospital. On the contrary, 660 patients (32.8%) died despite invasive mechanical support with ECMO. Finally, since 357 patients (17.7%) still needed ECMO support by the time these studies were being published, the final clinical outcome remains unknown.

DISCUSSION

We present a systematic review of publications on patients with severe SAR-CoV-2 infections treated with ECMO during 2020 since the beginning of the COVID-19 pandemic. This study includes one of the largest series of patients requiring ECMO due to severe SARS-CoV-2 infection published on the medical literature to this date.

The main clinical presentation of COVID-19 is a mild infection with dry cough and fever as the most common symptoms; the overall rate of ARDS is 3.4%.[12] However, after studying series of patients who develop pneumonia and require hospitalization, the rate of ARDS can be up to 17% to 21%.[13,14] The systemic inflammatory response of patients ith COVID-19 can affect, to a greater or lower extent, the pulmonary epithelium and endothelium.[15] However, the endothelium seems less affected by SARS-CoV-2, which produces fewer alveolar exudates, thus contributing to the production of dry cough. On the other hand, in patients with severe COVID-19 ARDS does not show the reduction of compliance that a standard ARDS would cause, suggestive that other mechanisms are responsible for severe hypoxemia.[15] This milder endothelial aggression can contribute to a small viral affectation of distal organs.[15]

Myocardial damage is present in 7.2% to 20% of the cases[15-18] and kidney injuries in 2.9% to 15% depending on the sources.[15] Myocardial damage can be associated with higher in-hospital mortality[16-18] and should tip us off to discard cardiogenic shock due to fulminant myocarditis in case of hemodynamic instability after severe SARS-CoV-2 infection[19]. Myocardial damage is multifactorial and could be the result of the virus direct cardiotoxicity on cardiomyocytes.[16] This possibility may be associated with the compatibility that exists between the virus and the angiotensin-II receptor, present in over 7.5% of cardiomyocytes. We should not forget the systemic inflammatory response following the infection that can cause the direct inflammation and suppression of myocardial contractility.[16] Similarly, the fewer visits to the emergency room due to acute coronary syndrome reported and the drop in the activity of the infarction code during the pandemic have both increased the rate of cardiogenic shock of ischemic origin.[20] This has reduced the healthcare activity provided during the pandemic with fewer coronary interventions being performed. This serious complication may have increased the need for ventricular assist devices, particularly ECMO, in the context of a lower availability of this device due to being used by patients with severe SARS-CoV-2 infection.

To fight severe COVID-19 cases due to ARDS refractory to protective invasive mechanical ventilation, muscle relaxation, and prone positioning or cardiogenic shock refractory to inotropic and vasopressor support, VV-ECMO or VA-ECMO are available options according to the guidelines recently published by the Extracorporeal Life Support Organization (ELSO).[7] The problem with this therapy is that it is an expensive and limited resource. Therefore, during this health crisis, it should be used in young populations with high mortality rates and fewer comorbidities.[7] Kidney disease is not an absolute contraindication and it should not be used in patients on invasive mechanical ventilation for more than 7 days because of the worse outcomes reported.[7] For all these reasons, thorough assessments prior to indicating the most appropriate ECMO support is needed in patients with severe SARS-CoV-2 infection.[21] The best time to implant this device is when protective invasive mechanical ventilation and prone positioning fail, and as long as the patient does not develop septic shock or multiorgan failure.[22] After implantation, it is recommended to assess the blood concentrations of IL-6 and lymphocytes because if the numbers of these markers do not improve with this therapy, these patients' prognosis is often less promising.[23]

The search conducted found higher mortality rates in patients who received ECMO due to ARDS after severe SARS-CoV-2 infection compared to those who developed the disease caused by the H1N1

Table 1. Registry of the studies available, number of patients on extracorporeal membrane oxygenation (ECMO), and number of patients released from the hospital, deceased, and still on ECMO by the time this study was being published

Study	Journal	Patients with COVID-19	Mean age, years (range)	Sex masculine/ feminine	Total Patients on ECMO	Patients on VV- or VVV/VA- or VAV-ECMO	Patients decannulated or released from the hospital (%)	Dead patients (%)	Patients still on ECMO (%)
Total		6636	54 (44-71)	1448/457	2007	1545/84	985 (49%)	660 (32.8%)	357 (17.7%)
Ahmadi ZH et al.[34]	*J Card Surg*	7	46	6/1	7	7/0	2	5	0
Akhtar W et al.[35]	*Indian J Thorac Cardiovasc Surg*	18	47	16/2	18	15/3	14	4	0
Alnababteh M et al.[36]	*Perfusion*	59	44	8/5	13	13/0	7	6	0
Barbaro RP et al.[24]	*Lancet*	1035	49	764/269	1035	978/57	599	380	56
Charlton M et al.[37]	*J Infect*	34	46	27/7	34	NA	18	16	0
Cousin N et al.[38]	*ASAIO J*	30	57	24/6	30	30/0	14	16	0
Falcoz PE et al.[39]	*Am J Respir Crit Care Med*	377	56	16/1	17	16/1	11	6	0
Guo Z et al.[40]	*J Cardiothorac Vasc Anesth*	667	63	7/1	8	8/0	4	4	0
Hu H et al.[41]	*Curr Med Sci*	55	50	4/5	9	9/0	5	4	0
Huang S et al.[42]	*J Clin Anesth*	3	62	1/2	3	3/0	0	2	1
Huette P et al.[43]	*Can J Anaesth*	12	NA	NA	12	NA	8	4	0
Jacobs JP et al.[44]	*ASAIO J*	32	52	22/10	32	26/5[b]	5	10	17
Kon ZN et al.[45]	*Ann Thorac Surg*	1900	40	23/4	27	27/0	11	1	15
Le Breton C et al.[46]	*J Crit Care*	13	58	10/3	13	13/0	11	2	0
Li J et al.[47]	*Am J Med Sci*	74	71	NA	2	NA	0	2	0
Loforte A et al.[48]	*ASAIO J*	4	49	4/0	4	4/0	1	2	1
Marullo AG et al.[31]	*Minerva Cardioangiol*	333	52	285/48	333	150/9[b,c]	54	57	222[c]
Miike S et al.[49]	*J Infect Chemother*	14	58	2/1	3	NA	2	1	0
Mustafa AK et al.[50]	*JAMA Surg*	40	48	30/10	40	NA	29	6	5
Osho AA et al.[51]	*Ann Surg*	6	47	5/1	6	6/0	5	1	0
Riera J et al.[52]	*Crit Care Explor*	19	50	16/3	19	19/0	13	4	2
Rieg S et al.[53]	*PLoS One*	213	65	NA	23	NA	9	14	0
Ruan Q et al.[19]	*Intensive Care Med*	150	67	NA	7	NA	0	7	0
Santos-Martínez S et al.[54]	*REC Interv Cardiol*	14	48	11/3	14	12/2	8	4	0
Schmidt M et al.[30]	*Lancet Respir Med*	492	49	61/22	83	81/2	52	30	1
Schroeder I et al.[55]	*Anaesthesist*	70	66	5/2	7	NA	1	6	0
Shen C et al.[56]	*JAMA*	5	36-65	1/0	1	NA	1	0	0
Sromicki et al.[57]	*Circ J*	9	59	6/3	9	7/2	7	2	0
Sultan I et al.[32]	*J Card Surg*	10	31-62[a]	7/3	10	10/0	2	1	7
Wu C et al.[58]	*JAMA Intern Med*	201	51	NA	1	NA	0	1	0
Xu Y et al.[59]	*Front Med (Lausanne)*	45	56	NA	10	NA	6	2	2

(Continues)

Table 1. Registry of the studies available, number of patients on extracorporeal membrane oxygenation (ECMO), and number of patients released from the hospital, deceased, and still on ECMO by the time this study was being published *(Continued)*

Study	Journal	Patients with COVID-19	Mean age, years (range)	Sex masculine/ feminine	Total Patients on ECMO	Patients on VV- or VVV/VA- or VAV-ECMO	Patients decannulated or released from the hospital (%)	Dead patients (%)	Patients still on ECMO (%)
Xuan W et al.[60]	*J Clin Anesth*	5	61	NA	5	4/1[b]	2	3	0
Yang X et al.[61]	*Crit Care Med*	21	58	12/9	21	NA	9	12	0
Yang X et al.[62]	*Lancet Respir Med*	52	59	NA	6	NA	0	5	1
Yang Y et al.[63]	*Card Fail Rev*	7	45	3/4	7	6/1[b]	6	1	0
Yankah CA et al.[64]	*Thorac Cardiovasc Surg*	42	51	30/12	42	42/0	17	7	18
Yao K et al.[65]	*J Infect Chemother*	101	60	NA	11	NA	9	2	0
Zayat R et al.[66]	*Artif Organs*	17	57	11/6	17	16/1	9	8	0
Zeng Y et al.[67]	*Critical Care*	12	51	11/1	12	NA	3	5	4
Zhang G et al.[13]	*J Clin Virol*	221	55	NA	10	NA	2	3	5
Zhang J et al.[68]	*ERJ Open Res*	43	46	20/13	43	43/0	29	14	0
Zhou F et al.[69]	*Lancet*	191	56	NA	3	NA	0	3	0

COVID-19, coronavirus disease-2019; ECMO, extracorporeal membrane oxygenation; NA, not available; VA, venoarterial; VAV, veno-arteriovenous; VV, venovenous; VVV, veno-venovenous.
[a] Study age range.
[b] Indication for VA- or VAV-ECMO not available.
[c] Incomplete data.

influenza virus in the United Kingdom during the pandemic of 2009: 32.8% vs 23%,[9] respectively. These findings are consistent with those from the registry conducted by Barbaro et al., one of the largest registries ever published, of 1035 patients with a 39% in-hospital mortality rate.[24] On the other hand, during the MERS-CoV pandemic of 2015, the mortality of the group that received ECMO therapy was analyzed (64% compared to 100% in the group without this device).[10] However, due to the lack of clinical trials in the medical literature with control groups of treatment without ECMO for the management of SARS-CoV-2-induced ARDS, we still should not say that its use is beneficial. Also, the high pressure exerted on the health centers at the beginning of the pandemic may have contributed to the worse results reported like the ones published by Ruan et al.[19] compared to other series that studied mortality with ECMO in these patients when this pressure on the healthcare system had probably gone down.[24,30]

During the first few months of 2020, 2 meta-analyses of patients with SARS-CoV-2-induced ARDS treated with ECMO were conducted. The first one included 4 Chinese studies and proved the poor benefits of this therapy in 17 patients since only 1 managed to survive.[25] The other meta-analysis includes 6 series of 17 patients in total. Fourteen of these patients died and mortality rate was close to 82.3%.[26] The limitation of these studies is the small number of patients included for analysis and both recommended conducting new studies.

There are reviews already currently available on the medical literature. However, one of them only includes 274 patients who required ECMO, meaning that mortality could not be properly analyzed since 45.6% of the patients remained hospitalized by the time the studies included were being published.[27] A different review of 479 patients from 25 studies showed a 19.83% mortality rate. However, the authors claim that it is just an estimate since some of the studies did not report on the mortality rate of the subjects.[28] Finally, Melhuish et al.[29] grouped 331 cases from 10 different studies and 4 database registries and estimated a 46% mortality rate. A common limitation of these studies is that none of them includes the registry conducted by Barbaro et al.[24] the largest published to this date. Our review widens and consolidates these findings after including the 3 largest series published to this date of 83, 333, and 1035 patients.[24,30,31] Although we found a higher mortality rate compared to the H1N1 pandemic of 2009,[8,9] ECMO support in these patients may be acceptable for the lack of another therapeutic option. However, every case should be treated individually; patients over 60 and with associated comorbidities like cardiovascular disease and diabetes have a higher mortality risk.[17,28,31]

Due to the complexity of ECMO support, the need for the proper learning curve and clinical experience, the results of this therapy can be biased. From 2003 through 2019, the number of centers that used this device across the world quadrupled, and the number of devices implanted has multiplied by a factor of 6.[32] This is so to such an extent that during an unexpected pandemic when resources need to be immediately restructured, the results obtained by the studies within the first few months of 2020 should be interpreted with caution. For example, during the pandemic of 2009, much more ECMO systems were used, which may have generated higher chances of recovery compared to the current limitation of resources available for the implantation of this device. This means that mortality results may be different too.[1]

Finally, we should mention that despite the fact that patients survive with the invasive support provided by ECMO, the chances of experiencing pulmonary fibrosis in the future are non-negligible with the corresponding higher mortality rate.[5] Further studies are needed to identify patients with greater chances of developing this

complication; also, antithrombotic therapy may be useful for the management of SARS-CoV-2 infections causing parenchymal pulmonary fibrosis.[5]

Limitations

The first limitation of our study is that unpublished multicenter registers on scientific journals were excluded.[33] Also, patients treated with ECMO from studies focused on analyzing ECMO related complications and isolated case reports were excluded. The characteristics of patients from each study or the methodologies used have not been compared because they were different.

CONCLUSIONS

We believe that invasive support with ECMO may be useful for certain patients based on the recommendations established by the clinical guidelines and the availability of resources despite the dissimilar results obtained. A randomized clinical trial comparing the use of ECMO to conventional invasive mechanical ventilation would bring further evidence on this regard.

FUNDING

This study received no funding whatsoever.

AUTHORS' CONTRIBUTIONS

N. Báez-Ferrer was involved in the reference search, data analysis, and writing of this manuscript. A. Bompart-Cairós, and D. López-Rial both participated in the reference search. P. Abreu-González, and D. Hernández-Vaquero participated in the review and writing of this manuscript. A. Domínguez-Rodríguez conducted the manuscript final review.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

- ARDS can be the clinical presentation of SARS-CoV-2 infection.
- Multiple drug therapies fail during the management of this entity. The use of ECMO is especially important in patients who are refractory to mechanical ventilation, muscle relaxation, and prone positioning.
- Since the beginning of the COVID-19 pandemic and all across 2020 several articles of patients with severe SARS-CoV-2 infection manifested as ARDS have been published. These articles have analyzed the mortality rate associated with ECMO therapy. However, to this date, no randomized clinical trial has assessed the clinical benefit of ECMO in these patients.

WHAT DOES THIS STUDY ADD?

- We presented the results of a systematic review of the studies published in 2020 during the COVID-19 pandemic to analyze the mortality rate of patients with SARS-CoV-2-induced ARDS requiring ECMO.
- A total of 41 publications were identified during 2020, and 2007 cases of patients with severe SARS-CoV-2 infection who required invasive support with ECMO were collected.
- Of all the cases collected, a mortality rate associated with ECMO in patients with severe SARS-CoV-2 was found to be 32.8%; 660 patients died despite therapy with invasive mechanical support.
- ECMO therapy may be useful in patients with SARS-CoV-2-induced ARDS. However, it would be interesting to conduct a randomized clinical trial to compare the use of ECMO to conventional invasive ventilation therapy during this pandemic.

REFERENCES

1. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. *PLoS Pathog*. 2020;16:1-24.
2. Actualización nº 291. Enfermedad por el coronavirus (COVID-19). 15.01.2021. Available online https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_291_COVID-19.pdf. Accessed 18 Jan 2021.
3. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:18-21.
4. Yan-Rong G, Qing-Dong C. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res*. 2020;7:11.
5. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*. 2020;8:807-815.
6. Thille AW, Esteban A, Fernández-Segoviano P, et al. Chronology of histological lesions in acute respiratory distress syndrome with diff use alveolar damage: A prospective cohort study of clinical autopsies. *Lancet Respir Med*. 2013;1:395-401.
7. Bartlett RH, Ogino MT, Brodie D, et al. Initial ELSO Guidance Document: ECMO for COVID-19 Patients with Severe Cardiopulmonary Failure. *ASAIO J*. Published online 2020:472-474.
8. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *J Am Med Assoc*. 2009;302:1888-1895.
9. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *J Am Med Assoc*. 2011;306:1659-1668.
10. Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care*. 2018;8:3.
11. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration*. Vol 62.; 2009.
12. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.
13. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. 2020;127:104364.
14. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
15. Li X, Ma X. Acute respiratory failure in COVID-19: Is it "typical" ARDS? *Crit Care*. 2020;24:1-5.
16. Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart*. 2020;106:1132-1141.
17. Li X, Guo Z, Li B, et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai, China. *ASAIO J*. 2020:475-481.
18. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5:802-810.

19. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-848.
20. Rodríguez-Leor O, Cid-Álvarez B, Ojeda S, et al. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. *REC Interv Cardiol*. 2020;2:82-89.
21. Khan R, Anandamurthy B, McCurry K, Krishnan S. Utility of extracorporeal membrane oxygenation in COVID-19. *Cleve Clin J Med*. 2020:1-3.
22. Li L, Li R, Wu Z, et al. Therapeutic strategies for critically ill patients with COVID-19. *Ann Intensive Care*. 2020;10:45.
23. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med*. 2020;8:e24.
24. Barbaro R, MacLaren G, Boonstra P, Iwashyna, TH, Slutsky A, Fan E. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396:1071-1078.
25. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care*. 2020;58:27-28.
26. Ñamendys-Silva SA. ECMO for ARDS due to COVID-19. *Hear Lung*. 2020; 49:348-349.
27. Oliveira TF de, Rocha CA de O, Santos AGG dos, et al. Extracorporeal Membrane Oxygenation in COVID-19 Treatment: a Systematic Literature Review. *Brazilian J Cardiovasc Surg*. 2021;8:84-123.
28. Haiduc AA, Alom S, Melamed N, Harky A. Role of extracorporeal membrane oxygenation in COVID-19: A systematic review. *J Card Surg*. 2020;35:2679-2687.
29. Melhuish TM, Vlok R, Thang C, Askew J, White L. Outcomes of extracorporeal membrane oxygenation support for patients with COVID- 19: A pooled analysis of 331 cases. *Am J Emerg Med*. 2020;39:245-246.
30. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020;8:1121-1131.
31. Marullo A, Cavaretta E, Biondi-zoccai G, et al. Extracorporeal membrane oxygenation for critically ill patients with coronavirus-associated disease 2019 : an updated perspective of the European experience. *Minerva Cardioangiol*. 2020;68:368-372.
32. Sultan I, Habertheuer A, Usman AA, et al. The role of extracorporeal life support for patients with COVID-19: Preliminary results from a statewide experience. *J Card Surg*. 2020;35:1410-1413.
33. The Extracorporeal Life Support Organization (ELSO): ECMO in COVID-19. Available online: https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx. Accessed 18 Jan 2021.
34. Ahmadi ZH, Jahangirifard A, Farzanegan B, et al. Extracorporeal membrane oxygenation and COVID-19: The causes of failure. *J Card Surg*. 2020;35: 2838-2843.
35. Akhtar W, Olusanya O, Baladia MM, Young H, Shah S. SARS-CoV-2 and ECMO: early results and experience. *Indian J Thorac Cardiovasc Surg*. 2021;37:53-60.
36. Alnababteh M, Hashmi MD, Vedantam K, et al. Extracorporeal membrane oxygenation for COVID-19 induced hypoxia: Single-center study. *Perfus (United Kingdom)*. 2020. http://dx.doi.org/10.1177/0267659120963885.
37. Charlton M, Dashey S, Stubbs A, Lai FY, Tang JW. Comparing SARS-CoV-2 and influenza A(H1N1)pdm09-infected patients requiring ECMO. A single-centre, retrospective observational cohort experience. *J Infect*. 2020. http://dx.doi.org/10.1016/j.jinf.2020.11.003.
38. Cousin N, Bourel C, Carpentier D, et al. SARS-CoV-2 versus influenza associated acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation support. *ASAIO J*. 2021 Feb 1;67(2): 125-131.
39. Falcoz P-E, Puyraveau M, Perrier S, et al. Extracorporeal Membrane Oxygenation for Critically Ill Patients with COVID-19–related Acute Respiratory Distress Syndrome: Worth the Effort?. *Am J Respir Crit Care Med*. 2020;202:460-463.
40. Guo Z, Sun L, Li B. Anticoagulation Management in Severe Coronavirus Disease 2019 Patients on Extracorporeal Membrane Oxygenation. *J Cardiothorac Vasc Anesth*. 2021;35:389-397.
41. Hu H, Xu S, Wang J, Rao X. Respiratory Support in Severely or Critically Ill ICU Patients With COVID-19 in Wuhan, China. *Curr Med Sci*. 2020;40: 636-641.
42. Huang S, Xia H, Wu Z, et al. Clinical data of early COVID-19 cases receiving extracorporeal membrane oxygenation in Wuhan, China. *J Clin Anesth*. 2021;68:110044.
43. Huette P, Beyls C, Guilbart M, et al. Extracorporeal membrane oxygenation for respiratory failure in COVID-19 patients: outcome and time-course of clinical and biological parameters. *Can J Anesth*. 2020;67:1486-1488.
44. Jacobs JP, Stammers AH, Louis J, et al. Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients. *ASAIO J*. 2020. http://dx.doi.org/10.1097/MAT.0000000000001185.
45. Kon ZN, Smith DE, Chang SH, et al. Extracorporeal Membrane Oxygenation Support in Severe COVID-19. *Ann Thorac Surg*. 2020. http://dx.doi.org/10.1016/j.athoracsur.2020.07.002.
46. Breton C Le, Besset S, Amouretti M, Billiet PA, Dao M. Extracorporeal membrane oxygenation for refractory COVID-19 acute respiratory distress syndrome. *J Crit Care*. 2020;60:10-12.
47. Li J, Xu G, Yu H, Peng X, Luo Y, Cao C. Clinical Characteristics and Outcomes of 74 Patients With Severe or Critical COVID-19. *Am J Med Sci*. 2020;360:229-235.
48. Loforte A, Dal Checco E, Gliozzi G, et al. Veno-venous extracorporeal membrane oxygenation support in covid-19 respiratory distress syndrome: Initial experience. *ASAIO J*. 2020;66:734-738.
49. Miike S, Sakamoto N, Washino T, et al. Critically ill patients with COVID-19 in Tokyo, Japan: A single-center case series. *J Infect Chemother*. 2021; 27:291-295.
50. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal Membrane Oxygenation for Patients with COVID-19 in Severe Respiratory Failure. *JAMA Surg*. 2020;155:990-992.
51. Osho AA, Moonsamy P, Hibbert KA, et al. Veno-venous Extracorporeal Membrane Oxygenation for Respiratory Failure in COVID-19 Patients: Early Experience From a Major Academic Medical Center in North America. *Ann Surg*. 2020;272:e75-e78.
52. Riera J, Argudo E, Martínez-Martínez M, et al. Extracorporeal Membrane Oxygenation Retrieval in Coronavirus Disease 2019: A Case-Series of 19 Patients Supported at a High-Volume Extracorporeal Membrane Oxygenation Center. *Crit Care Explor*. 2020;2:e0228.
53. Rieg S, von Cube M, Kalbhenn J, et al. COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. *PLoS One*. 2020;15:1-16.
54. Santos-Martínez S, Martín Moreiras J, Vázquez-Álvarez M, Peñasco Y, Uribarri A, Amat-Santos I. Oxigenador extracorpóreo de membrana con implante percutáneo durante la pandemia de COVID-19. Registro multicéntrico español. *REC Interv Cardiol*. 2020;2:312-314.
55. Schroeder I, Scharf C, Zoller M, et al. Characteristics and outcome of 70 ventilated COVID-19 patients: Summary after the first wave at a university center. *Anaesthesist*. 2020. http://dx.doi.org/10.1007/s00101-020-00906-3.
56. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. *J Am Med Assoc*. 2020;323:1582-1589.
57. Sromicki J, Schmiady M, Maisano F, Mestres CA. ECMO therapy in COVID-19: The Zurich experience. *J Card Surg*. 2021;36:1707-12.
58. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180:934-943.
59. Xu Y, Xu Z, Liu X, et al. Clinical Findings of COVID-19 Patients Admitted to Intensive Care Units in Guangdong Province, China: A Multicenter, Retrospective, Observational Study. *Front Med*. 2020;7:1-9.
60. Xuan W, Chen C, Jiang X, et al. Clinical characteristics and outcomes of five critical COVID-19 patients treated with extracorporeal membrane oxygenation in Leishenshan Hospital in Wuhan. *J Clin Anesth*. 2020;67: 110033.
61. Yang X, Cai S, Luo Y, et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome: A Multicenter Descriptive Study. *Crit Care Med*. 2020;3:1289-1295.
62. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475-481.
63. Yang Y, Rali AS, Inchaustegui C, et al. Extracorporeal Membrane Oxygenation in Coronavirus Disease 2019-associated Acute Respiratory Distress Syndrome: An initial US Experience at a High-volume Centre. *Card Fail Rev*. 2020;6:7-9.
64. Yankah CA, Trimlett R, Sandoval E, et al. COVID-19 Pulmonary Failure and Extracorporeal Membrane Oxygenation: First Experience from Three European Extracorporeal Membrane Oxygenation Centers. *Thorac Cardiovasc Surg*. 2021;69:259-62.
65. Yao K, Hasegawa S, Tagashira Y, et al. Experience of 101 patients with coronavirus infectious disease 2019 (COVID-19) at a tertiary care center in Japan. *J Infect Chemother*. 2021;27:413-417.

66. Zayat R, Kalverkamp S, Grottke O, et al. Role of extracorporeal membrane oxygenation in critically Ill COVID-19 patients and predictors of mortality. *Artif Organs*. 2020. http://dx.doi.org/10.1111/aor.13873.
67. Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: A retrospective case series. *Crit Care*. 2020;24:8-10.
68. Zhang J, Merrick B, Correa GL, et al. Veno-venous extracorporeal membrane oxygenation in coronavirus disease 2019: a case series. *ERJ Open Res*. 2020;6:00463-02020.
69. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.

REC Interv Cardiol. 2021;3(3):204-212
https://doi.org/10.24875/RECICE.M21000204

Review article

State-of-the-art and future perspective of percutaneous interventions for the management of STEMI

Luis Ortega-Paz, Salvatore Brugaletta, and Manel Sabaté*

Servicio de Cardiología, Hospital Clínic, Institut Clínic Cardiovascular, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

ABSTRACT

Ischemic heart disease is the most common cause of death worldwide. In patients with ST-segment elevation myocardial infarction (STEMI), optimizing primary percutaneous coronary intervention is crucial to improve prognosis. Over the years, many studies have been published on the value of second-generation stents, strategies to reduce myocardial damage, how to achieve complete revascularization and also on percutaneous mechanical circulatory support devices, which all are attractive therapeutic options to treat patients with STEMI complicated by cardiogenic shock. In this review we will be discussing how primary percutaneous coronary intervention can be optimized with respect to stent selection and revascularization strategy to reduce myocardial damage and improve clinical outcomes. In addition, we review published data on the use of mechanical circulatory support devices in patients with STEMI complicated by cardiogenic shock.

Keywords: ST-segment elevation myocardial infarction. Percutaneous coronary intervention. Drug-eluting stent. Cardiogenic shock.

Intervencionismo en el infarto de miocardio con elevación del segmento ST: estado actual y perspectivas de futuro

RESUMEN

La cardiopatía isquémica es la causa más común de mortalidad en todo el mundo. En pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST), la optimización de la intervención coronaria percutánea primaria es crucial para mejorar el pronóstico. Durante estos últimos años, se han publicado muchos estudios sobre el valor de los *stents* de segunda generación, sobre estrategias para reducir el daño miocárdico, sobre cómo conseguir la revascularización completa y finalmente también sobre dispositivos de apoyo circulatorio mecánico percutáneo que representan una opción terapéutica atractiva en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST) complicado con *shock* cardiogénico. En esta revisión discutimos cómo se puede optimizar la intervención coronaria percutánea primaria con respecto a la selección de *stents* y estrategia de revascularización, con el fin de reducir el daño miocárdico y mejorar los resultados clínicos. Además, revisamos los datos publicados sobre el uso de dispositivos de apoyo circulatorio mecánico en pacientes con IAMCEST complicado por *shock* cardiogénico.

Palabras clave: Infarto de miocardio con elevación del segmento ST. Intervención coronaria percutánea. *Stent* farmacoactivo. *Shock* cardiogénico.

Abbreviations

CS: cardiogenic shock. **DES:** drug-eluting stents. **IABP:** intra-aortic balloon pump. **LV:** left ventricle. **MVD:** multivessel coronary artery disease. **PCI:** percutaneous coronary intervention. **STEMI:** ST-segment elevation myocardial infarction. **VA-ECMO:** venoarterial extracorporeal membrane oxygenation.

* **Corresponding author:** Unidad de Cardiología Intervencionista, Departamento de Cardiología, Instituto Cardiovascular, IDIBAPS, CardioCV, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: masabate@clinic.cat (M. Sabaté).

Received 9 January 2021. Accepted 27 January 2021. Online: 16-03-2021.

INTRODUCTION

Ischemic heart disease is the leading cause of death across the world. Over the last few decades, thanks to the improvements made in reperfusion and antithrombotic therapies, and primary prevention, the relative rates of ST-segment elevation myocardial infarction (STEMI) and long-term and acute mortality have decreased significantly.[1] However, despite this reduction, the mortality rate of patients with STEMI is still substantial with in-hospital mortality rates ranging from 4% to 12%, and a 1-year follow-up mortality rate close to 10%.[2-4]

In STEMI patients, mortality depends on various factors like the Killip classification at presentation, old age, the presence of cardiovascular risk factors, left ventricular function, the spread of the disease in the coronary arteries, and the delayed administration of reperfusion therapy. An early diagnosis and restoration of myocardial blood flow from symptom onset are essential to optimize myocardial salvage and lower the mortality rate.[5] Primary percutaneous coronary intervention (PCI) is the reperfusion strategy of choice in STEMI patients if timely performed.[5] Optimizing the primary reperfusion strategy is essential to reduce myocardial damage and prevent further reperfusion lesions.

The objective of this review is to give a general overview on current and future percutaneous devices that can potentially improve the benefit of primary PCI including stents, revascularization strategies, and mechanical circulatory support devices for the management of STEMI complicated with cardiogenic shock (CS) like the intra-aortic balloon pump (IABP), the Impella device (Abiomed, Danvers, Massachusetts, United States), TandemHeart (Pittsburgh, Pensilvania, United States), and venoarterial extracorporeal membrane oxygenation (VA-ECMO).

THROMBUS ASPIRATION

Intracoronary thrombus can be found in most STEMI patients. Distal embolization has been reported in 5% to 10% of the cases and can cause obstruction what worsens the results.[6] Some time ago, the thrombectomy technique was proposed as a coadjuvant therapy to help restore the coronary blood flow at epicardial level by reducing the chances of distal embolization, the no-reflow phenomenon, and the size of the infarction. Also, it could reduce the thrombotic load prior to stent implantation, thus reducing the rate of associated complications due to stent malapposition. Manual thrombus aspiration was systematically recommended in primary PCI following small randomized clinical trials and a meta-analysis that showed reperfusion improvement with lower cardiovascular mortality rates.[7-9] However, after the publication of 2 large statistically powered randomized clinical trials to detect the superiority of routine manual aspiration vs PCI, only 1 change in the recommendation has occurred.[5] Neither the TOTAL (N = 10 732 patients) nor the TASTE (N = 7244 patients) clinical trials showed any differences with the thrombectomy in the clinical outcomes compared to the PCI alone.[10,11] Also, the TOTAL trial posed a safety issue associated with a higher risk of stroke in patients treated with thrombectomy compared to those treated with PCI alone.[12]

Based on these data, thrombus aspiration is now not recommended as a routine strategy in STEMI patients treated with a PCI primary PCI. However, it can be considered in patients with high thrombotic load after vessel recanalization. A subanalysis of the EXAMINATION trial (N = 1498) confirmed that the use of thrombectomy was associated with a higher rate of direct stenting, a lower rate of postdilatation, and a smaller number of stents implanted with a larger stent size.[13] However, the optimized angiographic result did not impact the long-term outcomes since no differences were seen in the clinical endpoints reported between the arms at the 2-year follow-up.

SELECTING THE TYPE OF STENT

Coronary stent implantation is the recommended therapy during a primary PCI for the management of STEMI patients. Direct stenting without predilatation in STEMI culprit lesions can reduce the embolization of the plaque components, the rate of no-reflow phenomenon, and increase myocardial perfusion.[14] This hypothesis was confirmed in the *post-hoc* analysis of the HORIZONS-AMI trial and the EUROTRANSFER registry; both showed a lower mortality rate at the 1-year follow-up associated with the use of direct stenting.[15,16]

Delayed stent implantation after restoring coronary flow has also been proposed through a minimalistic mechanical procedure to reduce the risk of no-reflow phenomenon.[17] Several observational trials showed benefits in terms of an improved left ventricular ejection fraction and a lower rate of adverse events with the delayed compared to the immediate stent implantation strategy in STEMI patients.[18,19] Also, a proof-of-concept randomized clinical trial (DEFER-STEMI, N = 411) reported a lower no-reflow phenomenon rate with the delayed stent implantation strategy in a population of patients with STEMI.[20] However, the DANAMI 3-DEFER trial randomized 1215 STEMI patients to receive delayed vs immediate stent implantation. At the 2-year follow-up no differences were seen in the primary endpoint of all-cause mortality, hospital admission due to heart failure, recurrent infarction, and any unplanned revascularizations between the study groups (18% vs 17%; hazard ratio [HR], 0.99; 95% confidence interval [95%CI], 0.76–1.29; $P = .92$).[21] Afterwards, the MIMI randomized clinical trial (N = 140), that excluded patients with a high thrombotic load, and the INNOVATION trial (N = 114) did not show any changes either in the infarction size or microvascular obstruction with the delayed compared to the immediate stent implantation strategy.[22,23] Finally, a meta-analysis of randomized and observational clinical trials found no improvement either in the rates of no-reflow, death, myocardial infarction or repeat revascularizations with the delayed stent implantation strategy for the management of STEMI.[24] Surprisingly, an improved left ventricular (LV) function was reported in the long-term. For all these reasons, to this date, the delayed stent implantation strategy is ill-advised in the primary PCI.

Another aspect to be taken into consideration before performing a primary PCI is what device should be implanted. Several randomized clinical trials and meta-analyses assessing first-generation drug-eluting stents (DES), whether sirolimus or paclitaxel, showed lower in-stent restenosis and target lesion revascularization rates compared to conventional bare metal stents (BMS).[25-32] However, safety concerns soon appeared given the high rate of late thrombosis associated with first-generation DES.[33-35]

To overcome this problem, second-generation DES with different drugs, thinner struts, and durable or bioresorbable polymers more biocompatible have been designed. The COMFORTABLE AMI clinical trial randomized 1161 STEMI patients on a 1:1 ratio to receive a BMS or a biodegradable polymer biolimus-eluting stent. At the 1-year follow-up a lower rate of major adverse cardiovascular events was reported in the biolimus-eluting group compared to the BMS group (4.3% vs 8.7%; HR, 0.49; 95%CI, 0.30–0.80; $P = .044$) mainly triggered by a lower risk of spontaneous myocardial infarction and target lesion revascularization.[36] Similarly, at the 2-year follow-up a lower rate of major adverse cardiovascular events was reported in the biolimus-elutin group (5.8% vs 11.9%;

HR, 0.48; 95%CI, 0.31–0.72]; $P < .001$).[37] Both at the 1- and 2-year follow-ups, the rates of definitive or probable stent thrombosis were also numerically lower with the DES although not statistically significant.[36,37]

The EXAMINATION clinical trial[38,39] randomized 1498 STEMI patients to receive a second-generation everolimus-eluting stent (EES) or a BMS. At the 1-year follow-up, the EES was superior to the BMS with a significantly lower rate of definitive thrombosis, and definitive or probable thrombosis (0.5% vs 1.9%, and 0.9% vs 2.5%, respectively; $P = .019$ for both]).[38] Also, at the 5-year follow-up, the rate of all-cause mortality was significantly lower in the EES group compared to the BMS group (9% vs 12%; HR, 0.72; 95%CI, 0.52–0.10]; $P = .047$)[39]. Also, a meta-analysis of both the EXAMINATION and the CONFORTABLE-AMI clinical trials found a significant reduction of the risk of definitive thrombosis with the use of the DES (HR, 0.35; 95%CI, 0.16–0.75; $P = .006$) compared to the BMS.[40] Given the conclusions of these clinical trials, the DES is currently the device of choice according to the recommendations established in the clinical practice guidelines published by the European Society of Cardiology on the management of STEMI.[5]

The researchers of the EXAMINATION trial investigators have recently reported that the 10-year follow-up results confirm the superiority of EES over BMS in terms of patient or device related cardiovascular adverse events. Between the 5- and the 10-year follow-up periods, a low rate of adverse cardiovascular events was associated with failed devices.[41]

Fully bioresorbable vascular scaffolds (BVS) were introduced to overcome the long-term limitation of the permanent presence of metal within the coronary artery. The data on their use for the management of STEMI is still limited. Although unavailable for clinical use, we believe the existing data should be discussed. The early experiences with the Absorb BVS (Abbott Vascular, Illinois, United States) for the management of STEMI showed positive and negative clinical results alike.[42-44] The TROFI II clinical trial randomized 191 STEMI patients to receive a BVS or a EES and found no differences between the 2 regarding scarring of the infarct-related artery.[45] However, other studies showed disturbing data following the high rate of thrombosis with the BVS device. In the BVS EXAMINATION clinical trial, the safety and efficacy profile of BVS vs EES was compared in STEMI patients. At the 1- and 2-year follow-up periods, no differences were found in the device-oriented composite endpoint between both groups.[46,47] We should mention that at the 2-year follow-up, the rate of definitive thrombosis was often higher in the BVS group compared to the EES group (3.3% vs 1.0%; $P = .081$). At the 5-year follow-up, the risk of the device-oriented composite endpoint was higher in the BVS group, indicative that the chances of obtaining favorable outcomes at a very long-term follow-up is low.[48]

The BVS STEMI STRATEGY-IT clinical trial was designed to reduce the rate of adverse events. It proved that a prespecified BVS implantation strategy in STEMI patients treated with a primary PCI was feasible and yielded good clinical outcomes at the 30-day and 1-year follow-up periods (rate of device thrombosis between 0.2 and 0.4%, respectively).[49,50]

We should mention that the long-term results of randomized clinical trials that proved a significantly higher rate of BVS thrombosis were the reason of their withdrawal from the market.[51-53]

The Magmaris (Biotronik, Bülach, Switzerland) is a magnesium-based bioresorbable sirolimus-eluting stent. It has shown promising early results at the 1-year follow-up in stable patients with very limited data on STEMI.[54] The MAGSTEMI trial is the only randomized clinical trial that compared the efficacy and safety profile of the Magmaris device in STEMI patients.[55] This study randomized 150 patients to receive a primary PCI with Magmaris vs sirolimus-eluting stents using a prespecified implantation technique. Compared to the sirolimus-eluting stent, the Magmaris device showed a greater capacity of vasomotor response to drug agents (whether independent from the endothelium or endothelium-dependent) at the 1-year follow-up. However, the Magmaris device was associated with a lower angiographic efficacy and a higher rate of clinical restenosis, but no thrombotic issues.[56] In the prespecified MAGSTEMI-optical coherence tomography substudy, both the Magmaris and the sirolimus-eluting stent showed a low degree of neointimal healing. However, lumen dimensions were smaller with the Magmaris at the 1-year follow-up. Although Magmaris advanced bioresorption state complicates the assessment of the scaffold, this seems to be the main mechanism of restenosis.[57,58] Cases of significant delayed resorption of the Magmaris device have been reported, and intraluminal scaffold remnants have been found 2 years after implantation.[59]

MULTIVESSEL CORONARY ARTERY DISEASE

Around 50% of STEMI patients show multivessel coronary artery disease (MVD).[60] Multiple clinical trials have studied the best revascularization strategy: treat the culprit lesion only vs complete revascularization. The PRAMI trial randomized 465 patients with STEMI and MVD to culprit lesion treatment only or revascularization of all obstructive lesions (angiographic stenosis > 50%) during the index procedure. Complete revascularization during the index procedure was associated with a 65% lower relative risk in the primary endpoint (cardiac death, infarction or refractory angina) compared to treating the culprit lesion only.[61] Similarly, the CvLPRIT trial (N = 269) showed that complete revascularization (angiographic stenosis > 70%) during the index hospitalization was superior to the PCI of the infarct-related lesion only in the composite endpoint of death, reinfarction, heart failure, and repeat revascularization at the 12-month follow-up.[62]

Measuring the fractional flow reserve of coronary flow to guide the need for non-culprit lesion revascularization has been proposed. The DANAMI-3-PRIMULTI trial (N = 627) proved that fractional flow reserve-guided complete revascularization significantly reduced the risk of future cardiovascular adverse events compared to any other invasive procedure after the primary PCI. This effect is due to a significantly lower number of repeat revascularization procedures because the rates of all-cause mortality and non-fatal reinfarction did not vary between the groups.[63] Also, the Compare-Acute trial (N = 885) proved that fractional flow reserve-guided complete revascularization during the index procedure significantly reduced the rate of cardiovascular adverse events.[64]

The COMPLETE clinical trial included 4041 patients randomized to complete revascularization vs culprit lesion therapy who were followed for up to 3 years. Complete revascularization was superior to the PCI only in the culprit lesion to reduce the risk of cardiovascular death or myocardial infarction, and the risk of cardiovascular death, myocardial infarction or ischemia-induced revascularization.[65] Currently, the BioVasc trial (NCT03621501) is studying how to optimize the treatment algorithm for patients with acute coronary syndrome with MVD to find out what the best time is to perform complete revascularization, whether immediate or delayed.[66]

According to the current guidelines of the European Society of Cardiology, during hospitalization and before hospital discharge, the complete revascularization of the non-culprit lesions of patients with STEMI and MVD should be considered.[5] However, this

Table 1. Technical characteristics of percutaneous mechanical circulatory support devices currently available

	BIAC	Impella	TandemHeart	ECMO-VA
Hemodynamic effect	Unloading of LV pressure and volume	Unloading of LV pressure and volume	Unloading of LV volume	Unloading of RV and LV pressure and volume
Mechanism	Aorta	LV to the aorta	LA to the aorta	RA to the aorta
Heart blood flow	0.3 L/min to 0.5 L/min	1 L/min to 5 L/min	2.5 L/min to 5 L/min	3.0 L/min to 7.0 L/min
Peripheral resistances	↓	↓	↑	↑↑↑
Size	8 Fr	13-Fr to 22-Fr	21-Fr inflow cannula and 15-Fr to 17-Fr outflow cannula	18-Fr to 21-Fr inflow cannula and 15-Fr to 22-Fr outflow cannula
Implantation complexity	Low	- Moderate with Impella 2.5 - High with Impella 5.0	High	High
Recommended use duration	Weeks	7 days	14 days	7 days
Contraindications	- Severe aortic regurgitation - Aortic dissection - Severe peripheral vascular disease	- Severe aortic valvular heart disease - Aortic mechanic valve - Thrombus in the LV - Severe peripheral vascular disease - Contraindication to anticoagulation	- Severe peripheral vascular disease - Thrombus in the LA - Contraindication to anticoagulation - Moderate-to-severe aortic regurgitation - Interventricular septal defect	- Moderate-to-severe aortic regurgitation - Severe peripheral vascular disease - Contraindication to anticoagulation
Complications*	- Thrombocytopenia - Thrombosis - Arterial flow obstruction due to incorrect positioning - Aortic dissection or rupture - Plaque or air embolism	- Hemolysis - Device migration - Lesion or aortic failure - LV perforation or tamponade - Ventricular arrhythmia	- Migration of the cannula - LV perforation or tamponade - Thromboembolism - Air embolism during the insertion of the cannula - Development of interatrial shunt	- Circuit thrombosis - Upper body hypoxia due to incomplete retrograde oxygenation - LV dilatation - Systemic gas embolism

* Complications that are common to all devices: bleeding and infections associated or not with puncture site, vascular complication, and neurological damage. Fr, French sizing; IABP, intra-aortic balloon pump; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

indication is likely to change after the publication of the upcoming COMPLETE trial clinical results.

In the specific case of CS-complicated STEMI patients, the CULPRIT-SHOCK trial randomized 1075 patients with CS-complicated STEMI with MVD to be treated with a PCI on the infarct-related artery or a multivessel PCI of all lesions (angiographic stenosis > 70%). Both at the 30-day and 1-year follow-up, the PCI performed on the culprit lesion only significantly reduced the risk of death or renal replacement therapy.[67,68] This difference was mainly triggered by a significantly lower mortality rate. In this sense, the European Society of Cardiology published an update of its guidelines on the management of STEMI where, in the presence of STEMI with CS and MVD only the culprit lesion of the acute event should be treated.[69]

CARDIOGENIC SHOCK

Around 5% to 8% of STEMI patients also show CS, which is defined as persistent hypotension (systolic pressure < 90 mmHg) with signs of peripheral hypoperfusion. CS is one of the leading causes of death with in-hospital mortality rates that can be over 50%.[70] In patients with CS refractory to drug therapy, percutaneous mechanical circulatory support can help reduce the LV workload and oxygen demand, keep organs and coronary arteries perfused, and stand as a bridging therapy to a more definitive therapy.[71,72] Currently, we have assist devices from the LV to the aorta (IABP and Impella), from the left atrium to systemic arterial circulation (TandemHeart), and from the right atrium to systemic arterial circulation (VA-ECMO). The technical characteristics of percutaneous mechanical circulatory support systems currently available are shown on table 1.

Left ventricular assist device to the aorta

Intra-aortic balloon pump

Intra-aortic balloon pump (IABP) has been the most commonly used mechanical support device until 2010. After this year, its use dropped significantly after some clinical trial results questioned its efficacy.[73] It requires an 8-Fr introducer sheath into the femoral or axillary arteries and consists of a balloon mounted over a catheter that is placed in the descending aorta. The balloon is inflated during diastole and deflated during systole. The IABP increases the diastolic aortic pressure, reduces the aortic systolic pressure, increases the mean systemic arterial pressure, reduces the LV volume and diastolic pressure, and increases the coronary perfusion pressure. However, the hemodynamic support provided by the IABP is strictly associated with the LV function since it is less effective when it shows severe dysfunction.

Observational trials and meta-analyses have traditionally supported the use of IABP in CS-complicated STEMI.[74-76] However, prospective clinical trials have showed no benefit whatsoever from the IABP therapy in patients with STEMI with or without CS. The CRISP AMI trial (N = 337) showed that IABP implantation right before the PCI to treat an anterior STEMI without CS did not reduce the size of the infarction or improve the short-term survival rate.[77] The TACTICS trial randomized 57 patients with acute myocardial infarction and 48 hours of fibrinolytic therapy to receive the IABP or optimal medical therapy. This trial found no differences in the mortality endpoint at the 6-month follow-up.[78] Also, the IABP SHOCK trial[6] randomized 45 patients with STEMI and CS for IABP implantation or standard medical therapy and found no significant hemodynamic improvements after additional therapy with the IABP.[79]

The IABP SHOCK II trial randomized 600 patients with STEMI and CS not associated with mechanical complications to compare IABP implantation the optimal medical therapy.[80] It was expected that all patients underwent early revascularization (predominantly with PCI) and received the optimal medical attention available. At the 30-day follow-up, no differences were seen in the all-cause mortality rate between the IABP and the optimal medical therapy (39.7% vs 41.3%; relative risk, 0.96; 95%CI, 0.79-1.17]; $P = .69$) or in the length of the stay in the intensive care unit, renal function, major bleeding, peripheral ischemic complications, sepsis or stroke.[80] At the 12-month follow-up, no differences were seen either in the mortality rate and secondary endpoints reported.[81] A meta-analysis of 12 randomized clinical trials and 15 observational studies found no benefits from the IABP therapy in the management of STEMI or in the 30-day mortality rate regardless of the presence (odds ratio [OR], 0.94; 95%CI, 0.69–1.28) or absence (OR, 0.98; 95%CI, 0.57–1.69) of CS. Currently, based on the available evidence, the European Society of Cardiology clinical practice guidelines always contraindicate the IABP in patients with CS.[5]

The Impella system

The Impella system is a continuous axial flow pump that is inserted into the LV in a retrograde fashion through the aortic valve and provides active support by expelling suctioned blood from the LV into the ascending aorta, thus restoring blood flow to ischemic organs.[82] The Impella device increases the mean arterial pressure, reduces the LV pressure and volume, and increases coronary flow. It comes in 3 different sizes: 2.5 (maximum output, 2.5 L/min), 3.7 (Impella CP, maximum output, 3.7 L/min), and 5.0 (maximum output, 5 L/min). The smallest devices can be placed percutaneously through a 12-Fr to 14-Fr introducer sheath and the 5.0 device through a 22-Fr introducer sheath.[82]

Two large registries confirmed the safety of the Impella 2.5 system in high-risk complex PCIs.[83,84] The ISAR-SHOCK trial randomized 26 patients with STEMI and CS to receive the Impella 2.5 system or the IABP. The endpoint, a change in the cardiac index from baseline to 30 min after implantation, improved significantly in the Impella group. However, secondary endpoints like lactic acidosis, hemolysis, and mortality at the 30-day follow-up did not vary between the 2 arms.[85] At the 30-day follow-up, the cohort overall mortality rate was 46%. The IMPRESS in Severe Shock clinical trial randomized 48 patients with mechanical ventilation associated with CS after STEMI to receive the Impella system or IABP implantation. We should mention that the device was implanted at the discretion of the treating physician. The trial proved that, compared to the IABP, the Impella system did not reduce the 30-day mortality rate, and the overall mortality rate at the 6-month follow-up was 50%.[86] Both vascular complications and major bleeding were more common in the Impella group.

We should mention that, to date, the Impella device has not been compared to standard therapy in patients with CS in a proper statistically powered randomized clinical trial regarding relevant clinical events. In this sense, the DanGer Shock clinical trial (NCT01633502) will include 360 patients with STEMI and CS who will be randomized to receive circulatory support with the Impella system or standard medical therapy.[87] The study is still recruiting patients and its primary endpoint is all-cause mortality at the 6-month follow-up.

Back in 2018 a groundbreaking idea was introduced: the use of the Impella system to unload the LV and, therefore, reduce the size of myocardial infarction in animal models with STEMI but without CS.[88] These animal models led to the design and conduction of the DTU-STEMI pilot study that randomized 50 STEMI patients without CS to LV unloading with the Impella CP device or optimal medical therapy. This trial revealed that LV unloading therapy prior to STEMI reperfusion with the Impella device was feasible and not associated with a significant delay in STEMI reperfusion.[89] However, the use of the unloading therapy was not associated with a reduced infarction size at 1-month follow-up. Currently recruiting patients, the DTU-STEMI clinical trial (NCT03947619) will be enrolling 668 patients to test the hypothesis of the use of the LV unloading therapy with the Impella CP device to reduce the infarction size as seen on the cardiovascular magnetic resonance imaging.

Left atrium-to-systemic circulation assist devices

TandemHeart

The TandemHeart is an extracorporeal ventricular assist device to aspirate oxygenated blood from the left atrium and pump it into the lower abdominal aorta or iliac arteries to avoid running through the LV. The 21-Fr inflow cannula is inserted via femoral vein access and advanced through the interatrial septum towards the left atrium. The 15-Fr to 17-Fr outflow arterial cannula and the system can provide up to 5 L/min of blood flow.[90] The device basically reduces the LV preload and left atrial volume by removing blood from the left atrium, thus reducing the LV stress and workload. It also increases the systemic mean arterial pressure and myocardial perfusion.

There is little experience regarding registries and studies on this device. Thiele et al.[91] informed on the use of this device in 18 patients with STEMI and SC. The device provided up to 4 L/min of assisted cardiac output. Patients improved their cardiac index and mean arterial pressure, and reduced their pulmonary artery pressure, pulmonary capillary wedge pressure, and central venous pressure with an average 4 days on ventilatory assistance. Kar et al.[92] published a series of 117 patients with CS treated with the TandemHeart device that quickly reversed the end-stage hemodynamic compromise seen in patients with STEMI and CS refractory to the IABP and vasopressor support. A randomized clinical trial included 42 patients treated with the IABP (N = 14) or the TandemHeart device (N = 19). The TandemHeart device improved the patients' hemodynamic parameters significantly even in IABP-refractory patients. However, the mortality rate was similar in both groups.[93] To this date, we do not know of any other randomized clinical trials on this technology.

Right atrium-to-systemic arterial circulation assist devices

Extracorporeal membrane oxygenation

VA-ECMO is a cardiopulmonary support system that aspirates blood from the femoral vein or internal jugular vein through a 21-Fr cannula. Through an artificial membrane lung, carbon dioxide is eliminated and oxygen is added to venous blood to later return to the arterial system through a 15-Fr to 22-Fr outflow cannula via the femoral or axillary arteries.[93] One of the greatest advantages of ECMO is that it can be implemented everywhere (emergency room, cath lab, etc.) since it is fully portable and does not require fluoroscopic or echocardiographic guidance for a successful implantation. This device provides circulatory support of up to 7 L/min in patients with circulatory and respiratory failure. Some of its limitations are that the VA-ECMO system cannot unload the LV, which can trigger an increased afterload, which is in turn associated with LV distension, worsening of LV function, LV thrombus, and swelling or untreatable alveolar hemorrhage.[94] For these reasons it has been proposed that ECMO should be administered with other devices like

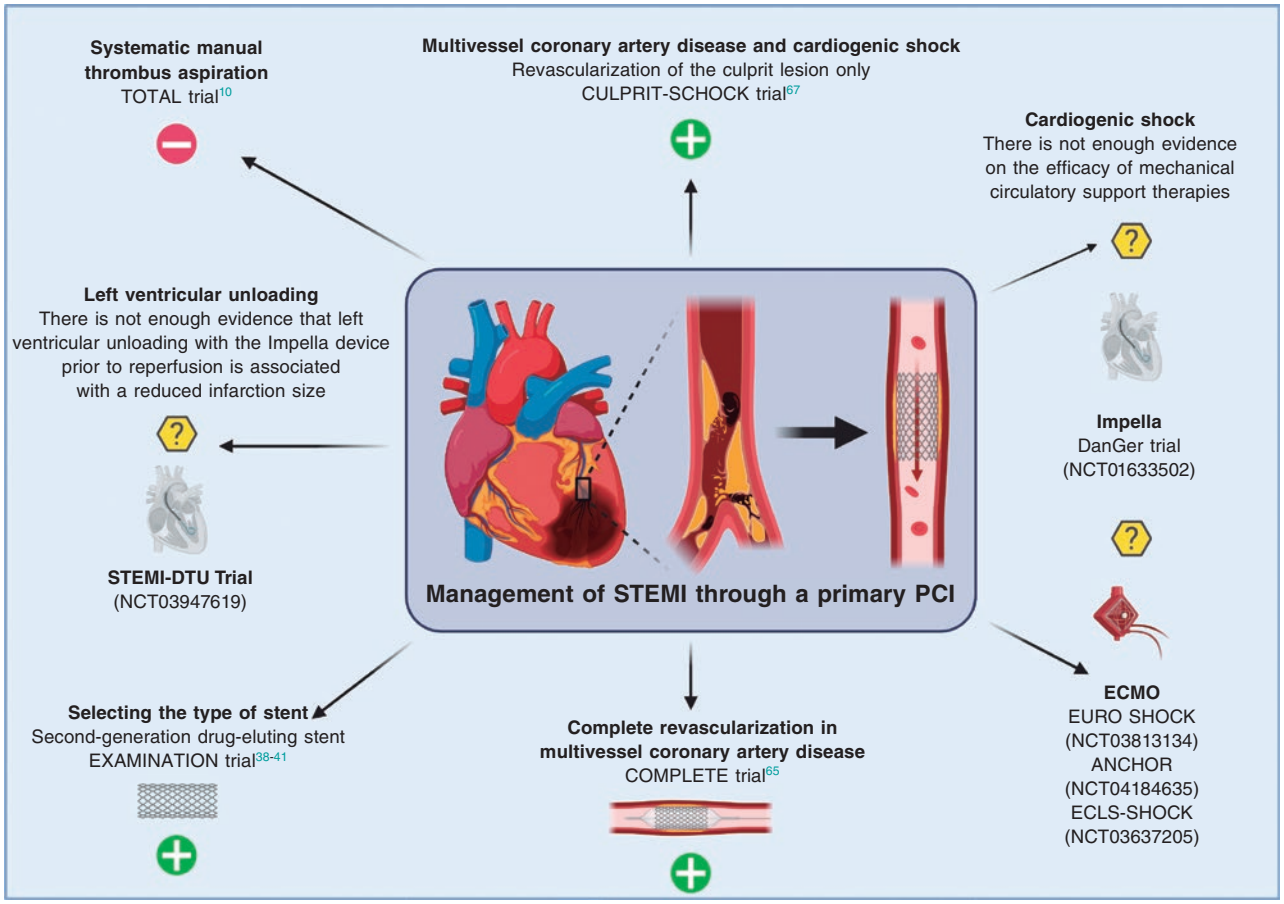


Figure 1. Current evidence and future perspectives of percutaneous coronary interventions for the management of ST-segment elevation myocardial infarction. The green + sign indicates that the procedure is recommended by the European Society of Cardiology clinical practice guidelines; the red minus sign (–) indicates that the procedure is not recommended; the yellow question mark (?) symbol indicates that there is not enough evidence (for or against) to recommend it. ECMO, extracorporeal membrane oxygenation; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

the IABP and the Impella to reduce pulmonary artery pressures and the dimensions of the LV.[95,96] A multicenter, international cohort study included 686 consecutive patients with CS (not due to STEMI exclusively) treated with ECMO. Those patients who underwent LV unloading with the Impella device had a better prognosis and a lower mortality rate, but also higher rates of implantation related bleeding and vascular complications.[97] Other authors also recommend procedures like percutaneous balloon atrial septostomy, to allow left-to-right shunting, or the administration of dobutamine to improve contractility and reduce the afterload.[94]

Aortic regurgitation, aortic dissection, severe peripheral arterial disease, and some ethical considerations are absolute contraindications to ECMO implantation.[90] Active bleeding is a relative contraindication because ECMO requires heparin for anticoagulation; however, it has been used in some high-risk patients without heparin since it was the only strategy to save the patient's life.[98] Complications are mainly vascular like lower limb ischemia, compartmental syndrome, major bleeding, stroke, air embolism, and serious infection.[90]

Yet despite ECMO is widely used in experienced centers, the data supporting its use in patients with acute myocardial infarction complicated with CS are mostly single-center small case-series. Sheu et al. conducted a single-center retrospective observational registry that compared the clinical outcomes of patients with STEMI treated with a primary PCI. The investigators studied 2 different timeframes:1993-2002 for the non-ECMO cohort and 2002-2009 for the ECMO cohort. The study proved that the ECMO assisted PCI improved results at the 30-day follow-up.[99] However, interpreting these results is difficult because of the significant discrepancies seen in the treatment strategies used between the groups. In a different study, Muller et al. included 138 STEMI patients treated with ECMO. They developed a mortality risk score in the intensive care unit setting called the ENCOURAGE score. The variables associated with worse prognosis were age > 60 years, female sex, body mass index > 25, Glasgow score < 6, elevated creatinine and lactate serum levels, and prothrombin times < 50%. Survival rates at 6-month and 1-year follow-up were 41% and 38%, respectively.[100]

Currently, the effects of the use of VA-ECMO on the mortality of patients CS-complicated STEMI is being studied in 3 randomized clinical trials: the EUROSHOCK (NCT03813134), the ANCHOR (NCT04184635), and the ECLS-SHOCK (NCT03637205) clinical trials.[101] On top of studying mortality, these clinical trials are an opportunity to analyze the indication, way, and effect of LV unloading.[102]

CONCLUSION

Despite the improvements made in reperfusion therapies, the mortality of STEMI patients is still high. Together with drug

therapy, the rapid restoration of coronary flow and stent implantation are the strategies recommended (figure 1). The routine use of manual thrombus aspiration is discouraged given the lack of clinical benefit compared to the PCI alone. Regarding the type of device selected, second-generation DES are the standard of choice in STEMI patients treated with a primary PCI since the short and long term results are better compared to BMS and first generation DES. In patients with STEMI and MVD, the current evidence recommends complete revascularization, although the optimal time to perform it remains unknown. Exclusively in the case of patients with CS, only the revascularization of the infarct-related artery is advised. Patients with CS-complicated STEMI is undoubtedly the clinical setting with less significant advances. Their mortality rate is still somewhere around 40% to 50%. To this date, several clinical trials are being conducted to assess the impact of circulatory assist devices like the Impella and VA-ECMO on these patients' mortality rate.

FUNDING

None.

AUTHORS' CONTRIBUTION

L. Ortega-Paz wrote the review draft on the current state of the interventional management of myocardial infarction. S. Brugaletta, and M. Sabaté conducted the critical review of the manuscript with the corresponding changes of content and format.

CONFLICTS OF INTEREST

M. Sabaté is a consultor for Abbott Vascular, and IVascular with no links to this study whatsoever. S. Brugaletta is a consultor for Boston Scientific, and IVascular with no links to this study. L. Ortega-Paz declared no conflicts of interest whatsoever.

REFERENCES

1. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001-2011. *J Am Heart Assoc*. 2015;4:e001445.
2. Kristensen SD, Laut KG, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J*. 2014;35:1957-1970.
3. Pedersen F, Butrymovich V, Kelbaek H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol*. 2014;64:2101-2108.
4. Fokkema ML, James SK, Albertsson P, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol*. 2013;61:1222-1230.
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
6. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344:1895-1903.
7. Sardella G, Mancone M, Bucciarelli-Ducci C, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol*. 2009;53:309-315.
8. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008;371:1915-1920.
9. Burzotta F, De Vita M, Gu YL, et al. Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J*. 2009;30:2193-2203.
10. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015;372:1389-1398.
11. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587-1597.
12. Jolly SS, Cairns JA, Yusuf S, et al. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. *Eur Heart J*. 2015;36:2364-2372.
13. Fernandez-Rodriguez D, Regueiro A, Brugaletta S, et al. Optimization in stent implantation by manual thrombus aspiration in ST-segment-elevation myocardial infarction: findings from the EXAMINATION trial. *Circ Cardiovasc Interv*. 2014;7:294-300.
14. Loubeyre C, Morice MC, Lefevre T, Piechaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol*. 2002;39:15-21.
15. Dudek D, Siudak Z, Janzon M, et al. European registry on patients with ST-elevation myocardial infarction transferred for mechanical reperfusion with a special focus on early administration of abciximab — EUROTRANSFER Registry. *Am Heart J*. 2008;156:1147-1154.
16. Mockel M, Vollert J, Lansky AJ, et al. Comparison of direct stenting with conventional stent implantation in acute myocardial infarction. *Am J Cardiol*. 2011;108:1697-1703.
17. Isaaz K, Robin C, Cerisier A, et al. A new approach of primary angioplasty for ST-elevation acute myocardial infarction based on minimalist immediate mechanical intervention. *Coron Artery Dis*. 2006;17:261-269.
18. Meneveau N, Seronde MF, Descotes-Genon V, et al. Immediate versus delayed angioplasty in infarct-related arteries with TIMI III flow and ST segment recovery: a matched comparison in acute myocardial infarction patients. *Clin Res Cardiol*. 2009;98:257-264.
19. Pascal J, Veugeois A, Slama M, et al. Delayed Stenting for ST-Elevation Acute Myocardial Infarction in Daily Practice: A Single-Centre Experience. *Can J Cardiol*. 2016;32:988-995.
20. Carrick D, Oldroyd KG, McEntegart M, et al. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). *J Am Coll Cardiol*. 2014;63:2088-2098.
21. Kelbaek H, Hofsten DE, Kober L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. *Lancet*. 2016;387:2199-2206.
22. Belle L, Motreff P, Mangin L, et al. Comparison of Immediate With Delayed Stenting Using the Minimalist Immediate Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study. *Circ Cardiovasc Interv*. 2016;9:e003388.
23. Kim JS, Lee HJ, Woong Yu C, et al. INNOVATION Study (Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment-Elevation Myocardial Infarction). *Circ Cardiovasc Interv*. 2016;9:e004101.
24. Qiao J, Pan L, Zhang B, et al. Deferred Versus Immediate Stenting in Patients With ST-Segment Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2017;6:e004838.
25. Spaulding C, Teiger E, Commeau P, et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). *JACC Cardiovasc Interv*. 2011;4:14-23.
26. Vink MA, Dirksen MT, Suttorp MJ, et al. 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial. *JACC Cardiovasc Interv*. 2011;4:24-29.
27. Violini R, Musto C, De Felice F, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. *J Am Coll Cardiol*. 2010;55:810-814.
28. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA*. 2005;293:2109-2117.

29. Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA*. 2008;299:1788-1799.
30. Di Lorenzo E, De Luca G, Sauro R, et al. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. *JACC Cardiovasc Interv*. 2009;2:515-523.
31. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med*. 2009;360:1946-1959.
32. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J*. 2007;28:2706-2713.
33. Holmvang L, Kelbaek H, Kaltoft A, et al. Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction). *JACC Cardiovasc Interv*. 2013;6:548-553.
34. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation*. 2007;115:1440-1455.
35. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
36. Raber L, Kelbaek H, Ostojic M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA*. 2012;308:777-787.
37. Raber L, Kelbaek H, Taniwaki M, et al. Biolimus-eluting stents with biodegradable polymer versus bare-metal stents in acute myocardial infarction: two-year clinical results of the COMFORTABLE AMI trial. *Circ Cardiovasc Interv*. 2014;7:355-364.
38. Sabate M, Cequier A, Iniguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet*. 2012;380:1482-1490.
39. Sabate M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387:357-366.
40. Sabate M, Raber L, Heg D, et al. Comparison of newer-generation drug-eluting with bare-metal stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials. *JACC Cardiovasc Interv*. 2014;7:55-63.
41. Brugaletta S, Lara JG, Ortega-Paz L, et al. TCT CONNECT-7 Everolimus-Eluting Stent Versus Bare-Metal Stent in ST-Segment Elevation Myocardial Infarction: 10-Year Follow-Up of the Multicenter Randomized Controlled Examination Trial. *J Am Coll Cardiol*. 2020;76(17 Supplement S):B4-B4.
42. Tousek P, Kocka V, Maly M, et al. Long-term follow-up after bioresorbable vascular scaffold implantation in STEMI patients: PRAGUE-19 study update. *EuroIntervention*. 2016;12:23-29.
43. Diletti R, Karanasos A, Muramatsu T, et al. Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study. *Eur Heart J*. 2014;35:777-786.
44. Cortese B, Ielasi A, Romagnoli E, et al. Clinical Comparison With Short-Term Follow-Up of Bioresorbable Vascular Scaffold Versus Everolimus-Eluting Stent in Primary Percutaneous Coronary Interventions. *Am J Cardiol*. 2015;116:705-710.
45. Sabate M, Windecker S, Iniguez A, et al. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. *Eur Heart J*. 2016;37:229-240.
46. Brugaletta S, Gori T, Low AF, et al. Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION Study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in the treatment of patients with ST-segment elevation myocardial infarction). *JACC Cardiovasc Interv*. 2015;8(1 Pt B):189-197.
47. Brugaletta S, Gori T, Low AF, et al. ABSORB bioresorbable vascular scaffold vs. everolimus-eluting metallic stent in ST-segment elevation myocardial infarction (BVS EXAMINATION study): 2-year results from a propensity score matched comparison. *Int J Cardiol*. 2016;214:483-484.
48. Brugaletta S, Gori T, Tousek P, et al. Bioresorbable vascular scaffolds versus everolimus-eluting metallic stents in patients with ST-segment elevation myocardial infarction: 5-year results of the BVS-EXAMINATION study. *EuroIntervention*. 2020;15:1436-1443.
49. Ielasi A, Campo G, Rapetto C, et al. A Prospective Evaluation of a Pre-Specified Absorb BVS Implantation Strategy in ST-Segment Elevation Myocardial Infarction: The BVS STEMI STRATEGY-IT Study. *JACC Cardiovasc Interv*. 2017;10:1855-1864.
50. Ielasi A, Campo G, Cortese B, et al. One-Year Results Following a Pre-Specified ABSORB Implantation Strategy in ST-Elevation Myocardial Infarction (BVS STEMI STRATEGY-IT Study). *Cardiovasc Revasc Med*. 2019;20:700-704.
51. Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016;388:2479-2491.
52. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. *N Engl J Med*. 2017;376:2319-2328.
53. Kereiakes DJ, Ellis SG, Metzger C, et al. 3-Year Clinical Outcomes With Everolimus-Eluting Bioresorbable Coronary Scaffolds: The ABSORB III Trial. *J Am Coll Cardiol*. 2017;70:2852-2862.
54. Haude M, Ince H, Abizaid A, et al. Sustained safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de novo coronary lesions: 12-month clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial. *Eur Heart J*. 2016;37:2701-2709.
55. Brugaletta S, Cequier A, Alfonso F, et al. MAGnesium-based bioresorbable scaffold and vasomotor function in patients with acute ST segment elevation myocardial infarction: The MAGSTEMI trial: Rationale and design. *Catheter Cardiovasc Interv*. 2019;93:64-70.
56. Sabate M, Alfonso F, Cequier A, et al. Magnesium-Based Resorbable Scaffold Versus Permanent Metallic Sirolimus-Eluting Stent in Patients With ST-Segment Elevation Myocardial Infarction: The MAGSTEMI Randomized Clinical Trial. *Circulation*. 2019;140:1904-1916.
57. Ortega-Paz L, Brugaletta S, Gomez-Lara J, et al. Target lesion revascularisation of bioresorbable metal scaffolds: a case series study and literature review. *EuroIntervention*. 2021;16:1100-1103.
58. Gomez-Lara J, Ortega-Paz L, Brugaletta S, et al. Bioresorbable scaffolds versus permanent sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction: vascular healing outcomes from the MAGSTEMI trial. *EuroIntervention*. 2020;16:e913-e921.
59. Ortega-Paz L, Brugaletta S, Sabate M. Very-late restenosis of a magnesium-based resorbable scaffold. *Eur Heart J*. 2020;41:2602.
60. Dziewierz A, Siudak Z, Rakowski T, Zasada W, Dubiel JS, Dudek D. Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry). *Am J Cardiol*. 2010;106:342-347.
61. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115-1123.
62. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015;65:963-972.
63. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665-671.
64. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376:1234-1244.
65. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381:1411-1421.
66. den Dekker WK, Van Mieghem NM, Bennett J, et al. Percutaneous complete revascularization strategies using sirolimus-eluting biodegradable polymer-coated stents in patients presenting with acute coronary syndrome and multivessel disease: Rationale and design of the BIOVASC trial. *Am Heart J*. 2020;227:111-117.
67. Thiele H, Akin I, Sandri M, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *N Engl J Med*. 2017;377:2419-2432.
68. Thiele H, Akin I, Sandri M, et al. One-Year Outcomes after PCI Strategies in Cardiogenic Shock. *N Engl J Med*. 2018;379:1699-1710.
69. Ibanez B, Halvorsen S, Roffi M, et al. Integrating the results of the CULPRIT-SHOCK trial in the 2017 ESC ST-elevation myocardial infarction guidelines: viewpoint of the task force. *Eur Heart J*. 2018;39:4239-4242.

70. Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc*. 2014;3:e000590.
71. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200.
72. Atkinson TM, Ohman EM, O'Neill WW, Rab T, Cigarroa JE, Interventional Scientific Council of the American College of Cardiology. A Practical Approach to Mechanical Circulatory Support in Patients Undergoing Percutaneous Coronary Intervention: An Interventional Perspective. *JACC Cardiovasc Interv*. 2016;9:871-883.
73. Helgestad OKL, Josiassen J, Hassager C, et al. Contemporary trends in use of mechanical circulatory support in patients with acute MI and cardiogenic shock. *Open Heart*. 2020;7:e001214.
74. Waksman R, Weiss AT, Gotsman MS, Hasin Y. Intra-aortic balloon counterpulsation improves survival in cardiogenic shock complicating acute myocardial infarction. *Eur Heart J*. 1993;14:71-74.
75. Bengtson JR, Kaplan AJ, Pieper KS, et al. Prognosis in cardiogenic shock after acute myocardial infarction in the interventional era. *J Am Coll Cardiol*. 1992;20:1482-1489.
76. Sjauw KD, Engstrom AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? *Eur Heart J*. 2009;30:459-468.
77. Patel MR, Smalling RW, Thiele H, et al. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA*. 2011;306:1329-1337.
78. Ohman EM, Nanas J, Stomel RJ, et al. Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial. *J Thromb Thrombolysis*. 2005;19:33-39.
79. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. *Crit Care Med*. 2010;38:152-160.
80. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367:1287-1296.
81. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet*. 2013;382:1638-1645.
82. Iannaccone M, Albani S, Giannini F, et al. Short term outcomes of Impella in cardiogenic shock: A review and meta-analysis of observational studies. *Int J Cardiol*.2021;324:44-51.
83. Sjauw KD, Konorza T, Erbel R, et al. Supported high-risk percutaneous coronary intervention with the Impella 2.5 device the Europella registry. *J Am Coll Cardiol*. 2009;54:2430-2434.
84. Maini B, Naidu SS, Mulukutla S, et al. Real-world use of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary intervention: the USpella Registry. *Catheter Cardiovasc Interv*. 2012;80:717-725.
85. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol*. 2008;52:1584-1588.
86. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump in Cardiogenic Shock After Acute Myocardial Infarction. *J Am Coll Cardiol*. 2017;69:278-287.
87. Udesen NJ, Moller JE, Lindholm MG, et al. Rationale and design of DanGer shock: Danish-German cardiogenic shock trial. *Am Heart J*. 2019;214:60-68.
88. Watanabe S, Fish K, Kovacic JC, et al. Left Ventricular Unloading Using an Impella CP Improves Coronary Flow and Infarct Zone Perfusion in Ischemic Heart Failure. *J Am Heart Assoc*. 2018;7:e006462.
89. Kapur NK, Alkhouli MA, DeMartini TJ, et al. Unloading the Left Ventricle Before Reperfusion in Patients With Anterior ST-Segment-Elevation Myocardial Infarction. *Circulation*. 2019;139:337-346.
90. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. *Lancet*. 2020;396:199-212.
91. Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation*. 2001;104:2917-2922.
92. Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The percutaneous ventricular assist device in severe refractory cardiogenic shock. *J Am Coll Cardiol*. 2011;57:688-696.
93. Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW, TandemHeart Investigators Group. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J*. 2006;152:469e1-8.
94. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of Mechanical Circulatory Support. *J Am Coll Cardiol*. 2015;66:2663-2674.
95. Petroni T, Harrois A, Amour J, et al. Intra-aortic balloon pump effects on macrocirculation and microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. *Crit Care Med*. 2014;42:2075-2082.
96. Cheng A, Swartz MF, Massey HT. Impella to unload the left ventricle during peripheral extracorporeal membrane oxygenation. *ASAIO J*. 2013;59:533-536.
97. Schrage B, Becher PM, Bernhardt A, et al. Left Ventricular Unloading Is Associated With Lower Mortality in Patients With Cardiogenic Shock Treated With Venoarterial Extracorporeal Membrane Oxygenation: Results From an International, Multicenter Cohort Study. *Circulation*. 2020;142:2095-2106.
98. Abrams D, Agerstrand CL, Biscotti M, Burkart KM, Bacchetta M, Brodie D. Extracorporeal membrane oxygenation in the management of diffuse alveolar hemorrhage. *ASAIO J*. 2015;61:216-218.
99. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med*. 2010;38:1810-1817.
100. Muller G, Flecher E, Lebreton G, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. *Intensive Care Med*. 2016;42:370-378.
101. Banning AS, Adriaenssens T, Berry C, et al. The EURO SHOCK Trial: Design, Aims and Objectives. *EuroIntervention*. 2020;EIJ-D-20-01076.
102. Lusebrink E, Orban M, Kupka D, et al. Prevention and treatment of pulmonary congestion in patients undergoing venoarterial extracorporeal membrane oxygenation for cardiogenic shock. *Eur Heart J*. 2020;41:3753-3761.

REC Interv Cardiol. 2021;3(3):213-215
https://doi.org/10.24875/RECICE.M21000212

Debate: Intervention on the mitral and the tricuspid valves. Perspective from interventional cardiology

A debate: Intervención sobre las válvulas mitral y tricúspide. Perspectiva desde la cardiología intervencionista

Dabit Arzamendi[a,b,*]

[a] *Facultad de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain*
[b] *Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M21000213

Question: What is the current status of percutaneous coronary interventions to treat functional mitral regurgitation (MR)?

Answer: To this date, transcatheter mitral valve repair therapies are backed by the highest scientific evidence. This has been confirmed by the new clinical practice guidelines[1] on the management of patients with valve disease published by the American Heart Association (AHA) where transcatheter repair (class IIa-Level of Evidence BR) is recommended for patients with functional MR and severe ventricular dysfunction. However, surgery is spared for cases that require concomitant coronary revascularization. We should not forget that transcatheter repair is the only technique on which there are randomized clinical trials available.[2,3] That is why it is indicated as the first-line therapy by the clinical practice guidelines. We should put the old sayings «regarding a case» or «in my hands, results are better» to sleep. Multicenter randomized clinical trials assess the reproducibility of the technique, and that is the key to generalize this or that therapy. In my opinion, the clinical cardiologist should place transcatheter mitral valve repair in the same level as cardiac resynchronization therapy. And, same as it happens with resynchronization, the right selection of patients is of paramount importance. When should repair be considered? In patients on optimal medical therapy who still remain symptomatic with severe functional MR, ventricular dysfunction, left ventricular end-diastolic diameter ≤ 70 mm, and with a suitable valvular anatomy as seen on the transesophageal echocardiography.

Q.: In your opinion, which would be the potential niche to combine techniques that target the leaflets or the annulus in this context?

A.: Winston Churchill used to say: « However beautiful the strategy, you should occasionally look at the results». Combined therapy is a very appealing idea, yet the experienced reported on this procedure is very limited with very few cases published to this date. It has probably encountered 2 main limitations so far: edge-to-edge mitral valve repair can alter the anteroposterior diameter of the mitral annulus and has a 5-year durability time limit compared to surgery; on the other hand, the combined procedure significantly increases risk, complexity, and the cost of the procedure.

With this mind and taking into consideration that in the future low-risk patients with primary MR will be treated, it is likely that we'll be seeing more reports on combined cases always with the objective of increasing the repair durability.

Q.: What does interventional cardiology have to offer to patients with organic MR who are not eligible for surgery? And what about the mitral annulus?

A.: The main advantage for patients with many comorbidities is that with transcatheter repair recovery is almost immediate (to this date, the average hospital stay is 48 hours) and the rate of complications is very low; the worst thing that can happen is unsuccessful repairs. That is why the main limitation is the impossibility of valvular replacement conversion with suboptimal results (actually something cardiac surgery allows).

Mitral annular calcification does not exclude transcatheter repair, but it can make it difficult due to the presence of less flexible leaflets, thus predisposing to a higher risk of leaflet tear and a greater final transmitral gradient. However, the wide array of devices available allows us to take on situations that we would have discarded in the past. In any case, this seems like the most interesting niche for transcatheter mitral valve repair.

Q.: What degree of clinical development have transcatheter mitral valves reached so far? In your opinion, which should be their indication with respect to repair techniques?

* **Corresponding author:** Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret 167, 08025 Barcelona, Spain
E-mail address: darzamendi@santpau.cat (D. Arzamendi).

Online: 26-04-2021.

A.: The first series with over 100 patients have already been published with positive results.[4] The main limitation here is the excessive selection of patients to guarantee positive results and avoid complications like left ventricular outflow tract obstruction. Over 60% of the patients assessed are eventually considered not eligible to undergo the procedure. Regarding the indication, for the time being, it should be spared for patients in whom the repair is not feasible or may be difficult. We still need data on valvular dysfunction and thrombosis at the follow-up.

Q.: Tricuspid regurgitation (TR) is a complex condition of often unsatisfactory management. What techniques are already available for the interventional cardiologist?

A.: That is true. Unfortunately, the mortality rate of isolated surgery on the tricuspid valve is high; actually, even higher regarding its repair (mortality rate > 10%). On the other hand, medical therapy is often limited by renal function. Also, if we consider that most TRs are functional, it seems like a perfect disease to use transcatheter techniques. That is why several devices we use nowadays to treat the mitral valve are also valid to treat tricuspid regurgitation.

For repair purposes, in the MitraClip device (Abbott Vascular, United States) the delivery sheath has been changed to approach the valve easier. The Triluminate study[5] used this version of the device (Triclip), and confirmed that TR was reduced by, at least, 1 grade in 86% of the patients with a 4% rate of adverse events at the 6-month follow-up. This possibility is also being explored with the Pascal device[6] (Edwards Lifesciences, United States), primarily with its ACE version, and the early results are similar to those published on the Triclip. The Cardioband[7] (Edwards Lifescience, United States) is also available for this use and the early experience with 30 patients reduced TR to less than moderate in 73% of the patients at the 6-month follow-up

On the other hand, the field of tricuspid valve replacement is clearly heading towards the use of the femoral access almost exclusively (currently, in the mitral valve, the most consolidated valve is the Tendyne [Abbott, United States] that is implanted via transapical access). Many of the valves intended for the mitral valve are also being used in the tricuspid one where right ventricular outflow tract obstruction does not seem be a problem.

Finally, we also have heterotopic valves available that are implanted outside the thoracic cavity. The main advantage of these devices is a relatively easy implantation, and the fact that they can be used when the etiology of TR is interference with wires coming from other devices such as pacemakers, automatic implantable cardioverter-defibrillators, etc.

Q.: Which is the optimal clinical indication and anatomical context to use these techniques?

A.: The main clinical indication is patients with severe TR with signs or symptoms of right congestion that are persistent despite medical therapy and without signs of severe pulmonary arterial hypertension. In our case, the typical subject is a patient operated on the mitral valve (probably due to atrial fibrillation) who has been dilating the tricuspid annulus for years and now has severe TR that he did not have when he underwent surgery.

With respect to the anatomical context, maybe the main limiting factor regarding repairs is the echocardiographic window. It is important to know whether we will be able to achieve good projections to guarantee a proper device implantation. There are times that multimodal images including transthoracic, transesophageal or intracardiac echocardiography are required. The main limitation of edge-to-edge repair devices is the size of coaptation defect (in the Triluminate, the cut-off value was 2 cm, but the truth is that in defects > 1 cm it is already assumed that we'll be needing more than 1 device), and in the case of the Cardioband the size of the annulus should be < 52 mm. Regarding valves, screening is performed through computed tomography scan and the limiting factor here is often the annular size. Heterotopic valves usually have very few limiting criteria.

Q.: What does the future of interventional cardiology have in store with respect to heart surgery? Where should we look into from one specialty and the other?

A.: From the medical point of view, we should probably not pay too much attention to which is the possible survival rate of this or that specialty, but where is the therapy heading to. Today's medicine favors prevention over intervention, and the least invasive procedures over the most aggressive ones. For example, let's look at the evolution surrounding the management of rheumatic mitral stenosis. We went from open commissurotomy as the early therapy to percutaneous valvuloplasty when it became available. However, thanks to early antithrombotic treatment there are fewer cases of mitral stenosis. This is the same path we should expect to follow with the remaining valve diseases we treat today.

We should focus on obtaining the most effective treatments causing the least possible damage to the patients. Therefore, it is our responsibility to work in order to *a)* use the least invasive access routes to boost the patients' early recovery; *b)* minimize the impact of the learning curve of this or that therapy through early focus and the proper dissemination; *c)* consistently assess the results of a new therapy while being patient at the same time (and not trying to know if it is effective with the first 10 cases at the 1-month follow-up); *d)* be actively involved in improving the procedures (whether through patient selection, device improvement or further medical management); and finally as Hippocrates used to say «foolish the doctor who despises the knowledge acquired by the ancients», in other words, let us benefit from the cumulative experience acquired over time to avoid making the same mistakes over again.

Once a therapy has become consolidated the proper training criteria should be established to be able to perform it, which leads us directly to accreditation. The proper criteria should be established and then incorporated to the proper training, and the corresponding legal validity achieved for accreditation purposes. This can be extrapolated to all the super-specialties within the different fields of medicine. Training is well regulated from college throughout the Internal Medicine Residency (MIR) program. However, once the specialty training is over, it is necessary to regulate further training.

Maybe we should work on how to approach cardiovascular disease from an overall perspective. We should have teams working on prevention, others on diagnosis, and other teams on therapeutics. Interventional cardiology and surgery should be included in the latter group.

FUNDING

None whatsoever.

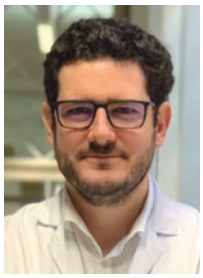
CONFLICTS OF INTEREST

D. Arzamendi is a proctor for Mitraclip and Triclip (Abbott), and Pascal (Edwards Lifescience).

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;14: e35-e71.
2. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med*. 2018;379:2307-2318.
3. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med*. 2018;379:2297-2306.
4. Badhwar V, Sorajja P, Duncan A, et al. Mitral regurgitation severity predicts one-year therapeutic benefit of Tendyne transcatheter mitral valve implantation. *EuroIntervention*. 2019;15:e1065-e1071.
5. Lurz P, Stephan von Bardeleben R, Weber M, et al. Transcatheter Edge-to-Edge Repair for Treatment of Tricuspid Regurgitation. *J Am Coll Cardiol*. 2021;77:229-239.
6. Lim DS, Kar S, Spargias K, et al. Transcatheter Valve Repair for Patients With Mitral Regurgitation: 30-Day Results of the CLASP Study. *JACC Cardiovasc Interv*. 2019;12:1369-1378.
7. Nickenig G, Weber M, Schüler R, et al. Tricuspid valve repair with the Cardioband system: two-year outcomes of the multicentre, prospective TRI-REPAIR study. *EuroIntervention*. 2021;16:e1264-e1271.

REC Interv Cardiol. 2021;3(3):216-218
https://doi.org/10.24875/RECICE.M21000213



Debate: Intervention on the mitral and the tricuspid valves. Perspective from surgery

A debate: Intervención sobre las válvulas mitral y tricúspide. Perspectiva desde la cirugía

Daniel Pereda[a,b,c,*]

[a] *Servicio de Cirugía Cardiovascular-Instituto Clínico Cardiovascular, Hospital Clínic, Barcelona, Spain*
[b] *Departamento de Cirugía y Especialidades Médico-quirúrgicas, Universitat de Barcelona, Barcelona, Spain*
[c] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M21000212

Question: What is the current status of percutaneous coronary interventions to treat functional mitral regurgitation (MR)?

Answer: Functional MR is one of the clinical conditions within cardiology that have experienced more changes over the last few years. Currently, not only the best way to treat it is under study including contributions from percutaneous techniques, but also its very definition is under review. Initially, cut-off values used to be selected to define its severity that were different from those of primary MR based on the results from longitudinal studies in populations that had suffered myocardial infarctions.[1] However, it has not been easy to confirm that by using these diagnostic thresholds, the therapeutic procedures yield consistent benefits.[2,3] As a matter of fact, to this date, it is recommended to use the same criteria as with primary MR (effective regurgitant orifice area ≥ 0.4 cm^2 and regurgitant volume ≥ 60 mL).

Another issue under discussion is whether the best therapeutic strategy is valve repair or replacement. Most clinical trials have studied the easiest repair strategy, that is, restrictive annuloplasty. It consists of annular remodeling with a rigid or semirigid annulus that is 1 or 2 sizes smaller than the patient's valve (usually determined by the intertrigonal distance or the anterior leaflet surface area). Despite the criticism received for the methodology used in the repair group and the results obtained after the procedure, several clinical trials conducted in the United States have shown no clear benefits of mitral valve repair over mitral valve replacement. However, a lower rate of MR has been reported in the group treated with valves.[4,5] Several authors suggest that this repair method is not the best one, especially if the etiology is ischemic and considering that myocardial damage and remodeling—the true culprit of valve disease—is often localized and highly variable.

My opinion is that this field has finally entered the adult age. It seems obvious that there is not an easy way to treat all patients. Also, that success depends on the right selection of patients and techniques including, in particular, the use of techniques for the subvalvular apparatus like repositioning or papillary muscle sling. Secondary MR is a ventricular disease; this is what we all say, but most surgeons and cardiologists still try to solve it by only acting on the valve alone.

Q.: Which are the most suitable techniques today to repair mitral valves with organ failure?

A.: The best way to treat primary MR is surgical valve repair when possible. Such is the case of almost all patients with myxoid degeneration treated in experienced centers. Also, it is the therapy of choice to treat other etiologies such as endocarditis and rheumatic disease. However, the repair rate is lower and depends on lesions associated with the valve and in the remaining structures.

The association between primary MR repair and the experience of the treating center is well known.[6] However, this experience is hard to gain; up to 50% of the patients who are eligible for valve repair keep are actually treated with valve replacements.[7] This opens the debate of whether patients should follow specific patterns of referral to centers experienced on mitral valve repair to guarantee optimal results, especially young patients and during the early stages of disease (asymptomatic, in sinus rhythm, and with a normal left ventricle) as the current clinical practice guidelines recommend.[8,9]

Q.: Are there good surgical options to treat mitral annular calcification?

A.: Annular calcification is relatively common in rheumatic disease and in advanced cases of myxoid degeneration and, in general, does not pose a significant problem. However, a minority of patients show very extensive calcification of the valvular annulus with deep infiltration and spread towards the ventricular myocardial tissue. These cases pose a problem not easy to solve. Incomplete annular

* **Corresponding author:** Cirugía Cardiovascular, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: dpereda@clinic.cat (D. Pereda).

Online: 26-04-2021.

decalcification leads to fewer chances of achieving successful repairs and a higher risk of suboptimal results regardless of the technique used: associated residual MR and stenosis in the case of mitral repair or paravalvular leaks and insufficient valvular size in valvular replacement.

The solution to this problem is performing extensive decalcification, which is a complex procedure with associated risks. It often involves the aggressive debridement of the posterior atrioventricular sulcus and further reconstruction with some type of reinforcement material (autologous or heterologous pericardium or synthetic tissues like Dacron). This type of reconstruction requires the proper selection of patients and a very precise technique since its main complication—the tear of the posterior sulcus—is associated with high morbidity and mortality rates.

An interesting option recently presented although with scarce information on the mid-term results is a combination of a minimally invasive approach to prepare the valve followed by implantation under direct vision of an expandable valve, which optimizes valve fixation and avoids left ventricular outflow tract obstruction.

Q.: What is your opinion on less invasive surgical techniques to treat MR?

A.: I think that today they are the method of choice to surgically treat mitral valves because the benefits are obvious. We recently published our own experience on the management of mitral prolapse with a successful repair rate (98%) and a perioperative mortality rate < 1% in *Revista Española de Cardiología*.[10] Minimally invasive thoracoscopic surgery was our preferred approach (more than 70% of the cases over the last few years) and is associated with less need for mechanical ventilation, shorter ICU stays, less blood loss, and less need for valve replacement at the 5-year follow-up (100% vs 95%).

Back in November 2019 we started our own robotic surgery program, the only one in Spain, with the Da Vinci system (Intuitive Surgical, United States), which basically focuses on mitral repair. By the time we were writing these lines, we had already treated 50 patients with very satisfactory results. In our early experience we think that the procedure is even less aggressive than thoracoscopy and is associated with further reductions of postoperative stays (median, 4 days).

There is no doubt in my mind that these minimally invasive techniques will keep growing and refining, and more patients will end up benefiting from repair surgeries less aggressively and with faster recovery times. Over the next few years, new robotic surgical platforms will be born for clinical use. Also, there will be new options for transapical neochord implantation without extracorporeal circulation. These advances will widen our current therapeutic armamentarium and join percutaneous techniques as part of our repertoire.

Q.: Tricuspid regurgitation (TR) is a complex condition of often unsatisfactory management. What does surgery have to offer these days and to who?

A.: TR has gradually been gaining the attention it deserves. One of the most important changes over the last few years is the confirmation of how important the early, prophylactic treatment actually is even when there is no left-sided valve disease when the procedure is performed.[8,9] This adds to the recognition of the need to treat severe primary TR in isolation in patients with symptoms of right-sided heart failure and in asymptomatic patients with progressive right ventricular deterioration.[9]

Same as it happens with secondary MR, the management of functional TR requires understanding right ventricular remodeling and other associated nonvalvular lesions. Secondary TR has been treated with surgery too often and in a superficial way without the same level of attention and detail paid to left-sided valve disease. Same as it happens with mitral valve repair, the management of secondary TR requires a high level of training and experience. The results of valve repair are excellent in the landmark centers, and sometimes the use of additional techniques is required on the leaflets (anterior leaflet repair with patch augmentation), the subvalvular apparatus (papillary muscle repositioning, chordal shortening or transposition or neochordal implantation), the right ventricle (free-wall and annular plication), and the right atrium. These less traditional techniques allow us to bring the benefits of repair to cases of very advanced functional TR, primary etiologies and, in the case of secondary TR, to repair the damage caused by device wiring or thoracic traumas. A good example of these more complex and advanced procedures is the Da Silva's cone repair technique in adult patients with Ebstein's anomaly.[11]

Isolated tricuspid valve or concomitant to mitral surgery can also be treated through minimally invasive and robotic thoracoscopic surgery in experienced centers in most of the patients. The concomitant ablation of atrial fibrillation can follow too.

Q.: What does the future of interventional cardiology have in store with respect to heart surgery? Where should we look into from one specialty and the other?

A.: I personally see a bright future ahead for the patients (which is the most important thing of all), cardiovascular surgeons, and interventional cardiologists. The magnitude of these improvements and how fast they will spread out will depend on our capacity to acquire the necessary knowledge and skills to coordinate ourselves and collaborate with one another.

My opinion is that surgery needs to move towards perfecting training regarding valvular repair and minimally invasive techniques so that more patients can benefit from the better options available. The current low rates of valve repair in the management of mitral valve disease simply cannot stand. Together with cardiology we need to reflect on the current patterns of patient referral and look for formulas so patients can be operated on (whether surgically or percutaneously) in experienced centers. Also, patients need to gain access to all therapeutic options, and all the techniques available should be performed with optimal results based on scientific evidence, auditing, and the public disclosure of results.

FUNDING

None whatsoever.

CONFLICTS OF INTEREST

D. Pereda is a proctor for minimally invasive surgery for Edwards Lifesciences.

REFERENCES

1. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation.* 2001;103:1759-1764.
2. Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med.* 2016; 374:1932-1941.

3. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178-2188.
4. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014; 370:23-32.
5. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med*. 2016;374:344-353.
6. Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. *Heart*. 2010;96:1964-1967.
7. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231-1243.
8. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38: 2739-2791.
9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72-e227.
10. Ascaso M, Sandoval E, Quintana E, Vidal B, Castellà M, Pereda D. Early and mid-term outcomes of mitral repair due to leaflet prolapse in a national referral center. *Rev Esp Cardiol*. 2021;74:462-4.
11. Fernández-Cisneros A, Ascaso M, Sandoval E, Pereda D. Cone repair for Ebstein's anomaly and atrial fibrillation ablation in an adult patient. *Multimed Man Cardiothorac Surg*. 2020. http://dx.doi.org/10.1510/mmcts.2020.064.

REC Interv Cardiol. 2021;3(3):219-226
https://doi.org/10.24875/RECICE.M20000158

Spontaneous coronary artery dissection and migraine crisis: an exceptional combination in male patients

Disección coronaria espontánea y crisis de migraña: una combinación excepcional en varones

Julio Echarte-Morales,* Tomás Benito-González, Carlos Minguito-Carazo, Samuel del Castillo García, Armando Pérez de Prado, and Felipe Fernández-Vázquez

Servicio de Cardiología, Complejo Asistencial Universitario de León, Leon, Spain

To the Editor,

Spontaneous coronary artery dissection (SCAD) is a misdiagnosed condition that has emerged as an important cause of acute coronary syndrome and sudden death, especially in women under 50. In these patients it is responsible for 30% of all the cases of such syndrome.[1] However, only between 10% and 15% of all SCADs are diagnosed in male patients.

This is the case of a male patient with SCAD in a migraine crisis setting. Informed consent was obtained from the patient for the proceeding and for the dissemination of his case in the article. The patient is a 55-year-old former smoker without a history of diabetes mellitus, arterial hypertension or previous heart disease. However, the patient has a past medical history of migraine treated with rizatriptan. The day of admission the patient presented with a migraine headache with left-sided hemicranial pain. Twenty minutes later, the patient showed clinical signs of oppressive central chest pain of 1-hour duration that radiated to the left upper limb and was associated with paresthesias, nausea, and vomiting. Upon arrival at the ER the patient's arterial blood pressure levels were 130/70 mmHg with no findings in the physical examination. The electrocardiogram showed ST-segment elevation in leads V1 through V4 with T-wave inversion. The ST-segment elevation came back to normal in the follow-up ECG performed 10 minutes after the index one with persistent T-wave inversion at the anteroseptal side. The blood test showed high troponin T and creatine kinase levels; the hemogram, coagulation test, the basic biochemistry, and chest x-ray all looked normal. The transthoracic echocardiogram performed revealed a slightly depressed systolic function (left ventricular ejection fraction of 50%) at the expense of akinesis in all apical segments. With the clinical, electrocardiographic, analytical, and imaging data it was decided to conduct an emergent hemodynamic study that confirmed the presence of a moderately diffuse stenosis in the mid left anterior descending coronary artery (figure 1); no images suggestive of thrombi or significant stenoses were seen. The lesion was assessed through optical coherence tomography and intravascular ultrasound (figure 2) that confirmed the presence of SCAD with intramural hematoma. During the index procedure, the renal angiography performed showed no signs suggestive of fibromuscular dysplasia.

During the patient's stay at the coronary unit, rizatriptan was changed for amitriptyline and antiplatelet therapy was withdrawn.

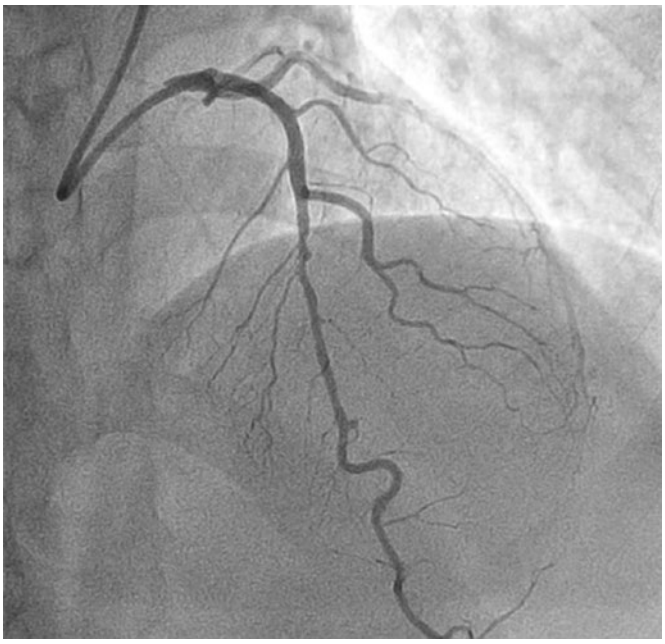


Figure 1. Moderate stenosis in mid left anterior descending coronary artery consistent with a type 3 spontaneous coronary artery dissection.

The transthoracic echocardiogram performed 48 hours after the index event showed a healthy-looking left ventricle with normal ventricular function, without altered segmental myocardial contractility or significant valvular heart disease. The patient was discharged without new episodes of chest pain or migraine crises during the hospital stay. The patient remains free from cardiovascular symptoms or associated events at the 16-month follow-up.

SCADs have been associated with fibromuscular dysplasia, pregnancy, emotional stress, extreme physical exercise, and connective tissue disorders.[2] Cohort studies conducted in patients with coronary dissections reveal that migraine is a risk factor in 37% to 46% of the cases.[3] This was also confirmed by a study with a series of patients with confirmed SCAD admitted to 22 hospitals from the United States. Thirty-two-point-five per cent of these patients had

* **Corresponding author:** Servicio de Cardiología, Complejo Asistencial Universitario de León, Altos de Navas s/n, 24071, Leon, Spain.
E-mail address: juliocecharte@gmail.com (J. Echarte-Morales).

Online: 21-09-2020.

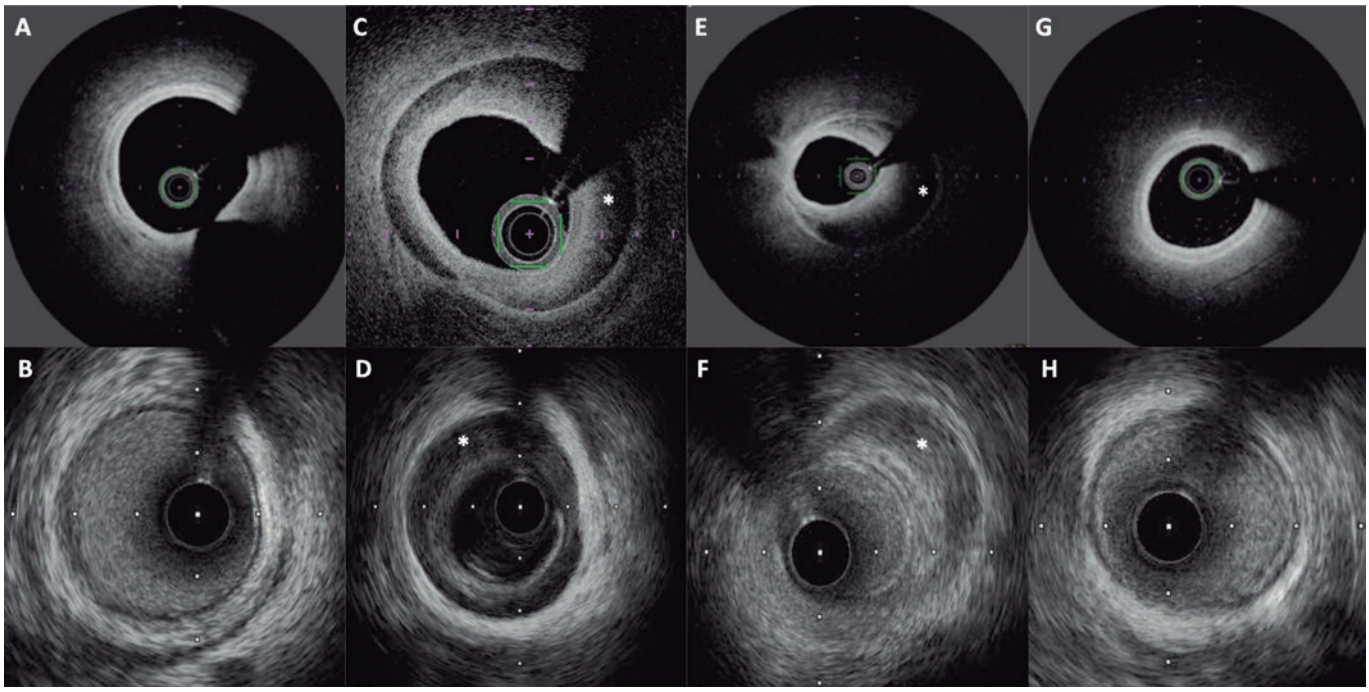


Figure 2. Optical coherence tomography (upper row) and intravascular ultrasound (lower row) showing the healthy proximal (**A, B**) and distal (**G, H**) segments of the left anterior descending coronary artery, and a spontaneous coronary artery dissection with intramural hematoma (asterisk) in the mid-segment (**C-F**).

a past medical history of migraine. In some studies, the presence of migraine was associated with new events of SCAD.

Migraine has been associated with mood swings such as anxiety and depression, which happen to be factors that increase cardiovascular risk.[4] Also, it has been associated with vascular phenomena like cerebral vasoconstriction, retinal vasculopathy, vertebral and cervical artery dissection, and cerebrovascular diseases.

The prevalence of SCAD was studied in a cohort of 585 patients with SCAD from Mayo Clinic. Previous migraine episodes were present in up to 40% of the cases. However, only 1 male patient had a past medical history of migraine when the SCAD was diagnosed.[4]

This case is relevant because of the exceptional combination of a migraine related SCAD in a male patient. To this day, this is the only case ever reported in the medical literature, probably due to the fact that the isolated prevalence of both conditions in males is very low.

FUNDING

The authors received no specific funding for this work.

AUTHORS' CONTRIBUTION

All authors contributed equally to the realization of this work.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

REFERENCES

1. Hayes SN, Kim CESH, Saw J, et al. Spontaneous coronary artery dissection: Current state of the science: A scientific statement from the American Heart Association. *Circulation*. 2018;137:e523-e557.
2. Adlam D, Alfonso F, Maas A, Vrints C. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD Study Group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. 2018;39:3353-3368.
3. Nakashima T, Noguchi T, Haruta S, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: A report from the Angina Pectoris-Myocardial Infarction Multicenter Investigators in Japan. *Int J Cardiol*. 2016;207:341-348.
4. Kok SN, Hayes SN, Cutrer FM, et al. Prevalence and clinical factors of migraine in patients with spontaneous coronary artery dissection. *J Am Heart Assoc*. 2018;7:e010140.

https://doi.org/10.24875/RECICE.M20000156

New technique for the emergent repositioning of the displaced Impella device

Nueva técnica para la recolocación emergente del Impella desplazado

Jorge García-Carreño,[a,b] Teresa Bastante,[b,c] Enrique Gutiérrez-Ibañes,[a,b,d,*] María Eugenia Vázquez,[a,b] Fernando Alfonso,[b,c] and Francisco Fernández-Avilés[a,b,e]

[a] *Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*
[c] *Servicio de Cardiología, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Madrid, Spain*
[d] *Departamento de Ingeniería Biomédica y Aeroespacial, Universidad Carlos III, Madrid, Spain*
[e] *Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain*

To the Editor,

The use of circulatory support has grown exponentially over the last decade, particularly for the management of cardiogenic shock in the setting of acute myocardial infarction.[1,2] The devices more often used like the Impella CP (Abiomed, United States) show good results in observational studies. These studies describe an improved survival rate when these devices are used as part of a well-defined program to treat cardiogenic shock.[3-5] However, this is not a risk-free therapy, and device displacement is a complication that can occur while the patient is being moved or transferred. Although rare, this complication can be deadly if not solved immediately because there is a loss of hemodynamic support. In these cases, the device needs to be retrieved due to the impossibility of crossing the aortic valve to proceed with a new implant.

We present a new technique for the emergent percutaneous repositioning of the Impella CP device as performed in 3 cases in 2 different hospitals. Informed consent was obtained from the patients or their relatives for the publication of their cases.

The complete displacement of the Impella CP device towards the aorta poses several technical difficulties regarding repositioning. In the first place, it is not easy to cross the aortic valve with the device just by pushing it; what will probably happen is that it will crash into 1 of the leaflets running the risk of damaging them. Secondly, it cannot be mounted over a conventional 0.035 in guidewire, only over a special 0.018 in guidewire, that happens to be unavailable in the cath lab. Also, it needs to be inserted through a guidewire that runs across the Impella CP device motor and can be retrieved after implantation, which is why a correct reinsertion is very difficult to achieve, if not impossible. Lastly, if the 14-Fr introducer sheath has been removed, as it is usually the case to extract and reinsert the Impella CP device, the artery needs to be recanalized with a new introducer sheath. For all these reasons, the way to reverse the Impella CP displacement is usually to replace it completely with the corresponding delay and high cost.

The reinsertion technique presented here consists of facilitating the aortic valve crossing through an easy maneuver that keeps it open for a few seconds. Using the radial access and a 0.035 in guidewire a 5-Fr/6-Fr pigtail catheter is advanced towards the left ventricle and pushed until it spins around the ventricle to eventually exit through the aortic valve. The guidewire should be kept inside the catheter for further support. This in-and-out loop keeps the valve open, which allows an easy advance of the Impella CP device until its correct positioning (figure 1); this last maneuver should be performed carefully to avoid vascular complications. If it encounters any sort of resistance in the valvular plane, it is pulled back just a few centimeters and a new attempt is made with a small rotation. In 1 of the cases reported the valve could not be crossed during the first attempt and in the other 2 cases, 3 or 4 attempts were needed. However, the valve was always crossed in a few minutes and without immediate complications (video 1 of the supplementary data). Although significant aortic regurgitation almost surely occurs while performing the maneuver, it was well tolerated in all cases, probably due to its short duration and added benefit of restoring circulatory support.

From December 2015 through December 2019, 97 Impella CP devices were implanted in our hospitals. In 7 of them (7.2%) catheter displacement was reported. In 3 of the cases, the displacement was limited to the outflow tract and repositioned at the intensive care unit. In the remaining 4 cases, the displacement was total, the catheter was retrieved from the left ventricle all the way to the aorta and hemodynamic support was lost. In 1 of these patients, support was being withdrawn, which is why the device was eventually removed. The remaining 3 required the emergent repositioning of the device using the technique described here. Table 1 shows the characteristics of these patients. The procedure was successful and without complications, and circulatory support was immediately recovered in the 3 cases. However, due to these patients' critical condition, 2 of them died a few days later of irreversible multiple organ failure.

* **Corresponding author:** Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo 46, 28007 Madrid, Spain.
E-mail address: egutibanes@gmail.com (E. Gutiérrez-Ibañes).

Online: 21-09-2020.

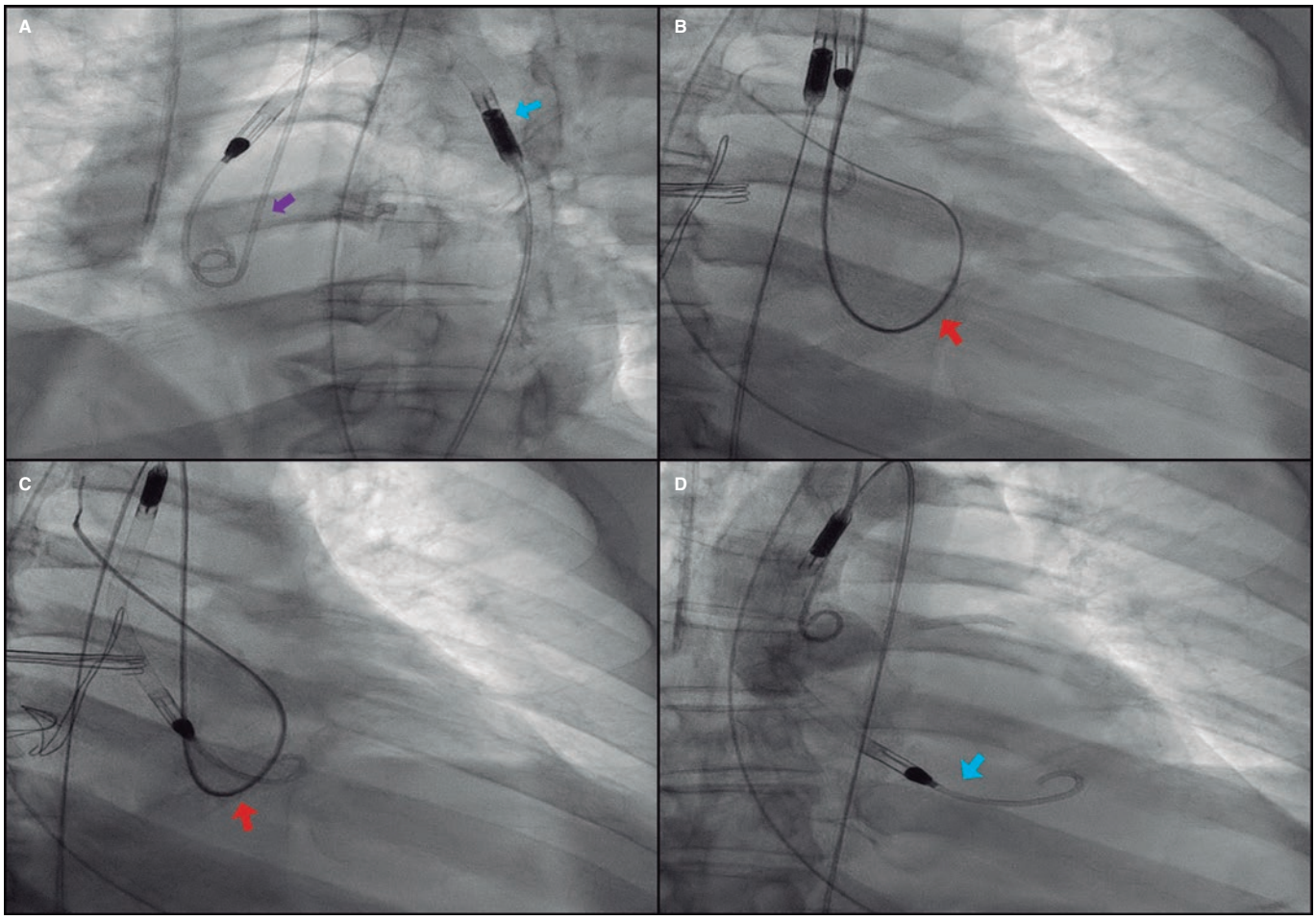


Figure 1. Impella CP device repositioning technique. **A:** pigtail catheter insertion (purple arrow) via radial access. Note how the Impella CP catheter has been displaced towards the ascending aorta (blue arrow). **B:** formation of intraventricular loop with the pigtail catheter keeping the 0.035 in guidewire to improve circulatory support (red arrow) while running across the aortic annulus, which facilitates its exit towards the aorta and keeps the valve open. **C:** afterwards, the Impella CP catheter (red arrow) is carefully advanced and pulled back by performing small rotations, if necessary, until reaching its final position (**D,** blue arrow).

Table 1. Characteristics of patients in whom the Impella CP device was repositioned

	Case #1	Case #2	Case #3
Age (years)	66	75	46
Sex	Male	Male	Male
Reason for the implant	Cardiogenic shock in the AMI setting	Electrical storm	LV unloading (APE after ECMO)
Previous LVEF (%)	20	20	5-10
Previous lactate (mmol/L)	5.1	4.2	> 15
Vasoactive drugs	NA + DBT	NA	NA + DBT
Additional support	ECMO	ECMO	ECMO
Impella access	Left femoral access	Right femoral access	Right femoral access
Cause of displacement	Transfer of the patient	Mobilization during x-ray	Accidental removal at the operating room
Successful repositioning	Yes	Yes	Yes
Hemodynamic improvement	Yes	Yes	Yes
Survival	No	No	Yes (transplant)

AMI, acute myocardial infarction; APE, acute pulmonary edema; DBT, dobutamine; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; LVEF, left ventricular ejection fraction; NA, noradrenaline.

In conclusion, we presented a safe, efficient, cost-effective, and rapid technique that could be widely used to solve the Impella CP device displacement, minimize its potential consequences, and reduce costs.

FUNDING

No funding has been received.

AUTHORS' CONTRIBUTION

M.E. Vázquez, T. Bastante, and E. Gutiérrez-Ibañes conducted the procedures. J. García-Carreño and E. Gutiérrez-Ibañes wrote the article. M.E. Vázquez, T. Bastante, F. Fernández-Avilés and F. Alfonso supervised and corrected the article.

CONFLICTS OF INTEREST

F. Alfonso is associate editor of REC: Interventional Cardiology. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000156.

REFERENCES

1. Berg D, Barnett C, Kenigsberg B, et al. Clinical Practice Patterns in Temporary Mechanical Circulatory Support for Shock in the Critical Care Cardiology Trials Network (CCCTN) Registry. *Circ Heart Fail.* 2019;12: e006635.
2. Amin AP, Spertus JA, Curtis JP, et al. The Evolving Landscape of Impella® Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention with Mechanical Circulatory Support. *Circ.* 2020;141: 273-284.
3. Basir MB, Kapur NK, Patel K, et al. Improved Outcomes Associated with the use of Shock Protocols: Updates from the National Cardiogenic Shock Initiative. *Catheter Cardiovasc Interv.* 2019;93:1173-1183.
4. Basir MB, Schreiber T, Dixon S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: The Detroit cardiogenic shock initiative. *Catheter Cardiovasc Interv.* 2018;91:454-461.
5. Tehrani B, Truesdell A, Singh R, Murphy C, Saulino P. Implementation of a Cardiogenic Shock Team and Clinical Outcomes (INOVA-SHOCK Registry): Observational and Retrospective Study. *JMIR Res Protoc.* 2018;7:e160.

https://doi.org/10.24875/RECICE.M20000162

Percutaneous closure of aortic pseudoaneurysm

Cierre percutáneo de seudoaneurisma aórtico

Francisco Pomar Domingo,[a,*] Margarita Gudin Uriel,[a] Alba López March,[b] Miguel Jerez Valero,[b] and Enrique Peris Domingo[a]

[a] *Servicio de Cardiología, Hospital Universitario de La Ribera, Alzira, Valencia, Spain*
[b] *Servicio de Cardiología, Hospital Manises, Manises, Valencia, Spain*

To the Editor,

Aortic pseudoaneurysm is a rare high-risk complication following surgery with aortic manipulation.

This is the case of a 66-year-old male patient with a past medical history of aortic valve replacement 16 years ago. He required a second surgery 3 months later due to prosthetic valve endocarditis with mechanical valve replacement with homograft valve implantation. Since then, the patient has remained asymptomatic until 1 year ago when he developed progressive dyspnea. The echocardiographic study revealed severe aortic regurgitation with heavily calcified valve and ascending aorta. A new surgical intervention was performed to replace the homograft by a bioprosthesis. Surgery was very complex due to the presence of significant calcification. Two months after this last intervention the patient was admitted with clinical signs of thoracic pain and hemoptysis. The computed tomography scan performed revealed the presence of a narrow-necked aortic pseudoaneurysm at the ascending aorta lateral wall, probably at the level of the cannulation performed during the previous surgery with a large periaortic hematoma (figure 1). Although the surgical repairment of the aortic pseudoaneurysm is the routine treatment, in this case it would have been the fourth reintervention. Instead, percutaneous treatment was decided.

Numerous articles have been published, most on isolated clinical cases, describing the closure of an aortic pseudoaneurysm with occluder devices different to the ones often used for the closure of septal defects, vascular plugs, etc. or coil embolization.[1,2] No comparative studies have ever been conducted on the different treatment options available. We only found an article in the medical literature published by Lyen et al.[3] that described a combined strategy in 7 patients with coil release and implantation of an occluder device in the same procedure. We also found a simple strategy with occluder device implantation in 5 patients with better results compared to the combined strategy. In our case, since the aortic pseudoaneurysm was large and the entry neck was small, a stepped combined strategy was decided of coil embolization and if

* **Corresponding author:** Unidad de Cardiología Intervencionista, Hospital Universitario de La Ribera, Ctra. Corbera km 1, 46600 Alzira, Valencia, Spain.
E-mail address: pomar_fra@gva.es (F. Pomar Domingo).

Online: 06-11-2020.

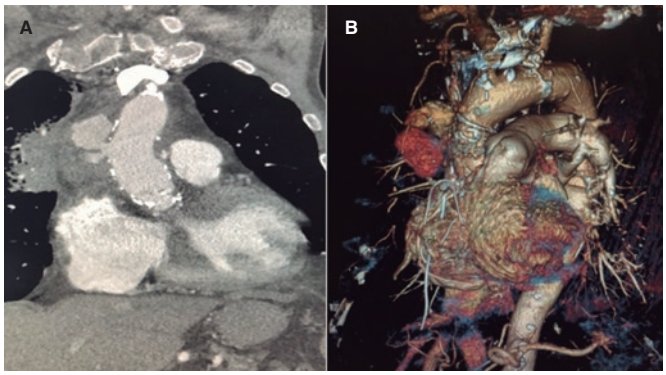


Figure 1. Coronary computed tomography angiography with contrast. Coronal view **(A)** and 3D reconstruction **(B).** Extensive atheromatous disease in the ascending aorta with diffuse calcification. Solution of continuity in the ascending aorta lateral wall with contrast extravasation contained by the tunica adventitia or surrounding tissues making up a partially thrombosed narrow-necked saccular pseudoaneurysm.

flow was persistent, followed by a second closure of the entry neck with an occluder device.

The procedure of coil embolization was uneventful, but the computed tomography scan with contrast performed 24 hours later showed flow persistence and progression of the size of the pseudoaneurysm (figure 2A), which is why percutaneous closure was decided with an occluder device.

The estimate size of the neck of the pseudoaneurysm was 8 mm. There are no protocols with criteria on how to choose the most suitable occluder device for the management of aortic pseudoaneurysms. However, it was thought that the ones used for the closure of atrial septal defects are designed to be implanted into low-pressure cavities, which means that the tissue of the device probably cannot stop high-pressure flows. Also, in the devices used to close atrial septal defects both discs are asymmetric in size, which would result in the implantation of the largest disc into the pseudoaneurysm, which could damage the wall of the sac. Therefore an 8 mm Amplatzer VSD Muscular occluder (Abbott, United States) with 2 discs of the same size was used.

The procedure was fluoroscopy and angiography guided. Because of the situation of the aortic pseudoaneurysm—similar to the location of anastomosis of right coronary artery grafts—the delivery sheath used was an 8-Fr Launcher JR4 guide catheter (0.090 in internal lumen) (Medtronic Launcher, United States) as it was the most suitable one to place it as coaxially as possible to the neck of the pseudoaneurysm. Using a standard 0.035 in guidewire via right femoral access the catheter was advanced towards the ascending aorta effortlessly. After a slight clockwise rotation, it entered directly into the pseudoaneurysm through the neck. No support guidewire was required (figure 2B). Afterwards, an Amplatzer VSD Muscular occluder device was implanted, 1 disc was placed inside the pseudoaneurysm and the other inside the aortic wall. The control angiography performed immediately after the implant showed no significant residual shunt (figure 2C). No periprocedural complications were reported and the patient was discharged 48 hours later. The patient remained asymptomatic and the computed tomography scan confirmed that the aortic pseudoaneurysm remained stable at the 4-week follow-up (figure 2D). However, 6 months after remaining asymptomatic, the patient died of severe hemoptysis, probably due to aortic pseudoaneurysm recurrence. The patient expressed his consent for his case to be published, respecting his right to privacy and the protection of personal data.

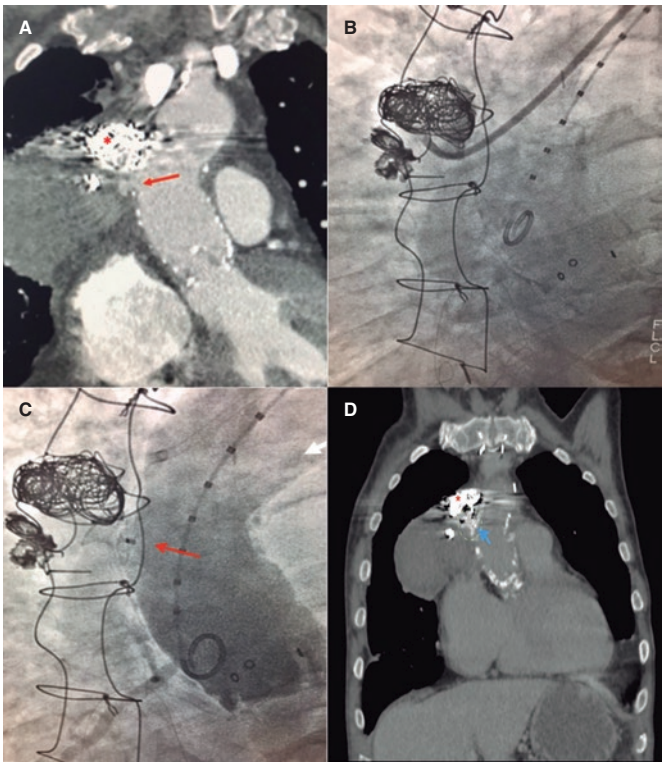


Figure 2. A: Coronary computed tomography angiography after coil release (asterisk) with presence of contrast in the cavity of the pseudoaneurysm indicative of incomplete occlusion. The entry neck (arrow) and larger size compared to the initial study can be seen. **B:** fluoroscopic imaging showing the distal border of the 8-Fr JR4 delivery catheter inserted into the pseudoaneurysm. **C:** post-implantation aortography. Occluder device (arrow) delivered inside the neck of the pseudoaneurysm. No significant passage of contrast to the inside is seen. **D:** thoracic computed tomography scan without contrast performed after 4 weeks. Occluder device (arrow) on the lateral wall of the aorta and coil metal artifact (asterisk) implanted in the main cavity of the pseudoaneurysm.

Although in our case the short-term outcomes were not satisfactory, the percutaneous closure of the aortic pseudoaneurysm with a combined technique of coils plus occluder device can be a valid therapeutic option for patients ineligible for surgery. That is so because it adds the coils prothrombotic effect to the entry flow reduction prompted by the occluder device. Further data are needed to determine whether this combined technique improves long-term survival compared to conservative treatment.

FUNDING

There is no funding.

AUTHORS' CONTRIBUTION

All authors have contributed to the conception, design and revision of the article.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Tang L, Lesser JR, Gössi M, et al. Transcatheter Closure of Complex Ascending Aortic Pseudoaneurysms After Cardiac Surgery. *Circ Cardiovasc Interv.* 2018;11:e007052.
2. Quevedo HC, Alonso A. Endovascular therapy for ascending aorta pseudoaneurysm. *Cardiovasc Revasc Med.* 2016;17:586-588.
3. Lyen SM, Rodrigues JC, Manghat NE, Hamilton MC, Turner M. Endovascular closure of thoracic aortic pseudoaneurysms: A combined device occlusion and coil embolization technique in patients unsuitable for surgery or stenting. *Catheter Cardiovasc Interv.* 2016;88:1155-1169.

https://doi.org/10.24875/RECICE.M20000163

Aortic prosthetic valve endocarditis as a cause of acute myocardial infarction

Endocarditis sobre prótesis aórtica como causa de infarto agudo de miocardio

José Valencia*

Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital General Universitario de Alicante, Alicante, Spain

To the Editor,

Compared to other causes, the most common cause of acute myocardial infarction (AMI) by far is atherosclerotic plaque rupture with its corresponding thrombosis and occlusion of the blood vessel. This is called type-1 AMI according to the latest guidelines by the European Society of Cardiology (ESC) published back in 2018 regarding the fourth universal definition of AMI. However, other cases reveal different and less common pathophysiological conditions as the cause of AMI. This is a very rare case of a patient with AMI associated with embolization of vegetation due to endocarditis that would correspond to a type-2 AMI according to the guidelines mentioned before.

This is the case of a 69-year-old male patient treated of aortic valve disease in 1994 implanted with a 25 mm Medtronic-Hall mechanical valve (Medtronic, United States). He was admitted to our hospital ER with clinical signs of high fever, poor general health status, and confusional syndrome of 48-hour duration. The cranial CT scan performed showed multiple images compatible with cortical and subcortical ischemic infarctions of possible embolic origin. The transthoracic echocardiography performed was inconclusive when it revealed vegetation at valve level, which is why a transesophageal echocardiography was performed that did show an image consistent with vegetation at valve ventricular level (figure 1A). Empirical antibiotic therapy was started with meropenem, daptomycin, rifampicin, and cloxacillin. A wait-and-see approach was established to see the patient's clinical progression and make a decision on the next therapeutic approach. Forty-eight hours after admission, the patient showed intense precordial pain and sweating, which is why an electrocardiogram was performed. It revealed the presence of overt ST-segment elevation in leads V2-V5 (figure 1B). Infarction code was activated, and the patient was referred to our unit to perform an emergency coronary angiography.

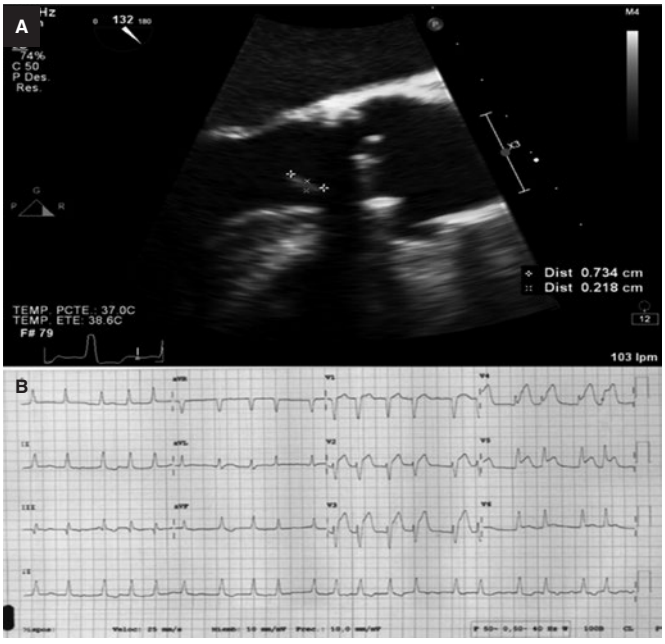


Figure 1. A: the transesophageal echocardiography shows a 7 mm × 2 mm long image of vegetation in the aortic valve ventricular side. **B:** the electrocardiogram shows an ST-segment elevation in leads V2-V5.

The coronary angiography was performed via radial access and showed an occluded distal left anterior descending coronary artery without other lesions and with mild atherosclerosis in the remaining coronary tree (figure 2A). A primary angioplasty was performed through percutaneous thrombectomy using a 6-Fr Pronto V4

* **Corresponding author:** Unidad de Hemodinámica y Cardiología Intervencionista, Servicio de Cardiología, Hospital General Universitario de Alicante, Avda. Pintor Baeza s/n, 03010 Alicante, Spain.
E-mail address: jvalenciam@hotmail.com (J. Valencia).

Online: 28-10-2020.

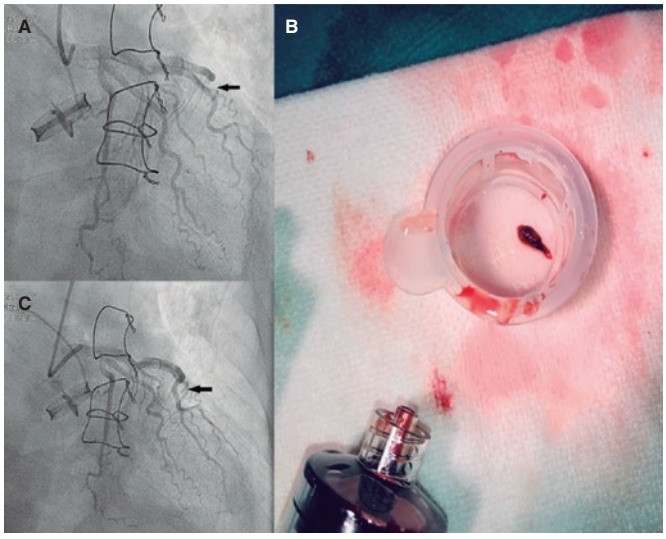


Figure 2. A: coronary angiography with distal left anterior descending coronary artery occlusion. **B:** material extracted after percutaneous thrombectomy. **C:** coronary angiography after thrombectomy with opening of the left anterior descending coronary artery.

catheter (Teleflex, United States). After a single distal-to-proximal retrieval passage of the catheter 1 thrombotic fragment was extracted (figure 2B). Thrombolysis in Myocardial Infarction coronary grade flow 2-3 was established with resolution of pain and repolarization alterations without stent implantation because there was no underlying lesion (figure 2C). After the procedure the patient gave his informed consent for the use of his clinical data for research purposes. The anatomopathological study of the sample revealed the presence of a fibrin-rich thrombus and scarce polymorphonuclear infiltration. The microbiological culture tested positive for *Staphylococcus aureus*, which was consistent with the blood culture tests run at admission. Anticoagulation only without antiplatelet therapy was advised as antithrombotic treatment. The day following the angioplasty, the patient's mechanical aortic valve was replaced for a biological one with good intraoperative outcome. Despite the initial clinical improvement that allowed the transfer of the patient to the hospital conventional ward, his further progression was torpid. The patient required surgical reintervention due to sternal suture dehiscence with sepsis due to *Pseudomonas aeruginosa*, which triggered progressive and irreversible impairment that led to the death of the patient 5 months after admission.

Although rare, there are other causes of AMI that both the clinical and interventional cardiologist should always be looking for. AMIs following the embolization of vegetation due to infectious endocarditis are very rare. Actually, there are no more than 100 cases published in the medical literature today. However, this entity should always be part of the differential diagnosis, especially for the lack of previous coronary artery disease. Prognosis is really somber and mortality rate is above 40%.[1,2] We should mention that this is often how clinical signs begin in over half of the cases of endocarditis with associated coronary embolism; also, embolic phenomena are often recurrent (as in this case), especially in patients with prosthetic valves or large vegetation. Although there is no such thing as a standard strategy for the management of these cases due to their scarce incidence, the rapid identification of clinical signs and an emergency percutaneous approach, preferably through thrombectomy (and if it fails through angioplasty balloon or stent) would be the strategy most highly recommended. Still, we should conclude that it is a feared complication with a very high mortality rate.

FUNDING

No funding.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Nazir S, Elgin E, Loynd R, Zaman M, Donato A. ST-Elevation Myocardial Infarction Associated With Infective Endocarditis. *Am J Cardiol.* 2019; 123: 1239-1243.
2. Singh M, Mishra A, Kaluski E. Acute ST-elevation myocardial infarction due to septic embolism: a case report and review of management options. *Catheter Cardiovasc Interv.* 2015;85:E166-171.

REC Interv Cardiol. 2021;3(3):227-232
https://doi.org/10.24875/RECICE.M20000188

Clinical case

Critical aortic coarctation in very low weight premature: primary angioplasty with coronary stent as bridging therapy

Coartación aórtica crítica en un prematuro de muy bajo peso: angioplastia con stent coronario como terapia puente

Diana Salas-Mera,[a,*] César Abelleira Pardeiro,[a] David Ortega Martínez,[b] Arturo Hernández de Bonis,[c] Felipe Gómez Martín,[c] and Federico Gutiérrez-Larraya Aguado[a]

[a] *Servicio de Cardiología Pediátrica, Hospital Universitario La Paz, Madrid, Spain*
[b] *Servicio de Pediatría, Hospital Clínico San Carlos, Madrid, Spain*
[c] *Servicio de Neonatología, Hospital Universitario La Paz, Madrid, Spain*

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M20000189
https://doi.org/10.24875/RECICE.M20000190

CASE PRESENTATION

Premature baby born by emergency caesarian section after 27 + 5 weeks of pregnancy due to premature rupture of membranes and umbilical cord prolapse. The patient's body weight at birth was 990 grams. The prenatal ultrasounds performed all looked normal. The patient required intubation and mechanical ventilation on his 6th hour of life due to hyaline membrane disease.

After the 24th hour of life, the functional echocardiogram performed revealed the presence of a 2.4 mm ductus arteriosus with left-to-right shunt. It was decided to start an ibuprofen cycle for pharmacological closure. Pressure curve damping in the umbilical artery, arm-leg blood pressure gradient, and lack of femoral pulse palpation were seen after the first dose. After discussion with the heart team aortic the presence of coarctation was confirmed with distal arch hypoplasia, and a 1 mm ductus arteriosus. It was decided to start the IV infusion of prostaglandins. The patient was transferred to our center on his 59th hour of life.

Upon arrival, the patient showed an arm-leg blood pressure gradient of 40 mmHg, a pre- and post-ductal saturation of 11%, preserved diuresis, and low lactic acid levels. The echocardiography performed revealed the presence of a small aortic arch, isthmus with posterior indentation, and preductal coarctation images with a maximum gradient of 60 mmHg, and diastolic prolongation of forward flow (figure 1 and figure 2, video 1 of the supplementary data). Also, a large ductus arteriosus irrigating the downstream aorta with systolic right-to-left shunt and pulsatile flow in the abdominal aorta with dampened systolic component and abolished diastolic component.

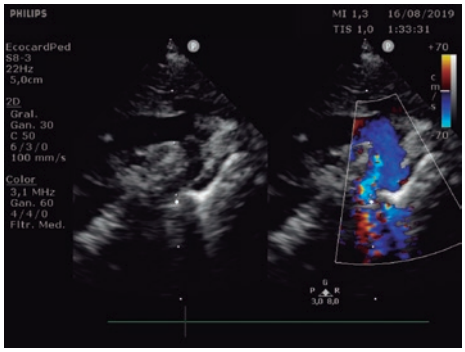


Figure 1. Small aortic arch and isthmus with posterior indentation.

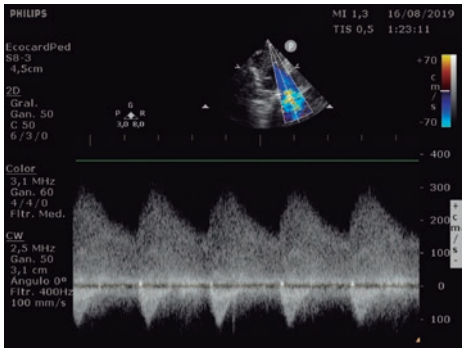


Figure 2. Continuous-wave Doppler echocardiography in the coarctation area with a maximum gradient of 60 mmHg and diastolic prolongation of forward flow.

*** Corresponding author:** Servicio de Cardiología Pediátrica, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.
E-mail address: diasalmer@gmail.com (D. Salas-Mera).

Online: 18-01-2021.

During the first few days following admission, the patient remained hemodynamically stable with the infusion of prostaglandins at maintenance dose. Arterial hypertension progressively developed with systolic pressure numbers in the upper limbs in between 90 mmHg to 100 mmHg followed by dilatation, hypertrophy, and further left ventricular systolic dysfunction on the control echocardiograms, which required the infusion of urapidil and dobutamine on day 9.

The patient's clinical condition deteriorated on his 13th day of life and he required respiratory support with high-frequency ventilation and further support with dobutamine. The echocardiogram confirmed the progressive deterioration of the left ventricle (video 2 of the supplementary data) with severe systolic dysfunction, appearance of moderate mitral regurgitation, and accelerated flow through the foramen ovale, which facilitated the estimation of left atrial pressure somewhere around 23 mmHg.

Since the clinical situation is so serious, an emergency procedure is proposed, but the patient is a high-risk candidate for surgery due to his prematurity, low body weight (29 + 4 weeks of postmenstrual age and 1200 grams at that time), hemodynamic instability, and severe left ventricular dysfunction.

FUNDING

The work has been carried out without funding.

AUTHORS' CONTRIBUTIONS

D. Salas-Mera, and C. Abelleira Pardeiro have drafted and corrected the text of this article. Mr. Ortega Martínez, A. Hernández de Bonis, and F. Gómez Martín have participated in the patient' care and have supervised the text. F. Gutiérrez-Larraya Aguado has supervised the text and contributed to the bibliography.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000188.

---

https://doi.org/10.24875/RECICE.M20000189

Critical aortic coarctation in very low weight premature: primary angioplasty with coronary stent as bridging therapy. How would I approach it?

Coartación aórtica crítica en un prematuro de muy bajo peso: angioplastia con stent coronario como terapia puente. ¿Cómo lo haría?

José Luis Zunzunegui Martínez*

Unidad de Hemodinámica Pediátrica, Hospital Gregorio Marañón, Madrid, Spain

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M20000188
https://doi.org/10.24875/RECICE.M20000190

* **Corresponding author:** Unidad de Hemodinámica Pediátrica, Hospital Gregorio Marañón, Dr. Esquerdo 46, 28007 Madrid, Spain.
E-mail address: zunzu69@hotmail.com (J.L. Zunzunegui Martínez).

Online: 18-01-2021.

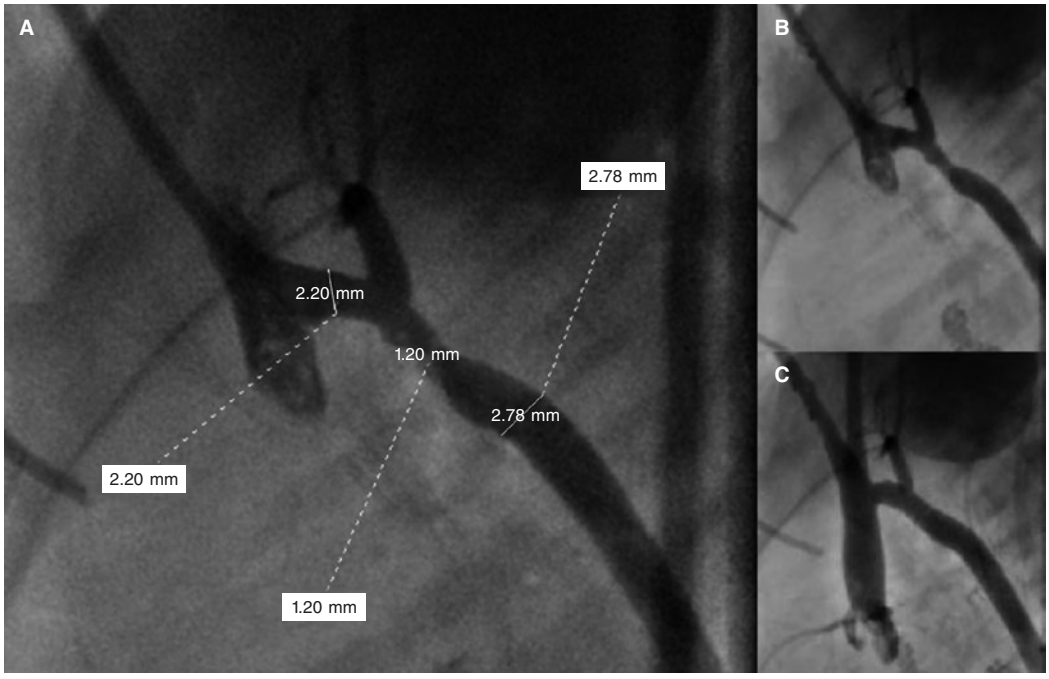


Figure 1. Aortic coarctation (AoC) treated with angioplasty and implantation of a 3.5 mm × 12 mm Absorb stent via carotid access in a newborn baby of 1400 grams of body weight. **A:** baseline angiographic measures; AoC, 1.2 mm; transverse arch, 2.2 mm; downstream aorta, 2.7 mm. **B:** angiography prior to implantation. **C:** result of the implant.

HOW WOULD I APPROACH IT?

The authors present the case of a preterm baby of 27 + 5 weeks of gestational age and 990 grams of body weight at birth. After an IV dose of ibuprofen to treat a ductus arteriosus with hemodynamic repercussion, a serious femoral pulse wave attenuation occurred with a systolic gradient of 60 mmHg in the aortic isthmus as seen on the Doppler ultrasound followed by significant diastolic prolongation of forward flow, and distal transverse arch hypoplasia. The diagnosis was severe aortic coarctation (AoC). Treatment was initiated with prostaglandins. Still, the arm-leg blood pressure gradient increased until the patient's condition got worse on his 13th day of life with a body weight of 1200 grams. Also, the patient's hemodynamic status got worse with severe left ventricular dysfunction and dilatation refractory to high-frequency ventilation and inotropic support with dobutamine.

The surgical approach of severe AoC in newborn babies with body weights < 2000 grams, especially in situations of multiorgan failure and coagulopathy, is often discarded in most centers because of the poor short and mid-term results; also, the incidence of brain injuries is very high. Over the last few years, balloon angioplasty has become a very popular bridging therapy to treat severe AoC in newborn babies. However, the incidence of a new AoC is fairly high.

Isolated, still promising, experiences have been published over the years regarding coronary stent implantation to treat AoC in newborn babies. This procedure has reduced the rate of new AoC significantly, postponed surgery until the baby's age and weight are more suitable, and facilitated the expansion of the transverse arch within the first months of life, thus reducing the need for more aggressive surgeries to expand the arch.[1]

However, retrieving a bare metal stent from the arch is not always easy. Our group has published the series with the largest number of pediatric patients to this date whose different vascular injuries were treated by implanting the Absorb bioresorbable coronary stent (Abbott, United States) built from a kind of lactic acid polymer. This series included a patient with 2.3 kilos of weight, AoC, and hemodynamic deterioration who received a 3.5 mm × 12 mm Absorb device. The patient was operated on 155 days later with termino-terminal anastomosis. The surgeons had no difficulty moving the structures and found no traces of any foreign material (figure 1). The resorption of this type of stent is associated with the absorption of water by the lactic acid in its structure. Usually, in adults the resorption of the stent occurs 2 years after the intervention. The fastest resorption reported in babies (in our patients after 5 months) may be due to the exposure of the endoprosthesis to higher blood flows in relation to coronary flow.[2] After this first case, our hospital has treated another 2 newborn babies with weights < 2000 grams and severe AoS through angioplasty with an Absorb device. Both patients underwent surgery 2 to 4 months later with good results. The consent necessary to carry out the procedure was obtained and the parents gave their consent for the reproduction of the images for scientific dissemination.

Unfortunately, we have not added more patients to this registry because the Absorb stent was removed from the market due to its unsatisfactory results treating coronary injuries. However, Sallmon et al.[3] have recently published the case of a newborn baby of 2100 grams of body weight and severe AoC implanted with a Magmaris bioresorbable coronary stent (Biotronik, Germany) with good results. It seems that the use of bioresorbable stents for the management of AoC in newborn babies is still promising because it improves the results of plain angioplasty and avoids the inconveniences associated with bare metal stents in postponed surgeries.

Therefore, the therapeutic approach in this patient would be to implant a bioresorbable stent. We would proceed with the surgical dissection of the right carotid artery followed by catheterization with a 5-Fr introducer sheath. Carotid access through dissection is our first option in patients < 3 kilos of weight who require aortic arch or aortic valve interventions since the incidence of vascular complications is lower. Also, it decreases the x-ray imaging exposure time.[1] The position of the tip of the i-ntroducer sheath would be verified under x-ray guidance and the downstream aorta would be catheterized using a 0.014 inches hydrophilic guidewire. Then, a 3.5 mm × 12 mm Magmaris stent would be mounted on the guidewire through the hemostatic valve. The introducer sheath side port would be used to perform the manual angiographies to check the position of the stent with respect to the AoC. The stent would progressively be dilated with increases of 2 atmospheres at a time until reaching 10 atmospheres. In the end, the final structural result would be tested on an angiography and the hemodynamic results on a transthoracic color Doppler echocardiography. This is how to avoid recrossing the stent with catheters and minimize the risk of stent displacement. At the end of the procedure, the surgical reconstruction of the carotid artery would be attempted (video 1 of the supplementary data).

FUNDING

No funding was received for this work.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000189.

REFERENCES

1. Lucas V. Stent treatment of neonatal coarctation: another option for critically ill or extremely small patients with unoperated coarctation or failed surgery. *Catheter Cardiovasc Interv.* 2010;75:562.
2. Rodríguez Ogando A, Ballesteros Tejerizo F, Sarnago Cebada F, Medrano López C, Gil Jaurena JM, Zunzunegui Martínez JL. Experience With the Absorb Bioresorbable Vascular Scaffold in Various Scenarios of Congenital Heart Disease. *Rev Esp Cardiol.* 2018;71:988-990.
3. Sallmon H, Berger F, Cho M-Y, Opgen-Rhein B. First use and limitations of Magmaris® bioresorbable stenting in a low birth weight infant with native aortic coarctation. *Catheter Cardiovasc Interv*. 2019;93:1340-1343.

---

https://doi.org/10.24875/RECICE.M20000190

Critical aortic coarctation in very low weight premature: primary angioplasty with coronary stent as bridging therapy. Case resolution

Coartación aórtica crítica en un prematuro de muy bajo peso: angioplastia con stent coronario como terapia puente. Resolución

Diana Salas-Mera,[a,*] César Abelleira Pardeiro,[a] David Ortega Martínez,[b] Arturo Hernández de Bonis,[c] Felipe Gómez Martín,[c] and Federico Gutiérrez-Larraya Aguado[a]

[a] *Servicio de Cardiología Pediátrica, Hospital Universitario La Paz, Madrid, Spain*
[b] *Servicio de Pediatría, Hospital Clínico San Carlos, Madrid, Spain*
[c] *Servicio de Neonatología, Hospital Universitario La Paz, Madrid, Spain*

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M20000188
https://doi.org/10.24875/RECICE.M20000189

* **Corresponding author:** Servicio de Cardiología Pediátrica, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.
E-mail address: diasalmer@gmail.com (D. Salas-Mera).

Online: 18-01-2021.

CASE RESOLUTION

Surgery was discarded due to the patient's critical condition and low body weight. Emergency cardiac catheterization with stenting was attempted to reduce the risk of early re-coarctation. Ultrasound-guided percutaneous access was used via right carotid artery (4-Fr introducer sheath). The angiography performed confirmed the critical preductal aortic coarctation and the ductus arteriosus (figure 1, video 1 of the supplementary data) with a 3.2 mm underdeveloped transverse arch and a 4.5 mm distal and diaphragmatic aorta. A 4 mm × 16 mm coronary stent was implanted, the distal transverse arch was slightly oversized, and the left subclavian artery was crossed resulting in the uneventful angiographic resolution of the coarctation (figure 2, video 2 of the supplementary data). Gradients were not measured due to the patient's unstable condition.

Over the following days, postaglandines and vasoactive support were withdrawn, and the patient was extubated. The early echocardiograms performed revealed the presence of residual mild gradients, left ventricular normalization, and the closure of ductus arteriosus. The patient developed occlusive thrombosis of the right common carotid artery and required bemiparin.

Due to the increasing arterial blood pressure levels and the presence of a gradient of between 45 mmHg and 50 mmHg according to the ultrasound data, the patient was re-catheterized when he was 70 days old (2100 grams) via right femoral artery. A gradient of 30 mmHg and endoluminal proliferation were seen (figure 3, video 3 of the supplementary data) as well as a 3.5 mm transverse arch. After dilatation with a 4.5 mm coronary balloon to solve the proliferation the angiography improved (figure 4, video 4 of the supplementary data) and the gradient dropped to 15 mmHg.

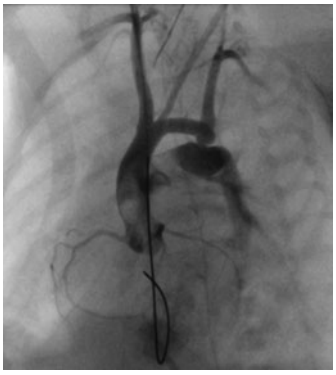


Figure 1. Critical preductal aortic coarctation and large ductus arteriosus.

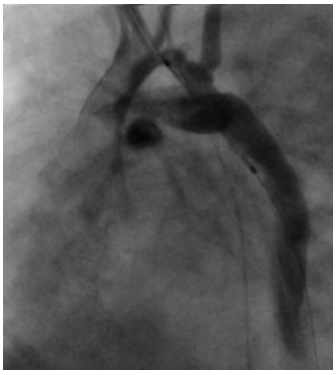


Figure 2. Resolution of coarctation after stent implantation.

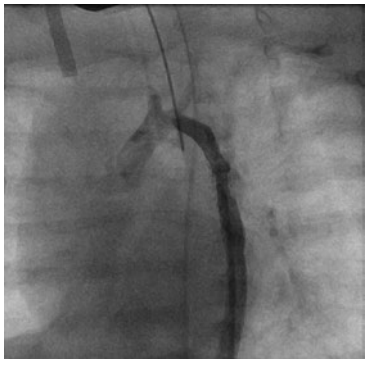


Figure 3. In-stent endoluminal proliferation.

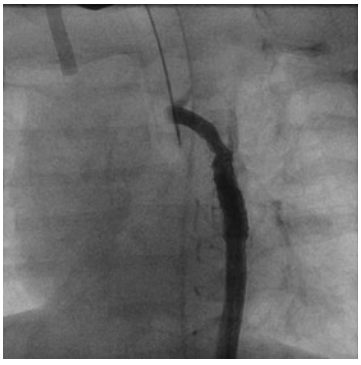


Figure 4. Improvement after angioplasty.

The patient was discharged from the hospital on his 100th day of life with a gradient of 30 mmHg according to ultrasound data, no diastolic prolongation of forward flow, and a normal left ventricular function. The patient remained on antiplatelet therapy with acetylsalicylic acid.

Six months later and with 5.4 kg of body weight the patient showed no signs of re-coarctation (clinical gradient < 20 mmHg, lack of arterial hypertension, and a peak gradient of 26 mmHg on the echocardiogram without diastolic prolongation of forward flow).

The surgical management of aortic coarctation in preterm babies with body weights < 1500 grams is associated with high morbidity, mortality, and re-coarctation rates. The primary angioplasty can be an option here, but with an associated early restenosis rate of up to 50%,[1] the risk of vascular damage and aneurysm formation. In a recent series of 5 preterm babies with body weights < 1500 grams treated with primary angioplasty via femoral arterial access, only 1 patient developed restenosis. Surgery was postponed in all the patients until

they weighed an average 5.5 kg without any surgical problems derived from the prior stent implantation.[2] All of them developed femoral artery thrombosis.

It was decided to attempt this strategy in our patient via carotid access, which allowed his clinical stabilization and postponed surgery for 6 months. However, this triggered a still unsolved carotid artery thrombosis.

Percutaneous treatment as a bridging therapy for the management of preterm babies allows us to postpone surgery and improve results. Although stent angioplasty can reduce the restenosis rate, our patient required reintervention due to endoluminal growth. Whether it should be the technique of choice compared to plain balloon angioplasty is still under discussion. The patient's parents agree with the publication of the clinical case respecting the privacy of the patient's personal data.

FUNDING

The work has been carried out without funding.

AUTHORS' CONTRIBUTIONS

D. Salas-Mera, and C. Abelleira Pardeiro have drafted and corrected the text of this article. Mr. Ortega Martínez, A. Hernández de Bonis, and F. Gómez Martín have participated in the patient' care and have supervised the text. F. Gutiérrez-Larraya Aguado has supervised the text and contributed to the bibliography.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000190.

REFERENCES

1. Rothman A, Galindo A, Evans WN, Collazos JC, Restrepo H. Effectiveness and safety of balloon dilation of native aortic coarctation in premature neonates weighing < or = 2,500 grams. *Am J Cardiol*. 2010;105:1176-1180.
2. Stegeman R, Breur JMPJ, Heuser J, et al. Primary coronary stent implantation is a feasible bridging therapy to surgery in very low birth weight infants with critical aortic coarctation. *Int J Cardiol*. 2018;261:62-65.

REC Interv Cardiol. 2021;3(3):233
https://doi.org/10.24875/RECICE.M20000164

Twisted left atrial appendage occlusion device

Retorcimiento de dispositivo de cierre de la orejuela

Felipe Hernández Hernández,[a,*] Esther Lázaro Fernández,[b] and José Moreu Burgos[b]

[a] *Unidad de Hemodinámica y Cardiología Intervencionista, Clínica Universidad de Navarra, Madrid, Spain*
[b] *Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Virgen de la Salud, Toledo, Spain*

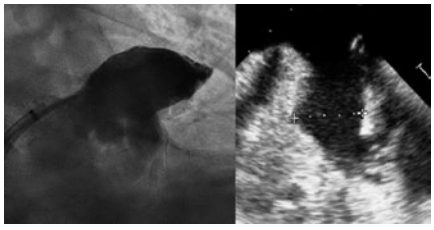


Figure 1.

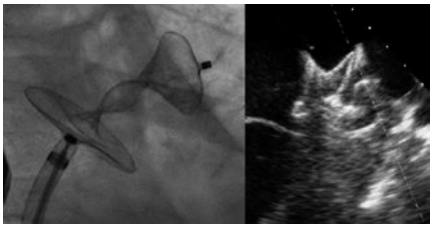


Figure 2.

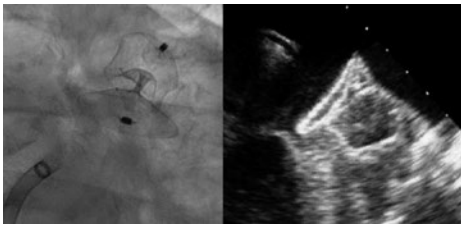


Figure 3.

An 80-year-old male with permanent atrial fibrillation (informed consent obtained) underwent a percutaneous procedure to close the left atrial appendage (LAA). He had required repeated admissions for severe anemia and chronic gastrointestinal bleedings while on different antithrombotic regimens (aspirin alone, clopidogrel alone, apixaban). He had a CHADS-VASC$_2$ score of 6 and a HAS-BLED score of 4. A transesophageal echocardiography (TEE) performed revealed the presence of Windsock morphology and no thrombus in the LAA. The diameters of the landing zone were between 23 mm and 25 mm (figure 1).

A 28-mm Amulet device was chosen to perform the procedure. A 14-Fr introducer sheath was advanced into the left atrium and, after a selective angiography, the device was deployed inside the LAA in a regular fashion. The first deployment did not achieve a good position (partially outside the appendage) and the device had to be recaptured. A second attempt was made with significant counterclockwise rotation of the sheath that achieved a peculiar "twisted" deployment of the body of the device (figure 2) whose distal part was actually deployed inside the appendage. It was carefully recaptured and after discarding pericardial effusion, it was re-implanted in a good position this time with no further need to change the device (figure 3). A transthoracic echocardiography performed the next day revealed no pericardial effusion. The TEE performed 1 month later revealed no leaks or thrombi on the device either.

The immediate complications described with LAA occluding devices are embolization, incomplete closure with residual leaks or the development of pericardial effusion and cardiac tamponade. Twisted malappositions are actually rare and could be predictors of short-term complications.

FUNDING

No funding source related to he manuscript.

AUTHORS' CONTRIBUTION

F. Hernández and E. Lázaro, procedure performance; all authors contributed in the drafting and revision of the manuscript.

CONFLICTS OF INTEREST

F. Hernández Hernández is a proctor for Abbott on issues concerning left atrial appendage occlusions.

*** Corresponding author:** Departamento de Cardiología y Cirugía Cardiaca, Clínica Universidad de Navarra, Marquesado de Santa Marta 1, 28027 Madrid, Spain.
E-mail address: felipeivus@hotmail.com (F. Hernández Hernández).

Received 7 May 2020. Accepted 24 July 2020. Online: 02-10-2020.

REC Interv Cardiol. 2021;3(3):234-235
https://doi.org/10.24875/RECICE.M20000166

Percutaneous closure of multiple mitral paravalvular leaks

Cierre percutáneo de múltiples fugas paravalvulares de prótesis mitral

Marcelo Gómez Silva,[a,*] Ignacio Cruz González,[b] Rodrigo Muñoz Di Vanni,[c,d] Rocío González Ferreiro,[b] Luis Javier Rodríguez Collado,[b] and Jean Núñez García[b]

[a] *Unidad de Hemodinámica, Hospital Dr. Gustavo Fricke, Viña del Mar, Valparaíso, Chile*
[b] *Unidad de Hemodinámica, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain*
[c] *Unidad de Hemodinámica, Hospital Dr. Sótero del Río, Santiago, Chile*
[d] *Clínica Alemana, Vitacura, Santiago, Chile*

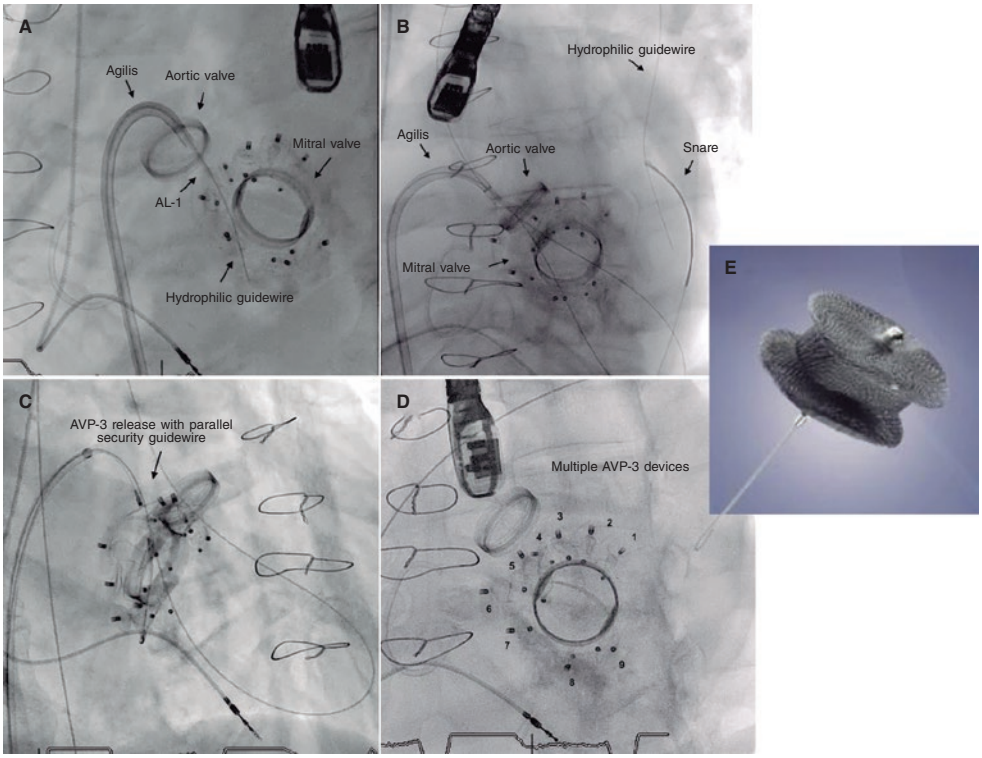


Figure 1.

Sixty-six-year-old male patient with a past medical history of mitral and aortic valve replacement in 1983. Back in 2005 he underwent a new aortic valve replacement due to prosthetic valve dysfunction. In 2018, also due to prosthetic valve dysfunction, a new mitral valve replacement was performed with a size 27 Bicarbon Fitline heart valve (Sorin Group, Italy).

Three months later the patient was hospitalized with functional class III-IV heart failure according to the New York Heart Association (NYHA) and hemolytic anemia with multiple mitral paravalvular leaks quantified as severe regurgitation. In a single medical-surgical session it was decided to perform percutaneous treatment due to the patient's high surgical risk. Informed consent was obtained for medical procedures and the use of anonymous clinical information. The percutaneous closure of the leaks was performed using 7 Amplatzer Vascular Plug III devices (figure 1E) that resulted in minimal residual leaks.

* **Corresponding author:** Unidad de Hemodinámica, Hospital Dr. Gustavo Fricke, Avda. Álvarez 1532, Viña del Mar, Valparaíso, Chile.
E-mail address: marceloalejandro.gomezsilva@gmail.com (M. Gómez Silva).

Received 28 April 2020. Accepted 4 August 2020. Online: 28-10-2020.

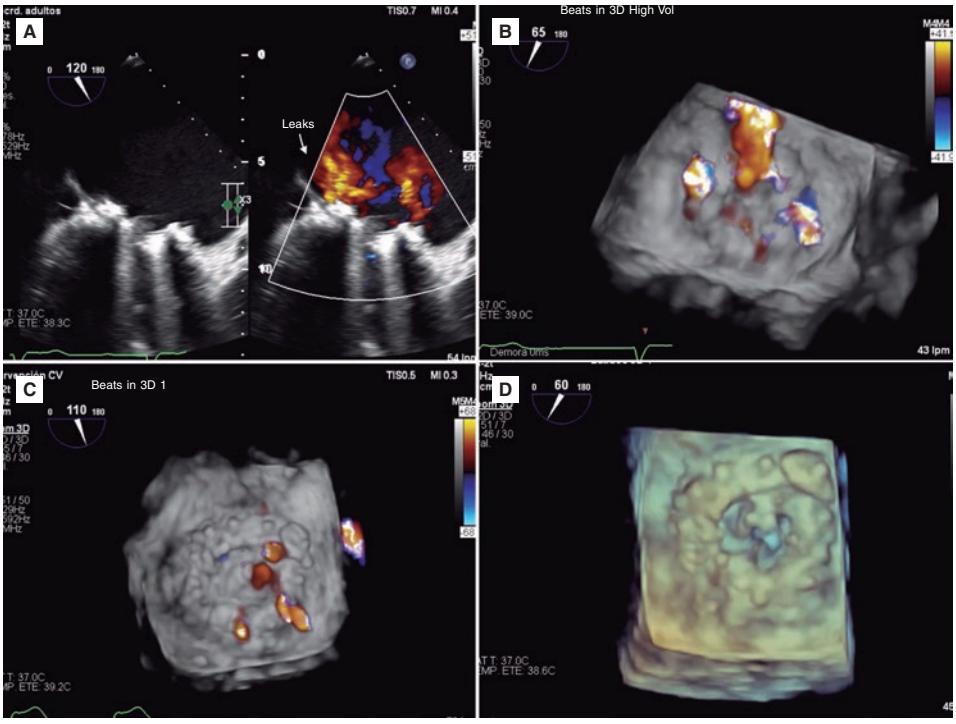


Figure 2.

In 2019 the patient presented with NYHA functional class III-IV and hemolytic anemia back again. The 3D echocardiogram performed revealed the presence of 2 severe mitral paravalvular leaks (figure 2A,B) (video 1 of the supplementary data). Percutaneous approach was attempted. An antegrade venoarterial circuit via transseptal puncture was built using a 0.035 in hydrophilic guidewire (figure 1A,B) (videos 2 and 3 of the supplementary data), 2 12/5 mm Amplatzer Vascular Plug III devices were implanted (figure 1C) (videos 4 and 5 of the supplementary data), and 9 devices of the same type surrounding the prosthetic circumference (figure 1D and figure 2D) (video 6 of the supplementary data). The procedure was completed uneventfully. The transesophageal echocardiography performed during the procedure confirmed the reduction of mitral paravalvular leaks now quantified as mild regurgitation (figure 2C) (video 7 of the supplementary data). Disease progression was good, and the patient was discharged with NYHA functional class II-III, corrected anemia (hemoglobin of 12 g/dL), and outpatient follow-up.

FUNDING

None.

AUTHORS' CONTRIBUTION

All authors have participated in the conception, design, data collection, analysis and interpretation of information.

CONFLICTS OF INTEREST

I. Cruz Gónzalez is proctor for Abbott.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000166.

REC Interv Cardiol. 2021;3(3):236-237
https://doi.org/10.24875/RECICE.M20000180

Comprehensive intracoronary physiological assessment of persistent angina

Evaluación integral de la angina persistente con fisiología intracoronaria

Andrés Provencio, Jesús Diz-Díaz, Juan Carlos Gómez-Polo, David Vivas, Javier Escaned, and Hernán Mejía-Rentería*

Servicio de Cardiología, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos *(IDISSC), Universidad Complutense de Madrid, Madrid, Spain*

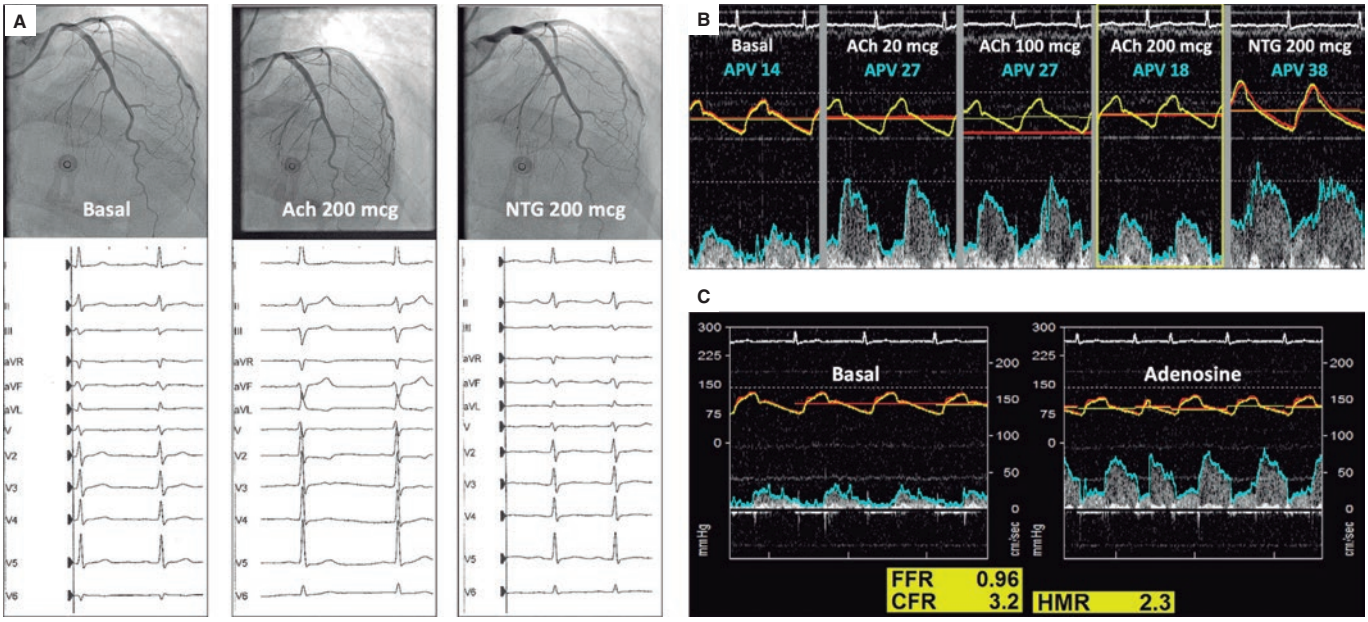


Figure 1.

Thirty-six-year-old male referred to the emergency room by the general practitioner with chest pain of 1-month duration. After the initial assessment revealed the presence of diffuse T-wave flattening, normal troponin levels, and a normal echocardiogram, the patient was discharged with a diagnosis of low-risk atypical chest pain. However, due to symptom recurrence and the fact that the treadmill test triggered angina-like symptoms and the ECG showed transient T-wave abnormalities, a coronary angiography was performed that ruled out the presence of epicardial stenosis (video 1 of the supplementary data).

The patient was readmitted a week later due to disabling oppressive chest pain related to low intensity exercise. Due to persistent angina without coronary stenosis, an intracoronary physiological assessment was scheduled with acetylcholine, adenosine, and simultaneous pressure and flow measurements in the left anterior descending coronary artery using a dual-sensor pressure and Doppler velocity guidewire. Acetylcholine (Ach) (200 mcg) triggered the patient's typical symptoms, the repolarization abnormalities seen on the ECG and the 50% decrease of coronary artery flow velocity (APV) without epicardial spasm (video 2 of the supplementary data). Intracoronary nitroglycerin (NTG) solved all abnormalities (figure 1A,B). The adenosine non-endothelium-dependent assessment revealed a normal fractional

* **Corresponding author:** Servicio de Cardiología, Hospital Clínico San Carlos, Prof. Martín Lagos S/N, 28040 Madrid, Spain.
E-mail address: hmejiarenteria@gmail.com (H. Mejía-Rentería).

Received 6 August 2020. Accepted 5 October 2020. Online: 21-12-2020.

flow reserve (FFR), hyperemic microcirculatory resistance (HMR), and coronary flow reserve (CFR) (figure 1C). Because of the clinical features present (acetylcholine-triggered angina with repolarization abnormalities seen on the ECG without epicardial spasm), microvascular vasospastic angina was diagnosed. Medical therapy adjustment with calcium channel blockers as first-line treatment improved the patient's symptoms at the follow-up.

This case illustrates the value of comprehensive intracoronary physiological assessment to evaluate specific pathways of vascular dysfunction in patients with persistent angina. This approach is supported by the 2019 ESC clinical practice guidelines on the management of chronic coronary syndromes in patients without obstructive coronary stenoses. The patient's consent was obtained to report his case anonymously.

FUNDING

The manuscript has not been funded.

AUTHORS' CONTRIBUTIONS

The text has been prepared and revised with the participation of all signatory authors.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M20000180.