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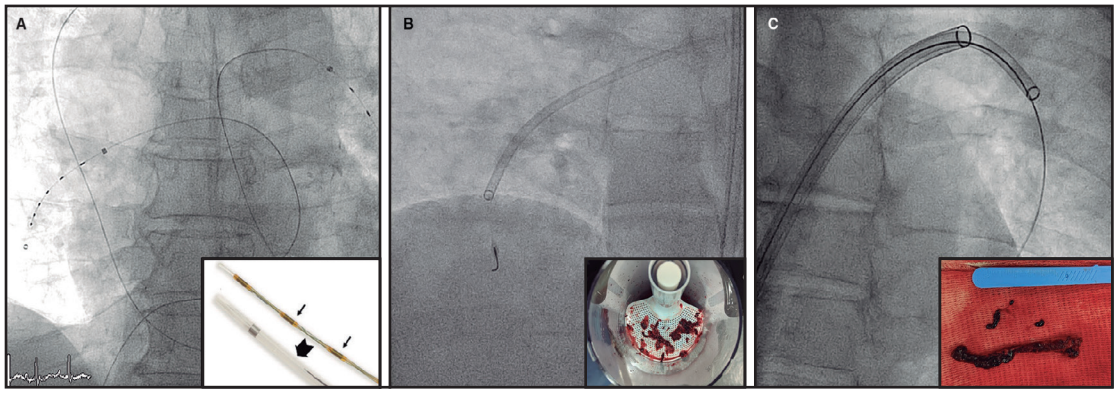

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REVISTA ESPAÑOLA DE CARDIOLOGÍA

REC: INTERVENTIONAL CARDIOLOGY

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Editorial

The challenging pathway to TAVI: in memory of Alain Cribier

El arduo camino hacia el TAVI: en recuerdo de Alain Cribier

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In 1998, in response to a comment on the limited durability of an aortic valvuloplasty performed during the last Madrid Interventional Cardiology (MIC) course, Alain Cribier insightfully stated: "We'll mount a stent on the valvuloplasty balloon, attach the leaflets, and problem solved." Four years and countless hours of work later, both at his hospital in Rouen, France, and at the animal experimentation center in Lyon, France, the recently deceased Alain Cribier (1945-2024) achieved a groundbreaking milestone.[1] On April 16, 2002, he performed the world's first surgery-free transcatheter aortic valve implantation (TAVI), prolonging the patient's life and revolutionizing heart valve surgery. This innovation dramatically improved the quality of life of a high percentage of patients with severe aortic stenosis who were ineligible for conventional heart surgery. Since then, more than a million patients have benefited from his technological innovation.

After this pivotal first case of TAVI,[1] isolated procedures were performed in selected patients in the following years, with few technical variations, and all via antegrade access. While interventional cardiologists were enthusiastic and had high expectations, critics predicted apocalyptic disasters due to alleged complications, such as vascular complications, valve instability and migration, coronary occlusion, strokes, annular and aortic rupture, paravalvular regurgitation, and concerns about the durability of the valve. In 2006, the first clinical trials (REVIVAL[2] in the United States and REVIVE[3] in Europe) changed the procedure strategy. The adoption of retrograde access, facilitated by the versatility of a flexible carrier catheter, considerably simplified the technique and contributed to its widespread adoption.

After a stay in Vancouver, Canada to acquire theoretical and practical training in the technique, and with Cribier's assistance, a team of interventional cardiologists from Hospital Gregorio Marañón, Madrid, Spain successfully implanted the first 2 aortic valves via transfemoral access in Spain on April 23, 2007 (figure 1). Throughout 2007, the team contributed to the REVIVE trial, successfully treating 10 patients with transfemoral TAVI, with no perioperative mortality or major complications. This success, with contributions from other European centers, paved the way for the approval of this technology for clinical use.

After standardizing and defining the complications associated with the procedure,[4] the randomized PARTNER clinical trials were conducted in inoperable patients and high-risk surgical patients.[5,6] These trials confirmed the safety and efficacy of TAVI, establishing

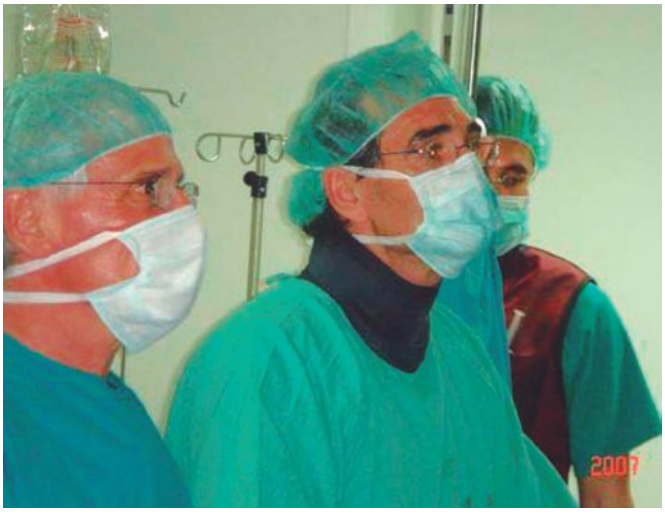

Figure 1. First transcatheter aortic valve implantation performed in Spain, on April 23rd, 2007. In the photograph, from left to right, Dr. Alain Cribier, Dr. Eulogio García, and Dr. Javier Ortal.

it as the treatment of choice for high-risk patients.[7] Eventually TAVI became the preferred treatment for all patients with aortic stenosis older than 75 years.[8-10]

In this exciting journey, we contributed a few technical improvements, demonstrating the safety of direct implantation without prior valvuloplasty[11] and improving the management of vascular access via contralateral access.[12] The gradual simplification of TAVI led to its classification as a "minimally invasive procedure". It is now available in all cath labs, with more than 1 million valves implanted in all 5 continents.[13]

Alain Cribier was technically elegant and efficient; meticulous, systematic, and generous in his teaching. His perseverance in the management of aortic stenosis drove him to seek a definitive solution. Bernard Guiraud-Chaumeil, former president of the French health assessment department, highlighted Cribier's exceptional contribution to the management of valvular heart disease, stating: "Revolutionary advances in medicine must be accessible to patients

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as soon as possible." Cribier's dedication, perseverance, and ingenuity changed the history of severe aortic stenosis; his legacy will not only save thousands of lives but will also improve the clinical practice of present and future generations of interventional cardiologists.

FUNDING

None declared.

CONFLICTS OF INTEREST

None declared.

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Editorial

Ventricular pressure-volume loop and other heart-function metrics can elucidate etiology of failure of TAVI and interventions

Las curvas de presión-volumen y otras métricas de función cardiaca pueden esclarecer la respuesta fallida al TAVI y otras intervenciones

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Aortic valve stenosis is one of the most acute and chronic cardiovascular disease conditions. Bicuspid aortic valve is the most common congenital heart abnormality and affected individuals have a 50% chance of developing severe aortic valve stenosis during their lifetime. In aortic valve disease (both aortic valve stenosis and bicuspid aortic valve), the heart valves are damaged and do not work properly. This condition can rapidly affect the pumping action of the heart and can progress to heart failure. Heart failure is a deadly disease affecting at least 26 million people worldwide and its prevalence is increasing with high mortality and morbidity.[1] Most importantly, aortic valve disease commonly coexists with other cardiovascular diseases, giving rise to the most general yet fundamentally challenging scenario: complex valvular, ventricular, and vascular diseases (C3VD). In C3VD, multiple valvular, ventricular, and vascular pathologies interact with one another, while the physical phenomena associated with each pathology amplify the effects of others on the cardiovascular system.

Left ventricle (LV) pressure-volume (P-V) loop analysis is a powerful tool to assess cardiac mechanics. This analysis can reveal the pathophysiological mechanisms of heart failure, including heart failure with preserved ejection fraction and myocardial and valvular diseases. It is, therefore, instrumental in the evaluation and management of heart failure and valvular heart disease and can also help explain the short- and long-term effects of valvular and other interventions with cardiac implications. In addition, ventricular P-V loop analysis can be used to monitor the cardiac effects of related medical devices, mechanical heart support, therapeutic interventions, and medications.[2-5] Indeed, ventricular P-V loop analysis has exceptional potential for integration into current clinical practice to advance the standard of care.

Aortic valvular disease increases LV pressure, LV end-diastolic pressure, LV workload, the stiffness of the systemic arterial system, and LV afterload, contributing to LV systolic and diastolic dysfunction,[6] an important cause of heart failure in such patients. While transcatheter aortic valve implantation (TAVI) provides positive outcomes and has markedly reduced the mortality rate, TAVI fails in nearly 25% to 35% of patients (patients either die or do not recover a reasonable quality of life after the procedure).[7] Indeed, the immediate intraprocedural as well the longitudinal hemodynamic changes affecting the aortic-left ventricular system after aortic valve replacement are poorly understood. While TAVI universally reduces the transvalvular pressure gradient, it is anticipated to improve systolic and diastolic LV function in the long-term. Despite the benefits, invasive LV P-V loop analysis revealed impaired LV systolic and diastolic function in the early phase following TAVI.[6,8] LV P-V loop analysis also revealed exacerbated heart failure despite successful TAVI procedures in many patients.[5,9] Indeed, LV P-V loop analysis elucidated that reductions in transvalvular pressure gradient post-TAVI were not always accompanied by improvements in LV workload. TAVI has been shown to have no effect on LV workload in many patients, while LV workload post-TAVI significantly rose in many others.[2,5,10]

In clinical settings, cardiac catheterization is the gold standard for evaluating pressure and flow through the heart to perform ventricular P-V loop analysis. However, due to its invasiveness, cost, and high risk, it is impractical for diagnosis in routine daily clinical applications or serial follow-up examinations. Most importantly, cardiac catheterization only provides access to the blood pressure in very limited regions rather than details of physiological flow and pressures throughout the heart and circulatory system. In addition, there is no method to invasively or non-invasively quantify the heart workload that can provide a contribution breakdown of each component of the cardiovascular diseases. This is especially crucial in the presence of TAVI and C3VD, in which quantification of left ventricular workload and its breakdown are important to guide the priority of interventions. Moreover, there is no noninvasive method for determining LV end-diastolic pressure, instantaneous LV pressure, and contractility. All these parameters provide valuable information about the patient's cardiac deterioration and heart recovery.

Keshavarz-Motamed[11,12] developed the first and the only Doppler-based noninvasive patient-specific diagnostic, monitoring, and predictive tool that can investigate and quantify the effects of interventions, medications, and C3VD constituents on the function of the heart and circulatory system at no risk to the patient (figure 1).

This novel method[4,10-15] offers several key capabilities (figure 2, sample results): *a)* quantifying details of physiological pulsatile flow and pressures through the heart and circulatory system; *b)* tracking cardiac and vascular states based on accurate time-varying models that reproduce physiological responses; *c)* performing LV P-V loop analysis and quantifying heart function metrics, specifically in

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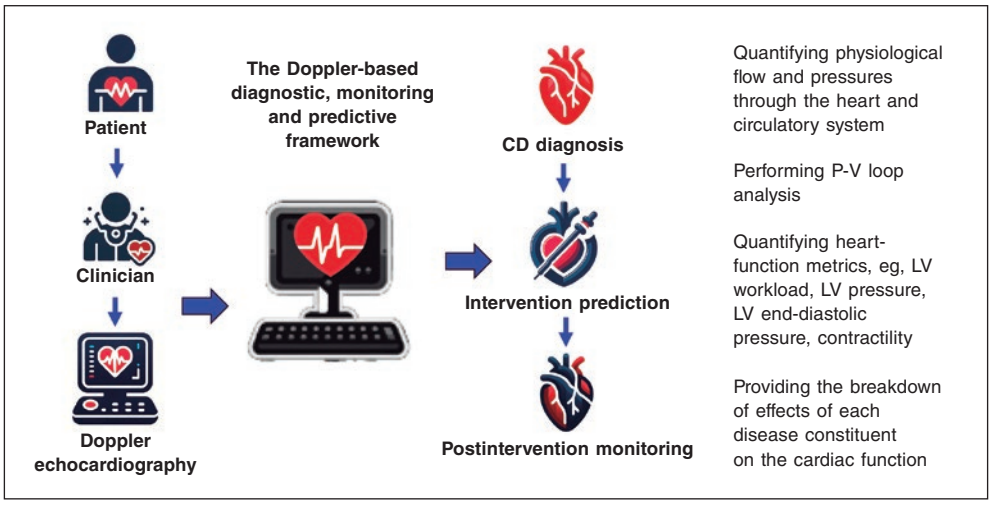

Figure 1. Doppler-based patient-specific diagnostic, monitoring, and predictive tool flowchart. The tool uses a few input parameters that can all be measured using Doppler echocardiography simply and reliably. This novel tool[4,10–15] was validated against cardiac catheterization and 4D flow MRI in patients with C3VD (so far ~ n = 600) with substantial inter- and intra-patient variability with a wide range of (adult and congenital) cardiovascular diseases. 4D, 4-dimensional; C3VD, complex valvular, ventricular, and vascular diseases; CD, cardiovascular disease; LV, left ventricular; MRI, magnetic resonance imaging.

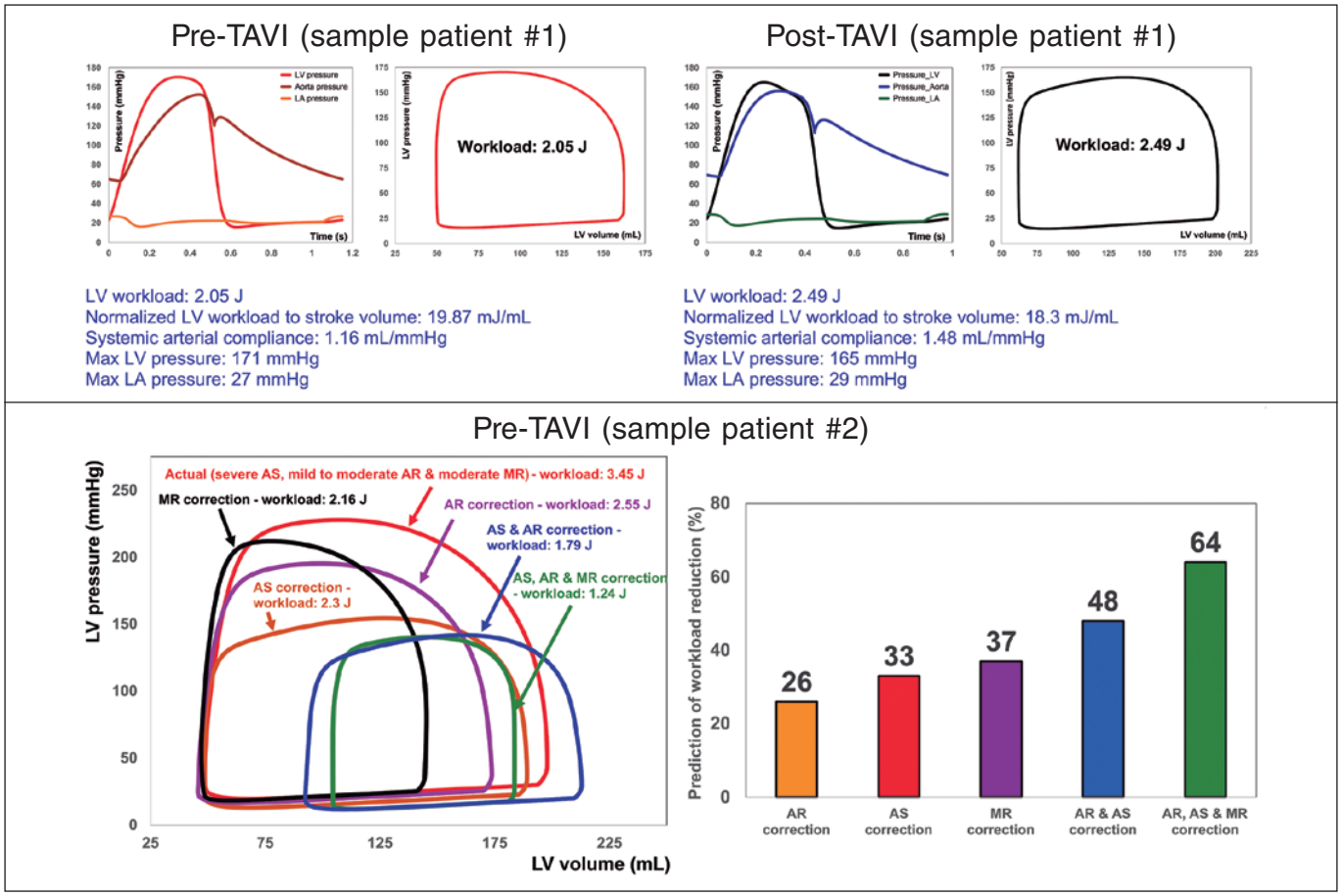

Figure 2. Diagnosis and monitoring in sample patient 1 from baseline to 90 days: this patient did not fully benefit form transcatheter aortic valve implantation (TAVI). Instead of improving the patient's heart condition by reducing LV workload, TAVI caused an increase in LV workload. Example of workload breakdown analysis and prediction for effects of interventions in sample patient 2: right: P-V loops of the actual disease condition and prediction of several valve interventions. Left: predicted percent decrease in LV workload following valve interventions. Both mitral valve regurgitation (38% increase) and aortic valve stenosis and regurgitation (48% increase) substantially contributed to increasing the workload. This patient only underwent TAVI. However, considering this calculation, the decision to also perform mitral intervention at the time of aortic valve intervention should have been evaluated. AS, aortic stenosis; AR, aortic regurgitation; MR, mitral regurgitation; LV, left ventricle; LA, left atrium. We retrospectively received patients' data from multicentre in which waiver of informed consent and data transfer were approved by their Institutional Review Boards.

terms of the heart workload; *d)* providing a breakdown of the effects of disease constituents on global heart function (eg, heart workload) to help predict the effects of interventions and plan the sequence of interventions in C3VD; *e)* quantifying other heart-function metrics, including LV end-diastolic pressure, instantaneous LV pressure, and contractility. None of the above metrics can be obtained non-invasively in patients, and when invasive cardiac catheterization is undertaken, the collected metrics cannot be as complete as what the novel method can provide. While such information is vitally needed for the effective use of advanced therapies to improve clinical outcomes and to guide interventions in patients, they are not currently accessible in clinical settings.

CONCLUSION

The novel method, developed and verified by Keshavarz-Motamed,[11,12] purposefully uses reliable and noninvasive input parameters measured by Doppler echocardiography to continuously calculate patient-specific hemodynamics to be used for diagnosis, monitoring, and prediction of cardiac function and circulatory status. This innovative method holds potential applications: *a)* in clinical trials, enabling the noninvasive analysis of cardiac and circulatory function metrics; *b)* as a diagnostic tool to noninvasively analyze cardiac function metrics for routine care, ambulatory care, or intensive and critical care units; *c)* as a patient monitoring tool, potentially integrated into personal wearable devices; and *d)* as a module incorporated into the software of Doppler echocardiography machines for enhanced diagnosis and prediction.

FUNDING

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CONFLICTS OF INTEREST

None.

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Editorial

Misconceptions and misunderstandings hampering medical research and progress

Errores y malentendidos que dificultan la investigación médica y el avance de la medicina

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INTRODUCTION

When scientific projects or articles are evaluated, objections are often raised that may prevent their performance or publication. Sometimes, the flaws noted may not be correct or relevant to the study. In this article, we review the most common types of objections that can hinder the progress of medical research and suggest ways to reduce them.

CLINICAL (OR PROCEDURAL) OBJECTIONS AND STATISTICAL/METHODOLOGICAL OBJECTIONS

The objections an evaluator can make to a research project can be grouped into 2 broad categories: clinical (or procedural) and statistical/methodological.

The former can be addressed and, if necessary, refuted by the author of the project as they relate to the clinical problem *per se*. In this regard, the author of the project has more expertise and sometimes more up-to-date knowledge than the evaluator on the issue in question. A common example could be the objection, "the project does not specify under which conditions baseline blood pressure should be measured, or the criteria chosen to define hypertension." The researcher can acknowledge the flaw in his/her protocol and correct it or argue that the objection is incorrect.

The situation is different with statistical/methodological objections. Researchers, whether acting as evaluators or persons who are evaluated, are not usually experts in research methodology and biostatistics. Below are a few examples of this type of objection.

Common erroneous statistical/methodological objections

Sample size

Contrary to what most researchers believe, the objection of an insufficient sample size is only relevant in highly specific situations. In some cases, it is not accurate; for example, if the result has a very small *P* value that constitutes strong evidence against the null hypothesis. It does not make any sense either in somewhat more complex situations.[1]

Statistical power

Statistical power depends on 4 parameters, whose value is often not predefined, so by choosing suitable values for these parameters, researchers can obtain almost any value for statistical power. In fact, when researchers are asked about the figure for statistical power, it is often insufficient to give a specific value, because the values of other parameters associated with such power are also necessary. Moreover, it is obvious that by slightly modifying these values within reasonable ranges, very different power values can be obtained.[2]

Test on the normal distribution of the response variable

In many cases, this objection may be doubly mistaken: either because the response variable is dichotomous and will be treated as such in the analysis, or because the sample size used is greater than, say, 30, and the central limit theorem guarantees a very good approximation to the normal distribution of the statistic used in the test. Naturally, it can never be guaranteed whether the variable has a normal distribution or not. Thus, in cases with a confirmed lack of normal distribution, the robustness of some parametric tests vs nonnormality must be taken into account.[3] In cases with a strong association and an extremely small *P* value in the test, it should be noted that if the true *P* value of the test were, say, 10 times larger or 10 times smaller than that found in the parametric test, the practical conclusion would be the same.

Control group and study validity

While a control group is a great asset in many situations, demanding its presence should not be a universally or undisputed mantra. In some situations—and when used appropriately—historical controls

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provide enough information to draw very interesting conclusions. In other cases, each patient serves as his/her own control, thus allowing the use of intraindividual variability, which is often less than interindividual variability and, therefore, provides more powerful tests in many cases.

Pilot trials

Randomized clinical trials (RCTs) add highly useful methodological refinements to effectively determine the safety and efficacy profile of a new drug or procedure. However, pilot trials can add these same methodological refinements and be controlled, randomized, and blinded to a point that the level of scientific evidence they provide can be equivalent to that of RCTs, with significant advantages regarding time and cost savings. In addition, in general, their size is not a determining factor that compromises their validity. Then, what is the main difference between the 2 designs? The difference lies not in the level of evidence they provide, but in the administrative process involved. RCTs require approval from external hospital, regional, or national committees, while pilot trials are endorsed by the expertise of the medical team involved in their design. For external evaluators, it is more challenging to make accurate assessments of each aspect of the project and provide a sound judgment. Moreover, if they have the authority to veto the study, there is a possibility of rejecting it based on insufficiently founded considerations.

Observational trials

Blinded RCTs are widely accepted as the best source of evidence on drug and treatment efficacy. However, observational studies can also provide information on long-term safety and efficacy, which is often lacking in RCTs. Additionally, they are less expensive, allow the study of rare events, and provide information more quickly than RCTs. New and ongoing developments in analytical and data technology offer a promising future for observational studies, which already play a key role in researching treatment outcomes. Data from large observational studies can clarify the tolerability profile of drugs and are particularly suitable for large and heterogeneous populations of patients with complex chronic diseases. RCTs and observational trials should, therefore, be considered to complement each other.

Case-control trials

Rothman[4] states that case-control trials have gone from "being the Cinderella of medical research to one of its brightest stars." In case-control designs, it is much more challenging to avoid the distortion caused by confounding factors. However, these issues are partially mitigated by segmentation, matching, and multivariate analysis techniques. In some cases, they can provide significant statistical evidence much faster and more cheaply than clinical trials. Let's consider an example of a disease that affects 1% of the population who do not follow a particular diet, and 5% of those who do follow it, knowing that 40% of the population follows that diet. A prospective trial would take 80 people from the diet group and another 80 from the control group, and after the agreed-upon time, we would measure the incidence of the disease in each of the 2 groups. The statistical power of this study for an alpha value of 0.05 would be 8%. A case-control trial would take 80 patients with the disease and 80 without it, and with very detailed health records, we would be able to determine the percentage of people who follow that diet in each of the 2 groups. The statistical power would be 93%.

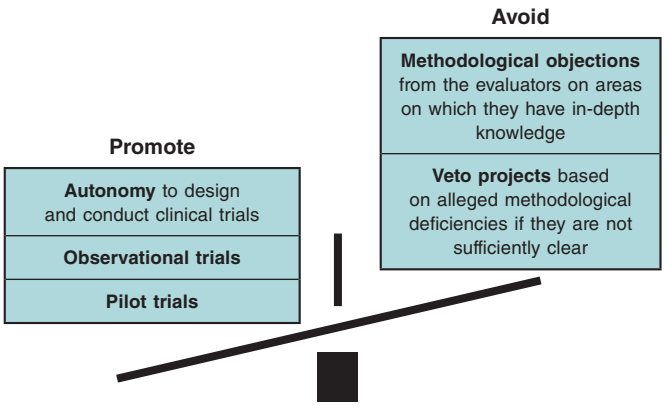

Figure 1. Measures to expedite medical research by promoting the autonomy of qualified physicians, avoiding unjustified methodological objections, and promoting the use of currently underrated designs.

The list of erroneous objections is much longer, however, and each would require a dedicated article to explain it.

CONCLUSIONS

Some of the methodological objections raised by the evaluators are incorrect. In most cases, the evaluated party assumes that his/her project has a major flaw and ends up abandoning it. Consequently, many projects that could have provided valuable information are unfairly discarded slowing down the progress of medicine.

We believe that this anomaly would largely be avoided if: *a)* evaluators raised methodological objections only in areas in which they have in-depth knowledge; *b)* whenever possible, the judgment issued by the evaluators from health agencies and bioethics committees was a suggestion instead of a veto; c) the fundamental role of observational trials, which can be highly effective and generally cheaper than clinical trials, was recognized; *d)* pilot trials were conducted in many cases where they are indicated, because they can be controlled, randomized, and blinded but without the restrictions associated with RCTs (figure 1).

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CONFLICTS OF INTEREST

None declared.

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Original article

Discordance between fractional flow reserve and nonhyperemic index with a fiber-optic pressure wire. READI EPIC-14

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ABSTRACT

Introduction and objectives: Functional assessment of coronary stenosis severity with the piezo-electric sensor pressure wire has shown a discrepancy of up to 20% between hyperemic and nonhyperemic indexes. No data are available with fiber-optic pressure wires. The aim of this study was to evaluate the incidence and factors related to the diagnostic discordance between these indexes with a fiber-optic pressure wire. Secondary aims were to assess diagnostic reproducibility in 2 consecutive measurements of fractional flow reserve (FFR) and diastolic pressure ratio (dPR) and evaluate the drift rate.

Methods: We conducted a prospective, observational multicenter study in patients undergoing functional assessment with a fiber-optic pressure wire. We took 2 consecutive measurements of the dPR (cutoff point 0.89) and FFR (cut-off point 0.80) in each lesion analyzed. The diagnostic correlation between 2 measurements with the same technique and between the 2 techniques (dPR and FFR) was assessed. Clinical and angiographic factors associated with discordance (FFR−/dPR+ and FFR+/dPR−) between the 2 techniques were analyzed.

Results: We included 428 cases of stenosis (361 patients). Diagnostic reproducibility was 95.8% for the dPR, with a correlation coefficient between the 2 measurements (dPR1 and dPR2) of 0.974 ($P < .0001$). For FFR, the diagnostic reproducibility was 94.9% with a correlation coefficient (FFR1 and FFR2) of 0.942 ($P < .0001$). The diagnostic discordance was 18.2% (FFR+/dPR− 8.2% and FFR−/dPR+ 10%). Among the variables analyzed, the factors significantly associated with FFR−/dPR+ discordance in the multivariate analysis were hypertension and intracoronary adenosine. The only factors significantly associated with FFR+/dPR− discordance were age < 75 years and stenosis > 60%. The drift rate was 5.7%.

Conclusions: Although FFR and dPR measurements with a fiber-optic pressure wire have excellent reproducibility and a low drift rate, the discordance rate remains similar to those in previous studies with a piezo-electric pressure wire. FFR−/dPR+ discordance is associated with intracoronary adenosine and hypertension. FFR+/dPR− discordance is related to age < 75 years old and stenosis > 60%.

Keywords: Coronary physiology. Fractional flow reserve. Nonhyperemic index. Discordance. Drift.

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Discordancia entre la reserva fraccional de flujo y el índice no hiperémico con guía de presión de sensor óptico. READI EPIC-14

RESUMEN

Introducción y objetivos: La valoración funcional de las estenosis coronarias con guías de presión de sensor piezoeléctrico ha mostrado hasta un 20% de discordancia entre los índices hiperémico y no hiperémico. No hay datos disponibles con guía de presión de sensor óptico. El objetivo del estudio es evaluar la incidencia y los factores relacionados con la discordancia diagnóstica entre estos índices con guía de presión de sensor óptico. Como objetivos secundarios se evaluó la reproducibilidad diagnóstica en dos determinaciones consecutivas de la reserva fraccional de flujo (RFF) y la *diastolic pressure ratio* (dPR). También se evaluó la tasa de *drift*.

Métodos: Estudio observacional, prospectivo, multicéntrico, en pacientes a quienes se realiza una valoración funcional con guía de presión de sensor óptico. Se hicieron dos mediciones consecutivas de dPR (umbral 0,89) y RFF (umbral 0,80) en cada lesión analizada. Se valoró la correlación diagnóstica entre dos mediciones con la misma técnica y entre ambas técnicas (dPR y RFF). Se analizaron factores clínicos y angiográficos asociados a la discordancia (RFF−/dPR+ y RFF+/dPR−) entre ambas técnicas.

Resultados: Se incluyeron 428 estenosis (361 pacientes). La reproducibilidad diagnóstica fue del 95,8% para dPR, con un coeficiente de correlación entre ambas mediciones (dPR1 y dPR2) de 0,974 (p < 0,0001). Para RFF la reproducibilidad diagnóstica fue del 94,9%, con un coeficiente de correlación (RFF1 y RFF2) de 0,942 (p < 0,0001). La discordancia diagnóstica fue del 18,2% (RFF+/dPR− 8,2% y RFF−/dPR+ 10%). Entre las variables analizadas, en el análisis multivariado, la hipertensión arterial y la administración intracoronaria de adenosina se asociaron de manera significativa con la discordancia RFF−/dPR+. Solo la edad < 75 años y la estenosis > 60% se asociaron de manera significativa con la discordancia RFF+/dPR−. La tasa de *drift* fue del 5,7%.

Conclusiones: Aunque las mediciones de RFF y dPR con guía de presión de sensor óptico tienen una excelente reproducibilidad y una baja incidencia de *drift,* la tasa de discordancia permanece similar a la de estudios previos con guía de presión de sensor piezoeléctrico. La adenosina intracoronaria y la hipertensión arterial se asocian con la discordancia RFF−/dPR+. La edad < 75 años y la estenosis > 60% se asocian a discordancia RFF+/dPR−.

Palabras clave: Fisiología coronaria. Reserva fraccional de flujo. Índice no hiperémico. Discordancia. *Drift*.

Abbreviations

dPR: diastolic pressure ratio. **FFR:** fractional flow reserve. **FOSW:** fiber-optic sensor wire. **iFR:** instantaneous wave-free ratio: **PPSW:** piezoelectric pressure sensor wire.

INTRODUCTION

Fractional flow reserve (FFR) measurement is an invasive procedure performed during coronary angiography to determine the functional significance of coronary stenoses.

In recent years, the instantaneous wave-free ratio (iFR) resting index has been developed to assess the functional significance of coronary stenoses without the need for adenosine administration. The optimal iFR cutoff value—equivalent to 0.80 in FFR—was initially established at 0.89.[1] In 2017, 2 clinical studies comparing FFR with iFR found no significant differences in clinical outcomes at follow-up.[2-3] After the publication of these 2 studies, the European Society of Cardiology guidelines on myocardial revascularization[4] assigned resting indices the same grade of recommendation as FFR for the functional assessment of coronary lesions.

Despite the validation of these 2 techniques in clinical trials and their inclusion in clinical practice guidelines, up to 20% discordance has been reported between iFR+/FFR− or iFR−/FFR+.[5] Several clinical factors, such as diabetes,[6] and anatomical factors, such as lesion location in the left main or proximal left anterior descending coronary arteries, have been identified in association with this discordance.[7]

Previous studies comparing FFR with iFR using a piezoelectric pressure sensor wire (PPSW) calculated the mean distal-to-aortic pressure ratio beginning 25% into diastole and ending 5 ms before end diastole.[1]

Recently, a new resting index—the diastolic pressure ratio (dPR)—has been developed to calculate the mean distal-to-aortic pressure ratio over the entire diastolic phase (from the lowest point of the dicrotic notch up to 50 ms before the onset of the upstroke of the next beat)[8] using a fiber-optic sensor wire (FOSW).

A study that compared the values of different resting indices (iFR, dPR, dPR25-75, dPRmid, iFRmatlab, iFR50ms, and iFR100ms) revealed that all were numerically identical,[8] meaning that the results obtained with the iFR can be extrapolated to other resting indices.

To date, no study has compared the agreement between dPR and FFR measured using a FOSW. One advantage of the FOSW over the PPSW is the lower loss of mean pressure matching in the wire compared with the measurement obtained in the guide catheter (drift).[9] Although various iFR studies state that drifts < ± 0.02 are considered acceptable, the drifts reported with the FOSW were even lower at < ± 0.01.[10]

The diagnostic reproducibility of PPSW decreases significantly when close to the threshold value of 0.80 and is approximately 80% when measurements are < 0.77 or > 0.83, and around 90% with values < 0.76 or > 0.84.[11] Since the FOSW is less sensitive to changes in humidity and temperature, greater reproducibility of results can be expected when the measurement is repeated.

Considering that most discordant measurements have been associated with cutoff values, the better reproducibility of measurements and practically nonexistent drift of the FOSW can more accurately determine FFR and dPR measurements and reduce discrepancies.

METHODS

Study design

In this prospective, observational, and multicenter registry of consecutive coronary stenoses, we conducted a study with FOSW based on our routine clinical practice.

We included consecutive patients with clinical signs and coronary angiography findings suggesting the need for a functional study with a pressure wire. We excluded patients with cardiogenic shock, heart failure, severe anemia (hemoglobin < 10 mg/dL), heart rate < 50 or > 100 bpm, baseline systolic blood pressure < 90 mmHg or > 160 mmHg, severe coronary artery lesions in distal segments, and contraindications for the administration of adenosine.

Objective

The aim of this study was to evaluate the incidence and factors related to diagnostic discrepancies between these indices using the FOSW. Secondary aims consisted of assessing the diagnostic reproducibility of FOSW in 2 consecutive measurements of FFR and dPR and evaluating the drift rate.

Procedure

The study was approved by the Drugs Research Ethics Committee of the Basque Country (internal code PS 2019039). All patients received information on the study and were asked to sign a written informed consent form prior to their participation in the study.

We performed coronary angiography using standard methods, with visual estimation of severity after intracoronary nitroglycerin administration. We included lesions with up to 50% to 75% percent diameter stenosis and collected data on the reference luminal diameter, minimum luminal diameter, lesion length, calcification, and vessel tortuosity for each studied lesion.

We performed 2 consecutive measurements of dPR (threshold, 0.89) and FFR (threshold, 0.80) for each studied lesion and analyzed the clinical and angiographic factors to determine their correlation with discordance (FFR−/dPR+ and FFR+/dPR−). We took dPR1 and FFR1 as reference values for discrepancy analysis.

We conducted the FOSW functional study with 5-, 6-, or 7-Fr guide catheters without side holes, using an OptoWire (Opsens Medical, Canada). After advancing the wire toward the tip of the guide catheter, we removed the introducer sheath and flushed the system with saline solution to prevent damping of the pressure wire resulting in equal pressure of the wire and the guide catheter at the tip of the catheter. After advancing the pressure wire distally, we administered 200 µg of intracoronary nitroglycerin before taking any measurements. We took the 2 dPR measurements after waiting the necessary time to obtain confirmation of a stable baseline distal-to-aortic coronary pressure ratio (Pd/Pa).

Subsequently, we took 2 different FFR measurements. Hyperemia was induced according to standard practice in each center (through intracoronary or IV adenosine infusion). If intracoronary adenosine was infused, for the second measurement, we waited until the baseline heart rate, blood pressure, and Pd/Pa were regained and then infused the same dose of adenosine. If IV adenosine was infused, the infusion was stopped until baseline heart rate, blood pressure, and Pd/Pa were regained, and then we infused adenosine at the same rate.

We evaluated the presence of drift upon removal of the pressure wire from the guide catheter. Drift was defined as a difference in Pd/Pa of at least ± 0.02 upon removal of the pressure wire from the guide catheter. In the presence of significant drift, measurements were repeated.

Cutoff values

The cutoff value was ≤ 0.80 for FFR and ≤ 0.89 for dPR.[10] We categorized all studied vessels based on dPR and FFR values into 4 groups: concordant positive group (FFR ≤ 0.80 and dPR ≤ 0.89), concordant negative group (FFR > 0.80 and dPR > 0.89), discordant FFR+/dPR− group (FFR ≤ 0.80 and dPR > 0.89), and discordant FFR−/dPR+ group (FFR > 0.80 and dPR ≤ 0.89).

Statistical analysis

Continuous variables are expressed as mean and standard deviation, while categorical variables are expressed as percentages. We measured the association between continuous variables using Pearson's correlation coefficient. To determine differences in variables in the FFR/dPR concordance groups we used ANOVA (for continuous variables) and the chi-square test (for categorical variables). We used the chi-square test to assess how each variable impacted FFR−/dPR+ and FFR+/dPR− discrepancies, and a multiple logistic regression model with backward elimination to determine the factors impacting FFR−/dPR+ and FFR+/dPR− discrepancies. On univariate analysis, we included variables with $P < .1$ in the logistic regression analysis and excluded those with a total n < 10. The analysis was conducted using SPSS software (version 20.1) and R (version 4.0.4).

RESULTS

We included a total of 428 stenoses in 361 patients. Table 1 and table 2 show the patients' baseline characteristics, clinical presentation, and procedural characteristics.

Sixty-seven percent of the patients received intracoronary adenosine; the mean doses of intracoronary adenosine administered were 324 µg (standard deviation [SD] ± 152) via the right coronary artery and 442 µg (SD ± 234) via the left coronary artery.

The medians of dPR measurements were 0.90 and 0.90 (SD ± 0.08) for the first and second measurements, with positivity rates of 27.4% and 27.9%, respectively. For FFR, the medians were 0.83 and 0.83 (SD ± 0.08) for the first and second measurements, with positivity rates of 28.1% and 30%, respectively.

The most widely studied vessel was the left anterior descending coronary artery (63%), followed by the left circumflex (20%) and right coronary arteries (16%).

The left anterior descending coronary artery showed a higher positivity rate (dPR+, 35.3%; FFR, 34%) than the left circumflex (dPR, 11.9%; FFR, 20.5%) and right coronary arteries (dPR, 15.9%; FFR, 17.4%).

Diagnostic reproducibility was 95.8% for dPR, with a correlation coefficient between the 2 measurements (dPR1 and dPR2) of 0.974 ($P < .0001$) and a mean difference of 0.019 (max, 0.12; min, −0.17). For dPR values < 0.86 or > 0.92, diagnostic reproducibility was 99.6%, decreasing to 90.7% when values were ≥ 0.86 or ≤ 0.92. For FFR, diagnostic reproducibility was 94.9%, with a correlation coefficient (FFR1 and FFR2) of 0.942 ($P < .0001$) and a mean difference

Table 1. Patients' baseline characteristics

	N = 361
Age (years)	65.80 ± 10.5
Male sex	76.9
Hypertension	63.3
Diabetes mellitus	31
Hypercholesterolemia	60.4
Active/former smoker	19.7/40.5
Previous acute coronary syndrome	30.5
Atrial fibrillation	14.7
Heart failure/dysfunction	15.4
Peripheral artery disease	10
Valvular heart disease, previous bypass, stroke	< 6

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

Table 2. Clinical presentation and procedural characteristics

	N = 361
Clinical presentation	N = 361
Chest pain	45.8
Acute coronary syndrome	23.1
Unstable angina	7.1
Left ventricular dysfunction	9.9
Others	14.2
Procedural characteristics	
Baseline systolic blood pressure (mmHg)	132 ± 24
Systolic blood pressure during hyperemia (mmHg)	125 ± 25
Baseline heart rate (bpm)	70 ± 12
Heart rate during hyperemia (bpm)	69 ± 15
Reference luminal diameter (mm)	3.09 ± 0.53
Stenosis (%)	54 ± 8
Lesion length (mm)	17.9 ± 12.2
IV/intracoronary adenosine	33/67
Catheter size (5-Fr/6-Fr)	17.5/81
Drift ≥ ± 0.02	5.7
dPR	0.90 ± 0.08
FFR	0.83 ± 0.08

dPR, diastolic pressure ratio; FFR, fractional flow reserve.
Data are expressed as No. (%) mean ± standard deviation.

of 0.029 (max, 0.14; min, −0.18) (figure 1). Values < 0.77 or > 0.83 showed a diagnostic reproducibility of 98.6%, decreasing to 86.4% when these values were ≥ 0.77 or ≤ 0.83.

The diagnostic concordance (figure 2) between FFR and dPR was 82%, with a correlation coefficient of 0.721 (P < .0001), while diagnostic discordance was 18.2% (FFR+/dPR−, 8.2% and FFR−/dPR+, 10.0%). In the FFR+/dPR− discordant group, FFR was 0.76 ± 0.04 and dPR, 0.93 ± 0.03. In the FFR−/dPR+ discordant group, FFR was 0.84 ± 0.03 and dPR, 0.86 ± 0.03.

Out of the 75 discordant results reported, the measurements at the cutoff value (7 stenoses with FFR 0.80 and 18 stenoses with dPR 0.89) showed a discordance rate of 72%, which decreased as it moved away from the cutoff value (figure 3).

Table 1 of the supplementary data illustrates the association between clinical and anatomical characteristics and the extent of agreement between FFR and dPR.

Out of all the variables analyzed in the multivariate analysis, hypertension (odds ratio [OR], 3.48, 95% confidence interval [95%CI], 1.01-11.98; P = .043) and intracoronary adenosine (OR, 7.04; 95%CI, 1.63-30.3; P = .001) were significantly associated with FFR−/dPR+ discordance. Age younger than 75 years (OR, 4.52; 95%CI, 1.03-20; P = .016) and percent diameter stenosis > 60% (OR, 6.69; 95%CI, 2.79-16; P < .001) were significantly associated with FFR+/dPR− discordance (table 3).

The drift rate was 5.7%.

DISCUSSION

We present the results of the first study conducted with a FOSW capable of measuring the diagnostic variability of 2 consecutive determinations of nonhyperemic and hyperemic indices, as well as the diagnostic discordance between the 2 techniques.

Previous discordance studies between the 2 indices with PPSW revealed discordance rates ranging from 12% to 22%,[12,13] largely depending on the proximity of the values to the cutoff point. In a study by Lee et al.,[12] the mean iFR and FFR values were 0.95 ± 0.10 and 0.87 ± 0.11, respectively, with a discordance rate of 12%, while in a study by Warisawa et al.,[13] the mean iFR and FFR values were 0.89 ± 0.05 and 0.80 ± 0.03, respectively, with a discordance rate of 22%. In our study, the discordance rate was 18.2%, with a mean dPR of 0.90 (SD ± 0.08) and a mean FFR of 0.83 (SD ± 0.08), which is a slightly lower discordance rate than that reported by previous studies on PPSW and mean iFR and FFR values close to the cutoff point, which may be indicative of the accuracy of measurements obtained with FOSW.

The main findings of this study were the excellent diagnostic reproducibility of the FOSW, the clinical and anatomical variables related to FFR/dPR discordance, and the low drift rate reported in the measurements.

Diagnostic reproducibility with the fiber-optic sensor wire

Diagnostic reproducibility with the FOSW was excellent, with a variation between 2 consecutive measurements < 0.02 for dPR and < 0.03 for FFR. This accuracy in measurement confers excellent diagnostic reproducibility. These data are better than those previously reported with PPSW.[11]

Clinical and anatomical variables associated with FFR/dPR discordance

For FFR+/dPR− discordance, in the multivariate analysis, only age younger than 75 years and percent diameter stenosis > 60% were significantly associated with FFR+/dPR− discordance. This discordance in participants younger than 75 years could be explained by a slower baseline flow and a greater coronary flow reserve in younger patients with preserved microvascular function.[14,15] Although discordance due to a higher percent diameter stenosis has already been described in previous studies,[15,16] such discordance requires a preserved coronary flow reserve.[6] When arterial flow velocity

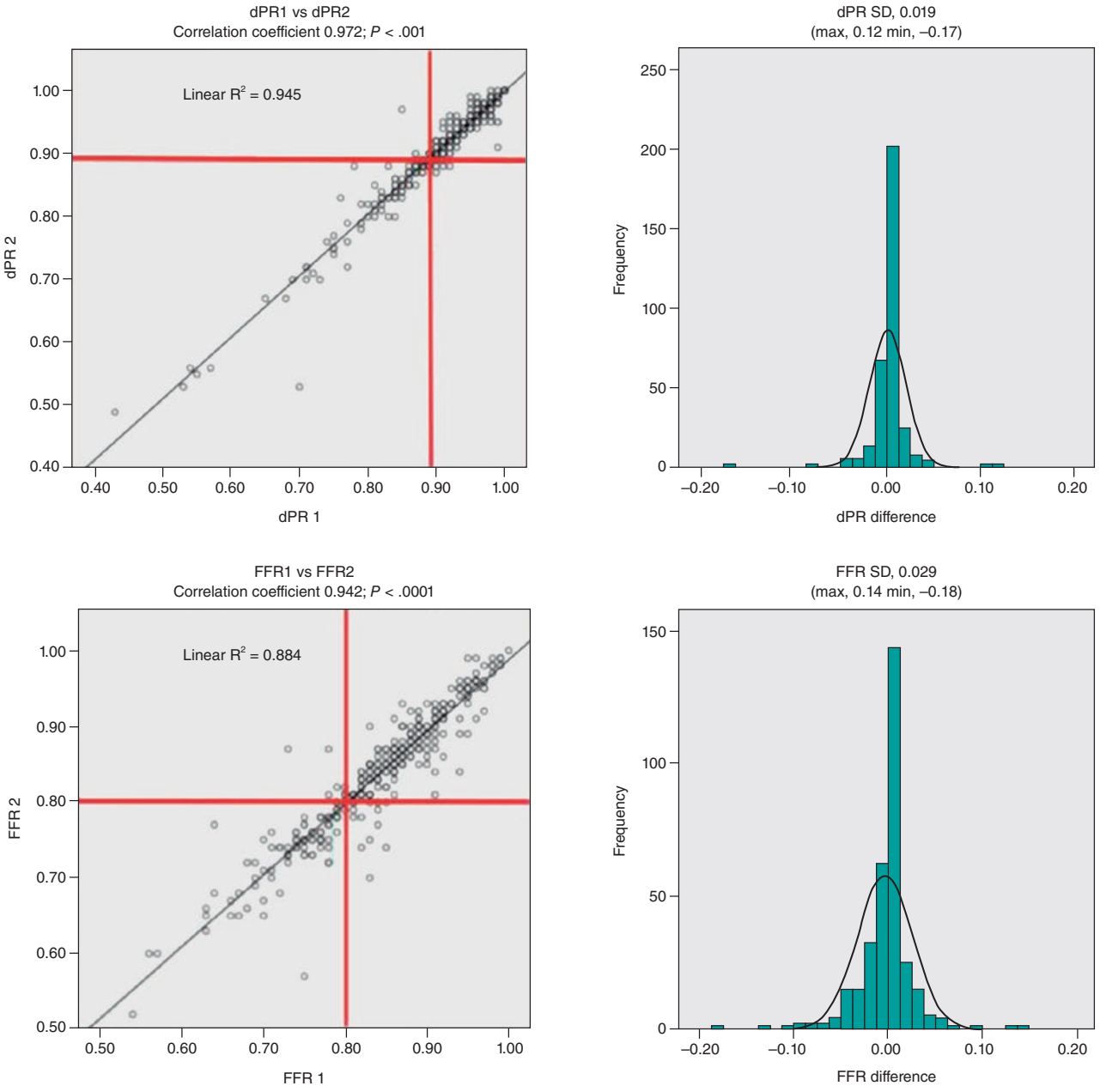

Figure 1. Correlation coefficient and histogram of the differences between the 2 dPR and FFR measurements. dPR, diastolic pressure ratio; FFR, fractional flow reserve; SD, standard deviation.

significantly increases during hyperemia, the pressure gradient does so too, decreasing distal coronary pressure during hyperemia substantially compared with baseline values, resulting in a low FFR value.

For FFR−/dPR+ discordance, in the multivariate analysis, the associated variables were hypertension and the administration of intracoronary adenosine. Although hypertension has not been associated with FFR−/dPR+ discordance in previous studies, it is known that patients with hypertension and left ventricular hypertrophy have a reduced coronary flow reserve[17] and a possible lack of vasodilatory response to adenosine due to an increased left ventricular end-diastolic pressure. These 2 factors could play a key role in the association between hypertension and FFR−/dPR+ discordance.

Although IV adenosine is the most widely studied route of administration to achieve maximum hyperemia, intracoronary adenosine at doses > 300 µg may be equally or more effective in achieving maximum hyperemia[18] and with fewer adverse events.[19] In our study, the FFR−/dPR+ discordance reported when intracoronary adenosine was used could be a result of a failure to achieve adequate hyperemia.

These variables related to discordance demonstrate that dPR and FFR measure different aspects of coronary circulation, which may be affected differently in distinct patients or myocardial territories, leading to discordant FFR values and nonhyperemic indices.[20]

Drift in the fiber-optic pressure wire

The incidence of drift in clinical studies of pressure wires is not well known, and the drift considered acceptable has varied over

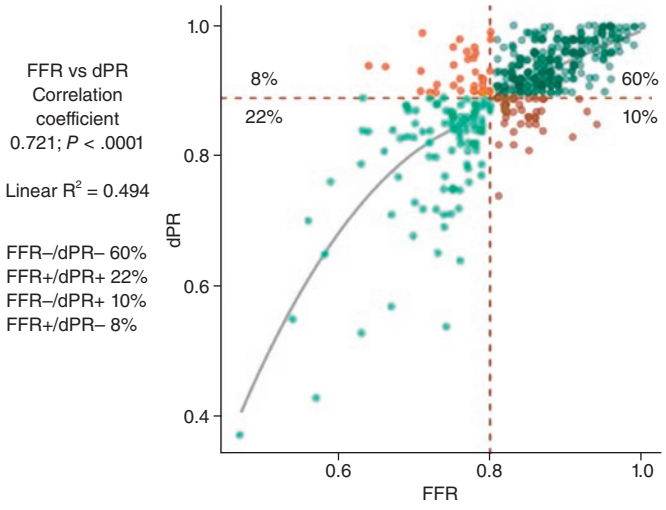

Figure 2. Distribution of lesions according to FFR and dPR, with the rate of concordant and discordant measurements. dPR, diastolic pressure ratio; FFR, fractional flow reserve.

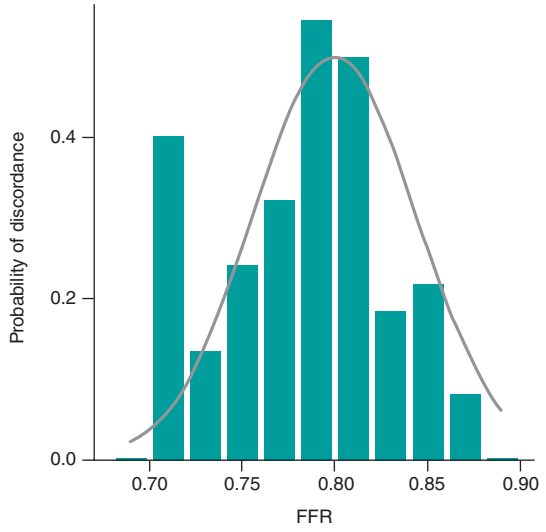

Figure 3. Probability of diagnostic discordance between FFR and dPR. The probability of discordance is close to 50% around the FFR cutoff point of 0.80 and decreases as it moves away from this point. Empirical model (bar chart) and model proposed by Petraco et al.[11] (in grey). dPR, diastolic pressure ratio; FFR, fractional flow reserve.

the years. Previously, FFR measurement was repeated when drift was > 5 mmHg,[21] while in more recent studies, drift > 3 mmHg has been considered significant. When FFR is between 0.77 and 0.82, drift ≤ 3 mmHg can reclassify 18.7% of stenoses,[22] and this reclassification may be higher when a nonhyperemic diastolic or whole-cycle index is used.[23] In the CONTRAST trial analysis of the PPSW, the drift rate (Pd/Pa ± 0.03) was 17.5%,[24] while a more recent study comparing drift between FOSW and PPSW revealed a significantly lower rate with the FOSW (4.8% vs 26.7%; $P = .02$).[9] In our study, the drift rate was 5.7%, which is consistent with other studies on FOSW, and much lower than that reported with PPSW, facilitating the use of pressure wire in routine clinical practice.

Limitations

Our study has several limitations. Both the severity and length of coronary lesions were quantified by the operator's visual estimation at the time of the procedure, and since this was a study without a core laboratory, we cannot rule out the possibility that some of the discrepancies found were due to technical problems in determining the indices. Since the study was based on our routine clinical practice, most patients received intracoronary adenosine, and the protocol did not specify the intracoronary infusion comprehensively, which may have resulted in the lower hyperemia reported in some patients.

Target lesion revascularization was based on dPR or FFR values according to the operators' decision. Patient selection for pressure guidance evaluation was also left to the treating physician's discretion, which may have resulted in biases. However, our intention was to study dPR and FFR indices under real-world conditions.

CONCLUSIONS

Although FFR and dPR measurements with FOSW have excellent reproducibility and a low incidence of drift, the discordance rate remains similar to that reported by previous studies with PPSW, and largely depends on the proximity of values to the cutoff point. Intracoronary adenosine and hypertension, which imply a lack of hyperemia or increased microvascular resistance, are associated with FFR–/dPR+ discordance. Age younger than 75 years and the severity of stenosis, which may be associated with a preserved coronary flow reserve, are related to FFR+/dPR– discordance.

FUNDING

This study received no funding.

ETHICAL CONSIDERATIONS

This study was approved by the Drugs Research Ethics Committee of the Basque Country (internal code PS 2019039) for its implementation. All patients received a patient information sheet about the study and signed an informed consent form before enrollment. The study took into consideration sex and gender variables before drafting this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used.

AUTHORS' CONTRIBUTIONS

M. Sádaba Sagredo drafted the protocol, included patients as the lead investigator of his center, and drafted the manuscript. A. Subinas Elorriaga and A. Quirós contributed to the statistical analysis and drafting of the manuscript. The remaining authors are lead investigators of the READI EPIC-14 trial in their respective centers and contributed to patient inclusion and article review.

CONFLICTS OF INTEREST

None declared.

Tabla 3. Univariate analysis and multivariate logistic regression of variables associated with discordance

Variables	FFR+/dPR–				FFR–/dPR+			
	Univariate analysis		Multivariate logistic regression		Univariate analysis		Multivariate logistic regression	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Age < 75 years	9.5 vs 3.3	.039	4.52 (1.03-20)	.016	7.1 vs 8.9	.347		
Female sex	5.7 vs 8.9	.231			11.4 vs 6.2	.079		
Hypertension	7.2 vs 10.4	.178			10 vs 2.2	.002	3.48 (1.01-11.98)	.043
Diabetes mellitus	7.3 vs 8.6	.406			11.7 vs 5.3	.018	2.11 (0.95-4.69)	.064
Dyslipidemia	7.5 vs 9.5	.304			7.1 vs 6.7	.525		
HF/LV dysfunction	4.4 vs 9.0	.154			11.8 vs 6.7	.118		
Valvular heart disease	7.7 vs 8.3	.635			19.2 vs 6.8	.037		
Coronary calcification	6.7 vs 8.6	.387			5.3 vs 8	.302		
Moderate/severe tortuosity	7.8 vs 8.3	.516			10.6 vs 5.7	.054		
Left main coronary artery	0 vs 7.9	.612			50 vs 6.9	.007		
Left anterior descending coronary artery	7.9 vs 7.6	.531			9.4 vs 4.4	.041		
Right coronary artery	10.8 vs 7.1	.176			2.4 vs 8.8	.029		
Left circumflex artery	4.3 vs 8.5	.179			2.9 vs 8.4	.081		
RLD > 3 mm	6.6 vs 13.3	.049			7.5 vs 8	.518		
Length > 20 mm	12.5 vs 5.4	.010			7.8 vs 7.3	.492		
Stenosis > 60%	16 vs 3	< .001	6.69 (2.79-16)	< .001	5.8 vs 8.3	.227		
Heart rate > 80 bpm	8.4 vs 8	.527			10.8 vs 6.8	.155		
Intracoronary adenosine	7.4 vs 8.5	.713			13 vs 3.8	.004	7.04 (1.63-30.3)	.001

95%CI, 95% confidence interval; dPR, diastolic pressure ratio; FFR, fractional flow reserve; HF, heart failure; LV, left ventricle; OR, odds ratio; RLD, reference luminal diameter. Data are expresed in %.

WHAT IS KNOWN ABOUT THE TOPIC?

- Determination of fractional flow reserve (FFR) is a widely used technique to establish the functional significance of coronary stenoses. In recent years, resting indices have been developed to assess the functional significance of coronary stenoses without the need for adenosine administration. The optimal cutoff value—equivalent to 0.80 in FFR—has been established at 0.89. Despite its validation in clinical trials and endorsement in clinical practice guidelines, discordant results are obtained in up to 20% of the cases between the 2 techniques.

WHAT DOES THIS STUDY ADD?

- Studies on discordance between hyperemic and nonhyperemic indices are conducted with piezoelectric pressure sensor wires. Fiber-optic sensor wires are not sensitive to temperature or humidity changes, making measurements more reproducible and drift rates very low.
- No previous studies have compared the concordance between hyperemic and nonhyperemic indices with the use of a fiber-optic sensor wire.
- Despite the low diagnostic variability of diastolic pressure ratio (dPR) and FFR (4.2% for dPR and 5.1% for FFR) in 2 consecutive measurements, and a similarly low drift rate (5.7%), the discrepancy between the 2 indices remains similar to that reported by previous studies (18.2%), indicating that discrepancies are more related to clinical and anatomical variables and proximity to the cutoff value than to the pressure wire used.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECIC.M24000448.

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Original article

Safety and efficacy of the Essential Pro paclitaxel drug-eluting balloon for the treatment of coronary in-stent restenosis

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ABSTRACT

Introduction and objectives: Drug-eluting balloons (DEB) are an established treatment option for in-stent restenosis (ISR). This study aimed to assess the safety and efficacy of a novel DEB in patients with ISR.
Methods: This prospective, single-center study enrolled a consecutive cohort of patients diagnosed with ISR who underwent coronary angioplasty with a new second-generation paclitaxel-eluting balloon. The 3 main endpoints were myocardial infarction, target lesion revascularization, and target vessel revascularization. Baseline variables were collected, including patient and procedure characteristics. Follow-up data were collected through medical records or telephone contact.
Results: The study included 160 consecutive patients with 206 treated lesions (mean age, 71.4 ± 14.9 years, 15.5% women) undergoing percutaneous coronary intervention with DEB for ISR. A total of 53.3% of patients had acute coronary syndrome. The average diameter of the treated vessel was 3.10 ± 0.7 mm. The DEB used had a mean diameter of 3.1 ± 0.6 mm and a mean length of 23.1 ± 6.8 mm. Predilatation was performed in 98% of the lesions, and a noncompliant balloon was used in 80%. Intracoronary imaging was used in 24% of cases. At the end of the procedure, 98.5% of patients had Thrombolysis in Myocardial Infarction flow grade 3, residual stenosis was > 30% in 3.4%, and dissection occurred in 1.4%. Bail-out stenting was required in 4.8% of patients. Mortality was nil during follow-up (maximum 768 days). The incidence of myocardial infarction, target lesion revascularization, and target vessel revascularization were 5.4% (95%CI, 0.69-10.1), 8.4% (95%CI, 0-17.8), and 14.2% (95%CI, 3.61-24.78), respectively.
Conclusions: In this cohort of patients with ISR treated with DEB, we observed a low rate of adverse events in both the short- and mid-term. These results support the safety and efficacy of this new generation of DEB for treating ISR.

Keywords: In-stent restenosis. Drug-eluting balloon. Paclitaxel.

Eficacia y seguridad del balón liberador de paclitaxel Essential Pro para el tratamiento de la reestenosis intrastent

RESUMEN

Introducción y objetivos: El balón farmacoactivo (BFA) es un tratamiento establecido para tratar la reestenosis intrastent (RIS). El objetivo de este estudio fue valorar la eficacia y la seguridad de un nuevo BFA en pacientes con RIS.
Métodos: Cohorte prospectiva, unicéntrica y consecutiva de pacientes con RIS tratados con angioplastia coronaria con un nuevo balón liberador de paclitaxel de segunda generación. Los 3 eventos principales del estudio fueron infarto de miocardio, revascularización de la lesión diana y revascularización del vaso diana. Se recogieron variables basales, incluidas las características del paciente y del procedimiento. Los datos referentes al seguimiento se obtuvieron de registros médicos o por contacto telefónico.
Resultados: Se incluyeron 160 pacientes consecutivos con 206 lesiones tratadas (71,4 ± 14,9 años, el 15,5% mujeres) que fueron tratados con una intervención coronaria percutánea con BFA debido a RIS. El 53,3% de los pacientes presentaban síndrome coronario agudo. El diámetro medio del vaso tratado fue de 3,1 ± 0,7 mm. El diámetro y la longitud del BFA empleado fueron de 3,1 ± 0,6 mm y 23,1 ± 6,8, respectivamente. El 98% de las lesiones se predilataron y en el 80% se empleó un balón no distensible. El 24% de las angioplastias fueron guiadas por imagen intracoronaria. El 98,5% de los pacientes presentaban un flujo *Thrombolysis in Myocardial Infarction* de grado 3 al final de la angioplastia. Hubo estenosis residual > 30% en el 3,4%, y el 1,4% presentaron

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disección. El 4,8% de los pacientes requirieron *stent* de rescate. Al finalizar el seguimiento (máximo 768 días), ningún paciente había fallecido. Las incidencias de infarto de miocardio, de revascularización de la lesión diana y de revascularización del vaso diana fueron del 5,4% (IC95%, 0,69-10,1), el 8,4% (IC95%, 0-17,8) y el 14,2% (IC95%, 3,61-24,78), respectivamente.
Conclusiones: En esta cohorte de pacientes con RIS tratados con BFA se observa una baja tasa de eventos clínicos adversos, tanto a corto como a mediano plazo. Estos resultados respaldan la eficacia y la seguridad de esta nueva generación de BFA para pacientes con RIS.

Palabras clave: Reestenosis intrastent. Balón farmacoactivo. Paclitaxel.

Abbreviations

DEB: *drug-eluting balloon*. **ISR**: *in-stent restenosis*. **TLR**: *target lesion revascularization*. **TVR**: *target vessel revascularization.*

INTRODUCTION

Patients with coronary in-stent restenosis (ISR) represent a clinical challenge.[1] Evidence indicates that these patients are at increased risk of recurrent symptoms, myocardial infarction, and repeated coronary revascularizations.[2] The use of drug-eluting balloons (DEB) is a novel alternative therapeutic strategy in patients with ISR.[1,3,4] The effect of DEBs in coronary angioplasty is based on the rapid and uniform transfer of antiproliferative drugs into the vessel wall using a single balloon through a lipophilic matrix without the need for permanent implants.[5]

Over time, new DEB technologies are developed and launched onto the market. The Essential Pro (iVascular, Spain) is a paclitaxel-eluting balloon catheter with advancements to enhance catheter pushability and drug delivery. We believe it is essential to report outcomes from real-world settings. In this study, we report our findings on the safety and efficacy of this new DEB in patients with ISR.

METHODS

Design and population

This prospective, single-center study included a cohort of consecutive patients undergoing DEB angioplasty with the Essential Pro. The center treating these patients performs more than 1500 percutaneous coronary interventions per year. The 2 inclusion criteria for this analysis were: *a)* use of an Essential Pro DEB and *b)* its application for ISR treatment. ISR was defined as stenosis more than 50% within the stented segment, and treatment was indicated according to the treating physician's judgment.[6] The use of the Essential Pro DEB was prioritized during the study period to treat all eligible patients for DEB angioplasty, while other DEB devices were rarely used due to inventory constraints. There were no exclusion criteria. Patients may have undergone stent coronary angioplasty of other lesions in the same or a different setting.

Drug-eluting balloon characteristics

The Essential Pro is a paclitaxel-eluting balloon with a uniform 3 µg/mm^2 eluting formulation, consisting of paclitaxel (80%) and a biocompatible amphiphilic excipient (20%).[7] The balloon incorporates the proprietary TransferTech technology (iVascular, Spain), which is based on the ultrasonic deposition of nanodrops, followed by a dry-off process, resulting in a homogeneous microcrystalline drug coating. This allows more uniform and complete treatment of the vessel with the antiproliferative drug. The microcrystalline structure, coupled with the lipophilic nature of both paclitaxel and the excipient, facilitates drug transfer within 45 to 60 seconds. The Essential Pro balloon has been designed with a smooth transition and a very low tip profile of 0.016 inches, enhancing flexibility, trackability, and device crossability. The balloon is compatible with 5-Fr sheaths in all available diameters.

Procedures

All procedures and decisions in this study reflect real-world clinical practice. Therefore, clinical indications, the use and selection of DEBs, procedural steps, and medical treatments were decided by treating physicians without following any specific guidelines. All coronary angiograms performed during follow-up were part of routine clinical practice and were assessed by our research team when available. Baseline and follow-up data were collected in a single anonymized dedicated database. Procedural aspects, as well as both baseline and follow-up angiograms, were independently evaluated by 3 different interventional cardiologists. Physicians were trained to consult senior staff if they had doubts when assessing angiograms or clinical records. Follow-up was conducted using clinical records, and patients with no on-site clinical visits during follow-up were contacted by telephone following standard clinical practice in our institution. This study was approved by our local institutional review board and patients provided consent for the use of their anonymized information for research purposes before inclusion. This was an investigator-initiated study with no sponsoring or funding.

Outcome definitions

Device delivery was defined as successful DEB insufflation in the affected coronary segment. Procedural, angiographic, and other standard outcomes were defined according to the Second Academic Research Consortium criteria.[8] Cardiovascular mortality was defined as any death without a clear noncardiovascular cause. Acute myocardial infarction was defined as any myocardial infarction meeting the fourth version of the Universal Myocardial Infarction Criteria.[9] Target lesion revascularization (TLR) was defined as any revascularization within or 5 mm beyond the treated segment.[8] Target vessel revascularization (TVR) was defined as revascularization of the index treated vessel.[8] Coronary-related hospitalization was defined as a new hospitalization in which a coronary origin was suspected as the main reason for admission. The 3 main efficacy outcomes were myocardial infarction, TLR, and TVR.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables as mean ± standard deviation (SD) when appropriate. Since the same patient may receive more than 1 DEB (for the same or different territory), the denominator for balloon-specific variables was based on the total DEBs used (such as treated vessel, vessel diameter, DEB diameter, and length), while the denominator of patient-level variables (such as age, sex, or clinical outcomes) was each single individual. Clinical outcomes during follow-up are presented at 30 days, 1 year, and total follow-up. The Kaplan-Meier method was used for estimating both the total follow-up risk and generating survival curves. Data were analyzed using IBM SPSS Statistics 25.

RESULTS

From December 2020 to June 2023, 290 patients with 352 coronary lesions were treated with DEB. Among them, 160 patients (206 lesions) underwent DEB angioplasty due to ISR. Out of the 160 patients receiving DEB for ISR, 46 patients (29%) received more than 1 DEB angioplasty for ISR, either during the same procedure or staged to a different lesion.

The patients' baseline characteristics are summarized in table 1. The mean age was 71.4 ± 14.9 years, 15.5% were women, and 35.5% had diabetes. Clinical presentation was stable angina in 29.7%, unstable angina in 30.5%, non–ST-segment elevation myocardial infarction in 9.9%, ST-segment elevation myocardial infarction in 12.9%, and 16.7% were asymptomatic.

Procedural characteristics are detailed in table 2. The most commonly treated vessel was the left anterior descending artery (48.7%), followed by the left circumflex (30.7%), and the right coronary artery (17%). Bifurcation was present in 10.7%. Lesion preparation was performed in 98.2% of cases (80% with a noncompliant balloon). Intracoronary imaging was used in 24% of patients. None of the patients underwent rotational atherectomy, and 2.4% underwent balloon lithotripsy before DEB delivery. The mean vessel diameter was 3.1 ± 0.65 mm. The mean DEB diameter was 3.1 ± 0.6 mm, and the mean length was 23.1 ± 6.8 mm. Device delivery was successful in 100% of cases (figure 1). The final angiographic assessment revealed a final dissection in 1.4%, Thrombolysis in Myocardial Infarction flow less than 3 in 1.5%, and residual stenosis more than 30% in 3.4%. Bail-out stenting was needed in 4.8%.

After discharge, 93.3% of the patients were successfully contacted. The median follow-up was 361 days, including censored patients, with a maximum of 768 days. At 30 days of follow-up, there were no deaths or TLR, there was 1 myocardial infarction (0.6%), TVR occurred in 0.6%, and 6 patients were readmitted to hospital due to a coronary syndrome (4.1%). At the 1-year follow-up, mortality was 0%, myocardial infarction occurred in 3.4%, TLR in 2.5%, TVR in 6.3%, and coronary-related rehospitalizations in 11.8%. At 18 months, the TLR rate was 4.3%. When all available follow-up was included (figure 2), mortality was 0%, myocardial infarction occurred in 5.4% (95% confidence interval [95%CI], 0.69-10.1), TLR in 8.4% (95%CI, 0-17.8), and TVR in 14.2% (95%CI, 3.61-24.78). During follow-up, none of the patients underwent surgical revascularization.

Table 1. Baseline characteristics

Patient characteristics	
Age, y	71.4 (14.9)
Sex women	20 (15.5)
BMI, kg/m^2	29.2 (10.5)
Hypertension	115 (87.7)
Active smoking	8 (6.1)
Diabetes mellitus	46 (35.3)
Previous MI	67 (51.5)
Previous CABG	26 (20)
Reduced LVEF (< 30%)	10 (7.6)
Laboratory parameters	
Hemoglobin, g/dL	13.9 (1.5)
GFR, mL/min/1.73 m^2	82.9 (25.4)
Active medication	
Aspirin	110 (84.6)
Clopidogrel	75 (57.6)
Ticagrelor	3 (2.3)
Prasugrel	2 (1.5)
Anticoagulation	20 (15.2)
Clinical presentation	
Silent ischemia	22 (16.7)
Stable angina	39 (29.7)
Unstable angina	40 (30.5)
NSTEMI	13 (9.9)
STEMI	17 (12.9)

BMI, body mass index; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as No. (%).

DISCUSSION

This is the first study to describe a real-world experience with the Essential Pro DEB for the treatment of ISR. In this cohort, all attempts at DEB delivery were successful, and less than 1 in 20 patients required bail-out stenting. The use of this new-generation DEB catheter was associated with high efficacy and a low incidence of adverse clinical outcomes during follow-up.

Patients with ISR are at higher risk of recurrent events than those undergoing non-ISR angioplasty.[10] The annual rate of ISR requiring TLR is around 2%,[3] representing up to 11% of all percutaneous coronary interventions performed in the United States.[11,12] Notably, 52% of patients presenting with symptomatic ISR have unstable angina, and up to 27% have an acute myocardial infarction.[12] Therefore, ISR poses a significant clinical challenge due to both its frequency and severity. The use of DEB in the ISR scenario avoids the addition of extra stent layers, which may have detrimental effects in the long term.

The use of DEB in ISR poses certain challenges. DEB platforms commonly have lower lesion crossability than regular coronary

Table 2. Characteristics of the treated lesion

Treated vessel	
LAD	100 (48.7)
LCx	63 (30.7)
Right coronary artery	35 (17)
Left main coronary artery	5 (2.4)
Graft	2 (0.9)
Anatomical characteristics	
Bifurcation lesion	22 (10.7)
Vessel diameter, mm	3.1 (0.65)
Procedural characteristics	
IVUS-guided PCI	51 (24)
Lesion predilatation	202 (98)
Predilatation with NC balloon	165 (80)
Intravascular lithotripsy	5 (2.4)
DEB diameter, mm	3.1 (0.6)
DEB length, mm	23.1 (6.8)
Result after DEB PCI	
Vessel dissection	3 (1.4)
TIMI flow 3	203 (98.5)
Residual stenosis > 30%	194 (3.4)
Bail-out stenting	10 (4.8)

DEB, drug-eluting balloon; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex artery; NC, noncompliant; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction. Data are expressed as No. (%).

balloon catheters. DEBs also have larger profiles than conventional balloons making it difficult to cross the lesion and requiring aggressive maneuvers that could lead to a loss of coating drug during delivery.[13] However, in our study, all attempted DEB deployments were successful. This high success rate may be due to improvements in second-generation DEBs, as well as better lesion evaluation and lesion preparation.

In the present study, TLR occurred in 2.5% of the patients and TVR in 6.3% at 1 year, while TLR occurred in 4.3% at 18 months. This event rate may seem low when compared with a prior systematic review of randomized and observational studies, which reported a TVR rate after DEB treatment of 11.3% with a calculated weighted mean follow-up of 18 months.[14] In a recent investigational device exemption randomized trial for a paclitaxel-coated balloon in ISR, the rate of TLR at 1 year was 13%.[15] However, prior evidence stems from diverse settings, designs, and populations, making it difficult to draw strong conclusions.

The rate of TLR with the previous generation of the Essential Pro DEB in a smaller cohort (n = 31) was 10% at 6 months.[16] While this rate may seem higher than that reported in our study, the small number of events (n = 3) makes comparisons challenging.

Limitations

This study has some limitations. First, it was based on a real-world cohort involving different operators from the same center, which does not follow specific protocols. Only a quarter of the patients underwent angioplasty assessment guided by intracoronary imaging. The lack of sponsorship to cover intracoronary imaging costs and its limited use reflects the usual clinical practice of this center. During the performance of this study, few patients with ISR were treated with other DEB catheters due to the lack of specific DEB sizes in stock. Since this situation was rare and was unrelated to clinical or medical coverage characteristics, it is unlikely to introduce significant bias. Since this was a substudy of a larger DEB cohort, some variables specific to ISR, such as the time from prior stent implantation or the type of stent used, were not available.

Second, there were no dedicated follow-up visits for this study. Although most of these patients were followed up by local cardiologists who maintained regular medical records, some required telephone contact for follow-up. Third, angiographic assessment was not duplicated, and no core lab was available. Finally, the number of events was low despite consecutive enrollment from late 2020, impacting the precision of Kaplan-Meier estimates for key clinical outcomes. Some limitations are related to real-world practice

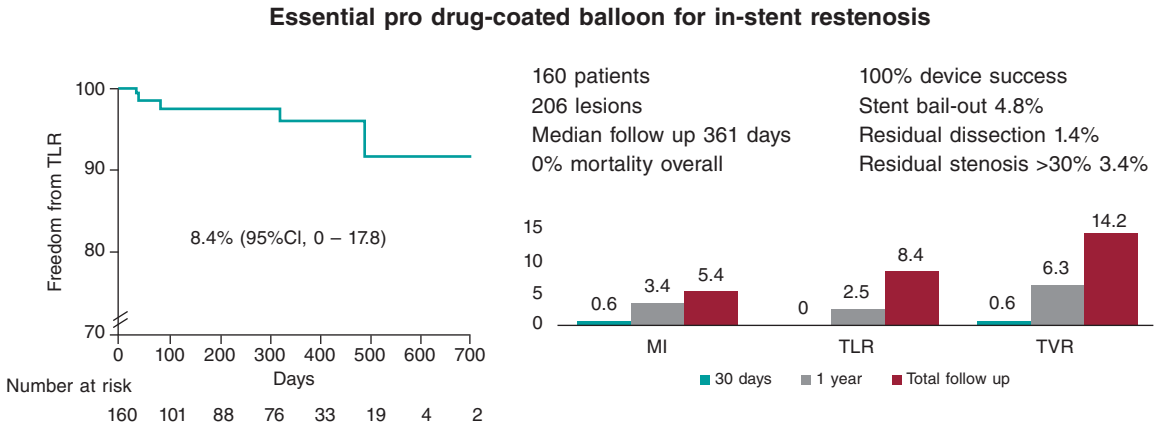

Figure 1. Central illustration. Main findings on the safety and efficacy of the Essential Pro drug-eluting balloon in patients with in-stent restenosis. Kaplan-Meier shows freedom from TLR. MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

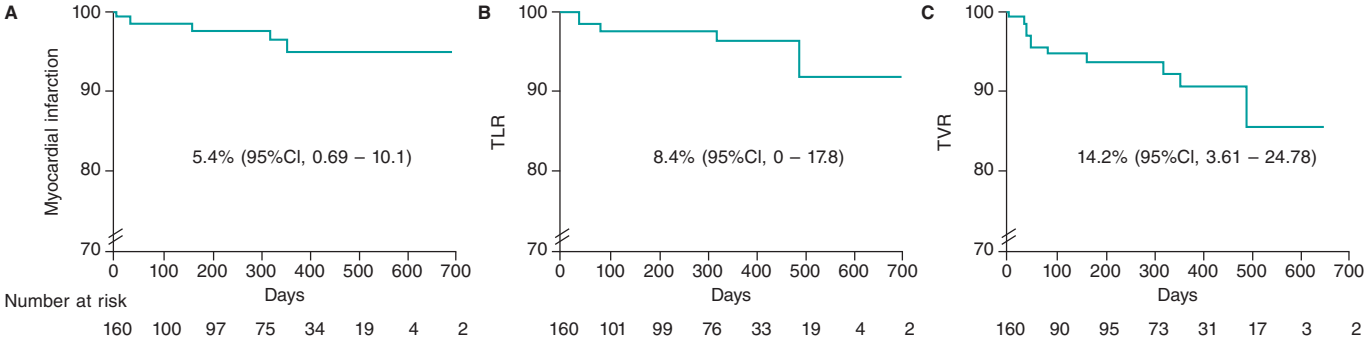

Figure 2. Survival curves of key clinical outcomes. Kaplan-Meier estimates for survival free from myocardial infarction (A), target lesion revascularization (B), and target vessel revascularization (C) in days. 95%CI, 95% confidence interval; TLR, target lesion revascularization; TVR, target vessel revascularization.

settings, which, on the other hand, enhance external validity with less selection bias compared with other more controlled designs.

CONCLUSIONS

Among patients with ISR, the Essential Pro DEB catheter had a high delivery rate and a low incidence of adverse clinical outcomes during follow-up. These results further underscore the safety and efficacy of this new-generation DEB for patients with ISR.

FUNDING

This work received no industry sponsoring or funding.

ETHICAL CONSIDERATIONS

This study was approved by our local institutional review board at the Instituto Cardiovascular de Buenos Aires, and patients provided written informed consent to use their anonymized information for research purposes before their inclusion. Possible sex/gender biases have been considered in the preparation of this paper.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used in the preparation of this study.

AUTHORS' CONTRIBUTIONS

L. Padilla conceived and oversaw all the process. F. Liberman, J. Tello, P. Rosas, P. Spaletra, G. Pedernera, P. Mascolo, S. Ordoñez, P. Santilli, and A. Candiello collected data and analyzed coronary angiograms. F. Cura and J. Belardi provided senior advice. P. Lamelas performed the statistical analysis and generated the first draft of the manuscript.

CONFLICTS OF INTEREST

L. Padilla has received proctoring and consulting honoraria from Terumo and Boston Scientific. P. Spaletra has received honoraria from Boston Scientific. F. Cura has received honoraria from Medtronic, Boston Scientific, Terumo, and Meril. P. Lamelas has received proctoring and consulting honoraria from Medtronic, Boston Scientific, Meril, Microport. The remaining authors have no conflicts of interest to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

– Patients with ISR are at high risk of recurrent events and are commonly treated with DEB. New or newer generation DEBs are frequently launched onto the market. It is important to report the real-world safety and efficacy of interventional devices. The Essential Pro is a second-generation paclitaxel-eluting balloon. Enhancements of this DEB include improvements in forward pushability, crossover capacity, and drug delivery capabilities.

WHAT DOES THIS STUDY ADD?

– Using this new-generation DEB, all attempts at treating ISR (n = 206) were successful. Intravascular ultrasound was used in 24%. The incidence of adverse events, from the procedure to mid-term follow-up, was infrequent and probably lower than that previously reported. These real-world results emphasize the safety and efficacy of this novel generation DEB for patients with ISR.

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Original article

Reperfusion therapies in patients with intermediate- and high-risk pulmonary embolism: insights from a multicenter registry

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ABSTRACT

Introduction and objectives: Most patients with acute pulmonary embolism (PE) receive anticoagulation only. Reperfusion is required in high-risk and a minority of intermediate-risk PE patients. Systemic thrombolysis (ST) is the first-line reperfusion therapy, but due to contraindications and major bleeding concerns, the use of catheter-directed therapies (CDT) is increasing as a suitable alternative. The objective of the present study was to detect predictors of the use of CDT compared with other therapies in patients with acute PE.
Methods: This registry included consecutive intermediate- and high-risk PE patients in 2 tertiary centers with a 24/7 PE response team from 2014 to 2022. The patients were grouped according to the primary treatment: anticoagulation only, CDT, or ST. We evaluated predictors of treatment assignment and safety endpoints.
Results: A total of 274 patients were included. Of them, 112 received anticoagulation only, 96 received ST as the primary treatment, and 66 underwent CDT first. Comorbidities were higher in the CDT group than in the other 2 groups. Patients undergoing ST/CDT had higher PE severity parameters at hospital admission. On multivariable analysis, independent predictors for the use of CDT were Charlson Comorbidity Index (OR, 1.29; 95%CI, 1.05-1.59), recent surgery (OR, 11.07; 95%CI, 3.07-39.87), and bilateral central PE (OR, 2.42; 95%CI, 1.10-5.32). Analysis of early safety outcomes showed that intracranial bleeding occurred only in the ST group (1.8% of patients).
Conclusions: This contemporary registry used CDT as the primary treatment in 24% of intermediate- and high-risk patients, mainly in comorbid and postsurgical patients. CDT was a safe and effective alternative to medical therapy in selected patients.

Keywords: Catheter-directed therapies. Pulmonary embolism. Systemic thrombolysis. Anticoagulation. Local thrombolysis.

Terapias de reperfusión en pacientes con embolia de pulmón de riesgo intermedio-alto y de riesgo alto: datos de un registro multicéntrico

RESUMEN

Introducción y objetivos: La mayoría de los pacientes con embolia pulmonar (EP) aguda reciben únicamente anticoagulación. La reperfusión es necesaria en los pacientes con EP de alto riesgo y en una minoría de pacientes con EP de riesgo intermedio-alto. La trombólisis sistémica (TS) es el tratamiento de reperfusión de primera línea, pero debido a las contraindicaciones y a la preocupación por las hemorragias graves, las terapias dirigidas por catéter (TDC) están surgiendo como una alternativa adecuada. El objetivo del presente estudio fue detectar predictores del uso de TDC con respecto a otras terapias en pacientes con EP aguda.
Métodos: Este registro incluyó pacientes consecutivos con EP de riesgo intermedio y alto en dos centros terciarios, con un equipo de respuesta a la EP, desde 2014 hasta 2022. Los pacientes se agruparon según la terapia inicial: solo anticoagulación, TDC o TS; y se evaluaron los predictores de selección de terapia y variables de seguridad.

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Resultados: Se incluyó a un total de 274 pacientes. De ellos, 112 recibieron solo anticoagulación, 96 recibieron TS como tratamiento primario y 66 fueron sometidos a TDC en un primer momento. Las comorbilidades fueron mayores en el grupo TDC que en los otros dos. Los pacientes sometidos a TS o TDC presentaban mayores parámetros de gravedad de la EP al ingreso hospitalario. Tras el análisis multivariable, el índice de comorbilidad de Charlson (OR = 1,29; IC95%, 1,05-1,59), la cirugía reciente (OR = 11,07; IC95%, 3,07-39,87) y la EP central bilateral (OR = 2,42; IC95%, 1,10-5,32) siguieron siendo predictores independientes del uso de TDC. En cuanto a los resultados precoces de seguridad, sólo se produjeron hemorragias intracraneales en el grupo TS (1,8% de los pacientes).
Conclusiones: Este registro contemporáneo utilizó TDC como terapia inicial en el 24% de los pacientes de riesgo intermedio y alto, principalmente en pacientes comórbidos y posquirúrgicos. La TDC fue una alternativa segura y eficaz al tratamiento médico en pacientes seleccionados.

Palabras clave: Terapia dirigida por catéter. Intervencionismo dirigido por catéter. Embolia pulmonar. Trombólisis sistémica. Anticoagulación. Trombólisis local.

Abbreviation

AC: anticoagulation alone. **CDT:** catheter-directed therapies. HR: high risk. **IHR:** intermediate-high risk. **PE:** pulmonary embolism. **ST:** systemic thrombolysis.

INTRODUCTION

Pulmonary embolism (PE) is the third leading cause of cardiovascular death and the first avoidable cause of death in hospitalized patients.[1] According to the European Society of Cardiology (ESC) guidelines, the treatment of PE is based on patient risk assessment.[2] Reperfusion therapy with systemic thrombolysis (ST) is indicated as the first-line therapy in patients with high-risk (HR) PE and in those with intermediate-high risk (IHR) PE who deteriorate on anticoagulant drugs.[2] However, ST is underused because of contraindications in roughly 30% of patients and even in those with HR-PE and no formal contraindications.[3-5] Moreover, this therapy carries a significant risk of major bleeding (≈10%-15%), especially in patients with advanced age, recent surgery, or active cancer.[3]

Catheter-directed therapies (CDT) have emerged as an alternative to ST for reperfusion in patients with acute PE.[6-10] These techniques may improve surrogate right parameters of ventricular failure and clinical outcomes with lower bleeding rates. In a meta-analysis of observational studies comparing catheter-directed thrombolysis vs ST, the risk of in-hospital death and intracranial hemorrhage was reduced in patients undergoing percutaneous intervention. [11] The current ESC guidelines state that CDT should be considered in patients with HR-PE an unsuccessful attempt at thrombolysis or a contraindication to this treatment, and as a rescue treatment for IHR-PE patients with clinical deterioration.[2] However, the penetration of interventional therapies is increasing, showing a discrepancy between guideline recommendations and clinical practice.

There is currently scarce evidence in the literature on the contemporary choice of reperfusion therapy, the parameters leading physicians to select one reperfusion therapy over the others, and the target population who may derive the greatest benefit from CDT. Therefore, the main objective of the present study was to identify the clinical factors associated with the choice of CDT as PE therapy in a contemporary cohort of patients with acute PE.

METHODS

Study design

This study was based on an ambispective multicenter registry that included consecutive patients with intermediate-risk (IR) and HR-PE, evaluated by local Pulmonary Embolism Response Teams (PERT), classified according to ESC guidelines,[2] and treated with CDT.[12] Two tertiary care centers also recruited patients evaluated by the PERT and treated medically, as previously reported in a single-center experience.[13] This study analyzed all consecutive patients evaluated by the local PERT in these 2 hospitals from 2014 to 2022.

The inclusion criteria were patients aged more than 18 years with a confirmed diagnosis of acute IR- or HR-PE (by computed tomography or transthoracic echocardiogram plus clinical suspicion in unstable patients unable to undergo computed tomography). We excluded patients with an uncertain diagnosis of PE, those with > 7 days from symptom onset to diagnosis, and those with low-risk PE according to ESC guidelines.[2] The registry was observational, with no recommendation on PE management. Thus, treatment was established according to the criteria of the treating physicians, and the use of CDT was chosen according to availability and the decision of the PERT. The reporting of this study adheres to the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guideline for cohort studies.[14]

Data collection and variable definitions

A secure web-based database stored anonymized data in both centers. Data were self-reported by local investigators from digital clinical records and included vital signs and laboratory values. Initial admission to the cardiac intensive care unit included more granular data with recording of hourly clinical vital signs, shock parameters at admission, and worsening during cardiac intensive care unit admission and subsequently after reperfusion (if the patient underwent reperfusion). After hospital discharge, structured follow-up was conducted with visits at 1-month, 3- to 6-months, and 12-months. However, 30-day follow-up results are included in this study. The right ventricle/left ventricle ratio was mainly derived from computed tomography except in patients with no baseline computed tomography due to instability. Bilateral central PE was diagnosed when a thrombus was detected in both main pulmonary arteries by computed tomography or angiography. PE risk was stratified according to ESC guidelines.[2] In all patients, we calculated the shock index, defined by the heart rate to systolic blood pressure ratio, Pulmonary Embolism Severity Index score,[15] Bova score,[16] and Charlson Comorbidity Index.[17] For most patients

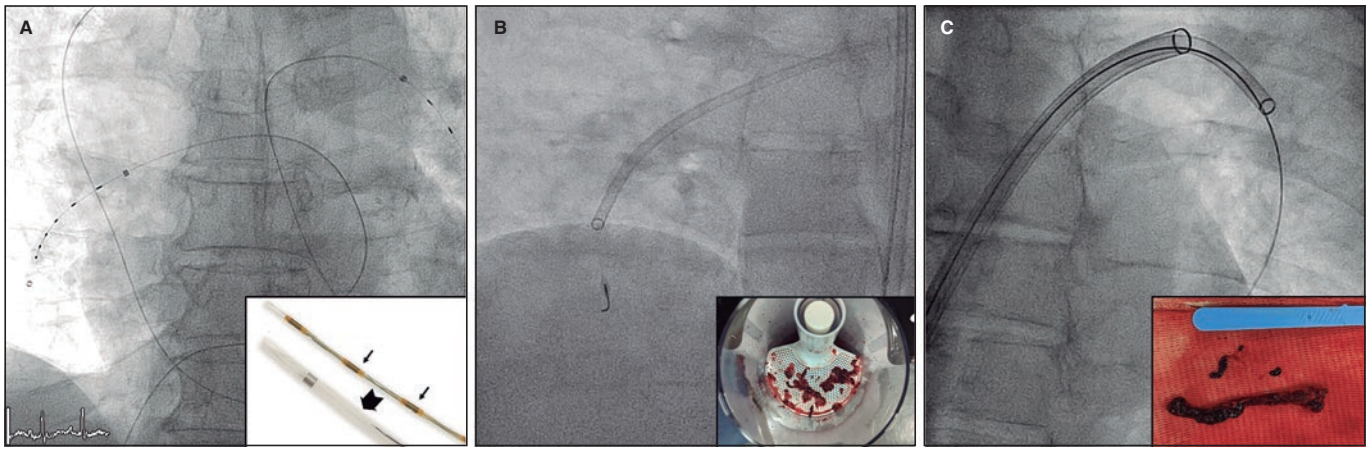

Figure 1. Catheter-directed therapies used in the study. Representative images of catheter-directed therapies. **A:** ultrasound-assisted thrombolysis, EKOS system (Boston Scientific, United States). **B:** percutaneous thrombectomy with Indigo system (Penumbra, United States). **C:** large-bore thrombus aspiration, FlowTriever catheter (Inari, United States).

who underwent CDT, hemodynamic parameters (such as systolic and mean pulmonary artery pressure) were measured invasively, with a catheter placed in the pulmonary artery.

Pulmonary embolism therapies

Parenteral anticoagulation was started immediately after PE diagnosis. ST was given through a peripheral vein following the doses recommended in the ESC guidelines.[2] CDT included: *a)* catheter-directed thrombolysis using a multiperforated catheter(s) inserted into the pulmonary artery and left for 6 to 24 hours to infuse low-dose thrombolytics (usually alteplase 0.25 mg/kg or the tenecteplase equivalent); *b)* mechanical thrombus fragmentation; *c)* thrombus aspiration using either nondedicated catheters (usually 8-Fr coronary guiding catheters) or dedicated catheters (Indigo 8-Fr [Penumbra, United States], Nautilus 10-Fr [iVascular, Spain], or FlowTriever 24-Fr [Inari medical, United States]); or *d)* a combination of them. The dose of fibrinolytic therapy (both for ST and catheter-directed thrombolysis) was decided by the treating physician. See figure 1 for an illustration of different CDT options.

Objectives

The main endpoint of the present study was to detect predictors of the use of CDT in patients with IR- or HR-PE requiring reperfusion therapy. Another endpoint was to compare the characteristics of the patients who received the different therapies for acute PE: anticoagulation alone (AC), ST, or CDT. If more than 1 reperfusion therapy was used, the patients were grouped according to the first administered therapy. The analysis focused on identifying variables associated with the choice of different therapies by the treating physician. Thirty-day all-cause mortality was reported as a safety outcome. We also analyzed in-hospital adverse events, such as bleeding events according to the International Society of Thrombosis and Hemostasis classification[18] and acute kidney injury. In patients undergoing CDT, we also recorded procedural results (eg, hemodynamic improvement).

Ethics and funding

The registry protocol was approved by the clinical research ethics committee at Hospital Clínico San Carlos as the central committee for the registry, following local research regulations (code 18/010-E). All prospectively included patients signed an informed consent form. An informed consent waiver was granted from the ethics research committee for patients recruited retrospectively. The investigation was an academic, unfunded, investigator-initiated study.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Group comparisons (AC, CDT, and ST) for continuous variables were performed using the ANOVA and chi-square tests for categorical variables. Comparisons between groups were performed with the Student t-test or Wilcoxon test, as appropriate, for continuous variables and the chi-square test for categorical variables. The predictors for using the different reperfusion techniques (ie, CDT or ST) were determined using a logistic regression analysis. The univariate analysis included baseline and clinical variables at PE diagnosis. Variables with P values < .10 in the univariable analysis were included in the multivariable model. Paired t-tests were used to analyze the change in hemodynamic parameters after transcatheter procedures. Missing values for covariates, if any, were not imputed. Statistical analyses were performed using Stata 16 (StataCorp, College Station, United States).

RESULTS

Baseline characteristics and risk stratification

From 2014 to 2022, a total of 274 patients were included in the registry (9.5% with intermediate-low risk, 74.7% with IHR, and 15.8% with HR-PE) (figure 2). Of them, 112 patients (40.9%) received AC only: 57% low molecular weight heparin and 43% unfractionated heparin. The remaining 162 patients (59.1%) underwent reperfusion therapy: 35% received ST as the primary treatment and 24% underwent CDT first. Of the ST group, all the patients received alteplase as fibrinolytic treatment and 5 patients underwent rescue CDT after unsuccessful ST. Notably, 58% of IHR-PE patients in our cohort received reperfusion therapies.

Patients' baseline characteristics according to the treatment strategy are shown in table 1. The study was well balanced regarding gender

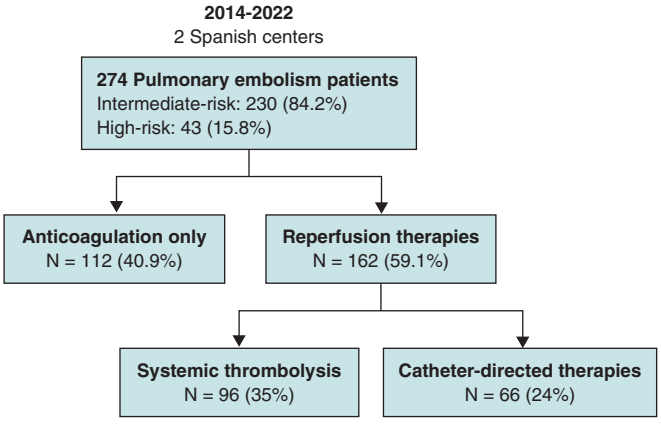

Figure 2. Study patients and selected therapy.

(52% men); however, there were more men in the AC group than in the ST group (58.0% vs 42.7%, $P = .027$). Patients in the AC and CDT groups were significantly older than those in the ST group (65.9 ± 16.2 and 62.3 ± 14.7 vs 57.4 ± 16.6 years, respectively, $P < .001$). Regarding comorbidities, previous cancer was more common among patients in the CDT group than in those in the ST group. The Charlson Comorbidity Index was higher in the CDT group than in the other 2 groups. Among precipitating factors for PE, a history of recent surgery was more frequent in patients in the CDT group than in the other 2 groups, while a recent hospital admission was more frequent in the AC and CDT groups than in the ST group.

Clinical and risk stratification parameters at hospital admission are shown in table 2. Patients who received reperfusion therapies, either with CDT or ST, had higher severity parameters than those in the AC group (eg, shock index, right ventricular involvement, or lactate levels). The Pulmonary Embolism Severity Index score, which incorporates comorbidities and PE severity parameters, was higher in CDT patients than in the other 2 groups ($P < .001$).

Reperfusion therapies

Figure 3 shows the trend in the choice between the 2 primary reperfusion therapies over time. There was a progressive increase in the use of CDT and a consequent decrease in the use of ST. The variables that might have led the treating physicians to choose between the 2 reperfusion therapies are shown in table 3. In the univariate analysis, the variables associated with the choice of CDT instead of ST were those reflecting comorbidities, such as older age, previous cancer, and the Charlson Comorbidity Index. Recent surgery and hospital admission were also associated with the choice of CDT. After multivariable analysis in this cohort of patients with acute PE, the only independent predictors of the choice of CDT over ST were the Charlson Comorbidity Index and recent surgery. In addition, this analysis showed that the presence of bilateral central PE was associated with the treating physician's choice of CDT instead of ST.

Procedural characteristics in the CDT group are displayed in table 4. The median treatment delay from diagnosis of acute PE to percutaneous treatment was 6.0 [interquartile range [IQR], 3.5-19.0] hours and the mean procedure length was 89.0 ± 44.4 minutes. Catheter-directed thrombolysis was used in 35 patients (53.0%), and the most frequently used thrombolytic drug was alteplase (71.4%), with a mean dose of 16.7 ± 7.2 mg. The median bolus dose in patients treated with alteplase was 4 [IQR, 2.9-6.3] mg and the

Table 1. Baseline characteristics

	Total	AC	ST	CDT	*P*			
	N = 274	N = 112	N = 96	N = 66	Global	AC vs ST	AC vs CDT	ST vs CDT
Male sex	142 (51.8%)	65 (58.0%)	41 (42.7%)	36 (54.5%)	.077	**.027**	.650	.138
Age, years	62.1 (16.4)	65.9 (16.2)	57.4 (16.6)	62.3 (14.7)	**< .001**	**< .001**	.136	.056
Body mass index (kg/m^2)	29.4 (6.7)	29.4 (6.0)	29.7 (8.8)	29.2 (5.0)	.921	.765	.890	.724
Obesity	133 (48.5%)	52 (46.4%)	54 (56.3%)	27 (40.9%)	.136	.167	.533	.078
Prior venous thromboembolism	53 (19.4%)	20 (17.9%)	22 (23.2%)	11 (16.7%)	.511	.345	.840	.316
Previous cancer	42 (15.3%)	15 (13.4%)	11 (11.5%)	16 (24.2%)	.065	.674	.065	**.032**
Hypertension	135 (49.5%)	55 (49.1%)	46 (47.9%)	34 (52.3%)	.857	.864	.681	.585
Diabetes mellitus	51 (18.7%)	18 (16.1%)	19 (19.8%)	14 (21.5%)	.628	.484	.362	.788
Heart failure	14 (5.1%)	8 (7.1%)	3 (3.1%)	3 (4.5%)	.411	.197	.487	.638
Chronic kidney disease	20 (7.3%)	10 (8.9%)	4 (4.2%)	6 (9.1%)	.342	.172	.971	.201
Charlson Comorbidity Index	1.0 (1.6)	0.8 (1.4)	0.9 (1.5)	1.5 (1.8)	**.026**	.676	**.010**	**.043**
Recent surgery	35 (12.8%)	12 (10.8%)	4 (4.2%)	19 (28.8%)	**< .001**	.074	**.002**	**<.001**
Recent immobilization	48 (17.5%)	14 (12.5%)	17 (17.7%)	17 (25.8%)	.080	.293	**.024**	.216
Recent hospital admission	28 (10.3%)	14 (12.6%)	4 (4.2%)	10 (15.2%)	**.044**	**.032**	.633	**.014**

AC, anticoagulation; CDT, catheter-directed therapies; ST, systemic thrombolysis.
Data are shown as mean (SD) for continuous variables and No. (%) for categorical variables. *P* values denote the significance of the differences between the groups for continuous variables analyzed by the ANOVA test and Student t-test, as appropriate. The chi-square test was used to assess the significance of between-group differences for categorical variables. Obesity was defined as body mass index ≥ 30 kg/m^2. Statistically significant values are highlighted in bold letters.

Table 2. Risk stratification parameters at hospital admission

	Total	AC	ST	CDT	*P*			
	N = 274	N = 112	N = 96	N = 66	Global	AC vs ST	AC vs CDT	ST vs CDT
Systolic blood pressure, mmHg[a]	118.7 (25.3)	126.8 (23.1)	114.5 (25.9)	110.8 (24.6)	**< .001**	**< .001**	**< .001**	.359
Heart rate, bpm	106.9 (18.8)	99.5 (19.7)	112.9 (16.3)	110.9 (16.2)	**< .001**	**< .001**	**< .001**	.459
Shock Index	0.96 (0.36)	0.82 (0.28)	1.06 (0.39)	1.07 (0.35)	**< .001**	**< .001**	**< .001**	.953
Respiratory failure	71 (28.9%)	28 (26.4%)	29 (34.9%)	14 (24.6%)	.314	.205	.796	.191
Syncope	57 (20.8%)	23 (20.5%)	18 (18.8%)	16 (24.2%)	.696	.747	.564	.399
Deep vein thrombosis	74 (27.6%)	34 (30.6%)	23 (24.5%)	17 (27.0%)	.612	.326	.612	.723
Right ventricular involvement	249 (94.0%)	93 (87.7%)	94 (98.9%)	62 (96.9%)	**.002**	**.002**	**.042**	.346
Bilateral pulmonary embolism	175 (63.9%)	70 (62.5%)	57 (59.4%)	48 (72.7%)	.204	.645	.163	.080
Lactate, mmol/L	2.9 (2.9)	2.2 (2.0)	3.7 (3.8)	3.0 (2.6)	**.006**	**.002**	**.039**	.315
Elevated troponin levels	209 (86.0%)	85 (83.3%)	73 (89.0%)	51 (86.4%)	.539	.271	.600	.642
Elevated NT-proBNP levels	167 (78.4%)	74 (77.9%)	57 (78.1%)	36 (80.0%)	.958	.977	.777	.804
High-risk PE[b]	43 (15.8%)	8 (7.1%)	18 (18.8%)	17 (26.2%)	**.002**	**.012**	**< .001**	.264
PESI score	105.1 (35.1)	97.6 (29.3)	104.9 (36.1)	118.2 (39.4)	**< .001**	.109	**< .001**	**.028**
Bova score	4.7 (1.5)	4.2 (1.5)	5.1 (1.4)	5.0 (1.5)	**< .001**	**< .001**	**.002**	.526

AC, anticoagulation; CDT, catheter-directed therapies; PE, pulmonary embolism; PESI, pulmonary embolism severity index; ST, systemic thrombolysis.
Statistically significant values are highlighted in bold. Data are shown as mean ± standard deviation for continuous variables and No. (%) for categorical variables. *P* values denote the significance of the differences between the groups for continuous variables analyzed by the ANOVA test and Student t-test, as appropriate. The chi-square test tested the significance of between-group differences for categorical variables.
[a]This variable reflects systolic blood pressure at hospital admission, but some of these patients were under vasopressors, and others were stable on admission and later deteriorated hemodynamically.
[b]As defined by the European Society of Cardiology guidelines.

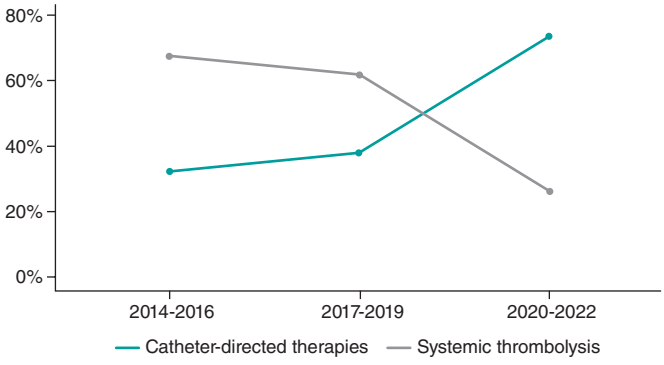

Figure 3. Choice of reperfusion therapy over the years.

median perfusion time of the remaining dose was 16.0 [IQR, 12.0-20.0] hours. In all patients treated with tenecteplase, the drug was administered as a bolus. Thrombus aspiration was performed in 42 patients (63.6%). The most commonly used aspiration devices were coronary catheters (42.9%), followed by FlowTriever catheter (Inari Medical, United States) (38.1%). A combined thrombolysis plus aspiration technique was performed in 11 patients. Systolic pulmonary artery pressure decreased from 57.9 ± 15.4 to 47.6 ± 12.6 mmHg (mean: −10.3 ± 11.3 mmHg, $P < .001$) after the percutaneous procedure, while the mean pulmonary artery pressure decreased from 35.0 ± 9.1 to 28.6 ± 8.8 mmHg (mean: −6.4 ± 6.8 mmHg, $P < .001$). Systolic blood pressure significantly increased after the procedure from 127.8 ± 23.4 to 138.8 ± 22.0 mmHg (mean: +11.0 ± 24.5 mmHg, $P = .028$).

Safety outcomes

Early clinical outcomes and in-hospital events according to the treatment strategy are shown in table 5. The median length of hospitalization was 8 [IQR, 6.0-13.0] days. In-hospital major bleeding, as defined by the International Society of Thrombosis and Hemostasis, occurred in 7 patients (7.3%) in the ST group and in 9 patients (13.6%) in the CDT group. Intracranial bleeding occurred in 5 patients, all of them in the ST group, during hospital admission. Vascular access complications, including minor and major events, were found in 6 (10.6%) of the patients who underwent CDT. Of note, 5 of these patients received catheter-directed thrombolysis (4 with alteplase and 1 with tenecteplase) and the tenecteplase-treated patient underwent aspiration with a nonspecific catheter. One of the vascular complications was a hematoma related to extracorporeal membrane oxygenation implantation and which, therefore, bore no direct relationship with the CDT procedure. The remaining events were 1 incident of femoral access bleeding leading to hypovolemic shock and eventual death (a local thrombolysis CDT case), 2 hematomas requiring transfusion, and another 2 hematomas not requiring transfusion. The incidence of 30-day all-cause mortality was 4.6%, 10.4% and 15.9% for the AC, ST and CDT groups, respectively ($P = .045$). Twenty-two patients died due to hemodynamic or respiratory deterioration related to PE, 2 patients died from anoxic encephalopathy (both in the CDT group), and 1 patient died from severe intracranial bleeding (ST group).

DISCUSSION

The present study explores the clinical characteristics, risk profile and outcomes of patients with IR and HR-PE in 2 tertiary care

Table 3. Univariate and multivariable predictors of the choice of CDT over ST or AC as a first-line therapy in acute pulmonary embolism

	Univariable		Multivariable	
Variables	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Male sex	1.61 (0.86-3.03)	.139		
Age (per year)	1.02 (1.00-1.04)	**.058***		
Body mass index (per kg/m^2)	0.99 (0.94-1.04)	.722		
Prior venous thromboembolism	0.66 (0.30-1.48)	.317		
Previous cancer	2.47 (1.06-5.75)	**.035***		
Hypertension	1.19 (0.63-2.24)	.585		
Diabetes mellitus	1.11 (0.51-2.42)	.788		
Heart failure	1.48 (0.29-7.55)	.640		
Chronic kidney disease	2.30 (0.62-8.49)	.211		
Recent surgery	9.30 (2.99-28.90)	**< .001**	11.07 (3.07-39.87)	**< .001**
Recent immobilization	1.61 (0.75-3.45)	.219		
Recent hospital admission	4.11 (1.23-13.72)	**.022**	1.25 (0.29-5.43)	.767
Systolic blood pressure (per mmHg)	0.99 (0.98-1.01)	.357		
Heart rate (per bpm)	0.99 (0.97-1.01)	.457		
Respiratory failure	0.61 (0.29-1.29)	.193		
Syncope	1.39 (0.65-2.97)	.400		
Deep vein thrombosis	1.14 (0.55-2.36)	.723		
Right ventricular involvement	0.33 (0.03-3.72)	.369		
Bilateral central pulmonary embolism	1.82 (0.93-3.59)	**.082**	2.42 (1.10-5.32)	**.028**
Lactate (per mmol/L)	0.94 (0.83-1.06)	.317		
Elevated troponin levels	1.00 (1.00-1.00)	.312		
Elevated NT-proBNP levels	1.12 (0.45-2.81)	.804		
Charlson Comorbidity Index	1.21 (1.00-1.47)	**.048**	1.29 (1.05-1.59)	**.018**

OR, ods ratio; 95%CI, 95% confidence interval.
Logistic regression was used to detect the predictors leading physicians to choose catheter-directed therapies instead of systemic thrombolysis as reperfusion treatment. Variables with *P* values < .10 in the univariable analysis were included in the multivariable model. Obesity was defined as body mass index ≥ 30 kg/m^2. Statistically significant values are highlighted in bold letters.
* Age and previous cancer were not included in the multivariable model despite being significant in the univariate analysis to avoid problems of collinearity because they are included in the Charlson Comorbidity Index.

referral centers with a 24/7 PERT team. The main findings were as follows: *a)* in this contemporary PE cohort, the factors associated with the choice of CDT over ST in the multivariable analysis were a higher Charlson Comorbidity Index, a history of recent surgery, and a proximal, bilateral PE; *b)* the choice of CDT as reperfusion therapy has increased; and *c)* CDT significantly improves hemodynamic parameters, suggesting that the effectiveness of the treatment is preserved in this comorbid population; nonetheless, the risk of complications is not negligible and should be considered in decision-making.

To our knowledge, this is the first study that focuses on the parameters associated with treating physicians' choice between the available treatment strategies in patients with acute IR and HR-PE. As expected, patients undergoing reperfusion had worse hemodynamic status and more frequently had right ventricular impairment or higher lactate levels. ST was more frequently used in patients with fewer comorbidities (eg, younger age, recent surgery, or hospital admission), which is in agreement with previous studies.[3,5] In contrast, CDT was chosen for patients with a greater number of comorbidities and probably with a higher bleeding risk (recent surgery). However, there were no differences in age, sex or previous comorbidities between the group of patients treated with AC and those who underwent CDT, with only PE severity as a driver for CDT reperfusion.

Catheter-directed therapies as an increasingly chosen option

In the last 10 years, CDT has emerged as a promising alternative to ST, but randomized studies vs standard medical therapy are lacking. The PE landscape currently has 2 scenarios on the opposite side of the innovation curve. On the one side, the early adopters (United States scenario) are using CDT with a very low threshold

Table 4. Procedural characteristics in the catheter-directed therapies group

Patients with percutaneous intervention (N = 66)	
*Therapy delay, hours**	6.0 [3.3-19.0]
Procedure length, minutes	89.0 (44.4)
Vascular access	
Femoral	64 (97.0%)
Brachial	2 (3.0%)
Maximum sheath diameter, French	8.0 [6.0-20.0]
Catheter-directed thrombolysis	35 (53.0%)
Thrombolytic drug	
Alteplase	25 (71.4%)
Tenecteplase	10 (28.6%)
Drug dose	
Alteplase, mg	16.7 (7.2)
Tenecteplase, units	3737.5 (1947.8)
Ultrasound-assisted	2 (5.7%)
Thrombus aspiration	42 (63.6%)
Catheter	
Coronary catheters	18 (42.9%)
FlowTriever	16 (38.1%)
Indigo	6 (14.3%)
Nautilus	2 (4.8%)
sPAP change, mmHg	−10.3 (11.3)
mPAP change, mmHg	−6.4 (6.8)
sBP change, mmHg	+11.0 (24.5)
mBP change, mmHg	+5.3 (17.6)

mBP, mean blood pressure; mPAP, mean pulmonary artery pressure; rTPA, alteplase; sBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TNK, tenecteplase.
Data are shown as mean ± standard deviation or median [interquartile range] for continuous variables, as appropriate, and No. (%) for categorical variables.
* Therapy delay was defined as the time that elapsed between diagnosis of pulmonary embolism and the procedure.

as an elective therapy for submassive PE (including the entire IR spectrum) despite the lack of randomized evidence or strong guideline recommendations. Conversely, awareness of CDT and its availability might be relatively low in late-adopter countries and nonacademic nontertiary centers, leading to inequalities in patients' access to advanced therapies for PE.

The rise in CDT treatments is due to the growing market and the promising results of early studies showing nearly immediate improvement in right ventricular function and hemodynamic status compared with conservative treatment,[7,10,19,20] with very low bleeding risk.[21,22] The variety of techniques (figure 1) might add some heterogeneity but discussion of the various CDTs is beyond the scope of this manuscript.

The significant number of patients treated with reperfusion in our cohort (59% of IHR-PE patients and 81% of HR-PE patients) may reflect that PERTs are currently activated only for a higher-risk segment of patients, but also reflects the optimal accessibility to reperfusion when ST and CDT are available together.

Systemic thrombolysis vs catheter-directed therapies

ST is the treatment of choice for patients with hemodynamic instability and PE-related cardiopulmonary arrest, although the mortality benefit is mainly based on a small clinical trial (n = 8) that was prematurely terminated.[23] Risk factors for PE are age, multiple comorbidities and especially past or active cancer,[24] which also confer an exceedingly high bleeding risk,[25] especially when treated with ST. Previous studies have shown that major bleeding occurs in ≈10% to 15% of acute PE patients treated with ST, while intracranial bleeding events occur in around 1.5% to 2% of this patient population.[3,4,26,27] It is probably for this reason that this treatment is not frequently applied in older patients with previous comorbidities, as shown in the present study and other previous publications.[3-5] Thus, managing older, comorbid and oncologic patients with ongoing acute PE remains a real challenge for clinicians, and in this particular scenario, CDT may be a safe and effective option for PE treatment. In fact, the multivariable analysis performed in our study showed that increasing comorbidities was an independent factor for the use of CDT over ST as the preferred reperfusion therapy. These results suggest a new choice for this group of highly vulnerable patients who would not otherwise be treated with reperfusion and therefore would have a higher mortality risk due to the conservative approach.[3] However, these results should be interpreted with caution because of the low percentage of patients treated with ST in the present study (35.0%) and the low percentage of HR-PE patients included (15.8%). Furthermore, given the large time period covered by the study, a significant percentage of IHR-PE patients undergoing ST were included. Following the publication of the PEITHO trial[28] and the emergence of specific catheters for PE treatment, the administration of ST in IHR-PE patients became less frequent, even in those with worse progress within this subgroup. Therefore, it is likely that our study population does not accurately represent patients in current clinical practice.

Postsurgical patients are especially complex because surgery is a risk factor for PE and is a formal contraindication for ST. Percutaneous thrombectomy has shown a low incidence of major bleeding in single-arm studies and seems a good alternative in these patients.[8,9,29] However, to use these devices, the thrombus must be in the proximal segment of the main pulmonary arteries. Indeed, bilateral central PE was an independent variable that prompted the choice of CDT in our study.

Anticoagulation vs catheter-directed therapies

Anticoagulation only is recommended for low-risk and stable IR-PE patients.[2] ST in IR-PE decreased the risk of hemodynamic decompensation but at a high cost of bleeding,[28] and consequently reperfusion therapies are intended for patients with hemodynamic deterioration.[2] Nonetheless, the irruption of transcatheter therapies, especially large-bore aspiration devices, could provide the advantages of pulmonary reperfusion observed in the PEITHO trial[28] without the worrisome adverse effects (mainly bleeding events). Our study shows that the use of CDTs has clearly increased in recent years but they were still being reasonably reserved for the higher-risk PE spectrum. Ongoing large clinical trials, such as PEERLESS (NCT: 05111613), HI-PEITHO (NCT: 04790370), and PE-TRACT (NCT: 05591118), will definitely clarify the indication for CDT in patients with acute IHR-PE.

Table 5. Early safety outcomes in patients with acute pulmonary embolism

	Total	AC	ST	CDT	*P*			
	N = 274	N = 112	N = 96	N = 66	Global	AC vs ST	AC vs CDT	ST vs CDT
Admission length, days	8.0 (6.0-13.0)	7.0 (6.0-11.0)	9.0 (6.0-12.5)	10.0 (6.0-23.0)	.132	0.394	.052	.178
In-hospital events								
Major bleeding*	18 (6.6%)	2 (1.8%)	7 (7.3%)	9 (13.6%)	**.008**	0.052	**.002**	.184
Intracranial bleeding	5 (1.8%)	0 (0.0%)	5 (5.2%)	0 (0.0%)	**.009**	**0.014**	-	.060
Acute kidney injury	22 (8.0%)	11 (9.8%)	9 (9.4%)	2 (3.0%)	.228	0.913	.093	.115
Vascular access complication	-	-	-	6 (10.6%)	-	-	-	-
30-day all-cause death	25 (9.3%)	5 (4.6%)	10 (10.4%)	10 (15.9%)	**.045**	0.110	**.011**	.310

AC, anticoagulation; CDT, catheter-directed therapies; ST, systemic thrombolysis.
Data are shown as median [interquartile range] for continuous variables and No. (%) for categorical variables.
* As defined by the International Society of Thrombosis and Hemostasis.

Early safety outcomes in patients with acute pulmonary embolism

Our study showed an incidence of 30-day all-cause mortality of 9.3%, which is lower than that in other observational studies.[21,30] However, the cited studies included only patients undergoing reperfusion therapies (either CDT or ST) and the present study also included patients undergoing conservative management, who can be expected to have lower severity and therefore better prognosis. In contrast to the findings of other published literature,[19,21,31] the incidence of in-hospital major bleeding and early all-cause death was relatively high in the CDT group in our cohort. These results can be explained by 2 main reasons: first, patients in the CDT group in our cohort were older and had more comorbidities, with 30% having a formal contraindication for ST; and second, the CDT group included almost 50% of patients receiving thrombolytic drugs, which are associated with a higher risk of bleeding than thrombus aspiration alone. Furthermore, among the group of patients who underwent catheter-guided thrombolysis, tenecteplase was used in 28.6%, with this drug demonstrating a high incidence of major bleeding in the PEITHO trial.[28] Finally, the vascular access used in the vast majority of patients in the present study was femoral (97.0%), with an incidence of vascular complications of 10.6% (all of them occurring in patients undergoing catheter-directed thrombolysis or aspiration with a nonspecific catheter). Previous studies have shown a low incidence of major bleeding when catheter-directed thrombolysis is performed through brachial access.[32] However, specific devices, especially large-bore aspiration devices, can currently only be used via femoral access due to their large caliber. In addition, there were no intracranial bleeding events in patients undergoing CDT in our cohort.

On the other hand, our study showed a significant hemodynamic improvement in patients who underwent CDT, in accordance with previous studies.[7-10,33] This benefit is important, but the futility of interventional treatments must be considered in very old and comorbid patients, balancing cost-effectiveness and clinical judgment.[34] More data are needed to establish the risk-benefit balance of CDT compared with anticoagulation and ST in older patients or patients with a high comorbidity burden.

Limitations

Several limitations should be considered when interpreting the results of this study. Due to its observational nature, the presence of unmeasured confounders could have influenced the conclusions of the study. The total number of patients admitted with PE in the study period in the 2 centers is unknown, and consequently a survival bias should be acknowledged. The percentage of intermediate-low risk patients included was relatively low, suggesting that PERT activation was selected for the most severe patients. Thus, a selection bias may have occurred in this study. Specific devices for the percutaneous treatment of PE were not initially available at the beginning of this study, and were incorporated as they became available (first specific devices in 2018). This was a registry with self-reported data without external monitoring, and consequently local investigators are responsible for the integrity of the data.

CONCLUSIONS

The results of this study show that the factors associated with the choice of CDT on multivariable analysis were a higher Charlson comorbidity index, a history of recent surgery, and proximal, bilateral PE. The choice of CDT over ST as reperfusion therapy increased during the study period. CDT was an effective option for older, comorbid patients with PE, but the management of acute PE patients is challenging and should be individualized.

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ETHICAL CONSIDERATIONS

The registry protocol was approved by the clinical research ethics committee at Hospital Clínico San Carlos as the central committee for the registry, following local research regulations (code 18/010-E). All prospectively included patients signed an informed consent form. An informed consent waiver was granted from the ethics research committee for patients recruited retrospectively. Sex but not gender data were included in the database design in 2018.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

C. Real designed the study outline, performed the statistical analysis, and drafted the article. C. Ferrera designed the study outline and drafted the article. M.E. Vázquez-Álvarez participated in data collection and data interpretation, M. Huanca, F.J. Noriega, E. Gutiérrez-Ibañes, A.M. Mañas-Hernández, N. Ramos-López, M. Juárez, P. Jiménez-Quevedo, J. Elízaga, and A. Viana-Tejedor participated in data collection and critically revised the manuscript. P. Salinas designed the protocol, database and study outline, coordinated the data analysis and interpretation, and critically revised the manuscript. All authors gave final approval of the version to be published.

CONFLICTS OF INTEREST

The authors report no conflicts of interest with respect to the content of this manuscript.

WHAT IS KNOWN ABOUT THE TOPIC?

- Catheter-directed therapies (CDT) have emerged as a safe and effective reperfusion therapy in patients with acute pulmonary embolism (PE). According to ESC guidelines, these therapies should be considered in patients with HR-PE and failed thrombolysis or a contraindication to this therapy and as a rescue treatment for IHR-PE patients with clinical deterioration. However, several studies aiming to establish the indication for these therapies in a broader spectrum of patients have been published in recent years. Furthermore, reperfusion therapy with systemic thrombolysis (ST) is known to be underused due to concerns about bleeding, and consequently CDT may be a feasible option in this profile of patients who would otherwise go untreated.

WHAT DOES THIS STUDY ADD?

- In clinical practice in two tertiary centers, the factors associated with the choice of CDT over ST were comorbidities, a history of recent surgery, and proximal, bilateral PE. However, the risk profile of patients treated with the 2 therapies was similar in each risk stratum. Therefore, we conclude that CDT could be a safe and effective alternative in patients requiring reperfusion therapy.

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Original article

Spanish cardiac catheterization in congenital heart diseases registry. Third official report from the ACI-SEC and the GTH-SECPCC (2022)

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ABSTRACT

Introduction and objectives: The Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) and the Interventional Working Group of the Spanish Society of Pediatric Cardiology (GTH-SECPCC) present their annual activity report for 2022.
Methods: All Spanish centers with catheterization laboratories and interventional activity in congenital heart diseases were invited to participate. Data were collected online and analyzed by an external company, together with the members of the ACI-SEC and the GTH-SECPCC.
Results: A total of 22 centers participated (19 public and 3 private). Interventional data on adult congenital diseases contributed by another 99 hospitals to the Registry of Cardiac Catheterization and Interventional Cardiology of the ACI-SEC in 2022 were incorporated into the analysis. A total of 1141 diagnostic studies (4.3% more than in 2021) and 2508 interventional catheterizations (61.5% more than in 2020) were registered. The most frequent procedures were atrial septal defect closure (1135 cases), percutaneous

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closure of patent ductus arteriosus (262 cases), and pulmonary branch artery angioplasty (234 cases). The most significant increases in volume were related to balloon aortic valvuloplasty (48.9%), atrial septal defect closure (45.2%), and ventricular septal defect closure (40.7%). Interventional procedures were successful in 97.6%, with major procedural complications occurring in 1.4% and in-hospital mortality in 0.2%.
Conclusions: This report is the third publication of the Spanish Cardiac Catheterization in Congenital Heart Diseases Registry. Both diagnostic and interventional procedures substantially increased, particularly in balloon aortic valvuloplasty, atrial septal defect closure, and ventricular septal defect closure. Most interventional techniques continue to demonstrate excellent safety and effectiveness outcomes.

Keywords: Atrial septal defect closure. Cardiac catheterization. Congenital heart disease. Percutaneous valve implantation.

Registro español de intervencionismo en cardiopatías congénitas. III informe oficial de la ACI-SEC y el GTH-SECPCC (2022)

RESUMEN

Introducción y objetivos: La Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC) y el Grupo de Trabajo de Hemodinámica de la Sociedad Española de Cardiología Pediátrica y Cardiopatías Congénitas (GTH-SECPCC) presentan su informe anual de actividad hemodinámica en cardiopatías congénitas correspondiente al año 2022.
***Métodos*:** Se invitó a participar a los centros españoles con laboratorio de hemodinámica y actividad intervencionista en cardiopatías congénitas. La recogida de datos se realizó mediante un cuestionario telemático. Una empresa externa analizó los resultados, que fueron revisados por miembros de la ACI-SEC y el GTH-SECPCC.
Resultados: Participaron en el registro 22 centros (19 públicos y 3 privados). Se incorporaron al análisis los datos de intervencionismo en cardiopatías congénitas del adulto aportados por otros 99 hospitales al Registro de Hemodinámica y Cardiología Intervencionista de la ACI-SEC del año 2022. Se registraron 1.141 estudios diagnósticos (un 4,3% más que en 2021) y 2.508 cateterismos intervencionistas (un 61,5% más que en 2021). Las técnicas con mayor casuística fueron el cierre de defectos interauriculares (1.135 casos), el cierre de ductus arterioso (262 casos) y la angioplastia de ramas pulmonares (234 casos). El incremento más significativo se comunicó en la valvuloplastia aórtica (48,9%), el cierre de defectos interauriculares (45,2%) y el cierre de comunicación interventricular (40,7%). La tasa de éxito en los procedimientos intervencionistas fue del 97,6%, con una tasa de complicaciones mayores del 1,4 % y una mortalidad intrahospitalaria del 0,2%.
Conclusiones: El presente trabajo es la tercera publicación del Registro Español de Intervencionismo en Cardiopatías Congénitas. Se ha comunicado un aumento muy significativo de la mayoría de los procedimientos terapéuticos, destacando el incremento de la valvuloplastia aórtica, del cierre de defectos interauriculares y del cierre de comunicación interventricular. Todas las técnicas intervencionistas han reportado excelentes datos de seguridad y eficacia.

Palabras clave: Cardiopatías congénitas. Cateterismo cardiaco. Cierre de comunicación interauricular. Implante percutáneo de válvula aórtica.

INTRODUCTION

The collaborative effort between the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) and the Interventional Working Group of the Spanish Society of Pediatric Cardiology (GTH-SECPCC), which was initiated in 2019, allowed the reactivation of a Spanish registry of cardiac catheterizations and interventional cardiology in patients with congenital heart diseases. The results of this collaboration have been published in the first 2 reports of the activity conducted from 2020 to 2021.[1,2] The main weakness highlighted in both reports is the inadequate estimation of interventional procedures performed in patients older than 18 years. Despite being highly representative of pediatric activity, the number of participating centers, did not seem sufficient to accurately reflect the activity carried out in adult congenital heart diseases in Spain.[3,4]

This article analyzes the current report, focusing on the activity conducted in 2022, and aims to consolidate the objective of reliably measuring the scope of interventional procedures to treat congenital heart diseases in all age groups. The results of this report were made public at the XXXIV ACI-SEC Congress held in Santander, Spain on June 7th, 2022.

METHODS

The data presented come from a retrospective, voluntary, unaudited, and annually updated registry. This year, a substantial and coordinated change has been made to the section on interventional procedures for the treatment of congenital heart diseases of the ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology to standardize data from the 2 registries and facilitate their incorporation into the study of its interventional activity in patients older than 18 years.[5]

All hospitals already participating in the ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology were invited to participate, as well as all pediatric hospitals represented in the GTH-SECPCC. Data were collected by the investigator of each participating hospital through the official website of the ACI-SEC.[6]

The registry results were managed and cleaned by an external company (Tride, Madrid, Spain), and were subsequently reviewed and compared with those obtained in previous years by members of the GTH-SECPCC and the ACI-SEC board. If the data were discordant, the center in question was contacted for clarification and error minimization.

Due to the methodological characteristics of the study and the fact that it was purely an activity registry, there was no requirement for approval from an ethics committee or processing of informed consent forms.

RESULTS

Resources and infrastructure

Twenty-two hospitals participated (6 more than in 2021), 19 from the publicly-funded health sector and 3 from the private sector (appendix 1 of the supplementary data). Data on cardiac catheterizations in adult congenital heart diseases from 2022 were provided by another 99 hospitals to the ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology of the and were included in the analysis (appendix 2 of the supplementary data).

Thirty-four cath labs with interventional activity for congenital heart diseases were included in the registry, of which 7 (20.8%) are pediatric cardiac cath labs exclusively; 9 of them with biplane image-guided systems and 14 with the possibility of implementing rotational angiography. The median number of monthly days dedicated by each hospital to interventional procedures for congenital heart disease was 6 [3-17] days vs 7 days in 2021. Fifteen (68.1%) of these hospitals have round-the-clock catheterization services, even for pediatric patients.

Data on medical staffing revealed that 67 interventional cardiologists with full-time dedication to the specialty were registered, of which 37 (55.3%) treated adults and 30 (44.7%) pediatric patients.

Diagnostic procedures

A total of 1141 diagnostic studies were reported, representing a 4.3% increase compared with the previous year. Age distribution was as follows: 37 (3.2%) cardiac catheterizations were performed in infants younger than 1 month, 127 (11.1%) in patients aged from 1 month to 1 year, 578 (50.7%) in patients from 1 to 18 years, and 399 (35.5%) in patients older than 18 years.

Sixty cardiac catheterizations (5.4%) were classified as emergency procedures. Regarding morbidity, 7 (0.6%) cases of serious complications were reported: 4 arrhythmias (2 with severe hemodynamic instability and cardiac arrest), 1 vascular event, and 1 cardiac tamponade; there was 1 procedure-related death.

Interventional procedures

The activity reported in this section increased by 61.5% compared with the previous year. In all, 2508 therapeutic catheterizations were reported and grouped into 13 categories with the following age distribution: 3 procedures (0.1%) were performed in the fetal period, 163 (6.4%) in infants younger than 1 month, 208 (8.3%) in patients aged from 1 month to 1 year, 754 (30.1%) in patients aged from 1 to 18 years, and 1380 (55%) in patients older than 18 years, of which 903 were added by incorporating data from the ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology of the (table 1 and table 2).

A total of 148 cardiac catheterizations were classified as urgent (9.7% of all procedures performed with this reported datum). The number of interventional procedures reported by each center was distributed as follows: 5 hospitals (21.7%) reported more than 150 catheterizations, 3 (13%) between 75 and 150 interventions, and 8 (47.1%) less than 75 catheterizations. The overall effectiveness of the various interventional techniques used was 97.6%, with most centers reporting effectiveness of more than 95% (table 3).

Percutaneous valvuloplasty procedures

Sixty-seven aortic valvuloplasty procedures were reported to treat congenital aortic stenosis (a 48.9% increase compared with 2021), including 2 fetal valvuloplasty procedures. Forty-two (62.6%) of these procedures were performed in patients older than 1 year, of which 20 (29.9%) were older than 18 years. Previously untreated native valves were dilated in 70% of cases.

In all, 138 pulmonary valvuloplasty procedures were reported, including 1 fetal valvuloplasty, representing a 32.7% increase compared with the previous year. Technical data were reported in 104 cases (85%): 95 (90%) were native valves; 7 (4.8%) were imperforate valves; and in 2 cases (1.9%), the procedure was associated with ductal stenting.

Lastly, there were no cases of mitral valvuloplasty that year.

Percutaneous angioplasty procedures

A total of 135 right ventricular outflow tract dilatations were reported (a 25% increase compared with 2021). Technical and anatomical data were reported for 96 (72.7%) procedures: surgical conduit angioplasty was performed in 62% of procedures and native tract angioplasty in the remaining 38%. Stent implantation was performed in 51% of cases, conventional balloon dilation in 43%, and cutting balloon in 5%.

There were 234 pulmonary branch angioplasty procedures. Technical data were obtained from 205 (87.6%) interventions: proximal branches were dilated in 191 interventions (93.1%) and peripheral arteries (lobar-segmental) in the remaining procedures. Stent implantation was performed in 102 (49.7%) catheterizations, conventional balloon dilation in 98 (47.8%), and cutting balloon dilation in 5 (2.4%).

Of 126 aortic angioplasty procedures, anatomical data were reported for 104 (82.5%) procedures: 70 (67.3%) were reinterventions and 34 (32.6%) were treatments on native aortas. The dilation substrate was the aortic arch/isthmus in all cases except for 1 angioplasty of the ascending aorta. The distribution of the technique used was as follows: conventional balloon angioplasty in 29%, implantation of uncovered stents in 18.5%, implantation of covered stents in 37.9%, and redilatation with a previously implanted stent balloon in 14.5%.

A further 100 catheterizations were reported in the category of "other angioplasty procedures," representing a decrease in their frequency by 9.1% compared with the previous year. The anatomical substrate of the angioplasty was reported in 73 cases, highlighting patent ductus arteriosus dilation in 25 cases, systemic veins in 16, Fontan conduits in 10, and surgical fistulas in 8. Fifty-five percent of the procedures were associated with stent implantation.

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

Variable	Total	Fetal	< 1 month	1 month to 1 year	1 to 18 years	> 18 years
Interventional procedures	2508	3 (0.1)	163 (6.4)	208 (8.3)	754 (30.1)	1380 (55.0)
Congenital aortic valvuloplasty	67	2 (3.0)	9 (13.4)	14 (20.9)	22 (32.8)	20 (29.9)
Congenital pulmonary valvuloplasty	138	1 (0.7)	34 (24.6)	39 (28.3)	34 (24.6)	30 (21.7)
Congenital mitral valvuloplasty	0	-	0	0	0	0
Pulmonary angioplasty	135	-	0	7 (5.2)	75 (55.6)	53 (39.3)
Pulmonary branch angioplasty	234	-	2 (0.9)	45 (19.2)	136 (58.1)	51 (21.8)
Aortic angioplasty	126	-	3 (2.4)	28 (22.2)	40 (31.7)	55 (43.7)
Other angioplasty procedures	100	-	26 (26.0)	22 (22.0)	37 (37.0)	15 (15.0)
Atrial septal defect/patent foramen ovale closure	1135	-	-	2 (0.2)[a]	130 (11.5)	1003 (88.4)
Patent ductus arteriosus closure	262	24 (9.2)[b]	17 (6.5)[b]	30 (11.5)[b]	147 (56.1)	44 (16.8)
Ventricular septal defect closure	38	-	-	1 (2.6)[a]	23 (60.5)	14 (36.8)
Other occlusions	91	-	2 (2.2)	8 (8.8)	39 (42.9)	42 (46.2)
Foreign body removal	23	-	3 (13.0)	0	18 (78.3)	2 (8.7)
Atrial septostomy	72	-	43 (59.7)	12 (16.7)	17 (23.6)	0
Transcatheter aortic valve implantation	87	-	-	-	36 (41.4)[c]	51 (58.6)

[a] In this case, infants younger than 1 month and from 1 month to 1 year are not shown separately and consequently the value corresponds to infants younger than 1 year.
[b] In patent ductus arteriosus closure, groups are premature (fetal), < 6 months (< 1 month), and 6 months to 1 year (1 month to 1 year).
[c] Reported as participants younger than 18 years and consequently the value corresponds to participants younger than 18 years.
Data are expressed as n (%).

Table 2. Number of interventional catheterizations performed in patients older than 18 years and distribution according to the source registry

Variable	> 18 years		
	Total	RICC[a]	RHCI[b]
Interventional procedures	1380	477	903
Congenital aortic valvuloplasty	20	19	1
Congenital pulmonary valvuloplasty	30	12	18
Congenital mitral valvuloplasty	0	0	0
Pulmonary angioplasty	53	21	32
Pulmonary branch angioplasty	51	26	25
Aortic angioplasty	55	33	22
Other angioplasty procedures	15	10	5
Atrial septal defect/patent foramen ovale closure	1003	221	782
Patent ductus arteriosus closure	44	11	33
Ventricular septal defect closure	14	4	10
Other occlusions	42	18	24
Foreign body removal	2	2	0
Atrial septostomy	0	0	0
Transcatheter aortic valve implantation	51	51	0

[a] Data provided by the 22 centers participating in ACI-SEC Spanish Cardiac Catheterization in Congenital Heart Diseases Registry (RICC) and the GTH-SECPCC (2022).
[b] Data provided by the 96 centers participating in the 2022 ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology Registry (RHCI).
Data are expressed as n.

Shunt closure and other occlusive procedures

There were 1135 atrial septal defect closures: 782 (68.8%) came from the incorporation of data from the ACI-SEC Spanish Registry of Cardiac Catheterization and Interventional Cardiology of the same year (table 2). Consequently, the volume of patients older than 18 years who underwent this technique was 83.8% overall. The predominant anatomical substrate of the defect was patent foramen ovale, with 705 (62.1%) cases. A total of 72.1% of atrial septal defects (ASD) were classified as complex, and the remaining ASD as simple. Data on procedure guidance were reported in 348 cases (28.3%): transesophageal echocardiography was used in 80.4%, intracardiac echocardiography in 12.6%, and angiographic measurements with balloon in 6.8%.

Patent ductus arteriosus closure accounted for 262 catheterizations. More than half of all procedures (56.1%) were performed in patients aged 1 to 18 years, while 9.2% were performed in premature infants (24 cases). The route of choice was antegrade venous access in 70% of closures. Occlusive devices were used in 88.4% of cases and controlled-release coil devices in the remainder.

Thirty-eight catheterizations for ventricular septal defect (VSD) closures were reported, increasing their frequency by 40.7% compared with the previous year. Data on the anatomical substrate of the VSD were reported in 28 (73.6%) cases, with the following distribution: 20 (71.4%) perimembranous, 6 (21.4%) muscular, and 2 (7.1%) postoperative. Occlusive devices were used in 89.2% of cases and coil-type occluders in the remainder. Two devices were implanted via a hybrid approach and the remaining devices via transcatheter access (93.3%).

Ninety-one catheterizations fell within the category "various occlusive procedures". Data on the type of occlusion were reported in

Table 3. Summary of reported efficacy of interventional procedures

Interventional procedures	n	Cases with success/ inefficacy data	Success	Inefficacy
Congenital aortic valvuloplasty	67	46 (68)	43 (93.5)	3 (6.5)
Congenital pulmonary valvuloplasty	138	118 (85)	117 (99.2)	1 (0.8)
Congenital mitral valvuloplasty	0	-	-	-
Pulmonary angioplasty	135	95 (70)	90 (94.7)	5 (5.3)
Pulmonary branch angioplasty	234	205 (87.6)	199 (97.1)	6 (2.9)
Aortic angioplasty	126	108 (85.7)	106 (98.1)	2 (1.9)
Other angioplasty procedures	100	95 (95)	91 (95.8)	4 (4.2)
Atrial septal defect/patent foramen ovale closure	1135	1024 (90.2)	1003 (97.9)	21 (2.1)
Patent ductus arteriosus closure	262	251 (95.8)	248 (98.8)	3 (1.2)
Ventricular septal defect closure	38	30 (78.9)	29 (96.7)	1 (3.3)
Other occlusions	91	66 (72.5)	65 (98.5)	1 (1.5)
Foreign body removal	23	23 (100)	22 (95.7)	1 (4.3)
Atrial septostomy	72	72 (100)	70 (97.2)	2 (2.8)
Transcatheter aortic valve implantation	87	87 (100)	84 (96.6)	3 (3.4)
Total	2508	2220 (88.5)	2167 (97.6)	53 (2.4)

Data are expressed as n.

65 (71.4%) cases, with closure of systemic-to-pulmonary collateral vessels in 40 (61.5%) cases, venous collaterals in 13 (20%), coronary fistulas in 3 (4.6%), and Fontan fenestrations in 2 (3%). The most widely used material was coil-type occluders (38.8%), followed by occlusive devices (36.1%), and particles as the only material or in combination with others (25%).

Atrial septostomy

Seventy-two atrial septostomy procedures were reported (a 33.3% increase compared with the previous year). Echocardiography was used for imaging guidance in 22.5% of cases, fluoroscopy in 28%, and a combination of the 2 imaging modalities in 49.2%. Forty-nine (68%) interventions were balloon atrial septoplasty procedures (Rashkind). There were also 7 procedures with radiofrequency-guided septal perforation, 7 with needle perforation, and 15 with septal stent implantation.

Percutaneous valve implantations

Eighty-seven procedures were reported, of which 51 (58.6%) were performed in patients older than 18 years. The hybrid approach was used in 2 cases, while the fully percutaneous approach was used in the remaining cases. The pulmonary position was predominant (96.5%), with 2 successful valve implantations being performed in the tricuspid position and 1 in the mitral position. The anatomical substrate of implantation in the pulmonary position had the following distribution: 33 in the surgical conduit, 31 in the native tract, followed by 20 valve-in-valve procedures.

Complications

Morbidity and mortality data were reported for 2401 interventional procedures, with 35 serious adverse events (table 4), including 6 deaths, which translated into a rate of major complication of 1.4% and a mortality rate of 0.2%. The categories associated with higher morbidity rates were percutaneous valve implantation (8%), other angioplasty procedures (6%), and VSD closure (5.2%). The most common complications were device embolizations (8 cases): 4 in ASD closures, 2 in patent ductus arteriosus closures, and 2 stents implanted in the setting of pulmonary angioplasty procedures; surgical removal of the embolized valve was required in only 1 case of ASD closure. Less frequent were vascular complications (6 cases), 3 of them being associated with pulmonary angioplasty procedures. There were 4 cases of severe arrhythmias, including 2 cases of cardiac arrest requiring bailout extracorporeal membrane oxygenation.

DISCUSSION

To date, one of the main weaknesses of this registry has been its limitations in adequately assessing the interventional activity carried out in the context of adult congenital heart disease. For this reason, and as the most significant novel addition to this report, we included data from 99 hospitals reporting their activities in adult congenital heart disease to the 2022 Spanish Registry of Cardiac Catheterization and Interventional Cardiology in the analysis of the various interventional categories. This has resulted in a significant increase in catheterization volume, totaling 3649 procedures (1002 more than in 2021). Their comparison with the activity conducted in previous years and the significant increase in registered procedures should be analyzed considering this methodological difference, and taking into account the increase in participating centers, 6 more than in 2021 (figure 1).

The total number of registered interventional procedures was 2508, with notable increases in techniques such as ASD closure, aortic and pulmonary valvuloplasty, atrial septostomy, and VSD closure.

Table 4. Distribution of major complications and reported deaths in various interventional procedures

Procedure	n	Major complications	Deaths
Congenital aortic valvuloplasty	67	3 (6.5) – 1 severe aortic regurgitation – 1 unspecified – 1 death	1
Valvuloplastia pulmonar congénita	138[a] (111)	2 (1.8) – 1 tricuspid valve rupture – 1 unspecified	0
Valvuloplastia mitral congénita	0	0	0
Angioplastia pulmonar	135[b] (102)	1 (0.9) – 1 unspecified	0
Angioplastia ramas pulmonares	227[c] (202)	6 (2.9) – 3 vascular dissections – 1 pulmonary hemorrhage – 2 stent embolizations	0
Angioplastia aórtica	124[d] (102)	3 (2.9) – 2 vascular dissections – 1 death	1
Otras angioplastias	100	6 (6) – 1 coronary thrombosis – 1 CPR-ECMO – 1 vascular dissection – 1 neurological event – 2 deaths	2
Cierre de comunicación interauricular/ foramen oval	1135	5 (0.4) – 4 embolizations (1 required surgery) – 1 neurological event	0
Cierre de conducto	262	3 (1.1) – 2 embolizations not requiring surgery – 1 death	1
Cierre de comunicación interventricular	38	2 (5.2) – 1 atrioventricular block – 1 CPR-ECMO	0
Otras oclusiones	91	0	0
Retirada de cuerpo extraño	23	0	0
Atrioseptostomía	72	1 (1.3) – 1 unspecified	0
Implantación de válvula percutánea	87	4 (8.0) – 1 vascular dissection – 1 pulmonary duct dissection – 1 ventricular tachycardia – 1 death	1
Total	2508[e] (2401)	35 (1.4)	6 (0.2)

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.
[a] Percentages calculated based on 111 reported cases.
[b] Percentages calculated based on 102 reported cases.
[c] Percentages calculated based on 202 reported cases.
[d] Percentages calculated based on 102 reported cases.
[e] Percentages calculated based on 2411 reported cases.
Data are expressed as n (%).

A total of 55% of cardiac catheterizations were performed in patients older than 18 years (compared with 32% in 2021), demonstrating an improvement in the representation of interventional procedures for adult congenital heart diseases. Once again, in the pediatric setting, we noted that fetal interventional activity in Spain is very limited, with only 3 reported cases (2 aortic valvuloplasty procedures and 1 pulmonary valvuloplasty procedure), despite evidence of its value and effectiveness in these and other prenatal scenarios, such as pulmonary atresia with intact ventricular septum and hypoplastic left heart syndrome.[7]

The reported data on the effectiveness of various interventional techniques yielded an overall success rate of 97.6% (compared with 95% in 2021) and a mortality rate of 0.2% (the same as in 2021), with 6 procedure-related deaths. These results are consistent with those reported from most international studies to date.[8,9] The rate of serious adverse events of 1.4% is the lowest reported so far (2% in 2020 and 2.7% in 2022), with a decrease in the frequency of all types of complications reported. Device embolizations continue to account for the highest number of cases, amounting to 22.5% overall, followed by vascular complications (20% overall).

The volume of valvuloplasty procedures has significantly increased with respect to 2021: a 48.9% increase in aortic valvuloplasty and a 32.7% increase in pulmonary valvuloplasty. For the first time, most cases involving one of these 2 techniques involved patients older than 1 year. In aortic valvuloplasty, the rate of serious events (6.5%) decreased compared with the previous year (11.1%), although with 1 associated death. The report shows that pulmonary valvuloplasty has become established as one of the techniques with the best results, with a 99.2% efficacy rate and a 1.8% complication rate. These data support the value of pulmonary valvuloplasty as the technique of choice in congenital pulmonary valve stenosis in our setting. However, its mid- and long-term outcomes may be influenced by unspecified anatomical and genetic factors.[10]

Both in pulmonary angioplasty procedures (of native tract or ducts) and pulmonary branch angioplasty procedures, stent implantation has surpassed conventional balloon dilation as the technique of choice, which has again reduced the use of cutting balloons. The most widely performed aortic angioplasty procedures continue to be aortic arch and isthmus dilatation, which are performed in almost all patients; of note, in this context, the increase in covered stent implantation, which, for the first time, has surpassed other dilation techniques. This increase could be explained by the intention to improve the safety of the procedure by reducing damage to the aortic wall in certain scenarios.[11] Furthermore, the availability of covered stents with lower implantation profiles has facilitated their use in pediatric patients of increasingly lower weight and younger age.[12]

ASD closure remained the most widely performed interventional technique in the registry (45.2% of all interventional catheterizations). The inclusion of patent foramen ovale closure as a procedure within this category and its classification as a congenital heart disease may be controversial but can be reevaluated in future reports. Its rarity in the pediatric setting contrasts with its increasing application in adults, confirming the maturity of the technique and the widespread acceptance of the scientific evidence supporting its use.[13] Transesophageal echocardiography guidance remains the usual imaging modality for ASD closure; both intracardiac echocardiography and balloon sizing of the defect are infrequent.

A notable finding was the increasing use of patent ductus arteriosus closure in the group of premature newborns (9.4% overall), as well as confirmation of the preference for the transcatheter option over

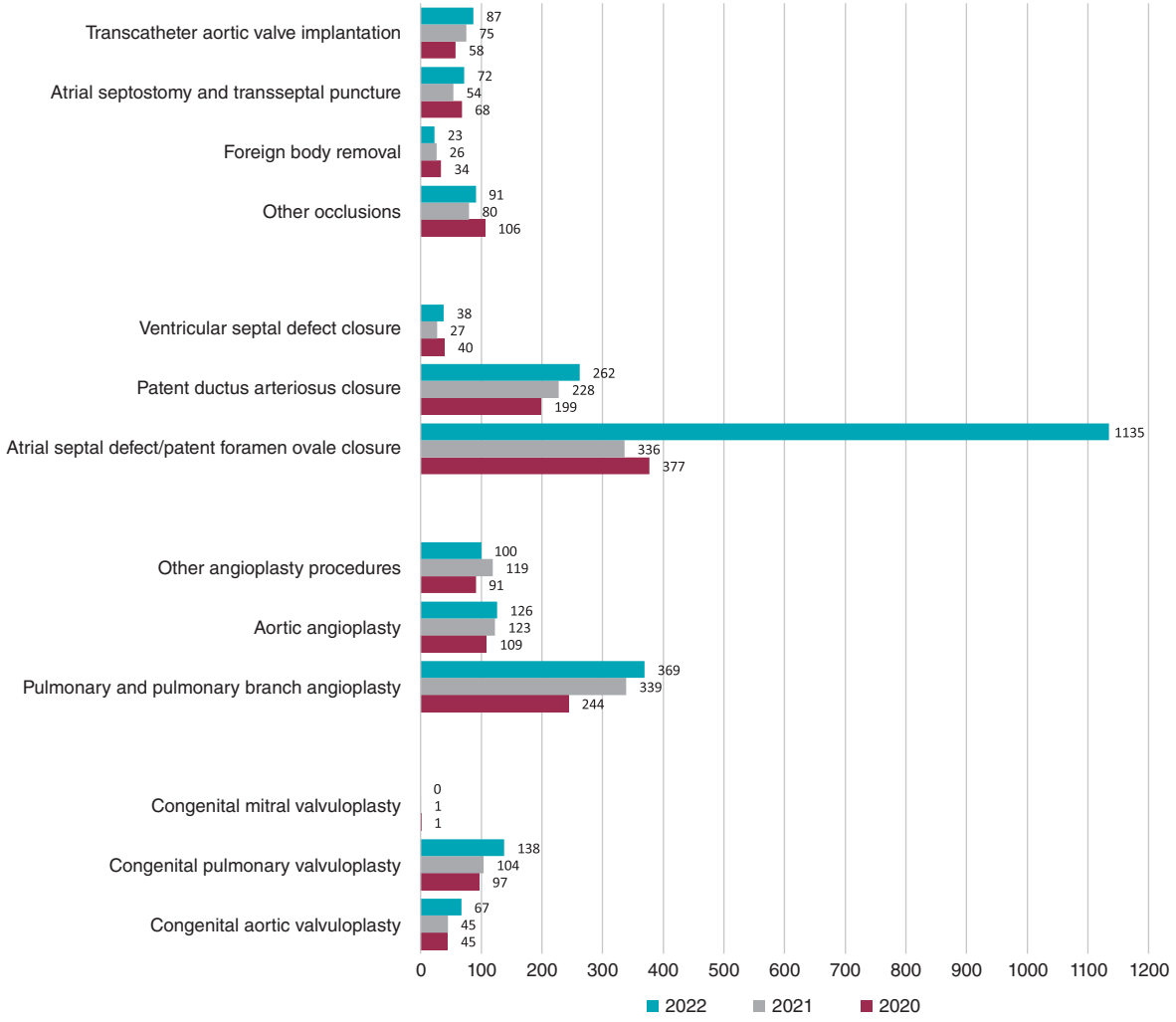

Figure 1. Comparison of the number of interventional procedures performed in 2020, 2021, and 2022.

surgery for these pediatric patients in our setting.[14] Antegrade venous access and the use of occlusive devices remain widespread procedures in a consolidated technique that has one of the best effectiveness rates in the registry (98.9%).

The reported data on the safety and efficacy of VSD closure show substantial improvement compared with previous reports: the major complication rate decreased from 18% in 2021 to 5.2% in 2022, while the success rate increased from 77.3% in 2021 to 96.7% in 2022. These figures reflect a change in trend, which could be related to the introduction of new closure devices, and the adoption of technical changes facilitating their approach.[15-17] All of this would facilitate the widespread use of the procedure, whose frequency has increased significantly by up to 40.7% compared with the previous year. The increase in the number of cases registered in patients older than 18 years was notable, reaching 38% overall (compared with 22% in 2021).

A 16% volume increase and a significant improvement in the reported safety and efficacy data of transcatheter aortic valve implantation were also reported, of which approximately 60% were performed in patients older than 18 years. There was a decrease in the tricuspid position as the anatomical substrate for implantation (from 10 cases in 2021 down to only 2 cases in 2022), at a time when transcatheter aortic valve implantation has reached an unprecedented growth as a structural heart procedure in Spain.[5] Access to new valves—especially self-expanding valves—and the continuous publication of scientific evidence endorsing the results of this technique, continue to enhance the expectations of the percutaneous management of patients with right ventricular outflow tract dysfunction in all anatomical scenarios.[18,19]

Limitations

The characteristics of this registry may be weakened by its retrospective, voluntary, and unaudited design. Expanding the collected data on certain techniques of special interest would help improve its quality and should be considered in future reports.

CONCLUSIONS

The main finding of this report is the significant increase in the number of interventional procedures recorded compared with previous years, which was closely related to the increase in participating centers. There has been significant growth in aortic valvuloplasty, ASD closure, and VSD closure procedures. The data

obtained provide a realistic overview of interventional activity in congenital heart diseases in Spain among all age groups. The reported safety and efficacy results demonstrate the consolidation of most techniques in our setting and are consistent with those published in other international studies.

The incorporation of a greater number of centers with interventional activity in congenital heart diseases into the registry will optimize the quality and reliability of the information generated.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

Due to the methodological characteristics of the study and its nature as solely an activity registry, there was no requirement for approval from ethics committees or signing of informed consent forms.

The characteristics of the present work exclude the consideration of possible variables of sex and gender.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to data collection and the critical review of this work. F. Ballesteros Tejerizo and F. Coserría Sánchez wrote the article.

CONFLICTS OF INTEREST

S. Ojeda Pineda is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure the impartial processing of the manuscript has been followed. The remaining authors declare no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Cardiac catheterization remains an indispensable procedure in the management of patients with congenital heart diseases.
- The existence of a national registry of pediatric percutaneous procedures and adult congenital heart diseases is essential to understand the current panorama of interventional cardiology in Spain and generate valuable information for professionals, patients, and families.
- The continuity of this registry allows understanding the level of implementation and results of various techniques, as well as their variation over time.

WHAT DOES THIS STUDY ADD?

- Some methodological changes and the gradual increase in the number of centers participating in the registry have enabled the collection of more realistic information on interventional activity for congenital heart diseases among all age groups in Spain.
- A highly significant increase in interventional procedures performed in 2022 was reported, with ASD and VSD closure and aortic valvuloplasty procedures being the techniques experiencing the greatest growth.
- The most widely performed procedures continue to be ASD closure, patent ductus arteriosus closure, and pulmonary artery branch angioplasty.
- The most frequent procedure-related adverse events were device embolizations and vascular complications.

SUPPLEMENTARY DATA

Supplementary data for this article can be found in the online version available at https://doi.org/10.24875/RECICE.M24000456.

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Original article

Left ventricular remodeling following transcatheter versus surgical aortic valve replacement: a speckle tracking study

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ABSTRACT

Introduction and objectives: Transcatheter aortic valve implantation (TAVI) has emerged as an alternative and less invasive treatment to surgical aortic valve replacement (SAVR). Left ventricular global longitudinal strain (LV-GLS) can reveal changes in left ventricular performance before involvement of ejection fraction. Our aim was to present and evaluate our center's experience regarding short- and long-term reverse left ventricular remodeling using two-dimensional-speckle tracking echocardiography-derived LV-GLS after TAVI compared with SAVR.
Methods: Our multidisciplinary cardiac team carefully evaluated 65 patients for SAVR who presented with severe symptomatic aortic stenosis and who had high, intermediate, or low surgical risk. The patients underwent either TAVI with an Evolut-R self-expanding valve or SAVR. Echocardiographic evaluation was performed before, 1 month, and 1 year after the procedure.
Results: TAVI was performed in 31 patients and SAVR in 34 patients. The incidence of valvular and paravalvular leak was higher in the TAVI group despite early favorable LV remodeling with a significant decrease in left ventricular mass index and E/e' shortly after the procedure and an early detectable improvement in LV-GLS from −8.18 ± 1.81 to −14.52 ± 2.52, reaching −16.12 ± 2.69 at 1 year ($P < .001$). This early improvement was not observed in the SAVR group. TAVI preserved right ventricular function without affecting tricuspid annular plane systolic excursion or increasing estimated pulmonary artery pressure.
Conclusions: Patients who underwent TAVI had earlier and significantly better LV remodeling with early reduction in left ventricular mass index, E/e' ratio, and significant early improvement in LV-GLS without concomitant impairment of left ventricular ejection fraction percentage or deterioration of right ventricular function.

Keywords: Left ventricular remodeling. Transcatheter aortic valve implantation. Surgical aortic valve replacement. Two-dimensional speckle tracking. TAVI. SAVR.

Remodelado del ventrículo izquierdo tras implante percutáneo o sustitución quirúrgica de válvula aórtica: estudio mediante *speckle tracking*

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica (TAVI) se ha establecido como una alternativa menos invasiva al recambio valvular aórtico (RVAo). El *strain* longitudinal global del ventrículo izquierdo (SLG-VI) puede detectar cambios en el funcionamiento ventricular izquierdo antes de que se deteriore la fracción de eyección. Nuestro objetivo fue presentar y evaluar la experiencia de nuestro centro en cuanto al remodelado inverso ventricular izquierdo a corto y largo plazo, utilizando el SLG-VI mediante rastreo de marcas, o *speckle tracking*, bidimensional, después de TAVI en comparación con los resultados tras RVAo.
Métodos: El equipo cardiológico multidisciplinario evaluó 65 pacientes remitidos para RVAo por estenosis aórtica grave, con riesgo quirúrgico alto, intermedio o bajo. Los pacientes se clasificaron según fueran tratados con TAVI (prótesis autoexpandible Evolut-R) o RVAo. Se realizó ecocardiograma antes del procedimiento, al mes y al año de llevarlo a cabo.
Resultados: 31 pacientes se trataron con TAVI y 34 con RVAo. En el grupo de TAVI hubo mayores tasas de regurgitación valvular y paravalvular. Se observó un remodelado ventricular izquierdo más favorable, con una disminución significativa del índice de masa del ventrículo izquierdo, un índice E/e' tras el procedimiento y una mejoría precoz del SLG-VI de −8,18 ± 1,81 a −14,52 ± 2,52, que al año fue −16,12 ± 2,69 ($p < 0,0001$), sin que esta mejoría precoz en dicho parámetro se evidenciara en el grupo de RVAo. En el grupo de TAVI se mantuvo la función ventricular derecha sin afectar al desplazamiento sistólico del plano tricúspide y sin aumentar la presión sistólica de la arteria pulmonar estimada.

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Conclusiones: Los pacientes que recibieron un TAVI tuvieron un mayor y más precoz remodelado ventricular izquierdo, con una reducción precoz del índice de masa del ventrículo izquierdo y del índice E/e', y una mejoría significativa precoz del SLG-VI, sin alteración de la fracción de eyección del ventrículo izquierdo ni deterioro de la función ventricular derecha.

Palabras clave: Remodelado ventricular izquierdo. Implante percutáneo de válvula aórtica. Recambio valvular aórtico. *Speckle tracking* bidimensional. TAVI. RVAo.

Abbreviations

AS: aortic stenosis. **LV:** left ventricular. **LVEF:** left ventricular ejection fraction. **LV-GLS:** left ventricular global longitudinal strain. **SAVR:** surgical aortic valve replacement. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Degenerative calcific aortic stenosis (AS) is the most common valvular heart disease worldwide. For severe symptomatic cases, surgical aortic valve replacement (SAVR) has been the gold standard procedure for decades.[1]

However, since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive alternative treatment with a shorter recovery time and lower perioperative mortality rate. Initially, the procedure was introduced for patients with high[2,3] and intermediate surgical risk.[4,5] However, advances in technique and operator skills have expanded its use to patients with low surgical risk.[6,7]

It is well-known that the main problem in people with isolated AS is an increase in afterload, resulting in diastolic dysfunction followed by systolic dysfunction of the left ventricle (LV).[8] The optimal timing of intervention, whether surgical or transcatheter, depends on the severity or grades of stenosis, symptoms, and LV dysfunction.[9] Aortic valve replacement, whether through TAVI or SAVR, significantly affects LV remodeling, reduces symptoms, and increases overall survival.[7]

The current guidelines use left ventricular ejection fraction (LVEF) percentage to assess LV systolic function. However, subclinical myocardial dysfunction may develop despite a normal LVEF percentage. Fibrotic changes induced by AS mainly affect LV longitudinal function, while ejection fraction is determined by radial myocardial function. Most cases of severe AS requiring intervention have preserved ejection fraction percentages before and after intervention, with reduced ejection fraction percentages only observed in late and neglected cases with poor prognoses when both radial and longitudinal functions are affected.[8] Therefore, assessment of LV function or remodeling before or after the intervention should not be based solely on LVEF. Another reliable method is needed to fully assess the impact of aortic valve replacement on LV function.[10]

Global longitudinal strain (GLS) analysis has proven useful in accurately characterizing regional and global myocardial systolic function. This analysis can detect changes in LV performance and overcome the limitations of ejection fraction, such as considerable interobserver variability, lack of subtle regional differences, and inadequate acoustic windows, with superior prognostic validity compared with LVEF percentage.[10]

At Tanta University Hospital, we recently introduced the TAVI procedure. The aim of this study was to present and evaluate the experience of our team and study the impact of aortic valve replacement on several factors. These included prosthesis hemodynamics, significant valvular or paravalvular leak, and the need for new pacemaker implantation. We also aimed to assess short-and long-term reverse LV remodeling by evaluating conventional echocardiographic parameters. In addition, we used the more reliable and accurate two-dimensional (2D) speckle tracking-derived left ventricle global longitudinal strain (LV-GLS) following the TAVI procedure and compared these parameters with the gold standard SAVR.

Patients and study design

Patient sample and inclusion criteria

This longitudinal, prospective, nonrandomized, single-center study was conducted in the Cardiology Department of the Faculty of Medicine at Tanta University Hospital between May 2022 and October 2023. Sixty-five patients diagnosed with severe symptomatic AS, categorized as high, intermediate, or low surgical risk and scheduled for aortic valve replacement, underwent thorough evaluation by the multidisciplinary heart team. Following selection of the appropriate procedure, eligible patients were allocated to undergo either trans-femoral TAVI with an Evolut-R self-expandable valve (Medtronic, United States) or SAVR.

Patients were classified into 2 groups as follows:

- Group I: patients with clinical symptoms, such as chest pain, syncope, or dyspnea, as well as echocardiographic evidence of severe AS (defined as a valvular area ≤ 1 cm^2 or indexed valve area ≤ 0.6 cm^2/m^2, mean pressure gradient ≥ 40 mmHg, and transaortic peak velocity ≥ 4 m/s).[9] Patients meeting these criteria were considered suitable candidates for TAVI.

- Group II: patients diagnosed with symptomatic severe AS based on clinical and echocardiographic findings, who were were deemed suitable candidates for SAVR.

Exclusion criteria

We excluded patients if they had any of the following conditions: concomitant significant valvular heart disease other than AS, severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m^2), prior biological or bare-metal valve replacement, significant carotid or coronary artery disease, abdominal aortic aneurysm, unstable heart failure, atrial fibrillation, atrial flutter, or any significant rhythm disturbance, predominant aortic regurgitation,

infective endocarditis, or severe LV dysfunction (ejection fraction < 35%). We also excluded patients who died during the study period or who lacked echocardiographic data before or after valve replacement.

METHODS

All patients underwent a full history and clinical evaluation. Data on the length of hospital stay, complications in the perioperative period, and clinical follow-up were collected by a review of medical records.

TAVI procedure

After the selection of suitable patients and valves, the procedure consisted of 5 sequential steps: access, valve crossing, balloon aortic valvuloplasty, valve implantation, and access closure. Additional considerations included the choice of anesthesia (local with sedation vs general anesthesia) and the placement of a temporary pacing wire in the right ventricle. Most patients underwent the procedure under conscious sedation. The devices used were the Evolut-R self-expandable valves (26, 29, or 34 mm).[11]

Standard echocardiography examination

Echocardiographic measurements were performed in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[12] Using the Vivid E9 ultrasound system (GE Vingmed Ultrasound, Norway), equipped with an M5S phased array transducer (2.5–5.0 MHz) and a dedicated software package, images and data were digitally stored for offline analysis before the procedure, shortly after (1 month), and 9 to 12 months after replacement. All echocardiographic parameters were acquired by 2 trained observers. Three to 5 consecutive beats were recorded and averaged.

LV dimensions, wall thickness, ejection fraction percentage and LV mass index were obtained. The transaortic peak and mean pressure gradients were calculated from the aortic velocity obtained through multiwindow continuous-wave Doppler evaluation using the modified Bernoulli equation.

The effective orifice area of the aortic valve was determined using the continuity equation and was indexed to body surface area as the stroke volume measured in the left ventricular outflow tract (LVOT) divided by the aortic time velocity integral measured by continuous-wave Doppler. LVOT stroke volume was calculated as the LVOT cross-sectional area multiplied by the LVOT time velocity integral, measured by pulsed-wave Doppler.

After aortic valve replacement, the LVOT velocity and diameter were obtained just apical to the prosthetic valve stent or sewing ring. The presence and quantification of any valvular or paravalvular leak were assessed using color and continuous-wave Doppler.

Additional echocardiographic parameters were obtained to assess LV diastolic function, particularly transmitral flow. This included measuring peak early (E) and atrial (A) flow velocities, as well as calculating the E/A ratio. The mean peak early diastolic (e′) velocity was acquired from the septal side of the mitral annulus in the apical 4-chamber view using tissue Doppler settings. The E/e′ ratio was then calculated, serving as an indicator of LV filling pressures.

Conventional parameters were used to assess right-sided function. This included measuring the tricuspid annular plane systolic excursion and evaluating the peak tricuspid regurgitation velocity with color Doppler flow imaging. The estimated systolic pulmonary artery pressure was calculated using the formula: estimated systolic pulmonary artery pressure = right atrial pressure + 4 V^2, where V represents tricuspid regurgitant velocity).

2D speckle tracking echocardiography, left ventricular global longitudinal strain

Global longitudinal peak systolic strain was assessed offline. Endocardial borders were manually traced and were visualized as a color-coded sequence in individual clips. Subsequently, they were combined in a bull's-eye plot. The software then calculated the regional and the average strain of the apical 2-chamber, 4-chamber, and 3-chamber views of the 17 segments at an end-systolic frame. Images with a frame rate < 50 were excluded.[13] The average peak GLS was then recorded and documented for each study.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 26 (IBM Corp., United States). Qualitative variables (eg, sex) are presented as frequencies, and the association of groups with categorical variables was assessed using the Pearson chi-square test for independence, the Fisher-Freeman-Halton exact test, or the Fisher exact test, as appropriate. Quantitative variables (eg, age and all echocardiographic measurements) are expressed as mean ± standard deviation (SD).

Differences in quantitative variables between the groups were assessed using either the independent samples T-test for baseline characteristics and measurements or mixed linear model analysis with treatment groups as a factor and baseline values as a covariate. Comparisons of repeated measurements within each group performed with the mixed linear model analysis for repeated measures with the time of treatment as a factor. The degree of mitral regurgitation between time points was compared using the McNemar test, while the degree of paravalvular leak was evaluated between time points using the marginal homogeneity test. A significance level of $P < .05$ was chosen for all statistical tests.

RESULTS

Table 1 shows the demographic data for the 2 groups: TAVI was performed in 31 patients and SAVR in 34. Age was older in the TAVI group ($P < .001$) than in the SAVR group.

The perioperative and postoperative course were uneventful in most patients, with reduced symptoms in both groups. However, several complications occurred during the periprocedural period and 1-year follow-up: 4 patients developed conduction abnormalities, presenting as complete heart block during their hospital stay and requiring the insertion of a dual-chamber permanent pacemaker; 3 patients developed contrast-induced nephropathy, which was corrected before discharge (2 of them had long-standing diabetes); 5 patients developed vascular complications in the form of mild to moderate bleeding from the access site, which did not require transfusion or intervention; and only 1 patient was readmitted due to hypertensive pulmonary edema (the patient had chronic uncontrolled hypertension) in the TAVI group. One patient died 10 days post-TAVI and was excluded.

In the SAVR group, 2 patients developed ischemic stroke due to ineffective anticoagulation and 2 others were readmitted due

Table 1. Demographic data, comorbidities and percentage of different complications in the 2 procedures

		TAVI (31)	SAVR (34)	*P*
Age	Mean ± SD	68.86 ± 2.61	66.00 ± 1.74	< .001*
Sex	Female	7 (22.6%)	9 (26.5%)	.716
	Male	24 (77.4%)	25 (73.5%)	
BMI	Mean ± SD	32.71 ± 3.13	32.83 ± 2.76	.893
Comorbidities	Hypertension	15 (48.4%)	18 (52.9%)	.714
	Diabetes	11 (35.5%)	13 (38.2%)	.818
	Dyslipidemia	13 (41.9%)	13 (38.2%)	.761
	CVD	7 (22.6%)	12 (35.3%)	.260
Complications Clinical outcome	No	22 (71.0%)	30 (88.2%)	.082
	Conduction disturbance	4 (12.9%)	0 (0.0%)	.046*
	Acute kidney injury	3 (6.4%)	0 (0.0%)	.103
	Neurological	0 (0.0%)	2 (5.9%)	.493
	Vascular-related complications	5 (16.1%)	0 (0.0%)	.021*
	Rehospitalization	1 (3.2%)	2 (5.9%)	.999

BMI, body mass index; CVD, cardiovascular disease; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; SD, standard deviation; TAVI, transcatheter aortic valve implantation.
* Significant at $P < .05$.

to warfarin toxicity complicated by gastrointestinal bleeding requiring admission for blood transfusion until the bleeding was controlled. None of the patients in this group developed acute renal injury, conduction abnormalities, or periprocedural vascular complications during their hospital stay (table 1).

In both groups, all echocardiographic variables were collected at baseline (before the procedure), and at 1 month, and 1 year postprocedure. These data are shown in table 2. A comparison of relative changes in each parameter at different evaluation times in the 2 groups is shown in table 3 and graphically represented in figure 1.

All baseline echocardiographic variables were comparable between the 2 groups.

Valve hemodynamics

After both procedures, there was a significant improvement in aortic valve maximum velocity (AV-V_{max}), aortic valve mean pressure gradient (AV-MG), and aortic valve area (AVA) ($P < .001$ for all). This improvement persisted throughout the year, while a relatively more pronounced early and 1-year improvement in AV-V_{max} and AV-MG ($P < .001$ for both) were observed in the TAVI vs the SAVR group. None of the patients in either group developed patient prosthetic mismatch.

Left ventricle dimensions and functions

There was a steady and significant improvement in LV septal thickness postprocedure in both groups at different evaluation times. There was also a slight but significant improvement in LV dimensions (LV end-diastolic dimension and LV end-systolic dimension) in the SAVR group at 1 year compared with the TAVI group. Specifically, LV end-diastolic dimension decreased from 5.15 ± 0.43 to 4.95 ± 0.29 ($P = .024$) in the SAVR group vs 5.09 ± 0.32 to 4.99 ± 0.29 ($P = .202$) in the TAVI group. Similarly, LV end-systolic dimension decreased from 3.51 ± 0.46 to 3.27 ± 0.21 ($P = .008$) in the SAVR group vs 3.30 ± 0.28 to 3.20 ± 0.22, $P = .064$ in the TAVI group.

A favorable early outcome was observed in the TAVI group, with a significant decrease in LV mass index and E/e' shortly after the procedure that persisted at 1 year. LV mass index decreased from 170.33 ± 14.10 to 152.14 ± 13.28 ($P < .001$) in the TAVI group vs 169.17 ± 11.39 to 169.63 ± 11.05 ($P = .999$) in the SAVR group. E/e' decreased from 15.81 ± 2.84 to 12.10 ± 1.92 ($P < .001$) in the TAVI group vs 14.13 ± 3.05 to 14.21 ± 2.67 ($P = .999$) in the SAVR group (figure 1).

Although mitral valve regurgitation showed a relative improvement in the TAVI group compared with the SAVR group at 1 month ($P = .028$) and 1 year of follow-up ($P = .020$), it did not significantly change within each group at different evaluation times. Mild mitral regurgitation was prevalent in both groups.

Right ventricular assessment

There was no significant change in tricuspid annular plane systolic excursion postprocedure in the TAVI group. However, in the SAVR group it significantly decreased shortly after the procedure from 2.14 ± 0.22 to 1.67 ± 0.22 ($P < .001$). As shown in figure 1, estimated systolic pulmonary artery pressure showed a significant reduction from 30.00 ± 6.32 to 27.14 ± 6.08 ($P = .001$) shortly after TAVI but was significantly increased from 29.79 ± 8.06 to 33.79 ± 7.49 after SAVR ($P = .005$).

Left ventricular global longitudinal strain

There was a statistically significant difference between the 2 groups ($P < .001$), favoring the TAVI group with an early detectable

Table 2. Echo-Doppler parameters for the 2 procedures at each stage of assessment

Variables		Baseline			1 month			1 year		
		TAVI	SAVR	*P*	TAVI	SAVR	*P*	TAVI	SAVR	*P*
LVEDD (cm)		5.09 ± 0.32	5.15 ± 0.43	.632	5.01 ± 0.33	5.13 ± 0.41	.133	4.99 ± 0.29	4.95 ± 0.29	.380
LVESD (cm)		3.30 ± 0.28	3.51 ± 0.46	.069	3.23 ± 0.28	3.50 ± 0.47	.136	3.20 ± 0.22	3.27 ± 0.21	.941
LVMI (g/m^2)		170.33 ± 14.10	169.17 ± 11.39	.760	152.14 ± 13.28	169.63 ± 11.05	< .001*	138.81 ± 15.16	138.54 ± 17.03	.952
LV sept (cm)		1.53 ± 0.12	1.52 ± 0.10	.707	1.44 ± 0.14	1.46 ± 0.13	.107	1.21 ± 0.17	1.25 ± 0.13	.280
LVEF %		63.33 ± 5.86	57.44 ± 13.66	.074	63.67 ± 6.05	59.71 ± 6.89	.207	64.48 ± 5.12	62.54 ± 4.29	.524
ESPAP (mmHg)		30.00 ± 6.32	29.79 ± 8.06	.924	27.14 ± 6.08	33.79 ± 7.49	< .001*	27.62 ± 6.21	28.54 ± 7.59	.491
E/A		0.63 ± 0.37	0.60 ± 0.39	.801	0.65 ± 0.43	0.62 ± 0.39	.899	0.67 ± 0.43	0.62 ± 0.38	.504
E/e'		15.81 ± 2.84	14.13 ± 3.05	.063	12.10 ± 1.92	14.21 ± 2.67	< .001*	10.10 ± 1.61	11.33 ± 1.90	.007*
TAPSE (cm)		2.06 ± 0.26	2.14 ± 0.22	.239	2.05 ± 0.26	1.67 ± 0.22	< .001*	1.97 ± 0.28	1.94 ± 0.23	.199
AV-V_{max} (m/s)		4.92 ± 0.22	4.95 ± 0.24	.655	1.64 ± 0.16	1.91 ± 0.15	< .001*	1.68 ± 0.16	1.85 ± 0.09	< .001*
AV-MG (mmHg)		58.38 ± 7.17	58.08 ± 7.67	.894	9.85 ± 1.65	13.23 ± 1.95	< .001*	9.21 ± 1.21	12.85 ± 1.93	< .001*
AVA-I (cm^2/m^2)		0.47 ± 0.10	0.47 ± 0.10	.984	1.20 ± 0.11	1.23 ± 0.07	.358	1.22 ± 0.10	1.26 ± 0.08	.201
LV-GLS %		−8.18 ± 1.81	−8.30 ± 1.99	.829	−14.52 ± 2.52	−8.82 ± 1.68	< .001*	−16.57 ± 2.52	−16.12 ± 2.69	.511
MR degree	Mild	26 (83.9%)	21 (61.8%)	.057	28 (90.3%)	23 (67.6%)	.028*	27 (87.1%)	21 (61.8%)	.020*
	≥ Moderate	5 (16.1%)	13 (38.3%)		3 (9.7%)	11 (32.4%)		4 (12.9%)	13 (38.2%)	
Degree of V or PV leak	None	–	–		17 (54.8%)	28 (82.4%)	.011*	15 (48.4%)	25 (73.5%)	.042*
	Mild	–	–		12 (38.7%)	6 (17.6%)		13 (41.9%)	8 (23.5%)	
	≥ Moderate	–	–		2 (6.5%)	0 (0.0%)		3 (9.7%)	1 (2.9%)	

AVA-I, indexed aortic valve area; AV-MG, aortic valve mean pressure gradient; AV-V_{max}, aortic valve maximum velocity; E/A, peak early diastolic mitral flow velocity/ late atrial diastolic mitral flow velocity; E/e', peak early diastolic mitral flow velocity/ pulsed-wave tissue Doppler-derived early diastolic velocity from the septal mitral annulus ratio; ESPAP, estimated systolic pulmonary artery pressure; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LV-GLS, Left ventricular- global longitudinal strain; LVMI, left ventricular mass index; LV sept, left ventricular septal thickness; MR, mitral regurgitation; SAVR, surgical aortic valve replacement; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation; V or PV leak, valvular or paravalvular leak.
* Significant at $P < .05$.
Values are expressed as mean ± standard deviation.

improvement of LV-GLS from −8.18 ± 1.81 to −14.52 ± 2.52, $P < .001$ at 1 month, reaching −16.57 ± 2.52 at 1 year. In contrast, this early improvement was not observed in the SAVR group, with the first detectable improvement being observed at 1 year (−8.30 ± 1.99 to −16.12 ± 2.69; $P < .001$) (figure 2).

Valvular or paravalvular leak

In the TAVI group, more patients developed mild or ≥ moderate paravalvular leak, with 12 (38.7%) and 2 (6.5%) patients, respectively, at immediate follow-up. These numbers increased to 13 (41.9%) and 3 (9.7%) patients, respectively, at 1 year. In the SAVR group, none developed ≥ moderate paravalvular leak, and only 6 (17.6%) patients had mild nonsignificant paravalvular leak at 1 month. Only 1 patient progressed from mild to moderate paravalvular leak at 1 year, with a statistically significant difference between the 2 groups ($P = .011$ at 1 month and $P = .042$ at 1 year).

Interobserver and intraobserver variability

The correlation coefficient for interobserver reproducibility of LV-GLS was 0.933 (95% confidence interval [95%CI]: 0.894-0.957), and that for intraobserver agreement was approximately 0.985 (95%CI, 0.976-0.991).

DISCUSSION

Echocardiography is the most effective approach for evaluating prosthetic valve performance, prosthesis-related complications, chamber geometry, remodeling, and cardiac function after any valve intervention, whether surgical or transcatheter.

Our study included all surgical risk categories. Whenever possible, TAVI was the preferred strategy for aortic valve replacement to increase our center's experience, unless contraindicated after heart team discussion (eg, inadequate annulus size, LV thrombus, asymmetric valve calcification, short distance between annulus and coronary ostium, inadequate vascular access, mobile thrombi in the arch or ascending aorta, bicuspid valve, concomitant significant valvular or coronary artery diseases requiring intervention, or due to unlikely improvement in quality of life after TAVI because of associated comorbidities). TAVI was found to be noninferior to SAVR regarding postoperative improvement in symptoms and enhanced valve hemodynamics with improvement of AV-V_{max}, AV-mean pressure gradient, and indexed aortic valve area, and even greater

Table 3. Comparison of repeated measurements at 1 month and 1year postintervention vs baseline measurements

	TAVI		SAVR	
	1 month vs baseline *P*	1 year vs baseline *P*	1 month vs baseline *P*	1 year vs baseline *P*
LVED	.092	.202	.999	.024*
LVESDD	.157	.064	.999	.008*
LVMI	< .001*	< .001*	.999	< .001*
LV sept	< .001*	< .001*	< .001*	< .001*
LVEF percentage	.999	.430	.736	.110
ESPAP	.001*	.036*	.005*	.752
E/A	.768	.117	.406	.761
E/e'	< .001*	< .001*	.999	< .001*
TAPSE	.999	.076	< .001*	.002*
AV-VMAX	< .001*	< .001*	< .001*	< .001*
AV-MG	< .001*	< .001*	< .001*	< .001*
AVA-I	< .001*	< .001*	< .001*	< .001*
LV-GLS	< .001*	< .001*	.443	< .001*
MR degree	.500	1.000	.500	1.000
-	-	1 year vs 1 month *P*	-	1 year vs 1 month *P*
Degree of V or PV leak	-	.083	-	.046*

AVA-I, indexed aortic valve area; AV-MG, aortic valve mean pressure gradient; AV-V_{max}, aortic valve maximum velocity; E/A, peak early diastolic mitral flow velocity/late atrial diastolic mitral flow velocity; E/e', peak early diastolic mitral flow velocity/pulsed-wave tissue Doppler-derived early diastolic velocity from the septal mitral annulus ratio; ESPAP, estimated systolic pulmonary artery pressure; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LV-GLS, left ventricular- global longitudinal strain; LVMI, left ventricular mass index; LV sept, left ventricular septal thickness; MR, mitral regurgitation; SAVR, surgical aortic valve replacement; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation; V or PV leak, valvular or paravalvular leak. *P* from mixed linear model analysis for repeated measures using time of treatment as a factor.
* Significant at $P < .05$.

improvement in AV-V_{max} and AV-mean pressure gradient during short- and long-term follow-up. These findings are supported by the recent update of the guidelines on indications for TAVI,[14] which have firmly established this approach as an alternative to SAVR in the treatment of AS in all surgical risk categories after the continued evolution of TAVI and the results of multiple randomized trials.

The major pathophysiological features of AS are increased afterload, LV remodeling, increased filling pressure, LV diastolic dysfunction, and heart failure symptoms. The diastolic dysfunction occurs earlier and is followed by an increase in LV mass.[15] After TAVI, there are immediate marked reductions in transvalvular pressure gradients, which translate into an immediate decrease in LV afterload, with an increase in E and e' that reflects early diastolic relaxation after TAVI compared with SAVR.

After SAVR, transient perioperative LV dysfunction related to cardiopulmonary bypass is a well-known factor that can adversely affect LV remodeling.[16] This transient LV dysfunction is associated with elevated biochemical markers, such as brain natriuretic peptides and troponin I soon after SAVR.[17,18] However, these consequences of cardiopulmonary bypass are absent after TAVI. Therefore, LV remodeling can be reduced shortly after the procedure due to less neurohormonal stimulation, which helps to improve preprocedure LV hypertrophy.[16]

Even with preserved systolic LV function after postcardiac surgery, the degree of the E/e' ratio has been shown to strongly correlate with brain natriuretic peptide levels. Consequently elevated left atrial pressure and diastolic dysfunction are major determinants of the release of brain natriuretic peptides in clinical settings.[19] The present study therefore highlights how the early recovery of LV filling pressure, as indicated by earlier reduction in AV-V_{max}, AV-MG, E/e' ratio, and LV mass index can positively affect LV remodeling. This translates into early improvement of LV-GLS deformation parameters even without significant changes in LVEF percentage after TAVI. These phenomena can help explain the evidence of better short-term prognosis in patients with severe AS undergoing TAVI.[20] At the 1-year follow-up, the initial mechanisms responsible for such better early outcomes were absent, and consequently the distribution of alterations in diastolic function in the SAVR group was comparable to that in the TAVI group.[15]

Mitral valve regurgitation did not appear to be significantly affected within the same group at different evaluation times but was improved in the TAVI group compared with the SAVR group.

These results contrast with previously published data from Gonçalves et al.[21] Although these authors calculated parameters of LV diastolic function before and minutes after TAVI, they did not include a comparison with a surgical group. They found a significant increase in E-wave deceleration time, E-wave velocity, and a marked decrease in LV end-diastolic pressure.

Additionally, Jin Ha et al.[22] compared the effect of TAVI vs SAVR immediately and 3 months after aortic valve replacement on LV function and diastolic parameters. They found that more patients showed improvement in LV diastolic function grade in the TAVI than in the SAVR group (42% vs 11%). Early improvement in diastolic function grade with a significant decrease in E/e' ratio and estimated systolic pulmonary artery pressure was seen immediately in the TAVI group. Similar to our study, LV end-diastolic dimension and LV end-systolic dimension were significantly changed at 3 months after SAVR. This result could be explained by the frequent use of diuretics following surgery to manage pleural effusion and possible pulmonary edema. In contrast, mitral valve regurgitation did not differ significantly between the groups, and LV mass index did not show an immediate significant change in either group and started to decrease after 3 months.

Guarracino et al.,[16] evaluated brain natriuretic peptides and LV diastolic function by mitral flow propagation velocity and mitral annulus early diastolic velocity, before and after valve procedures, and recorded improvement of LV diastolic parameters in the TAVI group with an increase in brain natriuretic peptides in the surgical group.

Similarly, Fairbairn et al.[23] reported early regression in mass and reverse LV remodeling after TAVI compared with SAVR.

In contrast, Ngo et al.[24] compared patients undergoing SAVR vs TAVI at 3 and 12 months and found a similar reduction in relative wall thickness in both groups and a more marked reduction in LV mass index in patients undergoing SAVR (17.5% vs 7.2%; $P < .001$).

In our study, patients who underwent TAVI showed little change in right ventricular function, with no change in tricuspid annular plane

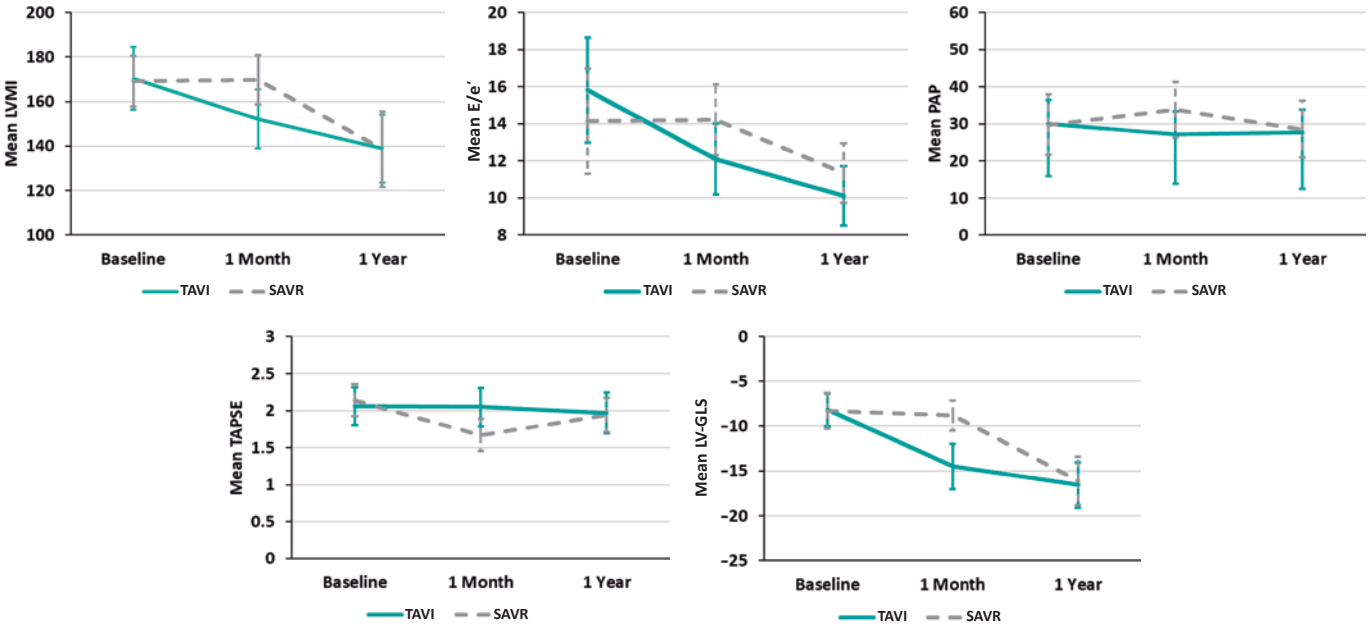

Figure 1. Relative changes of each parameter throughout the study from baseline to 1 year in both groups, with a relative decrease of LVMI, E/e, estimated systolic pulmonary artery pressure and relative increase in LV-GLS with no change in TAPSE shortly (1 month) after TAVI procedure vs no detectable changes in LVMI, E/e or LV-GLS and relative decrease in TAPSE and increase in estimated systolic pulmonary artery pressure in the SAVR group. At 1 year, the parameters were nearly equivalent in the 2 groups. E/e', peak early diastolic mitral flow velocity/ pulsed-wave tissue Doppler-derived early diastolic velocity from the septal mitral annulus ratio; LV-GLS, left ventricular-global longitudinal strain; LVMI, left ventricular mass index; PAP, pulmonary artery pressure; SAVR, surgical aortic valve replacement; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation.

systolic excursion or further increase in estimated systolic pulmonary artery pressure compared with those who underwent SAVR. Kempny et al.[25] confirmed that TAVI did not influence right ventricular function, but that it worsened in patients undergoing SAVR.

Increased LV mass and the higher relative wall thickness generated by increased LV afterload in patients with severe AS are associated with reduced LV regional and global myocardial deformation assessed by 2D speckle tracking echocardiography. Therefore, LV-GLS can accurately assess LV myocardial contractility and can detect subclinical changes in LV performance in patients with AS,[26] which improves after aortic valve replacement.[27]

Several studies have shown that TAVI is associated with a significant early improvement in LV strain parameters[28-30] and that this such improvement is associated with a more favorable prognosis.[25] Similar to our study, LV-GLS significantly improved immediately after TAVI while ejection fraction failed to show such a change.

Tsampasian et al.[31] assessed LV-GLS before and after TAVI in 85 patients, with a mean follow-up of 49 ± 39 days. TAVI resulted in an early significant improvement of GLS (from −13.96 to −15.25, P = .01) as well as early LV mass regression with no change in ejection fraction percentage. The type of valve had no effect on LV function or remodeling after TAVI.

Mild or persistent moderate paravalvular leak is a known predictor of poor outcomes after TAVI.[32] However, in our study, although more patients developed significant paravalvular leak after TAVI compared with SAVR in both short- and long-term follow-up, LV-GLS improved shortly after TAVI. This finding is supported by those of Kampaktsis et al.,[33] who studied the impact of paravalvular leak on LV remodeling and LV-GLS and reported significant improvement in LV-GLS regardless of paravalvular leak, at the same time as it negatively affected LVEF percentage, LV mass regression, and diastolic function. A small number of our included patients could have negatively affected the statistical power of these findings. Patients predominantly with aortic regurgitation, or severe LV dysfunction (EF < 35%) were excluded to eliminate the adverse effect of such confounding factors on LV remodeling.

Limitations

This study has some limitations. The first is the small sample size due to the limited number of TAVI patients in our center at enrolment. A larger sample size would have enhanced the statistical power and generalizability of the findings. Second, this is a single-center study with a lack of randomization, which could introduce selection bias and potentially affect the validity of the comparison between the 2 procedures. Third, we did not study other confounding factors affecting postoperative LV remodeling, such as hypertension, renal impairment, and baseline ventricular dysfunction. Fourth, the study reported follow-up data at 1 month and 1 year after the procedure. Longer-term follow-up would provide a more comprehensive understanding of LV remodeling outcomes.

CONCLUSIONS

Compared with individuals who underwent SAVR, those undergoing TAVI had earlier improvement of LV remodeling and LV diastolic function, with early reduction in LV mass index, E/e' ratio, and significant early improvement of LV-GLS without concomitant changes in LVEF percentage, while maintaining right ventricular function. Nevertheless, these patients also showed rapid valve deterioration and a higher incidence of valvular and paravalvular leak. More TAVI patients experienced complete atrioventricular block, requiring permanent pacemaker implantation, and vascular complication related to the access site.

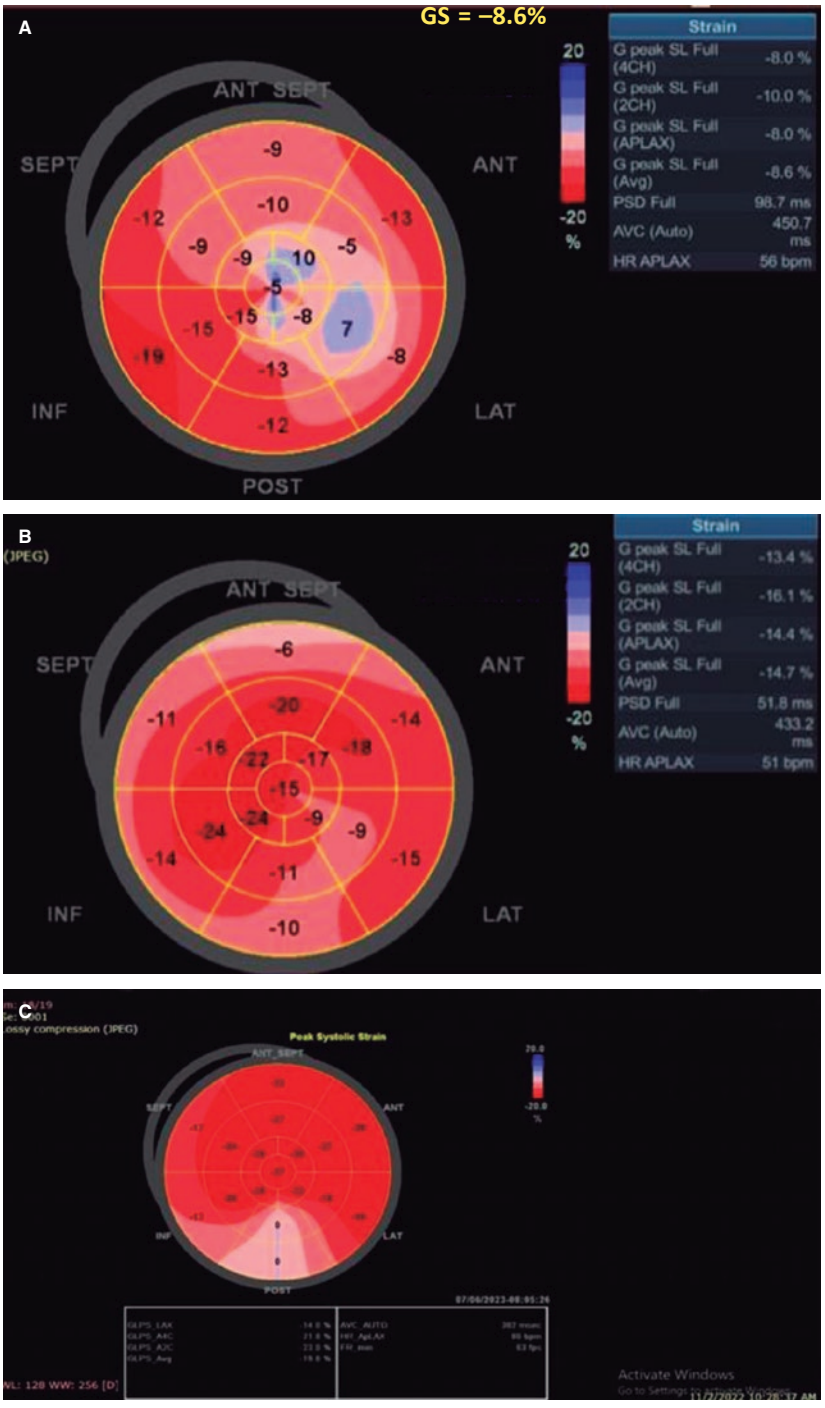

Figure 2. A, baseline: low LV-GLS before TAVI. B, 1 month after the procedure, LV-GLS significantly increased from –8.6 to –14.7. C, 1 year after TAVI, LV-GLS continued to improve from –14.7 to –19.8. SEPT, septal; ANT, anterior; ANT SEPT, anteroseptal; INF, inferior; POST, posterior; LAT, lateral.

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ETHICAL CONSIDERATIONS

Written informed consent was obtained from all study participants. The study was approved by the local Ethics Committee at the Faculty of Medicine, Tanta University (approval code: 36264PR12/1/23). Sex and gender variables were not taken into account in accordance with SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

S.B. El-Saied: design of the study, performing echocardiography for patients, and drafting the manuscript. R. Atlm and M. Elbarbary: data acquisition and analysis and revision of the manuscript and the results. A. Ghoneim and M.H. Sherif: contributed to manuscript drafting, data acquisition and analysis, and revision of the manuscript and the results. S.B. El-Saied, R. Atlm, A. Ghoneim, M.H. Sherif, and M. Elbarbary revised the work and approved the final version to be published.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

WHAT IS KNOWN ABOUT THE TOPIC?

- Degenerative calcific AS is the most prevalent valvular heart disease globally. SARV is the gold standard for severe cases.
- TAVI has emerged as an alternative, less invasive treatment with short recovery and lower perioperative mortality.
- Aortic valve replacement significantly impacts LV remodeling, reduces symptoms, and increases overall survival.
- Current guidelines use LVEF percentage to assess LV function, but subclinical myocardial dysfunction can develop despite a normal LVEF percentage.
- GLS analysis has been used to accurately characterize regional and global myocardial systolic function, overcoming the limitations of ejection fraction.

WHAT DOES THIS STUDY ADD?

- The study compared the impact of aortic valve replacement using TAVI vs SAVR on various parameters such as prosthesis hemodynamics, valvular leak, pacemaker implantation, and LV remodeling.
- TAVI showed earlier improvement in LV remodeling and diastolic function compared with SAVR, with reductions in LV mass index, E/e' ratio, and improvements in LV-GLS while maintaining RV function.
- However, TAVI was associated with valve deterioration, valvular leak, and a higher incidence of pacemaker implantation and vascular complications.

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Special article

Role of computed tomography in transcatheter coronary and structural heart disease interventions

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ABSTRACT

Computed tomography is a noninvasive imaging technique with high spatial resolution, providing excellent definition of calcium and intravascular space through the use of contrast media. This imaging modality allows both highly accurate measurements and virtual simulations for preprocedural planning in coronary and structural heart disease interventions. Computed tomography is currently the gold standard technique for patient selection and preprocedural planning in numerous scenarios, such as transcatheter aortic valve implantation, left atrial appendage occlusion, transcatheter mitral valve repair, and transcatheter tricuspid valve repair. This article reviews the role of computed tomography in transcatheter coronary and structural heart disease interventions.

Keywords: Computed tomography. Structural heart disease interventions. TAVR. LAAO. TMVR.

Papel de la tomografía computarizada en los procedimientos de cardiología intervencionista coronaria y estructural

RESUMEN

La tomografía computarizada es una técnica no invasiva, de gran resolución espacial, con excelente definición del calcio y del espacio intravascular al emplear medios de contraste, que brinda la posibilidad de realizar tanto mediciones como simulaciones virtuales de intervencionismo coronario y estructural. Se ha establecido como la técnica de referencia en la selección de pacientes y la planificación de procedimientos de intervencionismo transcatéter coronario y estructural en diferentes escenarios (implante percutáneo de válvula aórtica, cierre percutáneo de orejuela izquierda, reemplazo de válvula mitral transcatéter y reemplazo de válvula tricúspide transcatéter). El presente trabajo revisa el papel de la tomografía computarizada en el intervencionismo cardiaco coronario y estructural.

Palabras clave: Tomografía computarizada. Intervencionismo estructural. TAVI. LAAO. TMVR.

Abbreviations

CT: computed tomography. **ECG:** electrocardiogram. **LAAO:** left atrial appendage occlusion. **LVOT:** left ventricular outflow tract. **TAVI:** transcatheter aortic valve implantation. **TMVR:** transcatheter mitral valve replacement.

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INTRODUCTION

Coronary and structural heart disease interventions have traditionally relied on fluoroscopy and transesophageal echocardiography as the imaging modalities of choice, especially for intraprocedural monitoring. Imaging-based patient selection has also usually relied on echocardiography. However, the technological and knowledge advancements made in recent years have led to the incorporation of new imaging modalities—particularly computed tomography (CT) and, to a lesser extent, magnetic resonance—into the field of structural heart interventions.

Currently, CT is the imaging modality of choice before structural heart interventions in a wide range of procedures, as well as the screening technique for coronary artery disease, and even for planning coronary interventions.

This review examines the applications and indications of cardiac CT in transcatheter coronary and structural heart disease interventions.

GENERAL FEATURES OF CARDIAC COMPUTED TOMOGRAPHY

Cardiac CT is an optimal technique for evaluating patients prior to a structural heart intervention. This modality offers contrast-enhanced noninvasive imaging with excellent definition of calcium and intravascular space, submillimeter isotropic spatial resolution, and acceptable temporal resolution.

Like invasive coronary angiography, cardiac CT uses an X-ray source to create the image. Modern machines feature an O-shaped gantry ring with the X-ray tube positioned opposite a ring of detectors. The emitted radiation beam is attenuated and absorbed depending on tissue densities, with the captured energy reconstructed to form a medical image.

When acquiring tomographic images of heart structures and coronary arteries, it is important to consider their small-caliber, with each structure moving independently in all 3 spatial axes. Therefore, the equipment must be technically capable of producing conclusive studies. Table 1 outlines key technical parameters of CT generated images.

A cardiac CT scan should employ the ECG-gated technique to compensate for cardiac motion, with the study conducted during breath-holding to minimize respiratory movements. Acquisitions can cover the entire cardiac cycle or a preselected phase. Acquisition of the entire cardiac cycle (called "retrospective" in scanners with < 16 cm z-axis coverage) offers the advantage of allowing reconstruction of all phases, as well as functional assessments (volumes, ejection fraction, leaflet motion) and 4D reconstructions. However, this method requires higher radiation doses. This can be partially mitigated through retrospective acquisitions with dose modulation, acquiring high-quality images in 1 or more predefined phases while capturing the rest at lower quality, thereby reducing radiation exposure.[1]

Technological advances and the wider availability of CT scanners with cardiac acquisition software have allowed this imaging modality to be established as a standard in various structural interventional procedures. While it is widely acknowledged that the minimum equipment required includes an ECG-gated 64-slice CT scanner, the latest models offer superior image quality, decreased radiation exposure, and reduced contrast use. The latest generation of CT scanners follow various development paths: *a)* wide-detector CT scanners increase the scanned distance per heartbeat by incorporating more detectors; some scanners have more than 300 detectors, enabling cardiac coverage in a single heartbeat; *b)* high-pitch dual-source CT scanners use 2 radiation sources at a 90° offset and a high speed table to markedly enhance temporal resolution); *c)* spectral CT scanners use detectors with differing sensitivities or various energy levels from the emitter to capture images at different energy spectra, allowing a certain degree of tissue characterization; and *d)* photon-counting CT scanners eliminate the need for intermediate photoluminescent detectors, thus enhancing spatial resolution to 0.2 mm.

Table 1. Main basic concepts of computed tomography

Concept	Definition
Spatial resolution	The ability to visualize 2 separate points that are very close together. Depends on the size of the detectors; in modern CT scanners, it is < 1 mm.
Isotropism	Image composed of voxels with a similar size in all 3 spatial planes. Allows for image reformatting while minimizing the loss of resolution.
Temporal resolution	The shortest time required by the CT scanner to acquire an image. Depends on the gantry rotation speed and the acquisition method.

In addition to the CT scanner, an at least dual-phase injector is required to allow high flow (4-7 mL/s), a contrast agent with an iodine concentration around 350 mg/mL (ideally iso-osmolar), and a digital processing and image storage system in DICOM format (Digital Imaging and Communication in Medicine).

Preparing patients for a cardiac CT is essential to ensure high-quality diagnostic tests. Prior to the procedure, patients must provide informed consent and undergo an assessment to rule out any contraindications. A peripheral venous line is usually established in the right antecubital fossa (18-20 G). Patients are usually placed in the supine position with their arms raised above their heads. ECG electrodes are applied, ensuring excellent trace quality. It is important to explain and practice the breath-holding technique required during the scan with the patient, as well as to monitor ECG-quality during the breath-hold.

Depending on the indication of the study, if the patient's heart rate is high or the rhythm is irregular, premedication may be necessary, with the most common choice being IV beta-blockers. In studies that require assessing the coronary lumen, sublingual nitroglycerin is usually also administered. When performing a cardiac CT prior to structural intervention, it is important to remember that severe symptomatic aortic or mitral stenosis is a contraindication for nitroglycerin use. Beta-blockers should be administered with caution, under the supervision of qualified personnel, ensuring that advanced cardiopulmonary resuscitation can be performed if necessary.

APPLICATION TO STRUCTURAL HEART INTERVENTIONS

Coronary computed tomography angiography (CCTA) provides a detailed anatomical assessment of the coronary tree, including its origin and course, detects the presence of atherosclerotic lesions, quantifies affected segments, and determines the severity of stenosis and atherosclerotic burden. CCTA is the standard imaging modality to assess symptomatic patients and can be considered in selected high-risk asymptomatic patients. It has a sensitivity of 97% and a specificity of 78% when taking invasive coronary angiography in a population with a pretest probability of 56% as a reference. While

Table 2. Current indications for computed tomography of coronary arteries and measurement of coronary artery calcium based on the European Society of Cardiology clinical practice guidelines

Acute symptoms	Degree of recommendation	Level of evidence	Year	Ref.
Suspected acute coronary syndrome, normal or uncertain range troponins, normal electrocardiogram, and no recurrence of pain; may be considered as part of the initial diagnostic evaluation	IIA	A	2023	5
Systematic use in patients with suspected acute coronary syndrome	III	B	2023	5
Stable symptoms	**Degree of recommendation**	**Level of evidence**	**Year**	**Ref.**
Symptomatic patient with suspected coronary artery disease that cannot be clinically ruled out	I	B	2019	4
Risk stratification in patients with suspected or newly diagnosed coronary artery disease	I	B	2019	4
Patients with suspected vasospastic angina to study underlying coronary artery disease	I	C	2019	4
Screening for coronary artery disease in hemodynamically stable patients with aortic vegetations requiring cardiac surgery	I	B	2023	6
Patients with a low-to-intermediate probability of coronary artery disease and a previous equivocal noninvasive stress test	IIA	C	2021	7
Alternative to invasive coronary angiography prior to valvular cardiac surgery in patients with a low probability of coronary artery disease	IIA	C	2021	8
Patients with suspected cardiomyopathy for screening of coronary artery disease, or coronary anomalies that may be causing the cardiomyopathy	IIA	C	2023	9
Intermediate-to-high risk patients with prior nonemergency, noncardiac surgery: *a)* low-to-intermediate probability of coronary artery disease and suspected chronic or acute coronary syndrome without enzyme mobilization; *b)* patients ineligible for noninvasive functional tests	IIA	C	2022	10
Coronary computed tomography angiography is not recommended for the routine follow-up of patients with established coronary artery disease	III	C	2019	4
Asymptomatic	**Degree of recommendation**	**Level of evidence**	**Year**	**Ref.**
Calcium scoring as a risk modifier in asymptomatic patients with moderate cardiovascular risk	IIB	B	2019	4
Selected individuals with no history of coronary artery disease, high cardiovascular risk (SCORE > 10%, strong family history, familial hypercholesterolemia) and desire to start an intensive exercise program	IIB	B	2021	11
High cardiovascular risk (diabetes mellitus, family history, or previous test suggesting coronary artery disease)	IIB	C	2019	4
Asymptomatic adults (> 40 years) with diabetes mellitus	IIB	B	2019	4
Asymptomatic nondiabetic low-risk adults	III	C	2019	4

CCTA has the highest sensitivity compared with other invasive imaging modalities, functional imaging techniques such as stress magnetic resonance (80%), stress echocardiography (82%), and positron emission tomography (85%) have superior specificity.[2] Despite its lower specificity, the CT-based anatomical strategy has been proven to be noninferior in terms of prognosis compared with the ischemia test-based functional strategy (PROMISE trial).[3]

Due to its high negative predictive value, CT is recommended by clinical practice guidelines as a first-line imaging modality to rule out obstructive coronary artery disease in low-to-intermediate risk symptomatic patients.[4] Table 2 outlines the main indications for CCTA in various clinical scenarios.

Technological advances and the incorporation of new imaging modalities, such as stress CT perfusion and fractional flow reserve CT (FFR_{CT}) have increased specificity rates to 85% to 87%.[12] This enhances the positive predictive value of the imaging modality and allows meticulous evaluation of intermediate-to-high risk patients.

Landmark studies have been published on the prognosis of patients evaluated using CT. The SCOT-HEART trial[13] demonstrated a reduction in cardiovascular deaths and nonfatal myocardial infarctions at the 5-year follow-up with a CT-guided strategy with outcome-based treatment adjustment compared with a conventional management strategy. On the other hand, the DISCHARGE trial[14] showed a similar risk of major cardiovascular events during follow-up in patients with intermediate probability and stable chest pain randomized to CT vs invasive coronary angiography, with a lower rate of complications in the noninvasive imaging modality group. These studies support CT as a first-line imaging modality to rule out coronary artery disease, establish preventive treatment in patients with nonobstructive coronary artery disease, stratify patients with obstructive coronary artery disease, and offer an alternative to invasive coronary angiography in a wide range of patients.

In patients with a history of coronary artery disease, CCTA can be used to assess coronary artery bypass graft surgery, verify the patency of coronary stents in specific cases (proximal segments and

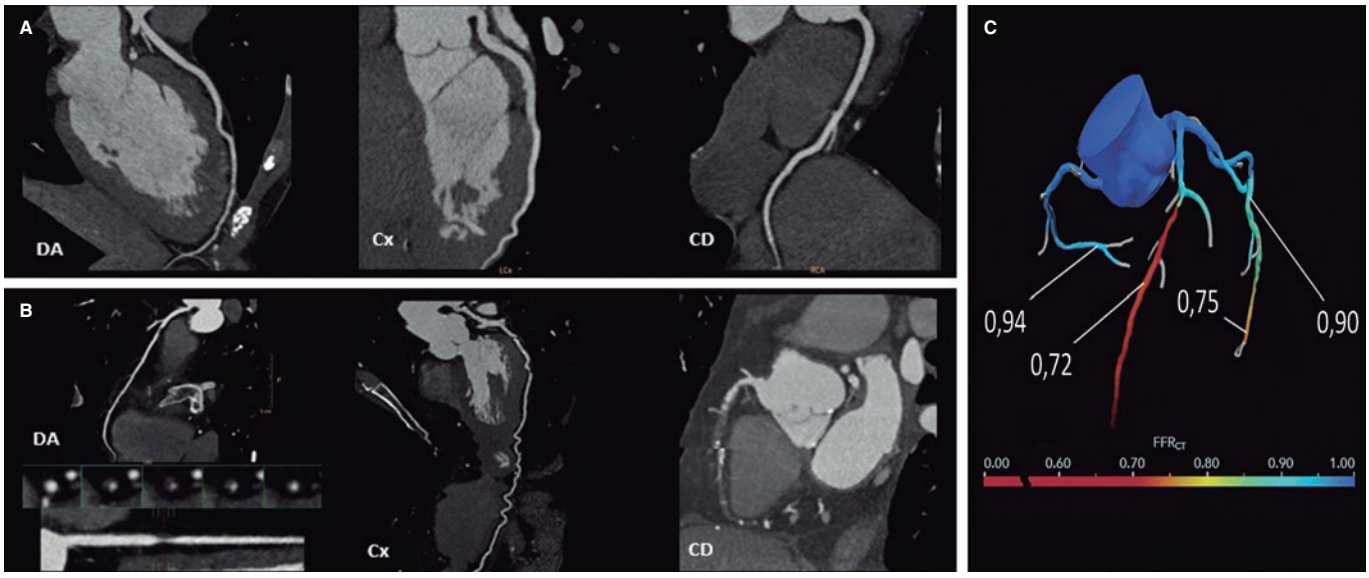

Figure 1. Computed tomography allows the study of coronary arteries to rule out the presence of coronary artery disease (**A**, normal coronary arteries), or to establish the severity and location of obstructive coronary disease (**B**, severe lesion in the proximal left anterior descending coronary artery [LAD] and chronic total occlusion in the mid and distal regions of the right coronary artery [RCA]). The functionality of the lesions can be assessed using computer simulation (**C**, fractional flow reserve computed tomography [FFR_{CT}], severe lesion in the mid LAD and distal left circumflex artery [LCx]).

stents > 3.0 mm), and assess chronic total occlusions prior to percutaneous coronary revascularization. In the BYPASS-CTCA trial,[15] which randomized patients with prior surgical coronary revascularization to undergo CT-based anatomical assessment and invasive coronary angiography, or isolated invasive coronary angiography, shorter procedures and fewer episodes of contrast-induced nephropathy were observed in patients with noninvasive assessment of coronary artery bypass grafts.

CCTA should adhere to the recommendations established by the Society of Cardiovascular Computed Tomography.[16] There are different image representation formats (axial, multiplanar reformatting, maximum intensity projection, curved multiplanar reformatting, or volumetric reconstruction), each with complementary uses. CCTA reading begins by assessing its quality, identifying potential artifacts, and visualizing the origin, course, and coronary dominance. The following are general principles for interpretation: *a)* cross-sectional systematic review of each coronary segment from multiple planes; *b)* vigilance for possible artifacts; *c)* evaluation of lesion morphology and composition; and *d)* grading lesion severity using high-resolution images in longitudinal and cross-sectional views of the vessel lumen. Following the modified distribution of the American Heart Association, coronary arteries are divided into 18 coronary segments. Identified lesions are listed based on the affected segment, the nature of the lesion (noncalcified, partially calcified, or calcified), and degree of resulting stenosis: normal (no lesion or stenosis), minimal (< 25% lumen reduction), mild (25%-49%), moderate (50%-69%), severe (70%-99%), or occlusion (> 99%).

Detailed analysis of the CT image enables the selection of a plan for transcatheter intervention and the materials to be used, and potentially reduces procedural length and complexity. This can be particularly useful when optimizing the fluoroscopy angle based on CT analysis in complex or bifurcated coronary artery lesions, as well as when performing complex cardiac catheterizations in patients with percutaneous aortic valve prostheses.[17]

The overall complexity of coronary artery disease can be represented by indices such as the coronary calcium score, or the number of segments with some degree of coronary artery disease, but several specific scales are available. Among these, the most widely used are the CAD-RADSTM (Coronary Artery Disease Reporting and Data System)[18] and its updated version, the CAD-RADSTM 2.0,[19] which incorporates parameters of perfusion and plaque complexity. Other more specific scales include the CT-SYNTAX[20] scale, which combines CT-based anatomical information with clinical data from the SYNTAX scale, and the Functional CT-SYNTAX[21] and Functional FFR_{CT}[22] scales, which add incorporate FFR_{CT}-based functional information. These scales help refine the decision between surgical and percutaneous revascularization strategies, with promising initial results.[23] Their prognostic validation in different scenarios, and their implementation in clinical practice, may represent a paradigm shift in the performance of invasive diagnostic imaging studies in stable patients.

In patients with chronic total coronary occlusions, preprocedural CT analysis allows estimation of the probability of success of percutaneous coronary revascularization; several prognostic scales have been developed for this purpose, such as the J-CTO,[24] the CT-RECTOR,[25] and the KCCT[26] (table 3). The parameters analyzed include the extent of calcification, vascular tortuosity, the morphology of the occlusion stump, the presence of multiple occlusions, and the length of the lesion.

APPLICATION TO STRUCTURAL HEART INTERVENTIONS

Transcatheter aortic valve implantation

After echocardiographic diagnosis of severe aortic stenosis, CT is the imaging modality of choice for a comprehensive assessment of patients eligible for transcatheter aortic valve implantation (TAVI).[27] In a single scan, CT can evaluate vascular access, verify the degree of aortic stenosis and valve morphology, measure the aortic annulus, assess the risk of coronary occlusion, and determine the optimal fluoroscopy angles, among other aspects. In addition, in a high percentage of cases, CT facilitates the screening of proximal obstructive coronary artery disease and assessment of extracardiac findings.[28]

Table 3. Prediction scales for the success and complications associated with the revascularization of chronic total occlusions by computed tomography

Score	Variables (points)	Classification
J-CTO	Tapered (0) vs blunt end (1)	Easy (0) Intermediate (1) Difficult (2) Very difficult (≥ 3)
	No calcification (0) vs some calcification (1)	
	Occlusion angle ≤ 45° (0) vs > 45° (1)	
	Occlusion length < 20 mm (0) vs ≥ 20 mm (1)	
	No previous failed revascularization attempts (0) vs with previous attempts (1)	
CT-RECTOR	< 2 occlusions (0) vs ≥ 2 complete interruptions (1)	Easy (0) Intermediate (1) Difficult (2) Very difficult (≥ 3)
	Tapered (0) vs blunt end (1)	
	< 50% calcification of vessel perimeter on short axis (0) vs ≥ 50% calcification at some point of the occlusion (1)	
	Occlusion angle ≤ 45° (0) vs > 45° (1)	
	No previous failed revascularization attempts (0) vs with previous attempts (1)	
	Duration of chronic total coronary occlusion < 12 months (0) vs ≥ 12 months (1)	
KCCT	Tapered (0) vs blunt end (1)	Easy (0) Intermediate (1) Difficult (2) Very difficult (3) Extremely difficult (≥ 4)
	No adjacent collateral branches (0) vs with collateral branches (1)	
	Occlusion length < 15 mm (0) vs ≥ 15 mm (1)	
	Occlusion angle ≤ 45° (0) vs > 45° (1)	
	Vessel calcification on the short axis < 180° of perimeter or < 50% of area (0) vs ≥ 180° of perimeter and ≥ 50% of area (1) vs complete central calcification of 360° of perimeter and 100% of area (2)	
	No previous failed revascularization attempts (0) vs with previous attempts (1)	
	Duration of chronic total coronary occlusion < 12 months (0) vs ≥ 12 months (1)	

Table 4. Main features that need to be included in the computed tomography report prior to transcatheter aortic valve implantation or percutaneous left atrial appendage occlusion

Transcatheter aortic valve implantation	
Aortic annulus	Measurement in systolic phase
	Area and perimeter
	Major and minor diameters,
	Optimal fluoroscopy view
Calcium and valve	Presence, morphology, and extent of calcium
	Valvular morphology
Aorta and accesses	Height of the origin of coronary arteries
	Minimum luminal diameter of each vascular segment
	Description of calcifications and vascular disease
Others	Coronary anatomy
	Extracardiac findings
Percutaneous left atrial appendage occlusion	
Thrombus	Screening for arterial/venous filling defect
Morphology and landing zone	Describe the morphology and presence of proximal lobes
	Measure the landing zone, maximum diameter
	Measure the depth and length of the appendage
	Optimal fluoroscopy view
Others	Anatomy of the interatrial septum
	Anatomy of the pulmonary veins
	Describe if there is pericardial effusion

Preprocedural assessment for TAVI includes: a) an optional noncontrast acquisition to quantify aortic valve calcium; b) ECG-gated acquisition in the systolic phase, at least in the region of the aortic valve complex; and c) depending on the speed and coverage of the equipment used, 1 or more acquisitions for iliofemoral access, without the need for ECG-gated synchronization in this region. The study requires the injection of contrast medium (50-90 mL, with a flow rate of 3-5 mL/s, subject to variations based on the equipment used and the patient's body surface area).[28]

The main aspects that should appear in the CT report prior to performing TAVI are listed in table 4.

Currently, there are 2 general designs of transcatheter aortic valve prostheses: balloon-expandable and self-expanding. Balloon-expandable TAVIs use radial force along with balloon inflation to fit their circular design to the oval shape of the aortic annulus. In contrast, self-expanding TAVIs expand on their own, due to nitinol memory, to fit over the annulus. In addition to technical and design differences, it is important to note that the sizing algorithms for these devices are not interchangeable. Sizing of balloon-expandable prostheses is based on the area of the aortic annulus, while that of self-expandig valves is based on the perimeter.

All the assessments necessary before TAVI are illustrated in Figure 2.

It is important to understand and analyze the anatomy of the aortic valve complex, which comprises the left ventricular outflow tract (LVOT), the Valsalva sinuses, the fibrous triangles between the aortic leaflets, and the leaflets themselves. A key measurement is the correct assessment of the plane of the aortic annulus, defined as the virtual plane aligned with the lowest insertion point of each aortic cusp or nadir. This involves determining the major and minor diameters, area, and perimeter of the aortic annulus. These measurements guide the selection of TAVI size. The aortic annulus undergoes changes in size and shape throughout the cardiac cycle, with mesosystole (30-35% R-R) often being the optimal time for measurement (larger size and reduced ellipticity).[29] Specialized software is available to automate these measurements and simulate the implant procedure, streamlining workflow and reducing inter- and intra-observer variability.

The landing zone for the prosthesis includes the aortic cusps, the aortic annulus, and the LVOT. Severe calcification in the LVOT and aortic valve increases the risk of subsequent periprosthetic regurgitation, while large nodular calcifications may pose a higher

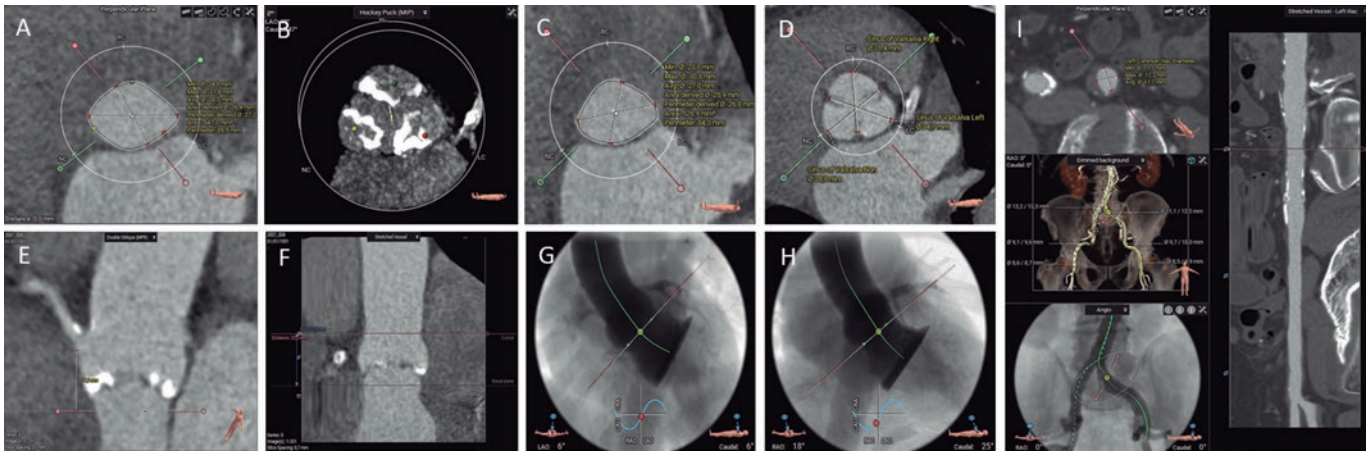

Figure 2. Preassessment for transcatheter aortic valve implantation using computed tomography and 3mensio CT analysis software: aortic annulus (**A**), aortic valvular calcium (**B**), left ventricular outflow tract (**C**), diameters of the Valsalva sinuses (**D**), height of the right coronary artery origin (**E**), height of the sinotubular junction (**F**), 3-cusp coplanar view (**G**), cusp-overlap view (**H**), and transfemoral accesses (**I**).

risk of aortic annulus rupture, especially with balloon-expandable prostheses.[30] It is essential to describe the location and extent of calcification in the aortic valve and the first 5 to 7 mm of the LVOT, as this area serves as the sealing zone for most available TAVIs. The morphology and degree of calcification of the aortic valve should be systematically reported, with particular attention to the presence of bulky calcification or partial fusion of the aortic commissures.[28]

The perpendicular height from the plane of the aortic annulus to the origin of the coronary arteries must be evaluated. Although absolute cutoff values have not been established, a coronary artery origin height of < 12 mm and sinuses of Valsalva < 30 mm are associated with a higher risk of TAVI-related coronary occlusion.[31]

The report should also include the optimal CT projections for valve deployment. Identifying these projections reduces radiation dose, contrast, and procedure duration.[29] Angulation should be reported to obtain a coplanar projection (3 cusps), aligning the cusps, and the angulation for obtaining an overlapping projection (cusp-overlap), with the left and right cusps overlapped. This plane deploys the LVOT and allows better control of implant depth during valve deployment, especially with self-expanding valves.[32]

CT allows assessment of vascular access in a single study, providing excellent resolution and detailed delineation of the presence and extent of calcifications. Vascular complications increase the morbidity and mortality associated with TAVI. Factors associated with the occurrence of vascular complications include the sheath-to-femoral artery ratio, the presence of moderate to severe calcification, and vascular tortuosity.[33] The report should include details on the minimum luminal diameters, the extent, distribution, and severity of calcification, as well as the presence or absence of vascular disease in all vascular segments between the aortic valve and the left and right common femoral arteries at the level of the femoral head.[28] If femoral accesses are deemed unsuitable, alternative accesses can be considered, with the most common being axillary/subclavian, carotid, transcaval, and transapical accesses.

Special attention should be paid to the bicuspid aortic valve, given its lower success rate in procedures and higher rates of periprosthetic regurgitation, albeit with similar clinical outcomes.[34] It is essential to determine the type of bicuspid valve (whether sinus fusion, 2 sinuses, or *forme fruste*),[35] presence of a raphe, calcium distribution, annulus size and eccentricity, as well as the origin and height of the coronary arteries. Measuring the aortic annulus can be particularly complex in 2-sinus bicuspid valves, requiring specific methodology.[28] The aortic annulus is defined as the virtual plane aligned with the lowest insertion point of the anterior/lateral cusp. Starting from this point, counterclockwise rotation to the lowest insertion point of the posterior/medial cusp is performed. Measurements should be taken at the line perpendicular to these 2 points, centered at the point where the smallest cross-sectional area is reached (as improper angulation can lead to inaccurate size estimation). The major and minor diameters, area, and perimeter of the aortic annulus are then determined. Algorithms have been developed for prosthesis size selection based on aortic annulus size, considering raphe length, calcium volume, and distribution (CASPER, calcium algorithm sizing for bicuspid evaluation with raphe).[36] Additionally, a method (LIRA, level of implantation at the raphe) has been proposed by delineating the perimeter of the bicuspid valve opening,[37] although its superiority over conventional measurements remains unclear.[38]

A variant of TAVI is the valve-in-valve implant, in which a percutaneous prosthesis is placed over a dysfunctional bioprosthesis. CT plays a key role in prosthesis size selection, especially when the model or size of the implanted prosthesis is unknown, but also in stratifying the risk of coronary occlusion. Among the main parameters for determining the risk of coronary obstruction are the level reached by the prosthesis cusps relative to the origin of the coronary arteries and the sinotubular junction, risk associated with the proximity of the valve to the sinotubular junction, < 2 mm distance from the virtual TAVI to the sinotubular junction, < 4 mm distance from the virtual TAVI to the origin of the coronary arteries, a prior supra-annular or supracoronary prosthesis, a surgical prosthesis with leaflets implanted outside the annulus (Mitroflow or Trifecta type), a prior implant in a high position, and the presence of moderate or severe commissural misalignment.[39,40]

After the TAVI procedure, CT allows assessment of the position and geometry of the prosthesis, as well as the thickness and mobility of the prosthetic leaflets. Following TAVI, a CT scan may be performed if prosthetic dysfunction or degeneration is identified by echocardiography, suspected thrombosis, infectious endocarditis, or periprosthetic regurgitation requiring anatomical assessment. The phenomenon of thickening with hypoattenuation and reduced mobility in the prosthetic leaflets has been described, which is associated with subclinical thrombosis and resolves with

anticoagulation therapy. This finding has been associated with a higher but nonsignificant tendency for embolic events, and consequently there is no consensus or established indication for systematic performance of CT after TAVI. Its occurrence is more common in valve-in-valve, balloon-expandable prostheses, and larger prostheses, as well as those with eccentric expansion due to bicuspid valves, for example.[41]

Lastly, there is the option of using CT scans to resolve diagnostic uncertainties regarding the severity of aortic stenosis. Assessing aortic valve calcium can be especially helpful in patients with low-flow, low-gradient aortic stenosis and preserved ejection fraction. Agatston scores ≥ 2000 in men and ≥ 1200 in women indicate severe degenerative aortic stenosis, while scores < 1600 in men and < 800 in women suggest the absence of severe degenerative stenosis.[8]

Percutaneous left atrial appendage occlusion

Percutaneous closure of the left atrial appendage (LAAO) is an alternative to oral anticoagulation in patients with atrial fibrillation and a contraindication to oral anticoagulation. The traditional technique used for patient selection is transesophageal echocardiography (TEE) to rule out the presence of thrombus in the appendage and to take measurements for device selection. Three-dimensional measurements (3D-TEE, CT) have consistently been shown to be more accurate in selecting device size than 2D-TEE. Therefore, CT is an alternative technique in patient selection, as it allows visualization of the presence of thrombus and evaluation of the anatomy and size of the appendage, as well as the interatrial septum.[42]

CT evaluation of LAAO should be performed with ECG-gated acquisition, ideally in the telesystolic phase (when the left atrial appendage is maximally expanded), and a second acquisition should be performed in the venous phase, 60 to 90 seconds after contrast administration, to assess the presence or absence of thrombus in the left atrial appendage.[43] The main features that should be included in a CT report for LAAO are listed in table 4. If the quality allows, it is advisable to perform an assessment of coronary anatomy.

The morphology of the left atrial appendage is highly variable and complex. Several devices for LAAO have been marketed, with the most commonly used being lobe and disc devices. Measurement of the landing zone is performed using multiplanar reformatting from 2-chamber and coronal planes. In the case of lobe devices, the landing zone extends from the circumflex artery to a point located 10 to 20 mm inside the ligament of Marshall.

The morphology of the left atrial appendage is highly variable and complex. Different devices for LAAO have been commercialized, with the most commonly used being lobe and disc devices. Measurement of the deployment zone is performed using multiplanar reformatting from two-chamber and coronal planes. In the case of lobe devices, the deployment zone extends from the circumflex artery to a point located 10-20 mm inside the ligament of Marshall. The depth is determined from the landing zone to the most distal end of the appendage. With disc devices, the landing zone is located 10 to 12 mm inside the ostium of the appendage, covering the course of the circumflex artery at its lower end. The depth in this type of device is defined from the ostium to the opposite wall of the appendage.[43] It is also important to assess the anatomy of adjacent structures, especially the ligament of Marshall, to assess the feasibility of fully covering it with a disc device and to avoid thrombus formation during follow-up,[44] as well as the anatomical characteristics of the pulmonary artery in relation to the left atrial appendage.[45]

Specific software has been designed to automate these measurements and simulate the implantation process (figure 3). Utilizing simulation software through computing enhances device selection and procedural outcomes.[46]

After LAAO, it is recommended to perform an imaging test 45 to 60 days postimplantation to verify the stability and positioning of the device, to search for residual leaks, and to rule out the presence of device-related thrombus. The most commonly used techniques are TEE and CT. CT allows better visualization of the position and deployment of the device, has equal thrombus detection capability, and has higher sensitivity in detecting residual contrast passage. The latter may be due to device malapposition, the presence of a peridevice leak, or the patency of the covering tissue.[47] The clinical relevance of residual leaks, as well as the importance of their size, are not entirely clear.[48]

Transcatheter mitral valve replacement

Within transcatheter mitral valve intervention, there are options for repair and replacement. Edge-to-edge repair techniques are clinically established, with patient selection and procedural monitoring conducted via TEE. In contrast, for various valve replacement techniques, CT is indispensable. CT with ECG-gated acquisition is required to cover and reconstruct the entire cardiac cycle after contrast administration with adequate opacification of at least the left chambers, and ideally the right chambers, as well as to enhance visualization of the anatomy and its relationships. Detailed recommendations for acquisition and optimization have been published.[49] CT allows evaluation of mitral annulus size and shape, selection of prosthesis type and size for implantation, virtual simulation of implantation, assessment of resulting neo-TSVI, selection of optimal fluoroscopy angles, and planning of vascular access (transseptal or transapical).[49] (figure 4). Specific measurements for each device are determined by the manufacturer.

Transcatheter mitral valve replacement (TMVR) has been described for native valve, prior surgical annuloplasty (valve-in-ring), dysfunctional bioprosthetic valve (valve-in-valve), and severely calcified native mitral annulus (valve-in-MAC).[50] CT is particularly useful to select prosthesis size and assess embolic risk in valve-in-MAC procedures by evaluating the thickness of the mitral annular calcium, its extension around the posterior perimeter or mitral trigones, and the damage to the mitral leaflets.[51]

The main complication to avoid during TMVR planning is LVOT obstruction after the procedure. The neo-LVOT refers to the distance or area between the lower edge of the virtual implant and the interventricular septum. The main predictors of neo-LVOT obstruction are detailed in table 5.[52] The neo-LVOT area should be assessed in meso-telesystole (40%-50% R-R; the smallest area during the cardiac cycle), with obstruction risk increasing as the neo-LVOT area decreases: < 170 mm² indicates very high risk, 170 to 190 mm² indicates high risk, 190 to 220 mm² indicates acceptable risk, and > 220 mm² indicates low risk. In selected high-risk cases, techniques such as laceration of the anterior mitral leaflet (LAMPOON) or interventricular septal ablation (alcohol septal ablation) can be employed to enlarge the neo-LVOT area.[53]

Transcatheter tricuspid valve replacement

Transcatheter procedures for the tricuspid valve mainly include edge-to-edge repair, annuloplasty, and both orthotopic and heterotopic valve replacement (valve prostheses in the venae cavae).

The acquisition process is similar to that of pre-TMVR CT (ECG-gated covering and reconstructing the entire cardiac cycle

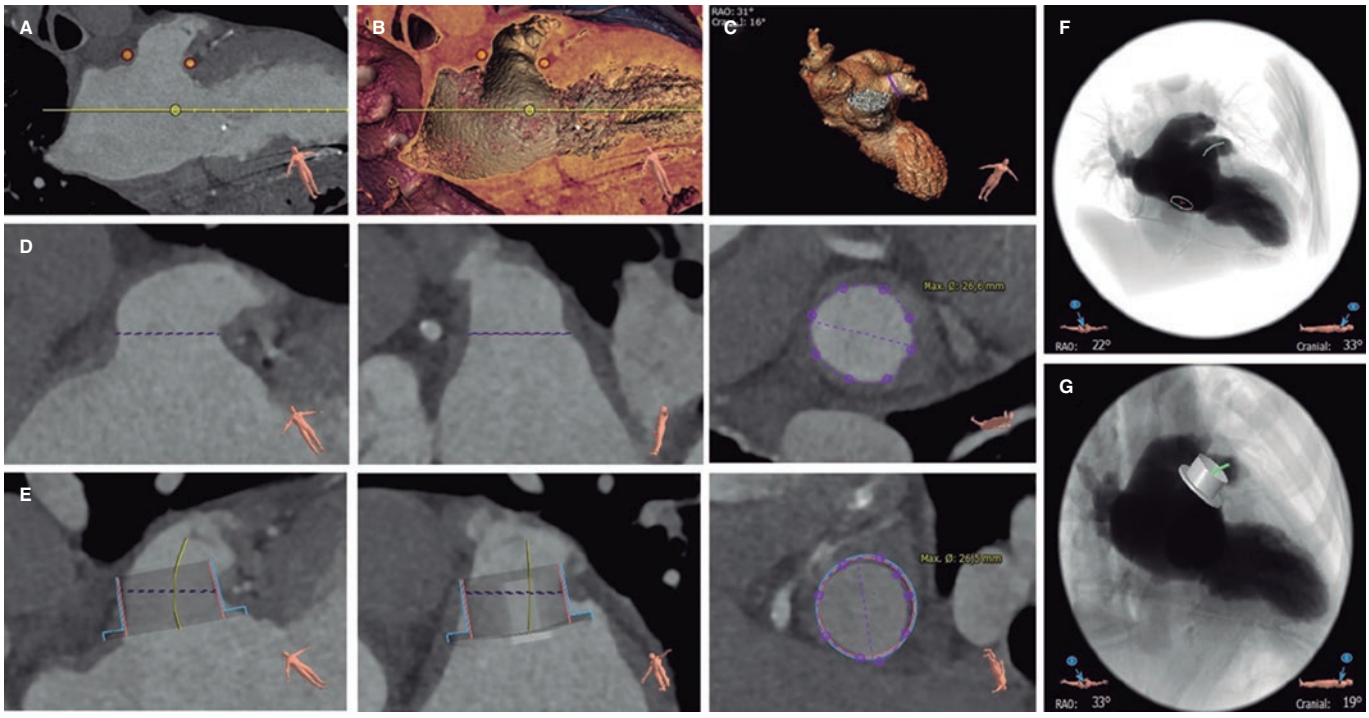

Figure 3. Planning for percutaneous left atrial appendage occlusion using computed tomography and 3mensio CT analysis software: identification of the left atrial appendage ostium (**A** and **B**), left atrial appendage morphology (**C**), measurement of the landing zone (**D**, longitudinal and cross-sectional views), simulation of the occluder device (**E**, longitudinal and cross-sectional views), simulation of the fluoroscopy view and position of the transseptal puncture (**F**), and simulation of the occluder device in fluoroscopy (**G**).

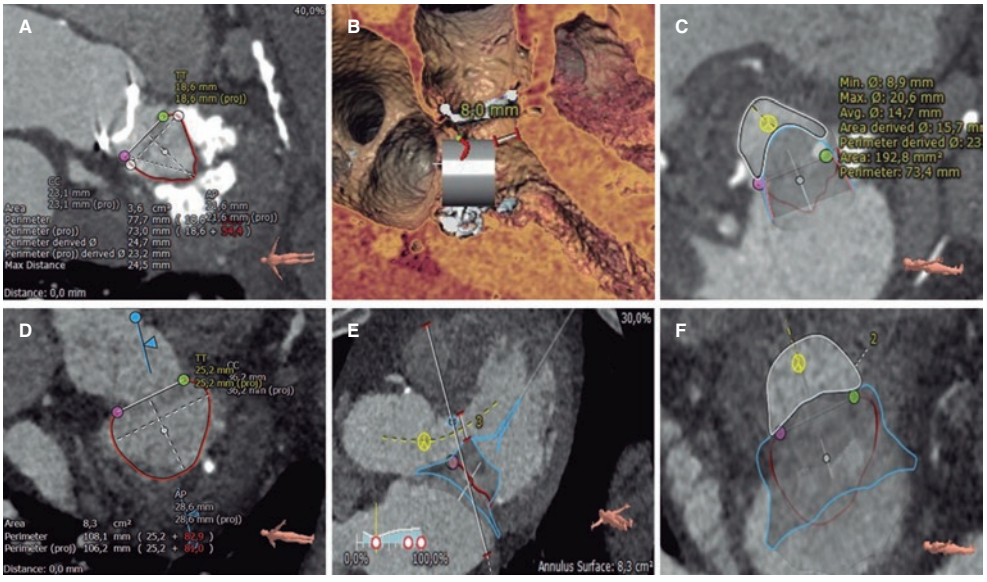

Figure 4. Several steps in the planning of transcatheter mitral valve replacement using computed tomography and 3mensio CT analysis software in 2 patients with valve-in-MAC (**A**-**C**) and native valve (**D**-**F**): delineation and measurement of the mitral annulus (**A** and **D**), evaluation of the distance from the virtual valve to the interventricular septum (**D** and **E**), and measurement of the neo-left ventricular outflow tract (**C** and **F**).

following contrast administration). However, it is optimized for contrast in the right heart chambers using triphasic injection protocols (a mixture of contrast and saline at different concentrations). Detailed recommendations for acquisition and optimization have been published.[49] CT imaging allows assessment of the tricuspid annulus geometry and size throughout the cardiac cycle, the morphology and mobility of the tricuspid leaflets, the position and relationship of the right coronary artery to the tricuspid annulus, right ventricular volume and ejection fraction, the optimal fluoroscopy angle, and vascular access[54] (figure 5).

CT imaging can also aid in assessing the position and relationship of pacing leads with the tricuspid leaflets in selected cases of edge-to-edge repair. However, its main role lies in patient selection and

Table 5. Predictors of left ventricular outflow tract obstruction in transcatheter mitral valve replacement

Obstruction predictors	Obstruction risk limit
Area of the neo-LVOT	< 1.9 cm²
Area of the neo-LVOT skirt	< 1.5 cm²
Sizes of the anterior mitral leaflet	> 25 mm
Protruding interventricular septum	Thickness > 15 mm
Distance between the mitral annulus and the interventricular septum	< 17.8 mm
Acute aortomitral angle	< 110°
Small left ventricle	End-diastolic diameter < 48 mm
Left ventricular hypertrophy	Indexed myocardial mass > 105 g/m²

LVOT, left ventricular outflow tract.

planning of annuloplasty and valve replacement procedures, in which it is the imaging modality of choice. In annuloplasty, CT imaging facilitates device sizing, allows certain possibilities to be ruled out via simulation of the interaction of anchoring systems and the course of the right coronary artery, and evaluates tricuspid leaflet tenting to assess potential residual regurgitation postprocedure.[54] In heterotopic replacement, CT enables sizing of the superior and inferior vena cava at different levels, assesses the anatomy and location of the suprahepatic veins, and determines the size of the right atrium, all of which determine the type and size of the device to be implanted.[55] Finally, in orthotopic replacement, the selection criteria largely depend on the chosen device; however, it is generally necessary to evaluate the annulus size, distance to the anterior papillary muscle or free wall of the right ventricle, the confluence position of the vena cavae, and the angles between these and the tricuspid annulus, as well as the access route.[56]

Other procedures

Paravalvular leak closure

CT has shown good diagnostic performance in detecting aortic and mitral paravalvular leaks, allowing definition of the number, location, shape, and size of the defects.[57] CT is especially useful in assessing infective endocarditis-related complications,[58] as well as for planning and supporting the closure of paravalvular leaks in the aortic position.[59] In addition, CT-based simulation prior to procedures can predict the occurrence of paravalvular leaks.[60]

Congenital heart diseases

Magnetic resonance imaging is the technique of choice in the diagnosis, evaluation, and follow-up of congenital heart diseases due to its ability to acquire any imaging geometry and perform anatomical and functional assessment, tissue characterization, and flow analysis, as well as the absence of radiation in a generally young population. CT is reserved for selected patients and cases.

Either CT or magnetic resonance can be used for patient selection, device choice, and sizing prior to intervention in congenital heart diseases. CT offers higher spatial resolution, enabling more precise delineation of calcification areas and proper sizing of prostheses. The use of CT or magnetic resonance is essential before transcatheter pulmonary valve replacement and percutaneous treatment of aortic coarctation. CT may also prove useful in cases of patent ductus arteriosus and complex fistulas. However, CT has lower added value in the closure of septal defects, such as atrial or ventricular septal defects.[61] Nevertheless, in postmyocardial infarction ventricular septal defects, CT can be highly useful for sizing the defect and assessing their morphology, extent, and borders, given the often intricate and complex nature of these defects, which hampers accurate evaluation by echocardiography.[62]

CT-fluoroscopy image fusion during structural heart interventions

The anatomical information and preprocedural planning can be integrated into procedural monitoring. Using specific software and a workstation, cardiac structures are semiautomatically segmented and coregistered with the patient's anatomy on the cath lab treatment table from 2 fluoroscopy projections. After coregistration, all CT information can be integrated into the procedure, allowing for expanded visibility, improved understanding of anatomical relationships, placement of markers or trajectories, and planning of optimal fluoroscopy angles.[63] However, these are static non-ECG- or respiratory-gated images (figure 6).

CT-fluoroscopy image fusion has been shown to reduce procedural length, contrast volume, and radiation exposure in TAVI and LAAO procedures, as well as a decreased need for intraprocedural device size adjustments in LAAO. The application and utility of CT- fluoroscopy image fusion have been reported in various procedures and have been shown to be particularly advantageous in complex interventions such as TMVR, transcatheter tricuspid valve replacement, transcaval TAVI, and paravalvular leak closure.[64]

CONCLUSIONS

CT is a high spatial resolution noninvasive imaging modality, providing excellent delineation of calcium and intravascular space using contrast media. The technique offers the possibility of performing measurements and virtual simulations for both coronary and structural interventions. CT has been established as the gold standard for patient selection and procedural planning in various scenarios of transcatheter coronary and structural interventions (such as TAVI, LAAO, TMVR, and transcatheter tricuspid valve replacement).

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

The manuscript was drafted by M. Barreiro-Pérez and I. Cruz-González and thoroughly reviewed and approved by all authors. Berenice Caneiro Queija and M. Barreiro-Pérez made corrections and editorial changes, and responded the reviewers.

CONFLICTS OF INTEREST

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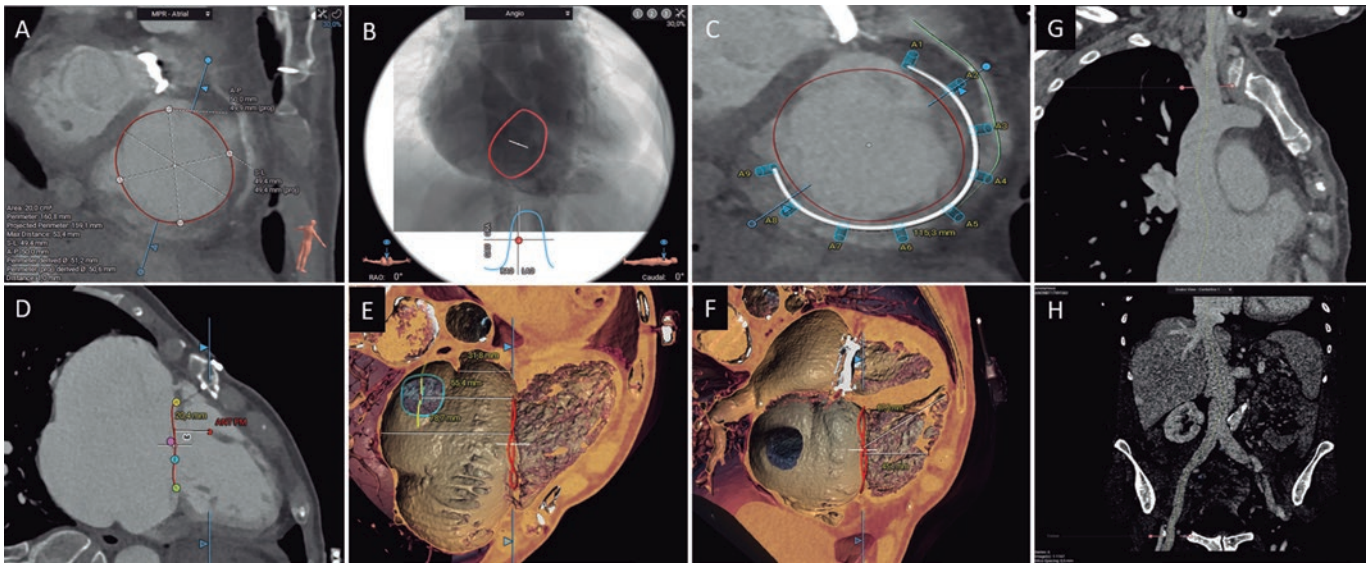

Figure 5. Evaluation of the tricuspid valve using computed tomography and 3mensio CT analysis software: measurement of the tricuspid annulus (**A**), simulation of the fluoroscopy view (**B**), simulation of the percutaneous annuloplasty anchors relative to the right coronary artery (**C**), distance from the tricuspid annulus to the anterior papillary muscle (**D**), distance from the tricuspid annulus to the roof of the coronary sinus, the inferior vena cava, and the roof of the right atrium (**E**), distance from the tricuspid annulus to the right ventricular free wall and apex (**F**), curved multiplanar reconstruction of the superior (**G**) and inferior venae cavae, and femoral accesses (**H**).

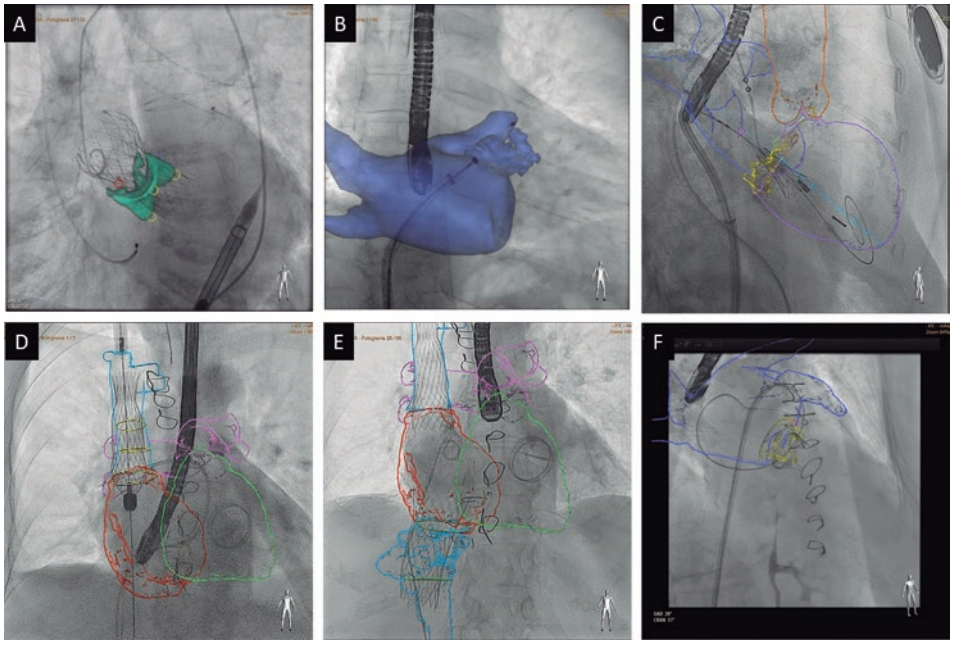

Figure 6. Examples of computed tomography and fluoroscopy image fusion in various procedures using Heart Navigator (Philips): transcatheter aortic valve replacement (**A**), left atrial appendage occlusion (**B**), transcatheter valve-in-MAC mitral valve replacement (**C**), valve implantation in the superior (**D**) and inferior venae cavae (**E**), and closure of mitral paravalvular leak (**F**).

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Review article

Use of cardiovascular registries in regulatory pathways: perspectives from the EU-MDR Cardiovascular Collaboratory

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ABSTRACT

On May 26, 2021, the European Medical Device Regulation (EU-MDR) entered into effect resulting in a major shift in the requirements for assessment of medical devices in Europe. The EU-MDR Cardiovascular Collaboratory (EU-MCVC) was founded to contribute to the development of faster, more efficient, and more effective pathways for innovation of cardiac medical devices. A registry is an organized system that collects uniform data and evaluates specified outcomes in a population defined by a disease, condition, or exposure. Most registries have been created to improve the quality of care and provide feedback to physicians, hospitals, and health providers. Clinical registries represent an ideal construct for scientific, clinical, and policy-making collaboration. We describe diverse experiences from 5 European countries and address the traditional quality components in clinical trials. Continued collaboration is expected among academics, clinical trialists, patient representatives, regulatory experts, research organizations, registry platforms, regulatory bodies, and industry partners. Data quality is a primary concern and registry leaders need to optimize data quality to become regulatory compliant. A collaborative approach among medical device stakeholders may improve quality of care, reduce costs, and provide faster access to innovative technologies, with the common objective of improving cardiovascular care and outcomes.

Keywords: Regulatory science. Clinical registries. Clinical trials.

Uso de registros cardiovasculares en procesos regulatorios: perspectivas del Colaboratorio Cardiovascular EU-MDR

RESUMEN

El 26 de mayo de 2021 entró en vigor el Reglamento Europeo de Productos Sanitarios (EU-MDR), que supuso un importante cambio en los requisitos de evaluación de los productos sanitarios en Europa. El EU-MDR Cardiovascular Collaboratory (EU-MCVC) se fundó con el fin de contribuir al desarrollo de vías más rápidas, eficientes y eficaces para la innovación de productos sanitarios cardiacos. Un registro es un sistema organizado que recoge datos uniformes y evalúa resultados específicos en una población definida por una enfermedad, afección o exposición. La mayoría de los registros se han desarrollado para mejorar la calidad de la atención y proporcionar información a médicos, hospitales y proveedores de servicios sanitarios. Los registros clínicos representan una construcción ideal para la colaboración científica, clínica y política. Describimos diversas experiencias de 5 países europeos y

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abordamos los componentes de calidad tradicionales en los ensayos clínicos. Se espera una colaboración continua entre académicos, especialistas en ensayos clínicos, representantes de pacientes, expertos en regulación, organizaciones de investigación, plataformas de registros, organismos reguladores y socios de la industria. La calidad de los datos es una preocupación primordial y los responsables de los registros deben optimizarla para cumplir con la normativa. Un enfoque colaborativo entre las partes interesadas en los dispositivos médicos puede mejorar la calidad de la atención, reducir los costes y proporcionar un acceso más rápido a tecnologías innovadoras, con el objetivo común de mejorar la atención y los resultados cardiovasculares.

Palabras clave: Ciencia reguladora. Registros clínicos. Ensayos clínicos.

Abbreviations

EMA: European Medicines Agency. **EU-MCVC:** European Medical Device Regulation Cardiovascular Collaboratory. **EU-MDR:** European Medical Device Regulation. **PMCF:** Post-marketing clinical follow-up. **RCT:** Randomized controlled trial.

INTRODUCTION

On May 26, 2021, the European Medical Device Regulation (EU-MDR) was enacted and the European Union underwent a major shift in the requirements for research and development of medical devices.[1] This coordinated regulatory upgrade, however, allowed each European country to adopt the regulation as understood locally, which introduced steep learning curves. Ethics committees, competent authorities, notified bodies, academic and nonacademic health institutions, as well as contract research organizations experienced delays, longer waiting times, increased workload, and loss of effectiveness. This resulted in some cases in manufacturers deciding to deprioritize Europe as a potential location for the development of new therapies. Three years after the implementation of EU-MDR, the learning curves have been overcome and Europe has been reprioritized. Nonetheless, increased requirements and higher costs call for alternative pathways for generating regulatory data.

A pertinent upgrade in this regulation is the need for manufacturers to conduct postmarket clinical follow-up (PMCF) activities requiring the collection of clinical data on the use of devices that are already commercially available. The purpose reflects the desire to confirm the safety and performance requirements under normal conditions of the intended use of the device, the evaluation of potentially rare adverse effects and the assurance that the risk-benefit, specific for each device, remains favorable.[1] Although postmarketing studies were common under the previous directive, the EU-MDR makes them mandatory. Beyond the financial consequences, these requirements inevitably result in an increased workload in the hospitals where the devices are used and/or implemented. This additional workload could potentially be mitigated by the establishment of public-private partnerships for efficient, effective, and high-quality data collection and reporting.

The successful management of cardiac conditions requires the use or implementation of medical devices, and the EU-MDR has had a fundamental impact on access to research, innovation, and improved therapies in European cardiology. In May 2023, the EU-MDR Cardiovascular Collaboratory (EU-MCVC) was initiated by Cardialysis (Rotterdam, The Netherlands) and established as an informal, voluntary, pro-bono international expert network bringing together European academics, clinical trialists, and regulatory experts to collaborate with clinical research stakeholders, both regionally and globally.[2] The purpose of EU-MCVC is to create a dynamic and open conversation to facilitate, in real time, effective implementation of clinical research in Europe with an emphasis on navigating the EU-MDR. Relevant stakeholders in this collaboration are cardiovascular research organizations, registry platforms, regulatory bodies, and industry partners.

The priority focus in 2023 to 2024 is the definition, requirements, and establishment of efficient, effective, and high-quality cardiovascular clinical registries as a valuable pathway for PMCF data collection. This article addresses the following 4 topics: *a)* the definition of registries and considerations related to informed consent; *b)* perspectives from 5 European leaders on the establishment and performance of clinical registries; *c)* the interplay between traditional clinical trial quality processes and clinical registries; *d)* registry data requirements and their potential and current use.

This perspectives document was drafted on the basis of voluntary contributions from all authors. The manuscript generation process had 2 components: *a)* a hybrid think-tank organized by EU-MCVC and Cardialysis, with faculty members attending primarily in-person (11/13), on September 8, 2023 in Rotterdam, The Netherlands; and *b)* the compilation of presentations, discussions, and conclusions, in a draft document that was critically reviewed and expanded by each of the authors.

Definition of clinical registries

The European Medicines Agency (EMA), the United States of America Food and Drug and the International Medical Device Regulators Forum provide guidance on defining clinical registries (table 1).[3-6] The common components of these definitions describe a registry as an organized system that collects uniform data and evaluates specified outcomes in a population defined by a disease, condition, or exposure. The International Medical Device Regulators Forum definition has a focus on quality of patient care, and thus requires a reasonably generalizable size, which would be most useful for informing policy decision-making. The United States of America Food and Drug Administration definition, however, adapts the goals to either scientific, clinical, or policy purposes. The EMA definition emphasizes the need to center the definition on the patient level, highlighting the focus of the registry on health information.

Table 1. Defining clinical registries

International Medical Device Regulators Forum (IMDRF) Definition
A registry is an organized system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes, and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (eg, international, regional, health system) with the primary aim of improving the quality of patient care
United States of America Food and Drug Administration (US FDA) Definition
A registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that services one or more predetermined scientific, clinical, or policy purposes
European Medicines Agency (EMA) Definition "Patient Registry"
Organized system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition, or exposure. The term 'patient' highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature
EU-MDR Cardiovascular Collaboratory (EU-MCVC) elements of a common clinical registry definition
Organized system
Collects uniform (continuously and consistently) data (clinical and other)
Evaluates specified (meaningful) outcomes
Population defined by a disease, condition, or exposure
EU-MCVC perspectives on clinical registry sizes
Single-center vs multicenter clinical registry
Exhaustive (all centers) vs nonexhaustive (selected centers) national clinical registry
Exhaustive (all centers) vs nonexhaustive (selected centers) international clinical registry
Clinical registry networks (multiple registries merging independent databases, either at patient-level or at registry-level)

When targeting EU-MDR requirements, a population is defined by exposure to a specific device, which has important consequences for the setting up of registry platforms in Europe. EMA defines at least 3 registry categories that, in ideal circumstances, could be interconnected. First, the EMA defines a disease registry as a patient registry whose participants are defined by a particular disease or disease-related patient characteristics, regardless of their exposure to therapies. A disease registry is purely observational. Second, the EMA defines a registry-based study as an investigation of a research question using a patient population within a patient registry. The interpretation of the EU-MCVC is that this refers either to investigational interventions or when the clinical investigation requires additional invasive or burdensome procedures or follow-up rules. A purely observational or descriptive analysis should ideally be defined within the umbrella of a disease registry. Third, the EMA refers to product or device registries, which generally apply to PMCF studies. PMCF studies are required to follow the regulations that apply to traditional clinical trials (eg, single-arm study) under MDR, unless no additional invasive or burdensome procedures are incorporated in the registry protocol.

The development of sustainable clinical registries may improve the quality of care, reduce costs, and provide faster access to better therapies. Figure 1 presents the conceptual framework for the implementation of a clinical registry.

Background of the utopian all-comers design and how registries may be the answer

Randomized controlled trials (RCTs) are the gold standard for evaluating the safety and efficacy of medical interventions, as, by design, they eliminate confounding factors as much as possible. RCTs are the standard for premarket evaluation, and typically select a narrow population by means of carefully selected eligibility criteria, which has 4 consequences: *a)* most confounders will be avoided and the purest possible estimates of "*therapy effects*" will be achieved; *b)* strict eligibility criteria may make it difficult to enroll patients, requiring more centers and more time to complete enrollment, although typically these studies require smaller sample sizes; *c)* the limited external validity of the intervention effect estimate, due to the highly selected population will require subsequent studies in larger populations, usually in the postmarket setting; and *d)* the design allows only limited information on potential rare adverse effects.

As a possible solution to challenges 2 and 3 above, the "*all-comers design*" was introduced, characterized by having simple eligibility criteria. This approach facilitates the enrollment of a more representative patient population. However, in a trial evaluating coronary stents,[7] at least 50% of eligible patients were still not enrolled after screening. The main reasons were related to the informed consent process (33% inability to provide informed consent, 19% refused to provide consent) and 27% did not meet the eligibility criteria. Furthermore, those who were not enrolled had poorer outcomes. Such observations have been replicated in many subsequent publications. Other potential issues to consider in the all-comers approach are: *a)* the addition of uncontrolled confounding factors that may lead to a 'dilution' of the therapy effect (initially designed for a specific and selected population) and an observed null-effect in a randomized comparison; and *b)* investigators tend to exclude the most severe presentations (eg, heart failure, cardiogenic shock). Thus, the all-comers approach still remains selective. The advent of registry-based research offers a unique opportunity to collect data on all patients, especially in purely observational studies, and to better understand outcomes in all subpopulations, particularly those traditionally excluded from clinical trials. The view of the EU-MCVC is that unselected populations should not be considered for early randomized comparisons unless a device is expected to benefit an unselected population. In contrast, if the effect of an intervention is primarily expected in a subgroup of patients, these subgroups of patients should be investigated first instead of launching an all-comers approach as the initial approach.

Informed consent

Patients who are admitted to or registered in a health care institution are not automatically aware that their clinical data may be used in multiple manners. However, they will generally presume that the most important function of health care data, as it relates to them personally, is to enable health care professionals to offer them the best care possible, to improve their well-being, quality of life, and life expectancy. However, depending on local health care frameworks, other users of their data can be insurance companies,

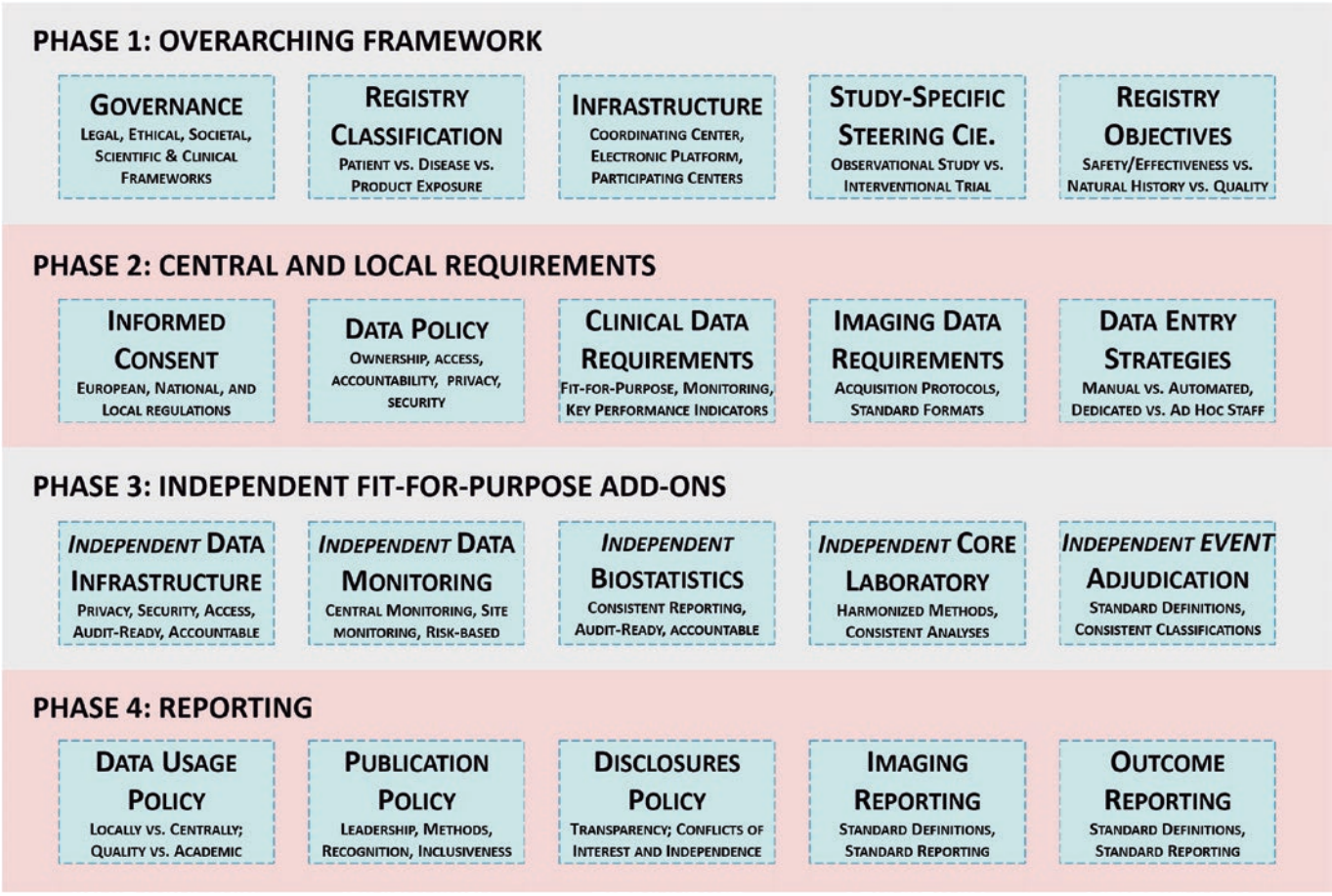

Figure 1. Conceptual framework for the implementation of a clinical registry. Phase 1 requires building a legal and scientific framework, as well as setting up agreements and designing the overall distribution of tasks among collaborators. Phase 2 touches upon the design and implementation of the registry, where most attention is paid to data requirements, and data quality should be a common denominator. Phase 3 presents optional activities to be provided by independent parties to increase consistency, quality, and long-term reliability. Phase 4 must be readily documented and available when results are expected. All phases shall be discussed and implemented simultaneously as the final product requires having assessed these 20 components. Detailed written documentation of agreements are to be held by the executive committee of the registry. All components of phases 1, 2 and 4 are required. Phase 3 components are optional.

national databases, partner organizations (eg, hospital networks), and quality-of-care databases.

When invited to participate in traditional clinical trials, patients should be informed in detail of the objectives of the study, the potential associated risks and benefits, extra burdens or commitments, and any other potentially relevant information. Under the EU General Data Protection Regulation, patients not only need to voluntarily provide their informed consent to enroll in a clinical investigation, but also need to voluntarily provide permission for each specific use of their data and may withdraw their consent at any time.[1] For the purposes of clinical trials and patient registries, patient data are typically coded or pseudonymized, which ensures that their personal identifiers will not be shared outside their treating health care institution. The use of coded personal data complies with the privacy requirements of the EU General Data Protection Regulation.

The question of whether informed consent is required for enrolling patients in a patient registry hinges on whether registry data collection is part of the standard of care (eg, quality registry) and defined in the terms and conditions of the institution, or whether the registry is beyond the scope of the standard of care. In the former, the registry may be part of the patient health care records, and institutional and regulatory national conditions may not require a registry-specific consent. In the latter, patients should be consented before entering a patient registry. EU-MCVC recommends always liaising with the local ethics committee to define the need for informed consent in the setting of a clinical registry.

Patient registries are expected to be purely observational. In the case of interventional registry studies (ie, with an experimental intervention) or in observational studies with additional invasive or burdensome procedures or follow-up rules, it is generally accepted that patients must be invited to participate and sign an informed consent form. Purely observational registries may also require the informed consent process depending on its objectives, and national and local requirements. An informed consent form for observational registries should clearly state that all coded data being collected might be used for multiple observational data analyses (either locally or in the full registry database), for which the patient will not be reconsented. Patients always retain the right to withdraw their informed consent.

Cardiovascular clinical registries: The Spanish experience

Spain has a long tradition of registry-based data collection in interventional cardiology under the motto "unity makes strength" in a population of more than 47 million people.[8] With one of the oldest interventional cardiology quality registries, the community has delivered impactful data based on registries. A nationwide registry in interventional cardiology has been published without interruption since 1990, collecting data through extensive surveys that are completed annually and reflect the volume of activity rather than patient-level data.[9,10] Consequently, from a research perspective, its value is highly limited.

Patient-level registries started as academic collaboration among colleagues who voluntarily and without external funding developed common databases to collect interventional cardiology procedural data and clinical outcomes at follow-up. Efforts started in 2004 and evolved from single-center registries to a multimodal academic interactive network. These voluntary contributions meant countless hours of structured data entry and follow-up plans. A salient example is the seminal article published in 2008 on stent thrombosis that included 23 500 patients enrolled in 20 Spanish centers.[11] Additional registries conducted in subsequent years led to more than 10 publications. From observational registries, this network expanded into randomized studies and interventional registries, with growing international collaborations.

In recognition of a clear trend toward collaborative research in the setting of complex disease and complex therapeutic approaches, the Spanish multimodal network has evolved into the EPIC Foundation (Education and Promotion of Investigation in Cardiovascular disease). EPIC was founded in 2016 and is currently engaged in academic research, industry-sponsored research, and observational studies with a track record of 47 projects, including 11 PMCF and Post-market surveillance under MDR. Currently, each registry is set up as a clinical study, following the traditional rules of ISO14155:2020, and including informed consent from patients. EPIC is expanding its capabilities in regulatory research in collaboration with local and international partners. Registries are funded by national grants or by industry. As an independent organization overseen by interventional cardiologists, EPIC is the only such platform in Spain as there is no national registry platform funded by the health authorities.

Cardiovascular clinical registries: The Belgian experience

Belgium has highly favorable conditions for registry-based research in a population of more than 11 million people. Notably, it is one of the rare examples where registry data collection is mandatory and funded according to national standard-of-care requirements. However, it also exemplifies the challenges related to governance in order to address the 3 main areas of interest as defined by the United States of America Food and Drug Administration: scientific, clinical, and policy-making. The Belgian interventional cardiology registry started as a physician-driven initiative that aimed to assess the effectiveness of therapies, regional disparities, and adherence to guidelines in order to improve patient outcomes and to advance scientific research.

In 1996 the Belgian working group of interventional cardiology started collecting a limited set of clinical and procedural data (by fax), which did not meet scientific rigor, as occurs with other quality-of-care registries. Since 2006, data entry shifted to a database hosted by the European Society of Cardiology, but owned and managed by the Belgian working group of interventional cardiology. In 2012, the Quality Electronic Registration of Medical acts, Implants and Devices (Qermid) database, hosted by health authorities, came into effect.[12] Data completion is mandatory for reimbursement of procedures and devices. This allows collection of ∼100% of procedures but adds a new administrative burden.

Qermid collects data for policy-making and quality-of-care, but currently the registry is not led or managed by the scientific community. This creates a paradox, where the ideal situation (full data collection) exists, but insufficient scientific advantage is taken from such a valuable infrastructure. Moreover, there are no dedicated resources for on-site data entry (currently performed by physicians or assistants) and data are not sufficiently monitored. Nevertheless, through the Belgian working group of interventional cardiology and Qermid, Belgium has been able to publish reliable metrics for more than 27 years, and provide nationwide real-world data on complex procedures,[13] and to elegantly describe the effect of the COVID-19 pandemic.[14]

Table 2. Connected databases that build up SWEDEHEART

Disease specific databases (eg, SCAAR for PCI)
Registries at the National Board of Health and Welfare
The national registry of causes of death
The national patient register (all ICD codes, all admissions since 1987)
The Swedish prescribed drug register (all dispensed drugs since 2005)
Central Bureau of Statistics (eg, marital status, country of birth, income, educational level)
The Swedish Social Insurance Agency (sick leave)
Other National Quality Registers (about 100 at present)

ICD, International Classification of Diseases; PCI, percutaneous coronary intervention; SCAAR, Swedish Coronary Angiography and Angioplasty Registry.

Cardiovascular clinical registries: The Swedish experience

The Swedish Coronary Angiography and Angioplasty Registry (SCAAR), within the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) platform, is seen as a role model among coronary registries.[15] The registry was founded voluntarily by physicians to improve quality of care. Data collection is nationwide, data entry is required for all procedures, and the health care system now supports the infrastructure. Moreover, Sweden mesmerized the cardiovascular community with the very first investigator-initiated, registry-based RCTs, published in top tier journals.[16,17] With a population of more than 10 million people, the SWEDEHEART quality registries capture over 80 000 procedures on a yearly basis. Data collection includes baseline, procedural, and outcome data, amounting to more than 300 variables on average. SWEDEHEART offers high compliance with > 95% data agreement when monitoring activities are performed.[15]

SWEDEHEART has certain characteristics that create ideal conditions. First, all patients who are treated at a hospital are included in the registry. Informed consent to enter the registry is not needed, but if the patient decides to leave the registry, it is still possible to

opt out. Second, a common patient identifier is used that allows the merging of multiple national databases, making the scope of data availability much wider than in a hospital-based registry (table 2). This allows for indefinite follow-up unless a patient leaves the country; the governance infrastructure takes into consideration the 3 elements (ie, scientific, clinical, or policy); more specifically, the process allows for feedback to the staff, the leadership, the patients, and the public.

Since 2018, SCAAR/SWEDEHEART have been approached by the medical device industry to support regulatory reports in the context of ongoing clinical follow-up and completeness of data. Since then, SCAAR/SWEDEHEART have been able to support most of the major PCI device companies with MDR reports. The existing experience allows for predefined reports, either at patient-level or device-level, as well as in patient subgroups (eg, older adults, diabetes) or lesion subgroups (eg, small vessels, long lesions). This platform is especially interesting for devices that are not commonly used (eg, left main devices, small stents). Currently the SWEDEHEART model is expanding in Europe through the European Society of Cardiology (ESC)-driven EuroHeart program. Some countries already had similar registries on different platforms, which is why one of the first important steps was to establish common data standards.[18]

Cardiovascular clinical registries: the Icelandic experience

Iceland has a population of around 400 000 people, and has an interventional cardiology center at Landspitali University Hospital (Reykjavik). This center has collaborated in SCAAR/SWEDEHEART since 2008, with prospective data collection. As a single-center experience and outside Sweden, Dr Guðmundsdóttir confirms that data collection in the SCAAR database is time-efficient and viewed as part of patients' essential health records. Patient and procedural data are entered by the treating physician and cath lab nurses immediately at the time of the procedure, which is accurate and time-efficient, given the simplified approach for data collection. The registry includes all treated patients, allows quality-of-care assessments, and represents a pathway for participation in multicenter registry-based clinical trials. The registry enables easy access to all Icelandic data for local research and quality control. However, a couple of the challenges observed are the following: *a)* Icelandic databases are not integrated as in the case of Sweden (table 2), and *b)* data aggregation and data sharing can be complex. Since routine data entry into the registry is seen as a part of patient care, it does not require informed consent. However, in the case of registry-based studies, ethics committee approval is a requirement and signed informed consent must be obtained from each participant. Iceland is collaborating in the EuroHeart program by providing data but is not currently using the EuroHeart platform.

Cardiovascular clinical registries: the Leiden experience on a noninvasive imaging databank

Leiden University was founded in 1575 and is the oldest university in The Netherlands. Leiden University Medical Center is highly involved with innovation and development, collaborating with organizations locally and globally. Its cardiology department is no exception and collaborates with 18 countries in research, PhD programs, and postgraduate training. In this environment, and due to adequate infrastructure and leadership, a powerful noninvasive imaging databank was established prospectively in 2000 and has collected retrospective data since 1990. By using standardized acquisition protocols according to care tracks (eg, patient disease or condition) and dedicated analysis efforts (powered by extensive work by research fellows and faculty), Leiden has offered the global scientific community a better understanding of disease natural history, identified populations at higher risk, and informed the design of clinical trials.

The Leiden experience offers 5 important lessons: *a)* individual centers collect a wealth of data that, if used properly, can change our understanding of disease and its management; *b)* consistent acquisition and analysis methodologies are required to compare data over time and, by spending time on a good acquisition, facilitate all future efforts; *c)* to adequately analyze these enormous amounts of data, countless hours are needed, which is facilitated by well-organized PhD programs; and *d)* collaboration among international imaging registries is especially powerful for less prevalent conditions and is most productive when good and high-volume centers are selected, standardized evaluation is in place, databases are well-organized, there are engaging professionals ready to grow in their academic career, and integration of multi-modality imaging techniques creates better possibilities to answer clinically relevant questions. Some examples include Leiden's experience of moderate aortic stenosis, bicuspid aortic valve disease, and acute myocardial infarction.[19-21]

Cardiovascular clinical registries: the European Cardiovascular Research Institute-Cardialysis Perspective

The European Cardiovascular Research Institute is a foundation bringing together a community of top clinical researchers and private/public partners in order to perform clinical investigations that improve cardiovascular health care. Since 2012, the European Cardiovascular Research Institute has performed some of the most ambitious European interventional cardiology trials, enrolling almost 30 000 participants and providing high-quality data that have impacted clinical guidelines around the globe. As an academic research organization, the European Cardiovascular Research Institute partners with Cardialysis, which is a quality-oriented, independent cardiac imaging core laboratory and a cardiology-focused research organization. Cardialysis has the largest track record on the conduct of interventional cardiology trials in Europe with more than 400 studies completed in 40 years with a total enrollment of more than 200 000 patients.[2] In this context, Cardialysis has experienced increased demand for both industry-initiated and investigator-initiated registries since 2021, in which it is pivotal to develop awareness and common acceptance of the quality required for various purposes (eg, premarket approval, postmarket follow-up, scientific research, guidelines). It has become a priority to define how registry platforms may be supported externally with specific quality components. The term 'Externally-Supported Clinical Registries' was introduced at the EU-MCVC's first think tank and refers to registry networks that use independent providers to boost the quality of the registry, depending on the objectives.

A call for quality and multi-stakeholder engagement

Cardiology is characterized by its very high standards in clinical research. Most research questions in cardiology are simple, binary comparisons. However, the wealth of information required to plan an adequate binary comparison leads to high complexity and requires the involvement of experts from different disciplines and

Table 3. Methodological components that add quality to cardiovascular clinical investigations

Trial design and protocol development according to international standards (eg, ISO 14155)
Use of standard definitions (eg, ARC definitions)
Independent and nonconflicted expert committees (eg, steering committees, clinical events committees, data and safety monitoring boards)
Independent and nonconflicted cardiac imaging core laboratories
Adequate site selection (eg, optimal research infrastructure)
Independent and nonconflicted site monitoring including data verification (eg, completeness, accuracy)
Consistent coding of adverse events (eg, MedDRA)
Regulatory-compliant electronic data capture system
Statistical analysis plan and predefined publication strategy
Independent statistical reporting or independent statistical validation
Timely use of public databases (eg, ClinicalTrials.gov)
Consistent quality assurance, regulatory compliance, and site audits
Clinical study reports according to international standards (eg, ISO 14155)

ARC, Academic Research Consortium; ISO, International Organization for Standardization; MedDRA, Medical Dictionary for Regulatory Activities.

backgrounds. Due to the latter, the establishment of standards has become an effective catalyst for innovation. These standards start with requirements from regulatory agencies,[3-6] definitions and trial design principles,[22] standard data elements, standard methodologies, and standard reporting. Failed adequately powered clinical trials continue to be a regular feature of the clinical trial landscape, as devices or strategies that held promise in initial trials with a limited number of patients sometimes have contradicting confirmatory data in subsequent larger trials. It is the view of EU-MCVC that confirmatory trials should be performed using high-quality standards. Methodological components that add quality to a clinical investigation are summarized in table 3.

In a recent systematic review, CORE-MD (Coordinating Research and Evidence for Medical Devices), published the results of their assessment of the 11 currently running European registries for coronary stents and transcatheter valve therapies.[23] They concluded that there is wide heterogeneity and incomplete public transparency to structure and methods, and a need to create a minimum set of quality criteria. They reported that on average, data quality and completeness criteria were met in less than 20% of the registries and that data on safety and performance was adequately addressed in less than 30%. This information confirms that the priority remains to improve the quality of data collection and that broadly accepted metrics need to be developed.

A consideration requiring further investigation is the need and relative value of on-site monitoring activities and on-site audits in the context of clinical registries. Automated and centralized mechanisms of data monitoring may offer efficiency; however, the effect of site monitoring visits on data completeness and quality is unknown. In general terms, on-site monitoring has been used in sponsor-driven device registries, but has generally not been used in academically-driven patient registries.

Table 4. Requirements for academic vs regulatory-compliant imaging core laboratories

	Regulatory-compliant imaging study[a]	Local academic imaging research
Image acquisition		
Study-specific imaging manual/protocol	Y	N/Y[b]
Study-specific personnel training/qualification	Y	N/Y[b]
Dedicated resources for image acquisition	Y	N/Y[b]
Imaging data management		
Anonymization of Protected Health Information	Y	N[c]
Secure image e-Transfer system	Y	N[c]
Adequate material handling and filing	Y	N[c]
Quality feedback and queries handling	Y	N
Image analysis		
Standardized analysis methodology (conforming to guidelines, accepted definitions, ensuring feasibility)	Y	N/Y[b]
Dedicated Image Workstation	Y	N/Y[b]
Primary reader – sonographer/imaging analyst	Y	N/Y[b]
Overread – imaging expert/supervisor	Y	N/Y[b]
Personnel training/qualification	Y	N/Y[b]
Reproducibility testing	Y	N
Imaging database		
Validated, study-specific electronic case report form	Y	N
High data entry requirements (automatic worksheet upload and queries, Part 11 compliant, audit trail)	Y	N
Data source verification and quality control	Y	N
Data release procedure after data base lock	Y	N

[a] Pamela Douglas – JASE.
[b] Not in registries, but possible academic studies.
[c] Not applicable in a local study.

Quality add-ons to traditional clinical registries

Independent core laboratory analyses

Establishing an independent core laboratory for a clinical trial increases quality by addressing the following quality requirements: *a)* optimizing image quality by developing a uniform image acquisition protocol for all participating centers. Adherence to the acquisition protocol may require confirmation that the image acquisition protocol was studied (or training received) and that a test-run is provided to confirm protocol adherence; *b)* ensuring that data are handled consistently (eg, pseudonymized, adequate privacy and security standards, adequate format, consistent analysis software); *c)* ensuring that data are analyzed consistently (eg, standard methodology, reproducible assessments, adequately trained personnel);

Table 5. Use of endpoint adjudication in registry-based randomized clinical trials

Study	Endpoint	Adjudication	Registry endpoints	Event trigger	Data collection	Other info
TASTE	All-cause death	No	Yes	N.A.	No	-
VALIDATE	MACE and major bleeding	Yes	N.A.	Site-reported	Yes, eCRF and hospital notes	-
DETOX	All-cause death	No	Yes	N.A.	No	-
iFR	MACE and major bleeding	Yes	N.A.	Site-reported	Yes, eCRF and hospital notes	Core Lab
HELP	Bleeding events	N.A.	Yes	N.A.	No	-
REDUCE	All-cause death and MI	N.A.	Yes	N.A.	No	-
Full REVASC	MI and unplanned revascularization	Yes	N.A.	SCAAR/Riks-HIA	Yes, eCRF and hospital notes	-
SPIRRIT	All-cause death and HF hospitalization	Yes	ICD codes	ICD codes and mortality register	Yes, eCRF and hospital notes	Simplified adjudication process
DAPA-MI	All-cause death and HF hospitalization	Yes	N.A.	Site-reported	Yes, eCRF and hospital notes	
INFINITY	Device-oriented composite endpoint	Yes	N.A.	Site-reported	Yes, eCRF and hospital notes	Core Lab

eCRF, electronic case report form; HF, heart failure; ICD, International Classification of Diseases; MACE, major adverse cardiac events; MI, myocardial infarction; Riks-HIA, Register of Information and Knowledge About Swedish Heart Intensive Care Admissions; SCAAR, Swedish Coronary Angiography and Angioplasty Registry.

d) ensuring that data adjudication is performed consistently (eg, regurgitation severity); and *e)* central availability of original datasets for regulatory audits.[24]

Imaging measurements and assessments obtained from real-world data (eg, site-reported) will not comply with the quality requirements mentioned in the prior paragraph and will be associated with increased variability of assessments and increased risk of investigator bias. For academic research, items 1 and 4 in the prior paragraph may be addressed, and the absence of the remainder may be acceptable as long as imaging data are not transferred outside the treating institution. For regulatory trials, however, all 5 are necessary, especially if imaging endpoints are part of the primary endpoint or main mechanism of action of the investigational device. In the setting of postmarket clinical registries, given the potential large number of patients, intermediate solutions need to be designed. Table 4 highlights the differences between a regulatory-compliant core laboratory and a local academic core laboratory.

Independent endpoint adjudication

Establishing an independent clinical events committee (CEC) increases quality by addressing the following quality requirements: *a)* adherence to standard definitions to ascertain and classify adverse events that potentially meet the definition of an endpoint for a given study. Having an expert committee for a given trial also offers consistency in the classification of complex events, such as periprocedural myocardial infarction and heart failure events; *b)* ensuring that assessments are performed utilizing a similar amount of information (eg, consistent checklist of documents and imaging materials required for adjudication); *c)* central availability of original source documents for regulatory audits; and *d)* importantly, given that device indications are largely based on primary endpoints that are clinical, the CEC must be shown to be independent from the manufacturer of a given device and have no perceived conflicts of interest to perform the tasks.[25]

In the context of premarket approval, it is the view of EU-MCVC that an independent CEC committee should be in place for the 4 reasons explained in the previous paragraph. In the context of a cardiovascular registry, however, it appears that site-reported data, especially when reporting is complete and uses standard definitions, might be sufficient from a quality perspective. Scientifically, it remains to be proven whether clinical outcome data from registries are sufficient without a CEC in place. Furthermore, in the context of registry-based randomized studies currently being set-up for regulatory purposes, it is the opinion of the EU-MCVC that a CEC should be in place, and its use and validity explored prospectively.

All-cause mortality, however, does not usually need endpoint adjudication. Especially if the specific registry or study has access to national mortality databases. It is not known whether subclassifications of death can be reliably documented using site-reported data or whether a CEC will provide additional value. Other endpoints for which there are ongoing efforts to clarify whether adjudication is or is not beneficial are myocardial infarction and revascularization, when coded as binary (yes/no). In the view of the EU-MCVC, most other endpoints (eg, heart failure, bleeding, subtypes of myocardial infarction, stent thrombosis, stroke, unstable angina, unplanned revascularization) do exhibit an advantage when undergoing adjudication, although this needs to be proven prospectively.

An example of adjudication of clinical events in a registry-based RCT is the Bivalirudin vs Heparin Monotherapy in Myocardial Infarction (VALIDATE SWEDEHEART) trial, which was a proof-of-concept of this methodology.[26] Furthermore, innovative adjudication approaches are being designed and tested with the aim of maintaining quality but lowering costs. For example, in the DAPA-MI trial, only death and heart failure hospitalization were adjudicated, while myocardial infarction, revascularization, and stroke were site-reported.[27] Additional examples are presented in table 5.

Table 6. Comparative table on the role of clinical registries in evidence-based medicine

Registries	Registry-based randomized controlled trials	Traditional randomized controlled trials
Purely observational Not adequate to support a conclusion on efficacy	Pragmatic Open-label evaluation of commonly used therapeutic alternatives in settings with existing registries	Highest level of scientific evidence Gold standard for comparative studies
True all-comers – representativeness Provide data on power calculation Clinically meaningful results Low risk populations Low frequency events	True all-comers – representativeness Provides information on characteristics and follow-up of patients randomized and noneligible individuals	Select eligible patients Attainment of patient consent Random assignment for treatment Control for confounders Detection and adjudication of clinical endpoints
Hypothesis generating	Causal inference To evaluate treatments, strategies, and devices or acute-phase pharmacological agents Evaluation of pharmaceutical agents for new indications	Causal inference
Resource effective	Low cost	Resource intense

Independent statistical analysis or validation

The assessment of appropriate trial databases goes beyond the locked statistical analysis database and includes a thorough assessment of a trial or registry design. From the perspective of a statistician, one must consider the study design, patient selection, choice of the comparator, regulatory compliance, description of the statistical methods, and finally both the assessment of the outcomes per se and the consistency among findings. The data quality gap between the evidence-based medicine paradigm and the real-world data paradigm is currently strikingly evident, and this is conceptually correct by design, given that real-world data refer to routinely collected data, which are by design of lower granularity and precision than clinical trial data. If real-world data are to be considered for use in regulatory pathways, they must comply with the following requirements: *a)* data sources are of demonstrated good quality; *b)* internal and external validity is expected; *c)* there is consistency across data sources; and *d)* data are adequate and precise. Regulatory documents using real-world data should also report on adjustment for potential confounders, identify potential for selection bias and information bias, describe how missing data are managed, and offer a robust data analysis.

Adequately designed and supported clinical registries offer multiple advantages from a clinical perspective, such as better insights into the natural history of diseases, better characterization of target populations, and the identification of new targets of therapies. In addition, registries offer the potential to introduce novel statistical approaches to pool and analyze data. When patient-level data are available within a single registry, traditional statistical approaches should be used, taking into account data limitations. When only registry-level data are available, meta-analytical methods can be implemented and may be used for policy decision-making or public health decision-making, but not for assessment of the safety, efficacy, or effectiveness or a device, which require the deepest granularity, which is not provided by registry-level meta-analytical data.

Role of clinical registries in European guidelines committees

The process of evidence generation that leads to the recommendations of the European clinical guidelines is well established and follows most robust standards, where adequately powered randomized controlled clinical trials represent the best source of information for decision-making. Ideally, a class IA recommendation should have more than one confirmatory, adequately powered clinical trial or at least one properly executed meta-analysis. In the absence of RCTs, however, other sources of data are used and ultimately contribute to the decision-making process of a committee.

With the aim of optimizing cardiovascular care and outcomes, the ESC has proposed a methodical approach for the development of quality indicators and, in collaboration with the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart), has proposed data standards for acute coronary syndrome and PCI, transcatheter aortic valve implantation, heart failure, and atrial fibrillation/flutter catheter ablation.[18] There has been rapid adoption with more than 40 000 cases of aggregated individual participant data collected in 2022 in 7 participating countries. This novel ecosystem is rapidly evolving and promises to have a high-impact on policy decision-making and public health priorities.

The existing strengths of adequately planned and supported clinical registries include being resource effective, offering a high representativeness, integration with clinical routine, and unselected consecutive recruitment. This setting, especially as implemented by SWEDEHEART, has opened pathways for registry-based RCTs that reduce workload, minimize selected bias, and provide better access for investigator-driven research and, recently, the opportunity for multinational trials. Continued research may better inform the scientific community and guideline committees on the use of registry-based RCTs results for decision-making, and their ultimate role in evidence-based medicine. A comparison between traditional registries, registry-based RCTs, and RCTs is available in table 6.

Limitations

The information presented and the organizations represented in this manuscript are limited to the experience of the participants of the Think Tank that took place in Rotterdam (September 8, 2023) and describes the perspectives of the coauthors. This is neither a consensus document nor a systematic review. Information on other organizations or countries involved in developing or currently running interventional cardiology registries was not captured or represented. The EU-MCVC welcomes voluntary participation of other established cardiovascular research organizations and/or

cardiovascular societies, and may be contacted through the corresponding author.

CONCLUSIONS

The EU-MDR has increased requirements for postmarket follow-up activities to be performed by all device manufacturers that market medical devices in Europe. Adequately planned and supported clinical registries have the potential to address the additional requirements by creating collaborative frameworks. Data quality is a primary concern and current registries and future registry platforms need to consider strategies to optimize data quality to become regulatory compliant. This collaborative approach may improve the quality of care, reduce costs, and provide faster access to innovative technologies. Existing registries, networks, standards, and procedures should be adopted and used consistently. The multiple potential uses of registry-based data collection make it an area that deserves continued and increased attention by all medical device industry stakeholders, with the joint objective of improving cardiovascular care and outcomes.

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AUTHORS' CONTRIBUTIONS

E. Spitzer and J.G.P. Tijssen contributed to the initiation, design and planning. E. Spitzer, J.M. de la Torre Hernández, I.J. Guðmundsdóttir, E. McFadden, C. Held, C. Hanet, E. Boersma, C.B. Ren, V. Delgado, D. Erlinge, A. Pérez de Prado, J. Bax, and J.G.P. Tijssen contributed with data/presentations. E. Spitzer compiled and drafted the manuscript, which was critically reviewed and revised by J.M. de la Torre Hernández, I.J. Guðmundsdóttir, E. McFadden, C. Held, C. Hanet, E. Boersma, C.B. Ren, V. Delgado, D. Erlinge, A. Pérez de Prado, J. Bax, and J.G.P. Tijssen. All authors approved the final manuscript.

CONFLICTS OF INTEREST

E. Spitzer reports institutional contracts for which he receives no direct compensation with Boston Scientific, Cardiawave, Edwards Lifesciences, Medtronic, Shanghai Microport Medical Co Ltd, NVT GmBH, Pie Medical Imaging, and Siemens Healthcare GmBH. C.B. Ren reports institutional contracts for echocardiography core laboratory analyses with Boston Scientific, Cardiawave, Edwards Lifesciences, NVT GmBH/Biosensors, for which she has received no personal compensation; and has received speaker fee from Abbott. V. Delgado received speaker fees from Edwards Lifesciences, GE Healthcare, Novartis, and Philips; and consulting fees from Edwards Lifesciences, Novo Nordisk and MSD. A. Pérez de Prado is President of the EPIC Foundation. J.G.P. Tijssen is Executive Board member at the European Cardiovascular Research Institute. Other authors have nothing to disclose.

A. Pérez de Prado is associate editor of REC: Interventional Cardiology. The journal's editorial procedure to ensure impartial processing of the manuscript has been followed.

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Review article

Functional assessment of coronary stenosis: alternative hyperemic, nonhyperemic, and angiographic indexes

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ABSTRACT

Assessment of the functional significance of coronary artery stenoses to guide percutaneous coronary intervention is widely performed using pressure wire fractional flow reserve during adenosine- or adenosine triphosphate-induced hyperemia. However, the use of fractional flow reserve may be limited by the contraindications and adverse effects of this hyperemic stimulus, as well as the potential risk of vessel damage from the pressure wire. This review will discuss alternative evaluation methods, including various hyperemic agents, nonhyperemic pressure ratios, and angiography-based indices.

Keywords: Angiography. Fractional flow reserve. Hyperemia. Percutaneous coronary intervention.

Evaluación funcional de las estenosis coronarias: índices alternativos hiperémicos, no hiperémicos y angiográficos

RESUMEN

La evaluación funcional de las estenosis coronarias para guiar los procedimientos de intervencionismo coronario percutáneo se realiza frecuentemente midiendo la reserva fraccional de flujo durante la hiperemia inducida por adenosina o trifosfato de adenosina. Las contraindicaciones de estos estímulos hiperémicos y la posibilidad de que se produzca daño vascular con la guía de presión pueden limitar la utilización de la reserva fraccional de flujo. Esta revisión discute los métodos alternativos de evaluación funcional: diferentes agentes hiperémicos, índices no hiperémicos e índices angiográficos.

Palabras clave: Angiografía. Reserva fraccional de flujo. Hiperemia. Intervención coronaria percutánea.

Abbreviations

FFR: fractional flow reserve. **iFR:** instantaneous wave-free ratio. **NHPR:** nonhyperemic pressure ratio. **PCI:** percutaneous coronary intervention. **PW:** pressure wire. **QFR:** quantitative flow ratio.

INTRODUCTION

The functional significance of coronary artery stenoses is widely assessed using fractional flow reserve (FFR), which is based on measurement of the pressure beyond the stenosis that is usually obtained with a pressure wire (PW) during adenosine- or adenosine triphosphate (ATP)-induced hyperemia. The use of FFR may be limited by the contraindications and adverse effects of this hyperemic stimulus and the possibility of damaging the vessel with the PW, despite its Class 1 recommendation to guide the revascularization of chronic coronary syndromes.[1] Consequently, various hyperemic drugs and alternative methods have been introduced overtime. This review will focus on: *a)* the relevant characteristics of hyperemic agents, and *b)* the diagnostic accuracy and outcome data of nonhyperemic pressure ratios (NHPRs) and angiography-derived indices.

HYPEREMIC AGENTS

Coronary flow is the critical determinant of ischemia and at rest is controlled to match myocardial oxygen demand and to counteract variations in coronary perfusion pressure by parallel changes in

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microvascular resistance, resulting in an autoregulatory plateau. Under maximal hyperemia, the relationship between coronary flow and pressure becomes curvilinear: it is straight within the physiological pressure range, but curves toward the pressure axis at lower pressures.[2]

Given this relationship, the ratio between mean distal coronary pressure and mean aortic pressure during maximal hyperemia (FFR) is used to estimate the ratio between maximum flow in stenosed coronary arteries and maximum flow in healthy arteries.

In animal studies, papaverine was the most potent pharmacologic vasodilator and this finding was also confirmed in humans, but given its adverse effects adenosine was validated.[3] Subsequently, adenosine or ATP became widely used in clinical studies evaluating the usefulness of FFR (eg, DEFER, FAME, FAME-2 trials).

Consequently, the use of adenosine or ATP is recommended unless patients consume caffeine (a competitive antagonist of all adenosine receptor subtypes) within 24 hours or have contraindications (eg, asthma and atrioventricular or sinus node dysfunction)[4]; in such cases, other drugs or a NHPR are particularly useful. The relevant characteristics of the hyperemic agents investigated to calculate FFR are shown in table 1 and below.

Papaverine

Efficacy

Although an overall comparison of hyperemic agents overall is lacking, papaverine (used at standard or higher doses) has been shown to be the most potent vasodilator compared with ATP or nicorandil; the FFR mean difference was 0.01 (P = .01, n = 50)[11] and 0.016 (P < .001, n = 40),[4] respectively.

In a group of 115 patients, FFR values after using the standard and higher doses of papaverine showed no significant difference.[5]

Adverse effects

The main adverse effect of papaverine, ventricular tachyarrhythmia, is linked to prolongation of the QTU interval. Risk factors for its development are sex (female), hypokalemia, and alkalosis.[5]

Hyperemia characteristics

The characteristics of hyperemia were evaluated in 46 patients without comparison with other agents: papaverine showed a time to achieve 90% of the hyperemic onset of 12 seconds, but about 50 seconds to achieve the maximum onset.[6]

Adenosine

In vascular smooth muscle, adenosine binds to purinergic type 1 receptors (subtype A2A), which are coupled to Gs-proteins. This coupling results in a subsequent increase in cyclic adenosine monophosphate, activation of protein kinase and inwardly rectifying potassium (K_{ir}) channels, leading to vasodilatation.

Adenosine is commercially available in 6 and 30 mg vials. Compared with the intracoronary (IC) route, the use of the intravenous (IV) route requires higher doses and consequently higher costs[8]; moreover, its preparation takes longer.

Efficacy

In a meta-analysis of 11 studies (n = 587), when high (120-600 µg) IC doses of adenosine were used, no significant FFR mean difference was observed compared with IV adenosine, which was infused between 140 µg/kg/min (the most widely used infusion rate) and 200 µg/kg/min.[8]

There is uncertainty regarding the optimal dose needed to achieve maximal hyperemia with IC adenosine: for instance, Leone et al.[13] and De Luca et al.[20] showed a dose-response relationship between FFR values and IC adenosine up to 600 µg and 720 µg, respectively.

Adjedj et al.[7] suggested a lower range of IC dose, allowing up to 98% of maximum hyperemia, which might represent the best compromise between diagnostic accuracy and safety (see "Standard dose" in table 1).

Adverse effects

Complete AV block, although transient, is more common with a high (> 100 µg) IC dose of adenosine is used than with IV infusion.[8] On the other hand, systemic adverse effects are more frequent with IV adenosine.[8]

Hyperemia characteristics

The times to achieve 100% hyperemia with adenosine (IC and IV), papaverine and ATP were evaluated in a study by De Bruyne et al.[9] (n = 21) and IV adenosine had the longest time, while the plateau phase of hyperemia was short for the IC route, making this route unsuitable to perform pressure pullback maneuvers. The latter are important to assess the presence of tandem stenoses or focal vs diffuse coronary artery atherosclerosis (diffuse disease is associated with suboptimal postpercutaneous coronary intervention [PCI] outcomes and more angina) and consequently to take PCI decisions.[21]

Adenosine triphosphate

ATP is a nucleoside triphosphate consisting of adenosine (formed by the nitrogenous base adenine and a ribose sugar) and 3 serially bonded phosphate groups. ATP binds to purinergic type 2 receptors and determines increased intracellular calcium in vascular endothelium, which indirectly leads to stimulation of smooth muscle K_{ir} channels. ATP is commercially available in 100 mg vials, which can facilitate its administration and may reduce costs compared with adenosine.

Efficacy

As shown, IV ATP has been demonstrated to be less potent than papaverine.[11] IV ATP efficacy was similar to that of IV adenosine[9] and lower or similar compared with nicorandil[10,17] (see "Nicorandil" section).

Adverse effects, hyperemia characteristics

They are similar to those of IV adenosine.[9,11]

Sodium nitroprusside

Efficacy

In a meta-analysis of 7 studies (n = 342), sodium nitroprusside (NPS) produced similar FFR measurements (weighted mean difference:

Table 1. Characteristics of hyperemic agents

Type of agent	Mechanism of action	Need to discontinue caffeine ≃ 24 h before	Standard dose	Route of administration	Vasodilatory efficacy	Main adverse effects	Time to achieve maximal hyperemia (sec)*	Plateau phase of hyperemia (sec)*	Reversing agent
Papaverine	Blocking of cAMP and cGMP phosphodiesterase	No	[12 mg (LCA), 8 mg (RCA)][5]	IC	>	Ventricular tachyarrhythmia (ventricular fibrillation 1.7%)[5]	Slightly less than 50 [referred to a dose of 12 to 16 mg (LCA), 8 to 12 mg (RCA)][6]	44 [referred to a dose of 12 to 16 mg (LCA), 8 to 12 mg (RCA)][6]	No
Adenosine	Nonselective stimulation of P1 (A1, A2A, A2B and A3) receptors	Yes	160 to 200 µg (LCA), 60 to 100 µg (RCA)][7]	IC	≃	AV block transient (complete 11.6%)[8]	15 [referred to a dose of 20 or 40 µg][9]	21 [referred to a dose of 200 ug (LCA)][7] 12 [referred to a dose of 100 µg (RCA)][7]	No
			140 µg/kg/min[8]	IV	≃	[AV block transient (complete 4.4%) Chest discomfort Dyspnea Flushing Nausea][8]	[80 (FV), 112 (PV)][9]	Depending on infusion duration	
Adenosine triphosphate	Stimulation of P2 receptors	Yes	150 µg/kg/min[10]	IV	≃	AV block transient Chest discomfort Dyspnea Flushing][11]	[76 (FV), 104 (PV) (referred to a dose of 140 µg/kg/min)][9]	Depending on infusion duration	No
Sodium nitroprusside	Induction of nitric oxide	No	[50 or 100 ug or 0.6 µg/kg][12]	IC	≃	Symptomatic hypotension (4%)[13]	About 15 [referred to a dose of 0.6 µg/kg][14]	51 [referred to a dose of 0.6 µg/kg][14]	No
Regadenoson	Selective stimulation of P1 A2A receptor	Yes	400 µg[15]	IV	≃	[Chest discomfort (20%) Flushing (16%) Headache (16%) Dyspnea (4%)][16]	34-59[15]	10-600[15]	Yes (150 mg aminophylline IV bolus)
Nicorandil	Opening of ATP-sensitive potassium channel Induction of nitric oxide	No	2 mg[4]	IC	≃	Chest discomfort/ dyspnea (5%)[10]	17-18[17,18]	27-32[17,18]	No
Nicardipine	Calcium channel blocker	No	200 µg[19]	IC	≃	[Chest discomfort (10%) Flushing (4%)][19]	13[19]	143[19]	No

ATP, adenosine triphosphate; AV, atrioventricular; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; FV, femoral vein; IC, intracoronary; IV, intravenous; LCA, left coronary artery; P, purinergic; PV, peripheral vein; RCA, righy coronary artery.
* When not specified, the characteristics of hyperemia refer to the standard dose of the hyperemic agent.

0.00) compared with IC adenosine (dose of 50 to 300 µg) or IV adenosine (standard dose); in the included studies, NPS was also administered in different doses (see "Standard dose" in table 1), which may have influenced its efficacy.[12]

Adverse effects

In the meta-analysis, NPS showed a significant reduction in adverse effects.[12]

Hyperemia characteristics

In 40 patients, the mean duration of the plateau phase was longer for 0.6 µg/kg NPS (51 seconds) compared with 60 ug adenosine (28 seconds).[14]

Regadenoson

Efficacy

In a meta-analysis of 5 studies (248 patients undergoing elective angiography) that compared regadenoson with IV adenosine (usually

at standard dose), the mean difference between FFR measurements was 0.001.[15]

Adverse effects

Transient AV conduction block, chest discomfort, shortness of breath, hypotension, flushing, and headache were higher with adenosine.[15] When regadenoson was reversed using intravenous aminophylline, no adverse effects were observed.[22]

Hyperemia characteristics

Compared with IV adenosine, IV regadenoson achieved maximal hyperemia in an interval that was approximately 30 seconds shorter. The shorter time to FFR in patients receiving regadenoson can potentially be explained by the nonweight-based dose of intravenous regadenoson and by its longer half-life (2-4 minutes).[15]

On the other hand, the length of the plateau phase of regadenoson varies, probably because of drug metabolism, which represents a limitation (together with its high cost).[15]

Nicorandil

Efficacy

In a pooled cohort of 429 patients, the hyperemic efficacy of an IC bolus of nicorandil 2 mg was similar to IV infusion of adenosine 140 µg/kg/min or ATP 150 µg/kg/min: the FFR mean difference was 0.002.[17]

In a single center study (n = 207), nicorandil 2 mg was even more effective in achieving maximum hyperemia than ATP 150 µg/kg/min; a potential reason could be ATP administration via a peripheral IV line.[10]

Adverse effects

Nicorandil caused no AV block and less chest discomfort than adenosine or ATP.[17,18]

Hyperemia characteristics

The time to the lowest FFR was lower than with IV adenosine or ATP.[17]

Nicardipine

Efficacy

When nicardipine was compared with a standard dose of IC adenosine in 159 patients, the FFR was slightly higher with nicardipine (median difference 0.02, $P = .246$) and the number of vessels with FFR < 0.80 was 28.5% with nicardipine and 32.1% with adenosine ($P = .016$).[19]

Adverse effects

Nicardipine produced less chest pain and flushing compared with adenosine and no AV block.[19]

Hyperemia characteristics

The time to the lowest FFR was similar for the 2 drugs, while the plateau time of an IC bolus of nicardipine was significantly longer than with IC adenosine.[19]

Summary

IC vasodilator administration requires lower doses (and costs) and shorter times for preparation and to reach maximal efficacy compared with IV administration; in contrast, it has the disadvantage of being harder to maintain maximum hyperemia, which is important for pullback maneuvers.

A suggested strategy to accurately assess functional significance is to use adenosine or ATP or nicorandil (in the event of caffeine intake within 24 hours or adenosine or ATP contraindications) as the first-line drugs and to reserve papaverine for doubtful cases (ie, FFR, 0.81-0.85).[4] However, nicorandil has the limitation of low availability.[17]

Nicorandil and NPS are valid first-line alternatives to adenosine or ATP on the basis of their safety, efficacy, and characteristics of maximal induced hyperemia. NPS has a longer hyperemia plateau phase than nicorandil (even if there is no a direct comparison). Moreover, the appropriate dose of NPS has not been well established.

Papaverine has high efficacy but an unfavorable safety profile and consequently it is useful especially in doubtful cases (FFR, 0.81-0.85) when there are no risk factors for ventricular tachyarrhythmia.

Regadenoson (due to variable duration of maximal hyperemia and cost) and nicardipine (due to its slightly lower efficacy) seem to be less valid alternatives.

NONHYPEREMIC PRESSURE RATIOS

NHPRs are evaluated with a 0.014″ PW or a pressure microcatheter (PMC) and various pieces of software without using hyperemic agents. Because they are independent of a steady-state hyperemia, they are useful in performing pullback maneuvers.

The definitions of NHPRs and some characteristics of the devices used to calculate them are shown in table 2.

The instantaneous wave-free ratio (iFR) is the most widely investigated and a value of 0.89 matched best with an FFR ≤ 0.80.[30] Its diagnostic accuracy compared with PW FFR will be discussed in the "Instantaneous wave-free ratio" section.

The resting distal coronary pressure to aortic pressure ratio (P_d/P_a) has a cutoff of 0.91 to predict functional significance, while the other NHPRs have the same cutoff as iFR (0.89); in a post-hoc analysis studies, these values were the best predictors of PW iFR, usually with very high diagnostic accuracy (which was somewhat lower for the diastolic pressure ratio $[dPR]_{micro}$), as shown in the "Resting P_d/P_a" to "Constant resistance ratio" sections.

Instantaneous wave-free ratio

When compared with adenosine FFR, iFR showed significantly less adverse procedural signs and symptoms (30.8% vs 3.1%), mainly chest pain and/or dyspnea,[31] as well as shorter procedural times (about 2-4 minutes of difference).[31,32]

Table 2. Definitions of NHPRs and characteristics of devices

Type of NHPR	Definition	Calculation period	Device (last version)	Manufacturer	Site of sensor (from the tip)*	Type of sensor	Coregistration (angiography and IVUS)
iFR	Average P_d/P_a[23]	Diastolic sub-cycle (wave-free period) that begins at the point 25% into diastole and ends 5 ms before end of diastole[23]	PW: OmniWire	Philips (the Netherlands)	3 cm	Piezoelectric (with conductive bands)	Yes (for IntraSight 7 Platform via SyncVision)
Resting P_d/P_a	Average P_d/P_a[24]	Whole cardiac cycle[24]	PW/PMC	Not proprietary technology	NA	NA	NA
dPR	Average P_d/P_a[25]	Whole-diastole that begins at the nadir of the dicrotic notch until 50 ms before the upstroke of the next heartbeat[25]	PW: OptoWire Deux	OpSens Medical (Canada)	3.5 cm	Optical	No
RFR	Lowest filtered P_d/P_a[26]	Whole cardiac cycle[26]	PW: PressureWire X	Abbott (United States)	3 cm	Piezoelectric	No
DFR	Average P_d/P_a (on 5 beats)[27]	Diastolic sub-cycle that begins when the P_a is less than the mean P_a and there is a down-sloping P_a[27]	PW: Comet II	Boston Scientific (United States)	3 cm	Optical	No
dPR_{micro}	Average P_d/P_a (on 5 beats)[28]	Diastolic point within diastole halfway between the peak of one waveform and the peak of the next waveform[28]	PMC: Navvus II	ACIST (United States)	5 mm	Optical	No
cRR	Average P_d/P_a[29]	Diastolic sub-cycle (wave-free period) identified by calculating the time derivative of P_d/P_a and finding the longest period when it equals zero[29]	PMC: TruePhysio	Insight Lifetech (China)	~2.5 mm	Piezoresistive microelectro mechanical system	No

cRR, constant resistance ratio; DFR, diastolic hyperemia-free ratio; dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; NA, not applicable; NHPR, nonhyperemic pressure ratio; P_a, aortic pressure; P_d, distal coronary pressure; PMC, pressure microcatheter; PW, pressure wire; RFR, resting full-cycle ratio.
* For PWs the sensor is just proximal to the radiopaque part.

iFR is the only index with the option of angio and intravascular ultrasound (IVUS) co-registration, which can favor evaluation of stenoses.

Diagnostic accuracy

Concordant results between iFR and FFR ranged from 79.4% to 88.2% in 3 studies (total n = 1259).[33-35]

Both hyperemic (FFR) and resting (NHPRs) measurements can be used to evaluate the significance of stenoses, even if FFR is evaluated during hyperemic flow, which falls with progressive stenosis severity with a consequent increase in transstenotic pressure gradient (TPG) and a decrease in FFR, while the NHPRs are evaluated during resting coronary flow, which is maintained in progressively worse stenoses (beyond a critical point of stenosis, resting flow is also expected to fall).[36] The maintenance of resting flow, however, is due to a compensatory reduction in microvascular resistance at the expense of distal coronary pressure, which falls with widening TPG; therefore, TPG increases with progressive stenosis severity in both hyperemic and resting measurements.[36]

Some factors may influence hyperemic and/or resting flow and explain the observed discordances, at least partly. Discordance between FFR and NHPRs (FFR high and iFR or resting full-cycle ratio (RFR) low) was seen in conditions that may give higher FFR values because of reduced vasodilation ability due to microvascular dysfunction (MVD): insulin-treated diabetes mellitus, lower estimated glomerular filtration rate, advanced age (because of its association with the latter comorbidities), atrial fibrillation (due to its association with advanced age and/or higher heart rate).[33] A similar discordance (FFR high and iFR low), as resting coronary flow increases with heart rate, was seen with elevated heart rate and/or absence of beta-blocker use,[34] which may therefore give lower iFR values. Other causes of FFR high and iFR low discrepancy may be severe aortic stenosis and myocardial infarction (MI).

The other kind of discordance (FFR low and iFR high) is affected by potentially high coronary flow reserve (CFR): indeed, left main (LM), proximal left anterior descending artery stenosis and male sex could result in greater coronary flow variation between resting and hyperemic conditions and consequently in greater discordance.[34,35]

Both kinds of discordance are more frequent among intermediate stenoses (41%-70%) than among mild or severe stenoses.[34,35]

Evaluation in specific clinical or angiographic conditions

Aortic stenosis: in patients with a severe defect, a blunted response to hyperemia is possible due to myocardial hypertrophy, elevated left ventricular diastolic filling pressure, and MVD. iFR seems more reliable in this context, although it might be reduced by increased oxygen demand and resting coronary flow due to hypertrophy.[33]

Diabetes mellitus: this condition is associated with MVD which may affect the reliability of FFR, and consequently NHPRs might be preferred in these patients.[33] On the other hand, in diabetic

patients in the DEFINE-FLAIR trial, iFR- and FFR-guided revascularization had a comparable risk of adverse events.

LM disease: discordance was even higher (25.0%) in a recent study in patients with isolated LM disease or with LM and concomitant downstream disease (36.2%); previous data suggest that both FFR and iFR can guide the decision to revascularize or defer LM lesions; if there are discordant results, performing IVUS and deferring the LM lesion can be considered only when the minimal lumen area is above 6 mm squared.[37]

MI: compared with stable angina patients, noninfarct-related arteries (non-IRA) of subacute non-ST-elevation MI/ST-elevation MI (NSTEMI/STEMI) showed increased resting flow and reduced CFR, while hyperemic flow was preserved. Moreover, the index of microcirculatory resistance (IMR), derived from pressure-temperature guidewires, was not increased and consequently the higher resting coronary flow in MI patients may have been the result of neurohumoral compensatory mechanisms triggered by the acute myocardial damage.[38]

According to the 1st study, these findings support the use of FFR in subacute MI,[38] but another study reported a significant FFR decrease in non-IRA in STEMI from the acute phase to the 1-month follow-up (mean difference 0.02, P = .001), together with an increased acute IMR.[39] In the same setting, iFR increased over time, although without significance (mean difference 0.01, P = .12).[39]

Eventually, both methods may be altered in patients with STEMI since lesion severity can be underestimated by FFR and overestimated by iFR. The 2023 European Guidelines recommended that PCI of non-IRA in STEMI patients be based on angiographic severity because the FFR-guided strategy does not usually reduce the risk of adverse events, whereas in patients with NSTE-acute coronary syndrome (ACS), the FFR-guided strategy has more favorable data compared with STEMI, and functional invasive assessment of non-IRA may be considered during the index procedure.[40]

Tandem lesions: these lesions are another cause of discordance between NHPRs and FFR, which can both be used for this evaluation; FFR may estimate TPG better in distinct lesions, while NHPRs may be less influenced by the interplay between serial stenoses.[21] Pullback can give a TPG for each lesion constituting tandem lesions and treating the lesion with the greatest TPG first and then reevaluating the other lesion is a reasonable approach.[21]

Outcome data

Two large randomized trials (DEFINE-FLAIR, n = 2492; iFR-SWEDEHEART, n = 2037) showed the noninferiority of an iFR vs an FFR-guided PCI strategy during follow-up at 1 year and 5 years, although iFR showed lower revascularization rates with almost significant P values.[31,32]

The rate of major adverse cardiac events (MACE) were 18.6% (iFR) vs 16.8% (FFR) (P = .63) after 5 years in deferred patients who presented with stable angina (n = 611) or nonculprit lesions of ACS (unstable angina and NSTEMI, n = 297). Moreover, there have been no significant differences in long-term event rates between stable angina and ACS.[41]

As regards deferred lesions with iFR-FFR discordance, they did not show an increased risk of adverse events at 5 years.[42]

Similarly, deferred lesions with discordant results between NHPRs (iFR, dPR, RFR) and FFR had a higher risk of vessel-related events at 5 years than those with concordant negative results but did not have a higher risk than revascularized lesions.[43] In patients with discordant results, meticulous follow-up was recommended with intensive medical treatment.[43]

Post-PCI: iFR ≥ 0.95 (n = 500) after successful stenting was associated with a significant reduction in the composite endpoint of cardiac death, spontaneous MI, or clinically-driven target vessel revascularization at 1 year compared with lower iFR.[44]

Resting P_d/P_a

Diagnostic accuracy

Resting P_d/P_a is evaluated throughout the cardiac cycle, which provides higher microvascular resistance and consequently a lower pressure gradient and potentially lower sensitivity than the diastolic wave-free period of iFR.[36] However, its diagnostic accuracy was high (93.0%) when compared with that of iFR (n = 627).[24]

Outcome data

Resting P_d/P_a and iFR showed similar associations with the risk of MACE at 2 years (1.5% for negative P_d/P_a vs 1.6% for negative iFR values; n = 375).[45]

Post-PCI: $P_d/P_a \leq 0.96$ poststenting was the best predictor of MACE at 30 months (n = 574).[46]

Diastolic pressure ratio (pressure wire)

Diagnostic accuracy

Diagnostic accuracy was approximately 97.0% in a study by Van't Veer et al. (n = 197).[25]

Outcome data

In the study by Lee et al.,[43] a sample of 435 patients showed similar vessel-related events at 5 years for negative dPR (7.9%), iFR (8.0%), and FFR (7.7%) values.

Post-PCI: not available.

Resting full-cycle ratio

Diagnostic accuracy

As shown in table 2, the RFR is calculated over the whole cardiac cycle. It was detected outside diastole in 12.2% of cases and consequently, according to the authors, lesions of potential significance might be missed by NHPR measured only during diastole.[26] However, the diagnostic accuracy of the RFR compared with iFR was 97.4% in the VALIDATE-RFR trial (n = 504),[26] and was therefore similar to that of diastolic NHPRs such as dPR and the diastolic hyperemia-free ratio.

Outcome data

In the same study conducted by Lee et al.,[43] negative RFR showed a similar percentage (8.1%) of adverse events.

Post-PCI: no data are available; the ongoing "PICIO (NCT04417634)" trial will evaluate the RFR in this setting.

Diastolic hyperemia-free ratio

Diagnostic accuracy

Diagnostic accuracy was 97.6% in the study by Johnson et al. (n = 833).[27]

Outcome data

In 926 patients, deferred lesion failure (cardiac death, MI, repeated revascularization) after 3 years was similar for negative diastolic hyperemia-free ratio (6.8%), iFR (6.9%), dPR (6.9%), RFR (7.1%) and FFR (5.9%).[47]

Post-PCI: not available.

Diastolic pressure ratio measured using a microcatheter (dPR_{micro})

Diagnostic accuracy

In a study by Arashi et al.[28] (n = 161), dPR_{micro} showed a mean bias of −0.028 and a diagnostic accuracy of 82.2% compared with PW iFR; this reduced value compared with the other NHPRs may have been influenced by the cross-sectional area at the lesion site of Navvus PMC, which is larger than the PW (and also compared with TruePhysio PMC) and this may have overestimated the stenoses.

Outcome data

Data are only available in the setting of post-PCI: $dPR_{micro} \leq 0.89$ was associated with significantly higher cardiac mortality at 2 years in 735 patients (of note due to the limited number of events, receiver operating characteristics analysis was not able to identify an optimal cutoff value and therefore the authors deliberately took the accepted ischemic threshold of 0.89).[48]

Constant resistance ratio

Diagnostic accuracy

Diagnostic accuracy was 97% with a mean bias of −0.0001 compared with PW iFR in an abstract by Li et al. (n = 86).[29]

Outcome data

No outcome data are available yet. The ongoing trial, SUPREME II (NCT05417763) will evaluate the implications of post-PCI constant resistance ratio.

Summary

Among NHPRs, iFR has the largest amount of evidence and showed noninferiority vs a FFR-guided PCI strategy over a long follow-up with less adverse procedural symptoms and procedural times. However resting P_d/P_a, dPR (PW), RFR, the diastolic hyperemia-free ratio and the constant resistance ratio showed very high diagnostic accuracy compared with iFR, and consequently they may be used to replace iFR.

In contrast, discordance results between NHPRs and FFR have been shown in a nontrivial percentage of cases. Patients with discordant results showed a worst outcome than those with concordant negative results and a meticulous follow-up with intensive medical treatment has been recommended, while revascularization of discordant lesions is uncertain.

ANGIOGRAPHY-DERIVED INDICES

Angiography-derived indices do not need PW or PMC use or drug-induced hyperemia, thus avoiding the potential risks of coronary injury and adverse effects. Moreover, they are not limited by pressure drift (the difference between initial pressure equalization and final check), which can be related to alterations in the pressure sensor (eg, due to temperature variations) and may lead to the need to repeat the measurements with both PW and PMC systems.

Angiography-derived indices share the same FFR cutoff value (0.80); a virtual pullback trace, which shows values along the interrogated vessel/vessels, is provided by all the systems.

Currently, the following indices have been evaluated: vessel fractional flow reserve (vFFR), quantitative flow ratio (QFR), coronary angiography-derived FFR (FFR_{angio}), computational pressure-flow dynamics-derived FFR (caFFR), angiography-based FFR (accuFFR-$_{angio}$), and Murray law-based QFR (μQFR).

These indices are calculated using various softwares through 3 dimensional (3D) reconstruction of the coronary artery based on 1 or more angiographic projections and estimated coronary flow velocity based on aortic pressure and/or frame count analysis. Aortic pressure measurement is needed for vFFR, FFR_{angio}, accuFFR$_{angio}$ and caFFR; in the latter case, a specialized pressure transducer (FlashPressure, RainMed Medical, China) connected to the guiding catheter is needed. Other details are reported in table 3. Diagnostic accuracy (compared with PW FFR) and outcome data are shown below.

Aortic-ostial lesions and significant vessel overlap are exclusion criteria for all the indices because they hamper software analysis.

Vessel fractional flow reserve

Diagnostic accuracy

In the multicenter FAST II study (n = 334, 39 NSTEMI), diagnostic accuracy was 90% compared with FFR ≤ 0.80 by a blinded independent core laboratory.[58]

Accuracy was maintained in specific subgroups such as patients with diabetes, bifurcations, moderate or severe calcifications, and tortuous lesions (NSTEMI subanalysis is not available).[58] The diagnostic accuracy of vFFR ≤ 0.80 in identifying LM lesions with IVUS minimal lumen area < 6.0 mm^2 was good (sensitivity 98%, specificity 71.4%).[59]

Outcome data

Outcome data are available only in post-PCI: lower (≤ 0.93) vFFR values were associated with a significantly increased risk of target vessel failure (TVF) at 5 years of follow-up (n = 748).[60]

Quantitative flow ratio

QFR is currently the index with the largest amount of evidence.

Table 3. Characteristics of angiography-derived indices

Type of index*	Software provider	Base of 3D reconstruction	Frame count analysis needed	Need for aortic pressure input	Type of 3D reconstruction	Simultaneous analysis of main vessel and side branches	Time to calculation (minutes)	Verification of an index to analyze microcirculation*	Verification of an index to differentiate focal and diffuse disease (quantitative method)*
vFFR	Pie Medical Imaging (the Netherlands)	2 projections at least 30° apart at 15 frames/s (eventually 7.5)[49,50]	No	Yes	Single-vessel	No	Not reported	No	No
QFR	Medis Medical Imaging (the Netherlands)/ Pulse Medical Imaging Technology (China)	2 projections at least 25° apart at 15 frames/s (eventually 7.5)[49,51]	Yes (for cQFR)	No	Single-vessel	No	5[52]	Yes: – IMR_{angio} – angio-IMR – A-IMR – nonhyperemic IMR_{angio}	Yes: – QVP – QFR-PPG
FFR_{angio}	CathWorks (Israel)	≥ 2 projections at least 30° apart at 10 frames/s[53]	No	Yes	Multi-vessel	Yes	9.6[54]	No	No
caFFR	RainMed Medical (China)	≥ 2 projections at least 30° apart at 15 frames/s[55]	Yes	Yes (with specialized pressure transducer)	Single-vessel	No	4.5[55]	Yes: – caIMR	Yes: – angio-FFR based PPG
$accuFFR_{angio}$	ArteryFlow Technology (China)	2 projections at least 25° apart at 15 frames/s[56]	Yes	Yes	Single-vessel	No	4.3[56]	Yes: – accuIMR	No
μQFR	Pulse Medical Imaging Technology (China)	1 projection at 15 frames/s[57]	Yes	No	Single-vessel	Yes	1.1[57]	Yes: – AMR	No

$accuFFR_{angio}$, angiography-based FFR; AMR, angiographic microvascular resistance; caFFR, computational pressure-flow dynamics-derived fractional flow reserve; FFR_{angio}, coronary angiography-derived fractional flow reserve; IMR, index of microcirculatory resistance; PPG, pullback pressure gradient; μQFR, Murray law-based QFR; QFR, quantitative flow ratio; QFR-PPG, QFR derived pullback pressure gradient; QVP, QFR virtual pullback; vFFR, vessel fractional flow reserve.
* All the listed indices are guidewire-free.

QFR was calculated from 3 models, obtaining fixed-flow QFR (fQFR), adenosine-flow QFR (aQFR), and contrast-flow QFR (cQFR), respectively; the latter is derived without induction of hyperemia using contrast flow velocity through the stenosis estimated using frame count analysis,[51] which is automatic in the latest software.

Diagnostic accuracy

cQFR and aQFR showed similar agreement with FFR and higher accuracy than fQFR.[51] The overall diagnostic accuracy was 87% in the meta-analysis by Westra et al.[61] (n = 819).

In the multicenter registry of Choi et al.[62] (n = 452), the diagnostic accuracy of cQFR was not reduced in nonculprit vessels in ACS (n = 153), while in the registry of Lee et al.[63] (n = 915), it was lower in nonculprit vessels in the acute MI group (n = 103) compared with the angina group (92.4% vs 96%), although without significance. A possible explanation is that its calculation is based on frame count analysis, which may be affected by transient MVD of infarct-related and noninfarct-related arteries.[63]

In the meta-analysis by Westra et al.,[61] diabetes, which may also cause MVD, showed a statistically significant ability to predict QFR values at least 0.10 lower than the corresponding FFR measurement, but the diagnostic accuracy of cQFR was not different in the diabetes subgroup in the registry by Choi et al.[62]

Accuracy was preserved in bifurcations and calcified and tortuous lesions,[63] but was reduced or preserved in tandem lesions in 2 different studies.[63,52]

Concordance was acceptable (90.7%) in intermediate LM lesions.[64]

The numerical agreement of QFR to FFR was negatively affected by low FFR[61]; similarly, in the case of 0.75 < FFR ≤ 0.85 QFR accuracy was reduced (91.2%) in the registry by Lee et al.[63] This could indicate difficulties in contouring more severe lesions with QFR.[61]

Outcome data

In a large (n = 3825) multicenter randomized trial (FAVOR III China) among patients undergoing PCI (ACS 63.5%), the composite endpoint of death from any cause, MI, or ischemia-driven revascularization at 1-year was significantly reduced in the QFR-guided group compared with the angiography-guided group (5.8% vs 8.8%).[65]

Post-PCI: the cutoff values of post-PCI QFR to predict the 1- to 3-year vessel-oriented composite endpoint ranged from 0.89 to 0.94 in a recent systematic review.[66]

Coronary angiography-derived FFR

In coronary angiography-derived FFR, the entire coronary tree including side branches (SBs) is evaluated, allowing FFR values to be obtained along each vessel. However, this may prolong computation times compared with indices with a per vessel approach (table 3).

Diagnostic accuracy

In a pooled analysis of 5 studies (n = 588, 59 NSTEMI), diagnostic accuracy was 93% by blinded operators and was consistent across nonculprit lesions of NSTEMI, diabetic patients, bifurcations, moderately/severely calcified or tortuous vessels, and tandem lesions.[67]

For lesions with FFR between 0.75 and 0.85, accuracy was somewhat lower (85.5%).[67]

Outcome data

In a cohort of 536 patients (approximately 50% with ACS), FFR_{angio}-guided treatment in the deferral group showed 2.5% of 1-year MACE, a rate consistent with previously reported data using FFR.[68]

Post-PCI: not available.

Computational pressure-flow dynamics-derived FFR

Diagnostic accuracy

In a multicenter trial (FLASH-FFR) in patients with stable or unstable angina pectoris (n = 328), diagnostic accuracy was 95.7% by an independent blinded core laboratory.[55]

The caFFR diagnostic accuracy was lower (89.9%) in 119 vessels with FFR between 0.75 and 0.85.[55]

Outcome data

In a small single-center study (n = 69), the 12-month outcome showed that caFFR-guided PCI deferral is safe (3.4% of patients had target vessel revascularization) and comparable to previous data on FFR-guided PCI deferral.[69]

Post-PCI: in a group of 136 patients, lower post-PCI caFFR (< 0.90) was associated with a higher rate of 9-month TVF.[70]

Angiography-based FFR

Diagnostic accuracy

In a single-center observational study of 300 patients with stable angina pectoris, the accuracy of $accuFFR_{angio}$ was 93.7%.[56]

Outcome data

Not available (ongoing trials).

Murray law-based quantitative flow ratio

The µQFR uses Murray bifurcation fractal law to reconstruct reference vessel size and a single angiographic projection (with a consequent time saving) to produce values along the main vessel and its SBs.

Diagnostic accuracy

The vessel-level diagnostic accuracy for µQFR to identify FFR ≤ 0.80 lesions was 93.0% in 330 main vessels in 306 patients (main presentation: stable/unstable angina pectoris); diagnostic accuracy was not evaluated in SBs.[57]

Outcome data

In 288 patients with true coronary bifurcations who underwent a provisional approach without SB treatment, after 3 years, TVF was 29.2% in the SB µQFR < 0.8 group vs 10.8% in the SB µQFR ≥ 0.8 group ($P < .05$).[71]

Post-PCI: in a group of 169 patients, µQFR ≤ 0.89 after treatment of in-stent restenosis with a drug-coated balloon was the best cutoff to predict the 1-year vessel-oriented composite endpoint and was associated with a 6-fold higher risk.[66]

Summary

Angiography-derived indices are a valid alternative to FFR in terms of clinical agreement. However, some angiographic characteristics have not been investigated. Diagnostic accuracy compared with FFR was good but was generally reduced at the borderline FFR zone. Direct comparison with FFR-guided treatment on outcomes is lacking, and reproducibility was variable.

Regarding the latter, QFR inter- and intraobserver reproducibility ranged from high to poor among trained operators and there was significant variability in vFFR values between nonexpert and expert operators; conversely, repeated FFR could be performed with close to zero imprecision in previous studies.[72]

The authors highlighted the importance of adherence to standard operating procedures and continuous feedback and training to achieve accurate computation.[72]

FUTURE PROSPECTS

In our opinion, the most important issues requiring clarification concern the need for PCI in lesions with discordant NHPR/FFR values and the comparison of angiography-derived indices vs FFR in guiding treatment. The value of these indices will be further established by the ongoing trials FAST III (NCT04931771), LIPSIASTRATEGY (NCT03497637), FAVOR III Europe Japan trial (NCT03729739), FLASH-FFR II (NCT04575207), NCT05209503 and NCT05202041, and ALL-RISE (NCT05893498), which will evaluate the risk of adverse events with vFFR, QFR, caFFR, $accuFFR_{angio}$, and FFR_{angio} vs FFR-guided revascularization.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial Intelligence was not used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

F. Vergni, G. Fiore, F. Pellone, and M. Luzi contributed to the design of the work. F. Vergni drafted and edited the work. F. Vergni, G. Fiore, F. Pellone, and M. Luzi revised the work and approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Debate. "Orbiting" around the management of stable angina. The interventional cardiologist's perspective

A debate. «Orbitando» en torno al abordaje de la angina estable. Perspectiva del intervencionista

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Question: In your opinion, what conclusions can be drawn from the 2 ORBITA trials?[1,2]

Answer: The 2 ORBITA studies aim to settle the debate on the utility of coronary revascularization in patients with stable chronic angina and coronary artery lesions causing ischemia in that territory. The first ORBITA trial[1]—a double-blind, multicenter clinical trial published in 2018—randomized 230 patients with stable angina and at least 1 severe coronary stenosis (> 70%) to undergo percutaneous coronary intervention (PCI) or receive placebo to assess the symptom relief of angina. After being included in the study, both groups received a strategy of medical therapy optimization 6 weeks prior to randomization. There were no significant differences at the 6-month follow-up in the primary endpoint of exercise tolerance between the 2 groups. The authors concluded that the efficacy of invasive procedures should be determined with placebo control only (without pharmacological optimization). This is precisely what the recently published ORBITA-2 trial[2] aimed to address. This trial randomized 301 patients in 14 centers in the United Kingdom to receive PCI or placebo. Two weeks before randomization, all antianginal drugs were discontinued. All patients were required to have significant coronary artery disease and evidence of ischemia in at least 1 vascular territory. Both groups received dual antiplatelet therapy (including the placebo group). The primary endpoint (assessment of angina, need for medication, and events after the 12-week follow-up) favored the PCI group vs the placebo group, with improvements in the follow-up ergometry and quality of life tests. The authors conclude that, in patients with stable angina, coronary artery disease, evidence of ischemia in that vascular territory, and not on antianginal drugs, PCI was more effective in reducing angina symptoms than placebo.

In my opinion, both studies confirm 2 issues: on the one hand, that the first-line therapy in patients with stable angina is optimal medical therapy; on the other hand, that PCI improves the symptoms, exercise capacity, and quality of life of patients who continue to experience angina or treatment-related adverse effects.

Q.: What would be the key features aspects of these 2 studies?

A.: Methodologically, the 2 studies have been conducted appropriately, but with very few patients. In the ORBITA trial[1], recruitment was not easy (230 patients in 4 years, in 5 major centers in the United Kingdom), meaning there is a patient selection bias (generally less severe patients). Coronary artery disease was estimated visually (lesions > 70%), without the use of intracoronary imaging, and not all lesions were proximal, which likely have a higher ischemic burden. Finally, 85% of patients who did not undergo PCI, were eventually treated with percutaneous coronary revascularization during follow-up.

The ORBITA-2 trial[2] addressed some of these limitations by using intravascular imaging and coronary physiology, which identify really significant lesions and avoid treating lesions that are functionally nonsevere, reducing events during follow-up.[3-5] However, once again, and in 14 centers, enrolling 300 patients took more than 4 years. Ethical aspects of the study have been criticized, as comparison vs placebo and not vs optimal medical therapy left the placebo group without any treatment for angina and exposed them to unnecessary bleeding risks due to dual antiplatelet therapy. Nevertheless, conducting the study in this manner seems timely, since both the true utility of PCI and even the foundations of coronary physiology were questioned following the results of the ORBITA trial,[1] suggesting that an increase in fractional flow reserve in an ischemic territory had no impact at all, which has been elucidated in the ORBITA-2 trial.[2]

Finally, perioperative myocardial infarction remains the weak point of coronary interventions in all clinical trials. The definition of

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"perioperative infarction" includes everything from Q-wave infarction related to loss of epicardial branch to mild troponin elevation (the threshold is 5 times higher than the upper limit, according to the current definition[6]) due to complications occurring during potentially treatable intervention with good final outcomes (branch dissection, no-reflow, compromised temporary flow, etc). Undoubtedly, this limits revascularization options (whether percutaneous or surgical) in all clinical trials. Therefore, it would be advisable to differentiate between the type of infarction, particularly those with the most prognostic implications.

Q.: What do you think these 2 studies contribute compared with the much larger ISCHEMIA trial?

A.: The ISCHEMIA trial,[7] published in 2020, was much larger, with more than 5000 patients with stable coronary artery disease and moderate-to-severe ischemia, randomized to an initial invasive strategy with coronary angiography and revascularization, when necessary, along with medical therapy, or to an initially conservative strategy, with medical therapy alone and angiography if insufficient. The aim of the study was prognostic—not symptomatic—assessment, with a composite endpoint of cardiovascular death, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. After a median follow-up of 3.2 years, the initial invasive strategy did not reduce the risk of cardiovascular ischemic events or all-cause mortality compared with the conservative strategy.

Setting aside the limitations and potential criticisms of the ISCHEMIA trial,[7] such as recruitment difficulties, very rigorous inclusion criteria, the absence of severe ischemia in a high percentage of cases, and that 25% of patients in the conservative treatment group eventually underwent revascularization, it is obvious that the aim of the study is very different from that of the ORBITA and ORBITA-2 trials.

In general, the prognosis of chronic coronary syndromes is good, but it is difficult to demonstrate prognostic differences in this subgroup of patients after a mean follow-up of just over 3 years. Furthermore, the ISCHEMIA trial included a group of patients who were heterogeneous in certain aspects features excluded those with more severe coronary artery disease (such as left main coronary artery disease) or ventricular dysfunction, in whom the prognostic impact of revascularization is known to be greater.

Another issue is symptom relief and quality of life. Indeed, the authors of the ISCHEMIA trial[7] reported clinical implications and improvements in terms of quality of life. Although 35% of patients remained asymptomatic, the invasive strategy was associated with an improvement in angina-related quality of life, especially in patients with complete revascularization.[8] This difference was greater for symptomatic patients.

The ORBITA trials focus on symptom relief in patients with chronic coronary syndromes, but with significantly fewer patients and shorter follow-up periods to demonstrate improvement in exercise capacity and quality of life, which were indeed observed in the secondary endpoints of the ISCHEMIA trial.

Q.: Based on all this evidence, what are the benefits, if any, of the invasive strategy over the conservative approach?

A.: The advantage of the invasive strategy over the conservative approach as first-line therapy has not been demonstrated in patients with chronic coronary syndromes. The cornerstone of therapy for patients with chronic angina is optimal medical therapy, as stated by clinical practice guidelines. In fact, the publication of the ORBITA trials has not changed these guidelines at all.

However, considering the results of these studies, we can be in no doubt that PCI is the best therapeutic option in patients who cannot control their symptoms with drugs, with drug-related adverse effects, or even those who simply do not want to continue taking drugs to control their symptoms. Revascularizing these patients is possible with good results and symptom relief.

We will have to wait for longer-term follow-up of the ISCHEMIA trial[7] to evaluate whether coronary revascularization in patients with stable chronic angina has any prognostic impact. For the time being, until further evidence becomes available for confirmation, we know that the patients included in the study treated with complete revascularization experienced fewer events (cardiovascular death or myocardial infarction) during follow-up than those undergoing incomplete revascularization or an initial conservative strategy.[9] Additionally, myocardial infarctions during follow-up (separating them from the perioperative infarctions with the above-mentioned implications) were also fewer in the group who initially underwent the invasive strategy.[10]

Finally, we should consider that all 3 studies included patients with generally low-risk chronic coronary syndromes, most with clearly demonstrated moderate ischemia, and single-vessel involvement, so their results are not generalizable to patients with more complex coronary artery disease, such as multivessel disease, left main coronary artery disease, or associated ventricular dysfunction.[11] Therefore, the correct identification and characterization of coronary artery disease are important, which almost always requires noninvasive coronary angiography, or invasive angiography if the former is inconclusive. Another question arises: once coronary artery disease has been accurately assessed, should the patient undergo revascularization or should a conservative approach to their lesions be pursued for symptom relief? Or, depending on the extent or severity of the coronary artery disease and the myocardial territory at risk, is a more aggressive approach necessary, with either percutaneous or surgical revascularization?

Q.: What indications do you take into consideration in your routine clinical practice to decide which invasive approach to use in a patient with stable angina?

A.: The results obtained in the ORBITA trials maintain medical therapy as the first option for patients with chronic angina and relegate the invasive approach to those with symptoms that cannot be resolved despite optimal medical therapy. This would, therefore, be the indication in stable chronic angina. However, such results cannot be extrapolated to patients with multivessel disease and severe ischemia, so it would be a mistake to take them as a reference to stop performing coronary angiograms, which would imply avoiding the revascularization of patients at higher risk than indicated by their symptoms. Therefore, as always in medicine, each patient should be individually evaluated to determine who requires an earlier invasive approach based on their symptoms and multiple other factors. We'll still have to wait for longer-term results, even for these lower-risk patients due to their lower ischemic burden, to see how the story ends.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

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CONFLICTS OF INTEREST

None declared.

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Debate. "Orbiting" around the management of stable angina. The clinician's perspective

A debate. «Orbitando» en torno al abordaje de la angina estable. Perspectiva del clínico

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Question: In your opinion, what conclusions can be drawn from the 2 ORBITA trials?[1,2]

Answer: The ORBITA trials focus on a specific aspect of the management of patients with acute coronary syndrome: the benefit in terms of symptom relief of angina.[1,2] The first ORBITA trial[1] is a double-blind, randomized, multicenter clinical trial, with 230 patients with severe single-vessel disease and ischemic symptoms that analyzed whether percutaneous coronary intervention (PCI) was associated with an improvement in angina-free exercise time compared with a placebo procedure.[1] There were no statistically significant differences in the primary endpoint (differences in exercise increment on the stress test) at the 6-week follow-up between the 2 groups. The second ORBITA trial[2], a double-blind, multicenter clinical trial, randomized 301 patients with exertional angina to undergo PCI or a placebo procedure.[2] The methodology differs from that of ORBITA trial: all patients discontinued antianginal medication 2 weeks before randomization and were only included if they experienced angina throughout this period (assessed by a complex scoring system through a mobile application).[3] Only patients with at least 1 severe coronary stenosis confirmed through physiological assessment were included; additionally, the 2 groups underwent the intervention (which was simulated in the group treated with the placebo procedure), and all patients received dual antiplatelet therapy. In total, 80% of patients had single-vessel disease, mostly involving the left anterior descending coronary artery, and complete revascularization was achieved in approximately 100% (using intracoronary imaging in 70% of PCIs). At the 12-week follow-up, patients treated with PCI experienced statistically significant greater angina relief, as well as improved exercise tolerance and quality of life than those in the placebo group.

Q.: What would be the key features of these 2 studies?

A.: Despite introducing the novel concept of simulating a PCI in the placebo group (thus avoiding the effect of attributing clinical improvement to the procedure *per se*), the main limitations of the first ORBITA trial were its small sample size and limited follow-up time. Moreover, the use of exercise tolerance with the stress test as the main study endpoint has been criticized due to its heterogeneity. Of note, 29% of patients had a negative functional flow reserve study (> 0.80), suggesting that there was no symptom improvement after PCI. Indeed, a prespecified substudy determined that, unlike angina (assessed by scores or exercise time), functional flow reserve did predict an improvement in ischemia (assessed by dobutamine stress echocardiography).[4] All in all, the possible impact of this study on clinical practice seems limited.

Unlike the first trial, the main criticism of ORBITA-2—which evaluated patients with lesions in more than 1 vessel—is the discontinuation of antianginal treatment (ie, it compared PCI with patients without pharmacological treatment, unlike ORBITA, in which patients remained on optimal medical therapy), against the recommendation of clinical practice guidelines.[5] Although the effect of PCI is expected to be immediate and sustained, the 12-week follow-up remains limited. Indeed, the main criticism that can be made of the study is its methodology: using a placebo procedure—not optimal medical therapy—for comparison may limit its clinical applicability. Nonetheless, the double-blind design of the study helps provide further evidence on PCI treatment in patients with coronary ischemia (both anatomical and functional) by improving the pathophysiology of the imbalance between oxygen supply and demand.

Q.: What do you think these 2 studies contribute compared with the much larger ISCHEMIA trial?

A.: In the context of chronic coronary syndrome, revascularization aims to provide 2 benefits: prognostic or symptomatic. In summary, the prognostic benefit of revascularization is well established in patients with severe left main or multivessel disease and left ventricular ejection fraction < 35%.[5,6] However, there is more uncertainty surrounding the prognostic benefit in patients with extensive ischemic territory (a topic of discussion in the ISCHEMIA trial) and in evaluating the symptomatic benefit of the intervention regarding angina. The ISCHEMIA trial, with a larger sample size

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than the ORBITA trials, randomized a total of 5179 patients with stable coronary artery disease and moderate-to-severe ischemia on stress testing to an initial invasive or conservative strategy.[7] After a median follow-up of 3.2 years, there were no significant differences between the 2 strategies in the primary endpoint (cardiovascular death, myocardial infarction, unstable angina hospitalization, heart failure, or resuscitated cardiac arrest). Although the multiple limitations of the study may affect the interpretation of its results (a high crossover rate between the 2 groups, up to 14% of the patients included in the study had mild or no ischemia, and the inclusion of perioperative infarctions which could bias the primary endpoint—more numerous in the invasive treatment group), patients randomized to the invasive treatment group showed greater symptomatic relief than those in the conservative treatment group. This benefit was greater in patients with more frequent episodes of angina at baseline and was less significant in asymptomatic patients, even with inducible ischemia.[8]

In my opinion, the main difference between the ORBITA and ISCHEMIA trials, beyond the sample size and limitations of the methodology of the former, is the blinding of patients undergoing invasive treatment in the ORBITA trials. Of note, symptoms are subjective and evaluating any intervention on cardiovascular events can have both a physiological component and a placebo effect. Therefore, we should welcome invasive studies to simulate the procedure in the control group because they allow testing the direct effect of the intervention on subjective endpoints, such as angina relief.

Q.: Based on all this evidence, what are the benefits, if any, of the invasive approach over the conservative approach?

A.: Current clinical practice guidelines (while awaiting the 2024 update from the European Society of Cardiology on the management of chronic coronary syndrome) state that the PCI should be reserved for patients who, despite being on optimal medical therapy, exhibit refractory symptoms,[5,6] and the aforementioned evidence does not indicate the need to change this indication. The ORBITA trials have demonstrated that the relationship between epicardial coronary stenosis, ischemia, and symptoms is more complex than we had initially thought, while the ISCHEMIA trial has revealed the questionable impact of relieving ischemia on the incidence of events. Indeed, the severity of ischemia is a reflection of the burden of atherosclerotic disease, which is why only revascularizing the identified blockages will not have any clinical impact, as the intervention cannot change the underlying process.[9] Moreover, an important point that should be made is that up to one-third of patients still experience angina symptoms despite successful revascularization.[10] In this scenario, even the cost-effectiveness of the invasive approach vs optimal medical therapy remains to be elucidated.[11] Therefore, beyond revascularization *per se*, an invasive hemodynamic study can provide valuable information to confirm the mechanism of ischemia (microcirculation abnormalities, vasomotor dysfunction, etc) and help optimize pharmacological treatment.

Q.: What indications do you take into consideration in your routine clinical practice to decide which invasive approach you should use in patients with stable angina?

A.: Setting aside scenarios where revascularization has previously shown prognostic improvement, as mentioned earlier, it seems reasonable to believe that the gold standard for stable angina should be pharmacological therapy. However, the fact that stable angina is a chronic disease, and the patient requires long-term antianginal drugs can complicate proper symptom control. Additionally, factors such as poor medication tolerability, suboptimal adherence, or the patient's own preference must be considered. In all these situations, the invasive approach may be the preferred option.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Not used.

CONFLICTS OF INTEREST

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Scientific letter

Computed tomography C-arm angulations for planning coronary cannulation after TAVI

Proyecciones angiográficas basadas en TC para planificar la cateterización coronaria después de un TAVI

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To the Editor,

Coronary re-access continues to be a challenge following transcatheter aortic valve implantation (TAVI). Commissural alignment of the prosthesis facilitates coronary re-access, especially in self-expanding prostheses.[1] Additionally, for certain devices, different techniques for coronary cannulation might be necessary if the previously implanted prosthesis has commissural misalignment.[2] By analyzing 3-cusp and left-to-right 2-cusp overlap (2-cusp) projections after TAVI, it is possible to estimate the degree of commissural alignment in prostheses with identifiable commissural posts on fluoroscopy.[3,4] This study aimed to describe the optimal projections for left and right coronary artery (LCA, RCA) cannulation in patients with previous TAVI.

We analyzed the pre-TAVI computed tomography scans of 105 consecutive patients referred to our center for TAVI implantation. Of these scans, 5 were excluded due to their poor quality or previous aortic valve replacement. The ideal projections for LCA and RCA catheterization were identified by using 3mensio software (Pie Medical Imaging, The Netherlands) and were defined as projections coplanar with the cross-sectional transverse plane of the aorta at the level of each coronary ostium and orthogonal to them, respectively. An en-face projection to the aortic annulus can be established intraprocedurally as a projection where the prosthesis is foreshortened, usually in a cranial (CRA) and right anterior oblique (RAO) angulation. The subsequent projection is useful for guiding clockwise or counterclockwise rotation of the catheter, which is particularly beneficial for determining whether the catheter crosses the stent frame within an aligned cell near the coronary ostium (figure 1).

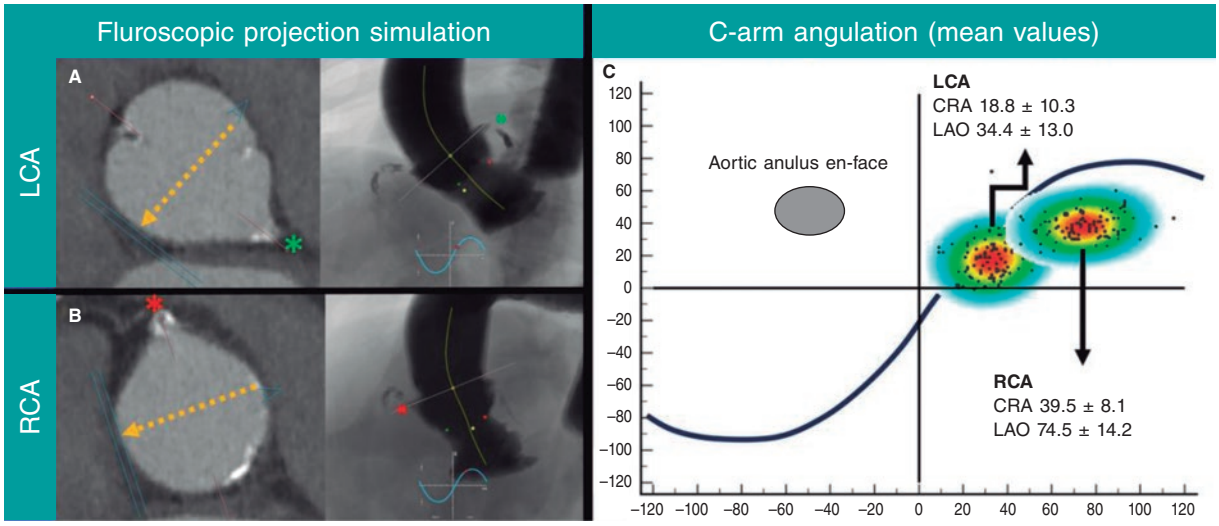

Figure 1. Computed tomography-derived fluoroscopic angulation. **A:** LCA cannulation (green asterisk; LCA ostia). **B:** RCA cannulation (red asterisk; RCA ostia). The yellow arrow indicates the direction of the C-arm projection at the en-face aortic root multiplanar reconstruction of the computed tomography scan. **C:** Scatter plot for LCA and RCA cannulation (grey ellipse; usual en-face projection to the aortic root); CRA, cranial; LAO, left anterior oblique; LCA, left coronary artery; RCA, right coronary artery.

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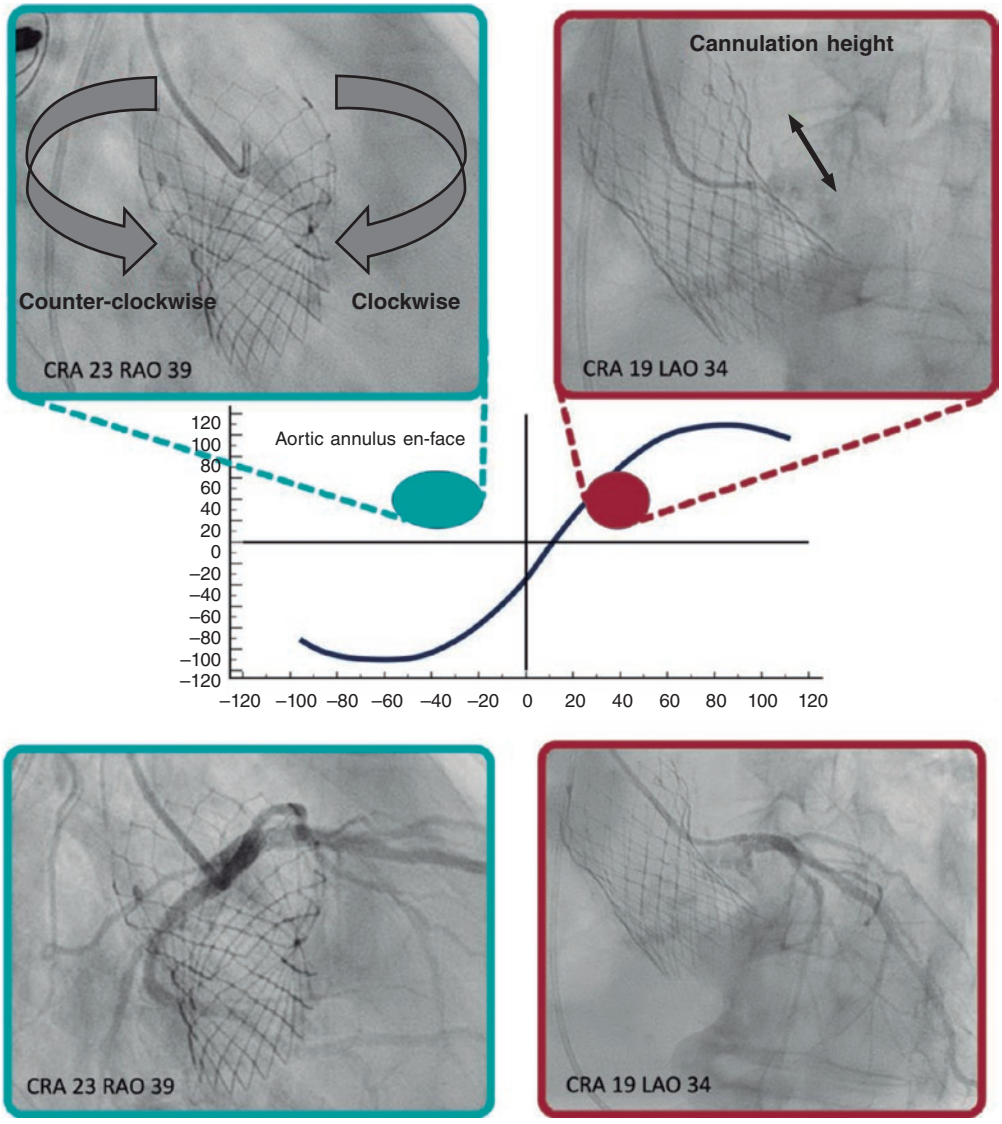

Figure 2. Example of LCA cannulation. CRA 19 LAO 34º projection was used to determine the height (purple arrow) of the cell for crossing in CRA angulation and RAO (blue ellipse) angulation assisted in the rotational orientation of the catheter either clockwise (blue arrow) or counterclockwise (red arrow). CRA, cranial; LAO, left anterior oblique; RAO, right anterior oblique.

The mean projections for LCA and RCA cannulation were as follows: CRA 18.8º ± 10.3º, LAO (left anterior oblique) 34.4º ± 13.0º, CRA 39.5º ± 8.1º, and LAO 74.5º ± 14.2º, respectively. Figure 2 illustrates the coronary cannulation of the LCA with a Judkins left 4.0 catheter in a patient with a previous Evolut PRO + 24 (Medtronic, United States) prosthesis using the proposed C-arm and en-face angulations.

As a result, we propose that when a post-TAVI patient is referred for a coronary angiogram, the first step should be to determine the TAVI alignment using previously described methods.[3] Coronary cannulation of the LCA might be attempted in CRA 18.8º LAO 34.4º and for RCA cannulation in CRA 39.8º LAO 74.4º, using an en-face projection to rotate the catheter clockwise or counterclockwise (figure 2). Different cannulation techniques should be considered based on the degree of commissural alignment.[2]

Furthermore, we suggest that after each TAVI procedure, the degree of commissural alignment should be noted. In addition, patient-specific RCA and LCA cannulation projections could be included in the report to facilitate subsequent coronary cannulation.

FUNDING

None.

ETHICAL CONSIDERATIONS

All patients signed the informed consent form, and the study was approved by the ethics committee of the hospital. Possible sex and gender variables were considered according to SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICAL INTELLIGENCE

No artificial intelligence tool has been used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

A. Redondo Diéguez and X. Irazusta Olloquiegui were involved in data collection. A. Redondo Diéguez drafted the manuscript. B. Cid Álvarez, R. Trillo Nouche, A. García Campos, and J.R González-Juanatey reviewed the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

R. Trillo Nouche is a proctor for Boston Scientific and Medtronic. None of the other authors have any conflicts of interest to declare.

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Scientific letter

Catheter-directed therapies for patients with acute pulmonary embolism: results from a multiparametric follow-up protocol

Terapias dirigidas por catéter para pacientes con embolia pulmonar aguda: resultados de un protocolo de seguimiento multiparamétrico

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To the Editor,

Anticoagulation alone has proven efficacy for the treatment of low- and low-to-intermediate- -risk acute pulmonary embolism (PE) patients.[1] Nonetheless, intermediate-high and high-risk PE are associated with a considerable risk of short-term circulatory collapse, death or chronic thromboembolic pulmonary hypertension, ranging from 3% to 10%, when treated with anticoagulation alone.[1] Although systemic fibrinolysis decreases this risk by 50%, this treatment significantly increases the risk of major bleeding, as seen in PEITHO trial (Fibrinolysis for patients with intermediate-risk pulmonary embolism),[2] which has limited the use of systemic fibrinolysis to high-risk patients, as recommended in the current guidelines.[3]

This limitation has led to growing interest in catheter-directed therapies (CDT) for patients with high-risk acute PE and a contraindication or failure of systemic fibrinolysis and patients with intermediate-high risk who develop worsening hemodynamics despite anticoagulation.[3] CDT allow faster resolution of perfusion defects and hemodynamic improvement without the systemic hemorrhagic effects of systemic thrombolysis.

Despite an increasing use of CDT, the clinical evidence of its benefits remains scarce, as there are no adequately powered randomized controlled trials and current studies have been limited to immediate hemodynamic improvement or imaging surrogate markers.[4-6]

This study aimed to assess the safety, feasibility, and mid-term effects of CDT. Between 2020 and 2022, we prospectively enrolled consecutive patients with high and intermediate-high-risk PE who underwent CDT at a single tertiary center. The selection criteria included high-risk patients with contraindicated or failed fibrinolysis and those with intermediate-high risk and worsening hemodynamics despite anticoagulation. We excluded patients with clinical onset of PE more than 2 weeks previously and/or with transit thrombus.

Right heart catheterization (RHC) and bilateral pulmonary angiography were performed through the femoral or right antecubital basilic vein before the intervention. The operators decided between in-situ fibrinolysis, mechanical thrombectomy, or both, based on thrombus burden, localization, hemodynamic status, and bleeding risk. Catheter-directed local fibrinolysis was performed using a 1 mg/h alteplase infusion for 12 hours, following a 1 mg bolus. The catheter-directed mechanical thrombectomy used the 8- and 12-Fr Indigo aspiration system (Penumbra, United States) to restore perfusion in as many branches as possible until a good angiographic result or blood aspiration of 300 to 350 mL was achieved. The follow-up protocol included an echocardiogram, computed tomography angiography scan, RHC, and pulmonary angiogram at 3 months after the CDT.

A total of 39 patients were analyzed. The baseline characteristics are presented in table 1, which shows increased levels of serum lactate in 30% of patients, troponin in 97%, and N-terminal pro-B-type natriuretic peptide in 92%. At admission, 18% of patients were stratified as high-risk. The admission echocardiogram revealed right ventricle (RV) dilation in 95% of patients, with RV systolic dysfunction in 69% of them.

Local fibrinolysis was performed in 71% of the patients, isolated penumbra aspiration in 10% and combined therapy in 18%. No major bleeding leading to death or requiring medical intervention or transfusion was observed during or after the procedure. There was 1 pulmonary artery dissection and 1 partial avulsion of the penumbra burr, both of which were managed conservatively with good outcomes. One patient developed persistent and refractory cardiogenic shock, leading to death. The procedural data are shown in table 1.

A total of 23 patients completed the 3-month follow-up, while 4 patients died, mainly from noncardiovascular causes. There was a significant rate of incomplete follow-up for various reasons, including 4 foreign patients who were unable to complete the

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Table 1. Baseline characteristics and procedure data

Baseline characteristics (n = 39)	
Age, years	60.0 ± 17.6
Gender, male	46.2% (18)
Previous VTE	12.8% (5)
Oncologic disease	10.3% (4)
Clinical and laboratorial findings (n = 39)	
Syncope at presentation	28.2% (11)
Dyspnea at presentation	76.9% (30)
Days from symptoms onset	1.0 [1.8]
High-risk pulmonary embolism	17.9% (7)
Failed systemic fibrinolysis	0%
Contraindication to fibrinolysis	10.3% (4)
Systolic blood pressure, mmHg	116 ± 26
Heart rate, bpm	102 ± 21
PaO_2/FiO_2 ratio	262 ± 96
Serum lactate, mmol/L (N < 1.8)	1.7 ± 1.6
hs-troponin I, pg/mL (N < 14)	262 [520]
NT-proBNP, pg/mL (N < 150)	2775 [3910]
Peak D-dimer, ng/mL (N < 500)	8835 [12 254]
Positive lactate	30.8% (12)
Positive troponin	97.4% (38)
Positive NT-proBNP	92.3% (36)
Imaging findings – initial work-up (n = 39)	
Central PE in angio-CT scan	34.2% (13)
RV/LV ratio angio-CT scan	1.4 ± 0.2
Dilated RV in TTE	94.6% (35)
RV dysfunction in TTE	69.4% (25)
Procedural data and complications (n = 39)	
Thrombectomy + local fibrinolysis	17.9% (13)
Isolated thrombectomy	10.3% (4)
Isolated local fibrinolysis	71.2% (28)
Any procedure complication	5.1% (2)
Cardiovascular death	2.6% (1)
Cardiogenic shock	2.6% (1)
Major bleeding	0%
Cardiac tamponade	0%
Pulmonary artery perforation	0%
Pulmonary artery dissection	2.6% (1)
Penumbra burr avulsion	2.6% (1)
Moderate-to-severe PR	0%
Moderate-to-severe TR (previous)	25.6% (10)
Moderate-to-severe TR (post)	7.7% (3)

CT, computed tomography; LV, left ventricle; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PE, pulmonary embolism; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; VTE, venous thromboembolism.
The data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

follow-up, 5 patients who withdrew their consent, and 3 who were lost to follow-up. Among the 23 patients who completed the follow-up, the hemodynamics showed significant improvement. The data from RHC revealed a mean drop of 3.6 mmHg, 16.8 mmHg, and 10.7 mmHg in right atrial, systolic pulmonary artery, and mean pulmonary artery pressures, respectively ($P < .001$). In addition, there was a mean increase of 1.61 L/min and 0.85 L/min/m^2 in cardiac output and index, respectively ($P < .001$), and a 1.65 Wood units decrease in pulmonary vascular resistance ($P = .012$). There was also an improvement in perfusion defects, with a mean drop of 8.7 points in the modified Miller index ($P < .001$). Improvement was also observed in RV function, with a mean decrease of 0.5 in the RV/left ventricle (LV) ratio on computed tomography (CT) scan ($P < .001$), a mean increase of 5.4 mm in tricuspid annular plane systolic excursion (TAPSE) ($P < .001$), and a mean increase of 5.0 cm/s in tricuspid annular s′ velocity ($P = .006$). These results are illustrated in figure 1. At 3 months, 9 out of the 23 patients (39%) had a mean pulmonary artery pressure above 20 mmHg.

During the follow-up period, 4 patients died, resulting in an overall mortality rate of 10.3%. However, only 1 patient died from a cardiac cause, which was secondary to worsening refractory cardiogenic shock. One patient died due to oncologic disease progression, and 2 patients died from noncardiovascular causes.

This study reports a minor procedural complication rate of 5.1%, which enhances the feasibility and safety of CDT. In the EXTRACT-PE trial (Indigo Aspiration System for Treatment of Pulmonary Embolism), a procedural complication rate of 2.5% was reported, with 1.7% being major bleeding and 0.8% being device-related pulmonary vascular injury.[5] Furthermore, both complications were nonfatal and managed conservatively, with good angiographic outcomes upon reevaluation. These complications were associated with the use of mechanical thrombectomy devices, and both occurred early in the learning curve of this device, leading the authors to believe that such complications may be minimized as operator experience increases. Despite the administration of catheter-directed fibrinolysis in nearly 90% of the patients, there were no major or life-threatening bleeding events in the first 48 hours after the procedure, possibly related to the low dose of alteplase.

Most previous trials have used imaging parameters as surrogate markers to evaluate the immediate effect of CDT. The most commonly used parameter is the RV/LV ratio, as seen in the SEATTLE II trial (A prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism), EXTRACT-PE and FLARE (A prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism) trials.[4-6] Our study provides more extensive and mid-term data on the benefits of CDT, including invasive direct assessment of hemodynamics instead of imaging surrogate parameters. At 3 months, we obtained a mean reduction in RV/LV ratio of 0.5, which is similar to the rates described in previous studies. Moreover, our study also reports a significant improvement in RV systolic function, as measured by transthoracic echocardiography, a significant reduction in pulmonary vascular pressures and resistance, and an increase in cardiac output, both measured invasively at 3 months after the procedure.

The optimal treatment for intermediate-risk PE is still not well established, and current guidelines recommend anticoagulation alone, with catheter intervention reserved for patients not responding to conservative therapy.[3] The PEITHO trial showed that systemic fibrinolysis significantly reduced the combined primary endpoint of death or clinical deterioration, at the expense of a significant increase in major bleeding and intracranial hemorrhage.[2] Although CDT has not been directly compared with anticoagulation

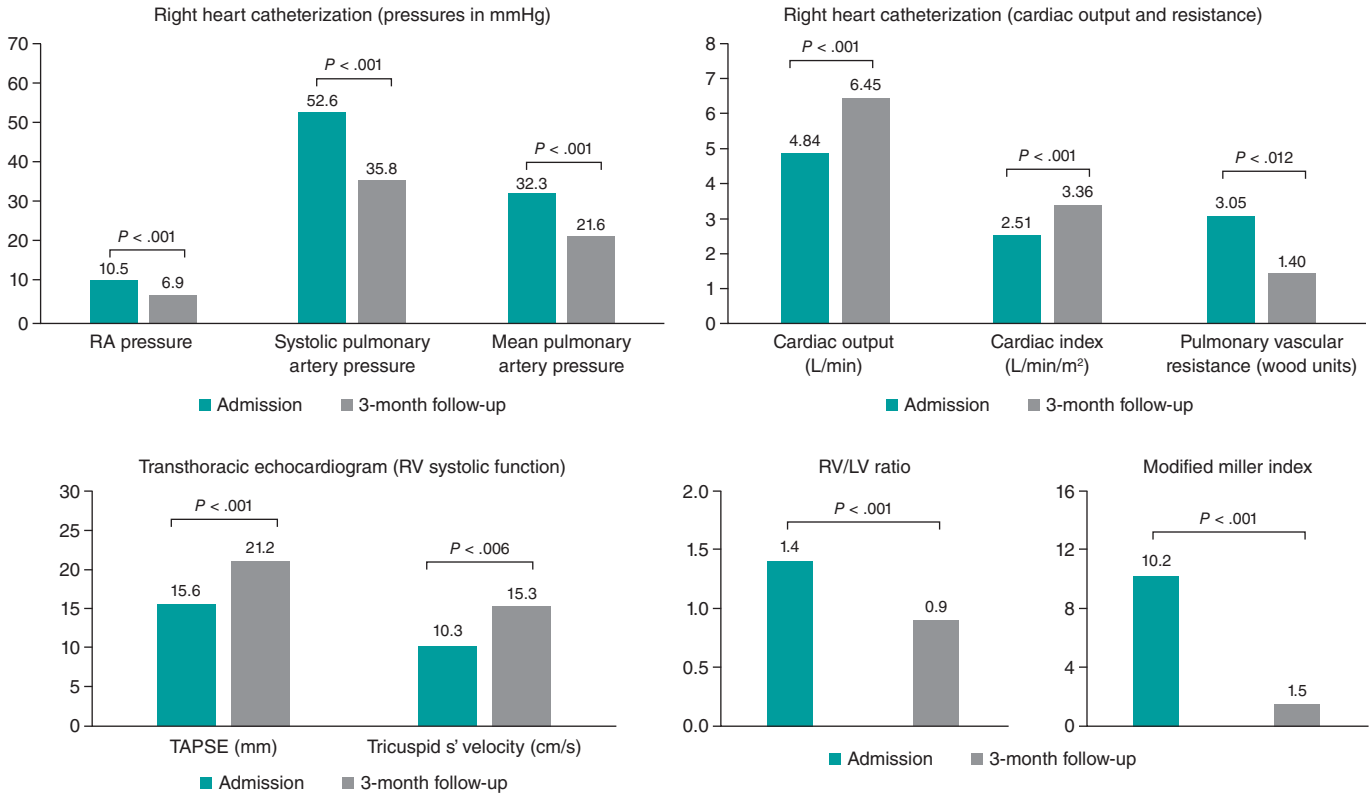

Figure 1. Invasive hemodynamic, echocardiographic, morphological, and thrombotic burden data on admission and at 3 months. LV, left ventricle; RA, right atrial; RV; right ventricle; TAPSE, tricuspid annular plane systolic excursion.

alone in these patients, the authors believe that CDT has several advantages. First, catheter-directed fibrinolysis may provide the same intrapulmonary benefits as systemic fibrinolysis without the risk of major bleeding. Second, aspiration systems allow for faster and more immediate reperfusion in main branches, preventing further irreversible deterioration in unstable patients. Third, catheter-directed mechanical thrombectomy is a safe and efficient alternative for patients who cannot receive fibrinolytic agents. Fourth, both techniques seem to have an additive benefit in long-term anticoagulation by reducing perfusion and pulmonary vascular pressures, thus reducing progression to chronic thromboembolic pulmonary hypertension.

The evaluation of hemodynamics at 3 months offers new insights into the high rates of patients who develop pulmonary hypertension. This is especially relevant when considering the new cutoff of 20 mmHg for the mean pulmonary artery pressure, as established by the 2022 ESC guidelines for pulmonary hypertension.

The main limitation of this study is the absence of a comparator arm. Other limitations are the incomplete follow-up in almost 33% of patients, the small sample size, and the use of 2 different catheter-directed strategies.

In conclusion, for patients with intermediate-high and high-risk PE, CDT is a feasible and safe treatment option that improves hemodynamics, RV function, and perfusion defects at 3 months after the procedure.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all participants involved in the study. The possible variables of sex and gender have been taken into account in accordance with the SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used during the performance of this study or during the drafting of this manuscript.

AUTHORS' CONTRIBUTIONS

A. Grazina and L. Almeida Morais designed the study protocol, with help from A. Fiarresga and D. Cacela. A. Grazina and B. Lacerda Teixeira collected and analyzed the data. A. Grazina and B. Lacerda Teixeira wrote the manuscript with support from L. Almeida Morais. A. Fiarresga and D. Cacela coordinated the project. All authors read and approved this manuscript.

CONFLICTS OF INTEREST

The authors declare that this is an original article and has not been previously published or submitted to another journal. The authors have no conflicts of interest.

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Scientific letter

Use of cutting or scoring balloons in patients with native coronary artery disease: systematic review and meta-analysis

Uso de balones de corte en pacientes con enfermedad coronaria de vaso nativo: revisión sistemática y metanálisis

José Antonio Sorolla Romero,[a] Julia Martínez Solé,[a] Andrea Teira Calderón,[a] María Calvo Asensio,[a] José Luis Díez Gil,[a,b] and Jorge Sanz Sánchez[a,b,*]

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To the Editor,

Calcified coronary lesions remain a procedural and clinical challenge associated with higher rates of procedural complications such as stent underexpansion and malapposition leading to an increased risk of target lesion revascularization (TLR), stent thrombosis, myocardial infarction (MI), and death.[1] While newer drug-eluting stents and advanced devices are considered safer and more effective, there is still a need for atherosclerotic plaque modification techniques that allow for adequate stent expansion and apposition when traditional techniques fail. Cutting and scoring balloons have been designed to treat complex lesions such as fibrotic plaque and calcified lesions.[2,3] However, their use may have been limited by problems of crossability and limited evidence supporting their efficacy and safety.[4] In addition, the available published literature is based on studies with noninferiority designs and small sample sizes,[5] which may not provide adequately powered analyses to evaluate the clinical efficacy of cutting and scoring balloons in patients with native-vessel coronary artery disease (CAD). Therefore, we performed a systematic review and meta-analysis to compare cutting and scoring balloons with conventional balloons (semi- and non-compliant balloons) in patients with native vessel CAD.

This meta-analysis was conducted according to the PRISMA guidelines for the reporting of systematic reviews. Two reviewers independently identified relevant studies through an electronic search of the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases (from inception to June 2023). Abstracts presented at major scientific conferences (American Heart Association, American College of Cardiology, European Society of Cardiology, EuroPCR, and Transcatheter Cardiovascular Therapeutics) were also reviewed. We also used backward snowballing (review of literature references within identified articles and relevant reviews). Inclusion criteria were: *a)* randomized controlled trials comparing percutaneous coronary intervention with cutting or scoring balloons with semi- or noncompliant balloons; *b)* study population including patients with native vessel CAD; *c)* the availability of clinical outcome data. This trial is registered with PROSPERO (CRD42023434007).

The primary endpoint was TLR. Secondary outcomes included MI, vessel perforation, and all-cause death.

Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated using the DerSimonian and Laird random effects model, and heterogeneity was estimated using the Mantel-Haenszel method. The presence of heterogeneity among studies was assessed using the Cochran Q chi-square test, and the I-squared test was used to assess inconsistency. A random-effects meta-regression analysis using the empirical Bayes method (Paule-Mandel) was performed to assess the interaction of percentage of drug-eluting stent (DES) use, percentage of intravascular ultrasound use, diabetes mellitus, and sex on treatment effects. We performed a subgroup analysis for the primary endpoint according to revascularization strategy (stent implantation or plain old balloon angioplasty [POBA]). The statistical significance level was 2-tailed $P < .05$.

A total of 1090 citations were screened and 8 studies with 2712 patients and a mean follow-up of 6.6 months were finally included.[2-8] Of the 8 studies, 2 included only calcified lesions,[2,3] while the remaining 6 included de novo lesions regardless of the severity of coronary calcification.[4-8] In addition, 4 studies used POBA as definitive therapy.[4-7] In all, 24.6% of patients were female, with a mean age of 61.6 years, of which 34.8% had a history of acute coronary syndrome. The most commonly treated artery was the left anterior descending artery (42.4%), and the mean vessel diameter of the target lesion was 2.8 mm. Intracoronary imaging was used in 18.8% of patients.

The use of cutting/scoring balloons was associated with a lower risk of TLR than that of conventional balloons (OR, 0.67; 95%CI, 0.53-0.85; I-squared, 0%) (figure 1). There were no differences between groups in the risk of all-cause death (OR, 1.31; 95%CI, 0.53-3.21; I-squared, 0%), MI (OR, 1.22; 95%CI, 0.48-3.08; I-squared, 50.1%), or vessel perforation (OR, 1.68; 95%CI, 0.37-7.74; I-squared, 0%). No significant effects were found for diabetes ($P = .337$), sex ($P = .896$), the percentage of intravascular ultrasound ($P = .178$), or the percentage of DES implantation ($P = .721$) on treatment effects. Our results remained consistent with the primary analysis after stratification by revascularization strategy (stenting or POBA) (figure 2).

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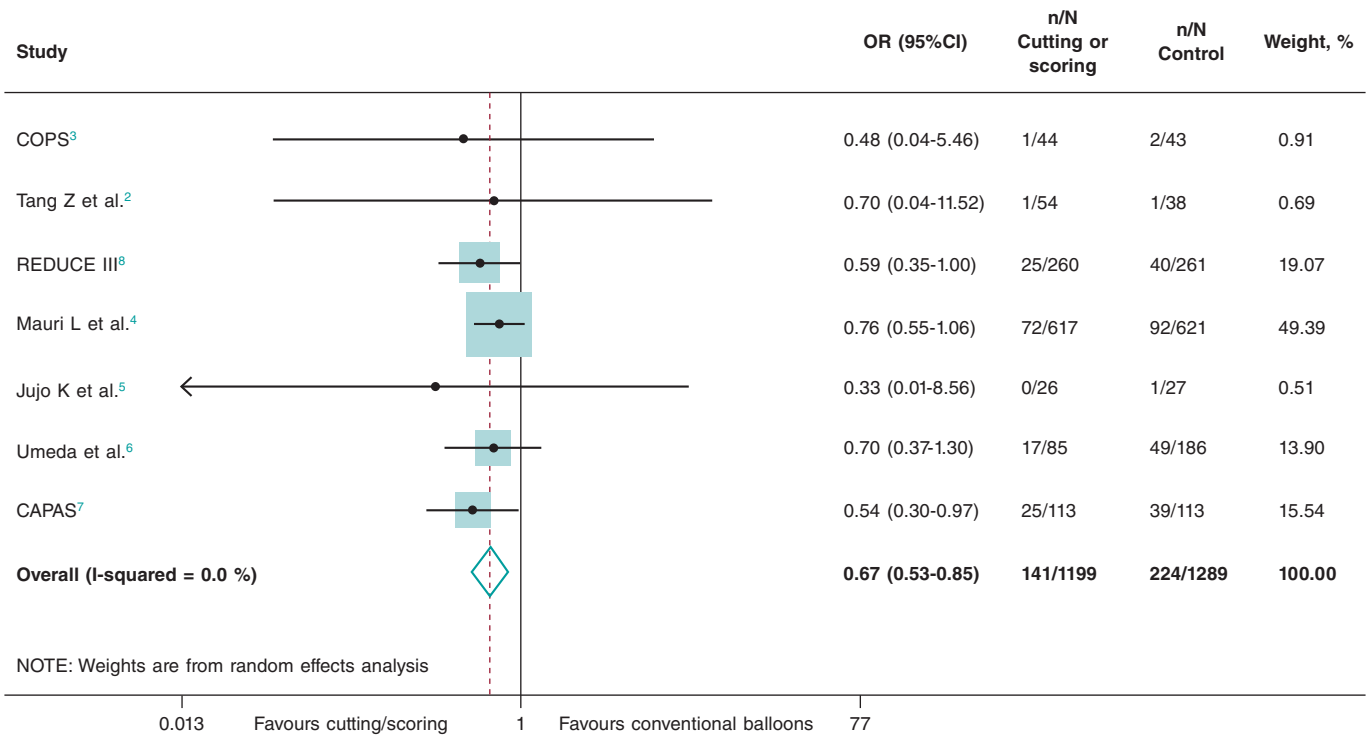

Figure 1. Forest plot reporting trial-specific and summary OR with 95%CI for the primary endpoint of target lesion revascularization. 95%CI, 95% confidence interval; CAPAS, Cutting balloon angioplasty vs plain old balloon angioplasty randomized study in type B/C lesions; COPS, Cutting balloon to optimize predilatation for stent implantation; OR, odds ratio; REDUCE, Restenosis reduction by cutting balloon angioplasty evaluation.

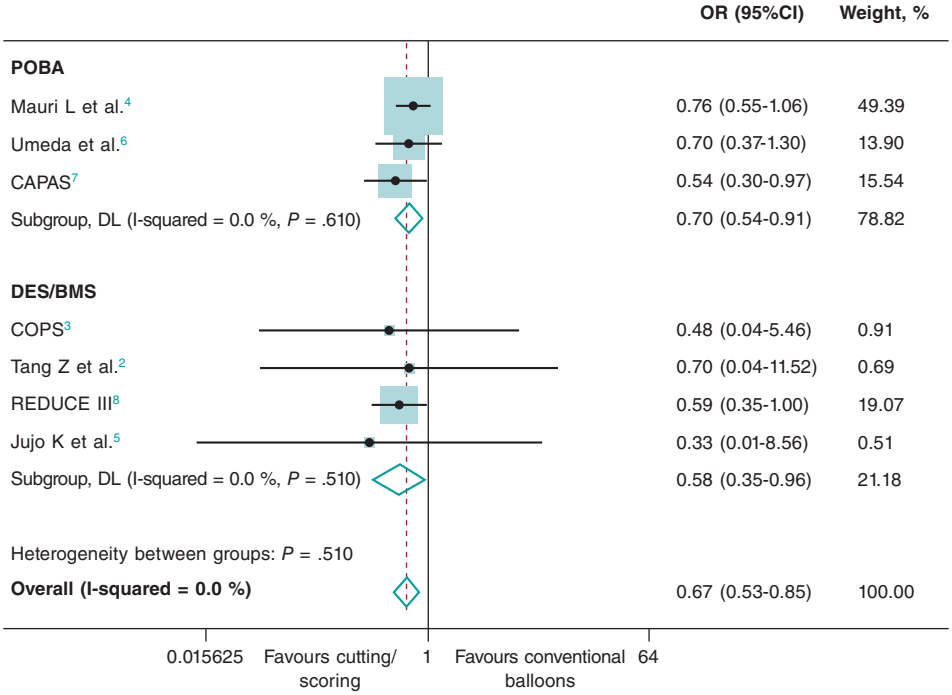

Figure 2. Subgroup analysis according to the revascularization strategy (stent implantation or plain old balloon angioplasty [POBA]) for the primary endpoint of target lesion revascularization. 95%CI, 95% confidence interval; BMS, bare metal stent; CAPAS, Cutting balloon angioplasty vs plain old balloon angioplasty randomized study in type B/C lesions; COPS, Cutting balloon to optimize predilatation for stent implantation; DES, drug eluting stent; OR, odds ratio; REDUCE, Restenosis reduction by cutting balloon angioplasty evaluation; POBA, percutaneous old balloon angioplasty.

The present study provides the first critical analysis of the available evidence on the use of cutting and scoring balloons in patients with native-vessel CAD. The use of cutting/scoring balloons was associated with a lower risk of TLR without an increased risk of clinical adverse events compared with conventional balloons. This benefit may be explained by the improved lesion preparation achieved with the use of cutting/scoring balloons. In addition, cutting/scoring balloons create discrete longitudinal incisions in the atherosclerotic target coronary segment, which may enhance drug diffusion and penetration into the arterial wall. Interestingly, a recent meta-analysis showed no significant differences in clinical or imaging outcomes in patients treated with cutting balloons compared with other techniques, including the same risk of repeat revascularization.[9] However, there are relevant differences with respect to this study that may explain the different outcomes: *a)* only patients with severely calcified lesions were included; *b)* studies comparing or combining cutting balloons with techniques such as rotational atherectomy or very high pressure balloons were included; and *c)* stent implantation was performed in all studies.

However, the present study should be interpreted in the light of several limitations. First, the lack of patient-level data prevented us from assessing the impact of baseline clinical characteristics (ie, degree of coronary calcification) on treatment effects. Second, some of the included older studies compared cutting/scoring balloon with POBA without stent implantation, which is not a contemporary strategy. Nevertheless, we found no effect of the percentage of DES implantation on treatment effects in the meta-regression analysis.

FUNDING

None.

ETHICAL CONSIDERATIONS

Ethics approval was not required for this meta-analysis as all data were collected and synthesized from previous studies and no informed consent was required as there were no patients involved in our work. The meta-analysis of RCTs was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines. We confirm that sex/gender biases have been taken into acount.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence software has been used.

AUTHORS' CONTRIBUTIONS

J.A. Sorolla Romero, J. Martínez Solé, A. Teira Calderón, M. Calvo Asensio and J. Sanz Sánchez contributed to the idea, design, drafting, and revision of the article. J.L. Díez Gil contributed to the critical revision of the intellectual content.

CONFLICTS OF INTEREST

None.

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An unusual etiology of shock after ECMO decannulation

Una etiología poco habitual de shock *tras decanulación de ECMO*

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Finalist case in the ACCIS 2023 Madrid course

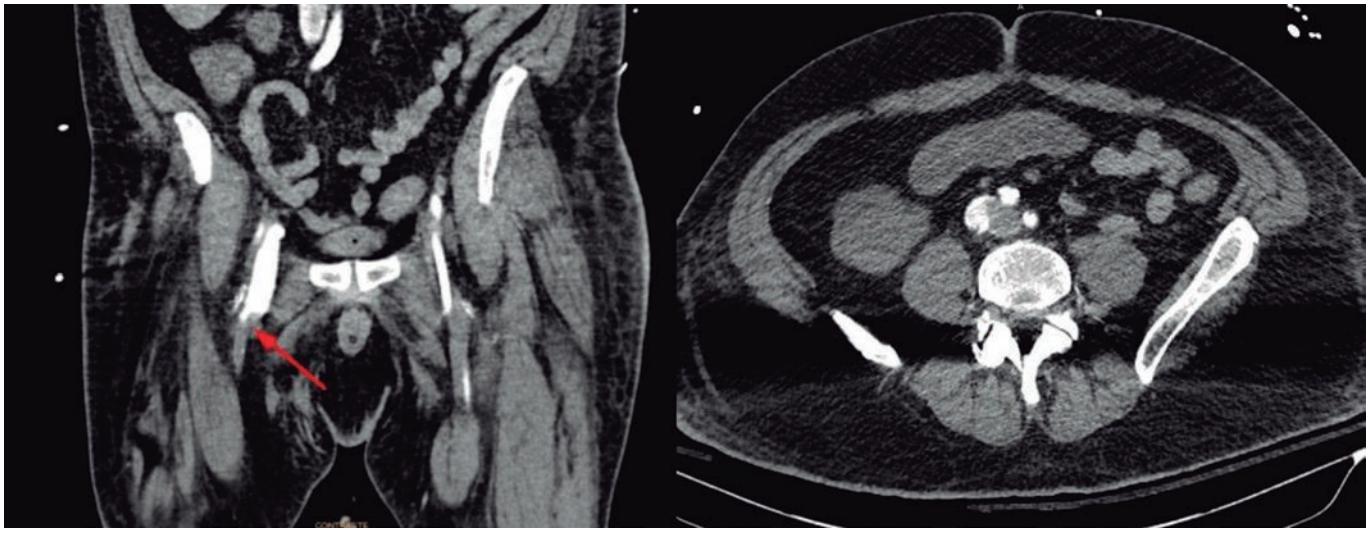

Figure 1.

We report the case of a 53-year-old male patient who required venoarterial extracorporeal membrane oxygenation (VA-ECMO) after a refractory cardiac arrest due to a ventricular fibrillation secondary to an anterolateral myocardial infarction. The cannulation was performed with a 25-Fr × 55 cm drain (right femoral vein) and a 17-Fr × 15 cm return (left common femoral artery). An intra-aortic balloon pump (IABP) was inserted through the right femoral artery (7-Fr). After stabilization, both the VA-ECMO and IABP were retrieved. The arterial insertion points were sealed with a Perclose ProGlide (Abbott, United States) system and the venous site with manual compression.

Shortly afterward, the patient developed shock accompanied by hypoperfusion in the right leg (indicated by near-infrared spectroscopy readings of 17% in the right leg vs 59% in the left leg). No changes were evident on electrocardiography, echocardiography, or coronary angiography. The arterial pressure waveform analysis revealed high cardiac output, increased central venous pressure, and a low systemic vascular resistance index. Computed tomography angiography revealed a high-flow arteriovenous fistula between the right femoral vein and artery (figure 1; red arrow shows a tubular communication between the 2 vessels). To assess the hemodynamic impact of the fistula, a 10-minute compression test was conducted (table 1 and figure 2), demonstrating an increase in mean arterial pressure, a decrease in cardiac output and left ventricular outflow tract velocity-time integral, and a significant reduction in central venous oxygen saturation.

After demonstrating the hemodynamic impact of the fistula, vascular surgeons treated it by surgically implanting an intravascular stent (Viabahn 8 × 100 mm, GORE, United States) in the right superficial femoral artery. The intervention resulted in significant hemodynamic and respiratory improvement and recovery of perfusion in the right leg.

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Table 1. Changes pre- and post-compression of AVF

	Pre-procedure	Post-procedure
Hemodynamic		
mPA (mmHg)	48	62
Heart rate (bpm)	98	95
Systolic volume (mL)	46	38
CO (L/min)	4,5	3,6
CI (L/min/m^2)	2,2	1,8
IVC (mmHg)	25	22
Echocardiogram		
LVOT-VTI (cm^2)	13,4	9,2
RVEDV (mm)	45	38
TAPSE (mm)	13	22
Gasometry		
SvO_2 (%)	87,9	60,7
$PpaO_2$ (mmHg)	97	104

Figure 2.

FUNDING

The authors did not receive support from any organization for the submitted work.

ETHICAL CONSIDERATIONS

This work was conducted following the ethics recommendations of our hospital, although no ethics review approval was required in human participants in accordance with the local legislation and institutional requirements. Oral consent was obtained from the patient and his family. The anonymity of the patient was respected at all times. In our research, we always try to adhere to the SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used to prepare this paper.

AUTHORS' CONTRIBUTIONS

P. Torrella and M. Vidal provided care for the study patient and conceived the study and its design. All authors critically reviewed and approved the study.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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Anterior AMI with an unusual angiographic image

IAM anterior con imagen angiográfica inusual

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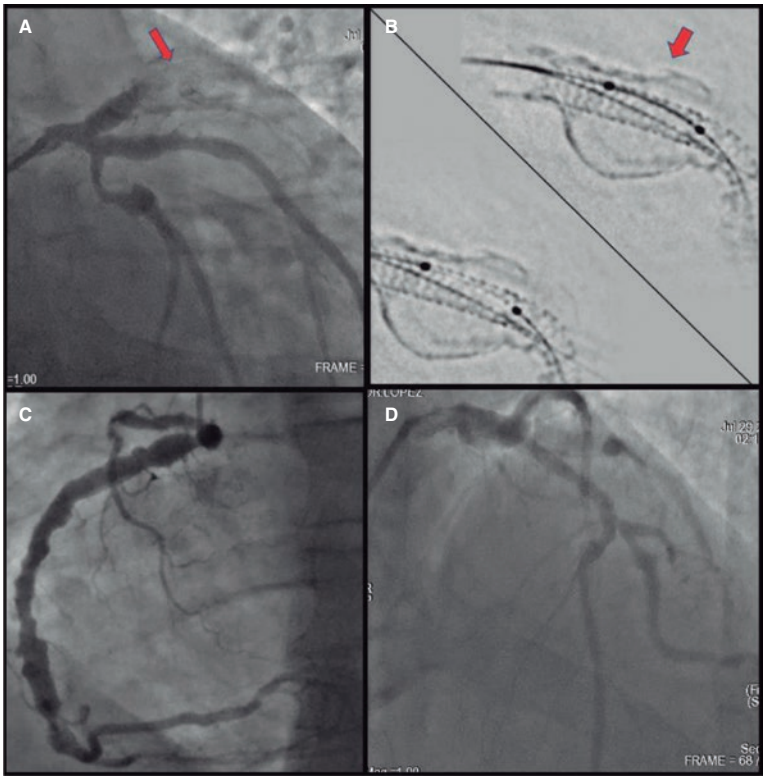

Figure 1.

A 53-year-old male smoker with hypertension and a family history of dyslipidemia and early ischemic heart disease in family members was diagnosed with anterior ST-segment elevation acute coronary syndrome (STEACS) in 2017. He was treated with a 4 mm × 18 mm everolimus-eluting stent implanted in the proximal left anterior descending coronary artery and 2 overlapping distal stents. The procedure was uneventful, and the remaining arteries showed ectasia with diffuse atheromatous disease. An echocardiogram revealed the presence of mild left ventricular systolic dysfunction. The patient was readmitted after experiencing a new anterior STEACS due to very late thrombosis of the previous stent in the proximal left anterior descending coronary artery, where an external calcified image was found around the stent (figure 1A,B: arrows). The study was completed with optical coherence tomography (figure 2A,B), which revealed the presence of abundant thrombotic content, and stent malapposition, without visualization of the surrounding arterial wall, indicating a large thrombosed and calcified aneurysm. Thrombus aspiration and a drug-coated balloon were used, along with glycoprotein IIb-IIIa inhibitors, resulting in final TIMI grade 3 flow. Computed tomography (figure 3: arrows) performed during admission confirmed the presence of a 24 mm coronary aneurysm with a thrombosed sac. The patient progressed favorably and was discharged from the hospital.

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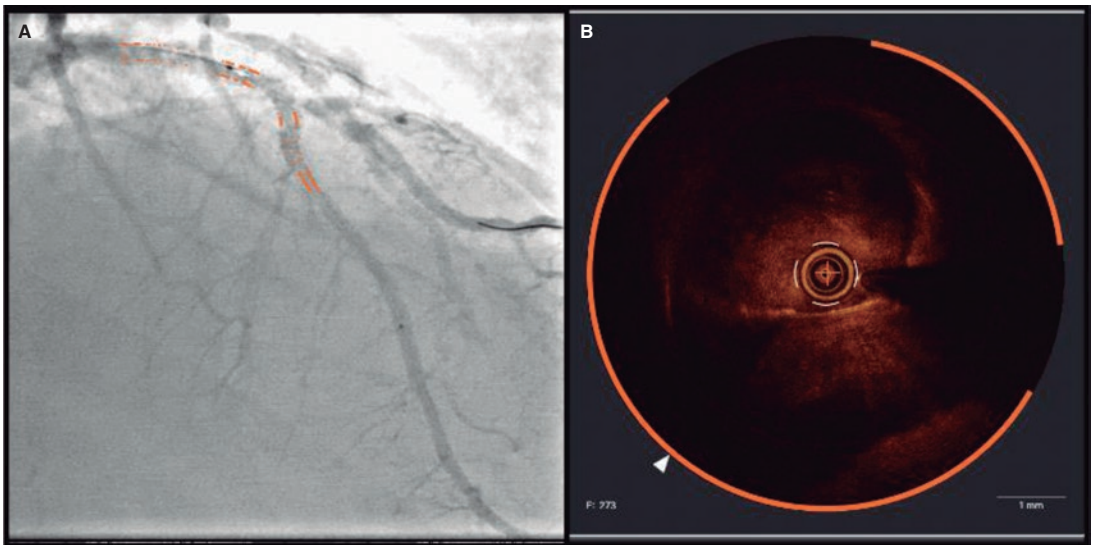

Figure 2.

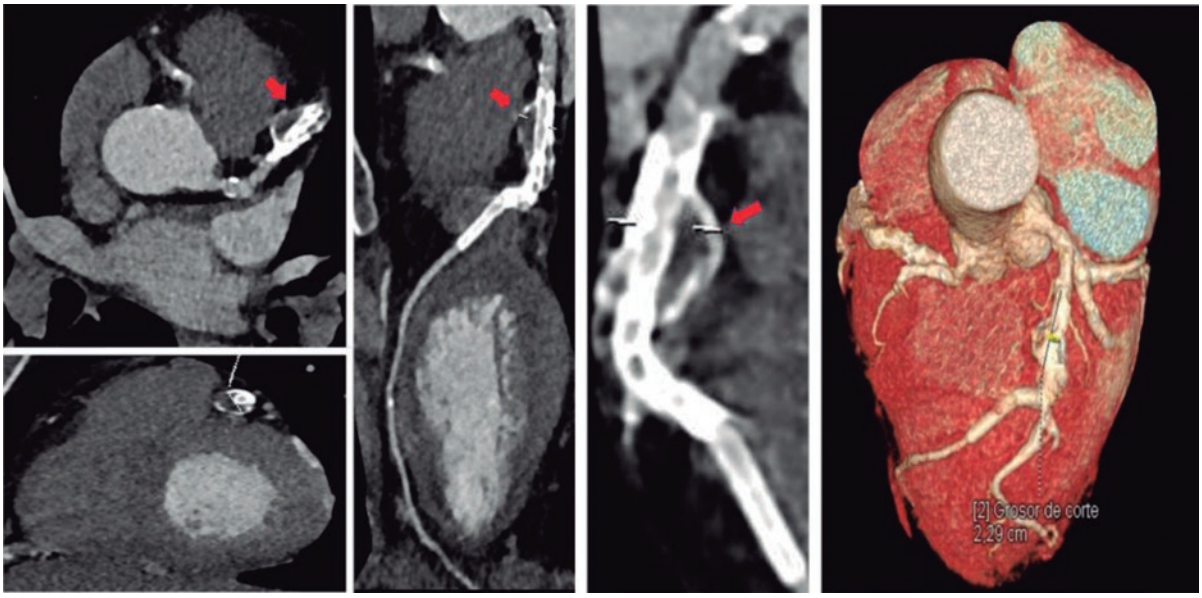

Figure 3.

Coronary aneurysms are a rare finding whose incidence ranges from 0.1% to 4.9%. The etiology can be atherosclerotic, congenital, or inflammatory. In our case, atherosclerotic etiology was suspected. However, it could have been intensified by an everolimus-related toxic effect due to hypersensitivity following stenting. This effect is less likely since it was not found in other treated segments, and ectasia was present in the remaining arteries (figure 1C-D; videos 1 and 2 of the supplementary data). Treatment consisted of indefinite dual antiplatelet therapy after confirming the absence of lack of endothelialization across the aneurysm neck.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The patient's prior written informed consent was obtained, and possible sex and gender variables were taken into account following SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

All authors contributed to the drafting of the article. A.T. Ariza-Mosquera, and F. Sabatel-Pérez wrote the text. F. Sabatel-Pérez, M. López-Pérez, and T. Gil-Jiménez were involved in the review and supervision process. G. Moreno Terribas and J. Caballero-Borrego critically revised the manuscript.

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.M23000422.

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Ductus arteriosus presenting as systemic and pulmonary embolism

Presentación de ductus *como embolia sistémica y pulmonar*

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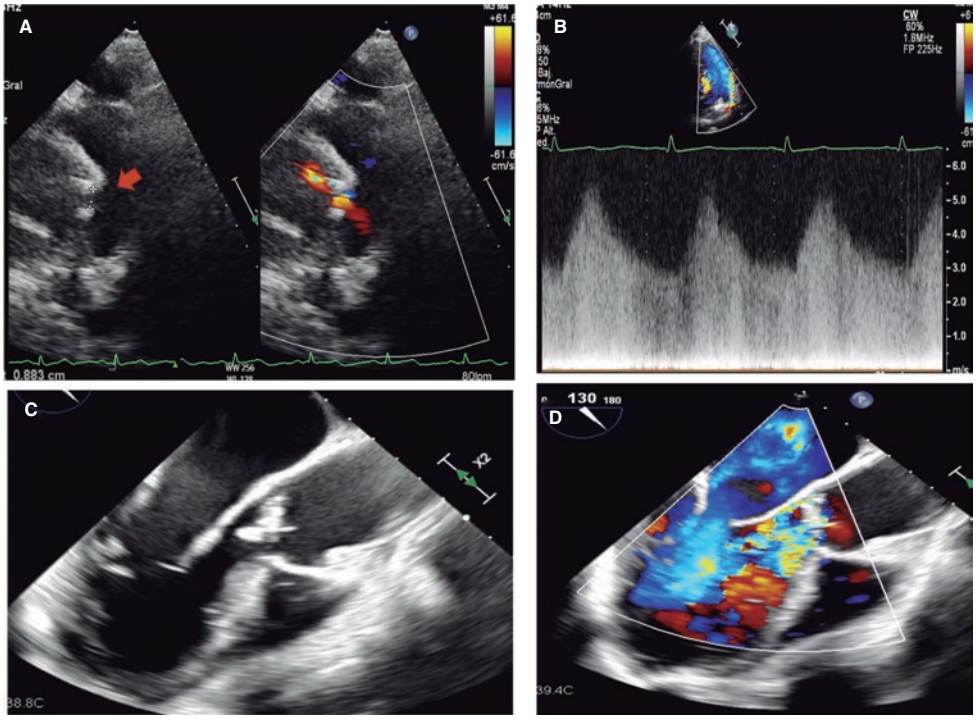

Figure 1.

A 52-year-old woman was admitted due to ischemic stroke treated with mechanical thrombectomy. She reported having a fever in the previous month, and a continuous systolic-diastolic murmur was identified during auscultation. An echocardiogram revealed the presence of a 7 mm x 5 mm persistent patent ductus arteriosus with hemodynamic repercussions (overload of left heart chambers) (figure 1A,B, arrow; videos 1 and 2 of the supplementary data). Additionally, a wart was found on the aortic valve with mild regurgitation. *Streptococcus sanguinis* was found in blood culture isolates. The thoracic coronary computed tomography angiography not only characterized the ductus, but also showed a vegetation on the pulmonary trunk, along with septic pulmonary emboli (figure 2A,D, arrow). A 4-week course of antibiotics was initiated. Due to worsening echocardiographic findings (vegetation growth, and progression of regurgitation) (figure 1C,D; videos 3 and 4 of the supplementary data), surgical intervention was decided to replace the aortic valve with a mechanical valve and close the ductus with a patch.

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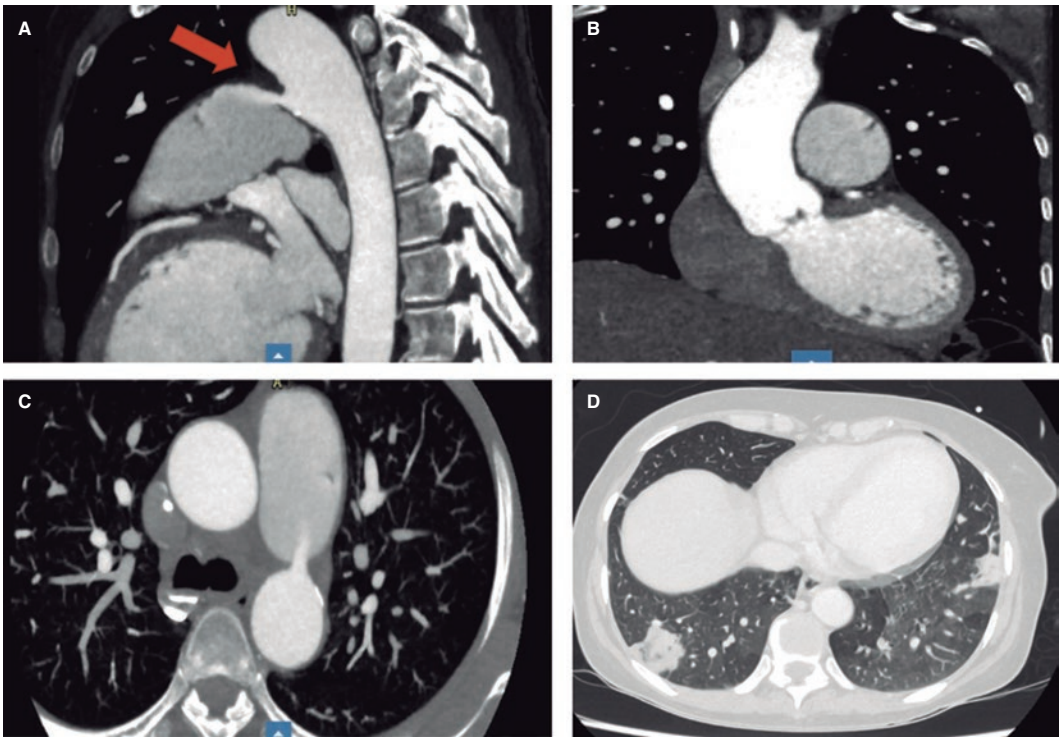

Figure 2.

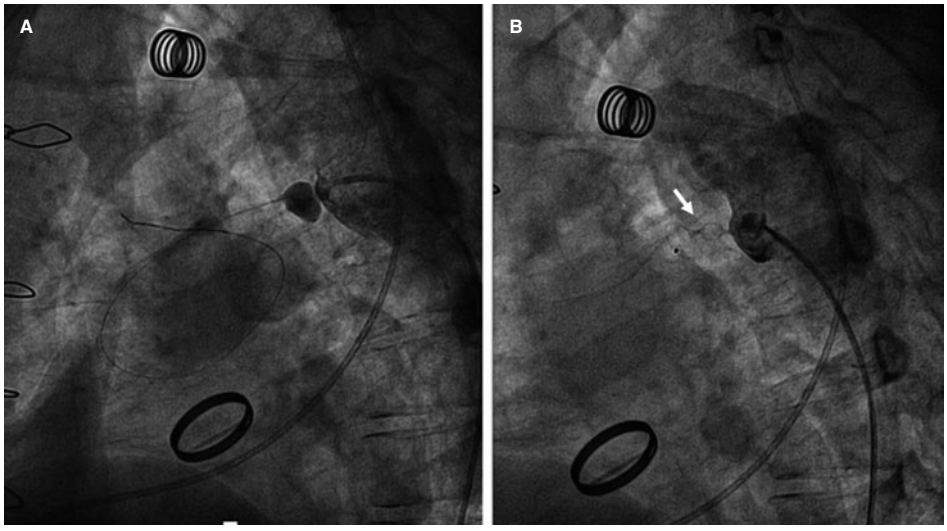

Figure 3.

In adults, the ductus can become calcified, thus hampering simple ligation. In this case, a small residual shunt remained, which was closed percutaneously 6 months later, following confirmation of the absence of inflammatory activity on positron emission tomography/computed tomography. After descending aorta angiography, crossing the ductus proved challenging because of its tortuosity and the presence of the patch. Microcatheter support and a 2.5-mm angioplasty balloon were used to finally implant an Amplatzer Duct Occluder II device (Abbott, United States) (figure 3A,B, J, arrow; videos 5 and 6 of the supplementary data).

The ductus is a rare cause of endocarditis because the turbulent flow jet causes endothelial damage that promotes bacterial invasion. "Preventive" closure of silent ducts is not included in clinical practice guidelines but is recommended by some groups recommend because it is a low-risk procedure.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the patient to publish her case. Since this is an isolated case report, most SAGER guidelines do not apply. The patient's gender (woman) has been specified. However, since this is a case report and not a research study, additional considerations were not deemed necessary.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used.

AUTHORS' CONTRIBUTIONS

A.T. Ariza, and P. Merás Colunga drafted the initial version of the manuscript, and selected and edited the images that would later be used. C. Merino, J. Ruiz Cantador, and R. Moreno were involved in the manuscript critical review, and approved its final version. I. Pinilla acquired the computed tomography images and approved the final version of the manuscript.

CONFLICTS OF INTEREST

R. Moreno is associate editor of *REC: Interventional Cardiology*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. No other conflicts of interests are declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000425.