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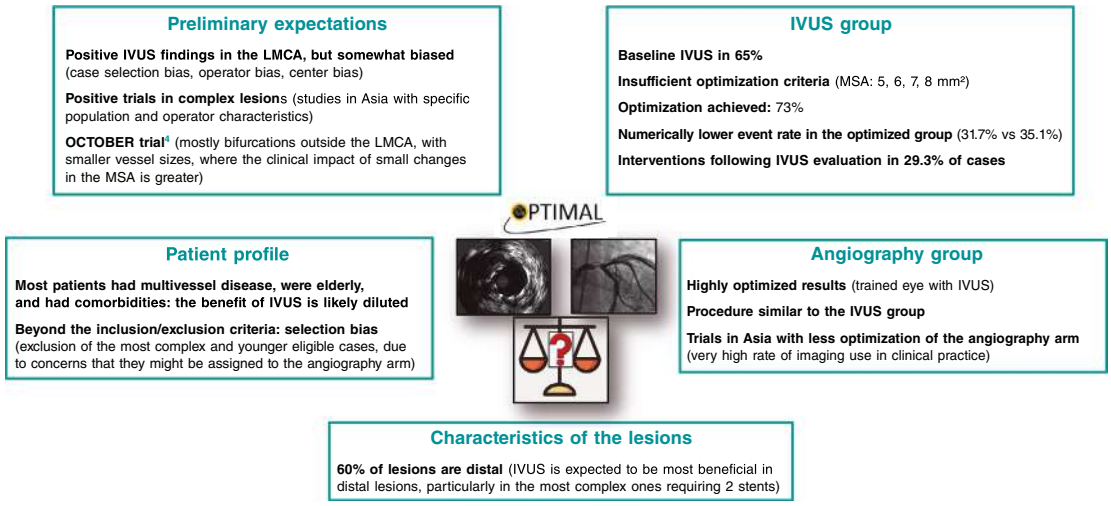

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How to get started in clinical research: notes from experience

Cómo iniciarse en la investigación clínica: apuntes desde la experiencia

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A few years ago I had the opportunity to write a review article for *Revista Española de Cardiología* together with Elazer R. Edelman.[1] In that paper, we reviewed the different stages and modalities of biomedical research, ranging from nonclinical studies in animal or computational models to randomized clinical trials and clinical registries. We also discussed the limitations and challenges they pose, while proposing potential solutions and alternative approaches to help overcome them.

Nearly a decade later, the aim of the present article is to offer a more personal perspective on clinical research in interventional cardiology, primarily intended for those who wish to being or are already taking their first steps in this field.

WHY CONDUCT RESEARCH?

All physicians should be involved in research in some capacity, although the degree of involvement may vary considerably. Clinical groups that actively conduct research also tend to improve the quality of their clinical care. Therefore, research should not be viewed as an optional activity within a medical team, but rather as an essential professional responsibility. Within each team, participation will naturally differ among members, encompassing both leadership and collaborative roles. Ultimately, research should serve first and foremost to improve patient care and, only secondarily, to enhance individual academic credentials.[2]

In my case, as in that of many physicians engaged in research, the motivations for undertaking research include the following:

- Because I ask questions.
- Because I wish to improve medical care.
- Because I wish to improve clinical outcomes.
- Because I feel fulfilled; it makes me feel better; it fascinates me.
- And yes, also because I find satisfaction in seeing my studies published.

The primary motivation for research is, ultimately, the desire to answer questions related to patients' cardiac diseases, including their diagnosis, treatment, and prognosis.[3]

If this is the case, however, why is it sometimes so difficult to initiate, sustain, or direct efforts toward research? Numerous barriers exist. Among the most notable are the scarcity of financial resources—often reflecting the limited sociopolitical priority given to research—the lack of a strong research culture and social motivation, the heavy clinical workload, the instability and job insecurity faced by researchers, and the limited professional and social recognition of research activities.[2,4] Additional obstacles include insufficient training in research methodology, lack of financial compensation, convenience, and simple lack of interest.

WHAT CAN I RESEARCH?

When beginning a research career—often modestly—one of the first questions we ask ourselves is: *what can I investigate that has not already been studied?* Frequently, particularly among younger physicians, there is a temptation to replicate previously conducted studies and reproduce them at a local level. In certain circumstances this approach may be appropriate, especially when prior studies have clear limitations and the proposed design offers meaningful improvements. However, this is often not the case, and such studies, even if completed, are unlikely to have a meaningful impact or achieve publication.

The proportion of recommendations in cardiology clinical practice guidelines supported by high-level evidence—defined as level A, typically derived from multiple randomized clinical trials or meta-analyses—is relatively low. In the clinical practice guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA), this proportion is approximately 8.5%.[5] In the European Society of Cardiology (ESC) guidelines, it ranges between 14% and 16%.[6]

Although much of the available clinical evidence is based on randomized clinical trials, these studies may also present certain limitations:

- Small sample size or inadequate representation of certain subgroups or specific clinical indications.
- Use of nonclinical (surrogate) endpoints or "soft" clinical outcomes (eg, outcomes that do not include death or myocardial infarction).

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- Short duration of follow-up.
- Use of a control group that does not represent the reference standard.
- Absence of an appropriate placebo (sham procedure) in trials involving certain interventional techniques.

In many settings, evidence derived from randomized clinical trials is lacking, and the available knowledge is based primarily on observational registries (level of evidence B). In cardiology, recommendations supported by level of evidence C—based on expert consensus, small studies, or retrospective registries—still account for a substantial proportion of clinical practice guidelines.

Therefore, it is undeniable that substantial knowledge gaps remain, and identifying them is essential for designing studies that, even if modest in scope, may still provide meaningful contributions.

Accordingly, there are numerous opportunities for clinical research, including the following:

- Registries evaluating the use of new technologies, including:
  - Outcomes in real-world clinical practice.
  - Outcomes in specific patient subgroups.
  - Assessment of rare complications.
- Comparisons between "old" and "new" technologies in clinical contexts that have not been addressed in previous trials.
- Clinical questions typically not addressed by industry-sponsored research, such as:
  - Conditions with very low case volumes.
  - Commercially "orphan" techniques.
- Evaluation of health care processes, including:
  - Safety and effectiveness of care delivery.

METHODOLOGICAL DESIGNS: STARTING WITH OBSERVATIONAL STUDIES

At the beginning of a clinical research career, conducting randomized clinical trials is often very difficult, particularly multicenter trials. However, other study designs are more feasible and accessible, and they provide valuable opportunities to develop and refine research skills.

Observational registries represent an excellent starting point. In order of increasing complexity of implementation—and, therefore, potential scientific value—the following study designs can be considered[1]:

- Single-center retrospective observational registries.
- Single-center prospective observational registries.
- Multicenter retrospective observational registries.
- Multicenter prospective observational registries.

In addition, hybrid study designs may also be used, such as ambispective registries, which incorporate both retrospective and prospective components.

Within these registries, the control group may be historical, based on a previous time series in which one treatment replaced another, or concurrent, when the treatments being compared coexist during the same time period. However, selection bias often limits the validity of comparisons between study and control groups, particularly when both treatments were available simultaneously. For this reason, registries frequently employ statistical adjustment techniques, such as methods based on the propensity score, to improve comparability between groups.[7]

A key question when designing a new observational registry is identifying where the opportunity lies. A real-world registry evaluating the use of a new drug or a new diagnostic or therapeutic technique may provide meaningful value if it meets at least one of the following conditions:

- It is the first registry addressing the topic.
- It includes a larger sample size than previously published studies.
- It provides longer follow-up than existing data.
- It explores new indications beyond established uses (off-label).
- It incorporates novel methods for evaluating or measuring outcomes.
- It evaluates its use in a specific national, regional, or local context.

COOPERATIVE, MULTICENTER, AND MULTIDISCIPLINARY RESEARCH

Modern medical research has evolved beyond the model of the solitary investigator toward a cooperative, multicenter, and multidisciplinary approach.

Multidisciplinarity

Many contemporary research projects require collaboration among cardiologists with different areas of expertise, cardiac surgeons, physicians from other specialties, nursing professionals, statisticians, bioinformaticians, and other specialists. This multidisciplinary framework allows cardiovascular diseases and interventions to be studied from multiple perspectives, fostering innovative solutions that would be difficult to achieve within a single discipline.

Multicenter approach

Research studies are increasingly conducted across multiple institutions to include larger and more diverse patient populations. This approach enhances statistical power and improves the generalizability of results to different populations worldwide. Multicenter collaborations frequently extend across countries and health systems. To develop such collaborations, establishing connections with professionals interested in the same field of research is essential. Scientific conferences and in-person courses provide valuable opportunities for networking, but they are not the only pathways. Currently, remote interaction and communication among professionals are widespread, both within countries and internationally. Email has facilitated these exchanges for decades, and more recently, online events and social media platforms have enabled researchers to connect, share ideas, and develop collaborative projects with colleagues around the world.

PROGRESSION OF THE CLINICAL RESEARCH CAREER

Earlier we highlighted the different levels of complexity of observational studies. This has important implications for how a research career may evolve, including the types of study designs undertaken and the strategies used to disseminate their results.

The sequence of progression I propose is the following. It should be considered illustrative rather than prescriptive, as research careers may follow different paths:

- Local observational studies conducted within one's own center:
  - Presentation at regional or national congresses.
  - Publication in regional or national journals.
- Multicenter retrospective and prospective observational studies:
  - Presentation at national or international congresses.
  - Publication in national or international journals.
- Randomized clinical trials (single-center or multicenter):
  - Submission as late-breaking trials to international congresses.
  - Publication in international journals.

As an example of this progression, the ESTROFA study group (*Estudio español sobre trombosis de stents farmacoactivos*) is noteworthy, having generated up to 10 publications. Focused on the investigation of clinical outcomes associated with drug-eluting stents, this collaborative project began with large multicenter retrospective registries, followed by prospective registries, and ultimately culminated in a collaborative randomized trial conducted together with a British research group.[8-10]

Another illustrative example is the LITRO study group (*Lesiones intermedias en tronco común*), which explored different aspects of the use of intravascular ultrasound in the assessment and management of left main coronary artery lesions.[11-13]

STATISTICS AND DATABASES

For basic and moderately complex analyses, it is often preferable to work independently or with a trusted collaborator, consulting external experts only for highly complex analyses that cannot otherwise be addressed. For this reason, training in biostatistics—through dedicated courses or master's programs—is highly valuable.

Statistical software used in clinical research can generally be divided into powerful commercial platforms and open-source or user-friendly tools designed for academic researchers.[14,15]

Among the most powerful commercial programs is SAS (Statistical Analysis System), which provides a robust biostatistical platform designed to meet strict regulatory standards. SPSS Statistics (IBM) is widely used in the health sciences because of its intuitive interface based on drop-down menus, making it suitable for analyses commonly applied in clinical research without requiring programming skills. MedCalc, designed specifically for biomedical research, is another commercial option that, although less comprehensive than other platforms, is among the most intuitive and therefore particularly suitable for beginners. Among free and open-source tools, R (and the RStudio environment) stands out as one of the most powerful and flexible statistical platforms currently available. It includes thousands of libraries specifically developed for biostatistical analyses and is widely used in academic research because it is freely available. However, its effective use requires greater training and programming experience.

Regarding databases, researchers often begin by creating them in Excel (Microsoft). Nevertheless, due to its limitations for research purposes, it is advisable to progress toward databases specifically designed for clinical research. Among these, REDCap (Research Electronic Data Capture) is particularly notable for its strong academic orientation. It is a secure, web-based platform designed for creating and managing online databases and surveys to facilitate data collection in research projects, especially in biomedical and academic settings. REDCap allows the design of complex studies—such as clinical trials and longitudinal studies—supports straightforward data import and export, and incorporates features such as branching logic, automated functions, and data validation. As a result, it has become an essential platform for researchers who need to manage sensitive information efficiently and securely.

ARTIFICIAL INTELLIGENCE AND CLINICAL RESEARCH

Artificial intelligence (AI) can assist research projects through general-purpose applications such as ChatGPT (OpenAI), which is widely used for writing, programming support, and general inquiries, as well as through other tools specifically oriented toward scientific research.[16,17]

- Literature search and review: traditionally, PubMed, the free public search engine maintained by the US National Library of Medicine, has been the most widely used resource for biomedical literature searches. However, AI-based tools are now emerging that allow clinical evidence to be identified more rapidly and efficiently than traditional search engines. One example is OpenEvidence, a platform designed to provide medical answers based exclusively on up-to-date clinical evidence.
- Data analysis: several AI tools are designed to process large volumes of medical information, including both structured and unstructured data. Amazon Comprehend Medical uses natural language processing to extract clinical information—such as diagnoses, medications, and symptoms—from unstructured medical notes. Owkin focuses on biomarker discovery and clinical trial design using machine learning models. PubMed.ai allows public health researchers to analyze and synthesize findings from multiple studies efficiently.
- Writing and editing of manuscripts: various applications assist with drafting scientific texts and ensuring compliance with academic standards. Paperpal provides real-time suggestions to improve academic writing and enhance the quality of scientific language. Jenny AI assists with article structure, proposes titles, and suggests citations based on the bibliography provided by the user. QuillBot is useful for paraphrasing and summarizing complex texts, helping improve clarity and reduce the risk of plagiarism. DeepL is a highly effective AI-based translation tool widely used in scientific writing.
- Workflow support: NotebookLM (Google) allows researchers to upload their own documents to ask specific questions, generate summaries, or create study guides. Scite.ai helps validate academic citations by indicating whether a study has been supported, cited, or contrasted by subsequent research.

Of note, although these tools can facilitate several steps of the research process, their outputs require careful verification and responsible, transparent use.

PUBLIC MASSIVE CLINICAL DATA SOURCES

Several public databases provide information on health care activity at the national level. Among these, the Minimum Basic Data Set (*Conjunto Mínimo Básico de Datos*, CMBD) is particularly relevant. This database is derived from hospital discharge reports, from which coding units at each hospital collect a standardized set of clinical and administrative variables. The main advantages of the CMBD include its large sample size, the high reliability of certain variables—such as age, sex, discharge diagnosis, and mortality—and the presence of a robust data auditing system that ensures overall data quality. However, several limitations must also be considered, including the potential undercoding of some variables and the absence of coding for others.[18]

THE SEARCH FOR FUNDING

The search for funding for cardiovascular research in Spain typically focuses on competitive public calls (national and regional), European programs, scientific societies, private foundations, and the pharmaceutical and medical device industry.

- Public funding (national and regional): the *Agencia Estatal de Investigación* (AEI), attached to the *Ministerio de Ciencia, Innovación y Universidades*, supports basic and translational research through annual R&D&i calls. The *Instituto de Salud Carlos III* (ISCIII) is the main source of funding for biomedical and clinical research in Spain through its Strategic Action in Health (*Acción Estratégica en Salud*, AES) programs.
- Scientific societies: the Spanish Society of Cardiology (SEC), including its associations and sections—such as the Interventional Cardiology Association of the SEC—offers grants, research awards, and funding for specific research projects.
- Centers of excellence: the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC) receives competitive funding, including the Severo Ochoa accreditation, to support research in cardiovascular prevention and treatment.
- Private foundations and other entities: examples include CaixaResearch, Fundación BBVA, and Fundación Ramón Areces, which provide competitive grants to support biomedical research.
- Independent research supported by industry: these are investigator-initiated clinical studies proposed and led by researchers outside the pharmaceutical or medical device industry that receive full or partial financial support from these companies.
- European funding: the European Research Council (ERC) offers grants to principal investigators of any nationality working in Europe. In addition, Horizon Europe, the European Union's framework program for research and innovation, includes substantial funding opportunities for health research. However, if obtaining funding at the national level is already challenging, applications for European funding typically involve considerably greater administrative and bureaucratic complexity.

ADMINISTRATIVE AND REGULATORY SUPPORT PLATFORMS

To conduct multicenter studies, whether prospective registries or randomized trials, particularly the latter, it is necessary to have appropriate expert support to manage, supervise, and develop the study while ensuring regulatory and ethical compliance. For this purpose, contract research organizations (CRO) are often used; however, their services are typically very costly. Consequently, alternative platforms developed by scientific institutions and foundations have emerged. Examples include the SEC's *Agencia de Investigación*[19] and initiatives promoted by foundations and research associations, such as Fundación EPIC[20] and Fundación FIC.[21] These platforms provide comprehensive support for study design, coordination, and regulatory management, offering a closer and more accessible framework for independent investigators working with limited research funding.

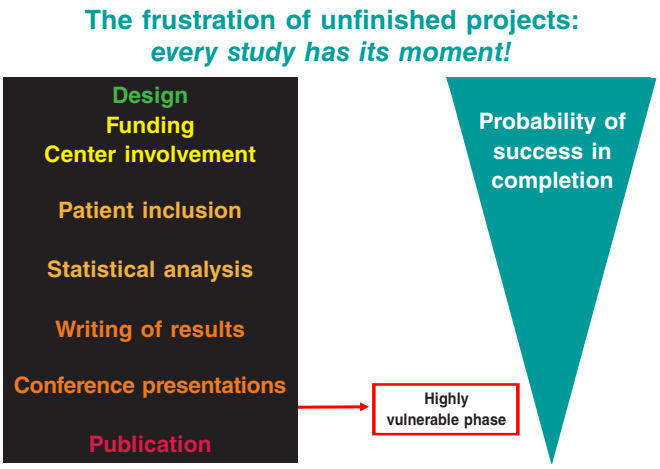

Figure 1. Stages of a study and levels of execution risk.

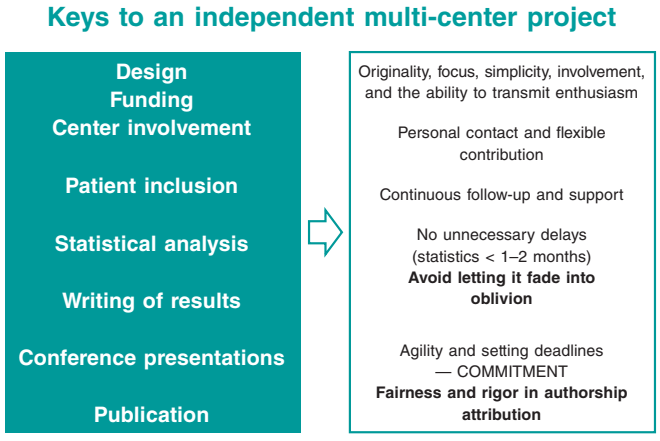

Figure 2. Essential aspects to guarantee success in an independent multicenter study.

FINAL REFLECTIONS

One of the greatest challenges in research is the substantial personal effort required, often combined with funding that is difficult to obtain or simply scarce. In addition, collaborations are frequently altruistic or poorly compensated, centralized data monitoring may be limited or absent, the quality of statistical analysis may vary, and the capacity for publication is often constrained. These difficulties commonly lead to a frustrating sequence of editorial rejections (figure 1).

To successfully undertake a clinical research project, it is essential to define a clear and original objective with practical implications and to design a study that interferes as little as possible with routine clinical practice. Only essential and well-defined information should be requested. Flexible and individualized contributions from participating centers should be encouraged, prioritizing data quality over quantity. Maintaining close communication with collaborators —offering support during patient enrollment and follow-up—is also crucial. Furthermore, investigators must demonstrate a genuine commitment to the dissemination and publication of results and establish authorship structures that reflect the magnitude of each contribution while avoiding any form of favoritism (figure 2).

Finally, as in any collaborative endeavor, the group of individuals involved in research largely determines the project's ultimate success. Each investigator should aim to build a collaborative network that includes both close colleagues and peers from other centers, while remaining willing to delegate tasks and assume shared responsibilities. The level of involvement and motivation among collaborators will inevitably vary; recognizing and managing these differences can help ensure the success of each project and foster durable research collaborations.

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None.

CONFLICTS OF INTEREST

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Editorial

Regarding the OPTIMAL study: analyzing the apparent disconnect between a clinical trial and real-world practice

A propósito del estudio OPTIMAL: analizando la aparente disociación entre un ensayo clínico y la práctica real

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Thirty years ago, in 1996, the concept of evidence-based medicine took hold; David Sackett, one of its leading advocates, defined it as the conscientious, explicit, and judicious use of the current best evidence for clinical decision-making. Since then, the properly designed randomized clinical trial has been the method par excellence for demonstrating the efficacy of medical interventions and generating robust evidence to inform the recommendations of scientific societies. However, over the past few decades, the scientific community has learned a great deal about the limitations of this methodology.

The results of the OPTIMAL trial have recently been published; the trial was designed to determine whether intravascular ultrasound (IVUS)-guided percutaneous revascularization of the unprotected left main coronary artery (LMCA) leads to better clinical outcomes than revascularization guided by conventional angiography alone.[1] In this trial, a total of 806 patients with a mean age of 71 years and a mean SYNTAX score of 30 were randomized to one of the two interventions; 78% of them were women. After a median follow-up of 2.9 years, the primary endpoint occurred in 135 patients (33.7%) in the IVUS-guided group and in 125 patients (30.9%) in the angiography-guided group. The incidence of death, myocardial infarction, or revascularization was similar in both groups. The incidence of stroke was higher in the IVUS group, although these events occurred at a median of 19 months, which may suggest a chance finding. The authors concluded that, among patients with LMCA disease, IVUS-guided percutaneous revascularization showed no additional benefit compared with angiography-guided revascularization. This is not the first time that trial results have conflicted with initial expectations.

For many years, I have been an advocate and promoter of the use of IVUS to guide drug-eluting stent angioplasty procedures in the LMCA, based on a conviction derived from my own experience, but primarily on the results of numerous observational studies, including some that we conducted in our country.[2,3] Therefore, being one of the principal investigators and the second author of the OPTIMAL trial manuscript places me in a unique position. On the one hand, I must accept the results of a trial that was executed flawlessly in every respect; on the other hand, I remain convinced that the use of IVUS can continue to add value in many cases of LMCA disease, especially when used appropriately. In the following paragraphs, I will attempt to explain and justify this position (figure 1).

EXPECTATIONS PRIOR TO THE OPTIMAL TRIAL

In recent years, several observational studies and corresponding meta-analyses have been published, all of which demonstrated that the use of IVUS in percutaneous revascularization of the LMCA was associated with a reduction in events, including cardiac death, myocardial infarction, and revascularization.[5] However, it is evident that the benefits observed in registries are often exaggerated, and this is due to certain biases. First, selection bias. Comparing cases in which IVUS was used versus those in which it was not within a registry implies selection bias, since that decision was based on certain variables, which ultimately affected certain characteristics of the patients and the lesions. Even with statistical matching techniques, it is very difficult to completely eliminate the confounding effect of partially hidden biases.[2] In this regard, the use of IVUS may have been more likely in patients in better clinical condition, who were more stable, and younger. This could explain the differences in overall mortality observed as early as the short- to medium-term between the IVUS and angiography groups in some registries.[6]

Another potential source of bias relates to the operator and the center. It is plausible that operators who used IVUS more frequently were also more meticulous in other technical and patient management aspects and were based at centers with higher patient volumes and greater experience. A large British registry found that the benefit of IVUS was greater when operators had higher case volumes, suggesting this bias.[6]

The positive results of some randomized trials, although not focused on the LMCA and conducted in Asian countries, also instilled considerable optimism.[7-10]

The OCTOBER trial, which compared optical coherence tomography-guided versus angiography-guided treatment of bifurcations, showed a lower incidence of the primary endpoint at 2 years (10.1% vs 14.1%).[4] It should be noted that these were mostly bifurcations that did not involve the LMCA and involved smaller vessels, where a greater effect of small changes in the minimum stent area (MSA) on clinical outcomes is expected.

PATIENT PROFILE

In the OPTIMAL trial, the mean age of patients was 71 years, 5 years older than that of patients in the OCTOBER trial.[1,4]

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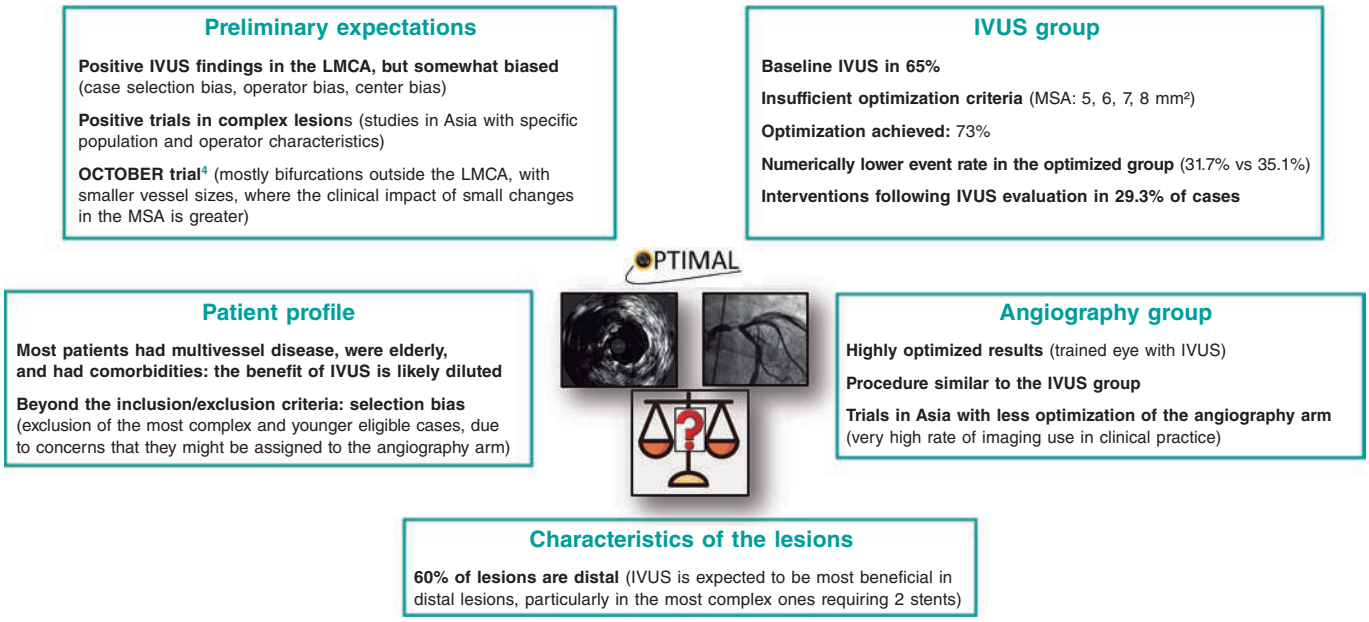

Figure 1. Various factors explaining the relative discrepancy between the expected results and those ultimately obtained in the OPTIMAL study. IVUS: intravascular ultrasound; LMCA: left main common artery; MSA: minimum stent area. The bibliographical references mentioned in this figure correspond to Testa et al.[1] (OPTIMAL trial) and Holm et al.[4] (OCTOBER trial).

Fifty-eight percent had three-vessel disease, with a mean SYNTAX score of 30. This explains the high incidence of events, exceeding 30% at 2.9 years.[1]

As is often the case in many trials, and especially when there are pre-existing biases, patient enrollment may have taken into account factors beyond the inclusion/exclusion criteria, leading to selection bias. Consequently, it is possible that some patients for whom IVUS was deemed necessary (such as those with more complex distal lesions or younger patients) were excluded.

CHARACTERISTICS OF LMCA LESIONS

In the OPTIMAL trial, 60% of the treated LMCA lesions involved the bifurcation. In a large Spanish multicenter registry, with two matched groups of 505 patients each, we found that the benefit associated with the use of IVUS in LMCA angioplasty with drug-eluting stents was greater in distal lesions and, particularly, in those requiring two stents.[2] Therefore, the inclusion of a relatively high proportion of non-distal lesions may have reduced the overall impact of IVUS in the OPTIMAL study.

In the recently published IVUS-CHIP trial, which evaluated the use of IVUS in 2020 patients with complex lesions and demostrated no differences compared with angiography, a trend toward a benefit from IVUS was observed in distal LMCA lesions.[11]

THE IVUS GROUP

IVUS is not a therapeutic tool, it is an imaging technique, and the benefit it may provide depends on how the operator uses it. The resulting clinical advantage derived from its use will be solely due to the corrective measures prompted by the imaging findings, the optimization criteria pursued, and the extent to which those criteria are met. In the OPTIMAL trial, the use of IVUS prior to the procedure was 65%, whereas a higher rate of use would have been expected to better understand the characteristics of the plaques and plan plaque management.

Among the optimization criteria, those related to expansion are particularly relevant, specifically the MSA cutoff values that were considered mandatory to achieve in this trial.[12] These values were 8 mm^2 for the LMCA, 7 mm^2 for the confluence polygon, 6 mm^2 for the left anterior descending artery, and 5 mm^2 for the left circumflex artery, which were acceptable at the time the trial was designed but have since been surpassed by more recent studies. Currently, the optimal MSA cutoff values are estimated at 10 mm^2 for the TCI, 7 mm^2 for the left anterior descending artery, and 6 mm^2 for the left circumflex artery.[13-17] In fact, just as this editorial was being written, the European Association of Percutaneous Cardiovascular Interventions and the European Bifurcation Club published a consensus document on the use of imaging in LMCA angioplasty that incorporates these new target values.[18]

In the OPTIMAL study, the final MSA in the LMCA was 12.99 ± 4.09 mm^2, 7.79 ± 2.43 mm^2 in the left anterior descending artery, and 6.75 ± 1.92 mm^2 in the left circumflex artery, indicating that in 15% of cases the MSA in the LMCA was less than 9 mm^2, less than 5.3 mm^2 in the anterior descending artery, and less than 4.8 mm^2 in the circumflex artery.[1]

However, in addition to establishing criteria, it is advisable to attempt, within the bounds of what is feasible and safe, to achieve these objectives. In the OPTIMAL study, corrective actions were observed in 29.3% of cases, and optimization was confirmed in 73%, with a numerically lower event rate in the optimized group (31.7% vs. 35.1%).[1] It should be noted that failure to achieve the targets cannot be attributed solely to lack of adherence but is often due to safety considerations. In this regard, it is noteworthy that there were no differences in periprocedural complications between the groups.

The consideration of appropriate criteria and their implementation under a standardized protocol provides a benefit compared to the non-protocolized use of IVUS.[3]

THE GROUP ASSIGNED TO ANGIOGRAPHY

Another striking aspect is the high degree of similarity between the groups regarding the technical aspects of the procedure, with a similar

rate of post-dilatation and similar device sizes. This may suggest that the operator working solely with angiography acted based on the knowledge and experience of someone who has performed many IVUS-guided procedures, which could be considered an angiography-guided intervention but inspired by prior experience with IVUS.

In this regard, while we previously noted that Asian trials[7-10] generally yielded more positive results than Western ones,[1,11,19] it is worth noting that the angiography group in the former shows clear differences from the intravascular imaging group, with much lower use of post-dilatation and selection of stents with significantly smaller diameters. It is likely that the very high use of IVUS in Asian countries may influence this different approach when angiography is the only option available. Furthermore, it cannot be ruled out that these operators adhered more strictly to the protocol for optimization based on intravascular imaging.

FINAL COMMENTS AND RECOMMENDATIONS

Further subgroup analyses of the OPTIMAL trial are needed to address issues such as the effect of IVUS in cases of isolated LMCA disease, to explore outcomes based on different MSA values, and, above all, to identify anatomical or clinical subgroups that benefit most from IVUS-guided procedures.

The conclusions drawn from these reflections are as follows:

- The routine use of IVUS to guide percutaneous revascularization in all cases of LMCA lesions is not clinically justified when operators have sufficient experience in performing the procedure.
- It is necessary to identify which LMCA lesion profiles benefit most from the use of intravascular imaging techniques (most likely distal lesions).
- Appropriate optimization criteria should be established.
- Efforts should be made to achieve these objectives within safety margins.
- The implementation of automated intravascular image assessment systems (based on artificial intelligence) can be of great help in this regard.
- It is essential to continue promoting training and the use of intravascular imaging techniques among less experienced professionals.

Finally, in my opinion, it would be advisable to conduct a new randomized trial that includes patients with distal LMCA lesions without a high SYNTAX score and uses the most up-to-date optimization criteria.

"Science never offers absolute certainties; rather, it is a dynamic process of conjecture and refutation."

Karl Popper

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Editorial

Transcatheter edge-to-edge repair for ventricular secondary mitral regurgitation: perfect synergy with optimal medical therapy

Reparación percutánea de borde a borde en la insuficiencia mitral secundaria ventricular: la sinergia perfecta con el tratamiento médico

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Secondary ventricular mitral regurgitation (MR) is a common valvular disorder resulting from ventricular dilation or dysfunction rather than primary leaflet abnormalities.[1] Progressive left ventricular (LV) dilation and spherical reshaping displace the papillary muscles laterally and apically, increasing leaflet tethering forces and restricting systolic closure. Moreover, annular dilation and flattening reduce leaflet coaptation, while impaired LV contractility diminishes closing forces across the valve. This imbalance between tethering and closing forces leads to incomplete leaflet apposition and regurgitant flow into the left atrium during systole. Thus, the regurgitation reflects geometric distortion of the mitral apparatus secondary to LV remodeling rather than intrinsic leaflet pathology.

Moderate-to-severe regurgitation is present in approximately one-quarter to one-third of patients with chronic systolic dysfunction, depending on the population studied and the echocardiographic definitions applied.[2] Its prevalence increases with progressive LV dilation, prior myocardial infarction, longer duration of heart failure, and inadequate reverse remodeling despite guideline-directed medical therapy (GDMT). Beyond its prevalence, secondary MR carries substantial prognostic implications. Numerous observational analyses have demonstrated that moderate-to-severe secondary MR is independently associated with increased all-cause and cardiovascular mortality, even after adjustment for LV ejection fraction and clinical markers of disease severity.[3] The hemodynamic burden imposed by regurgitant volume increases left atrial and pulmonary venous pressures, promoting congestion, recurrent heart failure hospitalizations, and progressive right ventricular dysfunction. Patients with significant secondary ventricular MR also exhibit reduced functional capacity and poorer quality of life.

Historically, mitral valve surgery has been considered the main interventional approach for patients with significant secondary MR. Over the past few decades, several studies, including randomized clinical trials and meta-analyses, have evaluated the role of mitral valve surgery in this setting. These investigations showed that although surgery can reduce MR severity and, in some cases, promote reverse ventricular remodeling, evidence supporting a survival benefit vs optimal medical therapy alone remained limited.[4] On the other hand, transcatheter interventions offer a less invasive alternative to open-heart surgery. Among these, percutaneous procedures, particularly transcatheter edge-to-edge repair (TEER), have been increasingly adopted. As supporting evidence grew accumulated, mitral TEER has been widely implemented in contemporary interventional practice worldwide. In recent years, 3 randomized clinical trials have compared GDMT plus mitral TEER with GDMT alone in patients with secondary significant MR. In a recent study published in *REC: Interventional Cardiology,* Paulino-González et al.[5] conducted a systematic review and meta-analysis of the main clinical endpoints evaluated in randomized clinical trials comparing mitral TEER and optimal medical therapy thus far. They conducted a systematic search of electronic databases and identified 3 randomized clinical trials including more than 1400 patients overall. The primary endpoints were all-cause mortality and heart failure hospitalization. An exploratory analysis excluding patients from the MITRA-FR study[6] was also performed to reduce heterogeneity between study populations. Overall, there was a trend towards lower all-cause mortality which did not meet statistical significance (risk ratio [RR], 0.80; 95% confidence interval [95%CI], 0.63–1.02; $P = .07$). Heart failure-related hospitalization rates were significantly lower among patients who underwent mitral TEER (RR, 0.71; 95%CI, 0.56-0.90; $P = .004$). In the exploratory analysis excluding MITRA-FR patients, both all-cause mortality (RR, 0.71; 95%CI, 0.59–0.86; $P = .0005$) and heart failure hospitalization (RR, 0.63; 95%CI, 0.55-0.72; $P < .00001$) were significantly reduced with the percutaneous approach, with minimal heterogeneity between studies. The reduction in the composite endpoint of heart failure-related hospitalization or death with mitral TEER was consistent among patients presenting grade 3+ and grade 4+ MR at baseline. There were no significant differences between mitral TEER and optimal medical treatment in terms of safety endpoints, including stroke and myocardial infarction.

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Several aspects of this meta-analysis merit further consideration:

- *Differences in baseline clinical features across the included studies*. When the COAPT trial[7] was published in 2018, it provided compelling evidence that TEER reduced both heart failure-related hospitalizations and mortality in carefully selected patients with symptomatic heart failure and moderate-to-severe or severe secondary MR. Importantly, COAPT required rigorous optimization of GDMT before enrollment and objective confirmation of persistent, significant MR. In contrast, the MITRA-FR trial, reported in the same year, failed to demonstrate a reduction in death or heart failure-related hospitalization.[6] At first glance, the results seemed contradictory to those of COAPT. However, closer examination reveals fundamental differences in trial design and patient phenotype. MITRA-FR applied broader MR severity thresholds and enrolled patients with substantially larger LV volumes. In these patients, MR severity was more proportionate to the degree of ventricular remodeling, suggesting that regurgitation was primarily a consequence, rather than a cause, of advanced myocardial disease.[8] The RESHAPE-HF2 trial[9] aimed to evaluate this comparison in a contemporary therapeutic landscape. Conducted in the era of more comprehensive GDMT, including greater uptake of sacubitril/valsartan, mineralocorticoid receptor antagonists, and SGLT2 inhibitors, its findings, showing reduction in heart failure events and symptomatic improvement, with a less pronounced mortality effect than COAPT), suggest that TEER may confer benefit across a broader spectrum of MR severity than that represented in COAPT, albeit with a smaller effect size.

- *Grades of residual MR after percutaneous intervention*. As the authors stated in the discussion,[5] MR reduction was less effective in the MITRA-FR trial. In conclusion, MR reduction to ≤ 2+ in MITRA-FR (75.6% MR ≤ 2+ at discharge) was markedly lower than that obtained in COAPT (94.8% MR ≤ 2+ at 12 months) and the RESHAPE-HF2 (90.4% MR ≤ 2+ at 12 months). In MITRA-FR the degree of MR reduction was modest relative to what has been observed in other studies, with many patients remaining with moderate residual regurgitation. Because baseline regurgitation in MITRA-FR tended to be less severe, based on effective regurgitant orifice area and regurgitant volume thresholds, and proportionate to LV dilation, the capacity of TEER to achieve a large absolute reduction in regurgitant volume was inherently limited. Analyses of residual MR in RESHAPE-HF2 suggest that the degree and durability of regurgitation correction remained an important determinant of clinical response: patients with sustained mild or lesser degrees of MR demonstrated the most favorable clinical outcomes, whereas those with persistent moderate regurgitation derived attenuated benefit.[10] Additional factors may also have influenced trial outcomes, including increasing operator experience and advances in device technology over time. For example, the G4 generation of the MitraClip system (Abbott, United States) utilized in the RESHAPE-HF2 trial enables independent leaflet grasping and provides a wider range of device sizes, ultimately enabling tailored device selection potentially improving treatment of complex mitral valve anatomies.

Overall, Paulino-González et al.[5] should be commended for their work and contribution to the field. Consistent with the findings of the abovementioned trials, this meta-analysis supports the fact that secondary ventricular MR is not merely an epiphenomenon of LV dysfunction but a modifiable contributor to adverse outcomes. Moreover, mitral TEER in combination to GDMT clearly constitute the best therapeutic strategy for improving clinical prognosis.

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Editorial

Rational application of excimer laser in complex percutaneous coronary intervention: beyond balloon failure

Uso racional del láser de excímeros en la intervención coronaria percutánea compleja: más allá del fracaso del balón

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Balloon failure during percutaneous coronary intervention (PCI), which occurs particularly in severely stenotic and extensively calcified lesions, remains one of the most complex and frustrating scenarios for the interventional cardiologist. In addition, initial balloon failure is associated with prolonged procedures, greater resource consumption, and an increased risk of complications.[1] All this occurs despite the development and availability of different plaque-modification techniques, including excimer laser coronary atherectomy (ELCA).[2,3]

Across different studies over the years, the concept of balloon failure has encompassed various scenarios, including both uncrossable and undilatable lesions. This terminological imprecision may affect the interpretation of the available results from these studies, which in turn may have an impact on decision-making in clinical practice.

In the context of PCI for complex uncrossable or undilatable lesions, a better understanding of the underlying anatomical mechanisms is essential. This may be facilitated by a more systematic use of intracoronary imaging modalities. Nevertheless, dedicated studies in this setting are clearly needed. Their results may help improve lesion characterization and optimize the therapeutic approach through more appropriate selection of plaque-modification techniques.[2,3]

In a recent article published in *REC: Interventional Cardiology*, Jurado-Román et al.[4] present the design of the LUDICO study (Coronary laser in undilatable and uncrossable lesions; NCT07206082), a prospective, multicenter, single-arm observational trial to evaluate the safety and efficacy profile of ELCA in 230 patients with an indication for PCI and lesions in which balloon failure has occurred. The main strength of the study lies in its methodological approach, as it explicitly distinguishes between uncrossable and undilatable lesions. This distinction may contribute to a better understanding of the role and positioning of this technique, given that in both scenarios—after failure to cross or dilate the lesion with a balloon—ELCA would represent the first plaque-modification strategy to be used. Another relevant aspect of the study is the recommendation to use intracoronary imaging, specifically optical coherence tomography. This approach allows assessment not only of procedural success but also of the structural changes induced in the lesion. Currently, these changes have been poorly characterized in the context of ELCA, particularly in cases of in-stent restenosis.[5]

The most evident limitation of the study, appropriately acknowledged by the authors, is the absence of a control group, which makes direct comparison with other plaque-modification techniques impossible. A comparison between these techniques has recently been performed in PCI for complex lesions in the randomized ROLLER COASTR-EPIC22 study (Rotational atherectomy, lithotripsy or laser for the treatment of calcified stenosis).[6] Such a comparison could also have been of interest in the specific context of the study under discussion. Another aspect worth noting is that the definition of an undilatable lesion is based on an objective criterion (balloon expansion < 80% after 1:1 noncompliant balloon inflation at 18 atm). In contrast, a stricter or more precise definition of an uncrossable lesion is lacking. In this study, an uncrossable lesion was defined after failure to advance a low-profile balloon despite adequate guide support at the operator's discretion. This approach may introduce a degree of variability that should be considered when interpreting the results.

From a broader perspective, the use of ELCA in clinical practice remains limited. This may be partly explained, in addition to the relatively scarce scientific evidence, by a certain paradox: although the technique is technically straightforward from the operator's standpoint, its application entails a degree of conceptual complexity. Specifically, the procedural parameters must be adjusted according to the clinical scenario in which the device is used. This may help explain its relatively limited adoption in catheterization laboratories across Spain.[6] Indeed, the safety and efficacy of ELCA largely depend on several procedural decisions that remain incompletely standardized. These include the optimal timing of ELCA use during the procedure, the selection of catheter diameter, the potential

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Table 1. Proposed excimer laser configuration in different scenarios

Clinical scenario	Frequency (Hz)	Energy (mJ/mm²)	Adjunctive use of contrast	Practical comments
Underexpanded stent	60-80 (high)	60–80 (high)	No, according to device labeling. Observational studies support the usefulness of contrast amplification in lesions resistant to ELCA with saline solution	Start with high parameters if saline solution is used. If contrast is used, it is prudent to initially reduce ELCA parameters (frequency 25–40 Hz, energy 30–45 mJ/mm²), and they may be progressively increased with caution
Severely calcified lesion	60-80 (high)	60–80 (high)	No, according to device labeling. Limited evidence supports the potential usefulness of contrast in lesions resistant to ELCA with saline solution	Start with high parameters if saline solution is used. The use of contrast is not well established; if used, it is reasonable to consider an initial reduction in frequency and energy, which may then be progressively increased with caution
Thrombotic lesion	25-40 (low/medium)	30–60 (low/medium)	No	In "pure" thrombotic lesions, low energy and frequency are generally sufficient. In cases of thrombus with a large plaque burden, energy and frequency parameters may be gradually increased

ELCA, excimer laser coronary angioplasty.

combination with other plaque-modification techniques, and the appropriate selection and modulation of device parameters. These parameters include energy intensity and frequency, application duration, total number of pulses, and even the adjunctive use of contrast medium (amplification).[7] Table 1 proposes a practical framework for adjusting ELCA parameters according to the clinical context in which it is used. In conclusion, although ELCA is not technically demanding from an operator-handling perspective, its optimal use requires a certain degree of experience. Maximizing its benefits depends on a thorough understanding of the predominant mechanism underlying each lesion, a process that can be facilitated by the performance and appropriate interpretation of intracoronary imaging.

When examining the available evidence on ELCA, which remains generally limited, the technique has demonstrated clearer usefulness in certain specific scenarios.[8] One of these is the treatment of uncrossable lesions,[9] in which ELCA can advance over the same angioplasty guidewire. This represents a clear advantage and suggests that ELCA could be considered one of the preferred plaque-modification techniques in this setting. Moreover, ELCA may facilitate subsequent device advancement in extremely hostile anatomies and assist in the management of undilatable lesions, particularly those related to stent underexpansion. In these cases, its ability to modify both the underlying plaque and resistant neointimal tissue may allow more effective subsequent expansion.[10] In another challenging scenario—the treatment of lesions with a high thrombotic burden—ELCA has also shown potential usefulness.[11] Supporting this application, a contemporary series of patients undergoing primary PCI demonstrated that ELCA can "vaporize" thrombotic material, reducing it to microscopic particles and improving coronary flow, thereby facilitating safer and more effective stent implantation.[12]

In conclusion, the LUDICO study represents a valuable initiative, and the investigators should be congratulated, since it will contribute very useful knowledge on the safety and efficacy of ELCA in a setting still marked by relatively limited scientific evidence. In the current landscape of PCI for complex and calcified lesions, in which several plaque-modification techniques coexist, progress will depend not only on the development of new devices, but also on the ability to use them in the most rigorous and precise way, ideally guided by strategies based on evidence provided by high-quality studies.

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Original article

Transcatheter mitral edge-to-edge repair vs optimal medical therapy in secondary mitral regurgitation: a meta-analysis

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ABSTRACT

Introduction and objectives: Mitral regurgitation is one of the most common heart valve diseases. Valve replacement surgery is a guideline-recommended option; however, in a significant proportion of patients, this option is not feasible. In such cases, mitral transcatheter edge-to-edge repair (M-TEER) is a potential therapeutic alternative. Nevertheless, the results of a randomized clinical trial have shown divergent results. Recently, the results of the RESHAPE-HF2 trial were published, providing additional insights. The objective of this work is to evaluate whether there are any differences between performing M-TEER and keeping patients under guideline-directed medical therapy (GDMT).
Methods: We conducted a meta-analysis following the PRISMA guidelines. We searched for studies across the PubMed, Embase, and Cochrane databases until February 2025. We establish the following inclusion criteria: patients with secondary mitral regurgitation, studies comparing M-TEER plus GDMT vs GDMT alone, and who reported hospitalization due to heart failure (HF) or mortality.
Results: A total of 3 randomized clinical trials meet the inclusion criteria, including a total of 1423 patients: 704 received M-TEER and 719, GDMT alone. M-TEER was associated with a reduced risk of HF-related hospitalization with a risk ratio (RR) of 0.71 (95%CI, 0.56-0.90; $P = .004$). We did not find any differences in all-cause mortality with a RR of 0.80 (95%CI, 0.63-1.02; $P = .07$).
Conclusions: In this meta-analysis, M-TEER plus GDMT shows a lower risk of HF-related hospitalization vs GDMT alone. We did not find any differences in the risk of all-cause mortality or cardiac death.
Registered at PROSPERO: CRD42025645047.

Keywords: Mitral regurgitation. Mitral transcatheter edge-to-edge repair. Heart failure. M-TEER.

Reparación mitral percutánea de borde a borde frente a tratamiento médico óptimo en regurgitación mitral secundaria: un metanálisis

RESUMEN

Introducción y objetivos: La regurgitación mitral es una de las valvulopatías cardiacas más comunes. La cirugía de reemplazo valvular es una opción recomendada por las guías clínicas. Sin embargo, en un porcentaje significativo de pacientes, esta opción no es viable. En estos casos, la reparación mitral percutánea de borde a borde (M-TEER) es una posible alternativa terapéutica. No obstante, los resultados de los ensayos clínicos aleatorizados han mostrado resultados divergentes. Recientemente se han publicado los resultados del estudio RESHAPE-HF2, que aportan información adicional sobre este tema. El objetivo de este trabajo fue evaluar si existen diferencias entre realizar M-TEER o mantener a los pacientes bajo tratamiento médico según las guías clínicas (TMSG).
Métodos: Se realizó un metanálisis siguiendo las guías PRISMA. Se buscaron estudios en las bases de datos PubMed, Embase y Cochrane hasta febrero de 2025. Se establecieron los siguientes criterios de inclusión: pacientes con insuficiencia mitral secundaria, estudios que comparaban M-TEER más TMSG frente a solo TMSG, y que indicaran hospitalización por insuficiencia cardiaca o mortalidad.

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Resultados: Tres ensayos clínicos aleatorizados cumplieron los criterios de inclusión, con un total de 1.423 pacientes, de los que 704 se trataron con M-TEER y 719 recibieron solo TMSG. La M-TEER se asoció con una reducción del riesgo de hospitalización por insuficiencia cardiaca con una razón de riesgo de 0,71 (IC95%, 0,56-0,90; p = 0,004). No se encontraron diferencias en cuanto a muerte por cualquier causa, con una razón de riesgo de 0,80 (IC95%, 0,63-1,02; p = 0,07).
Conclusiones: En este metanálisis, la M-TEER, en combinación con el TMSG, mostró una reducción del riesgo de hospitalización por insuficiencia cardiaca en comparación con el TMSG solo. No se hallaron diferencias en el riesgo de muerte por cualquier causa (muerte de causa cardiovascular o infarto agudo de miocardio).
Registrado en PROSPERO: CRD42025645047.

Palabras clave: Regurgitación mitral. Reparación percutánea de borde a borde. Insuficiencia cardiaca. M-TEER.

Abbreviations

MR: mitral regurgitation. **M-TEER:** mitral transcatheter edge-to-edge repair. **GDMT:** guideline-directed medical therapy. **HF:** heart failure. **NYHA:** New York Heart Association.

INTRODUCTION

Mitral regurgitation (MR) is a prevalent valvular heart disease associated with significant morbidity and mortality, particularly in patients with heart failure (HF).[1] Traditional management strategies include optimal medical therapy to treat symptoms and surgery for definitive correction.[2] However, current clinical practice guidelines only recommend mitral valve repair if the patient is undergoing another intervention such as coronary artery bypass graft or aortic valve replacement; nonetheless, many patients are at a high risk for surgery due to comorbid conditions, for this reason, alternative therapeutic options is required.[3]

Mitral transcatheter edge-to-edge repair (M-TEER) has emerged as a minimally invasive option for patients with symptomatic mitral regurgitation who are ineligible for surgery.[4] While M-TEER has shown promising results, its comparative efficacy vs guideline-directed medical therapy (GDMT) is still a matter of discussion.[5]

This meta-analysis aims to assess the impact of M-TEER plus GDMT vs GDMT alone on major clinical outcomes in patients with secondary MR. The primary endpoint evaluated was HF-related hospitalization. Secondary endpoints included all-cause mortality, cardiac death, improvement in New York Heart Association (NYHA) functional class (FC), and the incidence rate of stroke and myocardial infarction. These endpoints were selected for their clinical relevance and potential to inform therapeutic decision-making in this high-risk patient population.

METHODS

We conducted this meta-analysis in full compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[6] All the stages of this study were performed following the Cochrane Handbook for Systematic Reviews of Interventions, version 6.3.[7] The protocol for this meta-analysis was registered prospectively in PROSPERO on 10 February 2025 with protocol ID CRD42025645047.

Search strategy

We conducted a systematic search across 3 electronic databases (PubMed, EMBASE, and COCHRANE) from inception until February 2025. Search terms included combinations of the following keywords: *"transcatheter", "secondary", "mitral valve", "replacement", regurgitation", and "insufficiency".* These keywords were combined using Boolean operators AND, OR. The reference lists of eligible studies and previous reviews were checked to identify additional valuable articles.

Criteria of the included studies

Studies were considered for inclusion in the meta-analysis based on the following criteria: *a)* randomized clinical trials (RCT) or observational cohort studies in Spanish or English that *b)* compared transcatheter mitral valve replacement vs optimal medical therapy in adult patients with mitral valve regurgitation due to secondary causes; and *c)* studies that reported outcomes of interest such as the index HF-related hospitalization, HF-related readmissions or cardiac death, and all-cause mortality.

Studies were excluded if they were non-original articles such as systematic reviews, letters, abstracts, meta-analyses, case reports, or case series. Furthermore, studies were excluded if mitral regurgitation was due to primary causes or if prior surgical repair had been performed.

Although observational cohort studies were eligible, we only identified 1 cohort study that did not meet the inclusion criteria during full-text screening. As a result, only RCTs were ultimately included in the meta-analysis.

Data extraction

To ensure accuracy, we used Zotero to eliminate duplicate references. We screened each paper based on title and abstract as a first step, followed by a full-text review as the second step. Two authors (D.A. Navarro Martínez, and D. Paulino-González) independently screened each paper, with any disagreements being resolved by a third author (A.L. García Loera). In addition, references of the included studies were reviewed and added if they met our eligibility criteria. Data extraction was conducted using Excel spreadsheets capturing the following information: *a)* baseline characteristics of the studied population, including baseline medication, echocardiographic baseline characteristics, and comorbidities; *b)* summary of the characteristics of the included studies; *c)* outcome measures; and *d)* quality assessment domains.

Primary and secondary endpoints

The primary endpoints established for this meta-analysis included: *a)* all-cause mortality (hazard ratio [HR]), defined as all-cause mortality, assessed using time-to-event analysis,[8] and *b)* HF-related hospitalization, defined as hospital admission for worsening HF following the intervention (M-TEER or initiation of optimal medical therapy).[9]

Secondary endpoints included *a)* stroke, defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction;[10] and *b)* myocardial infarction, defined according to the Fourth Universal Definition.[11]

All endpoints were assessed as dichotomous categorical variables, which were reported in percentages. The risk ratio (RR) with its corresponding 95% confidence interval (95%CI) was calculated.

Assessment of heterogeneity

To assess heterogeneity, we used Cochrane's Q-statistic with a significance level of $P < .05$. Additionally, the I^2-statistic was used to quantify the proportion of variability due to heterogeneity, with values > 50% being considered indicative of high heterogeneity.[12]

Statistical analyses

To assess dichotomous data, we evaluated event frequencies and totals from each study group to calculate the RR and its 95%CI. Moreover, we obtained the HR and the 95%CI to calculate the standard error (SE).

The variables analyzed in this study were based on data reported in the original studies of the intention-to-treat principle. We implemented a random-effects model using the DerSimonian-Laird[13] method to account for variability and allow comparison across studies. Given the limitations and strengths of this method, we conducted a sensitivity analysis using the Hartung-Knapp-Sidik-Jonkman method. Forest plots were utilized as a visual representation of the estimated outcomes.

Considering the differences in the populations included in the clinical trials, we conducted an additional exploratory analysis that focused on the RESHAPE-HF2[14] and COAPT[15] trials for the primary endpoints by removing MITRA-FR[16] from the analysis.

All statistical analyses, including the calculation of RR and SE, were conducted using RevMan V.5.4.1 software.

RESULTS

The initial database search yielded a total of 164 potentially relevant articles. After removing duplicates, a total of 129 articles finally remained for title and abstract screening. Following this initial screening, 8 articles were identified as potentially eligible for full-text review. Finally, after a detailed evaluation of the full texts under the predefined inclusion and exclusion criteria, 3 studies were included. A summary of the study selection process is shown in the PRISMA flowchart figure 1.

Our analysis included 3 RCTs.[14-16] We consulted the extended report of the 2-year outcomes of the MITRA-FR trial[17] and 1 additional article on the RESAHPE-HF2 to obtain more data regarding hospitalization.[18] All included studies compared the use of M-TEER plus GDMT vs GDMT alone. To standardize the outcomes, the median follow-up was set at 24 months; only the NYHA FC was evaluated with 1-year results. All 3 included studies used the MitraClip (Abbott, United States) device.

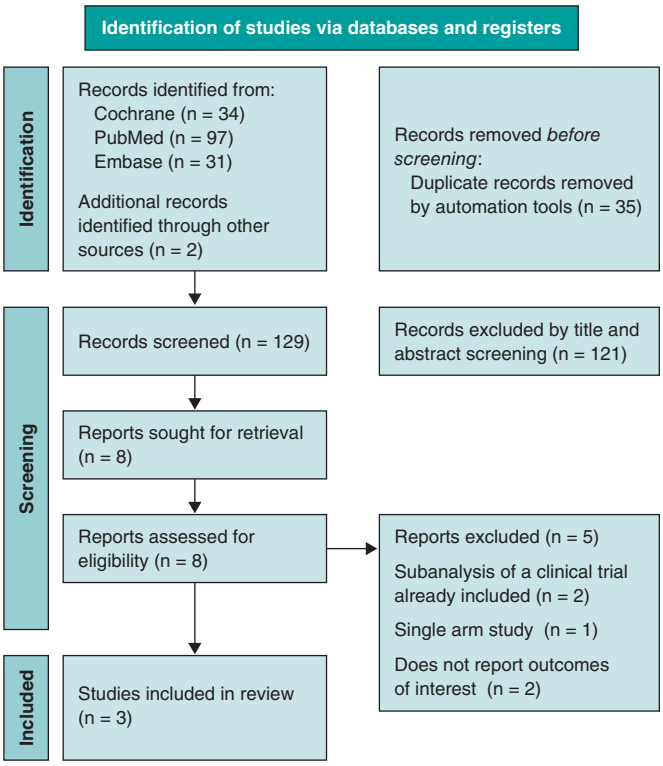

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Clinical baseline characteristics of the patients

We obtained a total population of 1423 patients; among them 704 received M-TEER and 719, GDMT alone. In the RESHAPE-HF2[14] the device group showed the following characteristics: mean age was 70 years old; left ventricular ejection fraction (LVEF), 32%; median left ventricular end-diastolic volume (LVEDV), 200 mL; median effective regurgitation orifice (EROA), 0.23 cm^2; median N-terminal pro-B-type natriuretic peptide (NT-proBNP), 2651; and brain natriuretic peptide (BNP), 556. In the COAPT[15] trial, median age was 71 years old; LVEF, 31%; LVEDV, 194 mL; median EROA, 0.41 cm^2; median NT-proBNP, 5174; and BNP, 1014. Finally in the MITRA-FR trial[16], mean age was 71 years old; LVEF, 33%; LVEDV, 136.2 mL; median EROA, 0.31 cm^2; median NT-proBNP, 3407; and BNP, 765. Regarding etiology, all trials enrolled mixed ischemic and non-ischemic etiology populations. Patient and study baseline characteristics, including comorbidities, drugs, and echocardiographic data, are shown in table 1, table 2, and table 3.

Risk of bias assessment

To evaluate the quality of the included randomized controlled trials, we used the Risk of Bias 2 (RoB2) tool from the Cochrane Handbook of Systematic Reviews of Interventions 6.3.[7] This methodology allowed us to systematically assess the methodological quality of each study, thereby strengthening the validity of our findings.

Of the 3 studies, 1 had a low risk of bias,[14] while the other 2 raised some concerns.[15,16] The studies with some concerns were limited by factors in their methodologies, as they were open-label studies (figure 2).

Table 1. Baseline characteristics of patients

Reference	Groups	N	Age	AF or flutter	Diabetes	Previous MI	Nonischemic etiology	Ischemic etiology	6-min walk distance	Beta-blocker	ACEI	ARB	ARNI	SGLT2i	MRA	Diuretics	Oral anti-coagulants	BNP	NT-proBNP	EuroSCORE II
RESHAPE-HF2[14]	M-TEER	250	70.0 ± 10.4	118 (47.2)	91 (36.4)	144 (57.6)	88 (35.2)	–	300 (220-382)	238 (95.2)	142 (56.8)	51 (20.4)	40 (16.0)	24 (9.6)	200 (80.0)	239 (95.6)	163 (65.2)	556 (312-1018)	2651 (1630-4918)	5.3 (2.7-8.9)
	Optimal medical therapy	255	69.4 ± 10.7	125 (49.0)	85 (33.3)	135 (52.9)	88 (34.5)	–	310 (200-378)	246 (96.5)	142 (55.7)	45 (17.6)	28 (11.0)	22 (8.6)	215 (84.3)	243 (95.3)	152 (59.6)	406 (231-874)	2816 (1306-5496)	5.3 (2.9-9.0)
COAPT[15]	M-TEER	302	71.7 ± 11.8	173 (57.3)	106 (35.1)	156 (51.7)	118 (39.1)	184 (60.9)	261.3 ± 125.3	275 (91.1)	138 (45.7)	66 (21.9)	13 (4.3)	NR	153 (50.7)	270 (89.4)	140 (46.4)	1014.8 ± 1086.0	5174.3 ± 6566.6	NR
	Optimal medical therapy	312	72.8 ± 10.5	166 (53.2)	123 (39.4)	160 (51.3)	123 (39.4)	189 (60.6)	246.4 ± 127.1	280 (89.7)	115 (36.9)	72 (23.1)	9 (2.9)	NR	155 (49.7)	277 (88.8)	125 (40.1)	1017.1 ± 1212.8	5943.9 ± 8437.6	NR
MITRA-FR[16]	M-TEER	152	70.1 ± 10.1	49/142 (34.5)	50 (32.9)	75 (49.3)	57 (37.5)	95 (62.5)	307 (212-387)	134 (88.2)	111 (73.0)	111 (73.0)	14/140 (10)	NR	86 (56.6)	151 (99.3)	93 (61.2)	NR	NR	7.33 ± 6.29
	Optimal medical therapy	152	70.6 ± 9.9	48/147 (32.7)	39 (25.7)	52 (34.2)	66 (43.7)	85 (56.3)	335 (210-410)	138 (90.8)	113 (74.3)	113 (74.3)	17/140 (12.1)	NR	80 (53.0)	149 (98.0)	93 (61.2)	NR	NR	6.57 ± 5.24

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BNP, B-type natriuretic peptide; M-TEER, mitral transcatheter edge-to-edge repair; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Table 2. Summary of included studies

Authors and year	Study design	Device	Population size	Compared interventions	Mean follow-up	Key findings
Anker et al. RESHAPE-HF2 2024[14]	RCT	MitraClip	505	M-TEER Optimal medical therapy	24 months	1. At 24 months, the rates of HF-related hospitalization or cardiac death were 37.0 vs 58.9 events per 100 patient-years in the device and control groups, respectively (RR, 0.64; 95%CI, 0.48-0.85; *P* = .002). 2. The KCCQ-OS score improved by 21.6 ± 26.9 points in the device group vs 8.0 ± 24.5 in the control group (mean difference, 10.9; 95%CI, 6.8-15.0; *P* < .001), with device-specific safety events occurring in only 1.6% of patients.
Stone et al. COAP 2018[15]	RCT	MitraClip	614	M-TEER Optimal medical therapy	24 months	1. At 24 months, the annualized rate of HF-related hospitalization was 35.8% per patient-year in the device group vs 67.9% in the control group (HR, 0.53; 95%CI, 0.40-0.70; *P* < .001) 2. All-cause mortality rate was 29.1% in the device group vs 46.1% in the control group (HR, 0.62; 95%CI, 0.46-0.82; *P* < .001)
Obadia et al. MITRA - FR 2018[16]	RCT	MitraClip	304	M-TEER Optimal medical therapy	24 months	1. At 12 months, the rates of cardiac death or HF-related hospitalization were similar across the groups: 54.6% in the intervention group and 51.3% in the control group (OR, 1.16; 95%CI, 0.73-1.84; *P* = .53) 2. Mortality rates were 24.3% vs 22.4%, respectively (HR, 1.11; 95%CI, 0.69-1.77), while HF-related hospitalization rates were 48.7% vs 47.4%, respectively (HR, 1.13; 95%CI, 0.81-1.56)

95%CI, 95% confidence interval; HF, heart failure; HR, hazard ratio; M-TEER, mitral transcatheter edge-to-edge repair; OR, odds ratio.

Table 3. Echocardiographic baseline characteristics

Baseline characteristics	RESHAPE-HF2[14]		COAPT[15]		MITRA-FR[16]	
	Device group	Control group	Device group	Control group	Device group	Control group
Severity MR Grade 3+, n,% (n)	141 (56.4) (250)	141(55.3) (255)	148 (49.0) (302)	172 (55.3) (312)	–	–
Severity MR Grade 4+, n,% (n)	109 (43.6) (250)	114 (44.7) (255)	154 (51.0) (302)	139 (44.7) (312)	–	–
LVEF, % (n)	32 (26-37) (250)	31 (25-37) (255)	31.3 ± 9.1 (302)	31.3 ± 9.6 (312)	33.3 ± 6.5	32.9 ± 6.7
LVEDV, mL (n)	137 (100-173) (250)	140 (104-176) (255)	135.5 ± 56.1 (302)	134.3 ± 60.3 (312)	–	–
LVEDV, mL (n)	200 (153-249) (250)	206 (158-250) (255)	194.4 ± 69.2 (302)	191.0 ± 72.9 (312)	136.2 ± 37.4	134.5 ± 33.1
LVESD, cm (n)	5.8 (5.3-6.5) (250)	5.9 (5.3-6.4) (255)	5.3 ± 0.9 (302)	5.3 ± 0.9 (312)	–	–
LVEDD, cm (n)	6.9 (6.3-7.6) (250)	6.8 (6.4-7.5) (255)	6.2 ± 0.7	6.2 ± 0.8	–	–
EROA, cm^2 (n)	0.23 (0.20-0.30) (250)	0.23 (0.19-0.29) (255)	0.41 ± 0.15	0.40 ± 0.15	0.31 ± 10*	0.31 ± 11*
Regurgitant volume, mL (n)	35.4 (28.9-43.9) (250)	35.6 (28.2-42.5) (255)	–	–	45 ± 13	45 ± 14

EROA, effective regurgitant orifice area; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation.
RESHAPE-HF2 data express median and interquartile range [IQR] in the COAPT trial. MITRA-FR data express median ± standard deviation.
* This data was originally expressed in mm^2 and has been converted to standardized meditation.

Outcomes

HF-related hospitalization

The analysis of this outcome showed a significant reduction, with a RR of 0.71 (95%CI, 0.56-0.90; *P* = .004). However, substantial heterogeneity was observed, with an I^2 value of 79%. Considering the differences in the MITRA-FR study population, we conducted an exploratory analysis excluding this trial. Results still demonstrated a significant reduction in the risk of hospitalization, with a RR of 0.63 (95%CI, 0.55-0.72, *P* < .00001), along with a marked improvement in heterogeneity (I^2 = 0%). Of note, this finding is exploratory and should be interpreted with caution.

The analysis, including all studies, is shown in figure 3A, and the exploratory analyses are shown in figure 3B. Furthermore, we analyzed HR for this endpoint and, given the limited number of studies, we conducted a sensitivity analysis using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method; all these analyses are provided in the supplementary data (figures S1-S4).

All-cause mortality

The RR for all-cause mortality was 0.80 (95%CI, 0.63–1.02; *P* = .07). However, substantial heterogeneity was observed across the studies (I^2 = 56%). In the exploratory analysis, a significant reduction in mortality was found, with an RR of 0.71 (95%CI, 0.59–0.86; *P* = .0005) and no heterogeneity across the studies (I^2 = 0%). The analyses, including all studies, are shown in figure 3C, and the exploratory analysis in figure 3D.

Both the HR analysis and the sensitivity analysis are provided in the supplementary data (figures S5-S8).

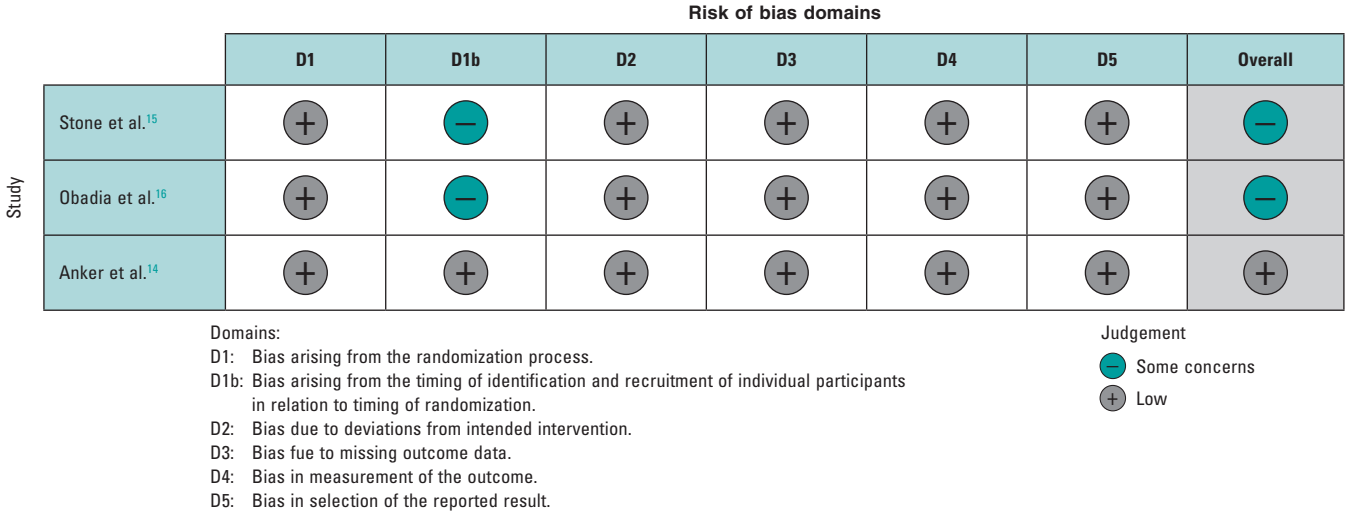

Figure 2. Risk of bias for each included randomized clinical trial. The bibliographical references mentioned in this figure correspond to Stone et al.,[14] Obadia et al.,[15] and Anker et al.[16].

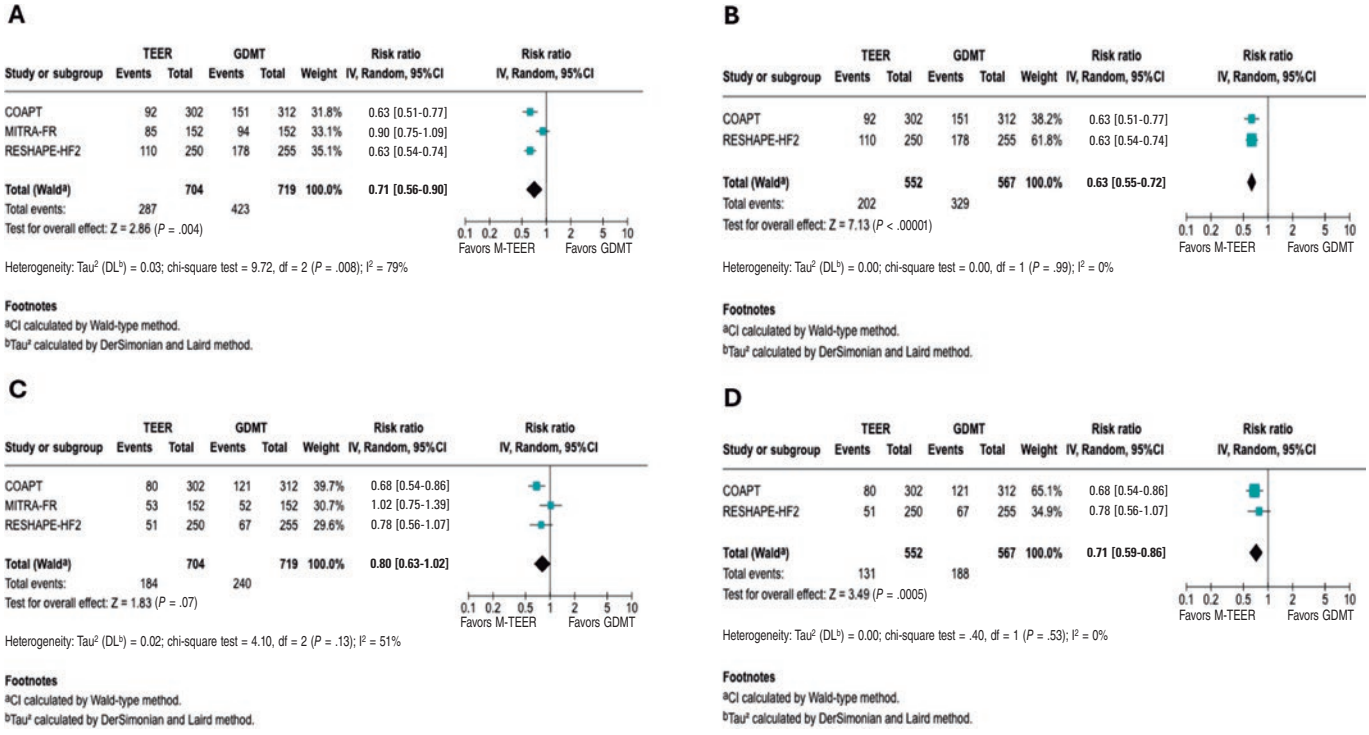

Figure 3. Forest plot of risk ratios (RR). Lines denote the 95% confidence intervals (95%CI) for each trial. **A:** forest plot of RR for HF related hospitalization. **B:** forest plot of exploratory RR for HF-related hospitalization. **C:** forest plot of RR for all-cause mortality. **D:** forest plot of exploratory RR for all-cause mortality. 95%CI, 95% confidence interval; GDMT, guideline directed medical therapy; M-TEER, mitral transcatheter edge-to-edge repair. The bibliographical references mentioned in this figure correspond to Stone et al.,[14] Obadia et al.,[15] and Anker et al.[16].

Cardiac death

The RR for death from cardiovascular causes was 0.81 (95%CI, 0.62–1.06, $P = .12$), with low to moderate heterogeneity ($I^2 = 48\%$). In the exploratory analysis, a significant reduction in cardiac death was observed, with an RR of 0.74 (95%CI, 0.55–1.00; $P = .05$) and low heterogeneity ($I^2 = 41\%$). The analyses, including all studies, are shown in figure 4A, while the exploratory analysis, in figure 4B. The sensitivity analysis and HR results are provided in the supplementary data (figures S9-S12).

NYHA FC

In this analysis of the NYHA FC, we observed that patients undergoing M-TEER are more likely to be found in NYHA FC I/II at 12 months, with a RR 1.26 (95%CI, 1.06–1.50; $P = .010$), respectively. Of note, the high heterogeneity ($I^2 = 72\%$). Furthermore, it is also essential to note that the NYHA FC is a subjective classification, which is why the findings of this outcome should be interpreted with caution. These results are shown in figure 4C.

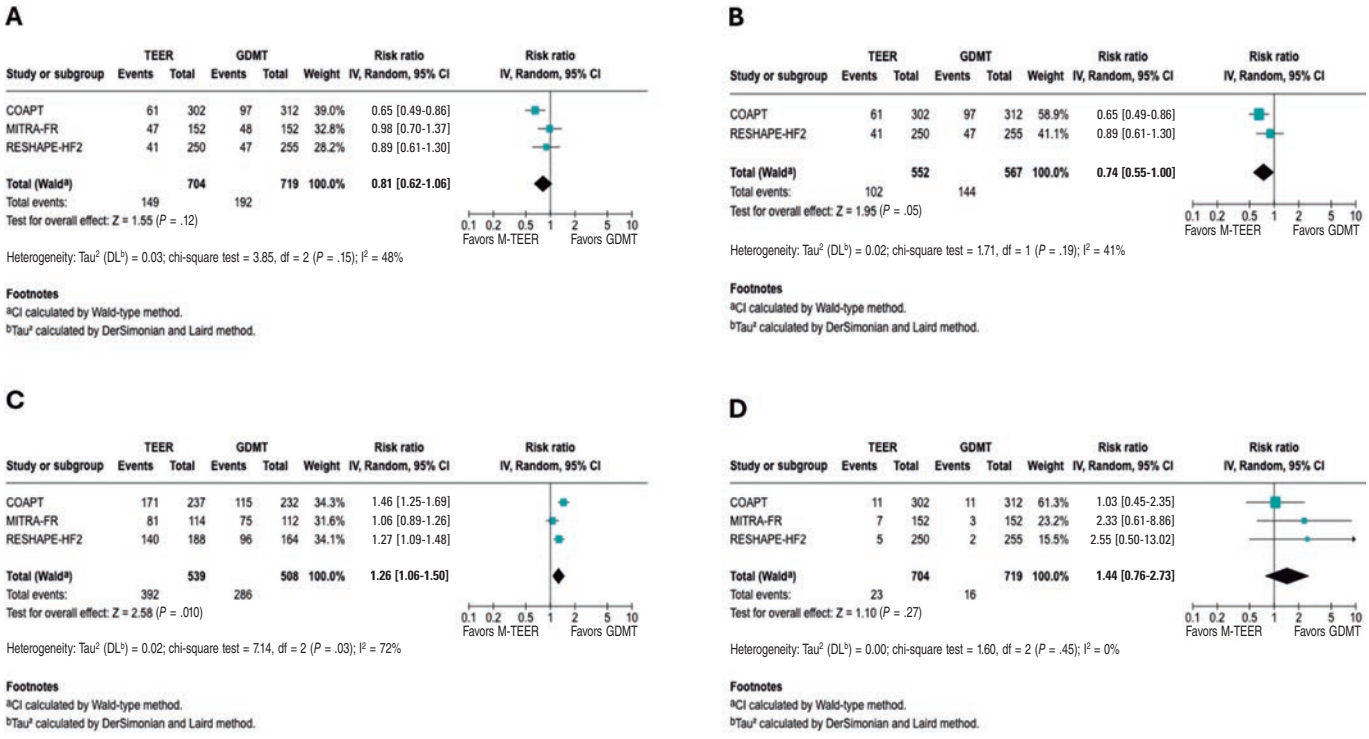

Figure 4. Forest plot of risk ratio (RR). **A:** forest plot of RR for cardiac death. **B:** forest plot of exploratory RR for cardiac death. **C:** forest plot of RR of NYHA FC I/II at 1 year. **D:** forest plot of RR for stroke. 95%CI, 95% confidence interval; GDMT, guideline directed medical therapy; M-TEER, mitral transcatheter edge-to-edge repair. The bibliographical references mentioned in this figure correspond to Stone et al.,[14] Obadia et al.,[15] and Anker et al[16]. Lines denote the 95%CI for each trial.

Stroke

There were no statistical differences between M-TEER and optimal medical therapy regarding stroke, with a RR of 1.44 (95%CI, 0.76 - 2.73, $P = .27$) without any heterogeneity being reported across the studies ($I^2 = 0\%$). These results are shown in figure 4D.

Myocardial Infarction

Regarding the risk of myocardial infarction, our analysis demonstrated no statistical difference between the M-TEER and optimal medical therapy groups (RR, 0.83; 95%CI, 0.43-1.61; $P = .58$). No heterogeneity among the studies was observed ($I^2 = 0\%$); this finding is shown in supplementary data (figure S13).

Exploratory analysis by severity

We conducted an exploratory analysis stratified by the baseline grade of mitral regurgitation. Data on the composite endpoint of all-cause death or HF-related hospitalization were available according to MR grade. For patients with MR 3+, the RR was 0.75 (95%CI, 0.56-1.00; $P = .05$; $I^2 = 12\%$). For those with severe MR 4+, data were available only from the RESHAPE-HF2 and COAPT trials, yielding a RR of 0.55 (95%CI, 0.42-0.73; $P = .0001$; $I^2 = 0\%$). This finding is shown in the supplementary data (figure S14 to figure S15).

DISCUSSION

Our meta-analysis provides an evaluation of 3 major RCTs, COAPT[15], MITRA-FR[16], and RESHAPE-HF2[14], evaluating M-TEER plus GDMT vs GDMT alone in patients with secondary MR. In patients with persistent symptoms despite adequate GDMT and who do not meet the criteria for definitive surgical replacement, mitral M-TEER has emerged as a promising alternative. In this updated meta-analysis, no statistically significant effect on all-cause mortality was found; however, the marked between-trial heterogeneity suggests that M-TEER provides meaningful clinical benefit when used in appropriately selected patients.

Our study showed that heterogeneity of results was mainly driven by MITRA-FR. COAPT and RESHAPE-HF2 have multiple similar differences compared with MITRA-FR, as evidenced in trial cohort baseline characteristics, methods, and outcome directions. This is better portrayed by an exploratory analysis comparing COAPT and RESHAPE-HF2 results, showing a 37% reduction in the risk of HF-related hospitalization risk and a 32% reduction in cardiac death (figure 3). The overall neutral mortality rate resulting from our study may be driven by heterogeneity across trials rather than a lack of intrinsic therapeutic benefit.

Among the main differences across trials, the MITRA-FR trial had broader inclusion of patients with tricuspid regurgitation, advanced LV remodeling, greater dilation, and smaller EROA vs the other 2 trials. Another key source of heterogeneity was baseline MR severity. COAPT and RESHAPE-HF2 primarily enrolled patients with grade 3+ and 4+ MR, whereas MITRA-FR is only focused on grade 4+, which may contribute to the observed outcome differences. In our exploratory analysis by MR grade, data showed consistent trends favoring M-TEER; however, these findings should be interpreted with caution due to limited subgroup data.

As proposed by Paul et al.,[19] one strategy to evaluate secondary MR is to consider the proportion between EROA and LVEDV. In

the MITRA-FR trial, many patients had smaller EROA with markedly dilated ventricles, a phenotype in which GDMT may have more impact than valve proceduren. In the COAPT and RESHAPE-HF2 trials, a greater proportion of patients had large EROA relative to the LVEDV,[20] making MR a primary driver of symptoms and outcomes, and, therefore, with potential for greater benefit from M-TEER.

In the trial-level subgroup analyses, the COAPT[15] and RESHAPE-HF2[14] trials reported no significant interaction between treatment assignment and ischemic vs non-ischemic etiology, which indicates consistency of benefit across etiologies. Similarly, the MITRA-FR[16] did not identify significant heterogeneity regarding etiology across prespecified subgroups. This suggests that ischemic vs non-ischemic alone should not be used to decide the treatment option in secondary MR. Instead, clinical decisions should prioritize other factors, such as the MR severity, the degree of LV dysfunction, symptom burden, and response to optimal medical therapy.[21]

Furthermore, differences between trials in procedural success are noteworthy, defined as achieving MR ≤ 2+. This was substantially lower in the MITRA-FR (75.6% MR ≤ 2+ at discharge) vs the COAPT (94.8% MR ≤ 2+ at 12 months) and the RESHAPE-HF2 (90.4% MR ≤ 2+ at 12 months). Multiple reasons could have influenced such differences; for instance, operator experience requirement in MITRA-FR (≥ 5 prior MitraClip cases) vs the high-volume and more experienced centers from the other trials. Similarly, post-approval data from the U.S. SSTS/ACC TVT Registry[22] demonstrated > 90% MR reduction to ≤ 2+ and survival rates consistent with trial outcomes, underscoring the reproducibility of clinical benefit in experienced centers. Furthermore, device technology is a main contributor to these differences, from first-generation clips in MITRA-FR, to second-generation in COAPT, to the fourth-generation in RESHAPE-HF2 with independent leaflet grasping and wider arm options, potentially explaining discrepant clinical results regarding MR durability and outcomes. Lastly, GDMT implementation differed across trials. MITRA-FR was conducted before the widespread use of ARNI and SGLT2 inhibitors; COAPT was conducted before the adoption of SGLT2 inhibitors; and RESHAPE-HF2 reflects the contemporary use of quadruple therapy.

Despite the differences in patient phenotypes across the trials, in many developing countries, access to transcatheter valve procedures remains limited, primarily due to their high cost and the need for specialized infrastructure.[23,24] The pronounced disparities in access to cutting-edge technologies, coupled with the centralization of these procedures in a few urban centers or high-specialty hospitals, a phenomenon observed even in high-income countries such as the United States, leave a substantial portion of the population without viable treatment options.[25] Consequently, the most impactful and broadly deployable intervention in these regions remains rigorous GDMT optimization and provider education. Nevertheless, patient phenotyping should still be performed to identify those who may potentially have an outsized benefit from future M-TEER referrals.

By integrating trial-level population characteristics with clinical outcomes, our work bridges the gap between isolated trial findings and real-world patient selection, thus offering a potential framework for future prospective studies and for refining guideline criteria. While the results from our study must be interpreted with caution, they provide hypothesis-generating evidence supporting the concept that patient selection, particularly considering the balance between EROA and LVEDV and GDMT optimization, may be critical to optimizing the benefit of M-TEER in secondary MR. This approach moves beyond the broad application of current guideline recommendations and points toward a more individualized strategy in which anatomical and functional parameters guide intervention.

Limitations

The primary limitation of this study lies in the heterogeneity of the populations enrolled in the randomized controlled trials, as evidenced by the I^2 observed in the analyses, which may influence the overall results. Second, differences in MR severity across trials represent a key limitation. While the COAPT and RESHAPE-HF2 trials mainly included patients with MR grade 3+ or 4, MITRA-FR enrolled a more severe grade, which may partly explain divergent results. Lastly, an individual patient-level meta-analysis could not be conducted due to lack of data; this level of analysis would further increase statistical power, especially in subgroup analyses, enhancing the robustness and generalizability of the findings.

CONCLUSIONS

In this meta-analysis, M-TEER plus GDMT shows a lower risk of HF-related hospitalization vs GDMT alone. We did not find any differences in the risk of all-cause mortality, cardiac death, stroke, or myocardial infarction.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This meta-analysis was performed using data from previously published studies. As it is based entirely on secondary data, no new data were collected from human or animal participants; on the other hand, the use of SAGER guidelines was not applicable in this study. All included studies were approved from the relevant center ethics committees. The authors confirm that all data utilized were publicly accessible, and no confidential information was used without proper authorization.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

During the preparation of this work, the authors used ChatGPT 4o to review the document's syntax and grammar. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

AUTHORS' CONTRIBUTIONS

D. Paulino-González: conceptualization; formal analysis, writing, review, and editing. A.L. García-Loera: methodology, investigation, writing, review, and editing. D.A. Navarro-Martínez: methodology, formal analysis. M.A. Pardiño-Vega: writing, review, and editing, supervision. K.P. Zúñiga-Montaño: investigation, writing, review, and editing.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Mitral regurgitation is a prevalent condition that negatively affects the patients' quality of life. M-TEER-has emerged as an alternative therapeutic option for patients who are ineligible for surgery. However, its benefit remains

unclear vs GDMT, as clinical trials evaluating this procedure have reported disparate results, with benefit in primary outcomes observed in the COAPT trial and in the recently published RHESAPE-HF2 trial, but not in the MITRA-FR trial; discrepancy in the results requires further study.

WHAT DOES THIS STUDY ADD?

– This meta-analysis provides a comprehensive evaluation of the evidence comparing M-TEER plus GDMT vs GDMT alone in secondary mitral regurgitation. Our findings confirm that M-TEER is associated with a significant reduction in HF-related hospitalizations. Of note, by examining trial populations in detail, we highlight how patient selection influences outcomes: in studies enrolling patients with less ventricular dilation and lower biomarker levels of congestion (such as the COAPT and RESHAPE-HF2 trials), M-TEER was associated with additional benefits in cardiac death and all-cause mortality. These results underscore the potential role of anatomical and functional parameters, such as the balance between EROA and LVEDV, in identifying patients most likely to benefit from this procedure.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M25000558.

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Original article

Design of the LUDICO study: effectiveness and safety of coronary laser in undilatable or uncrossable lesions

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ABSTRACT

Introduction and objectives: Excimer laser coronary atherectomy (ELCA) is increasingly used in complex percutaneous coronary interventions (PCI), particularly in cases of "balloon failure," which includes both uncrossable and undilatable coronary artery lesions. Although these 2 scenarios represent distinct technical and clinical challenges, they are usually evaluated using the same safety and efficacy endpoints. As a result, there is a lack of specific evidence on the safety and efficacy profile of ELCA in each of these situations. Furthermore, the role of intracoronary imaging in optimizing ELCA use remains insufficiently defined.
Methods: This will be an investigator-initiated, multicenter, single-arm, open-label, prospective observational study. Patients with an indication for PCI and undilatable (non-compliant balloon dilatation < 80% at burst pressure) or uncrossable (uncrossable with a "small-profile balloon" with adequate support, left to the operator's discretion) coronary artery lesions treated with ELCA will be included. Intravascular imaging will be highly advised and analyzed in a core laboratory. Device success, angiographical success, procedural success, clinical success and related complications will be evaluated. Patients will be postoperatively followed for 1 year and clinical events will be recorded.
Conclusions: The LUDICO study will be a multicentre, prospective study of ELCA therapy in uncrossable or undilatable coronary lesions. The study aims to evaluate the safety and efficacy profile of ELCA in these lesions as well as the clinical results at the 1 year follow-up in this setting. (ClinicalTrials.gov: NCT07206082).

Keywords: Percutaneous coronary intervention. Excimer laser coronary atherectomy. Intravascular imaging. Optical coherence tomography. Complex coronary intervention.

Diseño del estudio LUDICO: eficacia y seguridad del láser coronario en lesiones no dilatables o no cruzables

RESUMEN

Introducción y objetivos: La aterectomía coronaria con láser de excímeros (ELCA) se utiliza cada vez más en intervenciones coronarias percutáneas (ICP) complejas, en particular en caso de «fallo del balón», que incluye tanto lesiones coronarias no cruzables como no dilatables. Aunque estos 2 escenarios representan desafíos técnicos y clínicos distintos, con frecuencia se han evaluado utilizando los mismos criterios de efectividad y seguridad. Como resultado, existe una falta de evidencia específica sobre la seguridad y la efectividad de la ELCA en cada una de estas situaciones. Además, el papel de la imagen intracoronaria en la optimización del uso de la ELCA sigue estando insuficientemente descrito.

[◊] These authors contributed to the study equally and share first authorship.

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Métodos: Se trata de un estudio observacional prospectivo, abierto, multicéntrico e iniciado por los investigadores. Se incluirán pacientes con indicación de ICP y lesiones coronarias no dilatables (dilatación con balón no distensible < 80% a presión de ruptura) o no cruzables (no cruzables con un balón de bajo perfil y adecuado soporte, a criterio del operador) tratados con ELCA. Se recomendará el uso de imagen intravascular, que se analizará en un laboratorio central. Se evaluarán el éxito del dispositivo, el éxito angiográfico, el éxito del procedimiento, el éxito clínico y las complicaciones asociadas. Se seguirá a los pacientes durante 1 año tras el procedimiento y se registrarán los eventos clínicos.
Conclusiones: El estudio LUDICO será un estudio prospectivo y multicéntrico sobre el uso de ELCA en lesiones coronarias no cruzables o no dilatables. Su objetivo es evaluar la efectividad y la seguridad de la ELCA en estas situaciones, así como los resultados clínicos durante un seguimiento de 1 año. (ClinicalTrials.gov: NCT07206082).

Palabras clave: Intervención coronaria percutánea. Aterectomía coronaria con láser de excímeros. Imagen intravascular. Tomografía de coherencia óptica. Intervención coronaria compleja.

Abbreviations

ELCA: excimer laser coronary angioplasty. **IVUS:** intravascular ultrasound. **OCT:** optical coherence tomography. **PCI:** percutaneous coronary intervention. **RA:** rotational atherectomy.

INTRODUCTION

Excimer laser coronary atherectomy (ELCA) has been applied since the 1980s in multiple anatomical and clinical settings, with several studies supporting its safety and efficacy profile.[1,2] Common indications include in-stent restenoses, stent underexpansion, calcified coronary lesions, saphenous vein graft stenoses, thrombotic lesions, bifurcations, and chronic total coronary occlusions.[3-14] In practice, however, ELCA is predominantly used in the setting of balloon failure–specifically uncrossable and undilatable coronary artery lesions. However, historical studies have typically applied a uniform definition of device success across both lesion types, potentially overlooking important nuances that could influence outcomes and therapeutic decision-making.

Furthermore, despite growing recognition of the value of intracoronary imaging in optimizing complex percutaneous coronary intervention (PCI),[15] prior ELCA studies have largely underutilized this tool, limiting insight into the mechanisms of success or failure in balloon-resistant lesions.

The safety and efficacy profile of coronary laser in undilatable and uncrossable lesions (LUDICO) study is a real-world, observational study designed to evaluate the use of ELCA specifically in cases of balloon failure. The study has 2 primary objectives: *a)* to refine the definition of ELCA procedural success based on the type of balloon failure encountered—distinguishing between uncrossable and undilatable lesions—, and *b)* to emphasize the critical role of intracoronary imaging in guiding ELCA and interpreting procedural outcomes. By addressing these critical gaps, the study aims to provide a more precise and and clinically meaningful framework for the contemporary use of ELCA in complex coronary interventions.

METHODS

Study design and population

This is a prospective, multicentre, observational study including consecutive patients undergoing ELCA in undilatable (expansion < 80% of the distal vessel diameter after inflation of a 1:1 non-compliant balloon at 18 atm) and uncrossable coronary artery lesions (uncrossable after using a small-profile balloon with adequate support left to the operator's discretion). At least 15 national centers will be contacted to participate in the study. Participant centers will be required to have experience with ELCA and complex PCI, with a minimum of > 5 prior ELCA cases performed. Inclusion and exclusion criteria are described in table 1. This study was conducted in full compliance with the STROBE guidelines for observational studies.[16] The study protocol was registered in ClinicalTrials.gov (NCT07206082).

Procedure

PCI will be performed in accordance with current clinical practice guidelines on coronary revascularization.[15,17]

In uncrossable lesions, following successful guidewire passage and failed balloon crossing, ELCA will be performed (as described in the following section). PCI will be completed with optional predilatation at the operator's discretion, followed by stenting or drug-coated balloon implantation. Intravascular imaging [preferably with optical coherence tomography (OCT)] will be recommended after laser application to characterize the lesion substrate and evaluate the effect of the laser and at the end of the procedure.

In undilatable lesions, if balloon dilation is inadequate, an initial intracoronary imaging assessment will be conducted. Afterwards, laser atherectomy will be performed, followed by a second intracoronary imaging assessment to evaluate the effects of ELCA on the lesion. PCI will, then, be completed with balloon dilation and stenting or drug-coated balloon implantation, at the operator's discretion. A third intracoronary imaging pullback will be performed to assess the final procedural outcome (figure 1).

Laser atherectomy technique

ELCA procedure will be performed using the Spectranetics CVX300 (Spectranetics, United States) and the latest generation Philips Laser System Excimer (Philips, United States) System, which is based on pulsed xenon-chlorine laser catheters capable of delivering excimer energy (wavelength, 308 nm; pulse length, 185 ns) from 30 mJ/mm^2 to 80 mJ/mm^2 (fluencies) at pulse repetition rates of 25 Hz to 80 Hz.

The ELCA technique will be performed according to current recommendations.[18] The choice of laser catheter size will be left to the operator's discretion, selecting among the available rapid-exchange

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients ≥ 18	Patients with known allergies to ASA, clopidogrel, prasugrel, or ticagrelor
Patients with either stable coronary artery disease or acute coronary syndromes as the clinical presentation	Patients unable to provide informed consent, either personally or through a legal representative
Patients with severe coronary lesions (> 70% by visual estimation) in native vessels or coronary bypass grafts	Patients with clinical or hemodynamic instability defined as: sustained hypotension (SBP ≤ 90 mmHg for ≥ 30 minutes or use of pharmacological, or mechanical support to maintain an SBP ≥ 90 mmHg) or evidence of end-organ hypoperfusion including urine output of < 30 mL/h, cool extremities, altered mental status, or serum lactate > 2.0 mmol/L
"Uncrossable" coronary lesions (eg, lesions that cannot be crossed with a 0.7:1 balloon after successful guidewire passage) or "Undilatable" lesions (eg, those in which balloon dilation with a 1:1 non-compliant balloon at 18 atm results in < 80% expansion relative to the distal reference vessel diameter; this group includes both de novo lesions and in-stent restenosis or underexpanded stents)	Patients with significant comorbidities and a life expectancy of < 1 year

ASA, acetylsalicylic acid; SBP, systolic blood pressure.

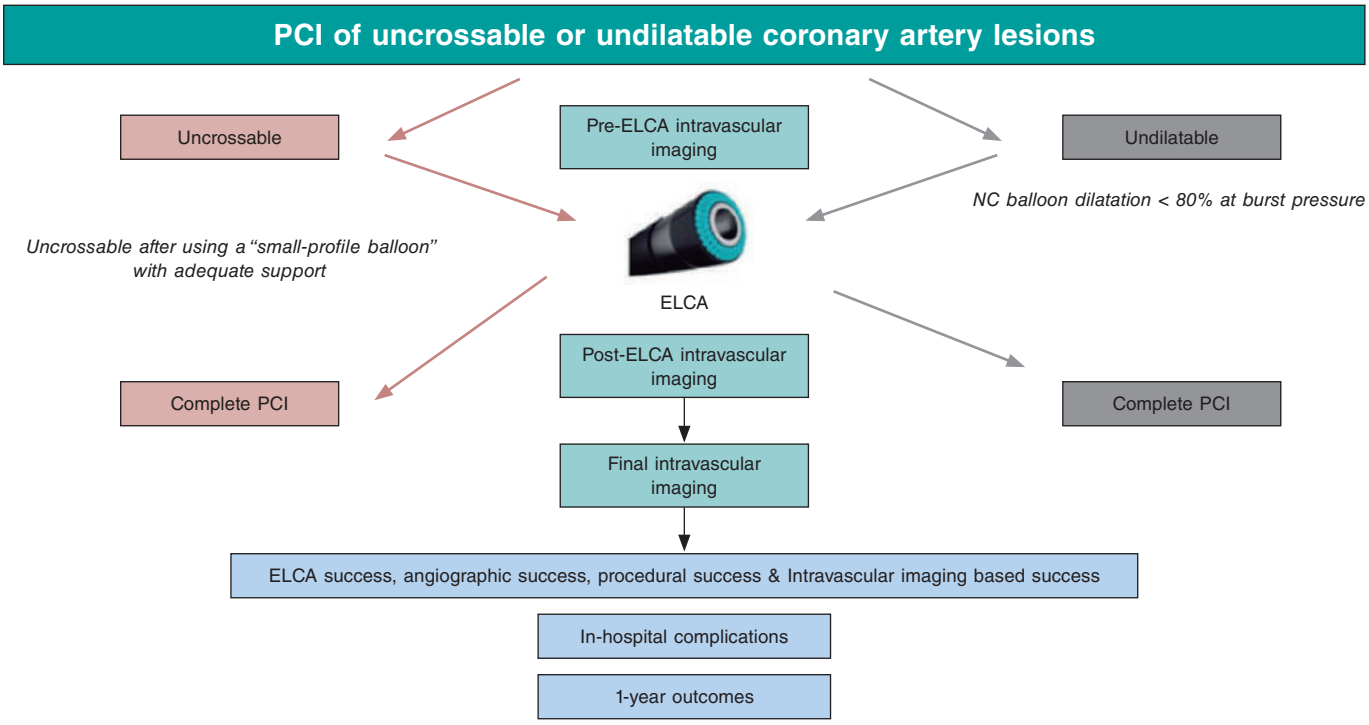

Figure 1. Central illustration. LUDICO study flowchart. ELCA, excimer laser coronary atherectomy; NC, non-compliant; PCI, percutaneous coronary intervention.

concentric probes (0.9 mm, 1.4 mm, 1.7 mm, or 2.0 mm). The selection of fluence, and repetition rate will be left to the operator's discretion. A saline infusion technique will be recommended, although application of laser with blood or contrast will be recommended in resistant lesions. In the event of unsuccessful initial therapy, additional plaque modification techniques may be employed at the operator's discretion and will be thoroughly recorded and described.

Clinical definitions and follow-up

Laser success will be defined differently for uncrossable and for undilatable lesions. For the former, laser success will be defined as the ability of the laser catheter to cross the lesion. Laser success will also be considered in cases where the laser catheter cannot cross the lesion but proximal laser application permits subsequent balloon crossing. For the latter, laser success will be defined as successful balloon dilation (sized 1:1 to the vessel diameter), with adequate expansion (> 80% in 2 orthogonal projections) following laser therapy without the need for other plaque modification technique.

Angiographic success will be defined as Thrombolysis in Myocardial Infarction (TIMI) grade-3 final flow and a percent diameter stenosis < 20%. Procedural success will be defined as angiographic success without severe procedural complications (death, coronary perforation, abrupt vessel closure, flow-limiting dissection).

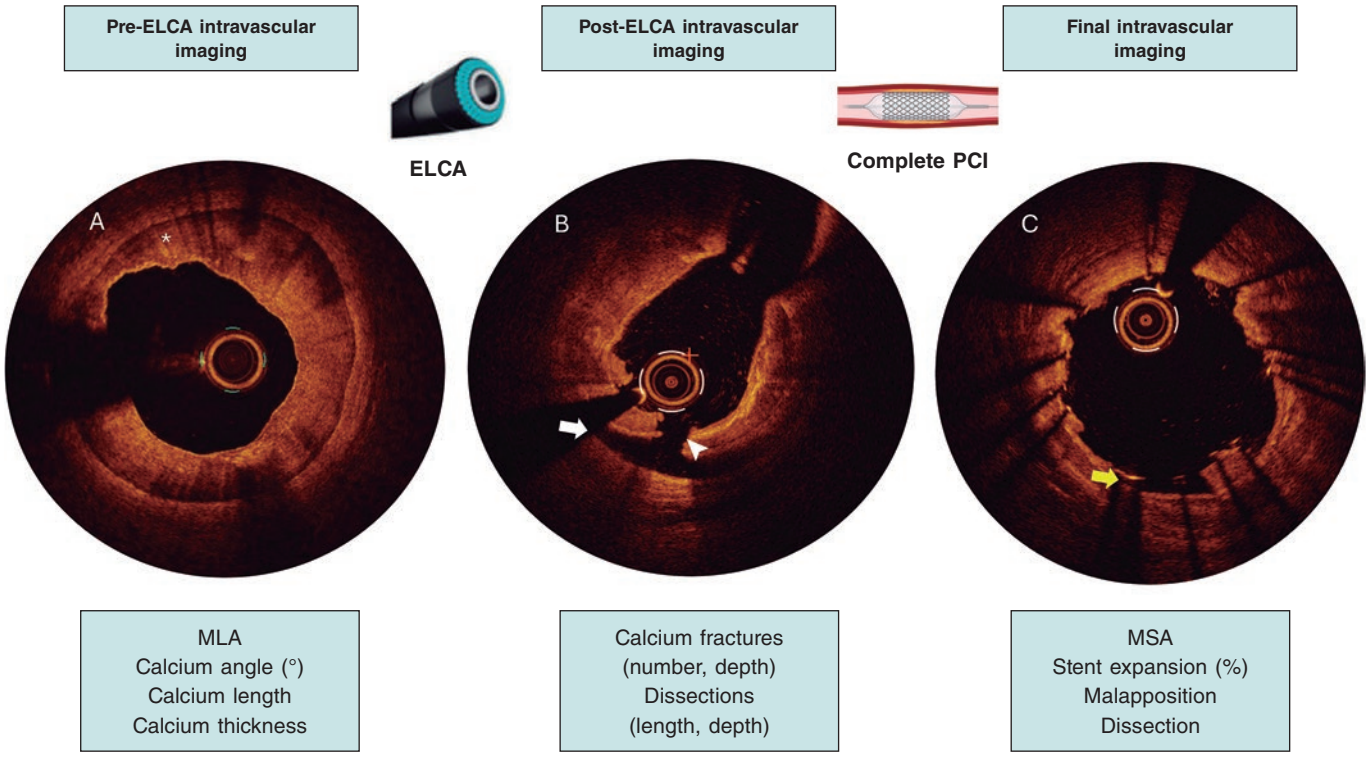

Figure 2. Example of the advised intracoronary imaging assessment in LUDICO study. **A**: baseline optical coherence tomography (OCT) image of a severely calcified lesion. The asterisk points to a calcium arc of 360° with a maximum thickness of 0.9 mm. **B**: OCT image after ELCA with contrast media. White arrow points to a dissection. The white arrowhead points to a deep calcium fracture. **C**: results after stenting. The yellow arrow points to a small area of malapposition. ELCA, excimer laser coronary atherectomy; MLA, minimal lumen area; MSA, minimal stent area; PCI, percutaneous coronary intervention.

Intracoronary imaging-based success will be defined as a stent expansion ≥ 80% (OCT or intravascular ultrasound [IVUS]) or a minimal stent area (MSA) ≥ 4.5 mm^2 in OCT or ≥ 5.5 mm^2 in IVUS.

Intracoronary imaging

Intracoronary imaging will aim to describe the lesion characteristics and identify potential predictors of adequate stent expansion and procedural result. Therefore, intracoronary imaging will be highly recommended and the advised imaging modality will be OCT as its better spatial resolution vs IVUS allows better tissue characterization, plaque modification assessment and visualization of stent failure etiologies.[19] A baseline intracoronary imaging evaluation is recommended, when possible, to describe the lesion characteristics and identify potential predictors of ELCA success or failure. Additionally, a second intracoronary imaging run is strongly advised immediately after laser therapy. This second run aims to describe the effect of ELCA in the coronary plaque. Evaluating and characterizing changes in the coronary plaque might help guide the optimal ELCA result and allow appropriate adjustment of therapy settings (fluence, repetition rate and infusion characteristics). Finally, a postoperative intravascular imaging run is strongly recommended once the final angiographic result is achieved. All intracoronary imaging data will be analyzed by a core laboratory. In the baseline intracoronary imaging run, lesion characteristics will be described as follows: minimum lumen area (MLA), minimum and maximum lumen diameter, lesion length, calcification angle, calcification thickness. In the post-ELCA imaging run the following parameters will be evaluated: MLA, number of calcium fractures and characteristics, presence of dissection, including its angle and length. In the final imaging run, MSA, stent apposition and dissections will be described. In both OCT and IVUS assessments, a dual-reference approach will be used: the proximal and distal reference lumen diameters will be identified, and MSA will be divided by each of these diameters separately. The final stent expansion index will be calculated as the mean of the 2 resulting values. Second, the tapered mode is only available in OCT: reference lumen profile is estimated based on the distal and proximal reference frame mean diameter and side branch mean diameter in between. With stent lengths > 50 mm, the dual method is preferred. With stent lengths < 50 mm the tapered method is often used. If the dual method is used, the stent expansion percentage of both segments will be recorded with the lower value of the two measurements used for analysis. The main variables to be evaluated by intravascular imaging are summarized and graphically shown in figure 2.

Follow-up

Follow-up will be conducted at 3 different timeframes: *a)* after PCI; procedural success and complications will be thoroughly documented, and all patients will be evaluated for any postoperative events, such as chest pain, heart failure, bleeding, or ischemic events; *b)* at hospital discharge, documenting clinical status, complications and antiplatelet therapy; and *c)* 1 year after the index PCI; clinical events and antiplatelet therapy will be recorded.

The primary endpoint at the follow-up will be the composite endpoint of major adverse cardiovascular events, defined as the occurrence of cardiac death, target vessel-related acute myocardial infarction, target vessel revascularization, or definite/probable stent thrombosis. Secondary efficacy endpoints will include all-cause mortality, cardiac death, non-fatal myocardial infarction, target lesion revascularization, and target vessel revascularization.

Table 2. Procedural and clinical definitions

Procedural definitions	
ELCA success	Uncrossable: defined as the ability of the laser catheter to cross the lesion or allow subsequent crossing with a predilatation balloon following laser application
	Undilatable: defined as successful balloon dilation with adequate expansion following laser therapy
Angiographic success	Defined adequate stent implantation and expansion, with residual stenosis < 20% and TIMI grade-3 flow, without crossover to another plaque modification technique
Procedural success	Angiographic success without severe procedural complications (death, coronary perforation, abrupt vessel closure, flow-limiting dissection)
Imaging based success	Defined as a stent expansion ≥ 80% (OCT or IVUS) or a MSA ≥ 4.5 mm^2 in OCT or ≥ 5.5 mm^2 in IVUS
Severely calcified coronary lesion	Angiographically: opacification in both sides of the artery before contrast administration
	Intracoronary imaging: > 180° calcium arc or calcium thickness > 5 mm
Clinical definitions	
MACE	Defined as the occurrence of cardiac death, target vessel-related acute MI, target vessel revascularization, or definite/probable stent thrombosis
Cardiac death	According to ARC definitions:[31] – Any death due to STEMI, arrythmia, heart failure, unexpected death or death from an unknown cause – Deaths related to cardiac procedures are included – Deaths related to vascular, but not cardiac death are included as well: stroke, aortic dissection, pulmonary embolism or peripheral arterial disease
Non-fatal MI	Third universal definition of MI.[32] In addition, procedure-related myocardial infarction—defined as a troponin elevation > 5 times the upper limit of normal in patients with previously normal troponin levels, or a ≥ 20% increase in patients with previously elevated troponin levels, along with electrocardiographic changes or new areas of myocardial necrosis detected by imaging—was included
Stent thrombosis	According to ARC criteria: – Definite: angiographically confirmed (TIMI grade-0 flow or thrombus image within the stent) + evidence of ischemia – Probable: unexplained death in the first 30 days after stenting or MI in the territory of the implanted stent – Possible: unexplained death beyond 30 days after stenting or MI with ischemia in the stented territory with no angiographic confirmation of thrombus
Stroke	New neurological focal deficit with imaging confirmation and assessed by a neurologist
TLR	New coronary artery lesion in the previously treated coronary lesion including 5 mm proximal and distal to the implanted stent
TVR	New coronary artery lesion in the previously treated coronary vessel
Hemorrhage	According to BARC classification[33]

ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; ECG, electrocardiogram; ELCA, excimer laser coronary atherectomy; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MI, myocardial infarction; MSA, minimal stent area; OCT, optical coherence tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

Secondary safety endpoints will include stroke and bleeding events (classified according to the Bleeding Academic Research Consortium [BARC] criteria). Endpoint definitions are shown in table 2.

Sample size estimation

The planned sample size of 230 patients was determined based on expected device success rates reported in prior studies of ELCA for undilatable and uncrossable lesions. Assuming a conservative laser success rate of 80%, a cohort of 230 patients would yield a 95% confidence interval with a precision of approximately ± 5% (estimated range, 74.8%–85.2%), which is considered adequate for reliably estimating procedural efficacy in the routine clinical practice. Moreover, this sample size ensures sufficient statistical power to support multivariable analyses of predictors of both intraoperative and follow-up outcomes. With an anticipated 40–50 events, the study would allow the inclusion of approximately 4 to 5 covariates in multivariable regression models while maintaining acceptable model stability. Based on the expected procedural volume at each participant center and the required sample size, the recruitment period is 2 to 3 years.

Statistical analysis

Quantitative variables following a normal distribution will be expressed as mean ± standard deviation. Those not following a normal distribution will be reported using the median and minimum and maximum values. Qualitative variables will be expressed as absolute numbers and frequencies.

A significance level of 0.05 will be considered, and 95% confidence intervals will be calculated for the primary outcome variables. Normality of the data will be assessed using the Kolmogorov-Smirnov test. Based on the distribution, appropriate statistical tests will be applied to compare relevant variables. For comparisons of means, the Student *t* test for independent samples will be used, or the

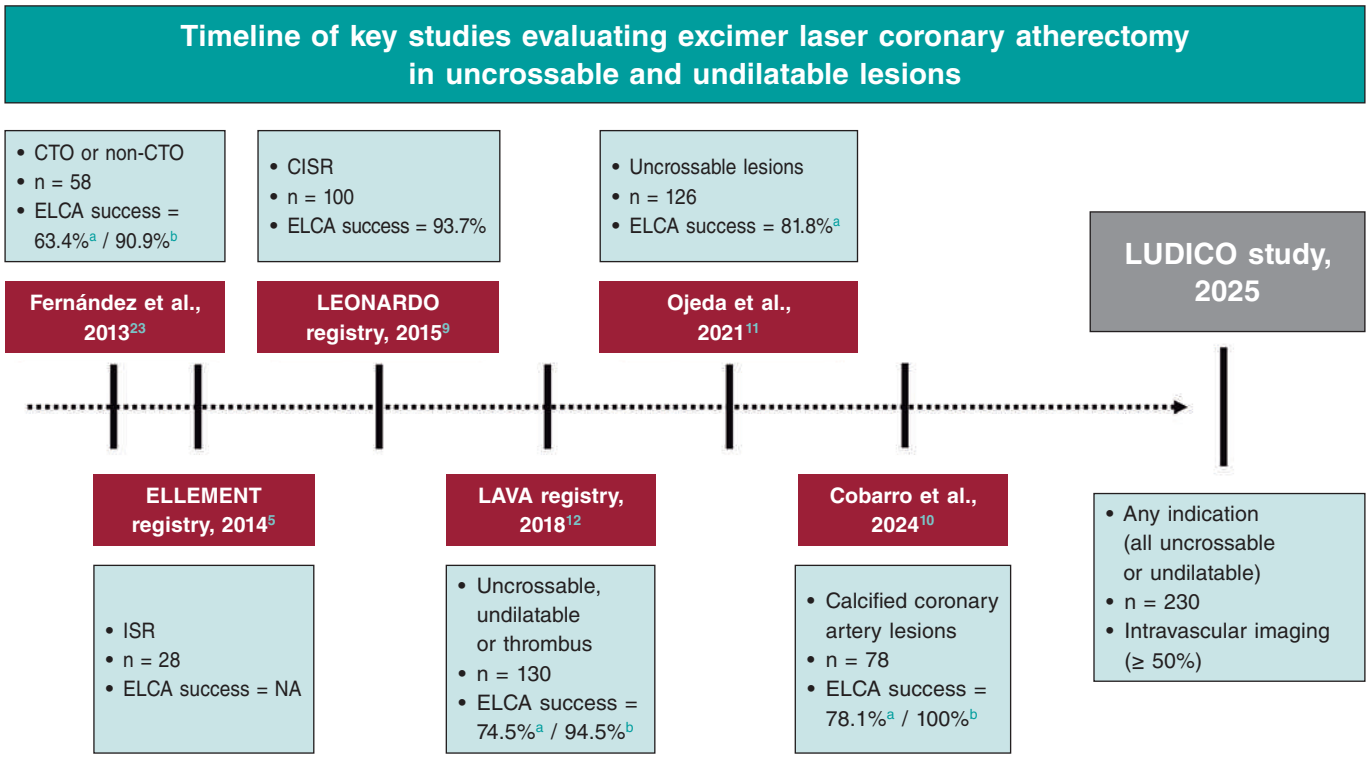

Figure 3. Timeline of key studies evaluating ELCA in uncrossable and undilatable lesions. CTO, chronic total coronary occlusion; ELCA, excimer laser coronary atherectomy; NA, not available; ISR, in-stent restenosis.
[a] Uncrossable lesions.
[b] Undilatable lesions.

non-parametric Mann-Whitney U test in case of dichotomous qualitative variables. For comparisons involving non-dichotomous qualitative variables, ANOVA or the non-parametric Kruskal-Wallis test will be employed. For bivariate analysis of qualitative variables, the chi-square test or Fisher's exact test will be used.

Multivariate analysis will be conducted using forward stepwise Cox regression analysis. Event-free survival curves will be constructed using the Kaplan-Meier method. Variables will be considered potential risk predictors in the multivariate model if they demonstrate a statistically significant association in the univariate analysis or show a trend toward significance. All statistical analyses will be conducted using Stata 16.1 (StataCorp, United States).

Ethical considerations

This study was conducted in full compliance with the principles outlined in the Declaration of Helsinki and with the International Council for Harmonization (ICH) Good Clinical Practice guidelines, including the most recent ICH E6 (R3) update. Before enrollment, patients or their legal representatives must be fully informed about the nature of the study and must provide written informed consent. The study protocol was approved by the Institutional Review Board at each participant center.

DISCUSSION

The LUDICO study will be a multicenter study to assess the safety, efficacy, and clinical outcomes of ELCA specifically in undilatable or uncrossable coronary artery lesions with lesion-specific endpoints and preferential use of intravascular imaging. We believe that this real-life approach will provide valuable insights into the 2 main clinical scenarios in which ELCA is currently used.

Three recent large registries confirmed ELCA to be a safe technique with an assumable rate of complications.[20-22] However, these studies analyzed the overall procedural performance but failed to describe the lesion specific characteristics or intravascular imaging data. The findings of studies reporting balloon failure scenarios[5,10-12,23,24] are summarized in figure 3. The LAVA multicenter registry set the main contemporary clinical indications for ELCA.[12] This registry analysed ELCA use in 130 lesions and stratified them in 3 scenarios: uncrossable, undilatable and thrombotic. The LAVA and other studies analyzing ELCA has shown good performance of ELCA in balloon-failure, with lower rates of ELCA success in uncrossable vs undilatable lesions. However, one significant limitation is present in these studies: situations of balloon-failure include undilatable, uncrossable, or lesions with both components. In the routine clinical practice, these 2 situations are distinct; however, ELCA success has often been defined uniformly, potentially confounding the real efficacy of the device. Consequently, the LUDICO study aims to address this issue by specifically defining 2 endpoints based on the type of balloon failure, uncrossable or undilatable.

Nonetheless, the definition of ELCA success in uncrossable lesions might be ambiguous in some cases. For instance, cases in which neither the ELCA catheter nor subsequent balloons are able to cross the lesion should not be considered procedurals failures if a microcatheter can subsequently cross and enable successful completion of the procedure using the RASER technique—a combination of ELCA and rotational atherectomy (RA). However, to simplify the

endpoint, we have considered this situation a crossover to RA. In contrast, for undilatable lesions, the definition of ELCA success is less prone to interpretation; however, clearly defining what constitutes an undilatable lesion remains essential. This highlights the importance of a compliance test —that is, performing an initial balloon dilatation to objectively demonstrate that the lesion cannot be adequately expanded. Such a test is critical to identify lesions that are likely to benefit from plaque modification techniques, including ELCA. Arguably, the results of some randomized controlled trials in plaque modification devices (such as ECLIPSE[25] using orbital atherectomy and ROLLERCOASTR[7] using ELCA, intravascular lithotripsy and RA) may have been influenced by the absence of "compliance test", potentially including coronary lesions in which plaque modification would not have been necessary after balloon testing, thereby reducing the differences across groups. Additionally, the recent CRATER trial showed that a total of 20.9% of patients in bailout RA group required crossover to RA because of balloon failure,[26] which highlights the high frequency of this situation and underscores the importance of its prompt identification to select the most appropriate plaque modification technique such as ELCA.

RA is the most extensively studied strategy for managing uncrossable coronary lesions, supported by wide clinical experience and robust evidence.[7,26,27] However, RA presents important limitations in specific scenarios where ELCA may offer clear advantages —such as in-stent restenosis or bifurcation lesions requiring side branch protection—given the risk of scaffold damage or distal embolization of debris.[28] Orbital atherectomy, although less studied in uncrossable lesions,[29,30] shares similar drawbacks due to its ablative mechanism. By contrast, ELCA is compatible with 6-Fr catheters, can be used over any standard guidewire, and has a less demanding learning curve.[18] Of note, while RA demonstrates limited efficacy against deep calcium, ELCA can affect both superficial and deep calcification.[4] Collectively, these features position ELCA as a uniquely valuable tool among plaque-modification techniques. Its capacity to safely treat in-stent restenosis, thrombotic lesions, uncrossable lesions, and bifurcations requiring side branch protection underscores advantages not readily attainable with RA or orbital atherectomy, thereby reinforcing ELCA as a superior alternative in selected complex PCI scenarios.

In conclusion, the use of intravascular imaging has been limited in most of the studies that have evaluated ELCA in balloon-failure, particularly those focused on uncrossable lesions. Additionally, none of these studies have described the findings of intravascular imaging before and after ELCA and identified potential predictors of success. In fact, the effect of ELCA in intravascular imaging remains an open question as there is a paucity of studies that have evaluated it and have been limited to in-stent restenosis.[4] Therefore, one of the aims of the LUDICO study is to evaluate the effects of ELCA by intravascular imaging (preferably by OCT, due to its better spatial resolution) and identify potential predictors of ELCA success or failure and its effect on the coronary plaque. We hypothesize that recognizing potential predictors in intravascular imaging could help operators guide the procedures and identify the anatomical characteristics that best predict a favourable outcome with ELCA, thereby optimizing patient selection and procedural planning.

Limitations

First, this multicentre prospective study will be conducted in a single country, which may limit the generalizability of its findings to other settings. However, these high-volume centres, with wide experience in complex PCI comply with the international recommendations and their practice is comparable to other similar centres. Second, because of to the nonblinded study design, selection bias may have occurred, whereby certain lesions, such as extremely calcified or highly complex, were preferentially treated with alternative techniques or revascularization strategies. Additionally, there will not be a control group to assess the efficacy of the ELCA therapy vs other therapies. Finally, although intracoronary imaging will be highly recommended, we foresee that the baseline evaluation will be limited to just a few cases. In fact, by definition, uncrossable lesions will rarely have a baseline evaluation. Besides, in the event of the patient having kidney disease, OCT runs could be avoided, conducting to less OCT runs, or even to the absence of intravascular imaging.

CONCLUSIONS

The LUDICO study will be a multicenter, prospective study of ELCA therapy in uncrossable or undilatable coronary artery lesions with specific success definitions for each indication. The study aims to evaluate the safety and efficacy profile of ELCA and the clinical outcomes during the follow-up. The OCT evaluation will provide insights into the effect of ELCA in this subset of coronary lesions.

FUNDING

The LUDICO study was supported by a non-restricted grant from Biomenco.

ETHICAL CONSIDERATIONS

The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki. Institutional Ethics Committee approval was obtained (institutional approval number: 5502), and all participants gave their written informed consent prior to enrolment. The confidentiality and anonymity of participants were strictly preserved throughout the study. Sex and gender considerations were addressed following the recommendations of the SAGER guidelines to ensure accurate and equitable reporting.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence assisted technologies were used exclusively to support language editing and improvement of style. No artificial intelligence tools were employed to generate, analyse, or interpret the data. The authors take full responsibility for the integrity, accuracy, and originality of the manuscript content.

AUTHORS' CONTRIBUTIONS

A. Jurado-Román and J. Zubiaur contributed to the study equally and share first authorship. A. Jurado-Román is responsible of the study conception and design. J. Zubiaur, A. Jurado-Román, and M. Basile were involved in the draft manuscript preparation. All authors reviewed the results 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; moreover, he has received consulting fees and honoraria/speaker fees from Abbott vascular, Boston Scientific, Medtronic, Terumo, and Biotronik. A. Jurado-Román reported

receiving consulting fees from Boston Scientific and Philips; honoraria/speaker fees from Abbott, Boston Scientific, Shockwave Medical, World Medica, and Philips; and serves as a proctor for Abbott, Boston Scientific, World Medica, and Philips. G. Galeote has received honoraria/speaker fees from Meril, Boston Scientific, Abbott SMT, and Biomenco. A. Gonzálvez-García has received honoraria from Abbott. J. Suárez de Lezo has received honoraria/speaker fees from Abbott and Philips. F. Hidalgo has received honoraria/speaker fees from Philips. M. Basile reported receiving consulting fees and speaking fees from Iberhospitex. B. Garcia del Blanco disclosed his role as a proctor for Edwards Lifescienses and his participation on the Advisory Board of Iberhospitex. All other authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- ELCA has demonstrated its usefulness across several challenging lesion subsets, including in-stent restenosis, stent underexpansion, calcified plaques, saphenous vein graft disease, thrombotic lesions, bifurcations, and chronic total coronary occlusions.
- However, in real-world practice, its main indication remains balloon failure, particularly in lesions that are either uncrossable or undilatable.
- Despite this, most earlier studies applied a uniform definition of device success for these distinct scenarios, potentially missing clinically relevant nuances that may affect outcomes and guide treatment strategies.

WHAT DOES THIS STUDY ADD?

- The LUDICO study is designed as a multicenter investigation to evaluate the safety, efficacy, and clinical outcomes of ELCA specifically in undilatable or uncrossable coronary artery lesions, incorporating individualized endpoints for each subset and emphasizing the use of intravascular imaging.
- This real-world strategy is expected to yield meaningful insights into the 2 primary clinical situations in which ELCA is currently employed: uncrossable and undilatable coronary artery lesions.

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Original article

Clinical utility of thrombus aspiration using the Hunter catheter in patients with acute myocardial infarction: the Hunted registry

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ABSTRACT

Introduction and objectives: Manual thrombectomy (MT) during primary percutaneous coronary intervention (PCI) aims to reduce thrombus burden. Our study evaluates the outcomes and predictors of successful MT.
Methods: The Hunted registry is a retrospective, single-center cohort study including patients who underwent MT during PCI using the Hunter catheter from July 2020 through February 2022. MT success was defined as an angiographic reduction to a Thrombolysis in Myocardial Infarction (TIMI) thrombus grade of ≤ 2, with clinical follow-up for major adverse cardiovascular events.
Results: Among 750 patients with acute myocardial infarction who underwent PCI, 401 (53%) received MT. The mean age of treated patients was 62 years (80% men). MT was effective in 327 patients (81.55%). Predictors of successful MT included larger vessel diameter ($P < .001$), high thrombus burden (TIMI grade ≥ 4 flow; $P < .001$), and non-circumflex target vessels ($P < .001$). Device-related complications occurred in 17 patients (4.3%). At follow-up, major adverse events occurred in 8.98% of patients at 1 year and in 9.97% at 2 years.
Conclusions: In patients with ST-segment elevation myocardial infarction undergoing PCI, MT with the Hunter catheter in selected cases with high thrombus burden (TIMI grade ≥ 4 flow), non-circumflex target vessels, and vessel diameters > 2.5 mm, is a safe and effective technique with a low rate of complications.

Keywords: ST-segment elevation myocardial infarction. Percutaneous coronary intervention. Manual thrombectomy. Thrombus burden.

Utilidad clínica de la tromboaspiración con catéter Hunter en pacientes con infarto agudo de miocardio: registro Hunted

RESUMEN

Introducción y objetivos: La trombectomía manual (TM) en la intervención coronaria percutánea primaria (ICPp) intenta reducir la carga trombótica. Este estudio evalúa los resultados y los factores predictores de éxito de la TM.
Métodos: El registro Hunted es un estudio de cohortes retrospectivo, unicéntrico, de pacientes tratados con TM en ICPp utilizando el catéter Hunter, desde julio de 2020 hasta febrero de 2022. El éxito de la TM se definió como una disminución angiográfica a grado ≤ 2 en la escala *Thrombolysis in Myocardial Infarction* (TIMI), con seguimiento clínico de eventos cardiovasculares adversos mayores.
Resultados: De los 750 pacientes con infarto agudo de miocardio tratados con ICPp, en 401 (53%) se realizó TM. Los pacientes tratados tenían una edad media de 62 años y el 80% eran varones. La TM fue efectiva en 327 (81,55%) pacientes. Los predictores de TM efectiva fueron un mayor diámetro del vaso ($p < 0,001$), una alta carga de trombo (TIMI ≥ 4; $p < 0,001$) y un vaso diferente de la circunfleja ($p < 0,001$). Se presentaron complicaciones relacionadas con el dispositivo en 17 pacientes (4,3%). En el seguimiento, el 8,98% presentaron eventos mayores a 1 año y el 9,97% a 2 años.
Conclusiones: En los pacientes con infarto de miocardio con elevación del segmento ST sometidos a ICPp, la estrategia de TM con catéter Hunter, en casos seleccionados con alta carga trombótica (escala TIMI ≥ 4), otros vasos que no fueran la circunfleja y diámetros > 2,5 mm, es una técnica eficaz y segura con una baja tasa de complicaciones.

Palabras clave: Infarto de miocardio con elevación del segmento ST. Intervención coronaria percutánea primaria. Trombectomía manual. Carga trombótica.

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Abbreviations

MACE: major adverse cardiovascular events. **MT:** manual thrombectomy. **PCI:** primary coronary intervention. **STEMI:** ST-segment elevation myocardial infarction. **TIMI**: Thrombolysis in Myocardial Infarction.

INTRODUCTION

In patients with ST-segment elevation myocardial infarction (STEMI), the treatment of choice is percutaneous coronary intervention (PCI) performed within the appropriate time window and by experienced operators. PCI has been shown to reduce mortality, reinfarction, and stroke compared with fibrinolysis.[1] Among other factors, this benefit may be attributed to greater epicardial reperfusion and higher TIMI (Thrombolysis in Myocardial Infarction) flow grades and myocardial blush grades achieved with PCI in the culprit artery, all of which are known to influence survival.[2,3]

PCI have distinctive characteristics, including the presence of a high thrombus burden and performance in patients in a markedly thrombogenic state. To reduce the local thrombus burden in the culprit artery, manual thrombectomy (MT) has been widely used during PCI to reduce thrombus load, prevent distal embolization, and improve final myocardial perfusion.[3,4] Despite its initial widespread adoption, routine use of MT in all patients undergoing PCI is no longer recommended, as randomized clinical trials have not demonstrated consistent clinical benefit.[3,4-7]

MT should be reserved for patients in whom it is most likely to provide benefit. To optimize the efficacy of PCI, the American[8] and European[9] clinical practice guidelines recommend MT in high-risk patients with a moderate-to-high thrombus burden who present with short ischemia times. Currently, however, there are no clearly defined criteria to precisely identify patients or thrombotic lesions that would derive the greatest benefit from MT.

The aim of our study was to evaluate the results of MT performed with the Hunter catheter (IHT–Iberhospitex SA, Barcelona, Spain), which has a high extraction capacity, in selected patients with STEMI undergoing PCI, and analyze the angiographic patterns associated with successful MT in our center.

METHODS

Study design and population

The Hunted registry is a single-center, observational, retrospective study. We included all patients diagnosed with STEMI who underwent PCI and in whom MT was performed using the Hunter thrombus aspiration catheter. This device was the first-choice catheter for MT in our center during the study period. The decision to perform MT was always left to the discretion of the operator performing the PCI, following homogeneous criteria among operators, subjectively based on angiographical evidence of a large angiographically visible thrombus. MT was not recommended in coronary vessels with a diameter < 2 mm or for the extraction of chronic thrombi or atherosclerotic plaques. The study period ranged from July 2020 through February 2022. Patients in whom MT was performed using a catheter other than the Hunter device were excluded.

The primary objective of the study was to evaluate the success of thrombus aspiration during PCI in patients with STEMI. Effective MT was defined as an angiographical reduction in thrombus burden, achieving a TIMI thrombus grade ≤ 2 (thrombus dimension < 50% of the vessel diameter). Moreover, angiographic factors associated with effective MT were assessed.

Secondary objectives included describing the clinical and angiographic characteristics of the patients and evaluating major adverse cardiovascular events (MACE) during hospitalization and follow-up.

MACE were defined as a composite endpoint of cardiovascular and noncardiovascular death, stroke, and acute myocardial infarction. Two follow-up time points were established at 1 and 2 years after PCI. Total ischemia time was defined as the interval, in minutes, between symptom onset and reperfusion, defined as passage of the intracoronary guidewire, in accordance with clinical practice guidelines.

Thrombus burden was graded according to the TIMI thrombus scale,[10] which includes 5 grades: grade 1, possible thrombus; grade 2, thrombus dimension < 50% of the vessel diameter; grade 3, thrombus dimension 0.5 to 2.0 vessel diameters; grade 4, thrombus dimension > 2.0 vessel diameters; and grade 5, total vessel occlusion by thrombus. Grades 4 and 5 were considered high thrombus burden.

Successful PCI was defined as achievement of TIMI grade 3 flow with residual percent diameter stenosis < 20%, without device-related complications or intraoperative MACE. For study purposes, patients were categorized into 2 groups according to whether MT was effective or not. Furthermore, these groups were compared to identify angiographic parameters that could predict MT success.

Data for the variables included in the Hunted registry were collected using a dedicated electronic case report form. Retrospective angiographic analysis was performed exclusively by 3 operators. All measures were taken to ensure confidentiality and protection of patient health record information. The study protocol fully complied with international recommendations for clinical research outlined in the Declaration of Helsinki and was approved by the hospital Ethics and Research Committee.

Characteristics of the Hunter device and aspiration technique

The Hunter thrombus aspiration catheter is a 140 cm rapid-exchange aspiration catheter compatible with a 6-Fr guiding catheter. Its tip has a slightly conical, low-profile, atraumatic design. The effective distal aspiration area measures 0.95 mm^2, and it can aspirate up to 1.92 mL per second, one of the highest capacities available. The distal segment is coated with a hydrophilic surface to facilitate device navigability.

The standard thrombectomy technique used in our center consisted of advancing the Hunter catheter to a segment proximal to the culprit lesion. Aspiration was always initiated proximal to the culprit lesion. The catheter was then slowly advanced across the lesion under continuous aspiration to reach the distal segment, while continuous filling of the syringe was observed. If filling stopped, the catheter was withdrawn until aspiration resumed or

removed completely if aspiration could not be reestablished. Continuous aspiration until removal from the guiding catheter was mandatory, as was thorough subsequent flushing of the guiding catheter, to prevent embolization of residual thrombotic material.

All retrieved material from the catheter and aspiration syringe was subsequently filtered using the filters provided with the device packaging. The procedure was repeated as many times as deemed necessary by the operator until the desired reduction in thrombus burden was achieved.

Statistical analysis

Qualitative variables are expressed as frequencies and percentages, and the quantitative ones as mean and standard deviation when normally distributed, and as median and interquartile range when distribution was nonnormal.

Qualitative variables were compared using the chi-square test, with odds ratios (OR) and 95% confidence intervals (95%CI) calculated. Quantitative ones were compared using the Student *t* test or nonparametric tests, as appropriate.

In univariate analysis, each variable was individually assessed for its association with effective MT. Variables showing a statistically significant association were included in the multivariate analysis. Multiple regression models were used to control for potential confounders and determine the independent effect of each variable on the outcome.

Survival curves were analyzed using the Kaplan–Meier method, and survival-related parameters were evaluated using Cox proportional hazards analysis. A 2-sided *P* value < .05 was considered statistically significant.

Statistical analyses were performed using STATA version 15 (StataCorp, United States).

RESULTS

During the study period, a total of 750 PCI were performed in patients diagnosed with STEMI. MT using the Hunter catheter was performed in 401 patients (53.47%). The clinical characteristics of the patients, STEMI features, and PCI are shown in table 1.

Angiographic analysis of the culprit lesion and flow in the infarct-related artery is shown in table 2. Initial TIMI grade flow in the infarct-related artery, prior to intracoronary guidewire passage was 0 in 83% of cases. A high thrombus burden was observed in 87.5% of patients, corresponding to TIMI thrombus grades 4 or 5; 53.4% had grade 5 and 34.2% had grade 4. Only 50 patients (12.5%) had a TIMI grade < 4 flow, defined as a low thrombus burden.

According to the predefined criteria, effective MT was achieved in 327 of 401 patients (81.5%). Thrombectomy was considered ineffective in the 6 patients who had initial TIMI thrombus grades 1 and 2. Final post-PCI coronary flow was TIMI grade < 3 flow in 15 patients (3.74%). Overall, the PCI was successful in approximately 97% of cases. Device-related complications were recorded in 17 patients (4.24%): severe arrhythmias (ventricular fibrillation or ventricular tachycardia) occurring during reperfusion in 10 patients; severe no-reflow due to distal thrombus migration that could not be successfully treated in 4 patients; and coronary dissection after passage of the MT catheter, which was successfully treated with stenting in 3 patients. There were no cases of perioperative stroke due to migration of aspirated thrombus.

Table 1. Clinical characteristics of patients and procedural variables

Clinical characteristics	n = 401
Age, years	62.38 ± 12.43
Male sex	319 (80)
Current/former smoker	163 (40.65)/35 (8.73)
Hypertension	207 (51.62)
Dyslipidemia	186 (46.38)
Diabetes mellitus	86 (21.45)
Kidney failure	7 (1.75)
Previous stroke	16 (3.99)
Peripheral vascular disease	8 (2.00)
Previous AMI	48 (11.97)
Previous PCI	50 (12.47)
Prior CABG	5 (1.25)
Infarct location	
Anterior	166 (41.50)
Inferior	207 (51.75)
Lateral	27 (6.75)
Killip-Kimball classification	
I	338 (84.71)
II	18 (4.51)
III	8 (2.01)
IV	35 (8.77)
Procedural variables	
Radial access	385 (96.01)
*No. of diseased vessels**	
1	233 (58.10)
2	111 (27.68)
3	57 (14.21)
Infarct-related artery	
Right coronary artery	183 (45.64)
Left anterior descending coronary artery	166 (41.40)
Left circumflex artery	48 (11.97)
Venous graft	1 (0.25)
Left main coronary artery	3 (0.75)
No. of stents implanted	
0	34 (8.47)
1	288 (71.82)
2	60 (14.96)
3	19 (4.74)
Drug-eluting stent (n = 367)	362 (98.64)
Total ischemic time	
< 90 min	43 (10.72)
91-180 min	167 (41.65)
181-270 min	82 (20.45)
271-360 min	42 (10.47)
> 360 min	67 (16.71)

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
* Left main coronary artery disease is counted as 2-vessel disease.
Data express n (%) or mean ± standard deviation.

Table 2. Angiographic analysis of patients treated with percutaneous coronary intervention and manual thrombectomy

Angiographic variables	
Vessel diameter	3.25 [3.00-3.50]
2.0-2.5 mm	61 (15.21)
2.6-3.0 mm	122 (30.42)
3.1-3.5 mm	124 (30.92)
3.6-4.0 mm	66 (16.46)
> 4.0 mm	28 (6.98)
Lesion length, mm	16 [15-20]
AHA/ACC lesion type	
B1	60 (14.96)
B2	161 (40.15)
C	180 (44.89)
Thrombus burden grade (TIMI)	
1	1 (0.25)
2	5 (1.25)
3	44 (10.97)
4	137 (34.16)
5	214 (53.37)
Pre-PCI IRA TIMI flow grade	
0	332 (82.79)
1	18 (4.49)
2	24 (5.98)
3	27 (6.74)
Post-PCI IRA TIMI flow grade	
0	2 (0.50)
1	3 (0.75)
2	10 (2.49)
3	386 (96.26)

AHA/ACC, American Heart Association/American College of Cardiology; IRA, infarct-related artery; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
Data express n (%) or median [interquartile range].

Comparative analysis of angiographic factors and ischemia time between patients with effective and noneffective MT is shown in table 3. MT was effective more frequently in patients with culprit coronary vessels > 3 mm in diameter (112 [34%] vs 12 mm [16%]; $P < .001$) and in those with a TIMI grade ≥ 4 thrombus burden (297 [91%] vs 54 [73%]; $P < .001$). Among the 61 patients with vessels < 2.5 mm, MT was ineffective in 36 (59.01%) vs 38 of 340 patients (11.2%) with vessels > 2.5 mm ($P < .001$). There were no statistically significant differences in ischemia time in relation to MT success.

The 1- and 2-year follow-up was completed in 100% of included patients. MACE occurred in 32 patients (7.98%) at 30 days, 36 patients (8.98%) at 1 year, and 40 patients (9.97%) at 2 years (table 4). Kaplan–Meier curves for event-free survival during follow-up and cardiovascular death according to effective vs noneffective MT are shown in figure 1 and figure 2, respectively. Individual components of MACE at 1 year are shown in figure 3.

DISCUSSION

In selected patients, MT using the Hunter catheter is a safe and effective strategy to reduce angiographically assessed thrombus burden during PCI.

Current clinical practice guidelines do not recommend routine MT during PCI but suggest considering it in patients with a high thrombus burden, based on individual assessment and operator experience.[8,9] In our series, MT was performed in 53.5% of patients with STEMI treated with PCI, a higher proportion than reported in other countries.[11-13] Only 12% of patients undergoing MT did not have a TIMI grade 4–5 thrombus burden on angiographic analysis.

In this selected population with high thrombus burden, 88% had TIMI grade ≥ 4 flow, which is similar to the 79% observed in the TOTAL trial,[14] with favorable results in both cases. In contrast, only 33% of patients from the TASTE trial[7] had a high thrombus burden.

A high thrombus burden appears to be a key determinant of achieving effective MT and may be associated with better clinical outcomes. In our cohort, although effective MT was achieved in 82% of cases, it was not significantly correlated with final procedural success (97% vs 95%; $P = .67$), likely due to the small sample size of the 2 groups. MT efficacy was higher in vessels with high thrombus burdens (TIMI grade ≥ 4 flow; $P < .001$), which is consistent with a meta-analysis showing less cardiovascular death in patients with STEMI undergoing PCI with MT in the high thrombus burden subgroup vs PCI alone (2.5% vs 3.2%; hazard ratio [HR], 0.81; 95%CI, 0.65–0.98; $P = .03$).[15] These findings reinforce the concept that appropriate patient selection is crucial to benefit from MT. Moreover, the same meta-analysis reported a higher risk of stroke (0.9% vs 0.5% in the PCI-alone group),[15] a complication that may be related to the TM technique used.

Strict adherence to proper technique is essential to minimize complications and maximize success. In our series, emphasis was placed on following a standardized and rigorous technique, as described in the Methods section, resulting in a low complication rate (4.3%). Many of these complications were not directly related to MT *per se* but rather to reperfusion, such as ventricular arrhythmias. MT-related stroke is a potential complication; in the TOTAL trial,[16] the stroke rate was 0.7%, twice that observed in the PCI-alone group, whereas in the large real-world SCAAR registry, there was no increase in the incidence rate of stroke across the groups,[17] which are findings more consistent with our results and possibly related to differences in MT technique.

To identify angiographic predictors of MT success, we compared the characteristics of patients with effective and noneffective MT. The former had significantly larger culprit vessel diameters; 48% of patients with noneffective MT had vessels measuring 2.5 mm. Although MT is generally discouraged in vessels < 2 mm, larger vessels may harbor greater thrombus burden and thus derive greater benefit from MT with the Hunter catheter, which has demonstrated higher in vitro aspiration capacity compared with other devices. Therefore, vessel size is a critical differentiating factor: in vessels < 2.5 mm, MT was ineffective in 59% of cases, a significantly higher proportion than the 11.2% of noneffective MT observed in larger vessels. The other major difference between

Table 3. Comparison of angiographic and procedural characteristics between patients with effective and noneffective manual thrombectomy

Procedural variables	Effective MT (n = 327)	Noneffective MT (n = 74)	*P*
Infarct-related artery			.008
Right coronary artery	153 (46.79)	30 (40.54)	
Left anterior descending coronary artery	140 (42.81)	26 (35.14)	
Left circumflex artery	30 (9.17)	18 (24.32)	
Saphenous vein graft	1 (0.31)	–	
Left main coronary artery	3 (0.92)	–	
AHA/ACC classification of the culprit lesion			.004
B1	51 (15.60)	9 (12.16)	
B2	142 (43.42)	19 (25.68)	
C	134 (40.98)	46 (62.16)	
Reference diameter of the culprit lesion			< .001
2.0 mm-2.5 mm	25 (7.65)	36 (48.69)	
2.6 mm-3.0 mm	101 (30.89)	21 (28.38)	
3.1 mm-3.5 mm	112 (34.25)	12 (16.22)	
3.6 mm-4.0 mm	64 (19.57)	2 (2.70)	
> 4.0 mm	25 (7.64)	3 (4.10)	
Thrombus burden grade (TIMI)			< .001
Low thrombus burden (TIMI < 4)	30 (9.18)	20 (27.03)	
High thrombus burden (TIMI ≥ 4)	297 (90.82)	54 (72.97)	
Pre-PCI TIMI grade flow			.031
TIMI grade 0-1 flow	291 (88.99)	59 (79.73)	
TIMI grade 2-3 flow	36 (11.01)	15 (20.27)	
Post-PCI TIMI grade flow			.61
TIMI grade 0-1 flow	2 (0.61)	3 (4.05)	
TIMI grade 2 flow	8 (2.45)	1 (1.35)	
TIMI grade 3 flow	317 (96.94)	70 (94.59)	
Time from symptom onset to reperfusion			.79
≤ 90 min	37 (11.31)	6 (8.11)	
91-180 min	139 (42.51)	28 (37.84)	
181-270 min	68 (20.80)	14 (18.92)	
271-360 min	33 (10.09)	9 (12.16)	
> 360 min	50 (15.29)	17 (22.97)	
Final procedural success	317 (96.94)	70 (94.59)	.61

AHA/ACC, American Heart Association/American College of Cardiology; MT, manual thrombectomy; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
Data express n (%).

Table 4. Incidence rate of the composite endpoint of major adverse cardiovascular events during follow-up

Cardiovascular events at the follow-up	
At 30 days	32 (7.98)
At 1 year	36 (8.98)
At 2 years	40 (9.97)

Data expressed n (%).

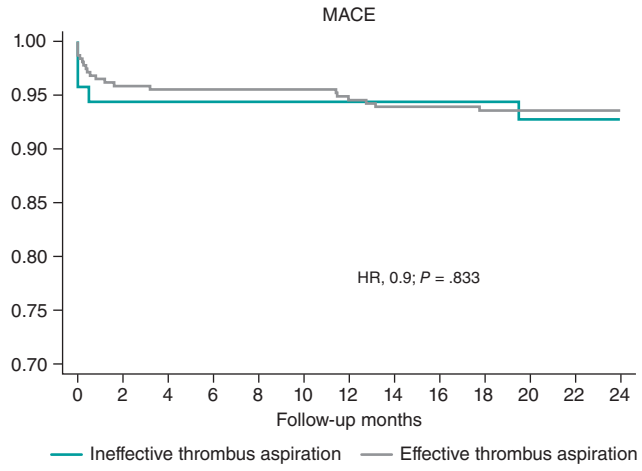

Figure 1. Kaplan–Meier curves for survival free from major adverse cardiovascular events (MACE). HR, hazard ratio.

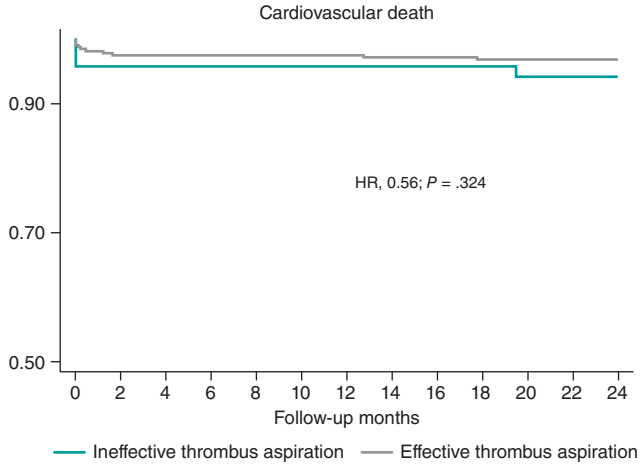

Figure 2. Kaplan–Meier survival curves for cardiovascular death. HR, hazard ratio.

groups was thrombus burden, as effective MT was achieved more frequently in patients with higher thrombus loads (TIMI grade ≥ 3 flow).[15] Furthermore, this factor represents a major difference among randomized clinical trials, in which the proportion of patients with high thrombus burden varied substantially.[15] More complex lesions, such as American Heart Association/American College of Cardiology type C lesions, those associated with calcification in addition to thrombus, long lesions, and left circumflex artery lesions were associated with higher rates of noneffective MT. These differences should be considered when selecting appropriate candidates for MT with the Hunter catheter, favoring patients with

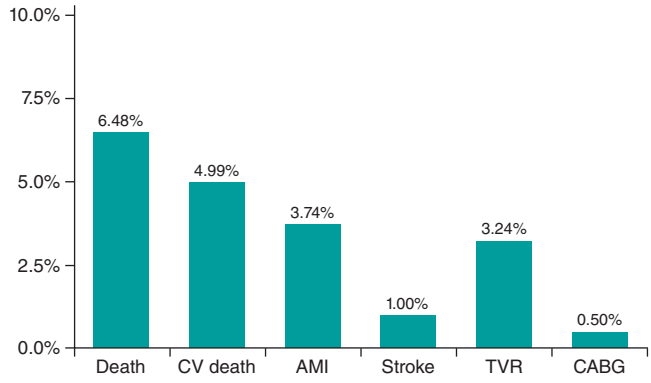

Figure 3. Individual components of major adverse cardiovascular events at the 1-year follow-up. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CV, cardiovascular; TVR, target vessel revascularization.

vessel diameters > 2.5 mm, abundant thrombus burden (TIMI grade ≥ 4 flow), and culprit arteries other than the left circumflex one.

Studies have shown that total ischemia time, which we believe may determine differences in thrombus composition,[18] may influence the efficacy of thrombus aspiration.[19] In our series, there were no differences between the effective and noneffective MT groups with respect to infarction duration.

When assessing whether effective MT impacted the outcome of the PCI, slightly different procedural success rates were observed: 97% for effective MT vs 95% for noneffective MT (P = .61). Statistical significance was not reached, possibly due to the small sample size. Only 4 patients experienced no-reflow that could not be resolved, with no differences across groups and without demonstrating that MT could prevent distal embolization, as suggested in former studies.[17-19]

Short- and long-term clinical outcomes in patients with STEMI who required MT were favorable, with a low 1-year cardiovascular death rate of 3.5%, comparable to that reported in randomized clinical trials. In the TASTE trial,[7] the 30-day mortality rate was 2.4% in the MT group and 2.9% in the PCI-alone group (HR, 0.84; 95%CI, 0.70–1.01; (P = .06). In the TAPAS trial,[20] the 30-day all-cause mortality rate was 2.1% in the MT group vs 4.0% in the conventional PCI group, reaching statistical significance at the 1-year follow-up (P = .07). Large registries have reported mortality rates similar to those observed in our series, with 2.8% vs 3.0% in the Swedish registry[21] and comparable findings in the Japanese registry.[22] The overall mortality rate observed in a meta-analysis with aggregated data from published MT studies was 3.7%.[15] When selecting patients with a high thrombus burden (TIMI grade ≥ 3 flow in the meta-analysis subgroup), the cardiovascular death rate was 2.5% (170 of 6872 patients) in the MT group vs 3.1% (205 of 6599 patients) in the PCI-alone group (HR, 0.8; 95%CI, 0.65–0.98; (P = .03).[15] Proper selection of this subgroup of patients with a high thrombus burden is, therefore, crucial to maximize the therapeutic benefit.

Limitations

As a single-center, observational, retrospective registry, this study has inherent limitations related to its design. First, because it reflects the experience of a single center—albeit with more than 15 years of experience in PCI—operator homogeneity may limit extrapolation of the results. The decision to perform MT was always left to the discretion of the operator, and no control group without MT was available for patient comparison. Because of the retrospective design of the analysis, we could not determine the cause of ineffective MT in all patients, which is why this variable could not be included in the analysis. This study should not be interpreted as an evaluation of thrombus aspiration in general, but rather as an assessment of outcomes in a selected population treated with the Hunter device; these selection criteria represent the primary contribution of this work to current scientific knowledge. The study did not incorporate systematic criteria to address sex- and gender-related variables during methodological development or result analysis. Although angiographic analysis was not performed by an independent core laboratory, it was conducted by 3 experienced analysts. In this analysis, MT success, procedural success, and baseline thrombus burden were defined using the TIMI scale.

CONCLUSIONS

In patients with STEMI undergoing PCI, selective use of MT with the Hunter catheter in cases with high thrombus burden (TIMI grade ≥ 4 flow), non-circumflex culprit vessels, and vessel diameters > 2.5 mm is a safe and effective strategy associated with a low complication rate. Further studies are needed to assess the impact of this strategy on PCI outcomes, MACE, and stroke.

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ETHICAL CONSIDERATIONS

The study was approved by *Hospital Universitari Germans Trias i Pujol* Ethics Committee (Barcelona, Spain) (CEIC code: PI-22-281) and conducted in full compliance with the principles outlined in the Declaration of Helsinki. SAGER guidelines were not applied to address gender bias.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

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

AUTHORS' CONTRIBUTIONS

D.G. Borraz-Noriega: angiographic analysis, data review, and manuscript drafting. J.F. Andrés-Cordón: angiographic analysis, data review, and statistical analysis. E. Cañedo: data collection and clinical follow-up. F. Panchano-Castro: angiographic analysis and data review. M. Trichilo: data collection and clinical follow-up. V. Vilalta: data collection and critical manuscript review. O. Rodríguez-Leor: data collection and critical manuscript review. E. Fernández-Nofrerias: critical manuscript review. I. Santos-Pardo: critical manuscript review. X. Carrillo: study design, overall supervision, and manuscript drafting. All authors reviewed and approved the final version.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THIS TOPIC?

- Routine use of manual thrombectomy has not demonstrated clear benefit. Current clinical practice guidelines recommend individualized use in selected patients with high thrombus burden. Clear angiographic criteria for identifying patients most likely to benefit from thrombectomy are lacking.

WHAT DOES THIS STUDY ADD?

- The Hunted registry provides specific evidence on thrombectomy performed with the Hunter catheter during PCI.
- It identifies angiographic predictors of thrombectomy success (vessel diameter > 2.5 mm, TIMI ≥ 4 thrombus burden, non-circumflex coronary arteries).
- The Hunter catheter, with its larger effective aspiration area, along with proper technique, demonstrates a low complication rate and favorable clinical outcomes.

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Original article

Feasibility of implementing reperfusion strategies in STEMI codes in a mountainous population remote from a PCI-capable center

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ABSTRACT

Introduction and objectives: ST-segment elevation myocardial infarction (STEMI) requires early coronary reperfusion to reduce mortality and improve prognosis. In rural areas, timely access to reperfusion therapies, including fibrinolysis or percutaneous coronary intervention (PCI) is frequently constrained by logistical and health care system-related factors.
This study aimed to identify factors associated with delays in reperfusion and those associated with mortality in patients with STEMI code activation in a mountainous European region.
Methods: This is an observational, retrospective, and quantitative study in Alt Pirineu-Aran region (Catalonia, Spain) from 2015 through 2020. Sociodemographic and geographic factors, clinical status, resource management and the treatment provided were analyzed using data from the STEMI code registry and the Catalan emergency medical system.
Results: During the study period, a total of 221 patients with STEMI code were treated in the Alt Pirineu-Aran region. Patients ranged in age from 27 to 96 years, with a mean age of 64.7 years; 72.4% were men. Of these, 47 received fibrinolytic therapy and 173 were transferred to a PCI-capable center, of whom 162 underwent PCI; in 11 cases the code was deactivated. Most patients transferred for PCI experienced delays of > 120 minutes from the diagnostic electrocardiogram. Helicopter transport improved treatment times, with the greatest benefit observed in primary transfers. The 15-day mortality rate was 8.1%.
Conclusions: Most fibrinolysis treatments and PCI were not performed within the times recommended by the European clinical practice guidelines. The study highlights the underutilization of fibrinolysis.

Keywords: ST-segment elevation myocardial infarction. Rural areas. Fibrinolysis. Percutaneous coronary intervention. Mountainous regions. Prehospital care.

Idoneidad de la implementación de la estrategia de reperfusión en los códigos IAM en zonas montañosas alejadas de una unidad de hemodinámica

RESUMEN

Introducción y objetivos: El infarto agudo de miocardio (IAM) con elevación del segmento ST requiere una reperfusión coronaria precoz para reducir la mortalidad y mejorar el pronóstico. En las zonas rurales, los tiempos de acceso a los tratamientos de reperfusión (fibrinolisis o intervención coronaria percutánea primaria [ICPp]) se ven comprometidos por aspectos logísticos y asistenciales. El objetivo de este estudio es determinar los factores asociados a los retrasos en la reperfusión y los asociados a la mortalidad en pacientes con código IAM en una región montañosa europea.

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Métodos: Se realizó un estudio observacional, retrospectivo y cuantitativo en la región del Alt Pirineu-Aran, en Cataluña (España), entre 2015 y 2020. Se analizaron los factores sociodemográficos y geográficos, el estado clínico de los pacientes, la gestión de los recursos y el tratamiento realizado, utilizando los datos del registro del código IAM y del Sistema d'Emergències Mèdiques.
Resultados: Durante el periodo de estudio, 221 pacientes con código IAM fueron atendidos en el Alt Pirineu-Aran. Los pacientes tenían entre 27 y 96 años, con una media de 64,7 años, y el 72,4% eran varones. De ellos, 47 pacientes recibieron fibrinolisis como tratamiento de reperfusión y 173 fueron trasladados a un hospital con unidad de hemodinámica, donde 162 recibieron ICPp; en 11 casos se desactivó el código. La mayoría de los pacientes trasladados para ICPp experimentaron un retraso superior a 120 minutos desde el electrocardiograma diagnóstico. El uso de helicópteros mejoró los tiempos de tratamiento, especialmente en los traslados primarios. La tasa de mortalidad a los 15 días fue del 8,1%.
Conclusiones: La mayoría de las fibrinolisis y de las ICPp no se realizaron dentro de los tiempos recomendados según las guías europeas. Se evidencia una marcada infrautilización de la fibrinolisis.

Palabras clave: Infarto agudo de miocardio con elevación del segmento ST. Zonas rurales. Fibrinolisis. Intervención coronaria percutánea. Zonas montañosas. Atención prehospitalaria.

Abbreviations

AMI: acute myocardial infarction. **ECG:** electrocardiogram. **EMS:** Emergency Medical Services of Catalonia. **PCI-capable center:** percutaneous coronary intervention capable center. **pPCI:** primary percutaneous coronary intervention. **STEMI:** ST-segment elevation acute myocardial infarction.

INTRODUCTION

Acute myocardial infarction (AMI) is a medical emergency that requires a rapid response to minimize cardiac damage and improve patient survival. Initial recognition and early treatment based on the optimal reperfusion strategy are key to survival; however, implementing this protocol in rural and mountainous regions is a major challenge.[1-4]

Primary percutaneous coronary intervention (pPCI) is recommended in all cases provided it can be performed within 120 minutes (ideally in less than 90 minutes).[4] If not contraindicated, fibrinolysis is the treatment of choice when this time frame cannot be guaranteed. Contraindications to fibrinolytic therapy may be classified as absolute or relative and should be evaluated on an individual basis. When fibrinolysis is contraindicated, primary angioplasty should be prioritized whenever feasible.[1,4] The STEMI code in Catalonia was implemented as a regional health care network in June 2009 designed to organize the management of patients with suspected ST-segment elevation myocardial infarction (STEMI).[5,6]

Several authors have linked delays in reperfusion treatment to the type of infarction, the timing of symptom onset, and complications.[7-9] Other studies suggest that a distance > 50 km to a PCI-capable center is associated with higher mortality rates vs early fibrinolysis.[10,11] Other experiences, such as sharing patient data during prehospital care, including electrocardiograms (ECG) and the use of nighttime helicopter transfer to the PCI-capable center have been associated with shorter diagnosis-to-treatment times; however, a reduction in mortality has not been demonstrated.[12] However, few studies have analyzed the factors causing delays in mountainous and hard-to-access geographic areas.

The main aim of this study was to determine the factors associated with delays in reperfusion treatment and those associated with mortality in patients treated under the STEMI code in a European mountainous area.

METHODS

Study design

We conducted an observational, retrospective, and quantitative study that included all STEMI code activations in the Alt Pirineu-Aran territory (Catalonia, Spain) from January 2015 through December 2020. The main sources of information were the STEMI code registry of the Department of Health of the Government of Catalonia[5,6] and the database of the medical Emergency Medical Services (EMS) of Catalonia, which were cross-referenced to obtain a comprehensive overview. Because the data were derived from preexisting registries and analyzed anonymously, informed consent was deemed unnecessary. The study was approved by the *Instituto Universitario de Investigación en Atención Primaria* (IDIAP) *Jordi Gol* Ethics Committee, code CEIm 22/238-P. The SAGER guidelines were followed regarding potential sex and gender bias.

Study setting

Alt Pirineu-Aran is a mountainous region comprising 6 counties and represents 18% of Catalonia's territory, yet it is home to less than 1% of its population. Population density is extremely low (12.6 inhabitants per km^2), and most towns are located between 500 and 800 meters above sea level, far from a specialized hospital center.

This regional health care system faces several challenges. Prehospital care is provided by the EMS, a public service that operates 24 hours per day and provides coverage throughout the entire territory. Each county is served by 1 advanced life support unit, and the region has access to 1 medicalized helicopter, 1 of the 4 operating in Catalonia. Alt Pirineu–Aran includes 4 county hospitals, all of which are non–PCI-capable centers (figure 1).

Hospital Universitario Arnay de Vilanova (Lleida, Spain) serves as the reference center for pPCI for Alt Pirineu-Aran, with the exception of the Cerdanya basic health area, where STEMI code patients are transferred to centers in the Barcelona metropolitan area (table S1).

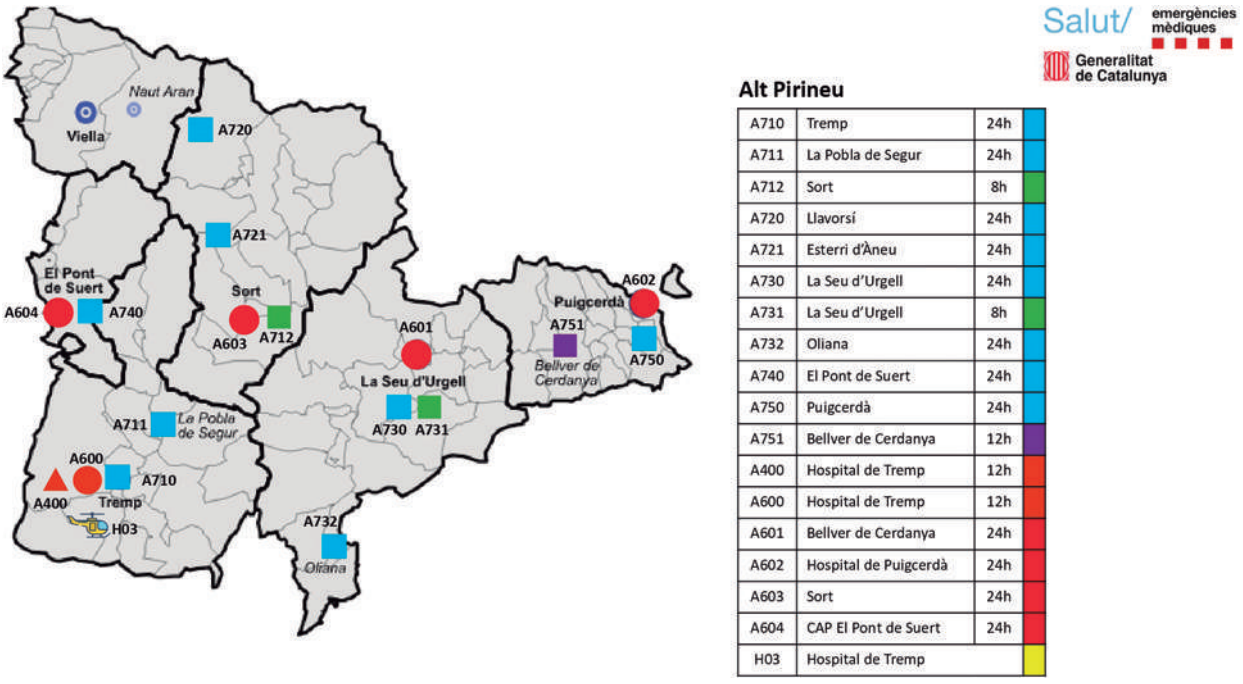

Figure 1. Alt Pirineu-Aran Health Region. H03: Tremp medicalized helicopter. H: county hospitals. Unit call signs are identified with A for Alt Pirineu; 1st number indicates the type of unit (7, basic life support; 4, advanced life support + nurse; and 6, advanced life support + physician); 2nd and 3rd numbers indicate the location of the units on the map.

Definitions and inclusion criteria

The definitions of "delay" used in the study were more than 10 minutes for fibrinolysis administration and more than 120 minutes for pPCI, measured from the time of ECG acquisition. These criteria were established on the basis of former studies and are consistent with current European clinical practice guideline recommendations.[1-4]

According to EMS protocols, a 90-minute transfer threshold—from ECG acquisition to arrival at the receiving hospital—is used to allow adequate time to perform pPCI and ensure compliance with the 120-minute target. To determine whether patients had a transfer time of less than 90 minutes to a PCI-capable center, a geographic analysis based on distance and estimate travel-time maps was performed.

Patients were included if the STEMI code was activated in Alt Pirineu–Aran and they were attended by EMS during the study period, as well as those who died after prior activation of the STEMI code.

Incomplete cases or those with coding errors were excluded, as were patients transferred to Toulouse (France) from Vall d'Aran.

Study variables

The variables analyzed included demographic, clinical, and logistical data. The primary time intervals assessed were symptom onset to first medical contact, time from first medical contact to ECG, and ECG to initiation of reperfusion treatment. The type of reperfusion strategy (fibrinolysis or pPCI) was recorded as well. Other relevant variables included the location of STEMI code activation, distance to the PCI-capable center, mode of transport to the PCI-capable center (ambulance or helicopter), and type of transfer (primary: direct care and transfer by a medicalized EMS ambulance; secondary: interhospital transfer; or delayed primary: initial assessment by a primary care physician or nurse-staffed ambulance followed by transfer to a medicalized ambulance or medical helicopter). Acute-phase complications and all-cause mortality at first medical contact, and at 24 and 48 hours, and at 15 days were also recorded.

Statistical analysis

The descriptive statistical measures used were absolute and relative frequencies for qualitative variables; mean and standard deviation for quantitative variables with normal distribution; and median and interquartile range for the remaining non-normally distributed quantitative variables, according to the Shapiro-Wilk test.

We analyzed a total of 4 binary outcome variables: use of fibrinolysis as the initial treatment, delays in fibrinolysis (> 10 minutes from ECG acquisition), delays in pPCI (> 120 minutes from ECG acquisition), and mortality. Furthermore, we evaluated associations between each outcome variable and patient- and care-related characteristics using the chi-square test for qualitative variables (or Fisher's exact test when expected frequencies were < 5), the Mann-Whitney *U* test for non-normally distributed quantitative variables, and the Student *t* test otherwise. In addition, we analyzed the importance of variables for treatment delay and mortality using the Boruta algorithm for variable selection. Only variables not rejected by this algorithm were selected for subsequent multivariable analyses to reduce the risk of overfitting. A conditional inference classification tree was constructing using a Monte Carlo test with a minimum terminal node size of 3.

All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Austria). *P* values < .05 were considered statistically significant.

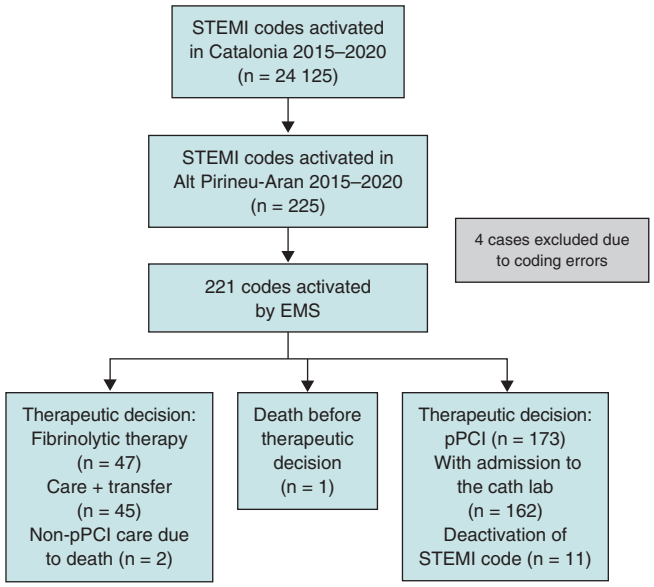

Figure 2. Flow diagram of STEMI codes. AMI, acute myocardial infarction; pPCI, primary percutaneous coronary intervention; EMS, Emergency Medical Services of Catalonia.

RESULTS

During the study period, a total of 24 125 STEMI codes were activated across Catalonia. The study analyzed 225 cases occurring in Alt Pirineu-Aran, representing less than 1% of the total. Four patients were excluded for not meeting STEMI code criteria (1 pulmonary thromboembolism, 2 coding errors, and 1 duplicate case) (figure 2).

The mean age of the 221 included patients was 64.7 years (range, 27–96). Of these, 72.4% were men and 67.4% resided in the study area. All STEMI codes were activated after ECG acquisition at first medical contact, either at a county hospital (51.6%), by EMS at the patient's home or in a public setting (28.9%), or at a primary care center (19.5%). The median time from first medical contact to ECG acquisition was 6 minutes, and from pain onset to ECG acquisition, 90 minutes (table 1).

The incident location had a mean altitude of 838 meters and was located at distances ranging from 81 km to 257 km from the PCI-capable center (median, 131 km). Overall, 76.5% of patients were situated more than 90 minutes from the PCI-capable center (median estimate transfer time, 106 minutes). Air advanced life support was used in 52.5% of the transfers (table 1).

Differences were observed in the time from ECG acquisition to pPCI according to mode of transport (Kruskal-Wallis; $P < .001$). The median time was 183 minutes for ground ambulance, 138 minutes for helicopter transport, and 140 minutes for combined transport (table 1). Pairwise comparisons using the Mann–Whitney U test showed significant differences compared with ground transport after adjustment for the false discovery rate.

We observed marked variability in the annual frequency of STEMI code cases, with a particularly high number in 2019, and in the proportion of first-assistance fibrinolysis performed from a minimum of 10.5% in 2020 to a maximum of 34.6% in 2017. The number of cases attended in 2020 (the year of the COVID-19 pandemic) was slightly higher than in 2015–2017 (38 cases [17.2%]) but lower than in 2019, which recorded 57 cases (25.8%) (table 1).

Delays in treatment

In 91.5% of patients in whom the therapeutic decision was to perform fibrinolysis at first medical contact, the time between ECG acquisition and treatment exceeded the recommended threshold (> 10 minutes).

When the therapeutic decision was to perform pPCI, the time between ECG acquisition and pPCI exceeded the recommended threshold (> 120 minutes) in 79.6% of cases (table 2).

Among patients located more than 90 minutes from a PCI-capable center who did not receive fibrinolysis at first medical contact, the reason for withholding treatment was not documented in 87 cases (68.5%). Although 76.5% of patients were situated more than 90 minutes from the PCI-capable center, a substantial underuse of fibrinolytic treatment was observed. Of note, patients with a longer time interval from symptom onset to ECG acquisition were more likely to receive fibrinolytic treatment earlier.

Interhospital transfers, incidents without participation of air advanced life support, and nighttime incidents located more than 90 minutes from the PCI-capable center showed greater delays in performing pPCI. Exclusive use of ground ambulance for transfer to the PCI-capable center was associated with a 96.9% rate of delay and emerged as the primary variable in the classification tree for delay between ECG acquisition and pPCI. Among helicopter transfers, delays were more frequent in interhospital transfers (85.4%). In primary or delayed primary transfers, delays were more common when the incident location was more than 90 minutes from the PCI-capable center (65.1%) compared with locations less than 90 minutes away (23.1%) (figure 3).

Mortality

A total of 18 patients (8.1%) died within the first 15 days. Mortality was significantly higher in patients who experienced a major event (asystole, intubation, shock, or ventricular fibrillation) within the first 24 hours. Age was significantly associated with mortality only at the 48-hour and 15-day follow-up. There were no significant differences in 15-day mortality between patients treated with fibrinolysis and those directly transferred for pPCI. Increased mortality was associated with treatment delays, particularly in the early mortality subgroup (< 24 hours); however, these differences did not reach statistical significance (table 3).

DISCUSSION

In our study, only 20.4% of patients who underwent pPCI received treatment within 120 minutes. Only 4 of the 47 patients treated with fibrinolysis received therapy within 10 minutes.

Several studies, such as the STREAM,[13] have shown that prehospital fibrinolysis followed by early pPCI may offer results similar to direct transfer for pPCI if patients are treated within the first 3 hours from symptom onset. In our analysis, we identified underuse of fibrinolytic therapy, along with insufficient documentation of the reasons for withholding treatment.

In contrast to the studies by Stopyra et al.[9,14] conducted in North Carolina (United States) in which 60.5% of patients underwent pPCI within ≤ 90 minutes, only 20.4% of patients in our study achieved reperfusion within a broader threshold (< 120 minutes). These findings underscore longer treatment delays in our region and support more frequent consideration of fibrinolytic therapy.

Table 1. Clinical characteristics and care times of activated STEMI codes and comparison according to therapeutic decision

Clinical and care characteristics	Total AMI (n = 221)*	No fibrinolysis (n = 173)	Fibrinolysis (n = 47)	*P*
Female sex	61 (27.6)	47 (27.2)	13 (27.7)	1
Age (years)	64.7 (13.7)	65.7 (13.7)	60.7 (12.7)	.023
Year				.201
2015	30 (13.6)	25 (14.5)	5 (10.6)	
2016	34 (15.4)	24 (13.9)	10 (21.3)	
2017	27 (12.2)	17 (9.83)	9 (19.1)	
2018	35 (15.8)	27 (15.6)	8 (17.0)	
2019	57 (25.8)	46 (26.6)	11 (23.4)	
2020	38 (17.2)	34 (19.7)	4 (8.51)	
Residents in Alt Pirineu i Aran health region	149 (67.4)	118 (68.2)	30 (63.8)	.695
Altitude (m)	838 [691;1202]	790 [659;1202]	974 [691;1202]	.08
Location of first medical contact				.01
Primary care center	65 (29.4)	57 (32.9)	8 (17.0)	
Home	20 (9.05)	18 (10.4)	2 (4.26)	
County hospital	94 (42.5)	63 (36.4)	30 (63.8)	
EMS or public setting	42 (19.0)	35 (20.2)	7 (14.9)	
Night shift	56 (25.3)	34 (19.7)	22 (46.8)	< .001
Sympton onset–first medical contact time (min)	80.0 [35.0;193]	82.0 [39.0;210]	60.0 [30.0;180]	.292
First medical contact–ECG acquisition time (min)	6.00 [1.00;12.0]	6.00 [1.00;12.0]	5.00 [2.50;12.0]	.807
Sympton onset–ECG acquisition time (min)	90.0 [45.0;216]	91.0 [49.0;253]	80.0 [37.5;192]	.182
Estimated time to PCI-capable center (min)	106 [93.0;112]	105 [84.0;109]	107 [96.0;114]	.061
Estimated time to PCI-capable center ≥ 90 min	169 (76.5)	127 (73.4%)	41 (87.2)	.074
Distance to PCI-capable center (km)	131 [116;143]	131 [100;142]	131 [127;149]	.393
Type of transfer				.036
Interhospital	123 (55.7)	89 (51.4)	33 (70.2)	
Delayed	71 (32.1)	63 (36.4)	8 (17.0)	
Primary	27 (12.2)	21 (12.1)	6 (12.8)	
Mode of transport				< .001
Ambulance	106 (48.0)	69 (39.9)	36 (76.6)	
Helicopter	56 (25.3)	49 (28.3)	7 (14.9)	
Ambulance + helicopter	59 (26.7)	55 (31.8)	4 (8.51)	
Past medical history				
Hypertension	104 (47.1)	85 (49.1)	18 (38.3)	.248
Diabetes	49 (22.2)	42 (24.3)	6 (12.8)	.135
Dyslipidemia	92 (41.6)	69 (39.9)	23 (48.9)	.343
Smoking	63 (28.5)	47 (27.2)	16 (34.0)	.458
Previous AMI	25 (11.3)	21 (12.1)	4 (8.51)	.663
Previous pPCI	25 (11.3)	22 (12.7)	3 (6.38)	.34
Stroke	16 (7.24)	14 (8.09)	2 (4.26)	.532
Previous antiplatelet therapy	40 (18.1)	35 (20.2)	5 (10.6)	.194
Treatment and prehospital complications				
Shock	8 (3.62)	5 (2.89)	2 (4.26)	.643
Ventricular fibrillation	6 (2.71)	4 (2.31)	2 (4.26)	.611
Asystole	6 (2.71)	3 (1.73)	2 (4.26)	.29
Intubation	7 (3.17)	4 (2.31)	2 (4.26)	.611

AMI, acute myocardial infarction; ECG, electrocardiogram; EMS, Emergency Medical Services of Catalonia; PCI-capable center, percutaneous coronary intervention capable center; pPCI, primary or secondary percutaneous coronary intervention.

* Includes 1 patient who died without therapeutic decision.

Distribution of totals, no fibrinolysis, and fibrinolysis. Values are expressed as percentage or median. Quantitative variables are expressed as mean (standard deviation) or median [25th percentile; 75th percentile].

Table 2. Factors associated with delay in reperfusion treatment

Clinical and care characteristics	Fibrinolysis (n = 47)	≤ 10 min	> 10 min	*P*	pPCI (n = 162)	≤ 120 min	> 120 min	*P*
Female sex	13 (27.7)	3 (75.0)	10 (23.3)	.059	45 (27.8)	6 (18.2)	39 (30.2)	.245
Age (years)	60.7 (12.7)	61.2 (13.8)	60.7 (12.7)	.943	65.3 (13.4)	65.3 (13.3)	65.3 (13.5)	1
Residents in Alt Pirineu i Aran health region	30 (63.8)	3 (75.0)	27 (62.8)	1	109 (67.3)	22 (66.7)	87 (67.4)	1
Altitude (m)	974 [691;1202]	946 [649;1202]	974 [691;1202]	.859	692 [640;1202]	692 [524;957]	838 [691;1202]	.079
Location of first medical contact				.13				.014
Primary care center	8 (17.0)	2 (50.0)	6 (14.0)		55 (34.0)	12 (36.4)	43 (33.3)	
Home	2 (4.26)	0 (0.00)	2 (4.65)		16 (9.88)	5 (15.2)	11 (8.53)	
County hospital	30 (63.8)	1 (25.0)	29 (67.4)		58 (35.8)	5 (15.2)	53 (41.1)	
EMS or public setting	7 (14.9)	1 (25.0)	6 (14.0)		33 (20.4)	11 (33.3)	22 (17.1)	
Night shift	22 (46.8)	3 (75.0)	19 (44.2)	.328	31 (19.1)	1 (3.03)	30 (23.3)	.017
Symptom onset–first medical contact time (min)	60.0 [30.0;180]	190 [180;200]	57.0 [28.5;152]	.047	82.5 [40.0;206]	60.0 [40.0;116]	90.0 [40.0;255]	.124
First medical contact–ECG acquisition time (min)	5.00 [2.50;12.0]	3.00 [0.75;7.50]	6.00 [3.00;12.0]	.421	6.00 [1.00;11.8]	6.00 [1.00;10.0]	6.00 [1.00;12.0]	.75
Symptom onset–ECG acquisition time (min)	80.0 [37.5;192]	198 [191;202]	60.0 [35.0;160]	.05	93.5 [50.0;250]	80.0 [43.0;117]	115 [57.0;309]	.053
Time to PCI-capable center (min)	106 (15.9)	101 (16.2)	106 (16.0)	.614	105 [82.5;110]	97.0 [71.0;108]	106 [94.0;111]	.309
Time to PCI-capable center ≥ 90 min	41 (87.2)	3 (75.0)	38 (88.4)	.432	118 (72.8)	19 (57.6)	99 (76.7)	.047
Distance to PCI-capable center (km)	131 [127;149]	132 [123;138]	131 [127;149]	.969	131 [100;143]	123 [85.0;137]	131 [123;143]	.085
Type of transfer				.342				.001
Interhospital	33 (70.2)	2 (50.0)	31 (72.1)		83 (51.2)	8 (24.2)	75 (58.1)	
Delayed	8 (17.0)	1 (25.0)	7 (16.3)		59 (36.4)	18 (54.5)	41 (31.8)	
Primary	6 (12.8)	1 (25.0)	5 (11.6)		20 (12.3)	7 (21.2)	13 (10.1)	
Mode of transport				1				< .001
Ambulance	36 (76.6)	4 (100)	32 (74.4)		65 (40.1)	2 (6.06)	63 (48.8)	
Helicopter	7 (14.9)	0 (0.00)	7 (16.3)		48 (29.6)	18 (54.5)	30 (23.3)	
Ambulance + helicopter	4 (8.51)	0 (0.00)	4 (9.30)		49 (30.2)	13 (39.4)	36 (27.9)	

ECG, electrocardiogram; EMS, Emergency Medical Services of Catalonia; PCI-capable center, percutaneous coronary intervention capable center; pPCI, primary or secondary percutaneous coronary intervention. Values are expressed as percentage or median. Quantitative variables are expressed as mean (standard deviation) or median [25th percentile; 75th percentile].

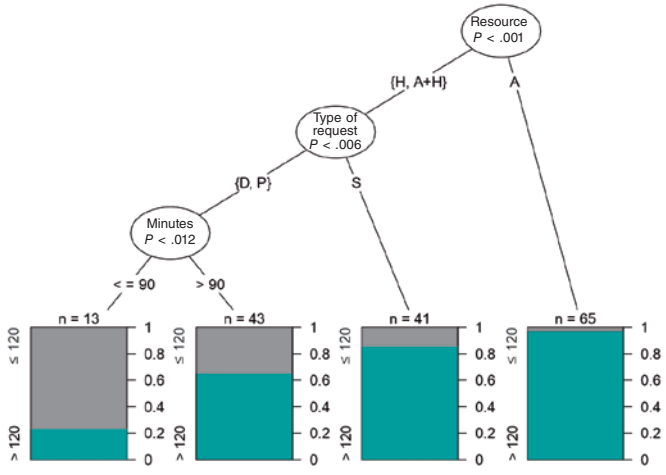

Figure 3. Classification tree for delay in primary percutaneous coronary intervention (pPCI). Three factors were significantly associated with delay: mode of transport (ambulance [A], helicopter [H], or combined use), type of activation (primary [P], delayed [D], or interhospital [S]), and estimated road travel time from the event location to the PCI-capable center in minutes (> 90 minutes < 90 minutes).

Although Aboal et al.[10,11] reported higher mortality rates associated with delayed pPCI, we did not observe a significant association in our study, despite a substantial lower proportion of patients undergoing pPCI within the target time (20.4% vs 42%). In addition, fibrinolysis was more frequently used in patients located more than 50 km from the PCI-capable center (66.7%), reflecting structural and logistical constraints specific to the Alt Pirineu-Aran region that influence treatment selection and reperfusion times.

In line with former evidence regarding mortality, the study results reinforce the clinical importance of time to care as a potential factor associated with worse prognosis, which is particularly relevant in early mortality (< 24 hours).

Compared with the study by Carol et al.,[15] in which 58% of patients underwent pPCI after more than 120 minutes, our data show a substantial higher proportion (79.6%). Factors associated with delay, such as intubation, initial shock, and nighttime care, were consistent between the 2 studies; however, other variables, including left bundle branch block, were not. A notable finding of our study is that the care delivered by the EMS was associated with shorter treatment times compared with county hospitals.

Table 3. Factors associated with mortality according to time from clinical course prior to death

Clinical and care characteristics	Pre-PCI-capable center (n = 3)	< 24 h (n = 8)	< 48 h (n = 12)	*P*	≤ 15 days (n = 18)	*P*
Female sex	1 (33.3)	2 (25.0)	4 (33.3)	.741	6 (33.3)	.587
Age (years)	67.7 (25.7)	69.8 (16.0)	74.4 (15.8)	.047	74.1 (14.1)	.008
Residents in Alt Pirineu i Aran health region	2 (66.7)	6 (75.0)	9 (75.0)	.755	13 (72.2)	.848
Altitude (m)	974 [721;1042]	832 [691;1014]	691 [468;1014]	.154	832 [691;1136]	.625
Location of first medical contact				.337		.514
Primary care center	0 (0.00)	1 (12.5)	1 (8.33)		3 (16.7)	
Home	0 (0.00)	1 (12.5)	1 (8.33)		1 (5.56)	
County hospital	2 (66.7)	4 (50.0)	7 (58.3)		9 (50.0)	
EMS or public setting	1 (33.3)	2 (25.0)	3 (25.0)		5 (27.8)	
Night shift	0 (0.00)	1 (12.5)	2 (16.7)	.735	4 (22.2)	1
Symptom onset–first medical contact time (min)	38.0 [19.0;246]	64.5 [22.0;488]	41.0 [22.0;488]	.502	65.0 [26.2;413]	.723
First medical contact–ECG acquisition time (min)	30.0 [17.0;11 542]	3.00 [0.00;11.2]	1.50 [0.00;11.2]	.152	2.00 [0.00;24.0]	.205
Symptom onset–ECG acquisition time (min)	42.0 [36.0;11 774]	66.5 [28.8;682]	45.0 [30.0;682]	.543	81.0 [42.8;518]	.962
Estimated time to PCI-capable center (min)	96.0 [90.5;113]	107 [95.8;107]	96.0 [81.5;107]	.242	96.0 [95.0;107]	.432
Estimated time to PCI-capable center ≥ 90 min	2 (66.7)	7 (87.5)	8 (66.7)	.483	14 (77.8)	1
Distance to PCI-capable center (km)	134 [108;149]	131 [130;132]	131 [85.0;131]	.15	131 [119;134]	.419
Type of transfer				.911		.938
Secondary	2 (66.7)	4 (50.0)	8 (66.7)		11 (61.1)	
Delayed	1 (33.3)	3 (37.5)	3 (25.0)		5 (27.8)	
Primary	0 (0.00)	1 (12.5)	1 (8.33)		2 (11.1)	
Mode of transport				.508		.734
Ambulance	1 (33.3)	3 (37.5)	5 (41.7)		10 (55.6)	
Helicopter	1 (33.3)	1 (12.5)	2 (16.7)		3 (16.7)	
Ambulance + helicopter	1 (33.3)	4 (50.0)	5 (41.7)		5 (27.8)	
Fibrinolytic therapy at first medical contact	2 (100)	2 (28.6)	2 (18.2)	1	4 (23.5)	.764
Delayed fibrinolytic therapy or pPCI	2 (100)	7 (100)	10 (90.9)	.693	16 (94.1)	.318
Past medical history						
Hypertension	1 (33.3)	4 (50.0)	7 (58.3)	.612	11 (61.1)	.317
Diabetes	1 (33.3)	2 (25.0)	3 (25.0)	.731	5 (27.8)	.558
Dyslipidemia	0 (0.00)	2 (25.0)	4 (33.3)	.765	7 (38.9)	1
Smoking	0 (0.00)	1 (12.5)	1 (8.33)	.186	4 (22.2)	.731
Previous AMI	0 (0.00)	1 (12.5)	2 (16.7)	.631	3 (16.7)	.437
Previous pPCI	0 (0.00)	1 (12.5)	2 (16.7)	.631	2 (11.1)	1
Previous stroke	0 (0.00)	0 (0.00)	0 (0.00)	1	1 (5.56)	1
Prior antiplatelet therapy	0 (0.00)	0 (0.00)	2 (16.7)	1	3 (16.7)	1
Treatment and prehospital complications						
Shock	2 (66.7)	3 (37.5)	4 (33.3)	< .001	6 (33.3)	< .001
Ventricular fibrillation	2 (66.7)	3 (37.5)	3 (25.0)	.002	3 (16.7)	.008
Asystole	3 (100)	5 (62.5)	5 (41.7)	< .001	5 (27.8)	< .001
Intubation	3 (100)	4 (50.0)	4 (33.3)	< .001	4 (22.2)	.001

AMI, acute myocardial infarction; ECG, electrocardiogram; EMS, Emergency Medical Services of Catalonia; PCI-capable center, percutaneous coronary intervention capable center; pPCI, primary or secondary percutaneous coronary intervention.
Values are expressed as percentage or median. Quantitative variables are expressed as mean (standard deviation) or median [25th percentile; 75th percentile].

Patient origin, geographic location, sex, number of resources involved, time required for therapeutic decision-making, and mode of transport influenced treatment times as well. Hakim et al.[16] suggest that helicopter transport is less effective than ground transport, especially for distances of less than 50 km. In our study, 71% of patients transferred by helicopter (all located more than 50 km from the PCI-capable center) received pPCI after more than 120 minutes, which may be associated with the lack of a helipad at the reference PCI-capable center, requiring additional ground transfer, and service hours, mainly daytime during the study period. In constrast to other studies conducted during the COVID-19 pandemic,[17,18] our series did not demonstrate a reduction in case volume or prolongation in alert time. However, 2020 was the year with the lowest use of fibrinolysis (4 cases, 10.5%).

Several studies indicate that delays in STEMI recognition and code activation have a direct impact on reperfusion time. One study highlights that training significantly improves these times,[19] suggesting that lack of training or skills among professionals may generate delays in care and lower use of fibrinolysis. Our study shows appropriate timing in ECG acquisition and emergency recognition by teams. Delayed primary transfers included the highest percentages of patients with optimal reperfusion times (table 2).

Our findings underscore the need to review and optimize action protocols, particularly in non-PCI-capable centers and geographic areas with greater delays. It is essential to optimize professional response to suspected STEMI, improve therapeutic decision-making time, and explore innovative solutions such as triage systems and STEMI code detection with technological support, optimization of air transport, and greater coordination between PCI and non-PCI capable centers.

Limitations and strengths

This study has limitations due to the small population size in the rural areas studied, which required extending the study period to 6 years to obtain the collected sample. This extension implies that data underwent several changes in record systems (from paper to digitized format) and organizational modifications (implementation of triage in emergency departments and nighttime helicopter flights). The sample of 221 patients remains limited and may have affected the statistical power to detect significant differences between analyzed variables. Similarly, distances from the incident location and estimated average travel times under optimal conditions were used, without accounting for any potential delays due to traffic or other unforeseen factors.

CONCLUSIONS

The results of this study demonstrate the need to increase the use of fibrinolysis in areas distant from a PCI-capable center to reduce reperfusion delays. Documentation of the reasons for not performing fibrinolysis should be improved, as this limits interpretation regarding therapeutic appropriateness. Joint initial care by primary care and emergency teams, as well as delayed primary transfers, reduce reperfusion times and avoid interhospital transfers. Finally, the low number of deaths during the study period prevents multivariate analysis and only allows identification of the variables or characteristics associated with mortality described in the results.

Despite these limitations, the study provides a comprehensive analysis of variables and describes in detail how the investigated population is managed and transferred, something unprecedented in this context. In addition, cross-referencing and thorough review of 2 databases provide valuable information to assess treatment delays. Therefore, this study is a solid basis for future advances in improving STEMI code management in rural areas.

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ETHICAL CONSIDERATIONS

This study was approved by the IDIAP Jordi Gol Ethics Committee, code CEIm 22/238-P. The SAGER guidelines were followed regarding potential sex and gender bias.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

ChatGPT was used to improve the wording of some paragraphs of the article. After using this tool, the authors reviewed and edited the content as necessary and take full responsibility for the final version.

AUTHORS' CONTRIBUTIONS

M. Navarra Llorens was responsible for study conception and design, overall supervision, and manuscript drafting. M. Martínez Alonso conducted the statistical analysis, interpreted the results, and critically reviewed the content. Y. Azeli was responsible for clinical analysis and critical review. S. Ferrandis Barrés collected data and contributed to the discussion and critical review. M. Canelles Seix collected data and reviewed the manuscript. L. Duch Grau participated in data collection, manuscript review, and final approval. A.M. Forradelles Rey collected data and performed critical review. M.A. Martínez Momblan supervised the project and critically reviewed the manuscript. X. Jiménez-Fàbrega supervised the project and provided intellectual contributions to the discussion. All authors approved the final text.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- STEMI requires early coronary reperfusion to reduce mortality and improve prognosis.
- In Catalonia, implementation of the STEMI code has optimized system response; however, in regions such as Alt Pirineu, delays have not been specifically evaluated.

WHAT DOES THIS STUDY ADD?

- This study shows significant underuse of fibrinolytic therapy, even among patients located far from a PCI-capable center. In additions, it highlights the absence of systematic documentation regarding the reasons for withholding fibrinolysis, thereby limiting the evaluation of therapeutic decision-making.

- The study demonstrates that joint initial care by primary care and emergency teams, along with delayed primary transfer, can reduce reperfusion times and avoid inter-hospital transfers, which are associated with longer delays.
- Similarly, it identifies the mode of transport as the main predictive variable for delay and shows that exclusive use of ground ambulance is the most critical factor.
- Although the low number of deaths prevents a robust multivariate analysis, characteristics associated with mortality are described, and the influence of delays is confirmed, reinforcing the need for adapted strategies.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M26000570.

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Original article

Out-of-hours presentation and 30-day myocardial infarction mortality in Mexico: a 2014-2023 retrospective study

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ABSTRACT

Introduction and objectives: Although acute myocardial infarction (AMI) remains a leading cause of death in Mexico, the impact of out-of-hours presentation on mortality remains understudied. The aim of this study was to evaluate the association between out-of-hours admissions (nights, weekends, holidays) and 30-day mortality in patients with AMI in Mexican hospitals, with a focus on the role of catheterization laboratories (cath lab).
Methods: We conducted a retrospective cohort study to analyze emergency admissions from December 2014 through August 2023. Admissions were classified as out-of-hours or during-hours and were stratified by hospital type (with or without cath lab). Cox regression models adjusted for sociodemographic, health, and temporal variables were used to analyze mortality risks.
Results: The study included a total of 29 131 cases: 4515 in percutaneous coronary intervention (PCI)-capable centers (group 1) and 24 616 in non-PCI-capable centers (group 2). Admissions outside regular hours accounted for 46.7% in group 1 and 53.6% in group 2. Adjusted analysis showed that although the presence of a cath lab was protective (HR, 0.25; 95%CI, 0.23-0.28), admissions outside regular hours increased the risk of mortality in both groups (group 1: HR, 1.25; 95%CI, 1.04-1.50; group 2: HR, 1.16; 95%CI, 1.11-1.22). Although overnight shifts increased the risk of death in both groups, weekends and holidays increased such risk only in non-PCI-capable centers.
Conclusions: Out-of-hours admissions were associated with higher mortality, and unlike in developed countries, the presence of a cath lab did not improve out-of-hours outcomes.

Keywords: Acute myocardial infarction. Out-of-hours. Mexico.

Presentación fuera de horario y mortalidad por infarto a 30 días en México: estudio retrospectivo 2014-2023

RESUMEN

Introducción y objetivos: El infarto agudo de miocardio (IAM) sigue siendo una causa principal de muerte en México, pero el impacto de su presentación fuera de horario sobre la mortalidad está poco investigado. El objetivo de este estudio fue evaluar la asociación entre las admisiones fuera de horario (noches, fines de semana y festivos) y la mortalidad a 30 días en pacientes con IAM en hospitales mexicanos, con énfasis en el papel de las salas de hemodinámica (SH).
Métodos: Se realizó un estudio de cohorte retrospectivo que analizó las admisiones en urgencias desde diciembre de 2014 hasta agosto de 2023. Las admisiones se clasificaron como fuera o dentro de horario, y se estratificaron según el tipo de hospital (con o sin SH). Se emplearon modelos de regresión de Cox ajustados por variables sociodemográficas, de salud y temporales para analizar el riesgo de mortalidad.
Resultados: El estudio incluyó 29.131 casos: 4.515 en hospitales con SH (grupo 1) y 24.616 en hospitales sin esta infraestructura (grupo 2). Las admisiones fuera de horario representaron el 46,7% en el grupo 1 y el 53,6% en el grupo 2. El análisis ajustado mostró que, aunque la presencia de un laboratorio de cateterismo fue protectora (HR = 0,25; IC95%, 0,23-0,28), las admisiones fuera de horario aumentaron el riesgo de mortalidad en ambos grupos (grupo 1: HR = 1.25; IC95%, 1,04-1,50; grupo 2: HR = 1,16; IC95%, 1,11-1,22). Los turnos nocturnos también incrementaron el riesgo de muerte en ambos grupos, pero los fines de semana y festivos solo lo hicieron en los hospitales sin laboratorio de cateterismo.
Conclusiones: Las admisiones fuera de horario se asociaron con mayor mortalidad y, a diferencia de los países desarrollados, la presencia de una SH no mejoró los resultados fuera de horario.

Palabras clave: Infarto agudo de miocardio. Fuera de horario. México.

Abbreviations

AMI: acute myocardial infarction. **Cath lab:** catetherization laboratory. **PCI:** percutaneous coronary intervention.

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INTRODUCTION

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide, despite advances in prevention and treatment.[1-3] Evidence suggests that patients with AMI admitted outside working hours–nights, weekends, and holidays–experience worse outcomes,[4-6] likely due to treatment delays,[7] limited specialist availability, and operational constraints.[4,8,9] While this association is well-documented in high-income settings, its impact in low- and middle-income countries such as Mexico, where health care resources are often constrained, remains less understood.[10-12]

Among Organisation for Economic Co-operation and Development (OECD) countries, Mexico reports the highest AMI mortality rate (23.7%), far exceeding the OECD average of 7%.[3,12] Throughout the past century, the Mexican public health system has evolved from fragmentation to institutional organization, with key institutions such as the Mexican Social Security Institute (IMSS) (est. 1943) and the Institute for Social Security and Services for State Workers or Civil Service Social Security and Services Institute (ISSSTE) serving formal and public-sector workers, respectively.[13,14] To address coverage gaps for the uninsured, programs such as *Seguro Popular* (2003), Institute of Health for Welfare (INSABI) (2020), and IMSS-BIENESTAR (2023) were established. In recent years, more than 53 million uninsured individuals, about 42% of the population, receive care through the Mexican Ministry of Health (SSA) across nearly 12 000 health centers and more than 680 hospitals.[13]

Despite system reforms, the management of AMI in Mexico remains hindered by limited access to specialized services, fragmented insurance coverage, and an underperforming emergency response system. These issues, exacerbated by socioeconomic disparities and insufficient preventive care, contribute to delays and reduced quality of treatment.[15,16] The main aim of the current study was to evaluate the association between out-of-hours presentation and 30-day AMI-related mortality in Mexican emergency departments.

METHODS

Study design, guidelines, and data source

We conducted a retrospective cohort study in full compliance with the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[17] The present study used information from the public database of emergency department admissions from December 2014 through August 2023 in Mexico, published and validated by the General Directorate of Health (DGIS).[18] This database compiles anonymous information from the SSA hospital registry (*Seguro Popular*/INSABI/IMSS-BIENESTAR programs) nationwide. Additional information on individual treatments (eg, percutaneous coronary intervention [PCI], thrombolysis, or door-to-balloon time), patient comorbidities, and delays in patient arrival was not available in the database.

Participants and sample size

The study included cases diagnosed with AMI (International Classification of Diseases [ICD-10, I21.0 to I21.9]), with lengths of stay of ≤ 30 days, classified as a qualified emergency, aged ≥ 18 years, and treated in a SSA hospital. Cases without complete information or not treated in the emergency department (referred to another health care unit, voluntarily discharged, or referred to outpatient care) were excluded from the analysis.

Definition of predictors and outcome

Sociodemographic (sex and age), time-related variables (admission and discharge dates), health care-related variables (type of emergency, discharge status, bed type, and AMI type according to ICD-10), and catheterization laboratories (cath labs) characteristics were collected. Several variables were grouped for analysis, including region of residence, death (yes/no), and length of stay (admission-to-discharge interval). The main predictor, out-of-hours, was defined as admissions during overnight shifts (19:00-6:59 h), weekends, or official holidays (per Article 74 of the Mexican Federal Labor Law).[19] Furthermore, the COVID-19 pandemic (from 23 March 2020 to 9 May 2023)[20] was considered. Hospitals were classified as PCI-capable and non-PCI-capable centers based on the SSA equipment database; and accurate and up-to-date information on PCI-capable centers was obtained; detailed definitions are provided in table S1.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. The primary sample was divided into 2 groups to observe the differences between PCI-capable and non-PCI-capable centers, and all analyses were systematically performed in each group. The chi-square and Student *t* tests evaluated the difference between the out-hours and on-hours groups. Univariate and multivariate Cox regression analyses were performed with proportional hazards adjusted for age, sex, year of admission, type of emergency, type of bed, territorial regions, type of AMI, admission during the COVID-19 pandemic, and characteristics of the cath lab. Moreover, Kaplan-Meier survival curves were constructed to estimate and visualize the cumulative mortality rate according to out-of-hours admission components. Statistical significance was set at $P < .05$. Confidence intervals (CI) were set at 95% (95%CI). Descriptive and analytical methods were performed in SPSS, version 25.0 (IBM, United States) and R software version 4.2.0 (R Foundation for Statistical Computing, Austria).

Ethical considerations

The study was based on data from the public emergency income database published by the DGIS.[4] Accordingly, the confidentiality of the subjects is governed by the Mexican standard NOM-012-SSA3-2012,[21] and the study is classified as risk-free research based on the principles of the General Law of Research for Health.[22] The research was approved by the Ethics Committee of the Women's Hospital, SSA (No. 202403-47).

RESULTS

General characteristics

The final dataset included a total of 29 131 cases: 4515 from PCI-capable centers (group 1) and 24 616 from non-PCI-capable centers (group 2) (figure 1). Out-of-hours admissions accounted for 46.7% in group 1 and 53.6% in group 2, with night admissions being the most frequent and holiday admissions the least common (table S2). Among PCI-capable centers, 32.2% provided nightshift coverage, while 53.1% offered weekend availability. Out-of-hours admissions were associated with a higher proportion of male patients, longer lengths of stay, greater use of shock beds, higher mortality, more pronounced regional differences, and a greater impact of the COVID-19 pandemic (table S3). Moreover, in PCI-capable centers, out-of-hours admissions were associated with a lower daily average number of procedures and fewer professionals per shift (table S4).

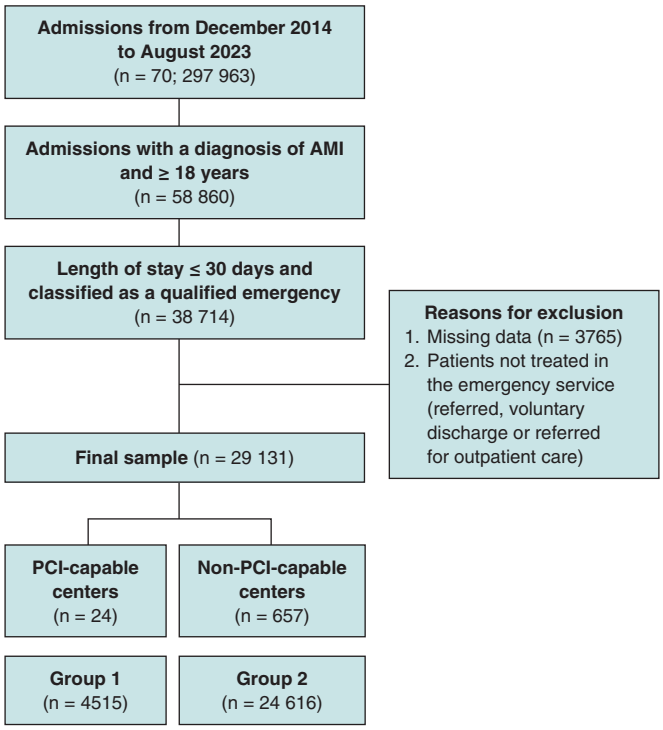

Figure 1. Flowchart of filtering process. Patients with AMI (ICD-10 I21.0-I21.9), aged ≥ 18 years, hospitalized ≤ 30 days in Ministry of Health (SSA) emergency services were included. Cases with incomplete data or not treated in emergency care were excluded. The final cohort was categorized as PCI-capable and non-PCI-capable centers, identified through percutaneous coronary intervention or cardiac catheterization records. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.

Association between out-of-hours care and the risk of death

Univariate analysis showed that the presence of a cath lab was protective (HR, 0.22; 95%CI, 0.204-0.246). Out-of-hours, overnight shifts, weekend admissions, and the COVID-19 pandemic were associated with higher mortality in both groups. The risks from out-of-hours (HR, 1.46; 95%CI, 1.21-1.73 vs HR, 1.18; 95%CI, 1.11-1.23) and night-shift admissions (HR, 1.18; 95%CI, 1.12-1.23 vs HR, 1.13; 95%CI, 1.08-1.18) were more pronounced in PCI-capable centers, and holidays increased mortality only in non-PCI-capable centers (HR, 1.21; 95%CI, 1.03-1.41) (figure 2). Among cath lab characteristics, higher mean procedure volume (HR, 0.888; 95%CI, 0.840-0.938), greater staffing (HR, 0.800; 95%CI, 0.760-0.842), and availability during afternoon (HR, 0.515; 95%CI, 0.427-0.620), night (HR, 0.290; 95%CI, 0.233-0.361), and weekend shifts (HR, 0.317; 95%CI, 0.264-0.380) were associated with reduced mortality.

After adjusting for potential confounders, the presence of a cath lab remained protective (HR, 0.25; 95%CI, 0.23-0.28), whereas out-of-hours, night-shift admissions, and the COVID-19 pandemic continued to be associated with increased mortality in both groups. Adjusted mortality risk from out-of-hours (HR, 1.25; 95%CI, 1.04-1.50 vs HR, 1.18; 95%CI, 1.12-1.23) and night-shift admissions (HR, 1.27; 95%CI, 1.06-1.53 vs HR, 1.11; 95%CI, 1.06-1.17) persisted, while weekend and holiday effects remained significant only in non-PCI-capable centers (figure 2). Regarding cath lab characteristics, only nightshift availability (HR, 0.149; 95%CI, 0.089-0.248) and mean health care staff per shift (HR, 0.770; 95%CI, 0.710-0.834) were significantly associated with reduced mortality. Kaplan-Meier survival curves are shown in figure 3.

DISCUSSION

Major findings

This nationwide study examined AMI admissions across a large number of Mexican hospitals, comparing PCI-capable and non-PCI-capable centers. Out-of-hours admissions were common and associated with higher mortality, longer lengths of stay, greater shock bed use, and a higher proportion of male patients. While the presence of a cath lab appeared generally protective after adjustment, out-of-hours and nightshift admissions showed a modest increase in mortality in both groups. Although weekend and holiday effects were more evident in non-PCI-capable centers, these results should be interpreted with caution given the absence of detailed clinical data, including reperfusion strategies, ST-segment elevation myocardial infarction/non-ST-segment elevation myocardial infarction (STEMI/NSTEMI) classification, and comorbidities.

A key finding is that PCI-capable centers did not fully eliminate excess mortality during out-of-hours periods. Advanced interventional capabilities may mitigate some risk during weekends and holidays; however, challenges remain during overnight shifts, as only 32.2% of studied centers offered cath lab availability during overnight shifts. Out-of-hours admissions were associated with fewer procedures, lower staffing, and limited specialized personnel compared with regular hours, which is consistent with former studies[4,8,9] (table S4). Additional factors likely contributing to poorer outcomes include reduced staffing, delays in care, limited access to specialized personnel, and the impact of human factors such as fatigue and sleep deprivation during nightshifts, despite the availability of advanced cardiac interventions.[4,8,9] Longer door-to-balloon times, limited 24/7 cath lab coverage, and the relatively low number of cath labs per capita in Mexico further exacerbate these challenges. Moreover, the increased out-of-hours risk from PCI-capable centers may reflect their role as referral centers, where longer patient arrival times and procedural delays are more frequent.[16]

Pre-hospital and COVID-19 challenges in the management of AMI

Several institutions in Mexico have implemented programs to standardize the management of AMI, such as the IMSS and SOCIME national "Code Infarction" (2015) and ISSSTE "*AsISSSTE Infarto*" (2018).[23,24] In contrast, SSA-affiliated institutions (Seguro Popular/INSABI/IMSS-BIENESTAR) follow more varied protocols, leading to disparities in care. Consequently, heterogeneity in the management of AMI management across institutions likely exacerbates challenges in pre-hospital care. Regulated, by NOM-034-SSA3-2013 and coordinated via Medical Emergency Regulatory Centers,[25] the pre-hospital system faces challenges such as poor inter-institutional coordination, insufficient ambulance equipment, and personnel shortages, especially in rural areas. These factors increase response times and complicate AMI emergency management.[26] Former studies report prolonged door-to-balloon times (up to 648 minutes) due to traffic, fragmented health care, and delayed diagnosis, with weekend and nighttime admissions independently predicting treatment delays over 12 hours. While this study does not examine treatment or pre-hospital delays, other research highlights these as major issues in Mexico. Araiza-Garaygordobil et al.[16] reported a mean door-to-balloon time of 648 minutes in a Mexico City referral hospital, 3 times longer compared with developed countries, due to traffic, health care fragmentation and delayed primary diagnosis. Baños-González et al.[15] found that patient delays, often from symptom unawareness or limited resources, led to late arrivals (> 12 hours), with 60% being transported by ambulance. Weekend and nighttime admissions independently predicted delays > 12 hours, with a mean 11-hour wait for first medical contact.

Source	HR (95%CI)
PCI-capable centers	**Unadjusted**
*** Off-hours	1.4 (1.22-1.76)
*** Overnight shift	1.39 (1.16-1.67)
** Weekend	1.32 (1.08-1.61)
Holiday	1.31 (1.68-2.53)
*** COVID-19 pandemic	1.63 (0.36-1.96)
Non-PCI-capable centers	**Unadjusted**
*** Off-hours	1.18 (1.12-1.24)
*** Overnight shift	1.13 (1.08-1.19)
*** Weekend	1.10 (1.05-1.16)
** Holiday	1.25 (1.07-1.46)
*** COVID-19 pandemic	1.16 (1.11-1.22)
PCI-capable centers	**Adjusted**
* Off-hours	1.25 (1.04-1.50)
** Overnight shift	1.27 (1.06-1.53)
Weekend	1.09 (0.89-1.34)
Holiday	1.41 (0.72-2.75)
*** COVID-19 pandemic	2.73 (1.84-4.03)
Non-PCI-capable centers	**Adjusted**
*** Off-hours	1.18 (1.12-1.23)
*** Overnight shift	1.11 (1.06-1.17)
*** Weekend	1.11 (1.05-1.16)
* Holiday	1.17 (1.00-1.37)
*** COVID-19 pandemic	1.64 (1.50-1.79)

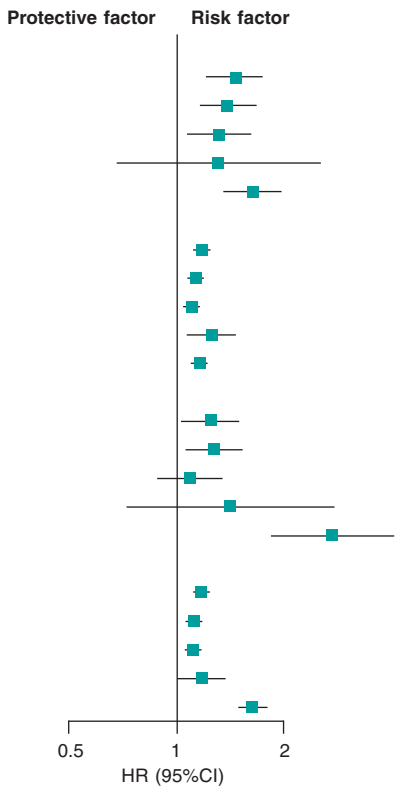

Figure 2. Mortality risk associated with out-of-hours admissions for acute myocardial infarction: analysis stratified by hospital type (PCI-capable and non-PCI-capable centers). The graph shows results from unadjusted and adjusted Cox regression models. Adjustments included age, sex, emergency type, bed type, region, year of admission, AMI type, and COVID-19 period. For PCI-capable centers, additional adjustments were made for cath lab availability by shift, angiography type, and number of specialists per shift. Points represent mortality HRs with horizontal lines for 95%CI. Results are shown separately for PCI-capable and non-PCI-capable centers. HR > 1 indicates increased mortality risk; HR < 1 indicates reduced risk. *P < .05; ** P < .01; *** P < .001. 95%CI, 95% confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; PCI, percutaneous coronary intervention.

The COVID-19 pandemic was associated with an increased AMI mortality in both hospital groups, with a more pronounced effect in PCI-capable centers. Globally, the pandemic disrupted health care delivery, reducing hospitalizations and PCI procedures, partly due to lower referral rates and patients' reluctance to seek care over concerns of viral exposure. Consequently, delays from symptom onset to first medical contact and prolonged door-to-balloon times occurred, both of which are known to adversely affect AMI outcomes.[27] In Mexico, Rodríguez-González et al.[28] reported a 51% decline in STEMI diagnoses in hospitals during early 2020, accompanied by longer arrival times and a 4.9%-6.8% increase in STEMI-related mortality. In other countries, such as Spain, PCI rates decreased by 10.1% during 2020.[29] A recent meta-analysis reported a significant reduction in the number of PCI (IRR, 0.72; 95%CI, 0.67-0.77), I^2 = 92.5%) and an increase in time from symptom onset to first medical contact by a mean 69.4 minutes ([11-127], I^2 = 99.4%) during the COVID-19 pandemic. However, no significant change was observed in door-to-balloon times (3.33 minutes [0.32-6.98]; I^2 = 94.2%).[30]

Although detailed clinical data were not available in our study, the impact of treatment on AMI mortality has been extensively investigated in Mexico. The nationwide RENASCA cohort[31] (21 826 patients, 2014–2017) reported high prevalence of diabetes (48%), hypertension (60.5%), smoking (46.8%), dyslipidemia (35.3%), and metabolic syndrome (39.1%) relative to multinational registries.[31,32] Patients with STEMI (14.9%) experienced higher cardiovascular mortality vs patients with NSTEMI (7.6%), reflecting referral patterns and more severe in-hospital complications, including cardiogenic shock and arrhythmias. Implementation of the IMSS "Code Infarction" program reduced patients without reperfusion from 65.2% to 28.6%, increased fibrinolysis to 40.1%, and PCI to 31.3%.[33] By comparison, Spain's well-structured "Code Infarction" protocol achieved a primary PCI rate of 87%, median door-to-balloon time of 193 minutes, and minimal pre-hospital delays, with 55.3% of patients receiving timely care and most remaining delays attributable to initial diagnosis (18.5%).[34]

Global trends in out-of-hours mortality: a comparison across regions

Compared with previous meta-analyses, which often lack data from developing regions such as Latin America, our findings highlight important disparities. Sorita et al.[4] reported higher short-term mortality rates and delayed PCI in patients with STEMI admitted outside regular hours, especially outside North America. Wang et al.[5] found a slight increase in short-term mortality but no effect on long-term outcomes or PCI risk. Other analyses showed no significant differences in mortality or door-to-balloon times.[35] Studies from developing countries such as Indonesia[36,37] reported no mortality differences by admission time, while in Iraq,[38] resource shortages and conflict led to higher out-of-hours mortality and limited reperfusion access. Latin American studies from Brazil[39-41] and Argentina[42] generally found no outcome differences by admission timing. Differences with our results are likely due to hospital infrastructure and staffing; Mexican public hospitals face substantial limitations after hours vs tertiary referral centers with 24/7 cath lab availability. Additionally, socioeconomic barriers and low awareness of AMI symptoms delay care, and the lack of standardized protocols further increases mortality risk.

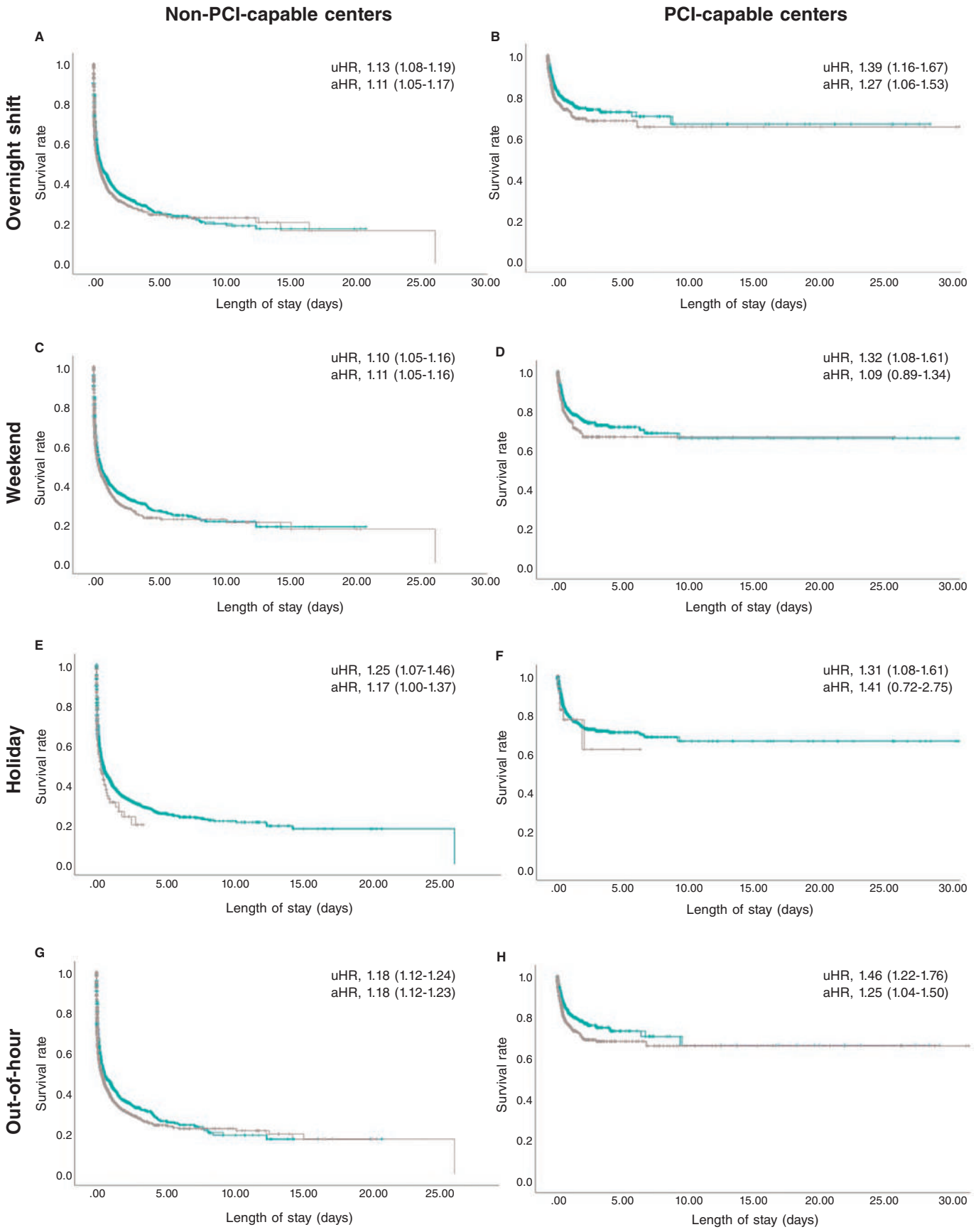

Figure 3. Kaplan–Meier analysis of mortality of out-of-hours acute myocardial infarctions by hospital type. Each column represents cath lab availability, while each row represents the components of out-of-hours admission. Each panel (A-H) shows the unadjusted (uHR) and adjusted mortality risk (aHR) with corresponding 95% confidence intervals.

Strategies to improve the out-of-hours management of AMI

The findings highlight several areas for improvement within the Mexican health care system, particularly regarding non-PCI-capable centers. All 3 components were associated with higher mortality, underscoring the need for enhanced pre-hospital and in-hospital management. Efforts should focus on early diagnosis, including increased availability of electrocardiography and the implementation of telemedicine platforms to allow cardiologists to promptly assess and guide treatment. Expanding access to thrombolytic therapy and ensuring experienced personnel are available during out-of-hours shifts can help reduce treatment delays. Furthermore, improving coordination across health centers through clear referral pathways, effective communication strategies, and standardized protocols, especially in hospitals serving uninsured patients, can streamline care and reduce variability in management. In PCI-capable centers, mortality was particularly elevated during overnight shifts, likely due to reduced cath lab availability within these hours. Despite existing protocols and optimized door-to-balloon times, strengthening nighttime staffing and training remains essential. This may include targeted training and incentives to encourage health care professionals to work during these shifts, thereby ensuring that high-quality care is maintained at all times.

Strengths and limitations

The present study is one of the largest cohorts to date examining the association between AMI-related mortality and time of presentation in Mexico. It provides valuable insights into the potential impact of out-of-hours admissions on outcomes, underscoring the importance of optimizing staffing, patient flow, and timely access to interventions such as PCI. Nevertheless, the findings should be interpreted with caution. The retrospective design, absence of detailed treatment information (eg, PCI, thrombolysis, door-to-balloon times), lack of comorbidity data, and inability to differentiate between STEMI and NSTEMI limit the depth and precision of the analyses. Furthermore, the study does not capture key factors such as patient-level delays, cath lab utilization patterns, or disparities in infrastructure and resource availability. Future research should integrate more comprehensive clinical and procedural data and explore the influence of provider fatigue, variability in care standards, and treatment delays to better delineate gaps in care.

CONCLUSIONS

Out-of-hours presentations were associated with high mortality rates, and contrary to findings in developed countries, the presence of a cath lab did not improve out-of-hours outcomes, which suggests that factors beyond cath lab availability, including systemic inefficiencies, resource limitations, and health infrastructure deficiencies, may profoundly affect patient outcomes in Mexico.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

Ethical approval for this study was granted by the Ethics Committee of the Women's Hospital, SSA (Approval No. 202403-47). The research used publicly available emergency income data published by the DGIS, for which subject confidentiality is governed by the Mexican standard NOM-012-SSA3-2012. In accordance with the General Health Research Law, the study is classified as risk-free research. Sex variable was defined as according to the definition of the Sex and Gender Equity in Research (SAGER) guidelines (table S1).

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No generative artificial intelligence (AI) tools were used in the conception, design, data collection and analysis of this manuscript. All content was produced entirely by the authors.

AUTHORS' CONTRIBUTIONS

D. Arriaga-Izabal contributed to the conceptualization, methodology, data curation, data analysis, investigation, and writing of the original draft. F. Morales-Lazcano was responsible for investigation, data curation, and drafting the original manuscript. A. Canizalez-Román provided supervision, project administration, and validation, and participated in the review and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Out-of-hours admissions (overnight shifts, weekends, holidays) are associated with higher AMI mortality, primarily due to treatment delays and reduced specialist availability.

WHAT DOES THIS STUDY ADD?

- Out-of-hours admissions in Mexican hospitals were associated with higher 30-day mortality rates, irrespective of cath lab availability. Although cath labs were generally protective, they did not fully mitigate risk during nights, weekends, or holidays, with increased mortality mainly observed in non-PCI-capable centers. The study is limited by the absence of detailed clinical data, including AMI type (STEMI/NSTEMI), reperfusion strategy, door-to-balloon times, and comorbidities, restricting conclusions regarding the precise impact of specialized care. Systemic factors, including staffing limitations and regional disparities, likely contribute to these outcomes, underscoring the need for improved out-of-hours AMI care.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M25000559.

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Special article

Device console programming in patients undergoing TAVI with preexisting cardiac implantable electronic devices: a practical guide

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) is established as the standard of care for patients across all surgical risk profiles, with expanding indications in younger and lower-risk populations. A substantial proportion of patients eligible for TAVI have preexisting cardiac implantable electronic devices (CIED). Temporary transvenous right ventricular (RV) pacing is routinely used during TAVI to facilitate procedural safety but carries inherent risks, including RV perforation, cardiac tamponade, and lead dislodgement. Alternative pacing strategies, such as left ventricular pacing via the valve delivery guidewire, have been proposed to reduce procedural complications. In patients with a preexisting CIED, leveraging the implanted device for procedural pacing represents a rational and potentially safer option. However, its adoption remains limited, largely due to unfamiliarity with device-specific programming. This article provides a detailed, step-by-step practical guide for programming rapid ventricular pacing using the most widely encountered CIED platforms: Biotronik, Medtronic, Abbott/St. Jude, Sorin, and Boston Scientific. The specific programming pathways for each manufacturer are summarized to facilitate safe, effective, and reproducible implementation during TAVI.

Keywords: TAVI. Pacing. Cardiac implantable electronic devices. Ventricular perforation.

Programación de dispositivos en pacientes con TAVI y dispositivos cardiacos implantables: una guía práctica

RESUMEN

El implante percutáneo de válvula aórtica (TAVI) se ha establecido como el estándar de atención para pacientes de todos los perfiles de riesgo quirúrgico. Una proporción significativa de los candidatos a TAVI son portadores de dispositivos cardiacos implantables (DCI). La estimulación ventricular derecha transvenosa temporal es una práctica habitual, pero conlleva riesgos como perforación ventricular, taponamiento y desplazamiento del electrodo. Para reducir las complicaciones se han propuesto estrategias de estimulación alternativas, como la estimulación ventricular izquierda a través de la guía de liberación de la válvula; sin embargo, en los pacientes con un DCI preexistente, aprovechar dicho dispositivo para la estimulación durante el procedimiento representa una opción racional y potencialmente más segura. No obstante, su utilización sigue siendo limitada, principalmente debido al desconocimiento de la programación específica de cada dispositivo. Este artículo ofrece una guía práctica detallada, paso a paso, para la programación de la estimulación ventricular rápida utilizando las plataformas de DCI más comunes (Biotronik, Medtronic, Abbott/St. Jude, Sorin y Boston Scientific) y se resume las rutas de programación específicas de cada fabricante para facilitar una implementación segura, eficaz y reproducible.

Palabras clave: TAVI. Marcapasos. Dispositivos cardiacos implantables. Perforación ventricular.

Abbreviations

CIED: cardiac implantable electronic device. **ICD:** implantable cardioverter defibrillator. **NIPS:** non-invasive programmed stimulation. **RV:** right ventricular. **TAVI:** transcatheter aortic valve implantation.

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as the preferred therapeutic option across the full spectrum of surgical risk, and more recently its indications have expanded to include younger patients and those at low surgical risk.[1-4] Patients undergoing TAVI are typically elderly and burdened with significant cardiovascular comorbidities, with a considerable proportion (8.7% to 23.1%) having preexisting cardiac implantable electronic devices (CIED).[5-6]

Temporary transvenous pacing is a well-established and integral component of TAVI, facilitating procedural success by reducing cardiac contractility during balloon aortic valvuloplasty and valve deployment. The target pacing rate varies according to the valve type: approximately 120 bpm for self-expanding valves and approximately 180 bpm for balloon-expandable valves.[7] In the 2 scenarios, the objective is to mitigate the risk of micro- or macro-dislodgement or embolization during implantation.

Notwithstanding its utility, temporary right ventricular (RV) pacing is associated with potential complications, including myocardial injury, RV dysfunction, and perforation, which may culminate in cardiac tamponade.[8-10] Furthermore, lead dislodgement and pacing failure have been reported among patients undergoing temporary pacing for a variety of indications, with incidence rates of approximately 4.6% and 9.5%, respectively. Although these figures are not specific to TAVI, they highlight that such complications are not rare and may result in ineffective pacing or sensing, thereby increasing the risk of critical intraoperative events, such as valve embolization or migration.[11]

To address these limitations, alternative pacing strategies have been proposed. Among them, left ventricular pacing via the valve delivery guidewire offers several advantages, such as elimination of the need for venous access, reduction of the risk of RV perforation, and potential reduction in procedural duration.[12,13]

In patients with preexisting CIED, use of the permanent device for procedural pacing appears to be a rational strategy to minimize complications.

The present article aims to address this unmet need by providing a concise and practical step-by-step guide for the use of the most widely encountered CIED programming consoles, thereby promoting safer and more efficient pacing management during TAVI.

USE OF ICD PROGRAMMING CONSOLES

This step-by-step guide for pacing patients with preexisting CIED during TAVI is derived from the routine clinical practice of our high-volume TAVI center, developed in close collaboration with our Electrophysiology Unit and in full compliance with the usage recommendations provided by our industry partners.

Biotronik (Germany)

Not all pacemaker models support electrophysiological testing. However, this limitation can be overcome by using the threshold measurement section. Select "Test", then "Pacing Threshold", and choose "Manual" (figure 1A,B). First, select the pacing mode (eg, VVI), then set the desired pacing rate (up to 200 bpm) and ensure the output is set to the maximum (7.5V) to guarantee proper capture. Once all parameters are configured, press the "Start" button to begin stimulation, which will continue until manually stopped. If the device supports rapid pacing, such as non-Invasive programmed stimulation (NIPS), overdrive pacing can be performed using the VVI or V00 mode (figure 1C). Select the desired mode and basic rate, then press the "Start Backup Program" button.

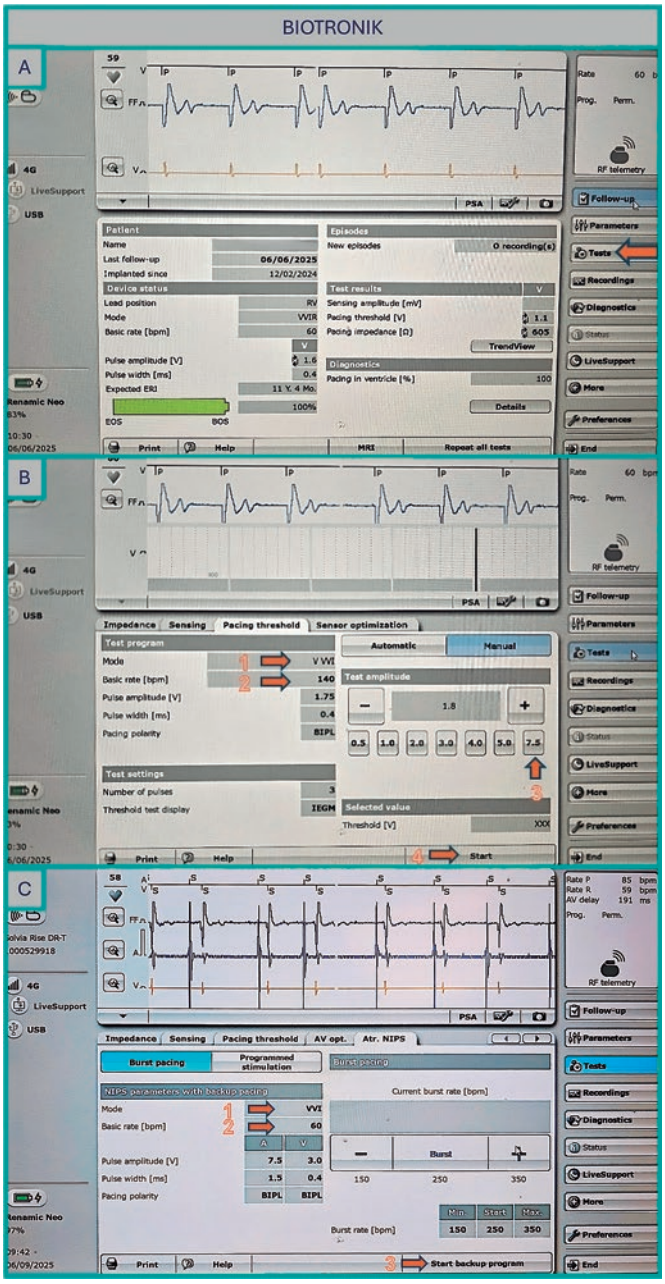

Figure 1. **A**: main screen of the Biotronik console. Select "Test" as indicated by the arrow to proceed to the pacing tests. **B**: to proceed to the pacing tests, select "Manual," then set the following parameters: pacing mode (arrow 1), basic rate (arrow 2), amplitude (arrow 3), and press "Start" to initiate pacing (arrow 4). **C**: configure the NIPS parameters by selecting VVI mode (arrow 1), setting the basic rate (arrow 2), and pressing "Start" to begin pacing (arrow 3). NIPS: Non-Invasive Programmed Stimulation.

Medtronic (United States)

Once on the main screen (figure 2A), press the "Test" tab, then navigate to "Electrophysiology Study" and select either "Fixed Burst" or "Burst" (figure 2B). The interface will prompt you to

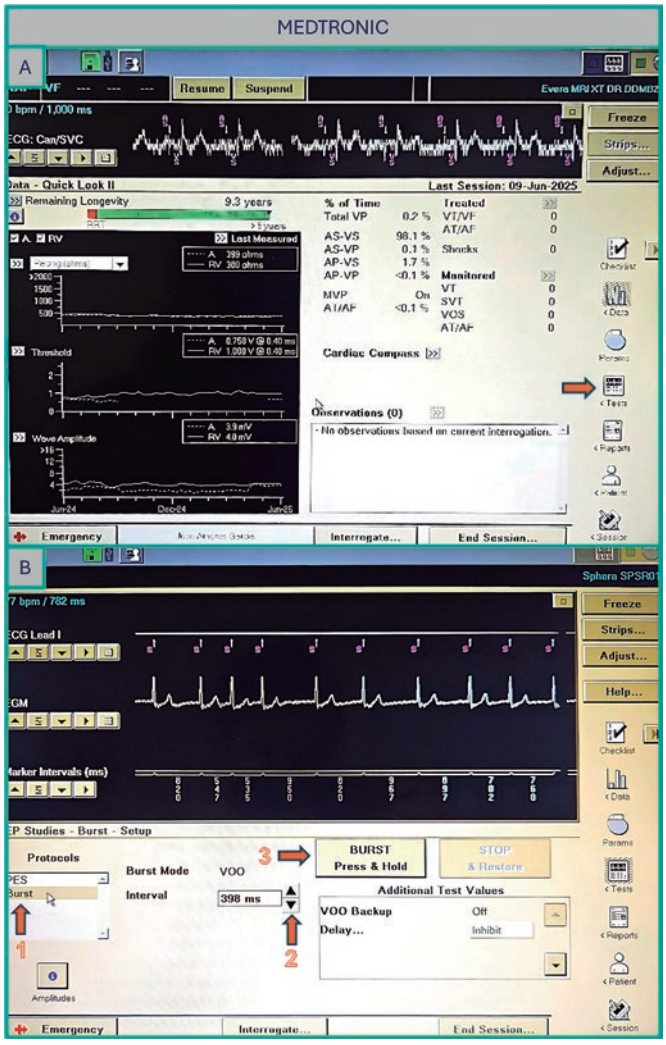

Figure 2. **A**: main screen of the Medtronic console. Press "Tests" (arrow) to access the electrophysiology study screen. **B:** select "Fixed Burst" or "Burst" (arrow 1), adjust the interval as needed (arrow 2), and press and hold the "Burst" button (arrow 3) to deliver pacing.

choose the chamber in which pacing will be applied — select "Right Ventricular". Adjust the interval to the desired value (as the interval decreases, the frequency increases — for example, 200 bpm corresponds to 300 ms). Once all parameters are set, press and hold the "Press and Hold" button to begin stimulation; release it to stop.

Abbott/St Jude (United States)

Once on the main screen (figure 3A), press "Test". There are 2 options to perform rapid ventricular pacing:

- NIPS (figure 3B): Click "Ventricular NIPS", then select "Burst", set the "Pulse Amplitude" (the output should be high to ensure capture), and adjust the pacing rate. In this case, the S1–S1 interval corresponds to the cycle length of the stimuli applied and must be set according to the desired heart rate. For example, 200 bpm corresponds to an S1–S1 interval of 300 ms.

- Temporary pacing (figure 3C): Select the pacing mode (in this case, VVI), the desired rate (up to 170 bpm), and the maximum

Figure 3. **A:** main screen of the Abbott/St. Jude console. Press "Test" to proceed to the electrophysiology study screen. **B:** ventricular NIPS screen. Select "Burst" (arrow 1), set the amplitude (arrow 2), adjust the S1–S1 interval (arrow 3), and press the green button to deliver pacing (arrow 4). **C:** temporary pacing screen. Select the pacing mode (arrow 1), desired rate (arrow 2), and pulse amplitude (arrow 3), then press the "Start Temporary" button (arrow 4).

output to ensure capture. Once all parameters are set, press "Start Temporary" to begin pacing. Stimulation will continue until manually stopped.

Sorin (Italy)

Select "Tests", then choose "NIPS". Under "Mode", select either ventricular pacing or ventricular burst, depending on the desired function. Next, set the "Basic Period" (figure 4A,B) by choosing the corresponding rate in milliseconds (for example, 200 bpm corresponds to 300 ms). Once all parameters are set, press "Start NIPS" to initiate the test.

Boston Scientific (United States)

Once on the main screen (figure 5A), select "Test", then choose "Temp Brady" (figure 5B) From there, select VVI mode and set the desired heart rate under "Lower Rate Limit." As in previous cases, ensure that the maximum output is selected to guarantee proper capture. After all parameters have been configured, press the "Start" button to begin.

DISCUSSION

While earlier permanent pacing devices had limitations in achieving instantaneous burst pacing —such as ramping up the ventricular rate instead of immediate increase and requiring time to reset the function—contemporary devices have largely overcome these issues.[14] Most current models allow rapid burst pacing up to 180 bpm with immediate start and stop, using electrophysiology program mode settings or whenever electrophysiology program is not available (especially in some pacemakers) via a threshold test with maximum output and maximum duration. In cases where this is not possible or does not ensure adequate rapid pacing, the placement of a temporary pacing lead should be considered. Table 1 lists several of the most widely used CIED in our routine clinical practice and specifies whether they provide the capability for rapid temporary pacing or electrophysiological testing). It is always required to ensure that any changes in device programming are reversed and individually optimized; therefore, verification of the device settings at the beginning of the procedure is recommended, and any changes or modifications at the end should be avoided. In patients with implantable cardioverter defibrillator or cardiac resynchronization therapy-defibrillator devices, tachyarrhythmia therapies should be deactivated before the procedure to avoid inappropriate shocks. Of note, some temporary pacing algorithms have a programmed duration limit, so it is essential to verify in advance that high-rate temporary pacing can be maintained for the entire time required for prosthesis deployment, as this may vary depending on the device and pacing mode used.

Given the high ventricular rates required during this process and the deactivation of therapies in patients with implantable cardioverter defibrillator or cardiac resynchronization therapy-defibrillator devices, these maneuvers should be undertaken in a controlled environment with continuous monitoring, immediate availability of cardiopulmonary resuscitation, and access to external defibrillation equipment.

Currently, temporary RV pacing remains a common clinical practice during TAVI in this patient subgroup despite growing evidence that pacing via an implanted CIED is safe and feasible and may reduce pacemaker-related complications, such as cardiac tamponade and hemorrhage vs temporary RV pacing.[9,15] However, certain challenges may arise, mainly of an organizational nature. During TAVI, a manufacturer-specific CIED programmer must be available, and the operator responsible for pacing should be adequately trained on how to operate the device programming functions. Because programming options vary by manufacturer and device type, operators must have thorough and specialized knowledge. In addition, the presence of trained nurses with specific expertise is essential to support device programming and ensure procedural safety. These devices can deliver rapid ventricular pacing through anti-tachycardia pacing functions but programming them often requires adjusting more complex parameters. Our proposed strategy is simpler and more practical, especially for professionals less experienced with advanced device programming.

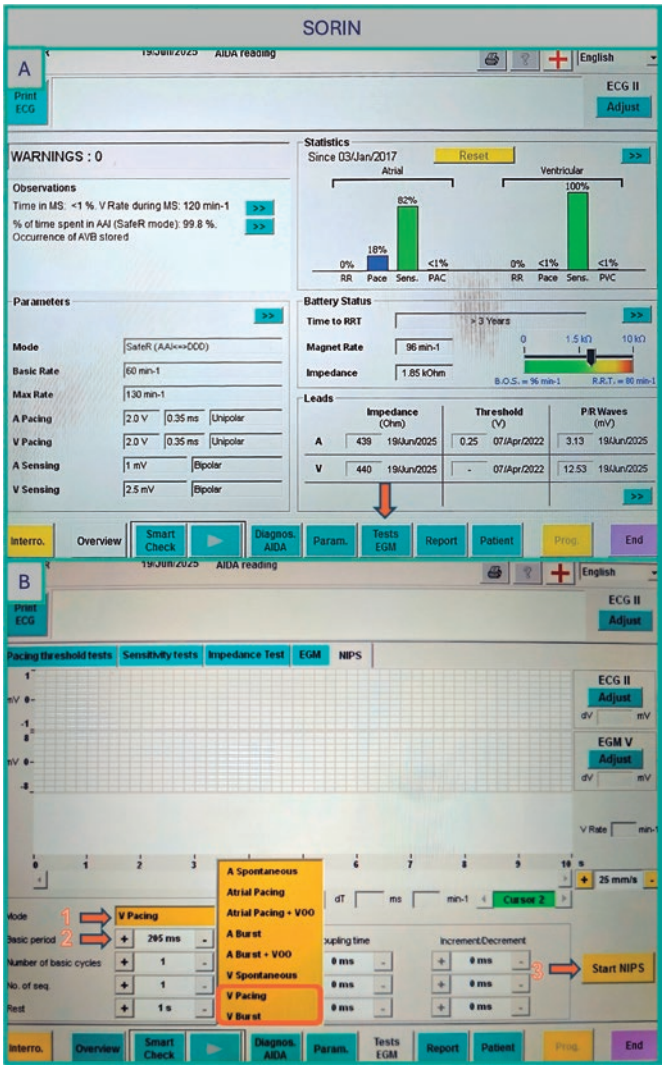

Figure 4. A: main screen of the Sorin console. Select "Tests EGM" (arrow) to access pacing options. **B:** "Tests EGM" screen. Select the pacing mode (arrow 1), the interval period (arrow 2), and then press the "Start NIPS" button (arrow 3).

CONCLUSIONS

In patients undergoing TAVI with preexisting cardiac implantable electronic devices, leveraging the implanted device for procedural pacing is a feasible and potentially safer alternative to temporary RV pacing. This strategy may reduce the risk of complications such as perforation, lead dislodgement, and bleeding. However, its broader adoption is hindered by the variability in device programming interfaces and limited operator familiarity. The step-by-step

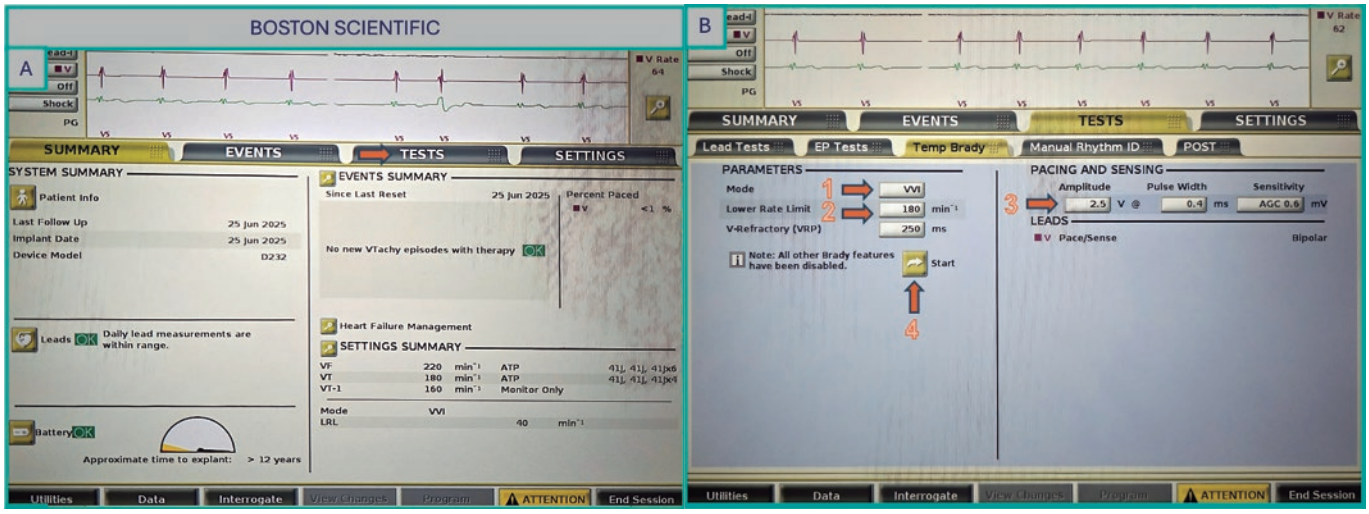

Figure 5. **A**: main screen of the Boston Scientific console. Select "Test" (arrow) to proceed to the pacing setup. **B:** select VVI mode (arrow 1), set the lower rate limit (arrow 2) and amplitude (arrow 3), then press the "Start" button to begin pacing (arrow 4).

Table 1. Characteristics of the main cardiac implantable electronic devices

Manufacturer	VVI-Pacemaker (EP study available yes/no)	DDD-Pacemaker (EP study available yes/no)	VVI-Defibrillator (EP study available yes/no)	DDD-Defibrillator (EP study available yes/no)	CRT-Pacemaker (EP study available yes/no)	CRT-Defibrillator (EP study available yes/no)
Biotronik	Ecuro SR (No) Enticos 4 SR (Yes) Edora 8 SR T (No) Evia SR T (Yes) Amvia Edge SR-T (Yes) Amvia Sky SR-T (Yes)	Amvia Sky DR-T (No) Amvia Edge DR-T (Yes) Edora 8 DR-T (No) Evity 8 DR T (No) Ecuro DR (No) Effecta DR (Yes) Enticos 4 DR (Yes) Evia DR (Yes) Solvia Rise DR-T (no)	Intica Neo 5 VRT (Yes) Iforia 3 VR-T (Yes)	Iforia 3 DR-T (Yes) Inlexa 3 DR-T (Yes) Intica 5/7 (Yes)	Edora 8 HF-T (Yes) Evia HF-T (Yes) Rivacor HF-T (Yes) Etrinsa 8 HF-T (Yes)	Intica HF-T (Yes) Rivacor HF-T QP (Yes)
Boston Scientific	Essentio SR (Yes) Advantio SR (Yes) Accolade SR (Yes)	Essentio DR (Yes) Advantio DR (Yes) Accolade DR (Yes) Ingenio (Yes)	Charisma EL ICD (Yes) Inogen VR (Yes) Punctua NE ICD (Yes) Vigilant EL VR (Yes) Resonate VR (Yes) Autogen VR (Yes) Energen VR (Yes)	Vigilant EL DR (Yes) Resonate (Yes) Energen (Yes)	Intua (Yes) Visionist CRT-P (Yes) Valitude CRT-P (Yes) Invive (Yes) Accolate CRT-P (Yes) Incepta CRT-P (Yes) Essentio CRT-P (Yes) Resonate X4 CRT-P (Yes)	Charisma CRT-D (Yes) Inogen CRT-D (Yes) Origen CRT-D (Yes)
Medtronic	Micra VR (No) Attesta SR (Yes) Sphera SR (Yes) Advisa SR (Yes) Ensura SR (Yes) Azure SR (Yes)	Azure DR (Yes) Adapta DR (Yes) Advisa DR (Yes) Attesta DR (Yes) Ensura DR (Yes) Sphera DR (Yes) Sensia DR (Yes) Relia DR (Yes)	Evera S VR (Yes) Maximo II VR (Yes/No) Protecta VR (Yes) Visia AF (Yes) Cobalt XT (Yes)	Evera DR (Yes) Protecta DR (Yes)	Serena CRT-P (Yes) Percepta CRT-P (Yes)	Brava CRT-D (Yes) Compia CRT-D (Yes) Cobalt CRT-D (Yes) Claria CRT-D (Yes)
Sorin	Reply SR (Yes) Kora SR (Yes)	Reply DR (Yes) Kora DR (Yes) Vega DR (Yes)	Resiliant (Yes) Platinum SR (Yes) Intensia VR (Yes) Paradym SR (Yes)	Platinum DR (Yes) Intensia DR (Yes) Paradym DR (Yes)	Platinum CRT-P (Yes) Kora CRT-P (Yes) Luna CRT-P (Yes) Resiliant CRT-P (Yes)	Platinum CRT-D (Yes) Paradym CRT-D (Yes)
Abbott/ St. Jude	Endurity Core (Yes) Assurity SR (Yes) Zephyr XL SR (Yes)	Assurity DR (Yes) Accent DR (Yes) Endurity (Yes) Sustain XL DR (No) Verity ADx XL DR (No)	Ellipse VR (Yes) Assura VR (Yes) Fortify Assura SR (Yes) Ellipse VR (Yes) Gallant VR (Yes) Neutrino (Yes) Entrant (Yes)	Ellipse DR (Yes) Assura DR (Yes) Fortify Assura DR (Yes) Ellipse DR (Yes) Gallant DR (Yes) Neutrino DR (Yes)	Quadra Allure CRT-P (Yes) Endurity CRT-P (Yes) Entrant CRT-P (Yes) Gallant CRT-P (Yes)	Quadra Assura CRT-D (Yes) Unify Assura (Yes) CRT-D Fortify Assura CRT-D (Yes) Ellipse HF CRT-D (Yes) Entrant HF CRT-D (Yes)

CRT, cardiac resynchronization therapy; CRT-P, cardiac resynchronization therapy pacemaker; CRT-D, cardiac resynchronization therapy defibrillator; DDD, dual-chamber pacing, dual-chamber sensing, and dual response to sensing; DR, dual chamber-rate; EP, electrophysiological; HF, heart failure; ICD, implantable cardioverter-defibrillators; SR, single rate; VVI, ventricular pacing, ventricular sensing, and inhibited response to a sensed event.

instructions provided in this guide aim to facilitate the practical implementation of this approach across the most widely encountered CIED platforms, ultimately promoting safer, more efficient, and complication-free TAVI procedures.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This is a step-by-step practical guide article; therefore, ethical committee approval was deemed unnecessary. No informed consent was required. Potential gender bias has been considered and excluded.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence has not been used in the development of this paper.

AUTHORS' CONTRIBUTIONS

F. Pensotti and L.J. Garnacho elaborated the manuscript under the supervision of I.J. Amat-Santos that revised and drafted the manuscript. All the remaining authors conducted a critical review. All authors approved the final version.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– Despite the fact that a substantial proportion of patients undergoing TAVI have a preexisting CIED, temporary pacing through these devices is rarely used. Instead, operators often prefer temporary RV pacing, which, however, carries inherent risks.

WHAT DOES THIS STUDY ADD?

– The step-by-step instructions of this guide are designed to help implement this approach on the most common CIED platforms, thereby ensuring safer, more efficient, and complication-free TAVI.

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Scientific letter

Outcomes of edge-to-edge mitral valve repair in patients with mitral regurgitation evaluated for heart transplantation

Impacto de la reparación mitral de borde a borde en pacientes con insuficiencia mitral evaluados para trasplante cardiaco

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To the Editor,

Advanced heart failure (HF) complicated by secondary mitral regurgitation is associated with a poor prognosis, and heart transplantation is the standard of care; however, donor scarcity requires bridge strategies.[1] The MitraBridge registry[2] evaluated the impact of transcatheter edge-to-edge repair (TEER) in patients considered for transplantation; however, its retrospective design and substantial loss to follow-up limit the strength of its conclusions.

The primary endpoint of our study was to assess the impact of TEER on mortality and the composite endpoint of death, need for heart transplantation or emergency left ventricular assist device placement, and index HF-related hospitalization in a cohort of patients with advanced HF and significant secondary mitral regurgitation who were evaluated for transplantation. The secondary endpoint was to compare the rate of HF-related hospitalizations before and after TEER.

We conducted a retrospective analysis of a single-center, prospective observational registry including all patients treated with TEER at a tertiary referral center in Spain. The Córdoba Research Ethics Committee approved the study, and all patients gave their prior written informed consent. We selected patients with advanced HF (defined as New York Heart Association [NYHA] functional class ≥ II, left ventricular ejection fraction ≤ 35%, at least 1 HF-related hospitalization, and age ≤ 70 years) who were assessed as potential candidates for listing on the transplant waiting list.

Kaplan–Meier curves were used to estimate overall and event-free survival, and the rate of HF-related rehospitalization was calculated per 100 patient-years.

A total of 191 patients underwent TEER from 2011 through 2023, 38 of whom met the inclusion criteria, with follow-up available until December 2024 (median, 35 months; 25th-75th percentile: 8–70). The mean age was 56 ± 12 years, and the rate of procedural success, 92%. Baseline, procedural, and follow-up characteristics are shown in table 1. A total of 17 patients died and 26 experienced the composite event during follow-up. At 24 months, the overall survival rate was 76.5%; and the event-free survival rate, 48% (figure 1). The rate of HF-related hospitalization decreased significantly from 108 to 33 per 100 patient-years (rate ratio, 0.31; 95%CI, 0.21–0.45; $P < .0005$) (figure 1). At last follow-up, 15 patients (40%) had died without transplantation and 5 (13%) had undergone transplantation (2 died). Of the remaining patients, 8 (21%) stayed on the waiting list, and 10 (26%) were not listed—4 due to contraindications and 6 due to clinical improvement (figure 1).

Our findings support the role of TEER as a bridge-to-transplant strategy in selected patients with fewer HF-related hospitalizations. Compared with the MitraBridge registry,[2] clinical and echocardiographic profiles were similar, although fewer patients from our study were in NYHA functional class III–IV (76.3% vs 93%). In the MitraBridge registry,[3] at 2 years, 27 of the 126 patients with complete follow-up had died, yielding an overall survival rate of 78.6%, which is similar to the 2-year survival rate observed in our study (75.6%), although that registry had a high loss-to-follow-up rate (17.6%). Such mortality figures are notable considering that, based on other studies,[4] the 1-year overall survival rate in patients with advanced HF is approximately 75%. In our study, the event-free survival rate was very similar to that of the MitraBridge registry at 2 years[3] (48% vs 47%) and that of other registries,[4] supporting the reproducibility of the strategy. The reduction in HF-related hospitalizations observed after TEER was even greater in our study than in the MitraBridge registry[3] (rate ratio, 0.31 vs 0.37), which may relate to the higher procedural success and lower proportion of patients in NYHA functional class III–IV in our series. Of note, 16% of our patients could be removed from the transplant waiting list because of clinical improvement, which is slightly lower than the 23% reported in MitraBridge,[3] but without loss to follow-up in our series. However, the number of patients who died or required transplantation or ventricular assist device placement was substantial in the 2 series, underscoring the importance of proper patient selection.

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Table 1. Baseline and procedural characteristics, and follow-up events of the patients in the series

Variables	Values
Clinical characteristics	
Age (years)	56 ± 12
Female sex	7 (19)
Smoker	11 (29)
Diabetes	17 (45)
Dyslipidemia	20 (52.6)
Hypertension	14 (37)
Peripheral arterial disease	2 (5)
Stroke	6 (16)
Atrial fibrillation	20 (52.6)
Anemia	8 (21.1)
Chronic obstructive pulmonary disease	7 (18.4)
History of cancer	2 (5)
Previous percutaneous coronary intervention	14 (37)
Previous coronary artery bypass graft	4 (11)
ICD/CRT	17 (45)
Ischemic mitral regurgitation	18 (47)
STS score (points)	2.4 [1.4–4.2]
NYHA functional class III–IV	29 (76.3)
Number of HF-related hospitalizations per patient	1.5 [1–3]
Body mass index (kg/m^2)	27 ± 4
Analytical characteristics	
Hemoglobin (g/dL)	14 ± 2
Leukocytes/mm^3	7551 ± 2138
Platelets/mm^3	187 833 ± 59 138
Creatinine (mg/dL)	1.2 ± 0.6
eGFR < 60 mL/min	13 (35)
NT-proBNP (pg/mL)	3200 [1241–5831]
Echocardiographic characteristics	
LV ejection fraction (%)	27 [22–31]
LV diastolic diameter (mm)	71 ± 8.5
LV systolic diameter (mm)	59 ± 10
Left atrium (mL/m^2)	61 [44–89]
Degree of mitral regurgitation	
Moderate–severe (III)	2 (5.3)
Severe (IV)	36 (94.7)
TAPSE (mm)	16 ± 3.6
Degree of tricuspid regurgitation	1 [1–2]
Pulmonary artery systolic pressure (mmHg)	47.5 [35–60]
Optimal medical therapy	
ACEI, ARB-II or ARNI	38 (100)
Mineralocorticoid antagonists	34 (92)
SGLT2i	11 (29)
Beta-blockers	37 (97.4)
High-dose diuretics	23 (69.5)
Anticoagulation	34 (92)
Procedural characteristics	
Procedural success	35 (92)
Residual mitral regurgitation	
Mild (I)	18 (47)
Mild-moderate (II)	16 (42)
Moderate-severe (III)	3 (7.9)
Severe (IV)	1 (2.6)
Number of clips	
1	16 (42)
2	19 (50)
≥ 3	3 (8)
Procedural time (min)	120 [66–186]
Type of clip (MitraClip)	38 (100)
Complications	1 (3)
Follow-up	
Events at 24 months	
Patients with HF-related hospitalization	19 (50)
Heart transplant	5 (13.2)
Left ventricular assist device	2 (5.3)
Death	9 (23.7)
Events at the end of follow-up	
Patients with HF-related hospitalizTION	24 (63.2)
Heart transplant	5 (13.2)
Left ventricular assist device	3 (7.9)
Death	17 (44.7)

ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitors; ACEI, angiotensin-converting enzyme inhibitors; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter type 2 inhibitors; TAPSE, tricuspid annular plane systolic excursion.
Data express absolute values and percentages (categorical variables), and mean ± standard deviation or median [25th–75th percentiles] (continuous variables).

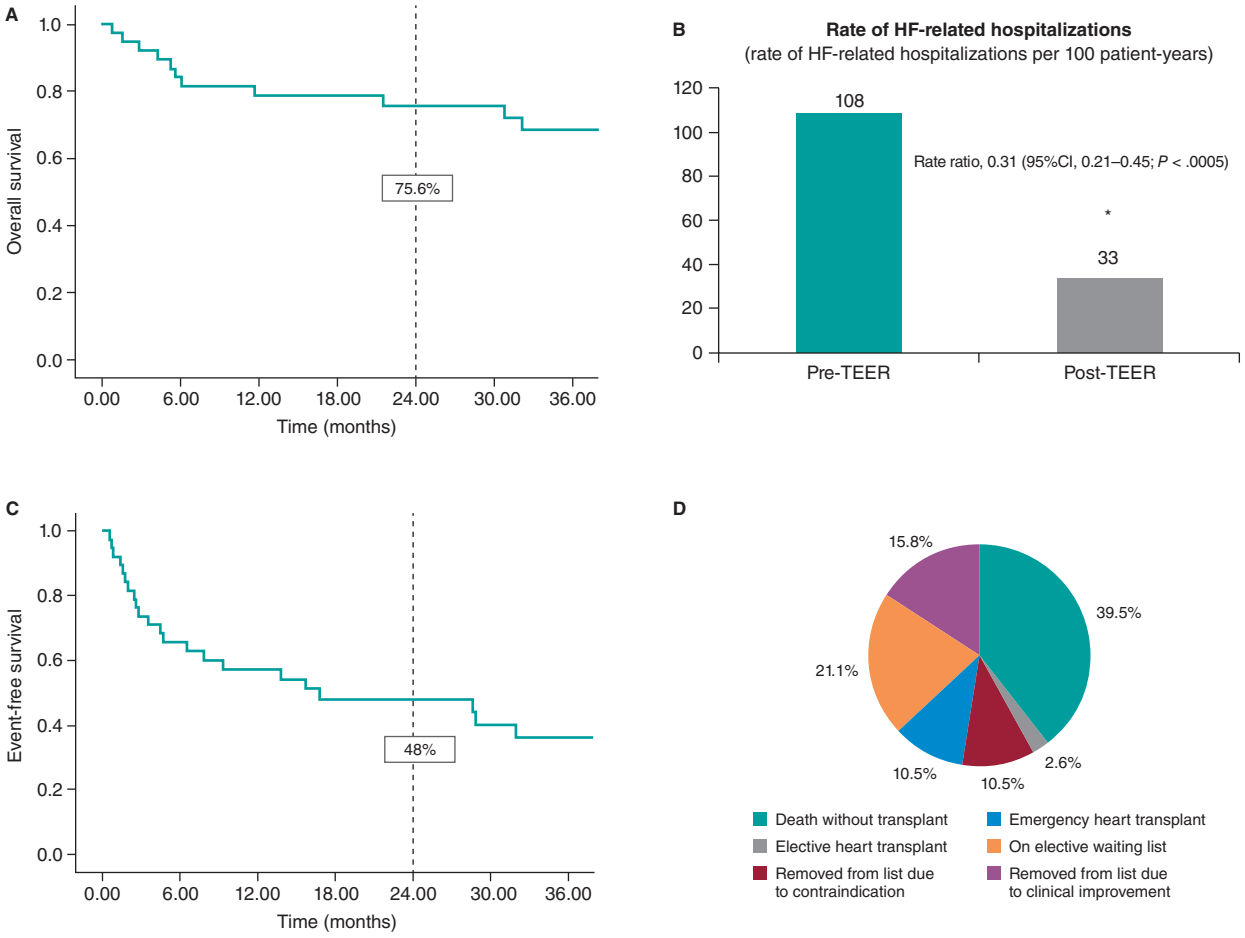

Figure 1. Overall survival (**A**) and event-free survival rates (**C**); pre- and postoperative rate of HF-related hospitalizations (**B**); and final status of patients in the series (**D**). 95%CI; 95% confidence interval; TEER, transcatheter edge-to-edge repair.

As a strength, although 3 Spanish centers participated in the MitraBridge registry,[2,3] this is, to our knowledge, the first study conducted in Spain to replicate its findings with consecutive patient inclusion and no loss to follow-up. These results support the use of TEER in patients with advanced HF not only in transplant centers but also in all centers equipped to perform the technique, as part of treatment optimization.

The main limitations of the study are its observational and retrospective design, absence of a control group, single-center nature, and small sample size.

In conclusion, TEER as a bridge to heart transplantation in patients with advanced HF and significant secondary mitral regurgitation is safe and effective, with a 2-year survival rate of 75%. Similarly, it significantly reduces HF-related hospitalizations and allows a meaningful proportion of patients to be removed from the transplant waiting list.

Randomized clinical trials are needed to confirm our findings and improve candidate selection.

DATA AVAILABILITY

Although the data supporting the findings of this study are not publicly available because of sensitivity concerns, they may be provided upon reasonable request to the corresponding author.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The study complied with the recommendations outlined in the Declaration of Helsinki and was approved by the Córdoba Research Ethics Committee. Informed consent was obtained from all participants. SAGER guidelines were followed regarding potential sex or gender bias.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

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

AUTHORS' CONTRIBUTIONS

F. Di Cosmo and L. Barreiro Mesa contributed equally to this work. D. Mesa Rubio and M. Ruiz Ortiz conceived and validated the study. M. Ruiz Ortiz administered the project and conducted the formal analysis. M. Pan Álvarez-Ossorio and D. Mesa Rubio supervised the conduct of the study. F. Di Cosmo and L. Barreiro Mesa

drafted the original manuscript. All authors contributed to research, reviewed and edited the manuscript, approved its final version, and are responsible for all aspects of the work.

CONFLICTS OF INTEREST

M. Pan Álvarez-Ossorio and D. Mesa Rubio declared to have received honoraria for sessions related to the topic of the manuscript. The remaining authors declared no conflicts of interest whatsoever.

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Scientific letter

Transfemoral TAVI in hostile access: experience with the paving and cracking technique

TAVI transfemoral en acceso hostil: experiencia con la técnica paving and cracking

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To the Editor,

Femoral access is the preferred route for transcatheter aortic valve implantation (TAVI), according to the most recent clinical practice guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS).[1] However, iliac vessel stenosis, tortuosity, and calcification may render transfemoral access unfeasible or lead to complications in up to 5%-10% of cases.[2]

To overcome these anatomical limitations, the paving and cracking (P&C) technique was described,[3] originally used in endovascular aneurysm repair. This strategy allows preparation of the iliac vessels using covered stents followed by postdilatation.[4] Other adjunctive techniques, such as intravascular lithotripsy,[5] modify iliac vessel calcification and facilitate the advancement of large-bore introducer sheaths.

We present our experience using the P&C technique to perform transfemoral TAVI in patients with hostile iliofemoral anatomy. We conducted a retrospective analysis of all patients who required adjunctive iliac endovascular treatment with covered stents (P&C technique) as part of transfemoral TAVI from 2021 through 2024 at our center. All cases were recorded in a prospectively maintained database including demographic variables, valve type and implantation characteristics, anesthetic technique, and procedural information. We analyzed preoperative computed tomography scans to assess maximum and minimum intraluminal iliac diameters, tortuosity, degree of calcification, and presence of thrombus. Because of the retrospective design of the study, the institutional Research Ethics Committee waived the requirement for specific informed consent.

Severe arterial tortuosity was defined as an angle > 90°, and grade 4 calcification as calcium involving > 75% of the vessel circumference. Vascular complications were defined according to the criteria outlined by the Valve Academic Research Consortium-3 (VARC-3).[6] Technical success was defined as successful completion of transfemoral TAVI. Quantitative variables were expressed as mean and standard deviation, and the qualitative ones as frequencies. We did not perform inferential analysis due to the limited sample size.

During the study period (2021-2024), a total of 739 transfemoral TAVI were performed, 6 of which (0.8%) required simultaneous iliofemoral endovascular treatment prior to valve implantation using the P&C technique (table 1). Evolut valves (Medtronic, United States) were used in all cases.

Table 1. Demographic, clinical, and anatomic characteristics of the 6 patients undergoing transfemoral TAVI using the paving and cracking technique

Variable	N = 6
Male sex	6 (100)
Age, years	77.5 ± 6 [68-84]
Smoking history	6 (100)
Peripheral arterial disease	4 (66.7)
Valve-in-valve procedure	3 (50.0)
Minimum luminal diameter, mm	3.5 (0.4-6.0)
Calcification (grade 3 or 4)	5 (83.3)
Severe tortuosity	2 (33.3)
Presence of thrombus	5 (83.3)
TAVI sheath profile	
14-Fr (Evolut Pro 23 or 26)	3 (50.0)
16-Fr (Evolut-R 34)	1 (16.7)
18-Fr (Evolut Pro+ 34)	1 (16.7)
22 Fr (Evolut FX 34)	1 (16.7)

TAVI, transcatheter aortic valve implantation.
Data are expressed as no. (%), mean ± SD, or median [interquartile range].

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Table 2. Procedural details, adjunctive endovascular and surgical techniques, and short- and mid-term clinical outcomes in the study cohort

Variable	N = 6
Fully transcatheter approach	4 (66.7)
Anesthesia	
Local	2 (33.3)
General	4 (66.7)
Use of intravascular lithotripsy	2 (33.3)
Endovascular procedure	
1 self-expanding stent[a]	2 (33.3)
2 self-expanding stents[b]	1 (16.7)
2 balloon-expandable stents[c]	1 (16.7)
1 self-expanding + 1 balloon-expandable stent[d]	2 (33.3)
Adjunctive surgical procedures	
Femoral endarterectomy	1 (16.7)
Iliofemoral bypass	1 (16.7)
Profundoplasty	1 (16.7)
Technical success	6 (100)
Minor complications (VARC-3)	1 (16.7)
Follow-up (months), median	25
Patency at end of follow-up	6 (100)

VARC-3, Valve Academic Research Consortium-3.
Data are expressed as No. (%) or median.
[a] Single 8 mm × 100 mm and 11 mm × 50 mm self-expanding stent (VIABAHN, W. L. Gore & Associates, United States).
[b] Combination of 2 self-expanding stents (11 mm × 100 mm VIABAHN + 11 mm × 50 mm VIABAHN).
[c] Two 10 mm × 59 mm + 10 mm × 39 mm balloon-expandable stents (VBX, W. L. Gore & Associates, United States).
[d] Combination of 1 self-expanding + 1 balloon-expandable stent (10 mm × 39 mm VBX + 10 mm × 100 mm VIABAHN; 11 mm × 79 mm VBX + 11 mm × 100 mm VIABAHN).

The anatomical characteristics of the treated iliac axes are shown in table 1. Iliac axis preconditioning was performed in 4 patients (67%) entirely percutaneously via ipsilateral femoral access. In 1 patient, intraoperative hemorrhage required conversion to open surgery with femoral endarterectomy, profundoplasty, and prosthetic patching. In 2 cases (33%), the endovascular procedure was complemented with open surgery on the common femoral artery: 1 endarterectomy and 1 bypass from the distal external iliac artery to the common femoral artery.

Additional details regarding the implanted stents are shown in table 2. In 2 patients, intravascular lithotripsy was performed prior to stent implantation using a 6-mm and 8-mm Shockwave M5+ catheter (Shockwave Medical, United States). We systematically performed postdilatation of all implanted self-expanding stents, using a balloon of the same diameter in 5 cases and a balloon 1 mm larger in 1 case.

Technical success was achieved in all patients. One patient developed a contralateral femoral pseudoaneurysm a few hours after the procedure, which was treated with ultrasound-guided thrombin injection. Follow-up ultrasound 20 days later showed partial persistence of the pseudoaneurysm and resulted in a 7 mm × 29-mm covered stent implantation (GORE VIABAHN VBX Balloon Expandable Endoprosthesis; W. L. Gore & Associates, United States) via contralateral femoral access. Two patients experienced major complications unrelated to vascular access: 1 case of aspiration pneumonia and 1 case of incomplete left bundle branch block.

All iliofemoral procedures remained patent during follow-up, with a mean follow-up of 25 months. Of note, 4 of the 6 patients (66.7%) died 5, 6, 24, and 28 months after the intervention.

In our series, P&C was used adjunctively to transfemoral TAVI in 6 patients, 3 of whom required adjuvant surgery (femoral endarterectomy with or without profundoplasty, or short iliofemoral bypass). Despite anatomical complexity, we achieved technical success in all cases, which confirmed the safety and efficacy profile of this strategy to enable femoral access in patients with severe atherosclerotic disease.

Endovascular treatment is the first-line option for complex aortoiliac occlusive lesions. In the TAVI setting, this approach expands the population eligible for transfemoral access. To optimize the procedure, ultrasound-guided puncture at the least calcified segment is recommended. Similarly, puncturing the common femoral artery 1-2 cm proximal to the bifurcation facilitates partial stent deployment within the femoral artery and simplifies potential surgical repair in case of injury.[4]

In cases requiring large-bore introducer sheaths (≥ 22Fr), large-diameter stents (10-11 mm) are typically used, and a bypass to the distal common femoral or profunda femoris artery may occasionally be required.[3] This location improves flow control by allowing more comfortable clamping of the stent. Moreover, the use of a radiopaque-tipped introducer sheath helps ensure stent deployment outside the introducer sheath. Balloon-expandable covered stents are recommended in the common iliac artery due to their high radial strength and precision, whereas self-expanding covered stents are preferred in the external iliac artery because of their flexibility and range of available lengths.[4]

If direct postoperative arterial closure is not feasible, a prosthetic bypass should be performed. Since previously available hybrid grafts are no longer on the market, reconstruction must be performed using a vascular prosthesis anastomosed end-to-end to the stent, with a recommended diameter of 10 mm to avoid size mismatch. When stent clamping is difficult, intraluminal balloon clamping (Fogarty or angioplasty balloon) may be used.

In patients treated with lower-profile devices, intravascular lithotripsy is a useful alternative that reduces the need for stent implantation; it uses a semi-compliant balloon with low inflation pressures and predictable recoil. Currently, devices up to 8 mm are available, expandable to 12 mm with the L6 balloon catheter.[5] However, in extensive, heavily calcified lesions requiring advancement of high-profile devices (>18-20-Fr), stent implantation is preferable, as it creates a smooth luminal surface that reduces friction and lowers the risk of arterial rupture. When multiple stents are required, proximal stents should be deployed first to avoid interference during device advancement.

Furthermore, treatment planning should assess hypogastric artery patency, given the risks associated with its occlusion. The P&C technique is typically used in patients with advanced iliofemoral disease, in whom the hypogastric artery is usually occluded or severely stenosed, allowing safe covered stent implantation from the external to the common iliac artery without risk of retrograde hemorrhage. If the hypogastric artery is patent, ischemic risk must be evaluated, including assessment of the contralateral hypogastric

artery and the inferior mesenteric artery. Moreover, in the event of arterial rupture, retrograde flow from a patent hypogastric artery may hinder endovascular hemorrhage control; thus, in the presence patency, prior embolization using oversized occluders (≈ 30%), coils, or other systems is recommended.[4]

The P&C technique is an effective tool to enable femoral access in patients with severe aortoiliac disease undergoing TAVI. Its success requires systematic planning based on imaging modalities and a multidisciplinary approach to optimize outcomes. This strategy expands transfemoral access options while keeping an acceptable safety profile, even in complex anatomies.

DATA AVAILABILITY

Although data supporting the findings of this study are not publicly available due to sensitivity concerns, they may be provided upon reasonable request to the corresponding author.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The study fully complied with the recommendations for medical research outlined in the Declaration of Helsinki. Given its retrospective design, the study was exempted from the need for an informed consent by our institutional Research Ethics Committee. Sex and gender were reported in accordance with the SAGER guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

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

AUTHORS' CONTRIBUTIONS

R. Vázquez Pérez, A. A. Zanabili Al-Sibbai, and F. Álvarez Marcos contributed equally to this work. R. del Valle Fernández and A. Alperi García validated the study. M. Alonso Pérez supervised its execution. R. Vázquez Pérez, A. A. Zanabili Al-Sibbai, and F. Álvarez Marcos prepared the original draft. All authors contributed to the research, reviewed, edited, and approved the final manuscript, and are accountable for all aspects of the work.

CONFLICTS OF INTEREST

R. del Valle Fernández has received honoraria for lectures and teaching activities from Medtronic and Merce V., as well as consultancy fees from Medtronic. A. A. Zanabili Al-Sibbai has received consultancy and educational honoraria from W. L. Gore & Associates, Shockwave Medical, and Medtronic. F. Álvarez Marcos has received consultancy and proctoring fees from Medtronic and Terumo Aortic. The remaining authors declare no conflicts of interest whatsoever.

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Scientific letter

Clinical and economic impact of FFR-CT–guided management in moderate coronary artery disease: an interventional simulation study

Impacto clínico y económico del tratamiento guiado por RFF-TC en la enfermedad coronaria moderada: estudio de simulación de intervención

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To the Editor,

Evaluation of chest pain remains a frequent clinical challenge, with ongoing debate surrounding the optimal diagnostic strategy. Among the available modalities, coronary computed tomography angiography (CCTA) has emerged as a reliable diagnostic imaging modality because of its high sensitivity and negative predictive value. However, its positive predictive value remains moderate (60%–70%) vs invasive coronary angiography (ICA) and stress imaging modalities. This limitation often results in increased downstream testing, as demonstrated by the PROMISE trial.[1] Recent technological advancements have enabled non-invasive assessment of the hemodynamic significance of coronary lesions, allowing fractional flow reserve derived from computed tomography (FFR-CT) to be calculated directly from CCTA images without the need for pharmacological stress agents or additional radiation exposure. Previous prospective trials have demonstrated a significant enhancement in the diagnostic accuracy of FFR-CT vs CCTA alone. As a result, the United States, the United Kingdom and European clinical practice guidelines currently endorse the use of FFR-CT. However, uncertainties remain regarding its clinical effectiveness and cost-efficiency across different health care systems and clinical settings.

We evaluated the potential clinical and economic impact of integrating FFR-CT into the routine practice in Spain vs standard care in patients with moderate stenosis on coronary computed tomography angiography (CCTA). We conducted a retrospective, observational, single-center intervention simulation study including outpatients with stable chest pain who underwent CCTA from July 2021 through December 2022 at a Spanish university hospital. Eligible patients had lesions classified as CAD-RADS 2.0 grade 3 (50%–69% stenosis) in vessels ≥ 1.5 mm,[2] body mass index (BMI < 35 kg/m^2) and coronary artery calcium score < 1000 Agatston Units (AU). Patients were identified through administrative databases, and electronic health records were reviewed to collect baseline clinical and imaging data. CCTA reports were independently reviewed by 5 clinical cardiologists, who recommended additional tests or treatments according to their clinical judgment. The same process was repeated after incorporation of FFR-CT to determine how functional information influenced decision-making. For each scenario, cardiologists answered questions, both before and after FFR-CT analysis: *a)* What additional diagnostic tests would you request? *b)* Would you recommend hospital admission, outpatient management, or discharge? *c)* What treatment strategy would you propose? *d)* Was the FFR-CT information useful? (figure 1). This structure enabled direct comparison of anatomical-only decisions vs those incorporating functional data. Significant FFR was defined as at least 1 vessel with FFR ≤ 80%.

CCTA images were acquired using a dual-source scanner (Somatom Drive, Siemens Healthineers, Germany) and interpreted by cardiologists and cardiovascular radiologists. FFR-CT analysis was performed by experts blinded to the original CCTA findings using DEEPVESSEL-FFR (Keya Medical Technology Inc; China), a new machine learning-based software platform that uses artificial intelligence and deep learning algorithms to generate FFR-CT values directly from CCTA datasets.[3]

The primary endpoint was total cost generated or saved after incorporating FFR-CT. Secondary endpoints included changes in tests utilization, hospitalizations decisions, adjustments in optimal medical therapy and physician-perceived satisfaction after FFR-CT analysis.

Baseline characteristics are expressed as frequencies and percentages for categorical data, and as mean ± standard deviation for continuous data. A cost analysis assessed the financial impact of the clinical decisions made in the intervention simulation, calculating total costs generated or avoided accordingly. Reference prices were obtained from our regional health care system and updated to 2024 using the Consumer Price Index.[4] The company-reported cost of each FFR-CT analysis was €400. All statistical analyses were performed using Stata 16.1; *P* values < .05 were considered statistically significant.

Among 631 outpatients who underwent CCTA, 43 (6.8%) met the inclusion criteria. Most were men, with a mean age of 64.7 ± 8.6 years. The mean Agatston score was 355.7 AU, reflecting a high coronary calcium burden. Dyslipidemia and hypertension were present in fewer than one-half of patients, and diabetes was documented in 11 (25.6%). The mean body mass index was 27.6 ± 4.3

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FFR-CT guided decision making in patients with moderate coronary artery disease: clinical and economic outcomes from a single-center intervention simulation study

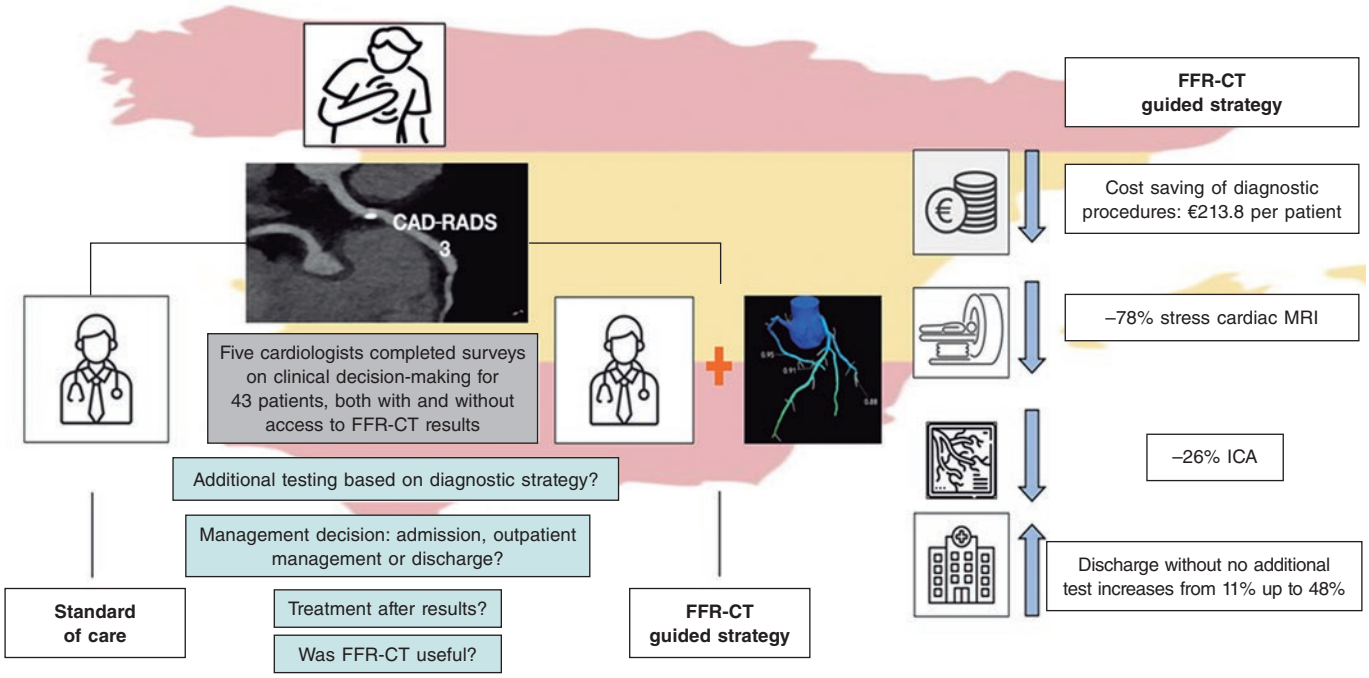

Figure 1. Study design and outcomes. CAD-RADS, coronary artery disease-reporting and data system; CT, computed tomography; FFR, fractional flow reserve; ICA, invasive coronary angiography; MRI, magnetic resonance imaging.

kg/m^2, and mean radiation exposure was low (1.9 ± 1.1 millisievert). A total of 83.7% of patients underwent single-beat acquisition (Flash); 7%, prospective ('step-and-shoot') acquisition; and 9%, retrospective acquisition. FFR-CT analysis was not feasible in 3 cases (7%) due to motion artifacts. Among successful analyses, 5 patients (11.6%) had a positive FFR-CT result.

In the clinical simulation analysis, 215 clinical scenarios were finally evaluated, corresponding to the individual assessment of all 43 cases by each of the 5 participating cardiologists. Prior to FFR-CT, additional testing was recommended in 89.9%, based solely on CCTA findings. The most frequently requested imaging modalities were stress cardiac magnetic resonance (CMR) (n = 118; 54.8%), and ICA (n = 46; 21%). After FFR-CT, the need for further testing dropped down to 28% (P < .01), with marked reductions in stress CMR (to 12%, -78%; P < .01) and ICA (to 15%, -26%; P < .01), respectively (table 1). This shift resulted in notable cost savings: total diagnostic costs decreased from €301 690 to €255 720, yielding savings of €45 976.64 (€213.84 per case). Discharge recommendations increased from 11% to 48% after FFR-CT (P < .01). Clinicians found FFR-CT helpful in 81% of scenarios. There were no significant changes in decisions regarding medical therapy.

This intervention simulation study provides several clinically relevant insights. First, FFR-CT was associated with lower health care spending and fewer downstream testing. Second, it enabled

Table 1. Cost analysis based on clinical simulation analysis

Complementary tests	Before CT-FFR, N (%)	Total cost (CT + additional tests[a]), €	After CT-FFR, N (%)	Total cost (CT + CT-FFR + additional tests[a,b]), €	*P*	Balance, €
ICA	46 (21)	80 865.99	32 (15)	69 024.64	< .01	
SPECT	9 (4)	9180.98	1 (0.5)	1420.11	.01	
Stress MRI	118 (55)	183 383.24	25 (12)	48 850.50	< .01	
Stress echocardiography	19 (8)	17 601.98	2 (0.9)	2652.04	< .01	
No test	23 (10)	10 649.92	155 (72)	133 768.1	< .01	
Total		301 692.04		255 715.4		45 976.64

CT, computed tomography; FFR, fractional flow reserve; ICA, invasive coronary angiography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography.

[a] Cost Regional Healthcare system December 2024 (updated to 2024 values based on the Consumer Price Index) (€): ICA = 1294.95; SPECT = 557.09; Stress MRI = 1091.16; CTA = 463.02; Stress echocardiography = 463.40.

[b] The cost of CT-FFR was estimated at € 400 per study.

completion of the diagnostic process in a high proportion of patients and was judged clinically useful in most cases. As the first study in Spain evaluating an FFR-CT–guided strategy, it suggests that routine implementation could decrease downstream investigations and associated costs in patients with stable chest pain.

Most cost-efficiency data comes from the United States and the United Kingdom, where FFR-CT adoption is higher. While in the United States, the PLATFORM study demonstrated cost reductions, primarily driven by decreased use of ICA,[5] evidence from the United Kingdom is more heterogeneous. While the latest NICE update projected £391 savings per patient, Mittal et al. reported higher costs vs stress imaging, although these findings have been questioned because most patients had stenoses outside the 50%–69% range—where additional testing and interobserver variability are more frequent—and the observed cost increase was largely attributable to higher ICA rates, findings that contradict earlier reports.[6] In our cohort, stress CMR (54.8%) and ICA (21%) decreased substantially after incorporation of FFR-CT (to 12% and 15%), resulting in savings of €213.84 per case.

In addition, FFR-CT effectively concluded the diagnostic process, increasing the discharge rate from 11% to 48% after FFR-CT ($P < .01$). This notable finding introduces an important dimension of organizational efficiency, as it may help optimize imaging resources and reduce waiting times for advanced diagnostic tests. Notably, previous cost evaluations have primarily focused on avoidance of unnecessary testing, and have not fully captured this potential management benefit. Furthermore, clinicians participating in the study considered FFR-CT highly useful in 87% of cases.

The main limitation of our study is its simulation-based design. Economic outcomes were influenced by local test utilization patterns and regional pricing structures, which may limit external validity and generalizability. Therefore, the results should be considered hypothesis-generating.

In conclusion, in this simulation study, incorporation of FFR-CT in patients with stable chest pain and moderate coronary stenosis on coronary CCTA was associated with reduced downstream testing, lower health care costs, and higher discharge rates within the Spanish National Health System.

DATA AVAILABILITY

The data underlying this study will be made available upon reasonable request. Requests should be directed to the corresponding author.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This study was conducted in full compliance with the principles outlined in the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on clinical research. As this was an interventional simulation study based on previously collected and fully anonymized data, formal ethical approval and informed consent were deemed unnecessary. Although this study included male and female patients alike, sex disaggregated analyses were not performed due to lack of expected sex related differences.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used in the development of this paper.

CONFLICTS OF INTEREST

None declared.

AUTHORS' CONTRIBUTIONS

Conceptualization, formal analysis, drafting of the original manuscript, and supervision were performed by J.A. Parada-Barcia and M. Barreiro-Pérez. Critical review and editing of the manuscript were undertaken by the remaining authors. All authors approved the final version of the manuscript for publication and accept all aspects of the work.

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Atrial septal defect closure with cor triatriatum sinister

Cierre del defecto del tabique auricular con cor triatriatum sinister

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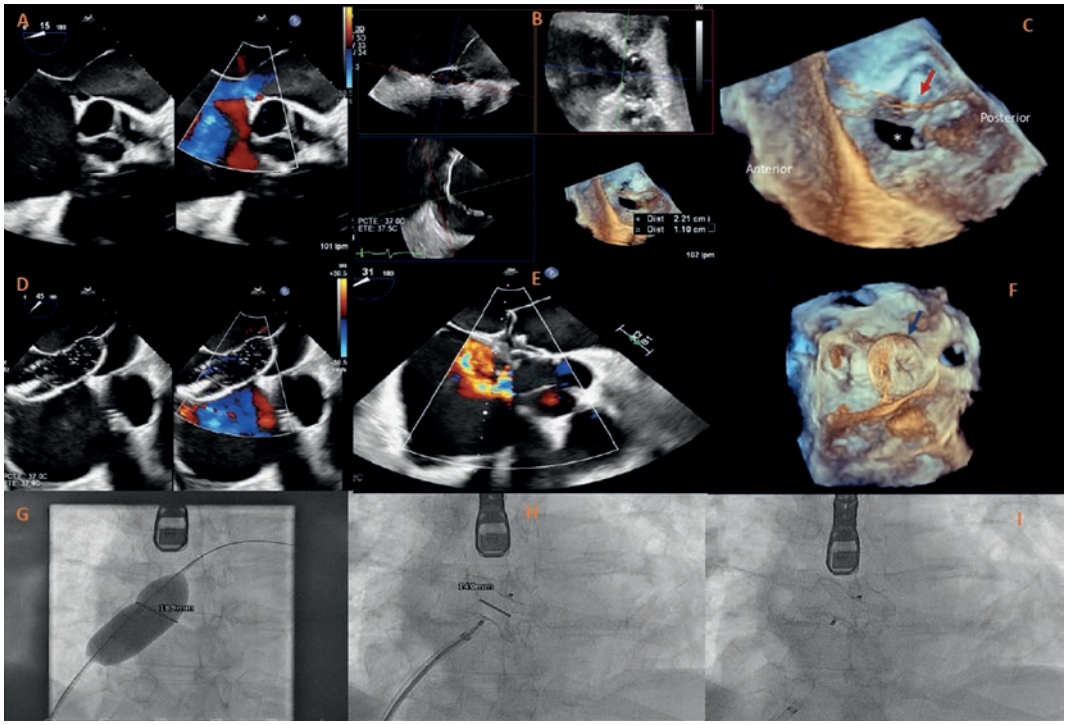

Figure 1.

This is the case of a 67-year-old man with signs of right heart failure due to an atrial septal defect (ASD) with right ventricular dilation, significant left-to-right shunt (Qp/Qs 1.5), and no significant pre-capillary pulmonary hypertension (mean pulmonary artery pressure, 26 mmHg; pulmonary vascular resistance, 2UW). Three-dimensional transesophageal echocardiography (3DTEE) revealed the presence of a cor triatriatum sinister (CTS) with a membrane extending from the upper-posterior end of the fossa ovalis to the pulmonary ridge, with multiple fenestrations, the largest measuring 24 mm (figure 1A). A 22 mm × 11 mm ostium secundum ASD was confirmed with the posterior rim partially covered by the membrane (figure 1B,C). Since the patient was technically suitable and had increased surgical risk due to cirrhosis, a percutaneous approach was undertaken. The procedure was performed under 3DTEE and fluoroscopy guidance, a 0.035-in guidewire and multipurpose catheter crossed the ASD, balloon sizing confirmed a 20 mm defect, and an 24 mm Amplatzer septal occluder (Abbott Structural Heart, United States) was successfully implanted (figure 1D,F). TEE confirmed accurate device placement, with no residual shunt and no left atrial flow obstruction. Informed consent was obtained.

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CTS is a rare cardiac malformation that can coexist with ostium secundum ASD in up to 33% of patients. Although transcatheter closure is preferred in suitable anatomies, the presence of CTS can complicate the device deployment due to inadequate margin definition, with increased risk of device instability and embolization. In this scenario, ASD closure was particularly challenging as the posterior rim was in direct continuity with the atrial membrane, raising concerns about proper device apposition. This case highlights the importance of advanced imaging, such as 3DTEE, in complex anatomies by allowing precise procedural planning and real-time guidance to ensure a successful intervention.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The patient gave his prior written informed consent for the procedure and for the publication of this case report, including all associated images. The SAGER guidelines have been followed with respect to possible sex/gender bias.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence, including language models, such as ChatGPT by OpenAI were used solely to support language editing of the manuscript. The scientific content, analysis, and interpretation were entirely produced by the authors.

AUTHORS' CONTRIBUTIONS

A. Abrantes was responsible for the study conception, literature review, manuscript writing, image processing, and figure preparation. E. Colón contributed to manuscript revision, image processing, and figure preparation. E. Pozo Osinalde performed the transesophageal echocardiography, acquired the echocardiographic images, and contributed to manuscript revision and figure preparation. D. García-Arribas was responsible for the patient's clinical follow-up and manuscript revision. L. Nombela-Franco and Pablo Salinas performed the interventional procedure and contributed to manuscript revision. All authors revised and approved the final version.

CONFLICTS OF INTEREST

None declared.

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Myocardial infarction due to late mammary artery occlusion

Infarto de miocardio por oclusión tardía de la arteria mamaria

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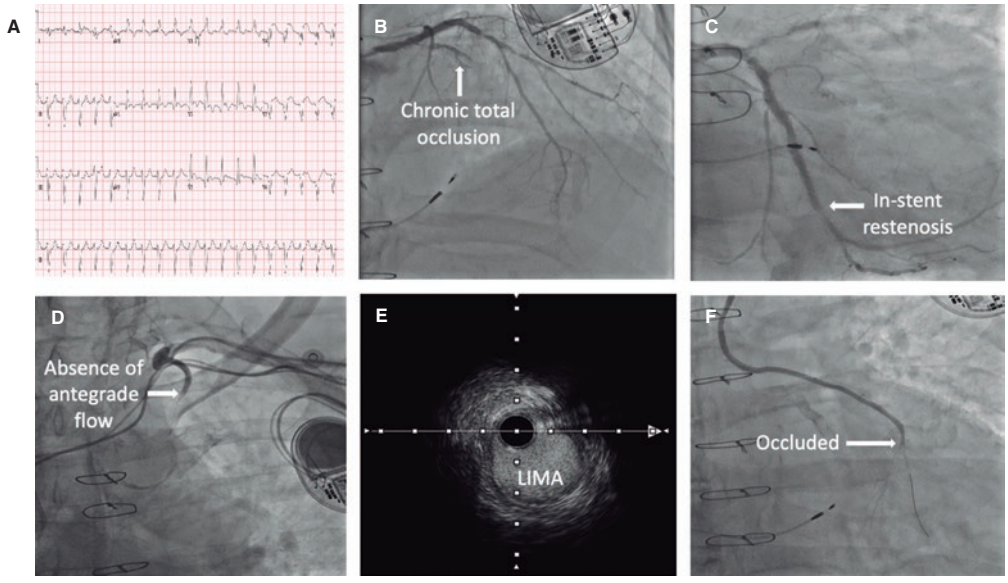

Figure 1.

A 77-year-old man with a history of severe in-stent restenosis (ISR) of the left anterior descending (LAD) and left circumflex (LCx) arteries, treated with coronary artery bypass grafting 4 years earlier, presented with acute chest pain, right bundle branch block, and anterolateral ST-segment elevation (figure 1A). His blood pressure was 90/60 mmHg, and echocardiography demonstrated severely impaired left ventricular function without mechanical complications.

Emergency angiography revealed a chronic total occlusion in the LAD (figure 1B, arrow), severe ISR in the LCx (figure 1C, arrow), and an occluded native right posterior descending artery. The graft to this artery was patent but diseased, and there was no antegrade flow in the left internal mammary artery (LIMA)–LAD graft (figure 1D; video S1). An intra-aortic balloon pump was inserted, and the LIMA–LAD graft was successfully wired with a workhorse guidewire. IVUS of the proximal to mid LIMA confirmed intraluminal position without evidence of dissection or graft disease (figure 1E).

Afterwards, a Thrombuster II (Kaneka Corp., Japan) aspiration device was advanced into the mid LIMA. Contrast injection revealed an occlusion at the LIMA–LAD anastomosis (figure 1F, arrow). Although thrombectomy restored flow, severe stenosis persisted at the anastomosis site. Balloon angioplasty was performed, followed by the deployment of a 2.0 mm × 30 mm Prevail (Medtronic, United States) drug-coated balloon (DCB) across the graft and native LAD (figure 2A, arrow). Final angiography demonstrated excellent runoff (figure 2B; video S2), ST-segment resolution, and hemodynamic improvement.

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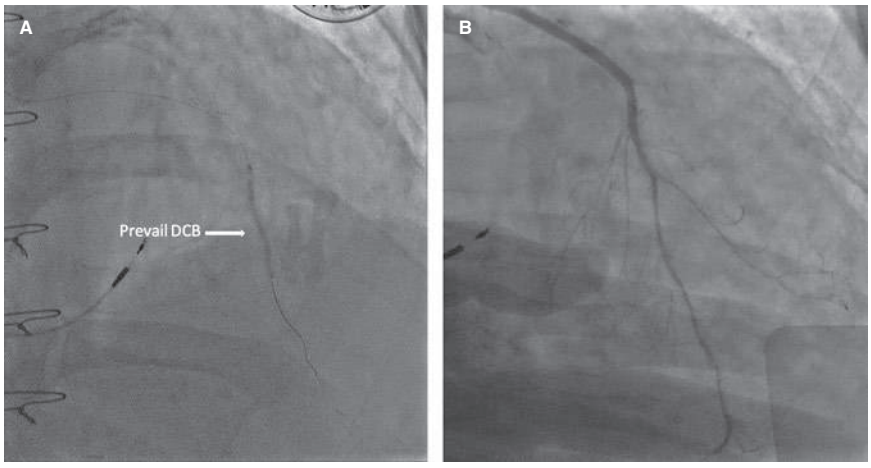

Figure 2.

Although LIMA grafts have excellent long-term patency, acute occlusion is rare but serious. In this case, acute native LAD plaque rupture distal to the LIMA anastomosis was a likely cause. Thrombectomy with DCB angioplasty enabled a scaffold-free revascularization strategy while preserving the integrity of the graft, illustrating a novel approach to acute LIMA–LAD graft occlusion.

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ETHICAL CONSIDERATIONS

Because this is an isolated case report, most SAGER guidelines recommendations are not applicable. The patient's age and gender have been specified. As this is a case report rather than a research study, no further considerations were required. Informed consent for diagnostic tests and for publication of the case was obtained.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used.

AUTHORS' CONTRIBUTIONS

S.C.H. Wong and B.V. Khialani drafted the initial version of the manuscript and selected and edited the images that would later be used. All authors collaborated in the manuscript critical review and approved its final version.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

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Interview

An interview with Lorenzo Azzalini

Una entrevista con Lorenzo Azzalini

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Lorenzo Azzalini is the Director of Interventional Cardiology Research and Professor of Medicine at the University of Washington, in Seattle (United States). His clinical and research focus is percutaneous coronary intervention (PCI) for chronic total occlusion (CTO), a field in which he is internationally recognized as a leading expert. He has authored more than 330 peer-reviewed publications, including numerous articles in *Journal of the American College of Cardiology*, *Circulation*, and *European Heart Journal*. Dr. Azzalini has received multiple international awards, performed live case demonstrations at major scientific meetings worldwide, and is deeply committed to education, training fellows and interventional cardiologists globally in advanced techniques for complex coronary revascularization.

What originally motivated you to pursue a career in medicine, and later to specialize in interventional cardiology?

During high school, I became fascinated by how incredibly complex and coordinated the human body is. The more I learned about physiology, the more I wanted to truly understand how things work—and what happens when they don't. I was drawn to medicine because it offered not only the opportunity to understand disease at a fundamental level, but also the ability to intervene and help "fix" what had gone wrong.

During medical school, I found myself especially drawn to cardiology. I was struck by how the dysfunction of a single organ could have such immediate and catastrophic consequences. At the same time, given the prevalence of cardiovascular disease, the potential to make a meaningful clinical impact was substantial.

I fell in love with interventional cardiology during my residency. while working night shifts, I cared for patients with acute myocardial infarction who would go straight to the cath lab. Seeing an interventional cardiologist open an occluded artery and watching a patient stabilize almost in real time was unforgettable. In those moments, I realized that I didn't just want to understand cardiovascular disease—I wanted to be a physician who could intervene during the most critical situations and make a difference.

Your training spanned Italy, Spain, Canada, and the United States. How did exposure to these different health care systems shape your development as a physician and scientist?

My training path has taken me through very different health care systems, each of which shaped me in a distinct way. In Italy, at the University of Padua, I developed a strong theoretical foundation in medicine. There is something powerful about training at an institution with an 800-year-long history—it instills a deep respect for the science of medicine and for the generations of physicians who came before us.

In Spain, at the *Hospital de la Santa Creu i Sant Pau* in Barcelona, I experienced significant clinical growth. I was exposed to the full spectrum of cardiology and developed a strong sense of responsibility for patient care. Both in Italy and Spain, I learned that medicine is fundamentally human. It's about being present for patients and their families, especially when we cannot offer a cure, and about sharing both hope and hardship.

My interventional training at the Montreal Heart Institute in Canada was transformative. I developed technical skills across a wide range of coronary and structural heart procedures and saw firsthand how careful planning and attention to detail can change a patient's trajectory in a single procedure.

Relocation to the United States, and particularly to the University of Washington, pushed me even further. The complexity of coronary artery disease here demands that we as interventional cardiologists learn different techniques to deal with very prevalent problems, including severe coronary calcification, chronic total occlusions, and revascularization in patients with prior coronary artery bypass graft surgery.

If there is a unifying theme in my journey it is this: medicine has required me to keep learning, adapting, and evolving—and that's exactly what continues to motivate me.

Complex coronary intervention, especially CTO PCI, requires a very particular mindset. What initially attracted you to this field, and specifically to CTO interventions?

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Lorenzo Azzalini (on the right), in a picture taken in the cath lab at the University of Washington Medical Center with an interventional cardiology fellow (September 2022).

I have always viewed CTO as incredibly complex puzzles—the kind that only a few people are willing to take on. What struck me early on was that many of these patients were simply told nothing could be done. As a result, they continued to experience significant symptoms and limitations, not because treatment was impossible, but because it required a very specific skill set. I felt strongly that these patients should have access to high-quality revascularization, which motivated me to pursue expertise in CTO intervention.

CTO work requires a particular mindset. Operators must be comfortable with long procedures, uncertainty, and constant problem-solving. It demands patience, edurance, and an obsessive attention to detail, because a single misstep at the wrong time can have serious consequences. It also requires deep familiarity with every device and technique, as well as the ability to anticipate and manage complications in a calm and systematic manner.

There is also a shared mindset among many operators in this field: we're drawn to challenges that others may avoid. We're willing to spend hours focused on opening a single lesion while others finish multiple cases and go home. It's demanding, sometimes humbling work, but incredibly rewarding.

I truly believe that high-level training in CTO PCI sharpens every aspect of your practice and ultimately makes you a better interventionalist in all coronary interventions.

You have authored numerous studies on CTO PCI, ranging from registries to reviews and consensus documents. Which contributions do you believe have had the greatest impact on daily practice or on how we conceptualize CTOs?

From early on in my CTO practice, I recognized that technical skill alone was insufficient. If I truly wanted to provide the best care, I needed to evaluate my outcomes, challenge my assumptions and share what we were learning with the broader community. That mindset led me to collaborate closely with colleagues and contribute to nearly 100 original studies on CTO PCI.

Several contributions stand out. In 2017, we published a large multicenter study examining CTO PCI in the setting of in-stent restenosis.[1] We showed that simply re-stenting these lesions had limited long-term durability. That work helped shift the conversation and opened the door to exploring alternative strategies, such as drug-coated balloons, for this challenging subset.

That same year, we reported outcomes of CTO PCI performed via ipsilateral, often epicardial, collaterals.[2] At a time of increasing enthusiasm for complex retrograde approaches, our data highlighted the higher risk of perforation and tamponade in this setting. I think that study contributed to a more balanced and cautious framework for procedural decision-making.

The study I am most proud of, however, is our recent randomized trial evaluating the subintimal tracking and re-entry (STAR) technique.[3] It was the first large trial comparing technical strategies in CTO PCI. We demonstrated that a bailout investment approach with STAR and deferred stenting can achieve high staged success rates without added risk, supporting a safer and more reproducible strategy. I believe this work is contributing to a shift in the field toward a paradigm that prioritizes procedural safety without compromising effectiveness, ultimately benefiting both operators and patients.

CTO PCI has not consistently demonstrated a mortality benefit in randomized trials, despite symptomatic improvement and observational signals. How should we interpret this apparent paradox?

As physicians, we are naturally oriented toward increasing survival: extending life is fundamental to what we do. But mortality represents only one outcome. For many of our patients, symptoms, functional capacity, and quality of life are equally important outcomes.

CTO PCI has a powerful and very consistent impact on quality of life. You truly understand this when patients return to the clinic after a successful recanalization. They tell you they can walk without stopping, travel again, or run after their grandchildren—things they had quietly given up on, assuming they were simply "getting older". That kind of transformation is real, even if it doesn't show up as a mortality curve on a trial report.

It's also important to maintain perspective. With the exception of primary PCI in the setting of ST-segment elevation myocardial infarction, PCI in stable patients has not consistently shown a survival benefit. If opening a severe but non-occlusive proximal left anterior descending artery doesn't clearly improve mortality in randomized trials, it is not unexpected that CTO PCI would yield similar findings.

I don't see this as a paradox. I see it as a reminder that the value of CTO PCI lies primarily in symptom relief and quality of life, and that we should hold it to the same standards, expectations, and honesty that we apply to PCI in general.

CTO PCI outcomes have improved substantially in recent years, with higher success rates and lower complication rates. In your view, what have been the most important drivers of this progress—whether in techniques, tools, or operator mindset?

Technology has certainly helped: better guidewires and microcatheters have expanded what we can do. But honestly, I think the biggest advances have happened in the minds of operators.

The development of techniques such as the retrograde approach and modern dissection and re-entry strategies fundamentally changed the field. Lesions that were once labeled "impossible" suddenly became treatable. But the real leap forward came when these techniques were organized into structured algorithms. Instead of improvising, operators began approaching CTOs with a clear, stepwise strategy. That shift brought consistency, efficiency, and better decision-making.

Organizers of the University of Washington Community CTO Event (July 2025). Left to right: William Lombardi, Kathleen Kearney, Primero Ng, Lorenzo Azzalini, Rachel MacDonald, and John Michael Maier.

In the last few years, progress has extended beyond wires and techniques. We have matured as a field. We've become more intentional about complication management: not only in prevention of complications, but also on how to recognize and recover from them calmly and systematically. Furthermore, greater emphasis has been placed on operator mindset, including mental resilience during long cases, and the importance of building strong CTO programs and collaborative communities rather than working in isolation.

Collectively, these changes—technical, strategic, and cultural—have worked together to turn CTO PCI not only into a more successful procedure, but also into a safer and more reproducible one than ever before.

From your perspective, which innovations are most likely to transform the way we approach CTO PCI in the coming years (e.g., new devices, imaging, robotics, or AI-based planning)?

Over the past two decades, we've seen many dedicated CTO crossing devices appear… and disappear. CTO PCI is simply too complex for a single tool to "solve" most cases. I don't think the next big leap will come from one single breakthrough tool.

Rather, I believe the real transformation will come from 3 areas.

First, education and training. Proctoring alone hasn't always been enough, but we're now seeing the impact of dedicated CTO fellowships and hands-on workshops. As we continue to invest in formal education, high-quality CTO PCI will become accessible to more operators, and therefore to more patients.

Second, imaging. Although intravascular imaging is already improving patient outcomes and the durability of recanalization, the real revolution is happening in procedural planning. Coronary computed tomography angiography (CCTA)-guided planning is changing the way we approach cases before we even scrub in. Understanding the anatomy in detail ahead of time can simplify strategy and reduce unnecessary escalation.

Finally, I think AI-assisted planning will play an important role. Rather than replacing operator judgment, AI can become a partner. If AI-based analysis of angiography and CCTA can identify key complexity features and suggest the most promising crossing and plaque modification strategies, it could make decision-making more consistent and help democratize CTO PCI.

Although AI won't think for us, it can sharpen our thinking. And that, in a field as nuanced as CTO PCI, could be truly transformative.

Interventional cardiology is both physically and emotionally demanding. How do you maintain balance outside the hospital?

The absolute pillar of my life, both inside and outside the hospital, is my family. My wife, Luz Maria, and my daughter, Lisa, are my grounding force. No matter how intense a day in the cath lab may be, coming home to them resets everything. Sharing life with them—the good moments and the difficult ones—gives me perspective and strength. It reminds me that medicine is what I do, not who I am. I find balance in the simple, everyday things: spending unhurried time together, traveling, hiking, sailing, and exploring new places as a family.

Those moments recharge me emotionally and physically, and they allow me to return to work focused, grateful, and ready to give my best to my patients.

Finally, what message would you offer to young interventional cardiologists aspiring to work in complex PCI?

First, know yourself. Understand who you truly are, what drives you, and what kind of physician you aspire to become. When you are grounded in that, decisions become clearer.

Don't build your career around impressing others or reacting to the noise around you. There will always be opinions—about what you should do, what is realistic, what is "possible." When I listened too closely to that noise, I sometimes drifted away from my own path.

Don't let anyone convince you that you are not good enough, or that something is impossible. Ambitious goals often live in that space between doubt and determination. If I had listened to the naysayers, I would not be where I am today, and where I will be tomorrow.

Whatever direction you choose, commit to it fully. Strive to be excellent. In the end, the only person you truly answer to is yourself. If you can look back and know you gave your best—intellectually, technically, and ethically—that is what defines a meaningful career.

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CONFLICTS OF INTEREST

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ABOUT THE AUTHOR

Soledad Ojeda is associate editor of *REC: Interventional Cardiology*. Her clinical and research interests include complex coronary intervention, particularly CTO PCI. She has collaborated with Lorenzo Azzalini on multiple research projects and peer-reviewed publications in this field.

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