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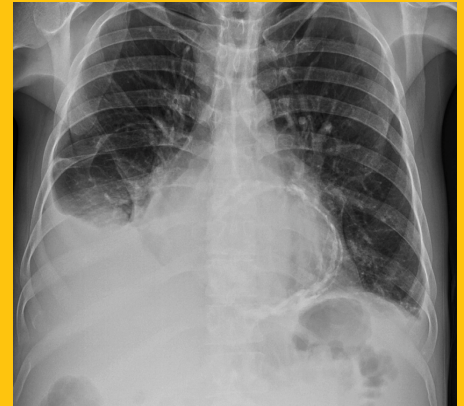
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Artificial Intelligence in Echocardiography: Five Clinical Challenges and a Roadmap Toward Responsible Integration by 2030

Ekokardiyografide Yapay Zekâ: Beş Klinik Zorluk ve 2030'a Kadar Sorumlu Entegrasyona Yönelik Bir Yol Haritası

ABSTRACT

Artificial intelligence (AI)-enabled echocardiography has demonstrated strong agreement with expert measurements across a broad range of cardiac functional parameters. However, the transition from technical validation to clinical impact remains incomplete. This structured narrative review employed a systematic literature search to identify the principal structural barriers to AI integration in echocardiography and to develop an expert-informed, evidence-grounded perspective on the priorities for responsible implementation by 2030. The methodological heterogeneity of the included studies, including retrospective and prospective designs, diverse outcome measures ranging from measurement agreement to workflow implementation, and multiple AI application domains, precluded quantitative pooling. Therefore, qualitative synthesis was selected as the primary prespecified analytical approach. PubMed/MEDLINE was searched for studies published between January 2015 and January 2026 addressing clinical AI applications, real-world validation, implementation science, and governance. Forty-six studies meeting predefined inclusion criteria underwent qualitative synthesis. Five interdependent domains were identified: reproducibility across clinical settings, generalizability beyond development datasets, the lack of outcome-focused evidence, regulatory and governance immaturity, and insufficient trust among clinicians and patients. Automated measurements of left ventricular function, strain, and valvular disease severity demonstrate close agreement with expert assessments. However, few studies have shown that AI-assisted echocardiography translates into improved patient outcomes. Based on the available evidence, the principal translational barrier appears to be not algorithmic capability itself, but rather the structural requirements necessary for accountable clinical integration. An expert-informed, evidence-grounded roadmap emphasizing decision-level reproducibility, rigorous external validation, outcome-linked evidence generation, continuous lifecycle governance, and human-centered design is proposed to guide the integration of AI into echocardiography and to support the development of a more durable and accountable clinical infrastructure by 2030.

Keywords: Artificial intelligence, clinical decision support systems, deep learning, echocardiography, implementation science, machine learning

ÖZET

Yapay zekâ (YZ) destekli ekokardiyografi, geniş bir kardiyak fonksiyon parametreleri yelpazesinde uzman ölçümleriyle güçlü bir uyum göstermiştir. Ancak teknik doğrulamadan klinik etkiye geçiş süreci henüz tamamlanmamıştır. Bu yapılandırılmış anlatı derlemesinde, ekokardiyografide YZ entegrasyonunun önündeki temel yapısal engelleri belirlemek ve 2030 yılına kadar sorumlu uygulama için önceliklere ilişkin uzman görüşüne dayalı, kanıt temelli bir bakış açısı geliştirmek amacıyla sistematik bir literatür taraması yapılmıştır. Dahil edilen çalışmaların retrospektif ve prospektif tasarımları, ölçüm uyumundan iş akışı uygulamasına kadar değişen çeşitli sonuç ölçütleri ve birden fazla YZ uygulama alanını içeren metodolojik heterojenliği, nicel birleştirmeyi mümkün kılmamıştır. Bu nedenle, nitel sentez önceden belirlenmiş birincil analitik yaklaşım olarak seçilmiştir. PubMed/MEDLINE'da Ocak 2015 ile Ocak 2026 arasında yayımlanan; klinik YZ uygulamaları, gerçek yaşam doğrulaması, uygulama bilimi ve yönetim konularını ele alan çalışmalar taranmıştır. Önceden tanımlanmış dahil edilme kriterlerini karşılayan 46 çalışma nitel senteze alınmıştır. Birbirine bağlı beş alan belirlenmiştir: klinik ortamlar arasında tekrarlanabilirlik, geliştirme veri setlerinin ötesinde genellenebilirlik, sonuç odaklı kanıt eksikliği, düzenleyici ve yönetim süreçlerindeki olgunlaşmamışlık ve klinisyenler ile hastalar arasında yetersiz güven. Sol ventrikül fonksiyonu, strain ve kapak hastalığı şiddetine ilişkin otomatik ölçümler, uzman değerlendirmeleriyle yakın uyum göstermektedir. Bununla birlikte, az sayıda çalışma YZ destekli ekokardiyografinin hasta sonuçlarında iyileşmeye dönüştüğünü göstermiştir. Mevcut kanıtlara dayanarak, temel translaşyonel engelin algoritmik kapasitenin kendisinden ziyade, hesap verebilir klinik entegrasyon için gerekli yapısal gereklilikler olduğu görülmektedir. Ekokardiyografiye YZ entegrasyonunu yönlendirmek ve 2030 yılına kadar daha dayanıklı ve hesap verebilir bir klinik altyapının geliştirilmesini desteklemek amacıyla, karar düzeyinde tekrarlanabilirliği, titiz dış doğrulamayı, sonuçlarla bağlantılı kanıt üretimini, sürekli yaşam döngüsü yönetimini ve insan odaklı tasarımı vurgulayan, uzman görüşüne dayalı ve kanıt temelli bir yol haritası önerilmektedir.

Anahtar Kelimeler: Derin öğrenme, ekokardiyografi, klinik karar destek sistemleri, makine öğrenimi, uygulama bilimi, yapay zekâ

REVIEW

DERLEME

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Echocardiography is the most widely used cardiac imaging modality in clinical practice, guiding diagnosis, risk stratification, and long-term management across the full spectrum of cardiovascular disease. Its portability, real-time imaging capability, and cost-effectiveness make it indispensable in settings ranging from primary referral centers to emergency departments and resource-limited environments. Nevertheless, the field faces a substantial structural challenge. Rising clinical demand, expanding quantitative assessment requirements, and persistent inter-operator variability are placing increasing pressure on echocardiographic services and threatening their long-term sustainability.¹

Manual assessment of left ventricular ejection fraction (LVEF), myocardial strain, chamber volumes, and Doppler hemodynamics is time-consuming and highly operator dependent. Even among experienced sonographers, reproducibility may vary considerably, particularly in high-volume laboratories and acute-care settings.²⁻⁴ These limitations represent not only technical constraints but also systemic vulnerabilities affecting quality, efficiency, and equitable access to cardiovascular care.

Artificial intelligence (AI) has emerged as a promising solution to these challenges. Automated LVEF quantification has been validated in both single-center and multicenter studies.^{5,6} Deep-learning platforms for point-of-care LVEF assessment have demonstrated strong agreement with expert measurements.⁷ Similarly, automated strain analysis and three-dimensional right ventricular quantification have shown encouraging reproducibility.⁸⁻¹⁰ Beyond ventricular function, AI applications have expanded to include valvular disease grading, hemodynamic assessment, and disease classification.^{11,12} Predictive models have also been developed to estimate the risk of left atrial thrombus in patients with atrial fibrillation and to facilitate the early detection of infiltrative cardiomyopathies such as light-chain amyloidosis.^{13,14}

Despite these technical advances, a more challenging reality remains. The translational pathway for AI in echocardiography is still fragmented. Most validation studies are retrospective, single-center investigations conducted in carefully selected populations.^{15,16} Dataset bias, vendor dependency, and reduced performance in suboptimal imaging conditions are recurring concerns.^{17,18} Furthermore, even multicenter studies have demonstrated meaningful variability in performance across institutions.^{19,20}

More importantly, few investigations have demonstrated improvements in patient-centered outcomes. Although AI systems can approximate expert consensus, evidence linking automation to reductions in morbidity and mortality, or sustained gains in healthcare efficiency remains limited.^{21,22} Based on the available evidence, the principal translational barrier appears to be not algorithmic capability per se, but the structural requirements necessary for accountable clinical integration. This review examines five structural challenges that will influence whether AI achieves meaningful clinical integration in echocardiography by 2030.

Terminology

Throughout this review, AI is used as the overarching term encompassing machine-based approaches to pattern recognition in clinical data. Machine learning (ML) refers

ABBREVIATIONS

AI	Artificial intelligence
AS	Aortic stenosis
DL	Deep learning
LVEF	Left ventricular ejection fraction
ML	Machine learning
RCT	Randomized controlled trial

specifically to statistical methods in which algorithms improve performance through exposure to data without explicit rule-based programming. Deep learning (DL) represents a subset of ML that employs multilayered neural networks. These terms are used precisely rather than interchangeably throughout this review, consistent with the terminology adopted in the cited studies.

Methodology

Review Design and Search Strategy

This structured narrative review was conducted using a systematic literature search and is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement.²³ The review design and eligibility criteria were predefined before the literature search was undertaken. Given the methodological heterogeneity of the included studies, including retrospective single-center cohorts, prospective multicenter trials, implementation science investigations, and governance analyses, quantitative pooling was not considered appropriate. Accordingly, qualitative synthesis was adopted as the primary prespecified analytical strategy, consistent with established guidance for narrative synthesis of heterogeneous evidence bases.²⁴ This review should be regarded as a structured narrative review incorporating a systematic search strategy and dual-reviewer study selection. It does not claim the analytical scope of a formal systematic review or meta-analysis. Consequently, its conclusions are presented as evidence-grounded interpretations rather than confirmatory findings. This distinction is stated explicitly to ensure alignment between the review's declared methodology and its actual analytical scope.

Note on Reference Structure: The 46 references cited in this manuscript comprise 44 primary AI studies included in the qualitative synthesis^{1-22,25-46} and two methodological guidance documents used to justify the review design^{23,24} (corresponding to PRISMA 2020 and the Joanna Briggs Institute [JBI] scoping review methodology, respectively). These methodological references are not primary clinical studies and were therefore excluded from the PRISMA flow diagram and synthesis totals. All quality appraisal and framework mapping described below apply exclusively to the 44 AI studies (Figure 1).

A structured literature search was conducted in PubMed/MEDLINE for studies published between January 2015 and January 2026. Search strategies were developed around three predefined domains: (1) clinical applications of AI in echocardiography, (2) real-world validation and implementation, and (3) regulatory, ethical, and governance considerations. The complete search strategy, including Boolean operators and search syntax, is provided in Supplementary Table 1.

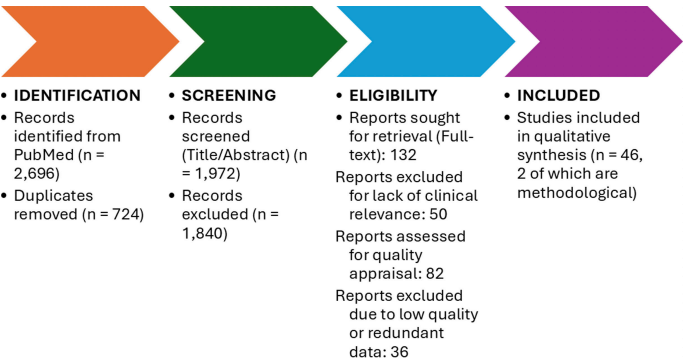


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the study selection process. A total of 2,696 records were identified through PubMed/MEDLINE. After removal of 724 duplicate records, 1,972 titles and abstracts were screened, of which 1,840 were excluded according to predefined eligibility criteria. Full-text review was performed for 132 articles, and 50 were excluded because of insufficient clinical relevance. Of the 82 studies that underwent appraisal, 38 were excluded (36 because of overlapping cohorts or limited validation and two because they failed to meet at least three predefined quality criteria). Ultimately, 44 primary artificial intelligence (AI) studies were included in the final qualitative synthesis. Two methodological references (PRISMA 2020 [23] and Joanna Briggs Institute (JBI) guidance [24]) are cited but are not included in the PRISMA flow. The complete reference list therefore contains 46 citations (two of which are methodological references).

Study Selection and Dual-Reviewer Process

Study selection was performed in two stages. In the first stage, two independent reviewers (a consultant cardiologist with expertise in echocardiography and a clinical researcher with experience in AI implementation science) screened all titles and abstracts according to predefined inclusion and exclusion criteria. Disagreements were resolved through consensus discussion, and no third-party adjudication was required. Inter-rater agreement for study inclusion and exclusion decisions was substantial (Cohen's κ = 0.81).

Studies were eligible for inclusion if they involved human subjects, reported external validation or prospective clinical data, and addressed clinical outcomes, workflow integration, implementation science, or governance-related topics. Pure algorithm-developed studies, simulation studies, phantom-model investigations, nonclinical engineering reports, conference abstracts, and non-peer-reviewed publications were excluded (Table 1).

In the second stage, all studies undergoing full-text review were subjected to a structured methodological appraisal based on five predefined quality criteria: (1) use of human subjects or prospectively acquired clinical data; (2) inclusion of an external or independent validation cohort; (3) application of a clinically meaningful reference standard; (4) reporting of a clinical endpoint or workflow-related outcome; and (5) disclosure of feasibility metrics. Studies meeting fewer than three of these criteria were excluded. Details of the appraisal process are provided in Supplementary Table 2.

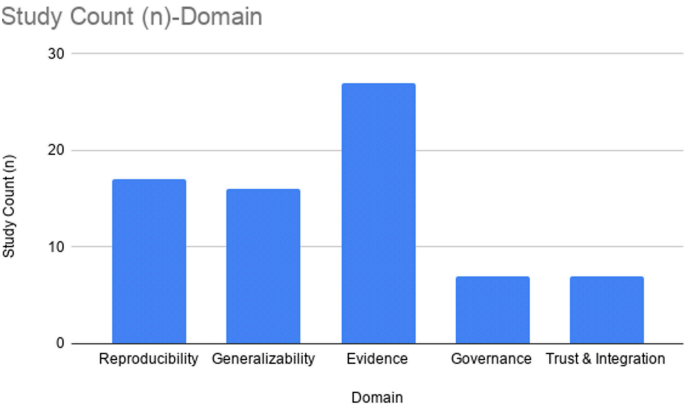


Figure 2. Evidence-to-framework mapping illustrating the distribution of the 44 included artificial intelligence (AI) studies across the five implementation-challenge domains. Studies informing multiple domains were counted in each relevant category. The unequal distribution of evidence, with the reproducibility and generalizability domains supported by the largest number of studies (n = 17 and n = 16, respectively) and the governance and trust domains supported by the fewest studies (n = 7 and n = 7, respectively), directly informed the relative depth of evidence synthesis across the manuscript. The two methodological references [23,24] are not represented in this framework mapping.

Quality Appraisal

Formal quality assessment was performed for all included studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool for diagnostic accuracy studies and the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool for observational implementation studies. Both assessments were conducted independently by two reviewers. Results are summarized in Table 2. A formal GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment was not performed because the review did not address a single focused clinical question suitable for graded evidence synthesis. Instead, a predefined five-level evidence hierarchy was applied as a descriptive quality stratification framework:

- Level I: Prospective multicenter randomized controlled trial (RCT) or meta-analysis;
- Level II: Prospective multicenter nonrandomized study;
- Level III: Retrospective multicenter study;
- Level IV: Prospective single-center study;
- Level V: Retrospective single-center study or technical pilot investigation.

This framework was used to characterize study quality and evidentiary strength in a manner consistent with structured narrative review methodology.

Framework Derivation

Consistent with established guidance for narrative synthesis of heterogeneous evidence, the five implementation domains were derived inductively through thematic analysis of the 44 included studies.²⁴ Two reviewers independently coded each

Table 1. Key clinical applications of artificial intelligence in echocardiography: Evidence summary and clinical readiness

Application domain	Clinical application	Key reference	n	Principal performance metric	External validation status	Clinical readiness
LV function	Automated LVEF assessment (multicenter handheld AI)	Kagiyama et al. 2024 ⁶	5,085	$r = 0.88$ – 0.92 ; bias 1.1% ; LOA $\pm 10.4\%$	Established	High (widely deployed)
LV function	DL-based point-of-care LVEF assessment	Asch et al. 2021 ⁷	700	ICC 0.93 ; MAE 4.1% ; feasibility 94%	Established	High
LV function	Blinded RCT of AI vs. sonographer LVEF assessment	He et al. 2023 ²⁶	3,495	Substantial change: 16.8% (AI) vs. 27.2% (sonographer); $P < 0.001$	Established	High
LV function	AI-based LV volume and EF quantification: real-time + large DB	Olaisen et al. 2024 ²⁵	$>5,600$	Acquisition time reduced by 77% ; ICC 0.91 (EF)	Established	High
Strain analysis	Automated LV GLS assessment (multicenter DL)	Salte et al. 2021 ⁸	437	Bias -0.3% ; LOA $\pm 1.8\%$; ICC 0.91	Partial	Moderate to high
Strain analysis	AI-based GLS assessment in a UK-wide dataset	Stowell et al. 2024 ¹⁷	4,108	ICC 0.87 ; site variability, SD 1.2%	Established	Moderate to high
Strain analysis	Real-time DL-based GLS workflow	Holmström et al. 2025 ²⁷	289	ICC 0.93 ; workflow time -22%	Absent	Emerging
RV function	Automated 3D RV quantification (pediatric vs. CMR)	Liu et al. 2025 ⁴	82	ICC 0.91 ; bias -3.2 mL; LOA ± 9 mL	Established	Emerging
Valvular disease	AI-based detection of severe AS by DL (multicenter)	Holste et al. 2023 [19]	5,257	AUC 0.94 – 0.95 (severe AS); generalizes to LG-AS	Established	Moderate
Valvular disease	AI-based assessment across the AS continuum	Park et al. 2025 ¹²	8,427	AUC 0.91 ; F1-score 0.84	Established	Moderate
Valvular disease	AI-based differentiation of LG-AS vs. moderate AS diagnosis	Wrzosek et al. 2026 ¹¹	900	AUC 0.87 ; sensitivity 81% ; specificity 84%	Partial	Emerging
Hemodynamics	AI-based RAP estimation	Zamzmi et al. 2023 ⁴⁰	255	Spearman $r = 0.82$; MAE 2.1 mmHg	Absent	Low to moderate
Hemodynamics	AI-assisted echocardiographic detection of PH	Salehi et al. 2025 ⁴¹	410	AUC 0.88 ; sensitivity 85% ; specificity 82%	Established	Moderate
Image acquisition	AI-guided image acquisition by novice operators (multicenter)	Trost et al. 2025 ³⁵	143	Diagnostic adequacy: 91% (AI) vs. 67% (control)	Established	Emerging
Image acquisition	AI-Echo RCT: workflow efficiency (RCT)	Sakamoto/Kagiyama et al. 2026 ²²	585	Examination time -9% ; daily scans $+18\%$; reduced fatigue	Established	Moderate
Disease classification	Amyloidosis detection from a single video clip	Slivnick et al. 2025 ³⁷	1,808	AUC 0.91 ; sensitivity 87% ; specificity 88%	Established	Emerging
Disease classification	ML-based prediction of LA thrombus	Xiong et al. 2025 ¹³	648	AUC 0.86 ; sensitivity 83% ; specificity 80%	Absent	Early
Outcomes/implementation	AI-assisted bedside echocardiography: inpatient RCT	Frydman et al. 2026 ²¹	388	Management change: 28% (AI) vs. 19% (control); $P = 0.04$	Established	Moderate
Outcomes/implementation	AI-assisted POCUS LVEF assessment: diagnostic accuracy	Motazedian et al. 2023 ⁴²	320	AUC 0.92 ; sensitivity 89% ; specificity 88%	Established	Moderate

AI, Artificial intelligence; AUC, Area under the receiver operating characteristic curve; CMR, Cardiac magnetic resonance; DL, Deep learning; GLS, Global longitudinal strain; ICC, Intraclass correlation coefficient; LOA, Limits of agreement; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MAE, Mean absolute error; PH, Pulmonary hypertension; POCUS, Point-of-care ultrasound; RCT, Randomized controlled trial; RV, Right ventricular. For detailed performance metrics and validation status of the studies cited in Table 5, see Table 1.

study's principal limitations and implementation barriers using an open-coding approach. Inter-rater agreement for thematic coding was substantial (Cohen's $\kappa = 0.76$), indicating acceptable reproducibility of the categorization process. Codes were subsequently grouped through iterative axial coding into broader

thematic categories. Five overarching domains emerged as the most consistently represented barriers across the literature: reproducibility, generalizability, evidence, governance, and trust (Figure 2). The complete mapping process is presented in Supplementary Table 2, which links each study to the domain(s)

Table 2. Risk-of-bias assessment of included studies using QUADAS-2 and ROBINS-I frameworks

Reference	n	Study design	Patient selection	Index test	Reference standard	Flow and timing	Overall risk
Kagiyama et al. 2024 ⁶	5,085	Retrospective multicenter	Low	Low	Low	Low	Low
Asch et al. 2021 ⁷	700	Prospective multicenter	Low	Low	Low	Low	Low
He et al. 2023 ²⁶	3,495	Blinded RCT	Low	Low	Low	Low	Low
Frydman et al. 2026 ²¹	388	Prospective multicenter RCT	Low	Low	Low	Low	Low
Holste et al. 2023 ¹⁹	9,483	Retrospective multicenter	Low	Low	Low	Low	Low
Olaisen et al. 2024 ²⁵	>5,600	Prospective multicenter	Low	Low	Low	Moderate	Low
Trost et al. 2025 ³⁵	143	Prospective multicenter	Low	Low	Low	Moderate	Low
Salte et al. 2021 ⁸	437	Retrospective multicenter	Low	Low	Low	Moderate	Low
Stowell et al. 2024 ¹⁷	4,108	Retrospective multicenter	Low	Low	Low	Moderate	Low
Slivnick et al. 2025 ³⁷	1,808	Retrospective multicenter	Low	Low	Low	Low	Low
Park et al. 2025 ¹²	8,427	Retrospective multicenter	Low	Low	Moderate	Low	Low
Wrzosek et al. 2026 ¹¹	900	Retrospective multicenter	Moderate	Low	Moderate	Moderate	Moderate
Sakamoto et al. 2026 ²²	585	RCT crossover	Low	Low	Low	Low	Low
Varudo et al. 2022 ²	120	Prospective single-center	Moderate	Low	Low	Moderate	Moderate
Zamzmi et al. 2023 ⁴⁰	255	Retrospective single-center	Moderate	Moderate	Moderate	Moderate	Moderate
Sveric et al. 2024 ¹⁶	310	Retrospective single-center	Moderate	Low	Low	Moderate	Moderate
Zhu et al. 2025 ¹⁵	1,832	Retrospective single-center	Moderate	Moderate	Low	Moderate	Moderate
Mou et al. 2026 ¹⁰	483	Retrospective single-center	High	Moderate	Moderate	High	High
Xiong et al. 2025 ¹³	648	Retrospective single-center	Moderate	Moderate	Moderate	High	High
Myhre et al. 2024 ²⁹	Multicohort	Retrospective multicenter	Low	Low	Low	Moderate	Low

Quality domains were adapted from the QUADAS-2 framework. Patient selection assesses the risk of inappropriate exclusions or the use of a case-control design; Index test assesses the risk related to knowledge of the reference standard during interpretation of the index test; Reference standard assesses the risk that the reference standard misclassifies the target condition; Flow and timing assesses the risk from inappropriate time intervals or incomplete analysis. Overall risk was classified as low (low risk across all domains), moderate (some concerns unlikely to substantially affect the conclusions), or high (serious concerns that may compromise study validity). Color coding: low (green), moderate (amber), and high (red).

it informed. The framework is presented as an evidence-synthesis tool rather than a novel theoretical construct. It is situated within established digital-health implementation frameworks, including Greenhalgh's NASSS (Nonadoption, Abandonment, Scale-up, Spread, and Sustainability) framework and previously published AI deployment taxonomies. Importantly, thematic coding was performed independently of the quality appraisal process, and the final domain structure was established before QUADAS-2 and ROBINS-I assessments were completed, thereby minimizing the risk of circular reasoning between evidence quality and framework development.

Study Selection Results

The initial search identified 2,696 records. After removal of 724 duplicates, 1,972 titles and abstracts were screened, of which 1,840 were excluded according to predefined criteria. Full-text review was performed for 132 articles, and 50 were excluded because of insufficient clinical relevance. The remaining 82 studies met thematic relevance criteria and underwent structured methodological appraisal using the five predefined quality criteria. Of these, 38 studies were excluded, including 36 because of overlapping cohorts or limited clinical validation and two because they failed to meet the minimum quality threshold of three criteria. Ultimately, 44 primary AI

studies fulfilled all evidentiary requirements and were included in the final qualitative synthesis (Figure 1). Two additional methodological references (the PRISMA 2020 statement²³ and JBI scoping review guidance²⁴) were cited in the Methods section but were not primary clinical studies and were not included in the synthesis totals. Consequently, the complete reference list contains 46 entries. Among the 44 included studies, 15 (34%) reported external or independent validation, 12 (27%) employed a prospective design, and 23 (52%) were retrospective single-center investigations. The distribution of AI application domains was as follows:

- Left ventricular (LV) function (n = 10),
- Strain and deformation imaging (n = 5),
- Valvular disease (n = 3),
- Right ventricular (RV) function (n = 3),
- Hemodynamic assessment (n = 2),
- Disease-specific classification (n = 4),
- Image acquisition and guidance (n = 5),
- Procedural planning (n = 3),
- Implementation and outcomes research (n = 6).

An additional study addressing clinician trust and acceptance ($n = 1$) was included as contextual evidence. The relatively small proportion of outcome-oriented and governance-focused investigations directly informs the five implementation challenges discussed in the subsequent sections.

Across the 44 included AI studies, a semiquantitative synthesis of key performance metrics revealed several patterns. In LV function assessment ($n = 10$), agreement between AI systems and expert readers was consistently high, with intraclass correlation coefficients (ICC) ranging from 0.87 to 0.93 for LVEF measurements. Mean absolute errors generally ranged from 3 to 5 percentage points, with narrow limits of agreement (LOA). The blinded RCT by He et al.²⁶ demonstrated the noninferiority of AI-assisted assessment compared with sonographer interpretation (16.8% vs. 27.2% substantially changed values; $P < 0.001$), representing the highest level of evidence in this domain. In strain imaging ($n = 5$ studies), automated global longitudinal strain (GLS) measurements demonstrated minimal bias (-0.3% to -0.5%), LOA of approximately 1.8% to 2.2%, and ICC ranging from 0.87 to 0.93. Nevertheless, interinstitutional variability remained evident in the UK-wide collaborative dataset.¹⁷ For valvular disease assessment ($n = 3$), the area under the receiver operating characteristic curve (AUC) for severe aortic stenosis (AS) detection ranged from 0.87 to 0.95. The multicenter model reported by Holste et al.¹⁹ ($n = 9,483$) demonstrated the strongest overall performance, including accurate identification of low-gradient phenotypes. Among disease-specific classification studies ($n = 4$), AUC values ranged from 0.86 to 0.91. Across implementation and outcomes studies ($n = 6$), both RCTs^{21,22} demonstrated statistically significant improvements in clinical management decisions and workflow efficiency. Overall study quality, assessed using QUADAS-2 and ROBINS-I, was rated as low risk in 14 studies (32%), moderate risk in 25 studies (57%), and high risk in five studies (11%). These quality assessments are integrated throughout the subsequent five-challenge synthesis. Domains supported by a greater proportion of low-risk studies are discussed with greater confidence regarding the strength and directness of the evidence. Conversely, domains dominated by moderate- or high-risk studies are interpreted more cautiously. Specifically, LV function assessment and workflow implementation are supported by the strongest evidence base, largely derived from multicenter studies with low risk of bias, whereas governance, trust, and disease-specific classification rely more heavily on moderate-risk retrospective and single-center investigations, a limitation explicitly acknowledged within the relevant sections.

Five Implementation Challenges Shaping AI in Echocardiography

Artificial intelligence in echocardiography has progressed well beyond the stage of early feasibility studies. Automated measurement of ejection fraction, strain quantification, disease classification, and image acquisition guidance are increasingly entering routine clinical practice.^{15,24} Nevertheless, five structural challenges will determine whether these technologies meaningfully transform clinical practice by 2030 or remain fragmented tools with limited system-wide impact. These domains are interdependent and reflect the ongoing tension between technological capability and clinical reality. Importantly,

the five domains described below are evidence-derived. They emerged through inductive thematic analysis of the 44 studies included in this review (Section 2.4) and are grounded in recurring limitations and implementation barriers reported in the literature rather than in author opinion or a priori theoretical categorization. Supplementary Table 2 maps each included study to the domain(s) it informs, thereby providing a transparent audit trail linking the evidence base to the thematic synthesis.

The Reproducibility Challenge: Automation without Consistency

Interobserver variability has long been a fundamental limitation of echocardiography. Manual assessment of LVEF, myocardial strain, and Doppler-derived parameters remains highly dependent on operator expertise and image quality.^{2,3,25} Consequently, discrepancies persist even among experienced readers.

Automated quantification platforms have substantially improved agreement with expert reference standards. Multicenter studies evaluating AI-assisted LVEF assessment have demonstrated high correlation with reduced intraobserver variability.^{6,7,26} In a randomized noninferiority trial, He et al.²⁶ showed that AI-assisted initial assessment of LVEF was noninferior to sonographer assessment and was associated with a lower proportion of substantially revised measurements (16.8% vs. 27.2%, $P < 0.001$ for superiority). Similarly, real-time deep learning-based GLS analysis has improved workflow efficiency without compromising measurement quality.²⁷ Automated three-dimensional RV quantification and strain analysis systems have also demonstrated encouraging reproducibility in selected patient cohorts.^{4,28}

However, improvements in reproducibility are not universal. Performance may decline in patients with severe remodeling, arrhythmias, prosthetic valves, or poor acoustic windows.^{16,29} Furthermore, agreement at the population level does not necessarily imply clinical interchangeability at therapeutic decision thresholds.¹⁶ A mean absolute error of only a few percentage points may alter clinical management in borderline cases. Emerging multitask learning frameworks that simultaneously assess ventricular structure and function may offer greater stability, although further external validation is required.³⁰

The reproducibility challenge therefore concerns not measurement capability, but measurement reliability across diverse and imperfect clinical environments. Automation reduces variability under controlled conditions; it cannot eliminate it entirely. Quality appraisal revealed an important asymmetry within this evidence base. The strongest reproducibility data derive from low-risk multicenter investigations, including those by He et al.,²⁶ Kagiya et al.,⁶ and Olaisen et al.²⁵, whereas several retrospective single-center studies were assessed as having a moderate risk of bias. Consequently, population-level agreement should not be interpreted as definitive evidence of decision-level stability in routine clinical practice.

2030 Priority: The available evidence suggests that future reproducibility assessments should focus on decision stability around clinically relevant thresholds, such as LVEF values of 35%–40% and GLS cutoffs for cardiotoxicity surveillance, rather than relying solely on population-level agreement metrics.

The Generalizability Challenge: From Single Centers to Real-World Diversity

Most AI systems in echocardiography are developed using retrospective datasets derived from single institutions.^{15,31} Although internal validation frequently yields excellent performance metrics, multicenter investigations consistently demonstrate variability when these models are deployed across independent clinical settings.^{16,17,19}

Model performance may be influenced by vendor-specific image processing, demographic variation, and differences in acquisition protocols.¹⁷ Spectrum bias further limits applicability when datasets disproportionately represent classical disease phenotypes.^{19,31} As a result, feasibility often declines when algorithms are applied outside their development environments.²⁹

This challenge is particularly evident in specialized patient populations. Holste et al.¹⁹ developed a deep learning model for AS detection using 5,257 studies from multiple centers and demonstrated excellent generalizability, with AUC values ranging from 0.94 to 0.95, including in the diagnostically challenging low-flow, low-gradient phenotype. However, studies incorporating rigorous multicenter external validation remain the exception rather than the norm. Similarly, AI models designed for congenital heart disease screening, fetal echocardiography, and complex procedural planning require validation across demographically and anatomically diverse populations.³²⁻³⁵

The generalizability challenge ultimately concerns ecological validity. Models that perform well under controlled validation conditions may exhibit reduced accuracy when confronted with the variability inherent in routine clinical practice. Among the studies informing the generalizability domain, QUADAS-2 assessment identified a moderate risk of patient-selection bias in several multicenter datasets, as cohorts frequently excluded patients with poor image quality, arrhythmias, or implanted devices, the very subgroups in which generalizability is most clinically relevant. This pattern underscores the need to interpret aggregate AUC and ICC values with caution when feasibility denominators are not clearly reported.

2030 Priority: The available evidence indicates that external validation across multivendor, geographically diverse datasets should be considered a prerequisite for widespread clinical adoption. At present, this standard is not consistently met.

The Evidence Challenge: Accuracy without Outcomes

The limited number of randomized outcome trials evaluating AI in echocardiography reflects several structural barriers. First, no regulatory agency currently requires outcome-based evidence for AI as a medical device in cardiac imaging; regulatory approval is generally based on technical equivalence to existing technologies. Second, the complexity of echocardiographic interpretation, which integrates multiple parameters in real time, makes blinding difficult and the assessment of endpoints challenging. Third, AI imaging systems are often protected by commercial confidentiality, limiting the data sharing required for independent validation. Fourth, software updates frequently occur more rapidly than traditional clinical trial cycles, meaning that a validated tool may undergo substantial modification before trial results become available. These challenges do not justify the

limited evidence base but help explain it. They also underscore the need to develop supporting research infrastructure, including adaptive trial designs and platform-neutral validation frameworks, alongside the technology itself.

Technical validation has advanced rapidly. Outcome-oriented evidence has not. Automated LVEF and GLS assessment platforms demonstrate strong agreement with expert readers.^{15,24} Likewise, AI classifiers for valvular heart disease and cardiomyopathies have achieved high discriminative performance.^{19,31} AI-enabled screening tools for cardiac amyloidosis based on single echocardiographic video clips represent an additional step toward disease-specific diagnostic automation.^{36,37}

Notable exceptions exist. In a prospective randomized controlled trial, Frydman et al.²¹ demonstrated that AI-assisted bedside echocardiography resulted in a significantly higher rate of management changes than standard care (28% vs. 19%, $P = 0.04$).²¹ Similarly, the randomized crossover AI-Echo trial conducted by Sakamoto and Kagiya et al.²² showed that AI assistance reduced examination time, increased daily scanning volume, and improved image quality without compromising diagnostic integrity. Together, these studies provide emerging evidence that AI may influence clinically meaningful process outcomes. Nevertheless, rigorous trials demonstrating improvements in patient-centered outcomes remain scarce.⁴³

This evidence challenge therefore reflects a fundamental assumption: that improved measurement accuracy necessarily translates into improved patient care. Of the six implementation and outcomes studies identified in this review, only the two RCTs^{21,22} were judged to have a low overall risk of bias according to the ROBINS-I assessment. The remaining four studies were rated as having a moderate risk of bias, largely because of concerns related to outcome ascertainment and flow and timing. The evidence base in this domain is therefore meaningful but limited and should be interpreted accordingly.

2030 Priority: Future validation efforts should link automation to therapeutic decision-making, resource utilization, and patient outcomes, rather than relying solely on agreement metrics.

The Governance Challenge: Regulation, Liability, and Drift

Two regulatory frameworks are particularly relevant to adaptive AI in echocardiography. The European Union (EU) Artificial Intelligence Act (2024) classifies high-risk AI systems in medical imaging as requiring conformity assessment and post-market monitoring, partially addressing the issue of model drift. The United States Food and Drug Administration's Predetermined Change Control Plan (PCCP) framework allows adaptive algorithms to be updated within predefined limits without requiring full reapproval. Both frameworks represent important progress; however, neither currently mandates continuous real-world performance monitoring, which is essential for detecting gradual performance drift in deployed models. Their practical implications for echocardiographic AI governance remain to be fully established.

As AI systems increasingly influence image interpretation and quantitative assessment, regulatory and medicolegal uncertainties become more prominent. Department-level studies have demonstrated the feasibility of integrating AI into

routine echocardiography workflows.¹ However, few studies have addressed lifecycle monitoring, post-deployment recalibration, or structured oversight mechanisms. Robotic and reinforcement learning-based acquisition systems introduce additional complexity because their autonomous behavior is more difficult to audit using conventional approaches.⁴⁴

Economic barriers are another important and often underrecognized obstacle to adoption. In many European and Middle Eastern healthcare systems, no formal reimbursement pathway currently exists for AI-assisted echocardiographic reporting as a billable service. As a result, institutions must absorb the costs of AI implementation without direct reimbursement, creating a structural disincentive unrelated to technical performance. Health-economic evaluations linking AI adoption to downstream resource savings are needed to generate the payer-focused evidence that regulatory approval alone cannot provide.

The governance challenge is fundamentally structural: technological advancement has outpaced the development of a corresponding governance framework. Governance and post-deployment monitoring were rarely primary study endpoints in the reviewed literature; most governance-relevant observations were reported incidentally within implementation studies. Consequently, the evidence base for governance relies disproportionately on expert commentary and observational data. Conclusions in this domain therefore carry greater interpretive uncertainty than those derived from the reproducibility or LV function domains.

2030 Priority: The available evidence suggests that continuous audit systems, recalibration protocols, and transparent liability frameworks should accompany the clinical deployment of adaptive AI systems to ensure safety and accountability throughout their operational lifecycle.

The Trust and Integration Challenge: Human Acceptance in a High-Stakes Field

Echocardiography is an interpretive discipline. Clinicians simultaneously integrate image quality, hemodynamic data, and clinical context when making diagnostic and management decisions. AI tools that lack transparency or are difficult to override risk resistance from frontline users.

Studies suggest that clinician trust increases when AI systems provide editable contours, visual overlays, and interpretable outputs.^{25,39} In contrast, rigid automation may provoke skepticism. Patient-perception studies indicate a general openness to AI support when it is presented as an adjunct to, rather than a replacement for, clinical expertise.⁴⁵

Training evidence further supports this perspective. AI-assisted guidance improves novice performance in acquiring standard apical views, and structured training programs incorporating AI support outperform traditional approaches in focused cardiac ultrasound skill acquisition.^{36,46} These findings suggest that trust develops most naturally when AI is introduced first as a teaching tool and subsequently as a clinical support tool.

Workflow integration is equally important. The AI-Echo (Artificial Intelligence-Echocardiography) RCT demonstrated that AI assistance reduced examination time (13.0 ± 3.5 min vs.

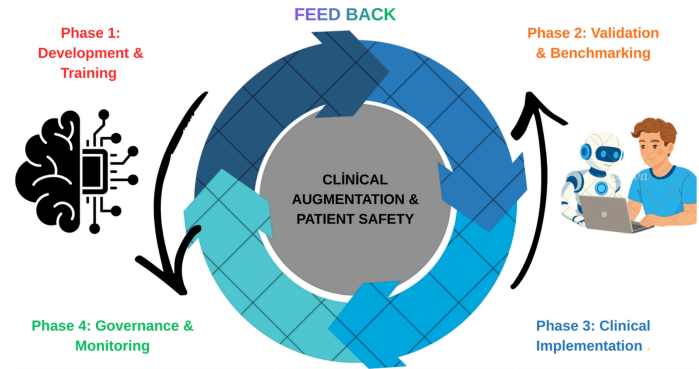


Figure 3. Conceptual framework illustrating a four-phase lifecycle for the responsible integration of artificial intelligence (AI) into clinical echocardiography, centered on clinical augmentation and patient safety. The framework comprises Phase 1 (Development and Training), Phase 2 (Validation and Benchmarking), Phase 3 (Clinical Implementation), and Phase 4 (Governance and Monitoring). Iterative feedback loops connect all phases to support continuous quality assurance and accountability.

14.3 ± 4.2 min, $P < 0.001$), increased daily examination volume, and reduced mental fatigue without compromising diagnostic integrity.²² However, vendor incompatibility and interoperability barriers continue to limit broader scalability.^{17,20}

The challenge of trust and integration is ultimately cultural. Even technically robust systems are unlikely to succeed without clinician confidence and seamless workflow integration. The single trust-and-acceptance study included in this review⁴⁵ was rated as having a moderate risk of bias according to the ROBINS-I assessment, and the trust domain overall is supported by the smallest body of direct evidence among the five challenges. Conclusions in this domain should therefore be viewed as interpretive and hypothesis-generating rather than practice-defining.

2030 Priority: AI should function as a transparent form of clinical augmentation, supporting rather than replacing professional judgment.

An Expert-Informed 2030 Roadmap: Evidence-Grounded Priorities

The five implementation challenges described above define the principal structural vulnerabilities of AI in echocardiography. Faster algorithms and larger models alone will not be sufficient. Progress will require methodological reform, regulatory maturation, workflow redesign, and cultural adaptation. Figure 3 illustrates the proposed lifecycle spanning development, validation, implementation, and governance. The priorities outlined in this section represent an expert-informed synthesis of the reviewed literature. They do not constitute a formal evidence-based forecast and should not be interpreted as a consensus-derived mandate. The year 2030 was selected as a pragmatic planning horizon for three converging reasons: the implementation timeline of the EU Artificial Intelligence Act (adopted in 2024, with phased enforcement through 2026–2027); the expanding FDA Predetermined Change Control Plan framework for adaptive medical AI, which is expected to

Table 3. Proposed validation and reporting standards for artificial intelligence in echocardiography

Domain	Recommended standard	Rationale	Supporting evidence	Priority tier
Dataset	Multicenter, multivendor training data	Reduces site-specific bias; improves generalizability	Kagiyama et al. 2024; ⁶ Stowell et al. 2024 ¹⁷	Required
Dataset	Subgroup analysis (sex, age, race, comorbidity)	Detects potential algorithmic bias	Wrzosek et al. 2026; ¹¹ Salehi et al. 2025 ⁴¹	Required
Annotation	Consensus ground truth from ≥ 2 expert readers	Reduces single-reader labeling bias	Zamzmi et al. 2023; ⁴⁰ Asch et al. 2021 ⁷	Required
Annotation	Prespecified reference standard with reported inter-reader agreement	Prevents post hoc favorable comparisons	Varudo et al. 2022; ² Trost et al. 2025 ³⁵	Required
Validation	Testing in an independent external cohort	Reduces overfitting and demonstrates real-world applicability	He et al. 2023; ²⁶ Olaisen et al. 2024 ²⁵	Required
Validation	Reporting of feasibility rates (cases excluded because of poor image quality or algorithm failure)	Reflects real-world performance	Sveric et al. 2024; ¹⁶ Myhre et al. 2024 ¹⁸	Required
Metrics	Bland-Altman agreement metrics (bias, LoA) AND classification metrics (AUC, sensitivity, specificity)	Reflects clinical reliability at decision thresholds	Varudo et al. 2022; ² Wrzosek et al. 2026 ¹¹	Required
Metrics	Stability analysis near therapeutic thresholds (e.g., LVEF 35–40%)	Identifies cases where AI errors may affect management	Kagiyama et al. 2024; ⁶ He et al. 2023 ²⁶	Recommended
Bias audit	Systematic subgroup performance analysis	Quantifies and mitigates algorithmic bias	Holste et al. 2023; ¹⁹ Slivnick et al. 2025 ³⁷	Required
Clinical outcomes	Prospective studies or RCTs linking AI to clinical outcomes	Demonstrates clinical benefit beyond measurement agreement	Frydman et al. 2026; ²¹ Sakamoto et al. 2026; ²² Levy et al. 2025 ⁴³	Required for deployment
Post-deployment	Post-deployment auditing and performance monitoring	Detects model drift and supports long-term safety	Lafitte et al. 2025; ¹ Holmström et al. 2025 ²⁷	Required for regulatory compliance
Post-deployment	Recalibration protocols and version control for adaptive models	Ensures accountability for evolving algorithms	Shida et al. 2025 ⁴⁴	Required for regulatory compliance

AUC, Area under the curve; CONSORT-AI, Consolidated Standards of Reporting Trials–Artificial Intelligence extension; LoA, Limits of agreement; LVEF, Left ventricular ejection fraction; PACS, Picture archiving and communication system; STARD-AI, Standards for Reporting Diagnostic Accuracy Studies–Artificial Intelligence extension. Required items are those whose absence substantially limits interpretability or clinical applicability. Recommended items enhance transparency and reproducibility.

reach greater regulatory maturity over a similar period; and the typical five- to eight-year duration required to complete and publish multicenter outcome trials. Together, these regulatory and research trajectories converge meaningfully around 2030, making it a useful, albeit inherently imprecise, reference point rather than a fixed predictive target.

Solving the Reproducibility Challenge: From Agreement Metrics to Decision Stability

Multicenter studies of LVEF and GLS have already demonstrated improved interobserver agreement with AI assistance.^{6,26} The blinded RCT by He et al.²⁶ provides the strongest evidence to date that AI-based initial assessment is noninferior to sonographer assessment within a real-world clinical workflow. Department-level experience further demonstrates that automated measurements can be integrated successfully into high-volume echocardiography services.¹ However, structured reporting of management impact remains uncommon. The available evidence suggests that reproducibility assessments should focus on classification stability near therapeutic thresholds, such as LVEF values of 35%–40% and GLS cut-offs used for cardiotoxicity monitoring, as well as treatment-decision concordance and case-level uncertainty, rather than

on population-level agreement metrics alone. Reproducibility is more meaningfully defined not as statistical similarity among expert readers, but as the consistency of clinical decisions across readers, centers, and time. Table 1 summarizes the validation profiles relevant to this standard.

Solving the Generalizability Challenge: Mandatory External Validation

Internal validation alone can no longer be considered sufficient evidence for clinical deployment. Single-center retrospective studies are valuable for hypothesis generation but are insufficient for practice-changing implementation.^{15,31}

Multicenter studies of automated LVEF and GLS assessment have shown that performance, although modestly attenuated, generally remains clinically acceptable under external validation conditions.^{16,17} Holste et al.¹⁹ developed a deep learning model for severe AS detection that was validated across multiple institutions and demonstrated excellent discrimination, including in low-gradient phenotypes. This study exemplifies the level of evidence to which future generalizability studies should aspire.

The reviewed evidence suggests that a credible minimum evidentiary threshold for widespread adoption should include

multivendor datasets, independent geographic validation, transparent reporting of feasibility rates, and subgroup performance analyses. This recommendation is not intended as a prescriptive policy statement; rather, it reflects recurring evidence gaps identified across the studies informing the generalizability domain. Table 3 provides a proposed framework.

Solving the Evidence Challenge: From Measurement to Outcomes

Technical equivalence does not necessarily translate into clinical benefit. Most AI applications demonstrate strong measurement agreement but stop short of evaluating clinical outcomes.^{15,24,31} The randomized trials by Frydman et al.,²¹ which demonstrated that AI-assisted echocardiography increased management change rates, and the AI-Echo randomized controlled trial by Sakamoto and Kagiya et al.,²² which demonstrated improvements in workflow efficiency, represent important advances in this area.

Drawing on the outcome-evidence gap identified across the reviewed studies, future research priorities should include pragmatic multicenter trials evaluating diagnostic reclassification, time to treatment, cost-effectiveness, and longitudinal patient-centered outcomes. Stepped-wedge trial designs embedded within routine clinical practice may offer a practical alternative to large randomized superiority studies. The underlying argument, grounded in the reviewed literature rather than in the authors' preferences, is that AI must demonstrate not only accurate measurement performance but also improvements in clinical care.

Solving the Governance Challenge: Lifecycle Oversight and Accountability

Current regulatory frameworks evaluate software largely at a single point in time. However, echocardiographic AI systems are dynamic and susceptible to performance drift.²⁵ The emergence of autonomous acquisition systems incorporating robotic navigation and reinforcement learning further heightens the governance challenge.⁴⁴ The governance and regulatory barriers identified in the reviewed literature are multifaceted and include unclear pathways for adaptive algorithms, diffuse liability frameworks, and the absence of reimbursement mechanisms in many healthcare systems. Table 4 summarizes these barriers and their proposed solutions across implementation domains, illustrating that governance reform cannot be separated from the technical, clinical, and economic factors required for sustainable deployment.

The governance gaps identified in the reviewed literature suggest that robust deployment frameworks should incorporate periodic performance audits, drift-detection protocols, transparent documentation of software updates, and clear delineation of clinician and developer responsibilities. These recommendations are not arbitrary; each addresses a specific vulnerability documented in the included studies, including model drift after deployment,^{25,44} uncertainty regarding liability when AI-assisted decisions cause harm,^{33,34} and the lack of structured post-market surveillance.¹ Regulatory maturity will depend on aligning technological innovation with enforceable monitoring standards, an objective increasingly reflected in both the EU Artificial Intelligence Act and the FDA PCCP framework.

Solving the Trust and Integration Challenge: Human-Centered Augmentation

Successful adoption of AI in echocardiography depends on clinician confidence. Systems that are difficult to override, poorly integrated into existing workflows, or insufficiently transparent are unlikely to achieve sustained uptake.²⁵ Training studies have shown that AI guidance can meaningfully improve image acquisition among novice operators, both for standard apical views and within broader focused cardiac ultrasound programs.^{36,46}

Three implementation principles emerge consistently from the reviewed literature as prerequisites for clinician trust and sustainable adoption. First, seamless integration into existing picture archiving and communication system (PACS) and reporting workflows. The AI-Echo RCT demonstrated that friction in data transfer and reporting interfaces was a major implementation barrier and that reducing this friction significantly improved examination efficiency and reduced reader fatigue.²² Second, AI systems should provide clear visualization of automated contours and measurements. Olaisen et al.²⁵ reported that visible and editable AI-derived contours were an important factor influencing echocardiographers' willingness to rely on automated GLS measurements.²⁵ Third, AI systems should provide immediate manual override capability. Multiple governance analyses identified the absence of a clear override pathway as a structural accountability gap when AI-assisted assessments resulted in disputed clinical decisions.^{33,34,45} Each of these principles is supported by evidence from the reviewed literature rather than by abstract design preferences. The available evidence suggests that human-centered augmentation, rather than end-to-end automation, represents the more durable design philosophy for the next phase of AI development. Table 5 contrasts current practice with AI-enabled capabilities across major echocardiographic domains.

A Coherent 2030 Vision

If these strategies are successfully implemented, echocardiography in 2030 could be substantially different. Quantitative measurements may become more standardized across institutions, interobserver variability in LVEF and GLS assessment may be reduced, and AI-guided image acquisition may expand access in under-resourced settings. Transparent audit systems could support ongoing performance monitoring, while stronger evidence frameworks could establish meaningful links between automation and clinical outcomes. The objective is not to replace clinical expertise, but to reinforce and standardize it.

Limitations

Several limitations of this review merit consideration. First, the literature search was restricted to PubMed/MEDLINE. Consequently, studies indexed exclusively in EMBASE, CINAHL, or the Cochrane Library may have been missed, potentially introducing database-level selection bias toward higher-profile English-language publications. Second, despite the use of independent dual screening, the qualitative synthesis and thematic categorization into five challenge domains necessarily involved interpretive judgments that cannot be entirely eliminated through methodological safeguards. Third, the five-domain framework represents an analytically derived conceptual

Table 4. Barriers and enablers for clinical implementation of artificial intelligence in echocardiography

Domain	Barrier	Impact	Representative evidence	Implementation priority	Proposed solution
Technical	Vendor incompatibility and lack of interoperability standards	Limited scalability across institutions	Kagiyama et al. 2024; ⁶ Stowell et al. 2024 ¹⁷	High	Mandatory DICOM–AI interoperability standards; open validation pipelines
Technical	Reduced performance in suboptimal imaging conditions (arrhythmias, prosthetics, poor windows)	Algorithm failure in real-world populations	Sveric et al. 2024; ¹⁶ Zhu et al. 2025 ¹⁵	High	Mandatory feasibility rate reporting; image-quality flagging
Technical	Lack of standardized external validation benchmarks	Unreliable cross-vendor comparisons	Holste et al. 2023; ¹⁹ Park et al. 2025 ¹²	High	Consensus benchmarking datasets (e.g., EchoNet-Dynamic)
Clinical	Limited clinician trust in opaque or non-editable outputs	Low adoption; clinician override of valid AI findings	Zamzmi et al. 2023; ⁴⁰ Huang et al. 2024 ⁴⁵	High	Explainable AI; editable contours; visualization of measurement uncertainty
Clinical	Lack of outcome-level evidence	AI deployment without demonstrated patient benefit	Frydman et al. 2026; ²¹ Levy et al. 2025 ⁴³	Critical	Pragmatic multicenter trials; stepped-wedge designs; CONSORT-AI reporting
Clinical	Algorithmic bias across demographic subgroups	Unequal performance and potential disadvantage for underserved populations	Holste et al. 2023; ¹⁹ Slivnick et al. 2025 ³⁷	High	Mandatory subgroup performance reporting; equity-audited training datasets
Training	Low AI literacy among clinical staff	Inappropriate reliance on AI and potential patient harm	Lau et al. 2025; ⁴⁶ Karni et al. 2025 ³⁶	Moderate	Structured AI education integrated into echocardiography training programs
Workflow	Poor integration with PACS and reporting software	Workflow disruption; reduced efficiency	Sakamoto et al. 2026; ²² Hollitt et al. 2025 ²⁰	High	Native PACS integration during development; human-centered design
Regulatory	Unclear pathways for adaptive/self-updating algorithms	Legal uncertainty; delayed access to improved models	Shida et al. 2025 ⁴⁴	High	FDA SaMD PCCP framework; compliance with the EU AI Act Article 50
Regulatory	Unclear liability when AI-assisted decisions cause harm	Litigation risk; institutional hesitancy	Mao et al. 2026; ³³ Trenkwalder et al. 2023 ³⁴	High	Explicit contractual delineation of responsibility among developers, institutions, and clinicians
Economic	Lack of reimbursement pathways for AI-assisted echocardiography	Restricted adoption; concentration of innovation in well-resourced centers	Wrzosek et al. 2026; ¹¹ Motazedian et al. 2023 ⁴²	Critical	Prospective health-economic studies; HTA submissions; CPT code development
Ethical	Inadequate informed-consent frameworks for AI-assisted diagnosis	Reduced patient autonomy and legal concerns	Huang et al. 2024 ⁴⁵	Moderate	Standardized AI disclosure frameworks; shared decision-making guidelines
Ethical	Risk of algorithm-assisted deskilling among trainees	Long-term decline in echocardiographic expertise	Karni et al. 2025; ³⁶ Lau et al. 2025 ⁴⁶	Moderate	AI-assisted training before clinical deployment; continued assessment of manual skills

Implementation priority ratings reflect the frequency and impact with which each barrier was identified as limiting clinical adoption in the reviewed literature. Critical = identified as a major barrier in ≥3 high-quality studies; High = identified in ≥2 studies; Moderate = identified in a single study or inferred from implementation context. Abbreviations: AI, Artificial intelligence; CPT, Current procedural terminology; DICOM, Digital Imaging and Communications in Medicine; EU, European Union; FDA, United States Food and Drug Administration; HTA, Health technology assessment; PACS, Picture archiving and communication system; SaMD, Software as a Medical Device; TAVR, Transcatheter aortic valve replacement.

structure rather than an empirically validated classification system; its descriptive value should not be conflated with confirmatory validity. Fourth, the 2030 roadmap is explicitly presented as an expert-informed perspective rather than a formally validated or consensus-derived projection. The 2030 horizon was selected because it aligns with three converging external timelines: implementation of the EU Artificial Intelligence Act and FDA PCCP framework, and the typical completion cycle of multicenter outcome trials. Nevertheless, technological, regulatory, and clinical developments remain inherently uncertain, and the

Table 5. Current echocardiography practice versus artificial intelligence-enhanced capabilities: a domain-by-domain comparison

Clinical domain	Current practice	AI-enhanced capability	Key reference(s)	Potential impact	Evidence maturity/limitations
LV function (LVEF)	Manual Simpson's biplane or visual estimation; LOA $\pm$ 10–15% between observers	Fully automated view selection, contour detection, and LVEF reporting; bias <2%; LOA $\pm$ 10%	Kagiyama 2024; ⁶ He et al. 2023; ²⁶ Olaisen et al. 2024 ²⁵	Reduces interobserver variability; enables point-of-care use	Deployment-ready; multicenter external validation established; outcome RCTs pending
Strain analysis (GLS)	Expert-dependent manual speckle-tracking analysis; vendor-specific outputs; often underutilized	Automated real-time GLS assessment standardized across vendors with DL-based with workflow integration	Salte et al. 2021; ⁸¹ Stowell et al. 2024; ¹⁷ Holmström et al. 2025 ²⁷	Standardizes deformation assessment; supports cardio-oncology monitoring	Multicenter external validation established (Myhre et al. [29]); prospective outcome data lacking
Valvular disease (AS)	Complex manual integration of Vmax, MPG, AVA; particularly challenging in LG-AS	DL-based detection of severe AS, including LG-AS; automated assessment across the AS continuum	Holste et al. 2023; ¹⁹ Park et al. 2025; ¹² Wrzosek et al. 2026 ¹¹	Reduces diagnostic uncertainty in LG-AS; supports earlier treatment decisions	Multicenter validation established; prospective outcome data for AS decision-making lacking
RV assessment	2D indices (TAPSE, FAC); RV geometry limits accuracy	Automated 3D RV volumetrics validated against CMR in adult and pediatric populations	Liu et al. 2025; ⁴ Mou et al. 2026 ¹⁰	Improves RV functional assessment and prognostication in PH	Pediatric external validation available; adult prospective multicenter data limited
Image acquisition	Prolonged supervised training required; highly operator-dependent; limited access in resource-constrained settings	Real-time AI guidance enabling novice operators to acquire diagnostic-quality images	Trost et al. 2025; ³⁵ Karni et al. 2025; ³⁶ Lau et al. 2025 ⁴⁶	Expands access to POCUS and resource-limited settings; accelerates training	Prospective RCT evidence available (Trost [35]); long-term retention data pending
Workflow efficiency	Manual measurement and report generation; average time >30 min per study	AI-assisted automation reduces measurement and reporting time by 50–77% and increases daily throughput	Sakamoto/Kagiyama et al. 2026; ²² Olaisen et al. 2024; ²⁵ Hollitt et al. 2025 ²⁰	Sustainable high-volume laboratories; reduces sonographer fatigue	RCT evidence for efficiency gains available (AI-Echo RCT [22]); single-center; scalability untested
Risk stratification	Conventional clinical risk scores; limited integration of echocardiographic data	Multimodal DL integrating echocardiographic and clinical data; phenogroup; mortality prediction	Mou et al. 2026; ¹⁰ Liu et al. 2023; ³¹ Anzai et al. 2025 ³⁸	Individualized risk prediction; phenogroup identification	Predominantly retrospective single-center studies; external outcome validation lacking; clinical utility unproven

AS, Aortic stenosis; AVA, Aortic valve area; CMR, Cardiac magnetic resonance; DL, Deep learning; GLS, Global longitudinal strain; LG-AS, Low-gradient aortic stenosis; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MPG, Mean pressure gradient; PH, Pulmonary hypertension; POCUS, Point-of-care ultrasound; RCT, Randomized controlled trial; RV, Right ventricular; TAPSE, Tricuspid annular plane systolic excursion; TAVR, Transcatheter aortic valve replacement. Detailed performance metrics and external validation data for the studies cited in Table 5 are provided in Table 1.

priorities outlined here may require revision as the field evolves. Accordingly, the roadmap should be interpreted as a structured synthesis of the current evidence base rather than as a policy mandate. Fifth, although quality assessment was performed using the QUADAS-2 and ROBINS-I tools, and domain-level quality patterns are discussed throughout the manuscript, the heterogeneity of study designs precluded formal weighting of evidence according to quality scores. As a result, the synthesis remains primarily thematic rather than quantitatively graded. Sixth, the AI literature in echocardiography is susceptible to publication bias favoring positive performance results, which may overestimate the strength of evidence for certain applications. Seventh, given the rapid pace of AI development in cardiac imaging AI, some referenced studies may have been updated or superseded since their inclusion in this review.

Conclusion

Artificial intelligence in echocardiography has progressed well beyond proof-of-concept investigations. Automated quantification of left ventricular function, strain analysis, right ventricular assessment, and AI-guided image acquisition are increasingly being incorporated into routine clinical practice.^{15,24,26} Technical feasibility is no longer the principal barrier to adoption. Prospective and randomized studies have demonstrated that AI can improve reproducibility, enable non-expert operators to acquire diagnostically adequate examinations, and reduce sonographer workload.^{22,35,36}

This review characterizes the current state of the field through five interdependent implementation challenges: reproducibility, generalizability, evidence, governance, and trust. Despite strong

agreement metrics under controlled conditions, performance variability persists across vendors, institutions, and patient subgroups.^{19,26,31} Most validation studies remain retrospective and single-centered in design. Outcome-focused evidence remains limited, although the first RCTs linking AI to clinical process outcomes and workflow efficiency have now been published.^{21,22} Regulatory pathways for adaptive systems continue to evolve, while structured post-deployment monitoring and drift surveillance remain inconsistently implemented.

This expert-informed 2030 roadmap highlights four key transitions, each grounded in evidence gaps identified across the reviewed studies. First, reproducibility assessment should shift from correlation-based metrics toward measures of clinical decision stability. Second, external validation across heterogeneous datasets should become the minimum evidentiary standard for widespread adoption. Third, future research should establish whether automated measurements improve patient outcomes and cost-effectiveness, building on the foundation provided by the first published RCTs. Fourth, governance frameworks should evolve toward continuous lifecycle oversight, incorporating clear accountability structures and routine performance auditing, developments already anticipated by emerging EU and FDA regulatory frameworks.

Cultural integration is equally important and often underestimated. AI tools that are transparent, editable, and seamlessly integrated into existing workflows are more likely to earn sustained clinician trust.^{25,39} The central question is no longer whether AI has a role in echocardiography. It clearly does. Rather, it is how responsibly, rigorously, and inclusively AI will be integrated into routine clinical care, and whether the necessary governance infrastructure will be established before the next generation of capabilities arrives.

Appendix Online File: [https://jag.journalagent.com/tkd/abs_files/TKDA-30071/TKDA-30071_\(0\)_supp.docx](https://jag.journalagent.com/tkd/abs_files/TKDA-30071/TKDA-30071_(0)_supp.docx)

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Prognostic Value of Myocardial Contraction Fraction for One-Year Cardiac Death After Transcatheter Aortic Valve Implantation in Severe Aortic Stenosis: A Simple Echocardiographic Metric for High-Risk Stratification

Miyokard Kontraksiyon Fraksiyonunun Prognostik Değeri: Yüksek Riskli Hastaların Belirlenmesinde Basit Bir Ekokardiyografik Ölçüt

ABSTRACT

Objective: Myocardial contraction fraction (MCF) is a volumetric index of myocardial shortening that relates left ventricular stroke volume to myocardial volume. In patients with severe aortic stenosis (AS), left ventricular ejection fraction (LVEF) may remain preserved despite advanced myocardial remodeling. This study aimed to evaluate the prognostic value of MCF for predicting 1-year cardiac death in patients undergoing transcatheter aortic valve implantation (TAVI).

Method: This retrospective, single-center study included 419 consecutive patients with severe AS who underwent TAVI at a tertiary center. MCF was calculated by dividing stroke volume by left ventricular myocardial volume and multiplying the result by 100. Left ventricular myocardial volume was derived by dividing left ventricular myocardial mass by the myocardial density, which was assumed to be 1.05 g/mL. The primary endpoint was 1-year cardiac death. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal MCF cutoff value, and the patients were divided into low- and high-MCF groups according to this threshold.

Results: The ROC-derived MCF cutoff value for predicting 1-year cardiac death was 24%, with an area under the curve of 0.783 (95% CI, 0.716–0.851), a sensitivity of 78.1%, and a specificity of 71.8%. Patients with $MCF \leq 24\%$ had lower LVEF and stroke volume index values, higher myocardial mass index and pulmonary artery pressure values, and larger left ventricular diameters than those with $MCF > 24\%$. One-year cardiac death occurred in 32 patients (7.6%) and was significantly more frequent in the $MCF \leq 24\%$ group than in the $MCF > 24\%$ group (18.7% vs. 2.5%; $P < 0.001$). In univariable Cox regression analysis, $MCF \leq 24\%$ was strongly associated with 1-year cardiac death. In multivariable analysis, higher MCF, evaluated as a continuous variable, remained independently associated with a lower risk of 1-year cardiac death.

Conclusion: Reduced MCF was associated with adverse left ventricular remodeling and increased 1-year cardiac death after TAVI. MCF may provide additional prognostic information beyond conventional echocardiographic parameters in patients with severe AS undergoing TAVI.

Keywords: Aortic valve stenosis, echocardiography, left ventricular function, mortality, transcatheter aortic valve replacement

ÖZET

Amaç: Miyokard kontraksiyon fraksiyonu (MKF), sol ventrikül atım hacmini miyokard hacmiyle ilişkilendiren volumetrik bir miyokardiyal kısalma indeksidir. Şiddetli aort darlığı olan hastalarda, ileri düzey miyokardiyal yeniden şekillenmeye rağmen sol ventrikül ejeksiyon fraksiyonu korunmuş olabilir. Bu çalışmanın amacı, transkateter aort kapak implantasyonu (TAVI) uygulanan hastalarda MKF'nin 1 yıllık kardiyak ölümü öngörmedeki prognostik değerini değerlendirmektir.

Yöntem: Bu retrospektif, tek merkezli çalışmaya, üçüncü basamak bir merkezde TAVI uygulanan şiddetli aort darlığı olan 419 ardışık hasta dahil edildi. MKF, atım hacminin sol ventrikül miyokard hacmine bölünmesi ve elde edilen değerin 100 ile çarpılmasıyla hesaplandı. Sol ventrikül miyokard hacmi, sol ventrikül miyokard kütlelerinin 1.05 g/mL olarak kabul edilen miyokard yoğunluğuna bölünmesiyle elde edildi. Birincil sonlanım noktası 1 yıllık kardiyak ölümdü. Optimal MKF kesim değerini belirlemek için alıcı işletim karakteristiği (ROC) eğrisi analizi kullanıldı ve hastalar bu eşik değere göre düşük ve yüksek MKF gruplarına ayrıldı.

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Bulgular: Bir yıllık kardiyak ölümü öngörmek için ROC analiziyle belirlenen MKF kesim değeri %24 olup eğri altında kalan alan 0.783 (%95 GA, 0.716–0.851), duyarlılık %78.1 ve özgüllük %71.8 idi. $MKF \leq \%24$ olan hastalarda, $MKF > \%24$ olanlara kıyasla sol ventrikül ejeksiyon fraksiyonu ve atım hacmi indeksi daha düşük, miyokard kütle indeksi ve pulmoner arter basıncı daha yüksek ve sol ventrikül çapları daha büyüktü. Bir yıllık kardiyak ölüm 32 hastada (%7.6) görüldü ve $MKF \leq \%24$ grubunda $MKF > \%24$ grubuna göre anlamlı olarak daha sıkı (%18.7'ye karşı %2.5; $P < 0.001$). Tek değişkenli Cox regresyon analizinde $MKF \leq \%24$, 1 yıllık kardiyak ölümle güçlü şekilde ilişkili bulundu. Çok değişkenli analizde, sürekli değişken olarak değerlendirilen daha yüksek MKF, daha düşük 1 yıllık kardiyak ölüm riskiyle bağımsız olarak ilişkili kaldı.

Sonuç: Azalmış MKF, TAVİ sonrası olumsuz sol ventrikül yeniden şekillenmesi ve artmış 1 yıllık kardiyak ölümle ilişkili bulundu. MKF, şiddetli aort darlığı nedeniyle TAVİ uygulanan hastalarda konvansiyonel ekokardiyografik parametrelerin ötesinde ek prognostik bilgi sağlayabilir.

Anahtar Kelimeler: Aort kapak darlığı, ekokardiyografi, sol ventrikül fonksiyonu, mortalite, transkateter aort kapak implantasyonu

Transcatheter aortic valve implantation (TAVI) has become an established treatment for symptomatic severe aortic stenosis (AS) across a wide range of surgical risk categories.^{1,2} Although procedural outcomes have improved considerably with greater operator experience, device refinement, and careful patient selection, mortality after TAVI remains clinically significant, particularly among patients with advanced myocardial remodeling, low-flow physiology, renal dysfunction, frailty, and a high comorbidity burden. Therefore, accurate preprocedural risk stratification remains an essential component of TAVI planning.^{3,4}

Left ventricular ejection fraction (LVEF) remains the most widely used measure of left ventricular systolic function. However, in severe AS, LVEF may not adequately reflect the true extent of myocardial dysfunction. Chronic pressure overload induces concentric hypertrophy, increased myocardial mass, diastolic dysfunction, myocardial fibrosis, impaired coronary microcirculation, and, eventually, low-flow physiology.^{5,6} Therefore, patients may have preserved or mildly reduced LVEF despite advanced myocardial remodeling and impaired forward flow. In this setting, parameters that integrate myocardial structure and pump performance may provide additional prognostic value.

Myocardial contraction fraction (MCF) is a volumetric index of myocardial shortening calculated as the ratio of stroke volume to left ventricular myocardial volume.^{7,8} Unlike LVEF, which expresses stroke volume relative to left ventricular cavity volume, MCF expresses stroke volume relative to the amount of myocardium generating it. Therefore, MCF may be particularly useful in diseases characterized by increased myocardial mass, including hypertensive heart disease, hypertrophic cardiomyopathy, cardiac amyloidosis, and severe AS.^{9,10}

Previous studies have shown that MCF is associated with cardiovascular outcomes and may identify myocardial dysfunction even when LVEF is preserved.^{11,12} In patients undergoing TAVI, reduced MCF has been associated with increased 1-year mortality, and in patients with low-gradient severe AS and preserved LVEF, MCF has been shown to improve risk stratification beyond conventional echocardiographic parameters.^{13,14} However, data on the prognostic value of MCF in real-world TAVI populations remain limited. Therefore, the present study aimed to evaluate

ABBREVIATIONS

AS	Aortic stenosis
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
LVEF	Left ventricular ejection fraction
MCF	Myocardial contraction fraction
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation

the role of MCF in predicting 1-year cardiac death in patients undergoing TAVI for severe AS.

Materials and Methods

Study Design and Population

This retrospective, observational, single-center study included consecutive patients with severe AS who underwent TAVI at a tertiary referral center between 2016 and 2025. During the study period, a total of 501 patients were screened. Patients were eligible if they had symptomatic severe AS, underwent TAVI, had preprocedural echocardiographic data available for MCF calculation, and had 1-year follow-up data available for cardiac mortality assessment. Patients with missing echocardiographic variables required for MCF calculation or unavailable follow-up data were excluded from the analysis. No additional exclusion criteria were applied. After excluding patients with incomplete preprocedural echocardiographic data that precluded MCF calculation and those with unavailable 1-year follow-up data, 419 patients constituted the final study population.

Severe AS was diagnosed according to contemporary guideline recommendations using standard echocardiographic criteria, including aortic valve area, indexed aortic valve area, transvalvular gradients, peak aortic jet velocity, and flow status, when appropriate.^{1,2} The decision to perform TAVI was made by the institutional heart team based on clinical, anatomical, and procedural considerations.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by Kocaeli University Non-Interventional Clinical Research Ethics Committee (Approval Number: KÜ GOKAEK-2026/06/21; Project

No. 2026/170; Date: 12.03.2026). Because of the retrospective design, the requirement for written informed consent was waived.

Clinical Data Collection

Baseline demographic, clinical, laboratory, echocardiographic, and procedural data were obtained from hospital records and the institutional electronic database. Clinical variables included age, sex, New York Heart Association (NYHA) functional class, AS type, hypertension, diabetes mellitus, peripheral artery disease, chronic obstructive pulmonary disease, prior stroke, malignancy, coronary artery disease, prior myocardial infarction, history of percutaneous coronary intervention, prior coronary artery bypass grafting, previous device implantation, and previous valvular interventions.

Laboratory parameters included serum creatinine, estimated glomerular filtration rate, hemoglobin, albumin, uric acid, C-reactive protein, N-terminal pro-B-type natriuretic peptide, and total cholesterol. Risk scores, including the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) and Society of Thoracic Surgeons (STS) score, were recorded when available.

Echocardiographic Assessment and MCF Calculation

All patients underwent comprehensive transthoracic echocardiography before TAVI. Echocardiographic parameters included LVEF, indexed aortic valve area, mean transvalvular gradient, peak aortic jet velocity, stroke volume index, left atrial diameter, left ventricular myocardial mass index, systolic pulmonary artery pressure, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and interventricular septal thickness in diastole.

Stroke volume was calculated using standard Doppler echocardiography by multiplying the left ventricular outflow tract area by the left ventricular outflow tract velocity-time integral. The left ventricular outflow tract area was derived from the left ventricular outflow tract diameter using the circular area formula. Left ventricular mass was calculated using the guideline-recommended linear echocardiographic method (Devereux formula), based on interventricular septal thickness, posterior wall thickness, and left ventricular end-diastolic diameter. Left ventricular myocardial volume was obtained by dividing left ventricular myocardial mass by the accepted myocardial density of 1.05 g/mL. MCF was calculated by dividing stroke volume by left ventricular myocardial volume and multiplying the result by 100.

MCF was calculated using the following formula:

$$\text{MCF (\%)} = \text{Stroke volume} / \text{Left ventricular myocardial volume} \times 100$$

where left ventricular myocardial volume = left ventricular myocardial mass / 1.05.

Severe AS phenotypes were classified according to baseline echocardiographic findings. High-gradient severe AS was defined as severe AS with a mean transvalvular gradient ≥ 40 mmHg and/or a peak aortic jet velocity ≥ 4.0 m/s. Non-high-gradient severe AS was defined as severe AS with an aortic valve area ≤ 1.0 cm² or an indexed aortic valve area ≤ 0.6 cm²/m² in the presence of a mean gradient < 40 mmHg and a peak aortic jet velocity < 4.0 m/s. Low-flow status was defined as a stroke volume index ≤ 35 mL/m². Patients with non-high-gradient severe AS were further classified as having classical low-flow, low-gradient AS

(LVEF $< 50\%$ and stroke volume index ≤ 35 mL/m²), paradoxical low-flow, low-gradient AS (LVEF $\geq 50\%$ and stroke volume index ≤ 35 mL/m²), or normal-flow, low-gradient AS (LVEF $\geq 50\%$ and stroke volume index > 35 mL/m²).

Receiver operating characteristic (ROC) curve analysis identified 24% as the optimal MCF cutoff value for predicting 1-year cardiac death. Patients were therefore divided into two groups: MCF $\leq 24\%$ and MCF $> 24\%$.

Endpoint Definition

The primary endpoint was 1-year cardiac death. Cardiac death was defined as death attributable to heart failure, sudden cardiac death, fatal myocardial infarction, fatal arrhythmia, valve-related death, or another documented cardiovascular cause. Mortality data were obtained from hospital records, institutional follow-up documentation, national health records, death registry information when available, and telephone follow-up. Because of the retrospective study design, events were not adjudicated by an independent clinical events committee.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation, whereas non-normally distributed variables were expressed as median and interquartile range. Categorical variables were expressed as numbers and percentages.

Comparisons between the MCF $\leq 24\%$ and MCF $> 24\%$ groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. ROC curve analysis was performed to evaluate the discriminatory performance of MCF for 1-year cardiac death. The optimal cutoff value was determined using the Youden index. The area under the curve, 95% CI, sensitivity, and specificity were reported.

Univariable Cox regression analysis was performed to identify predictors of 1-year cardiac death. Variables that were statistically significant in the univariable analysis (EuroSCORE II, LVEF, indexed aortic valve area, and MCF), together with clinically relevant variables, were entered as candidate covariates into the multivariable Cox regression model. Independent predictors were then identified using backward stepwise (Wald) elimination, and only variables retained in the final model are reported. In the multivariable model, MCF was entered as a continuous variable. Multicollinearity among the covariates was assessed using variance inflation factors and tolerance statistics. Kaplan-Meier survival analysis was performed to compare cumulative survival between the MCF groups, and differences were evaluated using the log-rank test. A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics

A total of 419 patients with severe AS who underwent TAVI were included in the study. The mean age of the study population was 76.3 ± 7.5 years, and 196 patients (46.8%) were male. According to the ROC-derived cutoff value, 134 patients (32.0%) had MCF $\leq 24\%$, whereas 285 patients (68.0%) had MCF $> 24\%$.

Baseline demographic and clinical characteristics according to MCF group are shown in Table 1. Age was similar between the MCF $\leq 24\%$ and MCF $>24\%$ groups (76.2 ± 8.1 vs. 76.3 ± 7.3 years; $P = 0.781$). Male sex was more frequent in the MCF $\leq 24\%$ group than in the MCF $>24\%$ group (56.0% vs. 42.5% ; $P = 0.010$). The distribution of NYHA functional classes did not differ significantly between the groups, although patients with low MCF had a numerically higher frequency of class IV symptoms.

Regarding AS phenotype, high-gradient severe AS was present in 374 patients (89.3%). The distribution of AS phenotypes differed significantly between the MCF groups ($P < 0.001$). High-gradient AS was less frequent in the MCF $\leq 24\%$ group than in the MCF $>24\%$ group (79.9% vs. 93.7%), whereas low-gradient AS phenotypes were more frequently observed among patients with reduced MCF. Classical low-flow, low-gradient AS was present in 35 patients (8.4%) and was more common in the MCF $\leq 24\%$ group than in the MCF $>24\%$ group (16.4% vs. 4.6%). Paradoxical low-flow, low-gradient AS was present in 10 patients (2.4%) and was also numerically more frequent in the MCF $\leq 24\%$ group (3.7% vs. 1.8%). No patient met the criteria for normal-flow, low-gradient AS. These findings are consistent with the lower stroke volume index and lower transvalvular gradients observed in patients with reduced MCF.

All TAVI procedures were performed using transfemoral vascular access. Valve type distribution was also evaluated. Self-expanding valves were used in 209 patients (49.9%), and balloon-expandable valves were used in 210 patients (50.1%). Self-expanding valves were numerically more frequent in the MCF $\leq 24\%$ group, whereas balloon-expandable valves were numerically more frequent in the MCF $>24\%$ group; however, this difference did not reach statistical significance ($P = 0.055$).

Hypertension was more common in the low-MCF group (95.5% vs. 88.8% ; $P = 0.025$). Diabetes mellitus, peripheral artery disease, malignancy, coronary artery disease, prior myocardial infarction, history of percutaneous coronary intervention, prior coronary artery bypass grafting, and previous valvular intervention were similar between the groups. Prior pacemaker or implantable cardioverter-defibrillator implantation was more frequent in the MCF $\leq 24\%$ group (14.2% vs. 7.0% ; $P = 0.019$).

Among the laboratory variables, serum creatinine was higher in patients with MCF $\leq 24\%$ than in those with MCF $>24\%$ (1.23 ± 0.70 vs. 1.13 ± 0.65 mg/dL; $P = 0.010$). Estimated glomerular filtration rate, hemoglobin, albumin, uric acid, C-reactive protein, N-terminal pro-B-type natriuretic peptide, and total cholesterol did not differ significantly between the groups. EuroSCORE II was higher in the low-MCF group ($P = 0.006$), whereas the STS score did not differ significantly between the groups.

Baseline Echocardiographic Findings

Baseline echocardiographic findings are summarized in Table 2. Patients with MCF $\leq 24\%$ had a less favorable echocardiographic profile than those with MCF $>24\%$. The indexed aortic valve area was lower in the MCF $\leq 24\%$ group (0.37 ± 0.10 vs. 0.40 ± 0.10 cm²/m²; $P < 0.001$). The mean transvalvular gradient was also lower in the MCF $\leq 24\%$ group (46.2 ± 15.8 vs. 51.2 ± 15.2 mm Hg; $P < 0.001$), consistent with the higher frequency of non-high-gradient AS phenotypes.

Left ventricular systolic function and forward flow were significantly worse in patients with low MCF. LVEF was lower in the MCF $\leq 24\%$ group than in the MCF $>24\%$ group ($48.9 \pm 18.3\%$ vs. $58.4 \pm 14.3\%$; $P < 0.001$). Stroke volume index was also markedly lower in the low-MCF group (31.7 ± 6.9 vs. 40.1 ± 7.4 mL/m²; $P < 0.001$).

Patients with MCF $\leq 24\%$ had significantly more advanced myocardial remodeling. Myocardial mass index was higher in the MCF $\leq 24\%$ group (172.8 ± 33.9 vs. 136.2 ± 29.2 g/m²; $P < 0.001$). Left atrial diameter was greater (48.8 ± 5.6 vs. 46.8 ± 6.2 mm; $P < 0.001$), systolic pulmonary artery pressure was higher (40.4 ± 15.7 vs. 36.9 ± 27.2 mm Hg; $P = 0.010$), left ventricular end-diastolic diameter was greater (53.9 ± 7.2 vs. 47.5 ± 6.2 mm; $P < 0.001$), and left ventricular end-systolic diameter was greater (36.6 ± 9.3 vs. 30.9 ± 7.5 mm; $P < 0.001$). Interventricular septal thickness in diastole was also greater in the low-MCF group (13.9 ± 2.1 vs. 13.1 ± 1.4 mm; $P < 0.001$).

Clinical Outcomes

Clinical outcomes according to MCF group are shown in Table 3. Length of hospital stay was similar between patients with MCF $\leq 24\%$ and those with MCF $>24\%$ (8.5 ± 5.5 vs. 8.6 ± 4.8 days; $P = 0.672$). The rates of renal failure and postprocedural pacemaker or implantable cardioverter-defibrillator implantation were also comparable between the groups.

During the 1-year follow-up, cardiac death occurred in 32 patients (7.6%). The rate of 1-year cardiac death was significantly higher in the MCF $\leq 24\%$ group than in the MCF $>24\%$ group (25 patients [18.7%] vs. 7 patients [2.5%]; $P < 0.001$).

ROC Analysis for MCF

ROC curve analysis was performed to determine the optimal MCF cutoff value for predicting 1-year cardiac death. The optimal ROC-derived threshold was 24% . An MCF $\leq 24\%$ predicted 1-year cardiac death with an area under the curve of 0.783 (95% CI, 0.716 – 0.851), a sensitivity of 78.1% , and a specificity of 71.8% .

Regression Analysis

Univariable and multivariable Cox regression analyses of predictors of 1-year cardiac death are presented in Table 4. In the univariable analysis, EuroSCORE II was significantly associated with 1-year cardiac death (hazard ratio [HR], 1.045 ; 95% CI, 1.018 – 1.073 ; $P < 0.001$). LVEF showed an inverse association with mortality risk (HR, 0.981 ; 95% CI, 0.963 – 1.000 ; $P = 0.044$), indicating a higher risk of cardiac death with decreasing LVEF. The indexed aortic valve area was also significantly associated with the endpoint. Among the variables evaluated, reduced MCF, defined by the ROC-derived cutoff value of $\leq 24\%$, showed the strongest association with 1-year cardiac death in the univariable analysis (HR, 8.155 ; 95% CI, 3.527 – 18.858 ; $P < 0.001$) (Figure 1).

Although patients with MCF $\leq 24\%$ had significantly lower LVEF than those with MCF $>24\%$ ($48.9 \pm 18.3\%$ vs. $58.4 \pm 14.3\%$; $P < 0.001$), the prognostic performance of MCF was not solely explained by reduced LVEF. After adjustment in the multivariable model, LVEF was no longer independently associated with 1-year cardiac death (HR, 1.006 ; 95% CI, 0.984 – 1.018 ; $P = 0.602$), whereas MCF remained independently associated with the endpoint.

Table 1. Baseline demographic and clinical characteristics of patients according to MCF group

Variables	All patients (n=419)	MCF ≤24% (n=134)	MCF >24% (n=285)	P
Age, years	76.3±7.5	76.2±8.1	76.3±7.3	0.781
Male sex, n (%)	196 (46.8)	75 (56.0)	121 (42.5)	0.010
NYHA functional class, n (%)				0.080
I	3 (0.7)	1 (0.7)	2 (0.7)	
II	30 (7.2)	7 (5.2)	23 (8.1)	
III	168 (40.1)	40 (29.9)	128 (44.9)	
IV	218 (52.0)	86 (64.2)	132 (46.3)	
AS type, n (%)				<0.001
High-gradient AS	374 (89.3)	107 (79.9)	267 (93.7)	
Classical low-flow, low-gradient AS	35 (8.4)	22 (16.4)	13 (4.6)	
Paradoxical low-flow, low-gradient AS	10 (2.4)	5 (3.7)	5 (1.8)	
Valve type, n (%)				0.055
Self-expanding	209 (49.9)	76 (56.7)	133 (46.7)	
Balloon-expandable	210 (50.1)	58 (43.3)	152 (53.3)	
Comorbidities				
Hypertension, n (%)	381 (90.9)	128 (95.5)	253 (88.8)	0.025
Diabetes mellitus, n (%)	195 (46.5)	69 (51.5)	126 (44.2)	0.163
Peripheral artery disease, n (%)	75 (17.9)	25 (18.7)	50 (17.5)	0.782
COPD, n (%)	145 (34.6)	55 (41.0)	90 (31.6)	0.057
Prior stroke, n (%)	34 (8.1)	14 (10.4)	20 (7.0)	0.230
Malignancy, n (%)	36 (8.6)	8 (6.0)	28 (9.8)	0.189
Coronary artery disease, n (%)	178 (42.5)	63 (47.0)	115 (40.4)	0.198
Prior myocardial infarction, n (%)	133 (31.7)	48 (35.8)	85 (29.8)	0.219
History of PCI, n (%)	133 (31.7)	50 (37.3)	83 (29.1)	0.093
Prior CABG, n (%)	76 (18.1)	20 (14.9)	56 (19.6)	0.242
Prior ICD or pacemaker implantation, n (%)	39 (9.3)	19 (14.2)	20 (7.0)	0.019
Prior MVR, n (%)	15 (3.6)	4 (3.0)	11 (3.9)	0.783
Prior AVR, n (%)	12 (2.9)	5 (3.7)	7 (2.5)	0.533
Prior TAVI, n (%)	7 (1.7)	2 (1.5)	5 (1.8)	1.000
Laboratory findings				
Creatinine, mg/dL	1.15±0.70	1.23±0.70	1.13±0.65	0.010
eGFR, mL/min/1.73 m ²	62.2±20.1	60.2±20.3	63.2±19.9	0.138
Hemoglobin, g/dL	11.8±1.8	11.7±1.8	11.9±1.8	0.296
Albumin, g/L	39.4±4.2	38.9±4.6	39.6±3.9	0.130
Uric acid, mg/dL	6.6±2.1	6.9±1.9	6.5±2.0	0.180
CRP, mg/L	3.6 (1.43-8.8)	4.4 (1.9-14.1)	3.4 (1.3-8.1)	0.096
NT-proBNP, ng/L	2210 (930-5455)	3300 (1480-7680)	1847 (848-4490)	0.119
Total cholesterol, mg/dL	173.5±44.8	168.9±43.3	175.5±45.4	0.160
Risk scores				
EuroSCORE II	9.5±8.2	9.9±6.7	9.2±8.7	0.006
STS score	12.9±3.8	13.2±4.1	12.8±3.6	0.149

Data are presented as mean±standard deviation, median (interquartile range), or n (%). AS, Aortic stenosis; AVR, Aortic valve replacement; CABG, Coronary artery bypass grafting; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ICD, Implantable cardioverter-defibrillator; MCF, Myocardial contraction fraction; MVR, Mitral valve replacement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation.

Table 2. Baseline echocardiographic findings according to MCF group in patients with severe AS

Variables	All patients (n=419)	MCF ≤24% (n=134)	MCF >24% (n=285)	P
Indexed AVA, cm ² /m ²	0.39±0.09	0.37±0.10	0.40±0.10	<0.001
Mean transvalvular gradient, mm Hg	49.6±15.6	46.2±15.8	51.2±15.2	<0.001
Peak aortic jet velocity, m/s	4.50±0.69	4.30±0.74	4.53±0.64	<0.001
LVEF, %	55.3±16.3	48.9±18.3	58.4±14.3	<0.001
Stroke volume index, mL/m ²	37.5±8.3	31.7±6.9	40.1±7.4	<0.001
Left atrial diameter, mm	47.5±6.1	48.8±5.6	46.8±6.2	<0.001
Left ventricular myocardial mass index, g/m ²	147.6±35.7	172.8±33.9	136.2±29.2	<0.001
Systolic PAP, mm Hg	38.1±24.2	40.4±15.7	36.9±27.2	0.010
Left ventricular end-diastolic diameter, mm	49.4±7.1	53.9±7.2	47.5±6.2	<0.001
Left ventricular end-systolic diameter, mm	32.8±8.6	36.6±9.3	30.9±7.5	<0.001
Interventricular septal thickness in diastole, mm	13.3±1.6	13.9±2.1	13.1±1.4	<0.001

Data are presented as mean±standard deviation. AS, Aortic stenosis; AVA, Aortic valve area; LVEF, Left ventricular ejection fraction; MCF, Myocardial contraction fraction; PAP, Pulmonary artery pressure.

Table 3. Clinical outcomes according to the ROC-derived MCF cutoff value

Variables	All patients (n=419)	MCF ≤24% (n=134)	MCF >24% (n=285)	P
Length of hospital stay, days	8.6±4.9	8.5±5.5	8.6±4.8	0.672
Renal failure, n (%)	55 (13.1)	18 (13.4)	37 (13.0)	0.899
Pacemaker or ICD implantation, n (%)	42 (10.0)	12 (9.0)	30 (10.5)	0.617
1-year cardiac death, n (%)	32 (7.6)	25 (18.7)	7 (2.5)	<0.001

Data are presented as mean±standard deviation or n (%). ICD, Implantable cardioverter-defibrillator; MCF, Myocardial contraction fraction; ROC, Receiver operating characteristic. Renal failure was defined as postprocedural stage 2 or 3 acute kidney injury according to Valve Academic Research Consortium/ Kidney Disease: Improving Global Outcomes criteria after TAVI.

In the final multivariable model, EuroSCORE II remained an independent predictor of 1-year cardiac death (HR, 1.041; 95% CI, 1.009–1.073; P = 0.011). The indexed aortic valve area was also independently associated with the endpoint (HR, 0.002; 95% CI, <0.001–0.164; P = 0.006). In this model, MCF was evaluated as a continuous variable, and each 1% increase in MCF was independently associated with a lower risk of 1-year cardiac death (HR, 0.882; 95% CI, 0.823–0.946; P < 0.001). These findings suggest that MCF provides prognostic information beyond conventional LVEF assessment in patients undergoing TAVI.

Kaplan–Meier Survival Analysis

Kaplan–Meier survival analysis demonstrated significantly lower 1-year survival among patients with MCF ≤24% than among those with MCF >24% (log-rank P < 0.001). The mean survival time was 10.71 months in the MCF ≤24% group and 11.76 months in the MCF >24% group (Figure 2). The survival curves showed early and persistent separation during follow-up, indicating poorer survival among patients with reduced MCF.

Mathematical Relationship Between MCF Components

Because MCF is calculated from stroke volume and left ventricular myocardial volume, differences in stroke volume index and myocardial mass index between the MCF groups are partly expected by definition. Therefore, these findings should not be interpreted as entirely independent observations but rather as confirmation that reduced MCF identifies a phenotype characterized by reduced forward flow relative to increased myocardial mass. The prognostic relevance of MCF in the present

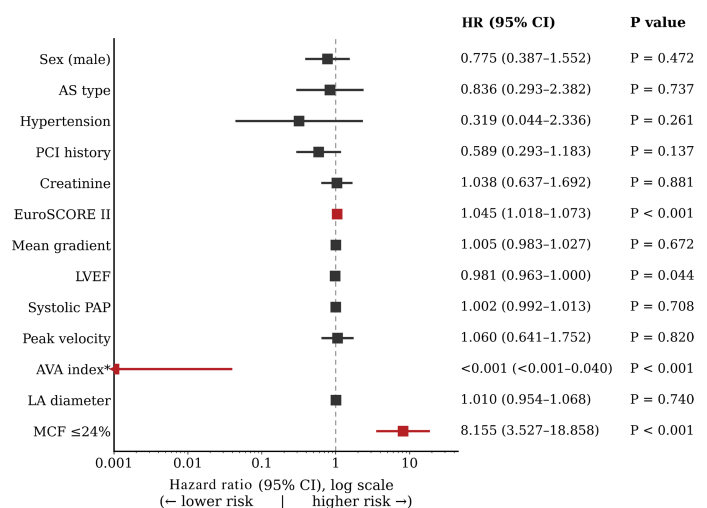
Univariable predictors of 1-year cardiac death

Figure 1. Forest plot of the univariable Cox regression analysis for predictors of 1-year cardiac death. Hazard ratios are plotted with 95% confidence intervals on a logarithmic scale; the dashed vertical line denotes a hazard ratio of 1. Statistically significant predictors are shown in red. Myocardial contraction fraction (MCF) ≤24% was the strongest predictor of 1-year cardiac death. *The indexed aortic valve area is expressed per 1 cm²/m²; its hazard ratio (<0.001) lies beyond the plotted range and is indicated by an arrow. AS, Aortic stenosis; AVA, Aortic valve area; LA, Left atrium; LVEF, Left ventricular ejection fraction; PAP, Pulmonary artery pressure; PCI, Percutaneous coronary intervention.

Table 4. Univariable and multivariable Cox regression analyses of predictors of 1-year cardiac death

Variables	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Male sex	0.775 (0.387–1.552)	0.472		
AS type	0.836 (0.293–2.382)	0.737		
Hypertension	0.319 (0.044–2.336)	0.261		
History of PCI	0.589 (0.293–1.183)	0.137		
Creatinine	1.038 (0.637–1.692)	0.881		
EuroSCORE II	1.045 (1.018–1.073)	<0.001	1.041 (1.009–1.073)	0.011
Mean transvalvular gradient	1.005 (0.983–1.027)	0.672		
LVEF	0.981 (0.963–1.000)	0.044	1.006 (0.984–1.018)	0.602
Systolic PAP	1.002 (0.992–1.013)	0.708		
Peak aortic jet velocity	1.060 (0.641–1.752)	0.820		
Indexed AVA	<0.001 (<0.001–0.040)	<0.001	0.002 (<0.001–0.164)	0.006
Left atrial diameter	1.010 (0.954–1.068)	0.740		
MCF	8.155 (3.527–18.858)	<0.001	0.882 (0.823–0.946)	<0.001

AS, Aortic stenosis; AVA, Aortic valve area; CI, Confidence interval; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, Hazard ratio; LVEF, Left ventricular ejection fraction; MCF, Myocardial contraction fraction; PAP, Pulmonary artery pressure; PCI, Percutaneous coronary intervention. Multicollinearity was assessed using variance inflation factors and tolerance statistics. Independent predictors were identified using backward stepwise (Wald) Cox regression. For MCF, the univariable estimate refers to MCF $\leq 24\%$ as a binary variable, whereas the multivariable estimate refers to MCF as a continuous variable per 1% increase.

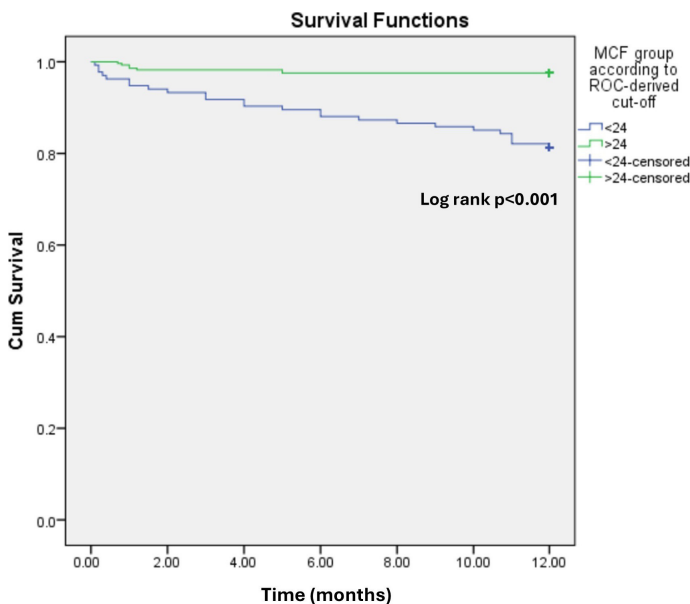


Figure 2. Kaplan-Meier survival curves for 1-year cumulative survival according to the receiver operating characteristic-derived myocardial contraction fraction (MCF) cutoff value of 24%. Patients with MCF $\leq 24\%$ had significantly lower 1-year survival than those with MCF $> 24\%$ (log-rank $P < 0.001$).

study is supported by its association with 1-year cardiac death and its independent relationship with the outcome in Cox regression analysis.

Discussion

In this retrospective, single-center study of patients undergoing TAVI for severe AS, reduced MCF was associated with adverse myocardial remodeling and a significantly increased risk of 1-year cardiac death. The principal findings were as follows: first, patients

with MCF $\leq 24\%$ had lower LVEF, lower stroke volume index, higher myocardial mass index, larger left ventricular diameters, greater left atrial diameter, and higher pulmonary artery pressure; second, an MCF threshold of 24% demonstrated good discriminatory ability for 1-year cardiac death; third, the rate of 1-year cardiac death was markedly higher in patients with MCF $\leq 24\%$ than in those with MCF $> 24\%$; and fourth, higher MCF, analyzed as a continuous variable, remained independently associated with a lower risk of 1-year cardiac death after adjustment for conventional clinical and echocardiographic variables.

These findings are pathophysiologically plausible. Severe AS causes chronic left ventricular pressure overload, leading to concentric hypertrophy, increased myocardial mass, impaired relaxation, interstitial fibrosis, and, eventually, systolic dysfunction and low-flow physiology.^{5,6} In this setting, LVEF may remain preserved despite substantial myocardial disease. MCF may partly overcome this limitation because it relates stroke volume to myocardial volume rather than to left ventricular cavity volume.^{9,10} Therefore, a lower MCF indicates that a larger myocardial mass generates a relatively smaller forward stroke volume, reflecting inefficient myocardial performance (Figure 3).

The concept of MCF was first described as a volumetric index of myocardial shortening using three-dimensional echocardiography.⁹ Subsequent studies showed that MCF may provide prognostic information in apparently healthy individuals and may identify abnormal myocardial performance in conditions associated with left ventricular hypertrophy.^{11,12} Cardiovascular magnetic resonance studies have demonstrated that MCF is reduced in hypertensive heart disease, hypertrophic cardiomyopathy, and cardiac amyloidosis despite varying degrees of LVEF preservation.¹² More recent three-dimensional echocardiographic studies have also supported the diagnostic utility of MCF in hypertrophic phenotypes with normal LVEF.¹⁰ These observations support the concept that MCF is not simply

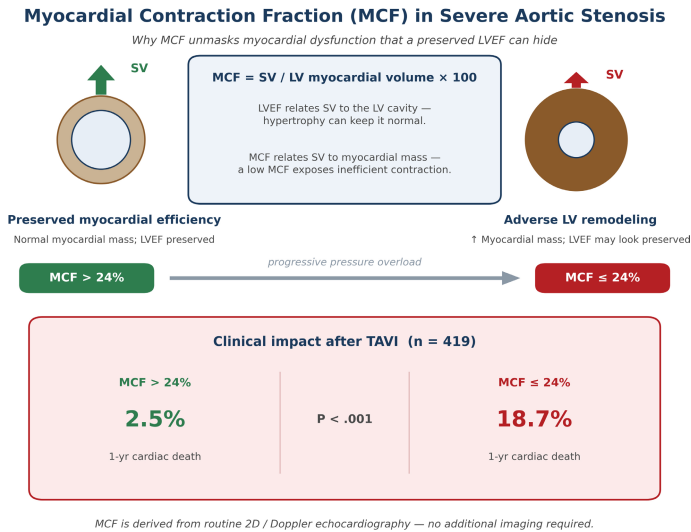


Figure 3. Mechanistic relationship between left ventricular remodeling and myocardial contraction fraction (MCF) in severe aortic stenosis. Chronic pressure overload causes concentric hypertrophy and increased myocardial mass, such that a larger myocardium generates a relatively smaller forward stroke volume (SV). Because left ventricular ejection fraction relates SV to cavity volume, it may remain preserved despite this remodeling, whereas MCF relates SV to myocardial volume and therefore reveals reduced myocardial efficiency. In this cohort, patients with MCF ≤24% had a markedly higher rate of 1-year cardiac death than those with MCF >24% (18.7% vs. 2.5%; P < 0.001). MCF is derived from routine two-dimensional and Doppler echocardiography without additional imaging.

another expression of LVEF but rather an integrated measure of myocardial shortening relative to myocardial mass. Consistent with this concept, LVEF lost its independent association with 1-year cardiac death after multivariable adjustment (P = 0.602), whereas higher MCF, analyzed as a continuous variable, remained independently associated with a lower risk. This dissociation suggests that MCF captures prognostic information beyond that conveyed by LVEF alone, which may be particularly relevant in severe AS, in which LVEF is frequently preserved despite advanced myocardial remodeling.

The clinical implications of these findings are important. MCF can be calculated using routinely available echocardiographic variables and does not require additional imaging, contrast administration, or advanced postprocessing. In contemporary real-world TAVI cohorts, residual mortality remains substantial despite high procedural success rates, underscoring the value of additional preprocedural risk markers.¹⁵ Moreover, although TAVI itself induces favorable changes in left ventricular function that can be monitored echocardiographically, baseline myocardial efficiency may better reflect the extent of preexisting remodeling than postprocedural changes alone.¹⁶ Therefore, MCF may be incorporated into preprocedural TAVI assessment as a simple marker of myocardial reserve and ventricular remodeling. Patients with MCF ≤24% may represent a high-risk subgroup requiring closer postprocedural follow-up, optimization of heart failure therapy, and careful surveillance for adverse outcomes. Moreover, reduced MCF may identify patients in whom valve intervention occurs after advanced or partially irreversible myocardial damage

has already developed, emphasizing the importance of timely referral before advanced myocardial remodeling occurs. Because MCF is derived entirely from standard two-dimensional and Doppler echocardiographic measurements, the proposed 24% threshold can be applied at the bedside without additional cost or expertise, which may facilitate its adoption into routine practice. Whether automated MCF calculation within echocardiography platforms could reduce measurement variability remains a question for future study; any such application would require prospective validation before clinical adoption.

Another strength of MCF is that it integrates two key components of AS pathophysiology: forward flow and myocardial hypertrophy. Conventional parameters such as LVEF, mean gradient, valve area, and stroke volume index each describe a single dimension of disease severity. MCF combines myocardial structure and function into a single index, making it particularly attractive in patients with discordant AS parameters, low-flow states, or preserved LVEF despite symptoms. In this respect, MCF may complement rather than replace existing risk scores such as EuroSCORE II. Similarly, adjunctive markers reflecting extracardiac organ dysfunction have been shown to improve mortality prediction beyond conventional risk scores in patients with severe AS, supporting a multiparametric approach to risk stratification.¹⁷

Study Limitations

This study has several limitations. First, it was a retrospective, single-center study; therefore, selection bias and unmeasured confounding cannot be excluded. Second, although the cohort included 419 patients, the number of 1-year cardiac deaths was limited, which may have affected the stability of the multivariable model. Third, MCF was calculated using echocardiographic measurements, which are subject to interobserver variability, particularly in the estimation of stroke volume and left ventricular mass. Fourth, the ROC-derived MCF cutoff value of 24% was obtained from this cohort and requires external validation before routine clinical use.

Fifth, several echocardiographic parameters with established prognostic value after TAVI, including global longitudinal strain, the E/e' ratio, left ventricular diastolic function grade, tricuspid annular plane systolic excursion, right ventricular function, and right ventricular-pulmonary artery coupling, were not systematically available and therefore could not be included in the analysis. Advanced imaging markers, such as cardiac magnetic resonance-derived fibrosis, extracellular volume fraction, and computed tomography-derived myocardial mass, were also unavailable. Sixth, frailty, nutritional status, postdilatation, residual transvalvular gradient, paravalvular leak severity, procedural complications, and postprocedural hemodynamic improvement may influence 1-year cardiac death but were not fully incorporated into the final multivariable model. Although valve type and vascular access were recorded and included in the descriptive analysis, the present study was primarily designed to evaluate the prognostic value of a preprocedural echocardiographic index of myocardial performance. Finally, cardiac death was determined retrospectively using available clinical records and follow-up sources, and events were not independently adjudicated by a clinical events committee.

Conclusion

Reduced MCF was associated with adverse left ventricular remodeling and a significantly increased risk of 1-year cardiac death in patients undergoing TAVI for severe AS. An MCF cutoff value of 24% identified a high-risk subgroup with markedly poorer survival. MCF remained independently associated with 1-year cardiac death after adjustment for conventional clinical and echocardiographic variables. As a simple echocardiographic index that integrates stroke volume and myocardial mass, MCF may improve preprocedural risk stratification in patients undergoing TAVI. Prospective multicenter studies are needed to externally validate the 24% threshold and determine whether incorporating MCF into preprocedural risk assessment improves clinical decision-making and outcomes.

Ethics Committee Approval: Ethics committee approval was obtained from Kocaeli University Non-Interventional Clinical Research Ethics Committee Approval Number: KÜ GOKAEK-2026/06/21; Project No. 2026/170; Date: 12.03.2026).

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Predictors of One-Year Restenosis After Percutaneous Mitral Balloon Valvuloplasty in Rheumatic Mitral Stenosis: Real-World Data From 555 Patients and the Limited Impact of Periinterventional Transesophageal Echocardiography

Romatizmal Mitral Darlığında Perkütan Mitral Balon Valvüloplasti Sonrası Bir Yıllık Restenozun Öngördürücüleri: 555 Hastalık Gerçek Yaşam Verisinde Periintervansiyonel Transözofageal Ekokardiyografinin Sınırlı Etkisi

ABSTRACT

Objective: Mitral balloon valvuloplasty remains an established first-line treatment for appropriately selected patients with rheumatic mitral stenosis. However, predictors of long-term restenosis and the additional value of periinterventional transesophageal echocardiography remain incompletely defined.

Method: This retrospective, single-center study included 555 patients who underwent percutaneous mitral balloon valvuloplasty for rheumatic mitral stenosis between January 2010 and January 2025 at Mehmet Akif Ersoy Heart Center, İstanbul, Türkiye. Patients were divided according to the presence or absence of restenosis at the 1-year follow-up. Restenosis was defined as a mitral valve area $<1.5 \text{ cm}^2$. Procedural success was defined as less than moderate mitral regurgitation at the end of the procedure and the absence of transeptal puncture-related complications. Clinical, echocardiographic, procedural, and laboratory variables were analyzed to identify predictors of restenosis and procedural success.

Results: Restenosis occurred in 94 patients (17%). The mean age of the overall cohort was 47.81 ± 12.29 years, and 467 patients (84.1%) were female. Patients with restenosis had higher preprocedural systolic pulmonary artery pressure, postprocedural transmitral gradient, postprocedural systolic pulmonary artery pressure, and preprocedural Wilkins score. In multivariable analysis, only the preprocedural Wilkins score remained an independent predictor of restenosis (OR: 1.907, 95% CI: 1.339–2.718, $P < 0.001$). Post-balloon transmitral gradient and postprocedural left atrial pressure $\geq 12 \text{ mmHg}$ were associated with procedural success. Periinterventional transesophageal echocardiography was not associated with restenosis or procedural success.

Conclusion: In patients undergoing percutaneous mitral balloon valvuloplasty for rheumatic mitral stenosis, the preprocedural Wilkins score was the only independent predictor of 1-year restenosis. Routine periinterventional transesophageal echocardiography did not significantly influence procedural success or long-term restenosis rates. These findings suggest that, in appropriately selected patients, percutaneous mitral balloon valvuloplasty can be safely and effectively performed under transthoracic echocardiographic guidance without routine periinterventional transesophageal echocardiography.

Keywords: Echocardiography, mitral valve, restenosis

ÖZET

Amaç: Mitral balon valvüloplasti, uygun şekilde seçilmiş romatizmal mitral darlığı hastalarında halen kabul görmüş birinci basamak tedavi seçeneğidir. Bununla birlikte, uzun dönem restenozun öngördürücüleri ve periintervansiyonel transözofageal ekokardiyografinin ek katkısı tam olarak tanımlanmamıştır.

Yöntem: Bu retrospektif, tek merkezli çalışmaya, Ocak 2010 ile Ocak 2025 tarihleri arasında İstanbul Mehmet Akif Ersoy Kalp Merkezi'nde romatizmal mitral darlığı nedeniyle perkütan

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mitral balon valvüloplasti uygulanan 555 hasta dahil edildi. Hastalar, 1 yıllık takipte restenoz varlığına göre gruplara ayrıldı. Restenoz, mitral kapak alanının $<1,5 \text{ cm}^2$ olması olarak tanımlandı. İşlem başarısı, işlem sonunda mitral yetersizliğinin orta dereceden az olması ve transeptal ponksiyona bağlı komplikasyon gelişmemesi olarak tanımlandı. Restenozun ve işlem başarısının öngördürücülerini belirlemek amacıyla klinik, ekokardiyografik, işlemel ve laboratuvar değişkenleri analiz edildi.

Bulgular: Restenoz 94 hastada (%17) görüldü. Tüm kohortun ortalama yaşı $47,81 \pm 12,29$ yıl olup 467 hasta (%84,1) kadındı. Restenoz gelişen hastalarda işlem öncesi sistolik pulmoner arter basıncı, işlem sonrası transmitral gradiyent, işlem sonrası sistolik pulmoner arter basıncı ve işlem öncesi Wilkins skoru daha yüksekti. Çok değişkenli analizde yalnızca işlem öncesi Wilkins skoru restenozun bağımsız öngördürücüsü olarak kaldı (OR=1,907; %95 GA: 1,339-2,718; $P < 0,001$). Balon sonrası transmitral gradiyent ve işlem sonrası sol atriyal basıncın $\geq 12 \text{ mmHg}$ olması işlem başarısı ile ilişkili bulundu. Perikardiyoskopi transözofageal ekokardiyografi, restenoz veya işlem başarısı ile ilişkili değildi.

Sonuç: Romatizmal mitral darlığı nedeniyle perkütan mitral balon valvüloplasti uygulanan hastalarda işlem öncesi Wilkins skoru, 1 yıllık restenozun tek bağımsız öngördürücüsüydu. Rutin perikardiyoskopi transözofageal ekokardiyografi, işlem başarısını veya uzun dönem restenoz oranlarını anlamlı ölçüde etkilemedi. Bu bulgular, uygun şekilde seçilmiş hastalarda perkütan mitral balon valvüloplastinin rutin perikardiyoskopi transözofageal ekokardiyografi olmaksızın, transtoraks ekokardiyografi rehberliğinde güvenli ve etkili bir şekilde uygulanabileceğini düşündürmektedir.

Anahtar Kelimeler: Ekokardiyografi, mitral kapak, restenoz

Mitral stenosis remains a significant global health problem, particularly among younger patients in developing countries. Rheumatic heart disease is the most common underlying etiology, although mitral stenosis may also occur as a result of severe mitral annular calcification or, less frequently, other conditions such as congenital abnormalities, systemic inflammatory disease, carcinoid syndrome, or prior chest irradiation.^{1,2} Invasive treatment is indicated in symptomatic patients with severe mitral stenosis, and mitral balloon valvuloplasty is considered the first-line therapeutic option in appropriately selected cases.^{3,4} The outcomes of mitral balloon valvuloplasty are influenced by both patient-related characteristics and operator experience.^{5,6} The procedure is usually performed under the guidance of either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE); however, evidence regarding the additional benefit of TEE over TTE in terms of procedural success and restenosis remains limited. We aimed to identify predictors of restenosis following mitral balloon valvuloplasty, as well as determinants of procedural success and long-term outcomes, in patients treated at a high-volume tertiary referral center in İstanbul, Türkiye.

Materials and Methods

This retrospective study included 555 patients who underwent percutaneous mitral balloon valvuloplasty for rheumatic mitral valve stenosis between January 2010 and January 2025 at Mehmet Akif Ersoy Chest, Heart and Vascular Surgery Training and Research Hospital, İstanbul, Türkiye. The pooled data were analyzed retrospectively. The study was conducted in accordance with the Declaration of Helsinki and was approved by the İstanbul Mehmet Akif Ersoy Chest, Heart and Vascular Surgery Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2025.11-108, Date: 30.12.2025).

ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
AVA	Aortic valve area
CAD	Coronary artery disease
CI	Confidence interval
HR	Heart rate
LA	Left atrium
LAA	Left atrial appendage
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
MVA	Mitral valve area
OR	Odds ratio
PAF	Paroxysmal atrial fibrillation
PAH	Pulmonary arterial hypertension
PHT	Pressure half time
SEK	Spontaneous echo contrast
SPAP	Systolic pulmonary artery pressure
TEE	Transesophageal echocardiography
TMG	Transmitral gradient
TTE	Transthoracic echocardiography

Data Collection

Demographic characteristics, comorbidities, electrocardiographic findings, hospitalization data, pericardiyoskopi data, peri- and postinterventional echocardiographic parameters, and laboratory values were obtained from electronic medical records. These parameters were compared between patients with long-term restenosis and those without restenosis. The decision not to use TEE in selected patients was based on adequate transthoracic image quality, an increased risk associated with general

Table 1. Baseline characteristics of the patients

Variables	All patients (n=555)	No restenosis (n=461)	Restenosis (n=94)	P
Age, years	47.81±12.29	48.12±12.54	46.28±10.96	0.185
Sex				
Female	467 (84.1)	382 (82.9)	85 (90.4)	0.054
Complaints				0.780
Dyspnea	430 (77.5)	359 (77.9)	71 (75.5)	
Dyspnea and palpitations	33 (5.9)	26 (5.6)	7 (7.4)	
Other	92 (16.0)	76 (16.5)	16 (17.0)	
Diabetes mellitus	48 (8.6)	39 (8.5)	9 (9.6)	0.729
Arterial hypertension	110 (19.8)	94 (20.4)	16 (17.0)	0.570
Hyperlipidemia	75 (13.5)	65 (14.1)	10 (10.6)	0.358
Pregnancy during the procedure	7 (1.3)	7 (1.5)	0 (0)	0.609
Ischemic cerebrovascular event	21 (3.8)	17 (3.7)	4 (4.3)	0.767
Thyroid dysfunction	30 (5.4)	23 (5.0)	7 (7.4)	0.349
CAD >50% stenosis	13 (2.3)	11 (2.4)	2 (2.1)	0.887
PAH	4 (0.8)	3 (0.6)	1 (1.1)	0.523

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. CAD, Coronary artery disease; PAH, Pulmonary arterial hypertension.

anesthesia due to concomitant respiratory disease, and the patient's preference to avoid general anesthesia.

Endpoints

The following endpoints were defined in this study.

Primary Outcome

The primary endpoint was restenosis, defined as a mitral valve area of less than 1.5 cm² at the 1-year follow-up.

Secondary Outcome

The secondary endpoint was procedural success. Procedural success was defined as less than moderate mitral valve regurgitation at the end of the procedure and the absence of transseptal puncture-related complications, such as cardiac tamponade.

Statistical Analysis

Categorical variables were presented as absolute frequencies and percentages. Continuous variables were expressed as mean±standard deviation or median with interquartile range, according to their distribution. Normality was assessed using the Kolmogorov-Smirnov test and visual inspection of histograms. Between-group comparisons were performed using the independent-samples Student's t-test or the Mann-Whitney U test for continuous variables, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test.

Procedural outcome and 1-year restenosis were defined and analyzed as two separate study endpoints. Patients were first compared according to procedural success, and a separate analysis was subsequently performed according to the presence or absence of restenosis at 1 year. To identify independent factors associated with procedural failure, univariable logistic regression analyses were initially performed. Variables considered clinically relevant and those showing a p value <0.10

in the univariable analyses were entered into a multivariable binary logistic regression model. A separate multivariable binary logistic regression model was constructed to identify independent predictors of 1-year restenosis. Periinterventional TEE was evaluated separately in both models to determine its adjusted association with procedural outcome and 1-year restenosis. The results of the logistic regression analyses were reported as odds ratios with corresponding 95% confidence intervals. P values and confidence intervals were calculated using the Wald method. Multicollinearity was assessed before construction of the multivariable models. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Data preparation and statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of the patients are summarized in Table 1. Among the 555 patients, restenosis occurred in 94 (17%). The mean age of the overall cohort was 47.81±12.29 years, and 467 patients (84.1%) were female. The proportion of female patients was higher in the restenosis group than in the non-restenosis group [90.4% vs. 82.9%, P = 0.054]; however, this difference was not statistically significant. All other baseline characteristics and comorbidities were comparable between the two groups. Preprocedural medications are summarized in Table 2. Patients with restenosis used diuretics more frequently than those without restenosis [67 (71.3%) vs. 273 (59.2%), P = 0.029]. The use of acetylsalicylic acid was also higher in patients with restenosis [56 (59.6%) vs. 223 (48.4%), P = 0.048]. The use of other medications was comparable between the two groups. Electrocardiographic parameters are summarized in Table 3. The prevalence of atrial fibrillation and postprocedural heart rate were comparable between the groups.

Table 2. Preprocedural medications of the patients

Medication	All patients (n=555)	No restenosis (n=461)	Restenosis (n=94)	P
Statin	42 (7.6)	38 (8.2)	4 (4.3)	0.159
Diuretics	340 (61.3)	273 (59.2)	67 (71.3)	0.029
Beta-blocker	430 (77.5)	354 (76.8)	76 (80.9)	0.390
ASA	279 (50.3)	223 (48.4)	56 (59.6)	0.048
Warfarin	181 (32.6)	144 (31.2)	37 (39.4)	0.126
Antiarrhythmics				0.818
Amiodarone	8 (1.4)	7 (1.5)	1 (1.1)	
Propafenone	3 (0.5)	3 (0.6)	0 (0)	
Sotalol	1 (0.2)	1 (0.2)	0 (0)	
Calcium channel blockers				0.106
Non-dihydropyridine	29 (5.2)	20 (4.3)	9 (9.6)	
Dihydropyridine	16 (2.9)	14 (3.0)	2 (2.1)	
Digoxin	24 (4.3)	18 (3.9)	6 (6.4)	0.268
ACEI/ARB	91 (16.4)	77 (16.7)	14 (14.9)	0.666

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. ASA, Acetylsalicylic acid; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

Table 3. Electrocardiographic parameters of the patients

Parameters	All patients (n=555)	No restenosis (n=461)	Restenosis (n=94)	P
Preprocedural ECG				0.604
Sinus rhythm	422 (76.0)	354 (76.8)	68 (72.3)	
AF	104 (19.0)	86 (18.7)	18 (19.1)	
Pacemaker rhythm	3 (0.5)	2 (0.4)	1 (1.1)	
PAF	23 (4.1)	17 (3.7)	6 (6.4)	
Preprocedural HR	78.38±17.53	77.66±16.86	81.86±20.76	0.221
PR interval (ms)	157.59±29.73	158.04±29.24	155.32±32.24	0.942
QRS duration (ms)	80.41±13.56	80.57±13.97	79.65±11.65	0.660
QTc interval (ms)	436.05±34.01	434.98±34.15	441.34±33.54	0.244
Postprocedural ECG				0.072
Sinus rhythm	426 (76.8)	360 (78.1)	66 (70.2)	
AF	117 (21.1)	94 (20.4)	23 (24.5)	
Pacemaker rhythm	3 (0.5)	2 (0.4)	1 (1.1)	
PAF	4 (0.7)	3 (0.7)	1 (1.1)	
Postprocedural HR	78.94±17.04	79.03±17.00	73.61±16.10	0.493
PR interval (ms)	156.46±29.16	156.56±28.34	155.85±33.52	0.593
QRS duration (ms)	82.19±32.87	80.47±12.91	90.66±73.39	0.258
QTc interval (ms)	440.99±35.21	440.54±33.65	442.46±42.04	0.754

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. ECG, Electrocardiography; AF, Atrial fibrillation; PAF, Paroxysmal atrial fibrillation; HR, Heart rate; ms, Milliseconds.

Echocardiographic parameters are summarized in Table 4. Regarding preprocedural TTE findings, systolic pulmonary artery pressure (SPAP) was significantly higher in the restenosis group [47.47±15.23 vs. 43.65±15.79 mmHg, P = 0.011]. Moderate aortic stenosis before the procedure was also more frequent in the restenosis group [4 (4.3%) vs. 6 (1.3%), P = 0.033]. Regarding postprocedural TTE findings, the transmitral gradient

(TMG) was higher in patients with restenosis [5.85±2.28 vs. 5.23±2.07 mmHg, P = 0.005]. Postprocedural SPAP was also significantly higher in the restenosis group [36.51±10.31 vs. 33.80±9.50 mmHg, P = 0.010]. Regarding TEE findings, only the preprocedural Wilkins score was significantly higher in the restenosis group [7.91±1.18 vs. 7.41±1.27, P = 0.001]. Other TEE findings were comparable between the groups.

Table 4. Echocardiographic parameters of the patients

Parameters	All patients (n=555)	No restenosis (n=461)	Restenosis (n=94)	P
Preprocedural LVEF	61.31±4.25	61.31±4.15	61.27±4.76	0.955
Preprocedural LA diameter	4.61±2.01	4.62±2.20	4.48±0.43	0.083
Preprocedural SPAP (TTE)	44.32±15.76	43.65±15.79	47.47±15.23	0.011
MR >grade I	156 (28.1)	131 (28.4)	25 (26.6)	0.720
TTE Wilkins score	7.86±1.49	7.81±1.57	8.02±1.08	0.654
Preprocedural MVA, planimetric (TTE)	1.20±1.37	1.21±1.51	1.13±0.22	0.828
Preprocedural MVA, PHT (TTE)	1.16±0.21	1.16±0.21	1.14±0.23	0.421
Preprocedural TMG (TTE)	11.36±4.74	11.25±4.61	11.93±5.34	0.282
Aortic valve stenosis				0.033
Mild	15 (2.7)	15 (3.3)	0 (0)	
Moderate	10 (1.8)	6 (1.3)	4 (4.3)	
Postprocedural LVEF	61.11±4.68	61.02±4.36	61.48±4.92	0.210
Postprocedural LA diameter	4.28±0.53	4.25±0.53	4.39±0.51	0.012
Postprocedural SPAP (TTE)	34.27±9.69	33.80±9.50	36.51±10.31	0.010
MR >grade I	203 (36.6)	167 (36.3)	36 (38.3)	0.713
Postprocedural MVA, planimetric (TTE)	1.81±0.34	1.82±0.33	1.79±0.38	0.896
Postprocedural MVA, PHT (TTE)	1.80±0.32	1.80±0.33	1.79±0.27	0.651
Postprocedural TMG (TTE)	5.34±2.12	5.23±2.07	5.85±2.28	0.005
Preprocedural SPAP (TEE)	48.85±15.88	48.54±15.67	50.43±16.95	0.169
Preprocedural MV mean gradient (TEE)	13.16±5.77	13.07±5.75	13.77±5.92	0.164
Preprocedural MVA, 3D (TEE)	1.08±0.57	1.10±0.63	1.01±0.25	0.131
Preprocedural MVA, PHT (TEE)	1.11±0.19	1.12±0.19	1.09±0.20	0.137
Preprocedural 3D MPR MVA (TEE)	1.15±0.34	1.16±0.34	1.05±0.34	0.137
LAA velocity (cm/s)	34.25±15.08	33.34±15.09	36.77±14.98	0.198
LAA thrombus or SEC				0.236
LAA thrombus	27 (4.9)	24 (5.2)	3 (3.2)	
LA SEC	73 (13.2)	56 (12.1)	17 (18.1)	
Preprocedural Wilkins score (TEE)	7.49±1.27	7.41±1.27	7.91±1.18	0.001

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. LVEF, Left ventricular ejection fraction; TTE, Transthoracic echocardiography; TEE, Transesophageal echocardiography; SPAP, Systolic pulmonary artery pressure; MR, Mitral regurgitation; MVA, Mitral valve area; TMG, Transmitral gradient; PHT, Pressure half-time; MV, Mitral valve; LA, Left atrium; LAA, Left atrial appendage; SEC, Spontaneous echo contrast; 3D, Three-dimensional; MPR, Multiplanar reconstruction.

Procedural success was also analyzed. Baseline characteristics according to procedural success are summarized in Table 5. Among the 555 patients, 51 had unsuccessful procedures. The reasons for procedural failure were severe mitral regurgitation in 16 patients (31.4%), pericardial effusion or tamponade in 11 patients (21.6%), failed atrial septostomy in 9 patients (17.6%), left atrial thrombus in 6 patients (11.8%), and other causes, including severe peripheral complications and severe pulmonary edema, in 9 patients (17.6%). Patients with unsuccessful procedures were significantly older than those with successful procedures [51.98±12.50 vs. 47.35±12.22 years, $P = 0.010$]. Other baseline parameters, including sex, preexisting hypertension, diabetes mellitus, coronary artery disease, and pulmonary arterial hypertension, were comparable between the two groups. Procedural characteristics, including contrast volume, procedure duration, and the use of TEE guidance, were also similar. The number of balloon inflations was lower in the

unsuccessful procedure group [1.29±0.89 vs. 2.00±0.72, $P = 0.001$]. The length of hospital stay was significantly longer in patients with unsuccessful procedures [7.06±6.71 vs. 3.01±1.75 days, $P < 0.001$]. Electrocardiographic and echocardiographic parameters according to procedural success are summarized in Table 6. Preprocedural heart rate was higher in the unsuccessful procedure group [86.18±22.38 vs. 77.56±16.89 bpm, $P = 0.018$]. Both preprocedural and postprocedural SPAPs were significantly higher in the unsuccessful procedure group ($P < 0.001$ and $P = 0.001$, respectively). Preprocedural TEE parameters were comparable between the groups, except for the presence of left atrial appendage thrombus or spontaneous echo contrast, which was significantly more frequent in patients with unsuccessful procedures ($P < 0.001$).

Outcomes

The primary outcome was restenosis. Univariable (Table 7) and multivariable (Table 8) analyses were performed to determine

Table 5. Baseline analysis according to procedural success

Variables	Successful (n=504)	Unsuccessful (n=51)	P
Age, years	47.35±12.22	51.98±12.50	0.010
Female sex	420 (83.3)	47 (92.2)	0.100
Complaints			0.472
Dyspnea	388 (77.0)	42 (82.4)	
Dyspnea and palpitations	30 (6.0)	3 (5.9)	
Other (edema, etc.)	66 (13.1)	3 (5.9)	
Diabetes mellitus	44 (8.7)	4 (7.8)	0.830
Hypertension	101 (20.0)	9 (17.5)	0.683
Hyperlipidemia	68 (13.5)	7 (13.7)	0.963
Pregnancy during the procedure	7 (1.4)	0 (0)	0.397
CVE	18 (3.6)	3 (5.9)	0.410
Thyroid dysfunction	25 (5.0)	5 (9.8)	0.145
CAD >50% stenosis	12 (2.4)	1 (2.0)	0.850
PAH	4 (0.8)	0 (0)	0.523
Diuretics	307 (60.9)	33 (64.7)	0.596
Beta-blocker	395 (78.4)	35 (68.6)	0.112
TEE-guided procedure	340 (71.3)	33 (76.7)	0.446
Procedure duration (min)	85.19±37.16	96.90±54.30	0.405
Fluoroscopy duration (min)	25.83±25.52	27.32±18.74	0.448
Radiation dose (mGy)	5749.43±587.36	477.86±353.42	0.736
Contrast volume (mL)	50.55±40.79	51.67±38.70	0.999
Balloon diameter (mm)	27.88±1.26	27.56±0.82	0.114
Number of balloon inflations	2.00±0.72	1.29±0.89	0.001
LA pressure before balloon inflation (mmHg)	12.69±5.09	15.50±9.01	0.581
LA pressure after balloon inflation (mmHg)	4.71±2.23	6.75±4.13	0.068
Postprocedural CVE	1 (0.2)	0 (0)	0.750
Postprocedural pericardial effusion (no intervention required)	7 (1.4)	3 (5.9)	0.022
Reason for procedural failure			0.730
Severe MR	—	16 (31.4)	
Pericardial effusion/pericardial tamponade	—	11 (21.6)	
Failed atrial septostomy	—	9 (17.6)	
Left atrial thrombus	—	6 (11.8)	
Other	—	9 (17.6)	
Length of hospital stay (days)	3.01±1.75	7.06±6.71	<0.001

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. CAD, Coronary artery disease; PAH, Pulmonary arterial hypertension; CVE, Cerebrovascular event; MR, Mitral regurgitation; LA, Left atrium; TEE, Transesophageal echocardiography.

predictors of restenosis. After adjustment for all relevant factors, only the preprocedural Wilkins score remained an independent predictor of restenosis [OR: 1.907, 95% CI: 1.339–2.718, $P < 0.001$].

The secondary outcome was procedural success. Univariable (Table 9) and multivariable (Table 10) analyses were performed to determine predictors of procedural success. Preprocedural transmitral gradient [OR: 1.156, 95% CI: 1.178–12.181, $P = 0.003$] and greater than mild mitral regurgitation [OR: 3.788, 95% CI: 1.020–1.311, $P = 0.025$] were associated with procedural success.

In this cohort, periinterventional TEE was not significantly associated with either procedural success or 1-year restenosis.

Discussion

In the present study, we evaluated predictors of long-term restenosis and procedural success in patients undergoing percutaneous mitral balloon valvuloplasty. The main findings of our study were as follows: first, the preprocedural Wilkins score was the only independent predictor of long-term restenosis after adjustment for potential confounders; second, the use of periinterventional TEE was not associated with a significant difference in procedural success or long-term restenosis; and third, comprehensive preprocedural imaging remains essential for optimal patient selection, anatomical assessment, and procedural planning.

Table 6. Electrocardiographic and echocardiographic analysis according to procedural success

Parameters	Successful (n=504)	Unsuccessful (n=51)	P
Preprocedural ECG			0.063
Sinus rhythm	390 (77.4)	32 (62.7)	
Permanent AF	89 (17.7)	15 (29.4)	
Pacemaker rhythm	2 (0.4)	1 (2.0)	
Paroxysmal AF/persistent AF	21 (4.2)	2 (3.9)	
Preprocedural HR (bpm)	77.56±16.89	86.18±22.38	0.018
PR interval (ms)	157.36±28.34	159.87±41.35	0.113
QRS duration (ms)	80.46±13.63	79.89±13.37	0.708
QTc interval (ms)	434.77±33.68	448.57±35.97	0.018
Postprocedural ECG			0.213
Sinus rhythm	392 (77.8)	34 (66.7)	
Permanent AF/persistent AF	103 (20.4)	14 (27.5)	
Pacemaker rhythm	2 (0.4)	1 (2.0)	
Paroxysmal AF	3 (0.6)	1 (2.0)	
Postprocedural HR (bpm)	78.14±16.48	84.60±16.40	0.019
Postprocedural QTc interval (ms)	439.48±34.16	455.25±42.53	0.007
Preprocedural LVEF (%)	61.26±4.35	61.71±3.11	0.662
Preprocedural LA diameter (cm)	4.61±2.10	4.66±0.63	0.162
Preprocedural SPAP (mmHg)	43.74±15.93	49.43±12.96	0.001
MR >mild	135 (26.8)	21 (41.2)	0.029
Preprocedural TTE Wilkins score	7.79±1.52	8.42±1.07	0.108
Preprocedural planimetric MVA (TTE) (cm ²)	1.21±1.45	1.10±0.19	0.212
Preprocedural MVA by PHT (TTE) (cm ²)	1.16±0.21	1.11±0.19	0.169
Preprocedural TMG (TTE) (mmHg)	11.23±4.70	12.66±5.02	0.029
Aortic valve stenosis			0.940
Mild AVS	14 (2.8)	1 (2.0)	
Moderate AVS	9 (1.8)	1 (2.0)	
Postprocedural LVEF (%)	61.22±4.26	58.88±7.15	0.085
Postprocedural LA pressure (mmHg)	4.26±0.53	4.49±0.49	0.052
Postprocedural SPAP (mmHg)	33.86±9.36	42.19±12.52	0.001
Postprocedural planimetric MVA (TTE) (cm ²)	1.82±0.34	1.67±0.45	0.146
Postprocedural MVA by PHT (TTE) (cm ²)	1.80±0.31	1.67±0.46	0.477
Postprocedural TMG (TTE) (mmHg)	5.24±1.95	7.295±3.87	0.012
Preprocedural SPAP (TEE) (mmHg)	48.67±15.71	50.63±17.54	0.329
Preprocedural TMG (TEE) (mmHg)	13.09±5.82	14.16±5.29	0.091
Preprocedural planimetric MVA (TEE) (cm ²)	1.08±0.61	1.08±0.22	0.402
Preprocedural MVA by PHT (TEE) (cm ²)	1.12±0.19	1.09±0.18	0.415
Preprocedural MVA by 3D TEE (cm ²)	1.15±0.35	1.11±0.26	0.560
LAA velocity (cm/s)	34.64±15.77	31.88±9.94	0.726
LAA thrombus/SEC			0.003
LAA thrombus	19 (3.8)	8 (15.7)	
LA SEC	64 (12.7)	9 (17.6)	
Preprocedural Wilkins score (TEE)	7.48±1.27	7.61±1.31	0.527

Values are presented as n (%), mean±SD, or median (first quartile, third quartile), as appropriate. ECG, Electrocardiography; AF, Atrial fibrillation; HR, Heart rate; bpm, Beats per minute; ms, Milliseconds; LVEF, Left ventricular ejection fraction; TTE, Transthoracic echocardiography; TEE, Transesophageal echocardiography; SPAP, Systolic pulmonary artery pressure; MR, Mitral regurgitation; MVA, Mitral valve area; TMG, Transmitral gradient; PHT, Pressure half-time; AVS, Aortic valve stenosis; LA, Left atrium; LAA, Left atrial appendage; SEC, Spontaneous echo contrast; 3D, Three-dimensional.

Table 7. Univariable regression analysis of predictors of long-term restenosis

Parameters	P	OR	95% CI
Preprocedural diuretic use	0.030	1.709	1.053–2.772
ASA use	0.049	1.573	1.002–2.468
LA pressure before MBV	0.015	1.071	1.014–1.132
LA pressure after MBV	0.020	1.149	1.022–1.292
Preprocedural SPAP (TTE)	0.048	1.014	1.001–1.026
Aortic valve stenosis (AVA <1.5 cm ²)	0.450	1.279	0.675–2.425
Postprocedural LA diameter	0.025	1.640	1.065–2.525
Postprocedural SPAP (TTE)	0.030	1.028	1.003–1.053
Postprocedural TMG	0.015	1.131	1.024–1.249
Preprocedural Wilkins score (TEE)	0.002	1.364	1.125–1.654
Triglycerides	0.050	0.992	0.989–1.000
INR	0.050	0.413	0.174–1.001

OR, Odds ratio; CI, Confidence interval; ASA, Acetylsalicylic acid; LA, Left atrium; MBV, Mitral balloon valvuloplasty; SPAP, Systolic pulmonary artery pressure; AVA, Aortic valve area; TTE, Transthoracic echocardiography; TMG, Transmitral gradient; TEE, Transesophageal echocardiography; INR, International normalized ratio.

Table 8. Multivariable regression analysis of predictors of long-term restenosis

Parameters	P	OR	95% CI
Preprocedural diuretic use	0.208	1.700	0.745–3.880
ASA use	0.111	1.902	0.863–4.194
LA pressure after MBV	0.634	1.039	0.888–1.216
Preprocedural SPAP (TTE)	0.779	1.003	0.982–1.025
LA pressure after MBV	0.202	1.610	0.774–3.351
Postprocedural SPAP (TTE)	0.779	1.003	0.982–1.025
Postprocedural TMG	0.076	1.202	0.982–1.471
Preprocedural Wilkins score (TEE)	<0.001	1.907	1.339–2.718

OR, Odds ratio; CI, Confidence interval; ASA, Acetylsalicylic acid; LA, Left atrium; MBV, Mitral balloon valvuloplasty; SPAP, Systolic pulmonary artery pressure; TTE, Transthoracic echocardiography; TMG, Transmitral gradient; TEE, Transesophageal echocardiography.

Percutaneous mitral balloon valvuloplasty remains an effective and well-established treatment option for selected patients with rheumatic mitral stenosis.^{3,4} The success and durability of the procedure are strongly influenced by mitral valve morphology, including leaflet mobility, leaflet thickening, calcification, and subvalvular involvement. These anatomical features are reflected in the Wilkins score, which has been widely used for preprocedural risk stratification and patient selection.⁷⁻¹⁰ In our study, the preprocedural Wilkins score was significantly higher in patients who developed restenosis and remained the only independent predictor of long-term restenosis in multivariable analysis. This finding supports the concept that the structural condition of the mitral valve before intervention is a major determinant of long-term valve durability after balloon valvuloplasty. In our cohort, several echocardiographic parameters differed between patients with and without restenosis. Preprocedural SPAP was higher in the

restenosis group, and postprocedural transmitral gradient and SPAP were also significantly higher in patients who developed restenosis. These findings suggest that patients with restenosis may have a greater hemodynamic burden both before and after the procedure. However, after adjustment, these parameters did not remain independent predictors of restenosis. This indicates that although hemodynamic variables reflect disease severity, anatomical valve morphology, as assessed by the Wilkins score, may have greater prognostic value for long-term restenosis.

Another important finding of our study was that periinterventional TEE did not significantly affect procedural success or long-term restenosis rates. TEE is commonly used before balloon valvuloplasty to exclude left atrial or left atrial appendage thrombus, assess mitral regurgitation, and provide additional anatomical information. It may also facilitate transseptal puncture by improving visualization of the interatrial septum and guiding catheter positioning, and several studies have suggested advantages of echocardiographic guidance over fluoroscopy alone in this setting.^{11,12} However, our findings suggest that the routine use of periinterventional TEE does not necessarily translate into improved procedural outcomes related to transseptal puncture or lower long-term restenosis rates. This may be explained by the fact that restenosis after balloon valvuloplasty is mainly driven by baseline valve morphology, rheumatic disease progression, commissural fusion, calcification, and subvalvular involvement rather than by the intraprocedural imaging strategy alone. Therefore, while preprocedural TEE remains essential for appropriate patient selection, exclusion of left atrial thrombus, assessment of mitral regurgitation, and identification of unfavorable anatomical features, routine periinterventional TEE may not provide additional benefit in all patients. In carefully selected cases with favorable anatomy and adequate transthoracic imaging quality, periinterventional guidance with TTE may be considered. This approach may also be relevant in patients for whom general anesthesia or deep sedation could carry additional risk, such as those with chronic obstructive pulmonary disease or significant comorbidities. Nevertheless, periinterventional TEE should remain available and should be used selectively in patients with complex anatomy, suboptimal transthoracic imaging, uncertain procedural findings, or increased safety concerns.

The role of TTE is also central to the evaluation of patients with mitral stenosis. TTE provides essential information regarding mitral valve area, transmitral gradient, pulmonary artery pressure, left atrial size, right ventricular function, and associated valvular lesions. In our study, preprocedural and postprocedural TTE parameters provided important clinical and hemodynamic information. In particular, higher postprocedural transmitral gradients and higher postprocedural SPAPs were observed in patients who subsequently developed restenosis. These parameters may help identify patients who require closer follow-up after balloon valvuloplasty, even if they do not independently predict restenosis after multivariable adjustment. From a clinical perspective, patients with higher preprocedural Wilkins scores should be considered at increased risk for long-term restenosis.^{3,4,10} These patients may benefit from more careful counseling before the procedure, closer echocardiographic follow-up, and earlier consideration of alternative treatment strategies when valve anatomy is unfavorable. Although balloon

Table 9. Univariable regression analysis of procedural success

Parameters	P	OR	95% CI
Age	0.011	1.031	1.007-1.055
Sex	0.110	2.350	0.825-6.698
Diabetes mellitus	0.830	0.890	0.306-2.585
Hypertension	0.683	0.855	0.403-1.814
Hyperlipidemia	0.963	1.020	0.441-2.357
Procedure duration	0.193	1.007	0.996-1.018
Fluoroscopy duration	0.835	1.002	0.982-1.022
Balloon diameter	0.194	0.826	0.620-1.102
Number of balloon inflations	<0.001	0.267	0.149-0.480
Preprocedural heart rate	0.005	1.023	1.007-1.040
Preprocedural SPAP (TTE)	0.020	1.020	1.003-1.036
MR >mild	0.032	1.913	1.059-3.457
LAA thrombus/SEC	0.004	1.593	1.163-2.180
TEE-guided procedure	0.447	1.330	0.638-2.772
Preprocedural LA pressure	0.143	1.082	0.974-1.202
Preprocedural LVEF	0.479	1.027	0.953-1.107
Preprocedural planimetric MVA (TTE) (cm ²)	0.171	0.366	0.087-1.542
Preprocedural MVA by PHT (TTE) (cm ²)	0.133	0.348	0.088-1.380
Preprocedural TMG	0.046	1.057	1.001-1.116
Preprocedural SPAP (TEE) (mmHg)	0.427	1.007	0.989-1.026
Preprocedural TMG (TEE)	0.221	1.031	0.982-1.082
Preprocedural planimetric MVA (TEE) (cm ²)	0.995	1.002	0.593-1.692
Preprocedural MVA by PHT (TEE) (cm ²)	0.390	0.505	0.106-2.397
Preprocedural 3D MVA (TEE) (cm ²)	0.662	0.663	0.105-4.193
LAA velocity	0.496	0.987	0.950-1.025
Preprocedural Wilkins score (TEE)	0.537	1.078	0.848-1.371

CI, Confidence interval; OR, Odds ratio; SPAP, Systolic pulmonary artery pressure; TTE, Transthoracic echocardiography; TEE, Transesophageal echocardiography; MR, Mitral regurgitation; LAA, Left atrial appendage; SEC, Spontaneous echo contrast; LA, Left atrium; LVEF, Left ventricular ejection fraction; MVA, Mitral valve area; PHT, Pressure half-time; TMG, Transmitral gradient; 3D, Three-dimensional.

Table 10. Multivariable regression analysis of procedural success

Parameters	P	OR	95% CI
Age	0.265	1.026	0.980-1.075
Number of balloon inflations	0.078	0.526	0.257-1.074
Preprocedural heart rate	0.378	1.013	0.985-1.041
Preprocedural QTc interval	0.247	1.009	0.994-1.025
Preprocedural SPAP	0.396	1.015	0.980-1.052
MR >mild	0.025	3.788	1.178-12.181
LAA thrombus/SEC	0.594	0.801	0.354-1.813
Preprocedural TMG (mmHg)	0.003	1.156	1.020-1.311

CI, Confidence interval; OR, Odds ratio; SPAP, Systolic pulmonary artery pressure; MR, Mitral regurgitation; LAA, Left atrial appendage; SEC, Spontaneous echo contrast; TMG, Transmitral gradient.

valvuloplasty may still provide symptomatic and hemodynamic improvement in selected patients with relatively high Wilkins scores, the expected durability of the procedure should be interpreted with caution.

This study has several limitations. First, it was a retrospective, single-center study, which may limit the generalizability of the findings. Second, although the overall cohort size was acceptable, the number of patients with restenosis was relatively limited, which may reduce the statistical power of the multivariable analysis. Third, the decision to perform periinterventional TEE may have been influenced by operator preference, patient characteristics, or image quality, introducing potential selection bias. Finally, long-term follow-up beyond 1 year would provide more comprehensive information regarding the progression of restenosis and clinical outcomes.

In this large real-world cohort of patients undergoing percutaneous mitral balloon valvuloplasty for rheumatic mitral stenosis, baseline mitral valve morphology, as assessed by the Wilkins score, was the main determinant of 1-year restenosis. Routine periinterventional TEE was not significantly associated with procedural success or restenosis in this cohort, suggesting that its use may be best considered on an individualized basis rather than as a routine requirement for all patients.

Ethics Committee Approval: Ethics committee approval was obtained from İstanbul Mehmet Akif Ersoy Chest, Heart and Vascular Surgery Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2025.11-108, Date: 30.12.2025).

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Indication Phenotypes and Short-Term Clinical Outcomes in Patients Undergoing Left Atrial Appendage Closure: A Single-Center Real-World Experience from Türkiye

Sol Atriyal Apendiks Kapama Yapılan Hastalarda Endikasyon Fenotipleri ve Kısa Dönem Klinik Sonuçların Değerlendirilmesi: Türkiye'den Tek Merkez Gerçek Yaşam Verisi

ABSTRACT

Objective: Left atrial appendage occlusion (LAAO) is widely used for stroke prevention in patients with atrial fibrillation who are unsuitable for long-term anticoagulation. However, whether clinical outcomes differ according to indication phenotype (bleeding-dominant versus ischemic-dominant) remains unclear. This study aimed to evaluate the association between indication phenotype and clinical outcomes following LAAO and to determine whether phenotype provides incremental prognostic value beyond traditional risk factors.

Method: In this retrospective single-center study, patients undergoing LAAO were classified as having either a bleeding-dominant or ischemic-dominant indication phenotype. The primary outcome was all-cause mortality. The secondary outcome was a net clinical benefit composite consisting of death, recurrent stroke, or major bleeding. Associations were assessed using Kaplan-Meier and Cox analyses, and the proportional hazards assumption was tested using Schoenfeld residuals. Sensitivity analyses were performed after excluding major bleeding from the composite outcome.

Results: A total of 109 consecutive patients were included. During a median follow-up of approximately 10 months, all-cause mortality occurred in 25.7% of patients, while the net clinical benefit composite occurred in 29.4%. No statistically significant association was observed between indication phenotype and mortality (adjusted hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.38–2.62) or the composite outcome (adjusted HR 0.73, 95% CI 0.30–1.78). However, the wide confidence intervals reflect the limited sample size and event burden.

Conclusion: Among patients undergoing LAAO, no statistically significant differences in short-term clinical outcomes were observed according to indication phenotype. Age emerged as the most consistent determinant of risk. Given the modest sample size, limited number of events, and relatively short follow-up duration, these findings should be interpreted cautiously and considered hypothesis-generating.

Keywords: Atrial fibrillation, clinical outcomes, indication phenotype, left atrial appendage closure, risk stratification

ÖZET

Amaç: Sol atriyal apendiks kapatma (LAAO), uzun süreli antikoagülasyon tedavisi için uygun olmayan atriyal fibrilasyon hastalarında inmenin önlenmesi amacıyla yaygın olarak kullanılmaktadır. Bununla birlikte, klinik sonuçların endikasyon fenotipine göre (kanama ağırlıklı ve iskemik ağırlıklı) farklılık gösterip göstermediği hâlâ belirsizdir. Bu çalışmanın amacı, LAAO sonrası endikasyon fenotipi ile klinik sonuçlar arasındaki ilişkiyi değerlendirmek ve fenotipin geleneksel risk faktörlerinin ötesinde ek bir prognostik değer sağlayıp sağlamadığını belirlemektir.

Yöntem: Bu retrospektif tek merkezli çalışmada, LAAO uygulanan hastalar endikasyona göre kanama dominant veya iskemik dominant olarak sınıflandırılmıştır. Birincil sonuç, tüm nedenlere bağlı mortaliteydi. İkincil sonuç ise ölüm, tekrarlayan inme veya majör kanamadan oluşan net klinik fayda bileşeniydi. İlişkiler Kaplan-Meier ve Cox analizleri kullanılarak değerlendirilmiş, orantılı riskler Schoenfeld kalıntıları ile test edilmiştir. Duyarlılık analizlerinde majör kanama, bileşenden hariç tutulmuştur.

ORIGINAL ARTICLE ARAŞTIRMA MAKALESİ

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Bulgular: Toplam 109 ardışık hasta çalışmaya dahil edildi. Nispeten kısa süreli bir takibi yansıtan yaklaşık 10 aylık medyan takip süresi boyunca, tüm nedenlere bağlı mortalite hastaların %25,7'sinde, net klinik fayda bileşeni ise %29,4'ünde görüldü. Endikasyon fenotipi ile mortalite (düzeltilmiş HR 1,00, %95 CI 0,38-2,62) veya bileşik sonuç (düzeltilmiş HR 0,73, %95 CI 0,30-1,78) arasında istatistiksel olarak anlamlı bir ilişki gözlenmemiştir. Ancak geniş güven aralıkları, sınırlı örneklem büyüklüğünü ve olay yükünü yansıtmaktadır.

Sonuç: LAAO uygulanan hastalarda, endikasyon fenotipine göre kısa vadeli klinik sonuçlarda istatistiksel olarak anlamlı bir fark gözlemlenmedi; buna karşın yaş, riskin en tutarlı belirleyicisi olarak ortaya çıktı. Mütevazı örneklem büyüklüğü, sınırlı olay sayısı ve nispeten kısa takip süresi göz önüne alındığında, bu bulgular dikkatli bir şekilde yorumlanmalı ve hipotez oluşturucu olarak değerlendirilmelidir.

Anahtar Kelimeler: Atriyal fibrilasyon, klinik sonuçlar, endikasyon fenotipi, sol atriyal apendiks kapatma, risk sınıflandırması

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major cause of ischemic stroke, contributing substantially to morbidity and mortality.¹ Oral anticoagulant (OAC) therapy, including vitamin K antagonists or direct oral anticoagulants, is the cornerstone of stroke prevention in patients with AF.² However, OAC therapy is associated with several important challenges, including treatment nonadherence, OAC-related bleeding, and ischemic events despite adequate anticoagulation.^{3,4}

The left atrial appendage is the predominant source of thromboembolism in patients with atrial fibrillation.⁵ Therefore, limitations or contraindications to OAC therapy have led to increasing interest in left atrial appendage closure. Percutaneous left atrial appendage occlusion (LAAO) is a device-based strategy for stroke prevention in AF.⁶ Several studies have shown that LAAO is noninferior for stroke prevention and is associated with a lower risk of bleeding.^{7,8} As procedural experience and case volume have increased over time, the role of LAAO has become more clearly established, and evidence regarding both short- and long-term outcomes has continued to accumulate.⁹

Published single-center real-world data from Türkiye remain limited. Therefore, this study aimed to identify bleeding- and ischemic-predominant indication phenotypes among patients undergoing LAAO and to compare their short-term clinical outcomes.

Materials and Methods

Study Population

This single-center, observational, retrospective cohort study was based on the analysis of consecutive patients who underwent LAAO at the İzmir Katip Çelebi University Cardiology Clinic between January 2020 and December 2025. Because this retrospective study used de-identified data, the requirement for additional informed consent for study participation was waived by the Ethics Committee. Written informed consent for the LAAO procedure had been obtained from all patients as part of routine clinical care. Clinical, laboratory, procedural, and follow-up data were retrospectively collected from the hospital information management system.

ABBREVIATIONS

AF	Atrial fibrillation
DOAC	Direct oral anticoagulant
INR	International normalized ratio
LAAO	Left atrial appendage occlusion
NOAC	Novel oral anticoagulant
NSAIDs	Nonsteroidal anti-inflammatory drugs
OAC	Oral anticoagulant
SAPT	Single antiplatelet therapy
TOE	Transesophageal echocardiography

Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- Age $\geq$ 18 years
- Diagnosis of atrial fibrillation
- Undergoing left atrial appendage occlusion
- Availability of clinical, laboratory, and follow-up data.

The exclusion criterion was missing clinical or follow-up data.

Patient Groups

Patients were categorized into two predefined indication phenotypes:

1. Bleeding-dominant phenotype: prior major bleeding, high HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol) score ($\geq$ 3), or intolerance to OAC therapy.
2. Ischemic-dominant phenotype: thromboembolism despite OAC therapy or contraindication to OAC therapy without a history of major bleeding.

Ethical Considerations

The study protocol was approved by İzmir Katip Çelebi University Health Research Ethics Committee (Approval Number: 0135, Date: 12.02.2026) and was conducted in accordance with the Declaration of Helsinki.

Left Atrial Appendage Closure Procedure

The LAAO procedure was performed according to the implantation protocol of the respective occluder device. In general, LAA anatomy was evaluated using preprocedural transesophageal echocardiography (TOE) and, when necessary, computed tomography. The presence of intracardiac thrombus was excluded before the procedure. Procedures were performed under general anesthesia with fluoroscopic and TOE guidance. The right atrium was accessed via percutaneous femoral venous puncture, followed by transseptal puncture to obtain access to the left atrium. A stiff guidewire was then advanced into the left upper pulmonary vein, and an appropriate delivery sheath was positioned. Left atrial appendage (LAA) angiography was performed using a pigtail catheter. Measurements of the LAA ostium, neck, landing zone, and depth were obtained from TOE and angiographic images. The appropriate occluder device type and size were selected and deployed within the LAA using the delivery system. After confirmation of appropriate device position by TOE and angiography, a tug test was performed, and the device was subsequently released.

Definitions

The CHA₂DS₂-VASc score was calculated by assigning points for congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), prior stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (1 point), age 65–74 years (1 point), and female sex (1 point).¹⁰

The HAS-BLED score was calculated based on the presence of hypertension, abnormal renal/hepatic function, prior stroke, bleeding history, age > 65 years, and concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs). Labile international normalized ratio (INR) was not applicable because the cohort predominantly received non-vitamin K antagonist oral anticoagulant (NOAC) therapy and was therefore coded as 0.¹¹

Statistical Analysis

Statistical analyses were performed using SPSS version 30.0.0.0 (IBM Corp., Armonk, NY, USA) and the R programming language (R Foundation for Statistical Computing, Vienna, Austria; version 4.5.2) within the RStudio environment (Posit PBC, Boston, MA, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Categorical variables are presented as counts and percentages. Student's t-test or analysis of variance was used for comparisons of continuous variables, whereas chi-square or Fisher's exact tests were used for categorical variables. The Kaplan-Meier method was used to estimate cumulative survival probabilities. Candidate variables for the multivariable Cox models included all covariates with a P value < 0.10 in univariable analyses (age, chronic kidney disease, carotid artery disease, left ventricular ejection fraction, hemoglobin, and CHA₂DS₂-VASc score), together with indication phenotype, which was included in all models irrespective of its univariable association. To minimize overfitting given the limited number of events, backward stepwise selection based on the Akaike information criterion was applied, and multicollinearity was assessed using variance inflation factors. Statistical significance was defined as a two-

sided P value < 0.05 . In the final parsimonious models, only age and CHA₂DS₂-VASc score were retained alongside indication phenotype. To explore the potential confounding effect of discharge antithrombotic therapy, additional Cox sensitivity analyses were performed among patients discharged on active antithrombotic therapy by adding direct oral anticoagulant (DOAC)-based versus antiplatelet-based discharge therapy to the base multivariable model.

Results

Study Population and Baseline Characteristics

A total of 109 consecutive patients undergoing left atrial appendage closure were included, of whom 58 (53.2%) were classified as bleeding-dominant and 51 (46.8%) as ischemic-dominant according to clinical indication. Baseline characteristics differed between groups in expected directions, with higher HAS-BLED scores and lower hemoglobin levels observed in the bleeding-dominant phenotype, whereas ischemic-dominant patients had a greater prevalence of prior thromboembolic events and higher CHA₂DS₂-VASc scores. Discharge antithrombotic regimens differed significantly according to indication phenotype, with single antiplatelet therapy (SAPT) used more frequently in the bleeding-dominant group and DOAC therapy used more frequently in the ischemic-dominant group. Other demographic and clinical variables were broadly comparable between groups (Table 1).

Procedural Characteristics

Procedural characteristics and in-hospital outcomes were comparable between phenotypes. Device distribution, procedural success, and length of hospital stay did not differ significantly between groups. Overall in-hospital mortality was low and did not differ according to indication phenotype (Table 2).

Follow-Up and Clinical Outcomes

During a median follow-up of approximately 293 days (IQR 176–468 days), representing relatively short-term follow-up, all-cause mortality occurred in 28 patients (25.7%). Among deceased patients, 10 deaths were classified as cardiovascular, 12 as noncardiovascular, one as periprocedural, and five as of unknown cause. Noncardiovascular deaths included malignancy ($n = 3$), pneumonia ($n = 5$), urosepsis ($n = 3$), and gastrointestinal bleeding ($n = 1$). The cohort was predominantly elderly: 13 patients (11.9%) were younger than 65 years, 40 (36.7%) were aged 65–75 years, and 56 (51.4%) were older than 75 years (Appendix 1). Recurrent stroke occurred in eight patients (7.3%), whereas major bleeding occurred in six patients (5.5%). The net clinical benefit composite endpoint, defined as the time to first occurrence of death, recurrent stroke, or major bleeding, occurred in 32 patients (29.4%).

When expressed as incidence rates, all-cause mortality occurred at approximately 27.9 events per 100 patient-years, recurrent stroke at 8.1 events per 100 patient-years, and major bleeding at 6.4 events per 100 patient-years. The net clinical benefit composite occurred at approximately 34.7 events per 100 patient-years (Appendix 2).

Outcome rates were numerically higher for major bleeding in the bleeding-dominant group, whereas mortality and recurrent stroke rates were similar between phenotypes (Table 3).

Table 1. Baseline characteristics according to indication phenotype

Variables	Bleeding-dominant (n = 58)	Ischemic-dominant (n = 51)	P
Age, years	74.30 ± 8.73	73.84 ± 9.50	0.797
CHA ₂ DS ₂ -VASc score [†]	4.00 [3.00-5.00]	6.00 [5.00-7.00]	< 0.001
HAS-BLED score [†]	4.00 [3.00-4.00]	3.00 [2.50-4.00]	< 0.001
LVEF, % [†]	60.00 [50.00-60.00]	60.00 [53.00-60.00]	1.000
BUN, mg/dL [†]	20.00 [15.00-28.50]	20.00 [16.00-26.50]	0.952
Creatinine, mg/dL [†]	1.17 [0.97-1.45]	1.11 [0.95-1.30]	0.386
Hemoglobin, g/dL [†]	10.50 [9.50-12.00]	12.60 [11.15-13.55]	< 0.001
CRP, mg/L [†]	8.50 [5.00-21.90]	7.00 [2.80-29.00]	0.501
Male sex	29 (50.0%)	30 (58.8%)	0.356
Current smoker	8 (13.8%)	7 (13.7%)	0.992
Diabetes mellitus	29 (50.0%)	20 (39.2%)	0.259
Hypertension	41 (70.7%)	37 (72.5%)	0.830
Coronary artery disease	0.704		
None	24 (41.4%)	17 (33.3%)	
Non-critical disease	14 (24.1%)	13 (25.5%)	
Prior PCI	12 (20.7%)	15 (29.4%)	
Prior CABG	8 (13.8%)	6 (11.8%)	
Heart failure	13 (22.4%)	5 (9.8%)	0.077
Chronic kidney disease	0.034		
None	25 (43.1%)	30 (58.8%)	
CKD	27 (46.6%)	21 (41.2%)	
Dialysis	6 (10.3%)	0 (0.0%)	
Prior stroke/TIA	15 (25.9%)	51 (100.0%)	< 0.001
Peripheral artery disease	3 (5.2%)	5 (9.8%)	0.470
Carotid artery disease	16 (27.6%)	45 (88.2%)	< 0.001
AF type	0.321		
None/unknown	1 (1.7%)	2 (3.9%)	
Paroxysmal	24 (41.4%)	27 (52.9%)	
Persistent	33 (56.9%)	22 (43.1%)	
Baseline anticoagulant therapy	0.263		
Apixaban	15 (25.9%)	15 (29.4%)	
Rivaroxaban	17 (29.3%)	21 (41.2%)	
Edoxaban	5 (8.6%)	4 (7.8%)	
Dabigatran	0 (0.0%)	1 (2.0%)	
VKA	5 (8.6%)	5 (9.8%)	
LMWH	3 (5.2%)	0 (0.0%)	
Discharge antithrombotic regimen	< 0.001		
DAPT	6 (10.3%)	4 (7.8%)	
DOAC	4 (6.9%)	31 (60.8%)	
SAPT	45 (77.6%)	14 (27.5%)	
No antithrombotic therapy	3 (5.1%)	2 (3.9%)	

AF, Atrial fibrillation; BUN, Blood urea nitrogen; CABG, Coronary artery bypass grafting; CHA₂DS₂-VASc, Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category; CKD, Chronic kidney disease, CRP, C-reactive protein; DAPT, Dual antiplatelet therapy; DOAC, Direct oral anticoagulant; HAS-BLED, Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; LMWH, Low-molecular-weight heparin; LVEF, Left ventricular ejection fraction; PCI, Percutaneous coronary intervention; SAPT, Single antiplatelet therapy, TIA, Transient ischemic attack; VKA, Vitamin K antagonist. [†]Values are presented as median (interquartile range (25-75th percentile)).

Table 2. Procedural characteristics and in-hospital outcomes

Variables	Bleeding-dominant (n = 58)	Ischemic-dominant (n = 51)	P
ICU stay, days	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.676
Length of hospital stay, days	6.00 [4.00-10.75]	8.00 [4.50-11.00]	0.510
Occluder type		0.307	
Amulet	26 (44.8%)	23 (45.1%)	
Lambre	32 (55.2%)	28 (54.9%)	
Contrast-induced nephropathy	2 (3.4%)	1 (2.0%)	1.000
In-hospital mortality	2 (3.4%)	0 (0.0%)	0.497

ICU, Intensive care unit.

Table 3. Follow-up clinical outcomes according to indication phenotype

Outcome	Bleeding-dominant (n = 58)	Ischemic-dominant (n = 51)	P
All-cause mortality	15 (25.9%)	13 (25.5%)	0.965
Recurrent stroke	4 (6.9%)	4 (7.8%)	1.000
Major bleeding	5 (8.6%)	1 (2.0%)	0.212
Net clinical benefit composite (death/stroke/major bleeding)	19 (32.8%)	13 (25.5%)	0.406
Recurrent MI	0 (0.0%)	2 (3.9%)	0.217
Heart failure hospitalization	4 (6.9%)	1 (2.0%)	0.369
Repeat revascularization	0 (0.0%)	0 (0.0%)	1.000

MI, Myocardial infarction. Additional descriptive analyses according to discharge antithrombotic regimen are presented in Appendix 3.

In descriptive analyses, discharge antithrombotic regimen was not significantly associated with all-cause mortality, recurrent stroke, major bleeding, or the net clinical benefit composite during follow-up (Appendix 3). Furthermore, exploratory Cox sensitivity analyses restricted to patients discharged on active antithrombotic therapy demonstrated that additional adjustment for DOAC-based versus antiplatelet-based discharge therapy did not materially alter the association between indication phenotype and either all-cause mortality or the net clinical benefit composite. DOAC-based discharge therapy was not significantly associated with either all-cause mortality or the composite outcome (Appendix 4).

Kaplan-Meier Analyses

Kaplan-Meier analysis demonstrated no significant difference in all-cause mortality between bleeding- and ischemic-dominant phenotypes (log-rank $P = 0.947$). Similarly, no significant difference was observed for the net clinical benefit composite outcome (log-rank $P = 0.352$) (Figures 1, 2). Survival curves showed substantial overlap between groups.

Cox Proportional Hazards Regression

All-Cause Mortality

In unadjusted Cox analysis, indication phenotype was not associated with mortality. In multivariable analysis adjusted for age and CHA₂DS₂-VASc score, no statistically significant association was observed between phenotype and mortality (hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.38-2.62, $P = 1.00$). Age showed a nonsignificant trend toward increased risk (HR 1.04 per year, $P = 0.11$), whereas CHA₂DS₂-VASc score was not associated with mortality.

Net Clinical Benefit Composite

For the composite outcome, phenotype was not significantly associated with events in the adjusted analysis (HR 0.73, 95% CI 0.30-1.78, $P = 0.49$). Increasing age was independently associated with a higher risk of events (HR 1.05 per year, $P = 0.039$), whereas CHA₂DS₂-VASc score was not significantly associated with the outcome.

Proportional Hazards Assumption

The proportional hazards assumption was evaluated using Schoenfeld residuals. No violations were observed at the global level for either the mortality or composite models. A borderline time-dependent pattern was noted for the CHA₂DS₂-VASc score, likely reflecting the limited number of events; however, this did not materially affect model validity (Appendix 5).

Event Rates per Patient-Years

Event rates per 100 patient-years were comparable between phenotypes for mortality and recurrent stroke. Major bleeding rates were numerically higher in the bleeding-dominant group, whereas overall composite event rates were similar between groups (Appendix 2).

Sensitivity Analysis

In a sensitivity analysis using an alternative composite endpoint consisting of death and recurrent stroke only, no statistically significant association was observed between phenotype and outcomes (HR 0.92, $P = 0.86$). Age showed a borderline association with risk, and proportional hazards assumptions remained satisfied, supporting the overall consistency of the primary findings during this relatively short follow-up period (Appendix 6).

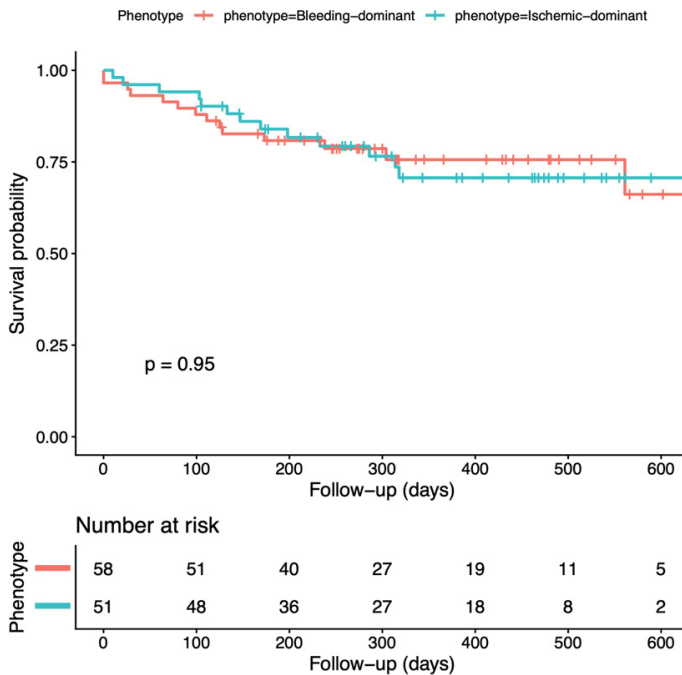


Figure 1. Kaplan-Meier curves for all-cause mortality according to indication phenotype. Kaplan-Meier survival curves illustrating the cumulative incidence of all-cause mortality in patients with bleeding-dominant and ischemic-dominant phenotypes. Differences between groups were assessed using the log-rank test.

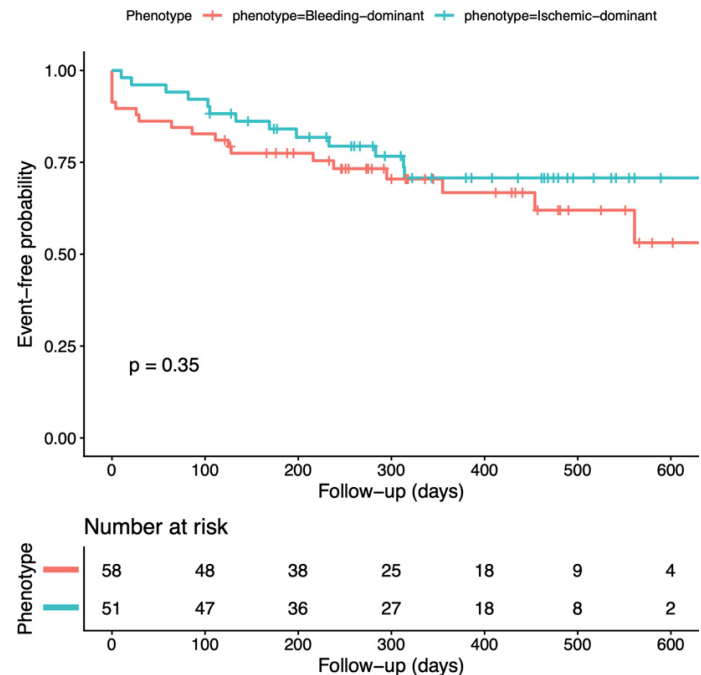


Figure 2. Kaplan-Meier curves for the net clinical benefit composite endpoint. Kaplan-Meier curves showing the cumulative incidence of the net clinical benefit composite endpoint, defined as death, recurrent stroke, or major bleeding, stratified according to indication phenotype. Group comparisons were performed using the log-rank test.

Discussion

Principal Findings

In this single-center cohort of patients undergoing LAAO, indication phenotype was not independently associated with either all-cause mortality or net clinical benefit during short-term follow-up. Across multiple models and sensitivity analyses, increasing age consistently emerged as the principal determinant of adverse outcomes. Importantly, the overall pattern of findings remained similar when major bleeding was excluded from the composite endpoint, although the modest sample size and limited follow-up duration warrant cautious interpretation.

Phenotype and Outcomes After LAAO

In our cohort, short-term clinical outcomes after LAAO appeared broadly similar between bleeding-dominant and ischemic-dominant phenotypes. However, given the modest sample size, limited number of events, and relatively short follow-up duration, these findings do not exclude potentially clinically meaningful differences between groups. Rather, they suggest that overall clinical vulnerability may be at least as important as the initial indication for closure during early follow-up. Larger multicenter studies with longer follow-up are needed to further evaluate this hypothesis. Rather than demonstrating a true "risk-equalizing" effect, these findings are only consistent with the hypothesis that LAAO may attenuate the prognostic impact of the index indication in highly comorbid patients.

Previous large registries, including the EWOLUTION registry (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure

Technology) and the Amulet Observational Study, have shown that outcomes after LAAO are influenced predominantly by baseline comorbidity burden rather than procedural indication alone.¹² In these studies, advanced age, renal dysfunction, and markers of frailty were consistently associated with mortality, whereas the initial indication for device implantation was less predictive of long-term outcomes.¹² Our findings extend these observations by directly comparing predefined indication phenotypes and suggest that phenotype classification alone may not provide substantial incremental prognostic information beyond traditional clinical risk factors during short-term follow-up.

High Short-Term Mortality and Competing Clinical Vulnerability

The relatively high all-cause mortality observed in our cohort should be interpreted in the context of advanced age, multimorbidity, and competing non-cardiovascular risks. More than half of the cohort was older than 75 years, and noncardiovascular causes accounted for a substantial proportion of deaths. In the recent EWOLUTION mortality analysis, the two-year all-cause mortality rate after LAAO was 16.4%, with 50% of deaths attributed to noncardiovascular causes. Independent predictors of mortality included older age, heart failure, vascular disease, valvular disease, abnormal renal function, and abnormal liver function.¹³ In the same analysis, mortality increased progressively with age, from 12.6% among patients aged 65–74 years to 21.1% among those aged 75–84 years and 29.1% among patients aged ≥ 85 years.¹³ These findings support the concept that mortality after LAAO in real-world populations is often driven by overall clinical vulnerability and competing

comorbidity-related risks rather than thromboembolic or device-related events alone. In our cohort, the distribution of deaths related to infection, malignancy, gastrointestinal bleeding, and unknown causes further supports this interpretation.

Role of Age as the Dominant Predictor

Age emerged as the most consistent predictor of adverse outcomes across both mortality and composite analyses. This finding is biologically plausible, as older patients undergoing LAAO frequently have a higher burden of systemic frailty, endothelial dysfunction, and competing risks, including noncardiovascular mortality.

Previous long-term follow-up analyses from the PROTECT AF (Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy) trials similarly demonstrated that age strongly influences survival after LAAO, independent of stroke risk scores.^{14,15} Moreover, contemporary real-world registries have emphasized that patients undergoing LAAO often represent a highly comorbid population in whom age reflects cumulative biological risk.¹⁶

Taken together, our findings reinforce the importance of prioritizing global risk evaluation, rather than procedural indication alone, in patient selection and prognostic assessment after LAAO.

Lack of Association with CHA₂DS₂-VASc Score

Interestingly, the CHA₂DS₂-VAsC score was not independently associated with outcomes in our cohort. This may reflect the fact that the score was originally developed to predict thromboembolic risk rather than mortality or overall clinical vulnerability after LAAO. Several previous studies have reported similar findings, suggesting that although the CHA₂DS₂-VAsC score remains useful for stroke risk stratification, it may have limited discriminatory value for broader clinical outcomes in LAAO populations.¹⁷

Clinical Implications

These findings may have several potential clinical implications:

1. Short-term risk stratification after LAAO may benefit from greater emphasis on age and overall comorbidity burden in addition to indication phenotype.
2. Our findings do not support relying solely on indication phenotype for prognostic assessment, although larger studies are needed before definitive conclusions can be drawn.
3. Early postprocedural follow-up strategies may benefit from incorporating frailty-focused assessment alongside conventional clinical characterization.

Collectively, these findings support a more holistic approach to outcome prediction after LAAO.

Sensitivity Analysis and Robustness

The consistency of findings across sensitivity analyses supports the internal coherence of the study results. Excluding major bleeding from the composite endpoint did not materially alter the association between phenotype and outcomes, suggesting that the overall pattern of findings was similar across different endpoint definitions during the available follow-up period.

However, the limited sample size and relatively short follow-up duration warrant cautious interpretation.

Methodological Considerations

The proportional hazards assumption was satisfied at the global level for all models, with only minor time-dependent patterns observed for the CHA₂DS₂-VAsC score, likely reflecting the limited number of events. These findings support the validity of the Cox modeling approach.

Limitations

This study has several limitations that should be acknowledged. First, the retrospective single-center design may limit the generalizability of the findings to other populations and practice settings. Additionally, the median follow-up duration was relatively short, restricting interpretation to short- to intermediate-term outcomes and precluding firm conclusions regarding longer-term prognosis after LAAO. Second, the sample size was modest and the number of clinical events was limited, resulting in wide confidence intervals and reduced statistical power. Accordingly, the study was not designed to establish equivalence or exclude clinically meaningful differences between indication phenotypes. Third, despite adjustment for key clinical variables, residual confounding cannot be excluded, particularly given the complex clinical profiles of patients undergoing LAAO. Although several baseline variables, including renal function, carotid artery disease, and left ventricular ejection fraction, differed between phenotypes and showed signals of association in univariable analyses, they were not retained in the final multivariable models because of collinearity with the CHA₂DS₂-VAsC score and the limited number of outcome events. Therefore, some degree of residual confounding by these factors remains possible. Discharge antithrombotic regimens also differed between indication phenotypes and were evaluated using descriptive analyses and exploratory Cox sensitivity models. Although these exploratory analyses yielded consistent findings, they should be interpreted cautiously because of the limited number of events and small treatment subgroups. Furthermore, longitudinal changes in antithrombotic therapy after discharge were not systematically captured and may have influenced clinical outcomes.

Fourth, event ascertainment relied on clinical documentation rather than centralized adjudication, which may have introduced misclassification bias, although all available records were systematically reviewed. Fifth, unmeasured variables such as frailty indices, inflammatory burden, malignancy status, or detailed anticoagulation management strategies were not available and may have influenced outcomes. Although causes of death were retrospectively categorized when possible, formal adjudication of cause-specific mortality was not performed, and the cause of death could not be determined in five patients. Sixth, although the proportional hazards assumptions were satisfied at the global level, minor time-dependent patterns observed for the CHA₂DS₂-VAsC score suggest that risk may evolve over time, particularly in small cohorts.

Finally, because the study was not powered to detect modest between-group differences or subgroup-specific effects, the absence of statistically significant differences should not be interpreted as evidence of true equivalence. Accordingly, these findings should be considered hypothesis-generating and require confirmation in larger multicenter cohorts with longer follow-up.

Conclusion

Among patients undergoing LAAO, indication phenotype was not significantly associated with short-term mortality or composite clinical outcomes, whereas age emerged as the most consistent determinant of risk. Given the modest sample size, limited number of events, and relatively short follow-up duration, these findings should be interpreted cautiously and considered hypothesis-generating rather than definitive evidence that prognosis is independent of indication phenotype. Further validation in larger multicenter cohorts with longer follow-up is needed.

Ethics Committee Approval: Ethics committee approval was obtained from Izmir Katip Çelebi University Health Research Ethics Committee (Approval Number: 0135, Date: 12.02.2026).

Informed Consent: Written informed consent for the clinical LAAO procedure was obtained from all patients as part of routine clinical care. For this retrospective analysis of de-identified data, the requirement for additional informed consent for study participation was waived by the institutional review board.

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Appendix 1. Age distribution and causes of death

Variables	n (%)
Age category	
< 65 years	13 (11.9)
65–75 years	40 (36.7)
> 75 years	56 (51.4)
Cause of death among deceased patients	
Cardiovascular death	10 (35.7)
Non-cardiovascular death	12 (42.9)
Periprocedural death	1 (3.6)
Unknown cause of death	5 (17.9)
Components of non-cardiovascular death	
Malignancy	3 (10.7)
Pneumonia	5 (17.9)
Urosepsis	3 (10.7)
Gastrointestinal bleeding	1 (3.6)

Percentages for age categories were calculated using the total study population as the denominator (n = 109). Percentages for causes of death were calculated using deceased patients as the denominator (n = 28).

Appendix 2. Incidence rates per 100 patient-years

Outcome	Group	Events	Person-years	Rate per 100 PY	95% CI
All-cause mortality	Overall	28	100.31	27.9	18.5–40.3
All-cause mortality	Bleeding-dominant	15	55.03	27.3	15.3–45.0
All-cause mortality	Ischemic-dominant	13	45.28	28.7	15.3–49.1
Recurrent stroke	Overall	8	99.25	8.1	3.5–15.9
Recurrent stroke	Bleeding-dominant	4	54.18	7.4	2.0–18.9
Recurrent stroke	Ischemic-dominant	4	45.08	8.9	2.4–22.7
Major bleeding	Overall	6	93.22	6.4	2.4–14.0
Major bleeding	Bleeding-dominant	5	48.08	10.4	3.4–24.3
Major bleeding	Ischemic-dominant	1	45.14	2.2	0.1–12.3
NCB composite	Overall	32	92.31	34.7	23.7–48.9
NCB composite	Bleeding-dominant	19	47.23	40.2	24.2–62.8
NCB composite	Ischemic-dominant	13	45.08	28.8	15.4–49.3

CI, Confidence interval.

Appendix 3. Follow-up clinical outcomes according to discharge antithrombotic regimen

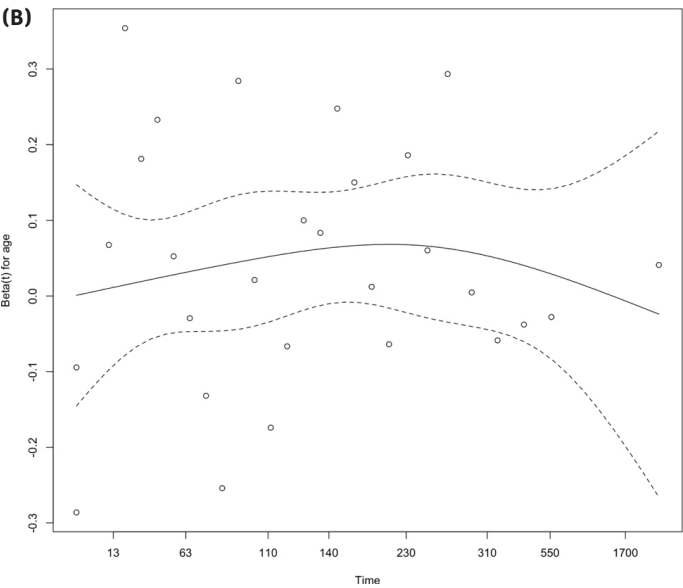
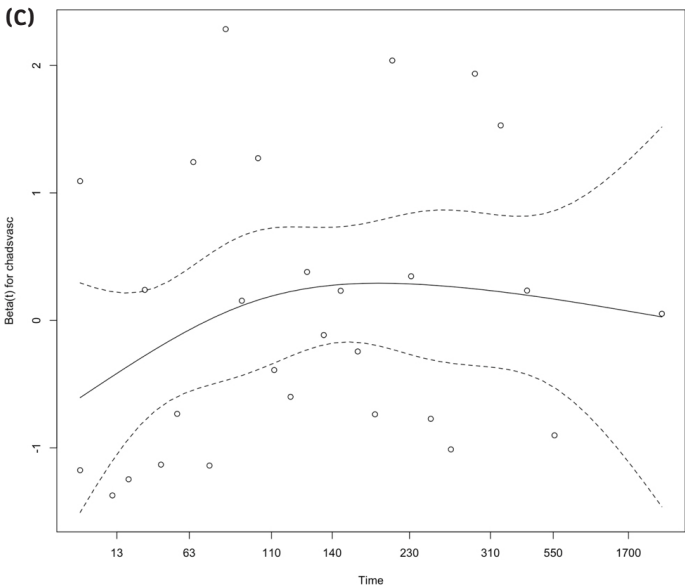
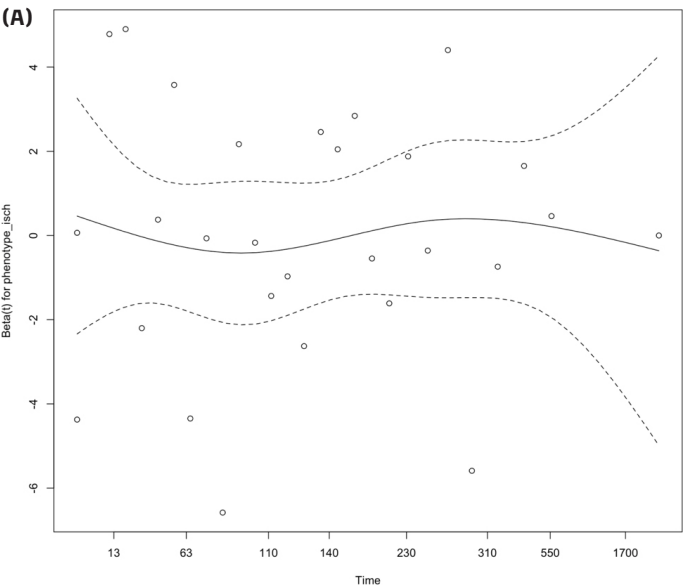
Variables	DAPT (n = 10)	DOAC (n = 35)	SAPT (n = 59)	P
All-cause mortality	4 (40.0%)	7 (20.0%)	13 (22.0%)	0.406
Recurrent stroke	1 (10.0%)	2 (5.7%)	5 (8.5%)	0.851
Major bleeding	1 (10.0%)	0 (0.0%)	4 (6.8%)	0.406
Net clinical benefit composite	4 (40.0%)	7 (20.0%)	17 (28.8%)	0.419

DAPT, Dual antiplatelet therapy; DOAC, Direct oral anticoagulant; SAPT, Single antiplatelet therapy. Descriptive comparisons were restricted to patients discharged on DAPT, DOAC, or SAPT. Patients discharged without antithrombotic therapy (n = 5) were excluded because of the very small sample size.

Appendix 4. Exploratory Cox models comparing DOAC-based versus antiplatelet-based discharge therapy

Outcome	Variables	HR	95% CI	P
All-cause mortality	Ischemic-dominant phenotype	0.98	0.30-3.27	0.978
All-cause mortality	Age, per 1-year increase	1.05	0.99-1.11	0.113
All-cause mortality	CHA ₂ DS ₂ -VASc score, per 1-point increase	1.10	0.79-1.54	0.556
All-cause mortality	DOAC-based discharge therapy	0.81	0.27-2.39	0.697
Net clinical benefit composite	Ischemic-dominant phenotype	0.76	0.25-2.32	0.632
Net clinical benefit composite	Age, per 1-year increase	1.06	1.01-1.12	0.028
Net clinical benefit composite	CHA ₂ DS ₂ -VASc score, per 1-point increase	1.08	0.80-1.45	0.626
Net clinical benefit composite	DOAC-based discharge therapy	0.71	0.25-2.03	0.519

CI, Confidence interval; HR, Hazard ratio. Patients discharged without antithrombotic therapy (n = 5) were excluded because of the very small subgroup size. Direct oral anticoagulant-based (DOAC-based) therapy included apixaban, rivaroxaban, edoxaban, and dabigatran. Antiplatelet-based therapy included dual antiplatelet therapy (DAPT), clopidogrel, and aspirin.



Appendix 5. Assessment of the proportional hazards assumption for key covariates. Scaled Schoenfeld residual plots demonstrating assessment of the proportional hazards assumption for indication phenotype (A), age (B), and CHA₂DS₂-VASc score (C). Solid lines represent smoothed estimates of time-varying effects, and dashed lines indicate approximate 95% confidence intervals. No meaningful deviations from proportionality were observed. The global test yielded P > 0.05 for all models.

Appendix 6. Sensitivity analysis using an alternative composite endpoint

Variables	HR (95% CI)	<i>P</i>	Patients included	Events
Ischemic-dominant phenotype (vs. bleeding-dominant)	0.92 (0.36-2.34)	0.863	109	30
Age (per 1-year increase)	1.05 (95% CI 1.00-1.10)	0.056	109	30
CHA ₂ DS ₂ -VASc score (per 1-point increase)	1.03 (0.76-1.39)	0.856	109	30

CI, Confidence interval; HR, Hazard ratio

Artificial Intelligence-Enhanced Risk Stratification in Non-ST-Segment Elevation Myocardial Infarction: The Incremental Prognostic Value of the Modified Glasgow Prognostic Score in Predicting 36-Month Mortality

ST Segment Yükselmesi Miyokard Enfarktüsünde Yapay Zeka Destekli Risk Katmanlaştırması: 36 Aylık Mortaliteyi Öngörmeye Modifiye Glasgow Prognostik Skoru'nun İlave Prognostik Değeri

ABSTRACT

Objective: Current clinical guidelines for non-ST-segment elevation myocardial infarction (NSTEMI) emphasize the duration of dual antiplatelet therapy (DAPT) based on scores such as the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score and the Dual Antiplatelet Therapy (DAPT) score. However, these anatomical and clinical models often overlook the "inflammatory gap," namely the contribution of systemic inflammation to both thrombotic and hemorrhagic risk. Although traditional models focus primarily on anatomical complexity, systemic inflammation may serve as a silent driver of adverse outcomes. We aimed to evaluate, using an artificial intelligence (AI)-enhanced approach, the incremental prognostic value of the inflammation-based Modified Glasgow Prognostic Score (mGPS) over a 36-month follow-up period, with particular emphasis on capturing non-linear interactions between biological markers and long-term outcomes.

Method: This study included 456 NSTEMI patients who underwent percutaneous coronary intervention (PCI). mGPS, DAPT, and PRECISE-DAPT scores were calculated for all patients. Prognostic performance was assessed using a Gradient Boosting Machine (GBM)-based machine learning (ML) framework. Analyses focused on improvements in the concordance index (C-index), Net Reclassification Index (NRI), and Integrated Discrimination Improvement (IDI), as well as three-year mortality assessed using Cox proportional hazards modeling to identify residual inflammatory risk. Model calibration was evaluated using the Brier score.

Results: At 36 months, mGPS emerged as the strongest independent predictor of mortality. Compared with patients with mGPS 0, those with mGPS 2 demonstrated a 6.18-fold higher risk of mortality (hazard ratio 6.18; 95% confidence interval 2.95–12.94; $P < 0.001$). Observed mortality rates increased markedly from 3.2% in the mGPS 0 group to 57.1% in the mGPS 2 group ($P < 0.001$). While mGPS was not significantly associated with the ischemic DAPT score ($P = 0.349$), it was strongly associated with high bleeding risk (PRECISE-DAPT ≥ 25), with all patients in the mGPS 2 category classified as high bleeding risk ($P < 0.001$). Incorporation of mGPS into the baseline AI model significantly improved discriminative performance, increasing the C-index from 0.72 to 0.81 ($P = 0.008$). Additionally, the model correctly reclassified 46% of patients (NRI 0.46, $P < 0.001$) and demonstrated significant predictive improvement (IDI 0.08, $P = 0.004$) compared with traditional scoring systems.

Conclusion: Systemic inflammation, as quantified by mGPS, is a critical biological modifier of cardiovascular risk that may help bridge the "inflammatory gap" in current scoring systems. AI-driven integration of mGPS into conventional clinical scores significantly improves 36-month prognostic reclassification. mGPS appears to function as a biological recalibrator, identifying high-risk individuals who may be misclassified by conventional scoring systems. These findings suggest that mGPS-guided personalized antiplatelet strategies—particularly early DAPT de-escalation in patients with elevated mGPS—may help reduce the high mortality and bleeding risk observed in this vulnerable population by addressing biological fragility in addition to anatomical risk.

Keywords: DAPT, machine learning, mGPS, NSTEMI, PRECISE-DAPT, systemic inflammation, three-year mortality

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ÖZET

Amaç: Güncel NSTEMI kılavuzları, ikili antiplatelet tedavi (DAPT) süresini PRECISE–DAPT ve DAPT gibi skorlamalar üzerinden anatomik ve klinik verilere dayanarak belirlemektedir. Ancak bu modeller, hem trombotik hem de hemorajik riski tetikleyen temel bir mekanizma olan "inflamatuvar boşluk" (inflammatory gap) olgusunu, yani sistemik inflamasyonun rolünü, sıklıkla göz ardı etmektedir. Geleneksel modeller anatomik karmaşıklığa odaklansa da sistemik inflamasyon, olumsuz olayların sessiz bir itici gücü olarak işlev görebilir. Bu çalışmada, biyolojik belirteçler ile uzun dönem sonuçlar arasındaki doğrusal olmayan etkileşimleri yakalamak amacıyla inflamasyon temelli Modifiye Glasgow Prognostik Skoru'nun (mGPS) 36 aylık takip sürecindeki ilave prognostik değerini yapay zeka (AI) algoritmaları aracılığıyla değerlendirmeyi hedefledik.

Yöntem: Çalışma, perkütan koroner girişim (PKG) uygulanan 456 NSTEMI hastasının AI entegrasyonlu analizini kapsamaktadır. Tüm hastalar için mGPS, DAPT ve PRECISE–DAPT skorları hesaplandı. Prognostik performans, "rezidüel inflamatuvar riski" tanımlamak amacıyla Gradient Boosting Machine (GBM) tabanlı bir makine öğrenmesi (ML) çerçevesi kullanılarak C–indeksi artışı, Net Yeniden Sınıflandırma İndeksi (NRI) ve Entegre Ayırım İyileştirmesi (IDI) üzerinden analiz edildi. Üç yıllık mortalite Cox oransal tehlikeler modellemesi ile değerlendirilirken model kalibrasyonu Brier skoru ile doğrulandı.

Bulgular: Otuz altı aylık takip sonunda mGPS, mortalitenin en güçlü bağımsız prediktörü olarak öne çıktı. mGPS 0 olan hastalarla kıyaslandığında, mGPS 2 grubundaki hastalar 6,18 kat artmış mortalite riski sergiledi (HR 6,18; %95 GA 2,95–12,94; $P < 0,001$). Gözlemlenen mortalite oranları mGPS 0 grubunda %3,2 iken mGPS 2 grubunda %57,1'e yükseldi ($P < 0,001$). mGPS, iskemik DAPT skoru ile anlamlı bir korelasyon göstermezken ($P = 0,349$), yüksek kanama riski (PRECISE–DAPT ≥ 25) ile güçlü bir ilişki sergiledi; mGPS 2 grubundaki hastaların tamamı (%100) yüksek kanama riski kategorisinde yer aldı ($P < 0,001$). mGPS'in bazal AI modeline entegrasyonu, ayırım gücünü anlamlı şekilde artırarak C–indeksini 0,72'den 0,81'e yükseltti ($P = 0,008$), hastaların %46'sını doğru şekilde yeniden sınıflandırdı (NRI 0,46; $P < 0,001$) ve geleneksel skorlara kıyasla belirgin bir prediktif kazanç sağladı (IDI 0,08; $P = 0,004$).

Sonuç: mGPS ile kantifiye edilen sistemik inflamasyon, mevcut risk skorlama sistemlerindeki "inflamatuvar boşluğu" kapatan kritik bir biyolojik modifikatördür. mGPS'in yapay zeka tabanlı modellere entegrasyonu, 36 aylık süreçte üstün bir prognostik yeniden sınıflandırma sunmaktadır. mGPS, geleneksel skorlar tarafından yanlış sınıflandırılan yüksek riskli bireyleri tanımlayan bir "biyolojik rekaliibratör" işlevi görür. Bu bulgular, mGPS rehberliğinde geliştirilecek kişiselleştirilmiş antiplatelet stratejilerinin, özellikle yüksek mGPS'li hastalarda erken DAPT de-eskale edilmesinin, anatomik riskin yanı sıra biyolojik kırılganlığı da hedefleyerek bu hassas kohorttaki yüksek mortalite ve kanama riskini azaltabileceğini düşündürmektedir.

Anahtar Kelimeler: DAPT, makine öğrenmesi, mGPS, NSTEMI, PRECISE–DAPT, sistemik inflamasyon, üç yıllık mortalite

Acute coronary syndromes (ACS), particularly non–ST-segment elevation myocardial infarction (NSTEMI), remain a leading cause of cardiovascular morbidity and mortality worldwide. Following percutaneous coronary intervention (PCI), determining the optimal duration of dual antiplatelet therapy (DAPT) is a major clinical challenge, requiring a careful balance between the prevention of recurrent ischemic events and the minimization of major bleeding complications.¹ Current guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommend the use of structured risk scores, including the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE–DAPT) score and the Dual Antiplatelet Therapy (DAPT) score, to guide the duration of antithrombotic therapy. Nevertheless, despite adherence to these recommendations, a substantial proportion of patients continue to experience residual risk events that are not adequately predicted by traditional models.^{2,3}

Although widely adopted, conventional scoring systems are largely based on clinical history, procedural characteristics, and baseline demographic variables. A major limitation of these models is the lack of direct incorporation of systemic inflammation, a key driver of atherosclerosis, plaque instability, and adverse clinical outcomes. This diagnostic blind spot may be conceptualized as the "inflammatory gap," in which subclinical systemic inflammation remains undetected by standard anatomical and clinical assessments. Previous studies have demonstrated that inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hs-CRP), are associated not only with increased ischemic risk but also with higher bleeding susceptibility through effects on vascular integrity and coagulation pathways.^{4,5}

The modified Glasgow Prognostic Score (mGPS), which combines serum C-reactive protein and albumin levels, is a validated marker of systemic inflammatory response and nutritional status. Unlike isolated biomarkers, mGPS captures a

broader state of "biological fragility" by integrating inflammatory burden (CRP) with host metabolic reserve (albumin). Although initially developed for oncological prognostication, mGPS has recently gained attention in cardiovascular medicine because of its ability to predict major adverse cardiovascular events (MACE) and mortality. However, the incremental value of mGPS in refining the risk-benefit assessment of DAPT, particularly within artificial intelligence (AI)-based predictive frameworks, remains insufficiently explored in NSTEMI populations.^{6,7}

In the era of precision medicine, AI-based algorithms offer the ability to identify complex, non-linear interactions between biological markers and clinical scores that may not be adequately captured by conventional statistical approaches. Traditional linear models may underestimate the synergistic effects of hypoalbuminemia and elevated C-reactive protein (CRP) levels on vascular outcomes. Integrating mGPS into established risk stratification systems may therefore help identify residual inflammatory risk that significantly modifies the prognostic utility of PRECISE-DAPT and DAPT scores.⁸

Accordingly, this study aimed to evaluate the incremental prognostic value of mGPS in NSTEMI patients during a 36-month follow-up period. Using an AI-enhanced framework, we investigated the relationship between systemic inflammation and conventional DAPT risk scores to establish a more comprehensive model for personalized antiplatelet therapy and long-term mortality prediction. We hypothesized that mGPS acts as a biological recalibrator, identifying high-risk individuals who may be misclassified by conventional anatomical risk models.^{9,10}

Materials and Methods

Study Design and Population

This retrospective, single-center, observational cohort study was conducted at the cardiology clinic of a tertiary care center. A total of 456 consecutive adult patients (≥ 18 years) diagnosed with NSTEMI between January 1, 2023 and September 30, 2023, were initially screened. Patient selection followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and is illustrated in the study flowchart (Figure 1). All enrolled patients underwent invasive coronary angiography followed by successful revascularization with either percutaneous coronary intervention or coronary artery bypass grafting (CABG). To ensure data integrity, all procedural and clinical records were independently reviewed and cross-verified by two cardiologists. The study protocol was approved by Ethics Committee of Giresun Training and Research Hospital (Approval Number: 23.07.2025/22, Date: 23.07.2025) and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Owing to the retrospective design of the study, the requirement for informed consent was waived by the institutional review board.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

1. Age ≥ 18 years;
2. Confirmed diagnosis of NSTEMI;
3. Successful invasive revascularization; and

ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndromes
AI	Artificial intelligence
C-index	Concordance index
CABG	Coronary artery bypass grafting
CRP	C-reactive protein
DAPT	Dual antiplatelet therapy
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GBM	Gradient Boosting Machine
hs-CRP	High-sensitivity C-reactive protein
IDI	Integrated Discrimination Improvement
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
mGPS	Modified Glasgow Prognostic Score
ML	Machine learning
NRI	Net Reclassification Index
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PRECISE-DAPT	Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy
STEMI	ST-segment elevation myocardial infarction
VIF	Variance inflation factor

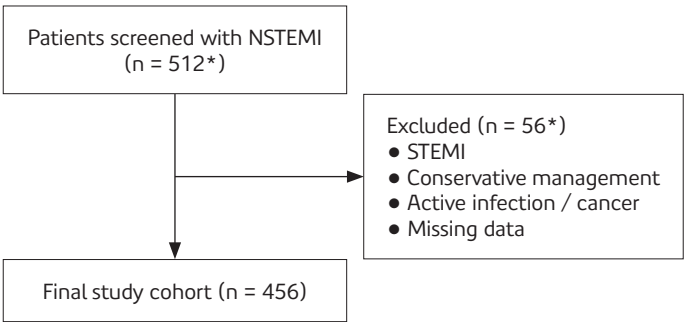


Figure 1. STROBE flowchart of patient selection.

Study flowchart of patient selection according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The diagram illustrates the process of identifying and enrolling 456 patients with non-ST-segment elevation myocardial infarction (NSTEMI) who underwent successful percutaneous coronary intervention (PCI). It also demonstrated the application of stringent inclusion and exclusion criteria, including the exclusion of patients with active infections or malignancies, to better isolate residual inflammatory risk.

4. Complete laboratory data, including CRP, albumin, and hematological parameters.
- To minimize confounding factors affecting systemic inflammation and to better isolate "residual inflammatory risk," the following exclusion criteria were applied:
1. ST-segment elevation myocardial infarction (STEMI);
 2. Conservative management without procedural treatment;
 3. Active infection, known malignancy, or autoimmune disease, which could distort baseline mGPS values; and
 4. Missing clinical or laboratory data required for score calculation.

Baseline Definitions and Scoring Systems

NSTEMI was defined according to the Fourth Universal Definition of Myocardial Infarction. Three validated scoring systems were calculated for each patient at admission:

- **Modified Glasgow Prognostic Score (mGPS):** Patients with CRP $10 \leq$ mg/L received a score of 0 regardless of albumin level. Patients with CRP > 10 mg/L and albumin ≥ 35 g/L received a score of 1, whereas patients with CRP > 10 mg/L and albumin < 35 g/L received a score of 2.
- **PRECISE-DAPT Score:** This score was calculated using age, creatinine clearance, hemoglobin level, white blood cell count, and history of spontaneous bleeding. A PRECISE-DAPT score ≥ 25 was defined as high bleeding risk.
- **DAPT Score:** The DAPT score was assessed 12 months after intervention and incorporated age, diabetes mellitus, smoking status, prior myocardial infarction or PCI, stent diameter (< 3 mm), stent type, and left ventricular ejection fraction. A score ≥ 2 was considered indicative of potential net benefit from prolonged DAPT.

For the AI modeling framework, mGPS, PRECISE-DAPT, and DAPT scores were analyzed as both categorical and continuous variables to capture the full spectrum of risk and improve predictive granularity.

Outcomes and 36-Month Follow-Up

The primary endpoint was all-cause mortality at 36 months, representing an extension of six months beyond the original 30-month thesis evaluation period to capture late clinical events. Clinical outcome data were obtained from electronic health records, national death registries, and telephone follow-up interviews conducted by investigators blinded to baseline risk scores to minimize bias.

Statistical Analysis and AI Modeling Framework

Statistical analyses were performed using JAMOVI (version 2.3.28; The jamovi Project, Sydney, Australia) and Python-based Scikit-learn frameworks. Continuous variables were assessed for normality using the Shapiro-Wilk test. To ensure the stability of the Cox models, the proportional hazards assumption was assessed using Schoenfeld residuals. Multicollinearity among predictors was assessed using the variance inflation factor (VIF), with values < 5 considered indicative of acceptable model stability. To evaluate the incremental prognostic value of mGPS, a three-tier analytical strategy was employed:

1. **Survival Analysis:** Thirty-six-month survival outcomes were analyzed using Cox proportional hazards regression to determine hazard ratios (HR) for mGPS relative to standard risk scores.
2. **AI-Driven Feature Importance:** Gradient Boosting Machine (GBM) and Random Forest algorithms were used to identify complex non-linear relationships and rank the predictive importance of each variable. To reduce overfitting and improve generalizability, 10-fold cross-validation was applied during model training. Hyperparameters were optimized by minimizing the Brier Score, with mGPS included as a key biological feature.

3. **Model Performance and Reclassification Analysis:** The incremental discriminative value of adding mGPS to a baseline model consisting of age, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and PRECISE-DAPT score was assessed using the concordance index (C-index), Net Reclassification Index (NRI), and Integrated Discrimination Improvement (IDI). These metrics enabled quantification of the clinical utility of mGPS in improving patient risk classification.

Model calibration was evaluated using the Brier score. To compare model performance, 95% confidence intervals for C-indices were calculated, and the DeLong test was used to assess incremental improvement. Reclassification performance was evaluated using the continuous NRI and IDI. To ensure model robustness, a GBM was used as the final predictive model, with hyperparameter optimization performed through a 10-fold cross-validation grid search aimed at minimizing the Brier score. A two-sided P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics and Risk Score Distribution

The study cohort consisted of 456 patients with NSTEMI, with a mean age of 66.7 ± 10.9 years. Most patients were male (76.3%). Baseline laboratory evaluation demonstrated a mean CRP level of 17.1 ± 31.1 mg/L and a mean albumin level of 41.3 ± 4.3 g/L. The distribution of mGPS indicated that more than one-third of the study population exhibited evidence of systemic inflammatory activation (mGPS 1 or 2)

- mGPS 0: 285 patients (62.5%)
- mGPS 1: 150 patients (32.9%)
- mGPS 2: 21 patients (4.6%).

With respect to dual antiplatelet therapy risk stratification, 31.2% of patients were categorized as high bleeding risk (PRECISE-DAPT ≥ 25), whereas 60.2% were classified as high ischemic risk (DAPT score ≥ 2) (Table 1).

Association Between mGPS and Clinical Risk Scores

A highly significant association was observed between systemic inflammation, as measured by mGPS, and the PRECISE-DAPT bleeding risk score ($P < 0.001$). Notably, all patients in the mGPS 2 category were classified as high bleeding risk, compared with only 9.0% of patients in the mGPS 0 group. In contrast, no significant association was observed between mGPS and the DAPT ischemic risk score ($\chi^2 = 2.11$, $P = 0.349$). This divergence suggests that inflammatory burden represents a distinct biological dimension that is largely independent of conventional anatomical and ischemic risk assessment.

Long-Term Outcomes and 36-Month Survival Analysis

At the initial 30-month follow-up, 36 deaths (11.8%) had been recorded. Extension to a 36-month follow-up period, incorporating the additional six months of data, further accentuated the prognostic differences among mGPS categories. Mortality rates increased progressively with inflammatory burden:

- 3.2% in mGPS 0
- 22.0% in mGPS 1
- 57.1% in mGPS 2 ($P < 0.001$).

Table 1. Baseline clinical, laboratory, and risk profile according to Modified Glasgow Prognostic Score (mGPS) groups

Variables	Total population (n=456)	mGPS 0 (n=285)	mGPS 1 (n=150)	mGPS 2 (n=21)	P
Demographics					
Age (years), mean±SD	66.7±10.9	65.4±11.2	68.1±10.4	72.3±8.1	<0.001
Male, n (%)	348 (76.3%)	217 (76.1%)	115 (76.7%)	16 (76.2%)	0.992
Laboratory parameters					
CRP (mg/L), mean±SD	17.1±31.1	4.2±2.8	32.4±15.6	82.3±44.2	<0.001
Albumin (g/L), mean±SD	41.3±4.3	42.8±3.1	39.7±3.4	31.2±2.8	<0.001
Clinical risk scores					
PRECISE-DAPT ≥25, n (%)	142 (31.2%)	26 (9.0%)	95 (63.3%)	21 (100.0%)	<0.001
DAPT Score ≥2, n (%)	274 (60.2%)	175 (61.4%)	87 (58.0%)	12 (57.1%)	0.349
Outcome					
36-Month Mortality, n (%)	54 (11.8%)	9 (3.2%)	33 (22.0%)	12 (57.1%)	<0.001

*The Dual Antiplatelet Therapy (DAPT) score is conventionally assessed at 12 months after percutaneous coronary intervention (PCI); however, in the present study, it was included as a baseline projection of anticipated 12-month ischemic risk to enable direct comparison with the biological baseline risk represented by the modified Glasgow Prognostic Score (mGPS). †Thirty-six-month mortality was defined as the primary clinical outcome and is presented in this table to provide a comprehensive overview of the prognostic divergence across mGPS groups. Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as n (%). P values were calculated using analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.

Table 2. Multivariate Cox proportional hazards model for 36-month mortality

Variables	HR	95% CI	P
mGPS 1 (vs 0)	3.42	1.85–6.32	<0.001
mGPS 2 (vs 0)	6.18	2.95–12.94	<0.001
PRECISE-DAPT score	1.05	1.01–1.09	0.024
DAPT Score	0.94	0.78–1.14	0.542
LVEF <40%	1.82	0.88–3.75	0.108
eGFR < 60 mL/min/1.73 m ²	1.12	0.65–2.14	0.412

*The multivariate model was adjusted for age, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score. †The proportional hazards assumption was confirmed using Schoenfeld residuals, and multicollinearity was excluded based on variance inflation factor (VIF) values < 5.0. CI, Confidence interval; HR, Hazard ratio; mGPS, Modified Glasgow Prognostic Score.

Multivariate Cox regression analysis identified mGPS as the strongest predictor of long-term mortality. Specifically, patients in the mGPS 2 group demonstrated a markedly increased risk of 36-month mortality compared with those in the mGPS 0 group (HR: 6.18; 95% confidence interval [CI]: 2.95–12.94; $P < 0.001$) (Table 2, Figure 2). The corresponding "number at risk" table for each follow-up interval is presented below the survival curves to ensure transparency in the longitudinal survival analysis.

AI-Driven Incremental Value and Reclassification

Integration of mGPS into the baseline predictive model, which included PRECISE-DAPT score and conventional clinical variables, resulted in substantial improvements in predictive performance within the AI-based framework (Figure 3).

Model discrimination improved significantly, with the C-index increasing from 0.72 (95% CI: 0.68–0.76) to 0.81 (95%

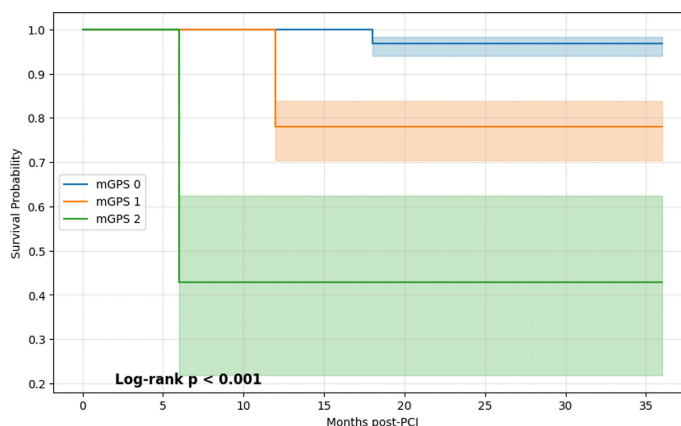


Figure 2. Kaplan-Meier survival curves for 36-month all-cause mortality stratified according to the modified Glasgow Prognostic Score (mGPS). The curves demonstrate significant divergence in survival across the 36-month follow-up period according to baseline inflammatory status. Patients in the mGPS 2 group, characterized by elevated C-reactive protein (CRP) and low albumin levels, exhibited the lowest survival rates, corresponding to a 6.18-fold increase in mortality risk compared with the mGPS 0 group ($P < 0.001$).

CI: 0.77–0.85) following the addition of mGPS ($P = 0.008$, DeLong test).

Incorporation of mGPS also resulted in a continuous NRI of 0.46 (95% CI: 0.28–0.64; $P < 0.001$) and an IDI of 0.08 ($P = 0.004$).

The final AI model demonstrated high predictive accuracy, with a Brier score of 0.091, indicating excellent agreement with the observed clinical outcomes (Figure 4).

Beyond traditional discrimination metrics, the clinical utility of the modified approach was further supported by improved patient reclassification. Incorporation of systemic inflammatory burden into the predictive model resulted in a significant incremental gain in classification accuracy (NRI: 0.46, $P < 0.001$).

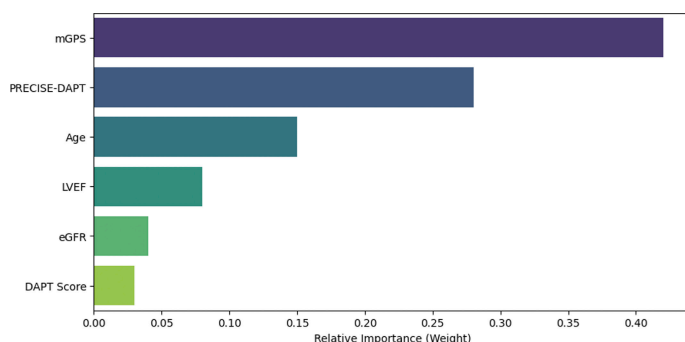


Figure 3. Artificial intelligence (AI)-driven feature importance ranking derived from the Gradient Boosting Machine (GBM) framework. The figure illustrates the relative predictive contribution of clinical and biological variables for 36-month mortality. The modified Glasgow Prognostic Score (mGPS) emerged as the strongest biological predictor, providing significant incremental prognostic value beyond traditional scoring systems, including the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score and the Dual Antiplatelet Therapy (DAPT) score.

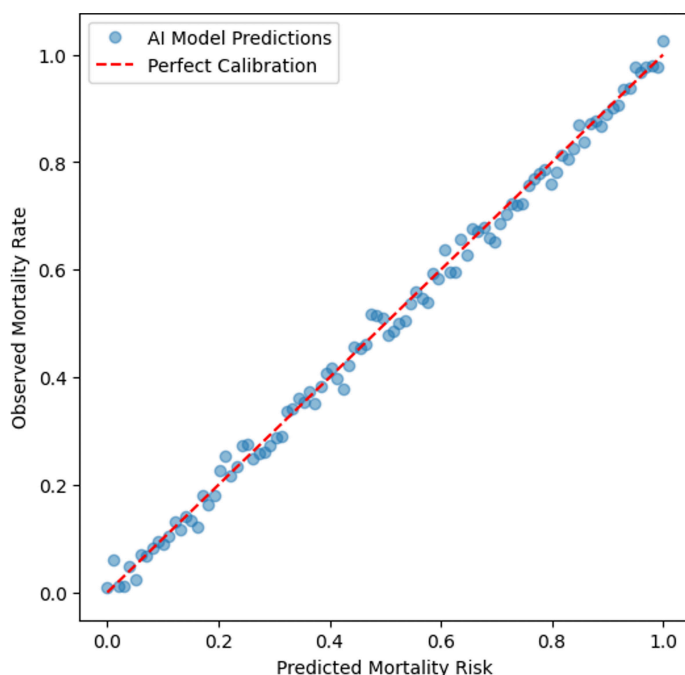


Figure 4. Calibration plot for prediction of 36-month mortality using the artificial intelligence-based model. The scatter plot and calibration curve demonstrate strong agreement between mortality risk predicted by the artificial intelligence (AI) model and the observed mortality rate (Brier score: 0.091).

Discussion

Our AI-enhanced analysis demonstrated a 46% improvement in the Net Reclassification Index for 36-month mortality following integration of the mGPS into standard risk stratification models. This finding is clinically important, as it suggests that nearly half (46%) patients with NSTEMI may be inadequately classified by current guideline-based approaches. Recent studies published in this journal have similarly emphasized the need to incorporate novel inflammatory biomarkers into acute coronary syndrome

risk stratification models to improve long-term prognostic accuracy in the contemporary PCI era.¹¹⁻¹³

The principal finding of this study is that mGPS, a simple and cost-effective marker of systemic inflammation, provides substantial incremental prognostic value beyond conventional clinical risk scores in NSTEMI patients. Integration of mGPS into the predictive framework significantly improved 36-month mortality discrimination and patient reclassification, highlighting the limitations of purely anatomical risk assessment models and emphasizing the importance of incorporating biological markers of inflammation into clinical decision-making. Furthermore, while mGPS demonstrated a strong association with high bleeding risk, it showed no correlation with anatomical ischemic risk, thereby identifying a distinct "inflammatory gap" within current risk stratification paradigms.¹³⁻¹⁶

The complete overlap between mGPS 2 and high bleeding risk further suggests that systemic inflammation is a major contributor to biological fragility. These findings are consistent with contemporary data from Turkish NSTEMI populations showing that bleeding complications and long-term mortality remain significant challenges despite advances in interventional techniques. Consequently, mGPS may serve as a "biological recalibrator," identifying high-risk patients who might otherwise remain undetected using anatomical risk scores alone.¹⁷

The Inflammatory Paradox: Bleeding Versus Ischemia

One of the most striking observations in our cohort was the complete overlap between mGPS 2 and high bleeding risk as defined by the PRECISE-DAPT score. This finding suggests that systemic inflammation, reflected by elevated C-reactive protein levels and hypoalbuminemia, is not merely a marker of cardiac injury but also an indicator of vascular and biological fragility. Although conventional scores such as the PRECISE-DAPT score focus on factors such as age and baseline hemoglobin level, they often overlook cytokine-driven endothelial dysfunction that may predispose patients to hemorrhagic complications.¹⁸

In contrast, the absence of a significant association between mGPS and the DAPT ischemic risk score ($P = 0.349$) indicates that inflammatory burden represents a distinct biological dimension that is largely independent of anatomical risk. While DAPT scores primarily reflect procedural complexity, mGPS appears to identify "biological fragility," which may contribute more directly to systemic mortality and bleeding risk through cytokine-driven endothelial dysfunction rather than recurrent stent thrombosis. Our findings suggest that, in patients with elevated mGPS, the potential ischemic benefit of prolonged DAPT may be outweighed by a disproportionately increased risk of bleeding and mortality, thereby creating a "biological mismatch" within conventional therapeutic decision-making frameworks.¹⁹

Prognostic Superiority of mGPS in Long-Term Mortality

The extended 36-month follow-up of our cohort further established mGPS as a powerful independent predictor of mortality, with patients in the mGPS 2 category demonstrating a 6.18-fold increase in mortality risk. Systemic inflammation is a well-recognized driver of adverse outcomes in acute coronary syndromes. Elevated CRP levels reflect active plaque inflammation and myocardial injury, whereas hypoalbuminemia

serves as a surrogate marker for both chronic malnutrition and the severity of the inflammatory response. Our findings are consistent with previous evidence suggesting that, in patients with NSTEMI, the inflammatory milieu may exert a greater influence on long-term survival than the severity of the index ischemic event itself.²⁰

Clinical Implications and AI-Driven Precision Medicine

Integration of mGPS into the AI-based predictive framework yielded a C-index of 0.81, representing a substantial improvement in discriminative performance compared with baseline models. These findings reinforce the growing recognition that a uniform approach to DAPT duration is increasingly inadequate in the era of precision medicine. Patients with elevated mGPS despite moderate anatomical risk may particularly benefit from earlier DAPT de-escalation strategies, such as transition to P2Y12 inhibitor monotherapy after one or three months, to reduce bleeding and mortality risk. Our AI-driven framework suggests that mGPS may function as a "biological recalibrator," capable of refining the decision thresholds of existing DAPT algorithms according to the patient's underlying systemic burden.^{21,22}

Limitations

A primary limitation of this study is the relatively small sample size of the mGPS 2 subgroup (n = 21). Although the observed hazard ratio was substantial (HR 6.18) and statistically significant (P < 0.001), these results should be considered hypothesis-generating and require validation in larger cohorts. Additionally, specific causes of death could not always be definitively adjudicated; therefore, mortality was analyzed as an all-cause composite endpoint. This study is also subject to the inherent limitations of a retrospective, single-center design. Although the 36-month follow-up period provides robust prognostic insight, external validation in larger multicenter prospective studies remains necessary. Finally, because systemic inflammation is dynamic, a single baseline measurement of mGPS may not fully capture temporal changes in inflammatory status during long-term follow-up.

Conclusion

Systemic inflammation, as quantified by mGPS, represents a critical yet frequently overlooked dimension of risk in patients with NSTEMI. By integrating this biological marker into conventional risk models through an AI-based framework, we achieved superior prediction of three-year mortality and improved patient reclassification. Incorporation of mGPS into routine clinical practice may facilitate more individualized antithrombotic treatment strategies and improve long-term outcomes in this high-risk population by helping bridge the "inflammatory gap" in contemporary risk assessment.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Giresun Training and Research Hospital (Approval Number: 23.07.2025/22, Date: 23.07.2025).

Informed Consent: The requirement for informed consent was waived by the institutional review board.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance: Artificial intelligence frameworks (including Gradient Boosting Machine and Random Forest via Scikit-learn/Python) were utilized for data analysis and predictive modeling to capture non-linear interactions between biological markers and mortality. No generative AI was used in this manuscript.

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The e-Consultation Paradox in Cardiology: The Conflict Between the Clinical Agility of Instant Messaging and Medicolegal Concerns Created by Current Legislation

Türkiye'de Kardiyolojide Anlık Mesajlaşma ile e-Konsültasyon: Klinik Kullanım, Veri Kalitesiyle İlişkili Tedavi Gecikmeleri ve Medikolegal Kaygı

ABSTRACT

Objective: To evaluate the clinical use of instant-messaging e-consultation among cardiologists in Türkiye, self-reported treatment delays attributed to the perceived quality of transmitted data, and variations in medicolegal concern according to professional seniority.

Method: A total of 253 cardiologists completed a cross-sectional online survey covering consultation patterns, acute myocardial infarction (AMI)-related support, types of shared data, data quality-related treatment delays, regulatory awareness, and the 15-item Medicolegal Implications of Digital Consultation in Cardiology Scale (MIDCCS). The primary analysis compared MIDCCS domain scores across seniority groups using the Kruskal-Wallis H test with Holm-Bonferroni correction; a single-item ordinal regression analysis of global concern was exploratory.

Results: Among current users, 86.9% (213/245) reported at least one AMI-related informal support activity: preliminary assessment, 71.5%; triage, 60.1%; catheterization laboratory activation support, 36.4%; and early management, 42.7%. The most frequently shared data type was the ECG (95.2%). A self-reported treatment delay attributed to perceived poor data quality was reported by 23.7% (58/245), most commonly involving ECG photographs. Medicolegal concern differed markedly across seniority groups after correction ($P < .001$ in every domain), with specialists and faculty members scoring higher than residents. In an exploratory ordinal model, a history of treatment delay was directionally but nonsignificantly associated with greater concern (common OR=1.711; 95% CI, 0.994–2.946). The MIDCCS demonstrated good internal consistency (Cronbach α =0.86).

Conclusion: Although e-consultation was widespread and clinically functional, data quality failures and seniority-related medicolegal concerns indicate important limitations. The findings highlight the need for a secure national e-consultation infrastructure integrated into Hospital Information Management Systems that is KVKK-compliant and end-to-end encrypted, while remaining as fast and user-friendly as WhatsApp.

Keywords: Cardiology, malpractice, ST-elevation myocardial infarction, telemedicine, text messaging

ÖZET

Amaç: Türkiye'deki kardiyologlar arasında anlık mesajlaşma yoluyla gerçekleştirilen e-konsültasyonun klinik kullanımını, iletilen verinin algılanan kalitesine atfedilen ve katılımcı beyanına dayanan tedavi gecikmelerini ve güvenli kurumsal bir altyapının yokluğunda ortaya çıkan medikolegal kaygının mesleki kıdeme göre değişimini değerlendirmek.

Yöntem: Sağlık kurumlarında çalışan 253 kardiyolog, kesitsel bir çevrim içi anket aracılığıyla; konsültasyon örüntüleri, akut miyokart enfarktüsü (AMI) ile ilişkili destek bileşenleri, paylaşılan veri türleri, algılanan veri kalitesine atfedilen katılımcı beyanına dayalı tedavi gecikmeleri, mevzuat farkındalığı ve 15 maddelik KDMEÖ açısından değerlendirildi. Birincil analiz, KDMEÖ alan skorlarının mesleki kıdem gruplarına göre karşılaştırılmasıydı (Kruskal-Wallis H; Holm-Bonferroni düzeltmesi). Tek maddelik genel medikolegal kaygı için yürütülen orantılı olasılıklar ordinal regresyon analizi ise keşfedici olarak ele alındı.

Bulgular: Aktif e-konsültasyon kullanıcılarının %86,9'u (213/245) AMI ile ilişkili en az bir informal destek etkinliği bildirdi: ön değerlendirme %71,5, triyaj %60,1, kateter laboratuvarı aktivasyon desteği %36,4 ve erken yönetim desteği %42,7. En sık paylaşılan veri türü

ORIGINAL ARTICLE

ARAŞTIRMA MAKALESİ

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elektrokardiyogramdı (EKG; %95,2). Algılanan düşük veri kalitesine atfedilen ve katılımcı beyanına dayanan tedavi gecikmesi %23,7 (58/245) oranında bildirildi; en sık ilişkili veri türü EKG fotoğrafıydı. Medikolegal kaygı skorları, çoklu karşılaştırma düzeltmesi sonrasında kıdem grupları arasında belirgin biçimde farklıydı (her alanda $P<0,001$); uzmanlar ve öğretim üyeleri asistanlara göre daha yüksek skorlar gösterdi. Keşfedici ordinal modelde, veri kalitesiyle ilişkili gecikme öyküsü daha yüksek kaygı düzeyleriyle yönsel olarak uyumluydu ancak istatistiksel anlamlılığa ulaşmadı (ortak OR=1,711; %95 GA, 0,994–2,946). KDMEÖ iyi düzeyde iç tutarlılık gösterdi (Cronbach $\alpha=0,86$).

Sonuç: E-konsültasyon yaygın ve klinik açıdan işlevsel olmakla birlikte, veri kalitesi sorunları ve kıdemle artan medikolegal kaygı önemli sınırlılıklara işaret etmektedir. Bulgular, Hastane Bilgi Yönetim Sistemlerine entegre, KVKK ile uyumlu ve uçtan uca şifreli, ancak WhatsApp kadar hızlı ve kullanıcı dostu, güvenli bir ulusal e-konsültasyon altyapısına yönelik öncelikli gereksinimi ortaya koymaktadır.

Anahtar Kelimeler: Kardiyoloji, malpraktis, ST elevasyonlu miyokart enfarktüsü, uzaktan tıp, kısa mesaj gönderimi

Digital health and telemedicine expanded considerably during and after the COVID-19 era.^{1–4} Smartphone-based messaging has become a widespread informal channel for clinical communication.⁵ In cardiology, where time-sensitive decision-making is critical in conditions such as ST-elevation myocardial infarction (STEMI), very-high-risk non-ST-elevation acute coronary syndromes, and malignant arrhythmias, e-consultation has become a routine component of daily clinical workflows.⁶ Cardiologists frequently rely on these platforms to receive and evaluate high-volume, complex medical data—ranging from electrocardiograms (ECGs) to coronary angiograms—sent by physicians from other specialties or by cardiology colleagues seeking a rapid second opinion. Although patient-sourced images may also circulate in real-world practice, this survey primarily captured physician-reported consultation workflows rather than a dedicated patient-to-physician telemedicine pathway. While this digital agility accelerates clinical decision-making in emergencies, it bypasses formal hospital information systems and cannot provide the institutional infrastructure required for the practice to be conducted securely.⁷

Data routinely shared in cardiology practice—a photographed ECG triggering catheterization laboratory activation, an echocardiographic loop reviewed on a smartphone, or a coronary cine image—constitute special-category personal health data.⁸ Processing these data through consumer messaging applications outside hospital information systems represents primarily not a criminal threat but an operational constraint arising from the lack of a systematic and integrated infrastructure. This exchange, which does not enter the official record and cannot be audited, results in fragmented medical records, uncertain data security, and medicolegal ambiguity. Current national regulations have made this gap even more visible by drawing attention to the secure processing of health data and the use of foreign-origin or informal channels.^{9–11} The resulting picture is a paradox: the very channel shown to shorten door-to-balloon time operates without the infrastructure—encryption, integration into the hospital system, and an auditable record—required for high-quality cardiac care and patient privacy.¹²

The global literature has documented that smartphone messaging is widely adopted among surgical teams and general medical staff.^{13,14} Structured physician-to-physician e-consultation services have demonstrably improved access

ABBREVIATIONS

AMI	Acute myocardial infarction
ECG	Electrocardiogram
HIMS	Hospital Information Management Systems
KMO	Kaiser-Meyer-Olkin
MIDCCS	Medicolegal Implications of Digital Consultation in Cardiology Scale
STEMI	ST-elevation myocardial infarction
TSC	Turkish Society of Cardiology

to specialty care across various health systems.^{15,16} Cardiology societies have also actively promoted formal digital pathways.^{17,18} Nevertheless, data on how highly dependent specialists such as cardiologists conduct this practice under current conditions remain extremely limited. Moreover, whether medicolegal concern differs according to professional seniority has not been examined to date. Therefore, this study aimed to evaluate the prevalence and patterns of e-consultation among cardiologists in Türkiye, characterize self-reported treatment delays attributed to the perceived quality of transmitted data, assess awareness of current national regulations, and identify the structural prerequisites of a secure national e-consultation platform integrated into the hospital system that protects both diagnostic accuracy and patient data privacy.

Materials and Methods

Study Design and Ethics Approval

This cross-sectional, survey-based study was conducted between May 21 and June 4, 2026. The protocol was approved by İzmir City Hospital Non-Interventional Ethics Committee (Approval Number: 2026/397, Date: 20.05.2026), and the online survey was activated only after approval. The study was conducted in accordance with the Declaration of Helsinki.¹⁹ Digital informed consent was obtained from all participants before enrollment. Reporting followed the STROBE statement for cross-sectional studies.²⁰ The CHERRIES statement for online surveys was also followed.²¹

Participants and Sampling

The target population consisted of cardiology residents, specialists, and faculty members actively working in Ministry of Health Training and Research Hospitals, University Hospitals, and State and Private Hospitals across Türkiye. A hybrid strategy

combining convenience and purposive sampling was used to ensure diversity in institutional representation; the survey was open to all actively working cardiologists regardless of whether they used instant messaging for clinical communication.

A total of 253 cardiologists actively working in 41 provinces of Türkiye were included using a snowball sampling strategy: cardiologists who received the survey invitation were asked to complete the survey and share it within their professional networks. According to Turkish Society of Cardiology (TSC) membership records, the number of registered cardiologists and cardiology residents in Türkiye is approximately 4,500; based on this reference population, a sample of 253 was considered descriptively adequate and acceptable for a descriptive survey study. Because recruitment relied on convenience and snowball sampling rather than probability sampling, this sample size does not support a formal claim regarding the margin of error or national representativeness. Explicit purposive efforts were made to ensure representation across the four institution types (Training and Research Hospital, State Hospital, University Hospital, and Private Hospital) and four academic titles (Resident, Specialist, Associate Professor, and Professor).

Because distribution through an open link prevented reliable determination of the number of physicians who viewed the invitation, view and response rates were not calculated. Inclusion criteria were being a licensed physician working in a cardiology department and actively participating in consultations; the exclusion criterion was an incomplete survey submission. The minimum sample size calculated using G*Power (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany) for a domain-level concern comparison among the three professional seniority groups, assuming a medium effect size and 85% statistical power, was approximately 205.^{22–24} The 253 complete and eligible responses obtained met this target.

Data Collection Instruments and Procedures

Data were collected using a structured, multi-section online survey prepared in accordance with design principles adapted for internet surveys.²⁵ To minimize duplicate entries, a single-response-per-device restriction was applied, and IP addresses were not stored to avoid collecting unnecessary personal data. The survey consisted of three sections, provided in full in Supplementary Material S1:

- Sociodemographic and Professional Profile: age, sex, academic title/seniority, duration of professional experience in the specialty, and institutional tier.
- e-Consultation Practices and Regulatory Awareness: This section recorded the frequency of informal consultation (never, monthly, weekly, daily, or more than once a day), its predominant direction (mostly sender/requester, mostly consulted specialist, or both), the primary platform (WhatsApp, Telegram, or other), and whether communication involved only physician-to-physician or also patient-to-physician data transfer. Clinical support for suspected acute myocardial infarction (AMI) was divided into four non-mutually exclusive components: preliminary assessment, triage, catheterization laboratory activation support, and early management support; these items were asked of the entire sample (n=253), because

even participants without current informal channel use may have participated in a time-sensitive AMI episode. Types of shared data—ECGs, echocardiography loops, coronary angiography cine images, and laboratory/biomarker reports—were recorded among current users. A data quality-related treatment delay was operationally defined as any delay in diagnosis, treatment, referral, or catheterization laboratory activation attributed to inadequate or degraded transmitted data resulting from factors such as missing ECG leads, low resolution, poor framing, glare, motion artifact, or missing clinical context; when a delay was reported, the primary modality, estimated duration (0–9 minutes, 10–30 minutes inclusive, or ≥ 31 minutes), and immediate operational outcome were recorded. Two 5-point Likert items assessed general awareness of the Personal Data Protection Law (KVKK) provisions regarding health data sharing and awareness of the January 2026 KVKK announcement restricting foreign-origin applications in public institutions.¹⁰

- Medicolegal Implications of Digital Consultation in Cardiology Scale (MIDCCS): a purpose-developed 15-item instrument covering three a priori domains—Perceived Legal Liability, Clinical Data Security, and Institutional Telemedicine Trust—each rated on a 5-point Likert scale (1=“Strongly disagree,” 5=“Strongly agree”).^{26,27} The full English wording of the items is presented in Supplementary Table S2. The initial MIDCCS items were generated through a review of the relevant literature and expert consensus among a local panel of cardiologists. Before full-scale deployment, the draft items underwent pilot testing for face validity and clarity with a network of practicing cardiology specialists and residents, which led to minor phrasing adjustments to ensure alignment with daily clinical workflows. To ensure that a higher total score consistently indicated greater medicolegal concern, the Institutional Telemedicine Trust items were reverse-coded. The scale demonstrated good internal consistency in this sample (Cronbach $\alpha=0.86$ for the total scale).

Statistical Analysis

Statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous data distributions was assessed using the Shapiro–Wilk test. Continuous data that were not normally distributed were summarized as the median and interquartile range (IQR), and categorical data were summarized as frequencies (n) and percentages (%); key prevalence estimates were reported with Wilson score 95% confidence intervals (CIs). For between-group comparisons of continuous data, the Mann–Whitney U or Kruskal–Wallis H test was used according to the number of groups being compared; significant Kruskal–Wallis H test results were further examined using the Bonferroni-corrected Dunn post hoc test. Categorical data were compared using the chi-square test or Fisher exact test. To control the Type I error rate in multiple comparisons, the Holm–Bonferroni correction was applied. The internal consistency of the scale was evaluated using the Cronbach α coefficient, and its factor structure was assessed using exploratory factor analysis following the Kaiser–Meyer–Olkin (KMO) and Bartlett tests of sphericity.²⁸ The primary analytic emphasis was the comparison of MIDCCS domain scores according to professional seniority. The multivariable analysis based on a separate, single-item global

Table 1. Comparison of MIDCCS domain scores according to professional seniority

Domain, median (IQR)	Resident (n=53)	Specialist (n=130)	Faculty member (n=62)	χ^2	P	ε^2
Perceived legal liability	2.80 (2.40–3.20)	4.20 (3.80–4.40)	4.40 (4.20–4.60)	151.98	<0.001	0.603
Clinical data security	3.20 (2.80–3.60)	3.80 (3.40–4.20)	4.10 (3.80–4.60)	89.80	<0.001	0.356
Institutional telemedicine trust	2.40 (2.20–2.80)	2.00 (1.80–2.40)	1.60 (1.40–2.00)	76.81	<0.001	0.305

Values are presented as medians and interquartile ranges (IQRs). The P column shows raw Kruskal-Wallis P values; all three comparisons remained statistically significant after Holm-Bonferroni correction applied across the nine domain-level comparisons. For seniority-based comparisons, the four academic titles were reduced to three groups; the Faculty Member group was formed by combining Associate Professors (n=44) and Professors (n=18) to ensure adequate cell sizes (n=62). Seniority-based comparisons were restricted to active e-consultation users (n=245). All eight participants excluded on this basis held faculty positions (3 Associate Professors and 5 Professors), accounting for the difference between the academic title distribution in Table 1 (n=253) and the group sizes shown here. IQR, interquartile range; MIDCCS, Medicolegal Implications of Digital Consultation in Cardiology Scale; χ^2 , Kruskal-Wallis H test statistic; ε^2 , rank-based effect-size estimate.

concern outcome was designed as exploratory; to model this five-level ordinal outcome, proportional-odds ordinal logistic regression was used, with common odds ratios (ORs), 95% CIs, and McFadden pseudo- R^2 reported, and the proportional-odds assumption tested using the parallel lines test.²⁹ A two-sided $P < .05$ was considered statistically significant. Because of anticipated small cell sizes, Associate Professors and Professors were combined into a single "Faculty Member" category for all seniority-based comparisons (Table 1). Because the seniority gradient could be confounded by age, years of professional experience, institutional setting, consultation workload, and regulatory awareness, multivariable linear regression models were fitted for each MIDCCS domain score, with seniority (reference: resident), age, years of experience, institution type, on-call status, consultation direction, consultation frequency, and both KVKK awareness items entered simultaneously.

Results

Study Population

A total of 253 cardiologists from 41 provinces participated. Of the sample, 70.4% were male (n=178) and 29.6% were female (n=75); the most populous age stratum was 36–45 years (41.1%). Specialist cardiologists constituted the majority (51.4%), with the remainder distributed among Residents (20.9%), Associate Professors (18.6%), and Professors (9.1%). Approximately half of the sample (45.5%) worked in Training and Research Hospitals, 30.4% in State Hospitals, 16.6% in University Hospitals, and 7.5% in Private Hospitals. The majority (62.8%) maintained active in-hospital on-call duties. All demographic characteristics are presented in Table 2.

Clinical Use of e-Consultation and Data Quality-Related Treatment Delays

e-Consultation via instant messaging was frequently reported in this sample. At least one AMI-related support activity was reported by 86.9% (213/245) of current e-consultation users (denominator: current users, n=245); component frequencies, calculated across the entire sample (n=253) as described in the Methods, were 71.5% for preliminary assessment, 60.1% for triage, 36.4% (95% CI, 30.7–42.5) for catheterization laboratory activation support, and 42.7% for early management support (denominator: entire sample, n=253). This composite variable is not clinically homogeneous: in addition to the more common activities of preliminary assessment and triage, it includes catheterization laboratory activation support, which is less frequent but carries substantially greater clinical and medicolegal weight (Table 3).

Table 2. Demographic and professional characteristics of participating cardiologists (n=253)

Variables	Category	n	%
Sex	Male	178	70.4
	Female	75	29.6
Age (years)	25–35	74	29.2
	36–45	104	41.1
	46–55	75	29.6
Academic title	Resident	53	20.9
	Specialist	130	51.4
	Associate professor	47	18.6
Institution type	Professor	23	9.1
	Training and research hospital	115	45.5
	State hospital	77	30.4
	University hospital	42	16.6
	Private hospital	19	7.5
On-call status	Active in-hospital	159	62.8
	Home/remote	44	17.4
	None	50	19.8

Data are presented as frequencies (n) and percentages (%).

Among current users, the most frequently shared data type was the ECG (233/245; 95.2%; 95% CI, 91.6–97.4); this was followed by echocardiography loops (68.2%), coronary angiography cine images (54.7%), and laboratory/biomarker reports (50.6%). A self-reported treatment delay attributed to the perceived poor quality of the transmitted data was reported by 23.7% of users (58/245; 95% CI, 18.5–29.5). Among cases involving a delay, the most common modality was an ECG photograph (34/58; 58.6%); most delays were estimated to last 10–30 minutes (51.7%), and the most frequent operational outcomes were re-requesting the data (48.3%) and a delayed referral or catheterization laboratory activation decision (29.3%).

Medicolegal Concern and Regulatory Awareness According to Professional Seniority

A substantial majority of participants (72.7%; n=184) endorsed the global item indicating concern about legal noncompliance or malpractice arising from informal digital consultation. By contrast, regulatory awareness was low: only 32.0% of participants (n=81) were aware of the January 2026 KVKK public announcement restricting foreign-origin applications in public

Table 3. Clinical e-consultation patterns, data quality risks, and subjective professional burdens

Survey items and clinical variables	Frequency, n (%) / agreement (%)
e-Consultation frequency	
Never	8 (3.2%; 95% CI, 1.6–6.1)
Monthly	29 (11.5%; 95% CI, 8.1–16.0)
Weekly	85 (33.6%; 95% CI, 28.1–39.6)
Daily	131 (51.8%; 95% CI, 45.6–57.9)
Direction and dyad	
Both sender and consulted physician	110/245 (44.9%; 95% CI, 38.8–51.2)
Mostly consulted physician	86/245 (35.1%; 95% CI, 29.4–41.3)
Mostly sender/requester	49/245 (20.0%; 95% CI, 15.5–25.5)
Physician-to-physician only	207/245 (84.5%; 95% CI, 79.4–88.5)
Involving patient-to-physician data	38/245 (15.5%; 95% CI, 11.5–20.6)
Primary platform	
WhatsApp	231/245 (94.3%; 95% CI, 90.6–96.6)
Telegram	11/245 (4.5%; 95% CI, 2.5–7.9)
Other	3/245 (1.2%; 95% CI, 0.4–3.5)
AMI-related informal support components	
At least one AMI-related support activity among current e-consultation users	213/245 (86.9%; 95% CI, 82.0–90.9)
Preliminary assessment	181 (71.5%; 95% CI, 65.7–76.7)
Triage	152 (60.1%; 95% CI, 53.9–65.9)
Catheterization laboratory activation support	92 (36.4%; 95% CI, 30.7–42.5)
Early management support	108 (42.7%; 95% CI, 36.7–48.8)
Data types shared via e-consultation (non-mutually exclusive)	
Electrocardiogram (ECG)	233/245 (95.2%)
Echocardiography loops	167/245 (68.2%; 95% CI, 62.1–73.7)
Coronary angiography cine images	134/245 (54.7%; 95% CI, 48.4–60.8)
Laboratory/biomarker reports	124/245 (50.6%; 95% CI, 44.4–56.8)
Data quality-related treatment delay	
Self-reported treatment delay attributed to perceived poor data quality	58/245 (23.7%; 95% CI, 18.5–29.5)
Primary delay modality among cases with delay (n=58)	
ECG photograph	34 (58.6%; 95% CI, 45.8–70.4)
Echocardiography loop	11 (19.0%; 95% CI, 10.9–30.9)
Coronary angiography cine image	8 (13.8%; 95% CI, 7.2–24.9)
Laboratory/biomarker report	3 (5.2%; 95% CI, 1.8–14.1)
Multiple/uncertain	2 (3.4%; 95% CI, 1.0–11.7)
Estimated delay duration among cases with delay (n=58)	
0–9 minutes (<10 minutes)	19 (32.8%; 95% CI, 22.1–45.6)
10–30 minutes (inclusive)	30 (51.7%; 95% CI, 39.2–64.1)
≥31 minutes	9 (15.5%; 95% CI, 8.4–26.9)
Immediate operational outcome among cases with delay (n=58)	
Re-request of data only	28 (48.3%; 95% CI, 35.9–60.8)
Delayed referral or catheterization laboratory activation decision	17 (29.3%; 95% CI, 19.2–42.0)
Conservative management until clarification	7 (12.1%; 95% CI, 6.0–22.9)
No immediate operational outcome/other or unspecified	6 (10.3%; 95% CI, 4.8–20.8)
Selected MIDCCS perceptions (% agreement)	
Informal channels create 24/7 availability pressure and burnout	215/253 (85.0%; 95% CI, 80.1–88.9)
Formal institutional channels would provide vital legal protection	206/253 (81.4%; 95% CI, 76.2–85.7)
I routinely experience malpractice concern when sharing patient data	184/253 (72.7%; 95% CI, 66.9–77.8)

Unless otherwise stated, percentages were calculated using the entire study population (n=253). Percentages for consultation direction/dyad, platform, and shared data types were calculated among current e-consultation users (n=245), excluding participants who did not report current e-consultation use. Component-level AMI support variables are non-mutually exclusive; therefore, their sum may exceed the composite proportion. The composite proportion for “at least one AMI-related support activity” uses current e-consultation users (n=245) as the denominator, whereas the four individual components use the entire study sample (n=253) as the denominator because these items were asked of all participants regardless of current channel use (see Methods). This difference in denominators is intentional and should not be interpreted as a data inconsistency. Delay modality, delay duration, and outcome percentages were calculated among participants reporting a delay (n=58). AMI, acute myocardial infarction; CI, confidence interval; ECG, electrocardiogram; MIDCCS, Medicolegal Implications of Digital Consultation in Cardiology Scale.

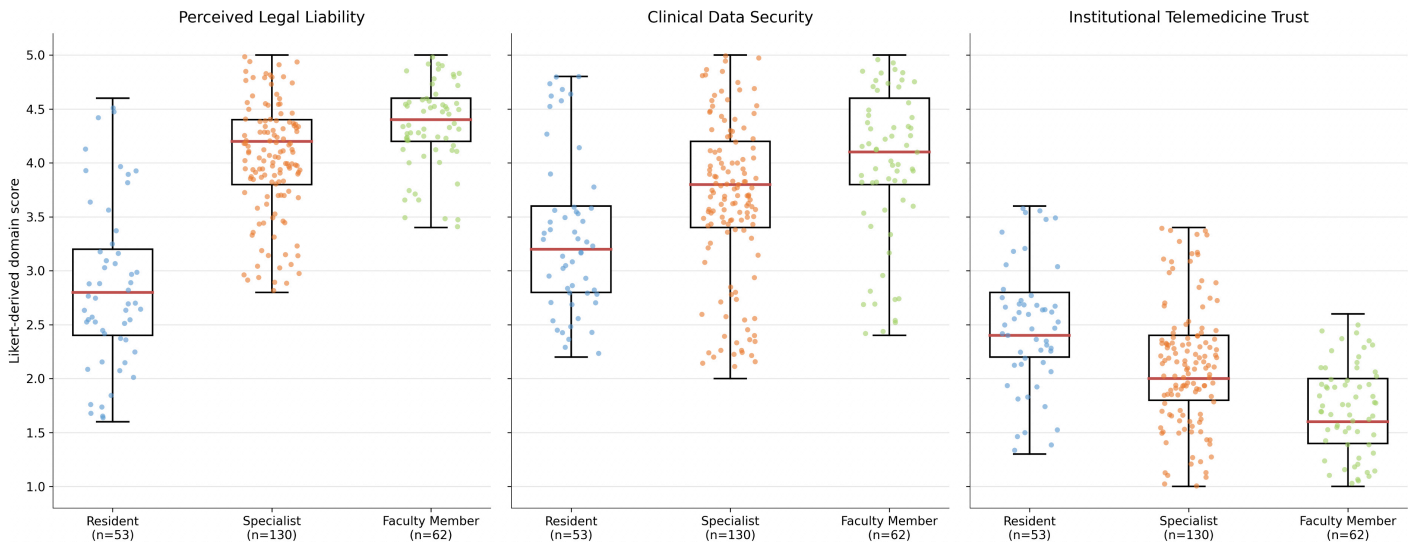


Figure 1. Box plots with overlaid individual data points showing the distribution of MIDCCS (Medicolegal Implications of Digital Consultation in Cardiology Scale) domain scores according to professional seniority (residents, specialists, and faculty members). Analyses were restricted to active e-consultation users (n=245); group sizes are shown beneath each group label (residents, n=53; specialists, n=130; faculty members, n=62). The figure is provided as a separate high-resolution file (≥300 dpi).

institutions.¹⁰ General KVKK awareness regarding health data sharing was 56.1% (n=142). In terms of domain scores, the median Perceived Legal Liability score was high, whereas the median Institutional Telemedicine Trust score was low (Table 1).

After Holm–Bonferroni correction, none of the domain comparisons by sex or institutional tier remained statistically significant; by contrast, strong differences according to professional seniority persisted across all three domains (Holm-corrected $P < 0.001$ for each domain). The associated effect sizes were largest for Perceived Legal Liability ($\epsilon^2 = 0.603$), followed by Clinical Data Security ($\epsilon^2 = 0.356$) and Institutional Telemedicine Trust ($\epsilon^2 = 0.305$). Bonferroni-corrected Dunn post hoc comparisons showed that specialists and faculty members had significantly higher Perceived Legal Liability and Clinical Data Security scores and lower Institutional Telemedicine Trust scores than residents ($P < 0.001$ for all resident–senior comparisons). The distribution of domain scores according to professional seniority is shown in Figure 1.

To examine whether the observed seniority gradient was confounded by age, experience, or institutional and workload-related factors, multivariable linear regression models were fitted with each MIDCCS domain score as the dependent variable. After simultaneous adjustment for age, years of experience, institution type, on-call status, consultation direction, consultation frequency, and regulatory awareness, the seniority gradient remained strong and statistically significant across all three domains. Compared with residents, specialists scored 6.1 points higher on Perceived Legal Liability (95% CI, 4.9–7.4; $P < 0.001$), 3.6 points higher on Clinical Data Security (95% CI, 2.2–4.9; $P < 0.001$), and 1.7 points lower on Institutional Telemedicine Trust (95% CI, –2.8 to –0.6; $P = 0.003$); faculty members differed by 6.1, 5.5, and 3.7 points, respectively (all $P < 0.001$). Neither age nor years of experience was independently associated with Perceived Legal Liability ($P = 0.996$ and $P = 0.114$, respectively), suggesting that the seniority effect was not merely a proxy for chronological age or professional tenure.

Ordinal Model for Global Legal Noncompliance/Malpractice Concern

In the proportional-odds ordinal model for the 5-level global concern item, a self-reported history of delay attributed to the perceived poor quality of the transmitted data was directionally associated with higher concern levels but did not reach the prespecified significance threshold, and the confidence interval included the null (common OR=1.711; 95% CI, 0.994–2.946; $P = 0.053$). Specialist seniority was associated with higher concern compared with residents (common OR=1.988; 95% CI, 1.181–3.347; $P = 0.010$), whereas faculty membership was not independently significant ($P = 0.330$). The explanatory power of the model was low (McFadden pseudo- $R^2 = 0.015$); therefore, the ordinal model should be interpreted as exploratory rather than confirmatory, and the principal findings rest on comparisons of MIDCCS domain scores according to seniority. Given this nonsignificant association and the low explanatory power of the model (McFadden pseudo- $R^2 = 0.015$), the ordinal model provides limited additional information beyond the primary domain-score comparisons and should not be relied upon as evidence of a delay–concern relationship. User-restricted, institutional tier-, age-, and experience-adjusted, and domain-level sensitivity models did not alter the direction of the delay estimate but yielded no additional statistically significant findings. The high endorsement of the global item across all seniority groups (64.4% among residents, 77.1% among specialists, and 77.8% among faculty members) makes it less discriminative than the multi-item Perceived Legal Liability domain.

Discussion

This study is among the first clinically grounded investigations to evaluate, in a digitally reached sample of cardiologists in Türkiye, e-consultation via instant messaging together with its associated data quality risks and emerging medicolegal concerns. While cardiologists adopt these platforms for clinical agility, the combination of professional seniority and recent

regulatory developments—the December 2025 amendment to the Regulation on Personal Health Data and the January 2026 KVKK announcement—was associated with a marked seniority-related gradient in medicolegal concern.^{9,10} Because the study is cross-sectional, this gradient should not be interpreted as longitudinal maturation within the same physicians.

That three-quarters of participants reported at least one AMI-related informal support activity indicates that these platforms are highly visible in the sample; however, this should not be interpreted as an unbiased estimate of national prevalence. The component-level distribution is clinically distinguishable: while preliminary assessment and triage are widespread, catheterization laboratory activation support is less frequent but carries substantially greater clinical and medicolegal weight. In STEMI, very-high-risk non-ST-elevation acute coronary syndromes, and malignant arrhythmias, where minutes matter, the clinical agility offered by instant messaging in contrast to the bureaucratic barriers of existing formal telemedicine infrastructures appears to be the principal factor driving physicians toward these channels despite the known legal risks. This tendency has a demonstrated clinical rationale: in a multicenter Turkish experience, WhatsApp-based STEMI triage between a non-PCI rural hospital and a tertiary PCI center shortened door-to-balloon time and reduced inappropriate catheterization laboratory activations.¹² The international literature similarly reports high adoption rates among emergency surgical teams and general medical staff.^{6,13,14} The very large seniority-based separation in the Perceived Legal Liability domain ($\epsilon^2=0.603$) should be interpreted not as a population-level estimate but as a strong descriptive gradient within this sample; the overlaid raw distributions in Figure 1 make this separation transparent.

Cardiology's fundamental distinction from this literature lies in the nature of the shared data. Among physicians, 23.7% self-reported delays that they attributed to perceived poor data quality; the most frequently associated modality was the ECG photograph, whereas echocardiographic and angiographic cine loops constituted a smaller but technically higher-fidelity subset in which compression or frame loss may be clinically meaningful. Most delays were estimated to last 10–30 minutes and generally resulted in re-requesting the data or in a delayed referral or catheterization laboratory activation decision. These findings suggest that instant messaging has ceased to function merely as a communication tool and has evolved into an unregulated diagnostic platform through which ECGs, echocardiograms, and coronary angiograms are transmitted.^{5,7} Although the association between delay and higher concern in the ordinal model was directionally consistent, it did not reach the significance threshold, and the confidence interval included the null. Because delay and concern were measured concurrently, this association should not be interpreted as causal and should instead be regarded as hypothesis-generating. The study also lacks a counterfactual measure of delays that might occur through formal hospital information systems; therefore, the data cannot estimate the net benefit or harm of informal channels with respect to delays relative to formal pathways.

One of our most distinctive findings is the seniority-related gradient in medicolegal concern. Although younger physicians are known to adapt rapidly to digital technology, the lower

medicolegal risk perception observed among residents may reflect the institutional reality of the medical hierarchy. Senior cardiologists who bear primary legal and administrative responsibility as department heads, training supervisors, or senior consultants may adopt a more cautious and protective approach toward recent regulatory developments.^{9,10} The more modest effects observed in the global-item model should not be interpreted as contradicting the domain-score findings; the single-item measure, which was highly endorsed across all seniority groups, is naturally less discriminative than the multi-item domain, and the gradient is substantially stronger when the within-scale legal-liability item is examined. Because professional seniority also encompasses generational, institutional, and role-based differences, the observed gradient cannot be disentangled from generational effects in this cross-sectional design. The persistence of this gradient after multivariable adjustment for age, experience, institution type, on-call burden, consultation role, and regulatory awareness further suggests that the observed difference is attributable to the institutional responsibilities and medicolegal exposure accompanying professional seniority rather than to demographic or workload-related confounding alone.

Our study points to a clear asymmetry between the speed at which physicians integrate technological innovations into clinical practice and their level of compliance with existing legal frameworks. That 72.7% endorsed concern regarding legal noncompliance or malpractice despite continuing to rely on e-consultation suggests that clinical pragmatism may override the deterrent effect of regulatory warnings; this attitude-behavior gap is consistent with technology-acceptance frameworks in health care, in which perceived clinical usefulness outweighs perceived risk.³⁰ Notably, only one-third of participants—most of whom (92.5%) work in public institutions that were the direct addressees of the January 2026 KVKK announcement—were aware of that announcement; thus, while concern increases with seniority, regulatory literacy remains inadequate across all levels of professional seniority. An opposing interpretation must also be considered: faster activation pathways may reduce treatment delays, but rapid decisions based on incomplete or low-quality ECG/image data may also increase inappropriate triage, false-positive catheterization laboratory activation, or delayed correction of an initial misclassification.³¹ This study did not objectively measure false activations or clinical outcomes.

This picture also reveals a structural gap between the focus of current regulations and clinical reality. The December 2025 regulatory amendment and the January 2026 KVKK announcement largely regulate appointment-based telemedicine services at the outpatient level and e-Nabız-based institutional integrations—that is, the planned and formal channel—whereas they do not directly address the instant, informal crisis-management dynamic in which a STEMI ECG is transmitted via WhatsApp at 03:00.^{9,10} The paradox lies precisely here: the regulated channel is not the channel actually used in an emergency, while the informal channel shown to shorten door-to-balloon time remains in a legal gray area.¹² Consequently, the core problem is not merely physicians' compliance with regulations, but also the failure of the regulatory framework to provide a usable formal alternative suited to the speed and nature of emergency cardiac care.

Implications for Clinical Practice and Health Policy

The following recommendations extend beyond our descriptive findings; they are policy proposals grounded in the implications of the study rather than conclusions directly supported by the data.

Given that cardiologists cannot relinquish the clinical agility provided by e-consultation, while senior physicians in particular report greater medicolegal concern under the current regulatory burden, the following steps are proposed for the practical implementation of a structural solution to this dilemma:

- **Establishment of an Integrated National Telemedicine Platform:** Based on the finding that the great majority of participants seek a formal framework, a user-friendly e-consultation module should be developed within the Ministry of Health. This module should be fully integrated with e-Nabız and Hospital Information Management Systems (HIMS), use end-to-end encryption on domestically managed infrastructure, and comply with the principle of data sovereignty.^{32,33} The demonstrated effectiveness of structured physician-to-physician e-consultation services in other health systems supports this approach.^{15,16,34} International experience with secure messaging also suggests that the relevant comparison is not between consumer chat and no communication, but between consumer chat and an institutional infrastructure that combines encryption, recipient authentication, clinical-system integration, and auditable delivery.³⁵⁻³⁷
- **Mobile-Accessible, High-Fidelity ECG and Cardiovascular Imaging Support:** The proposed platform should provide smartphone-compatible access to ECGs, echocardiography loops, and angiography cine images without loss of clinically meaningful resolution, frame order, or acquisition metadata. For ECGs, the priority should be standardized digital 12-lead transmission or, where photographs are unavoidable, a minimum acquisition protocol that prevents missing leads, glare, distortion, and absent calibration; for echocardiography and angiography, DICOM-preserving or lossless transmission pathways should be available when diagnostic interpretation depends on frame-by-frame fidelity.
- **Forensic Informatics Standards and Time-Stamping:** All physician-to-physician consultations conducted through the platform should be sealed with time stamps compliant with forensic informatics standards and automatically entered into the patient's official HIMS electronic health record. This would confer formal legal status on the medical opinions provided and eliminate existing legal gray areas.
- **Regulation of Workload and Physician Rights:** To mitigate the "24/7 availability" pressure created by informal platforms and the associated risk of burnout, digital consultation processes should be formally incorporated into physicians' legal working hours and workload definitions. This should be accompanied by clear ethical and administrative guidelines defining urgency criteria and mandatory response times.

Study Limitations

This study has several limitations. Because the design is cross-sectional, the findings represent a snapshot of a single time

point, and causality cannot be established; the seniority-related difference in concern may also reflect generational and role-based differences rather than changes within the same physicians over time. Because the data rely on physicians' self-reports, informal use and delays may have been underreported because of legal concerns or social desirability; delay durations were also based on recall and were not linked to measured door-to-balloon times or patient outcomes. Because delay and concern were assessed concurrently, it cannot be determined which occurred first; therefore, the association between them should be considered hypothesis-generating rather than causal. Recruiting participants through professional messaging groups may have overrepresented digitally active cardiologists who were likely already more comfortable with and reliant on instant-messaging-based consultation; therefore, the reported use and support rates are frequencies specific to this sample rather than estimates of national prevalence. The dependent variable in the multivariable model was a single, unvalidated concern item that was highly endorsed across all seniority groups. The explanatory power of the model was low, it should not be used for individual-physician risk prediction, and the near-threshold association between delay and concern should not be interpreted as evidence of "no association." Subgroup differences by sex and institutional tier should be regarded as exploratory only. The MIDCCS is also a newly developed scale; although its internal consistency is adequate, its structure has not yet been validated in an independent sample, and the validity panel consisted only of cardiologists without input from a health-law or forensic-medicine expert; psychometric details are presented in Supplementary Table S3. Independent confirmatory validation of the MIDCCS in a separate cohort, ideally incorporating input from health-law or forensic-medicine experts, is required before the scale can be adopted more broadly. Formal cognitive interviewing, independent confirmatory factor analysis, and structured input from a health-law or forensic-medicine expert were not performed as part of the present study; we plan to address these steps in a dedicated future validation study rather than presenting the MIDCCS here as a fully validated instrument.

In conclusion, in this digitally reached sample of cardiologists, e-consultation via instant messaging is widespread and clinically functional; however, data quality failures and medicolegal concern that increases with seniority suggest that this practice, in its current form, has important limitations. These policy recommendations are grounded in participants' perceptions and the study's descriptive findings rather than in a direct evaluation of clinical effectiveness, patient safety, platform security, or the operational feasibility of a national system, none of which were assessed here; the legal and regulatory interpretations offered are intended as a starting point for multidisciplinary discussion and should ideally be reviewed by a health-law or forensic-medicine expert before policy implementation. The solution is not to eliminate clinical agility but to transfer it to a secure infrastructure: there is a priority need for mobile institutional e-consultation interfaces integrated into HIMS that are KVKK-compliant and end-to-end encrypted, yet as fast and user-friendly as WhatsApp. Until such an infrastructure is provided, physicians will continue to be forced to choose between legal security and patient safety.

Appendix Online File: [https://jag.journalagent.com/tkd/abs_files/TKDA-23495/TKDA-23495_\(0\)_TKDA-23495_\(0\)_2148-suppp.docx](https://jag.journalagent.com/tkd/abs_files/TKDA-23495/TKDA-23495_(0)_TKDA-23495_(0)_2148-suppp.docx)

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Assessment of Patients' Awareness of Anticoagulant Use in Atrial Fibrillation: A Cross-Sectional Survey

Atrial Fibrilasyonda Antikoagulan Kullanımına Yönelik Hasta Farkındalığının Değerlendirilmesi: Kesitsel Bir Çalışma

ABSTRACT

Objective: Atrial fibrillation (AF) increases thromboembolic risk, and oral anticoagulants (OACs) substantially reduce this risk; however, their safe and effective use requires adequate patient knowledge. We aimed to assess AF- and OAC-related awareness among Turkish patients and to identify predictors of knowledge.

Method: This single-center, cross-sectional survey was conducted between July 1, 2024 and January 1, 2025, and included consecutive adults with non-valvular AF receiving warfarin or direct OACs for at least three months. A structured questionnaire collected data on demographic characteristics, comorbidities, medication use, adherence, and knowledge across six domains: dosing frequency, treatment indication, side-effect awareness, treatment-duration awareness, drug-interaction awareness, and food-interaction awareness. A composite knowledge score (range, 0–6) was calculated. Multivariable linear regression was used to evaluate predictors of knowledge, including age, sex, and education level. Ethics approval was obtained, and all participants provided written informed consent.

Results: A total of 261 patients were included (median age, 67 years; 50.2% women). Hypertension and diabetes mellitus were present in 64.8% and 32.2% of patients, respectively. Direct oral anticoagulants (DOACs) accounted for 72.4% of prescriptions, whereas 27.6% of patients received warfarin. Although 36% of participants had AF for more than six years, only 16.5% could correctly name their arrhythmia. While 92% knew they were taking an anticoagulant, only 75.1% correctly identified the indication for anticoagulation. Knowledge of side effects was limited, with 68% reporting no awareness. Awareness of interactions was poor: 88% reported no knowledge of drug-drug interactions, and 71% were unaware of food interactions. Most patients knew their dosing schedule (92.3%) and reported that they would not double a missed dose (99.6%). Self-reported adherence was high (94% "always" and 4% "often"), and taking medication with meals was associated with better adherence ($\chi^2 = 17.0$, $P < 0.001$). The mean knowledge score was 2.8 ± 1.3 (Cronbach's $\alpha = 0.50$). Higher educational attainment and female sex were associated with greater knowledge, whereas age was inversely associated with knowledge.

Conclusion: Despite high self-reported adherence, substantial knowledge gaps persist among patients receiving anticoagulation for AF, particularly regarding side effects and drug or food interactions. Targeted, health-literacy-sensitive educational strategies may improve medication safety and clinical outcomes in patients receiving anticoagulation for AF.

Keywords: Atrial fibrillation, oral anticoagulants, patient knowledge

ÖZET

Amaç: Atrial fibrilasyon (AF), tromboembolik riski artırır ve oral antikoagulanlar (OAK) bu riski önemli ölçüde azaltır; ancak bu ilaçların güvenli ve etkili kullanımı, hastaların yeterli bilgi düzeyine sahip olmasını gerektirir. Bu çalışmada, Türk hastalarda AF ve OAK ile ilişkili farkındalığın değerlendirilmesi ve bilgi düzeyinin belirleyicilerinin saptanması amaçlandı.

Yöntem: Bu tek merkezli, kesitsel araştırma 1 Temmuz 2024 ile 1 Ocak 2025 tarihleri arasında gerçekleştirildi ve en az üç aydır varfarin veya direkt OAK kullanan non-valvüler AF'li ardışık erişkin hastalar çalışmaya dahil edildi. Yapılandırılmış bir anket ile demografik özellikler, komorbiditeler, ilaç kullanımı, tedavi uyumu ve altı bilgi alanı değerlendirildi: ilaç akma sıklığı, tedavi endikasyonu, yan etkiler hakkında bilgi, tedavi süresi hakkında bilgi, ilaç etkileşimleri hakkında bilgi ve gıda etkileşimleri hakkında bilgi. 0–6 arasında değişen bileşik bir bilgi skoru hesaplandı. Yaş, cinsiyet ve eğitim düzeyi dahil olmak üzere bilgi düzeyinin belirleyicileri çok değişkenli lineer regresyon ile değerlendirildi. Etik kurul onayı alındı ve tüm katılımcılardan yazılı bilgilendirilmiş onam elde edildi.

ORIGINAL ARTICLE

ARAŞTIRMA MAKALESİ

The preliminary results of the study conducted on a pilot sample of 50 patients were presented at the 40th Turkish Cardiology Congress held on November 6–10, 2024.

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Bulgular: Toplam 261 hasta çalışmaya dahil edildi (medyan yaş 67 yıl; %50,2 kadın). Hipertansiyon ve diabetes mellitus sırasıyla hastaların %64,8 ve %32,2'sinde mevcuttu. Direkt oral antikoagülanlar (DOAK) reçetelerin %72,4'ünü oluştururken, hastaların %27,6'sı varfarin kullanıyordu. Katılımcıların %36'sında AF süresi altı yıldan uzun olmasına rağmen, yalnızca %16,5'i aritmisinin adını doğru olarak ifade edebildi. Katılımcıların %92'si antikoagülan kullandığını bilirken, sadece %75,1'i antikoagülasyon endikasyonunu doğru bir şekilde tanımladı. Yan etkilere ilişkin bilgi sınırlıydı ve katılımcıların %68'i bu konuda herhangi bir bilgisi olmadığını belirtti. Etkileşimlere ilişkin farkındalık da düşüktü; hastaların %88'i ilaç-ilaç etkileşimlerini, %71'i ise besin etkileşimlerini bilmiyordu. Hastaların çoğu doğru dozlama şemasını biliyordu (%92,3) ve neredeyse tamamı unutulmuş bir doz sonrasında çift doz almayacağını bildirdi (%99,6). Öz bildirilen tedavi uyumu yüksekti (%94 "her zaman", %4 "sıklıkla") ve ilacın yemekle birlikte alınması daha iyi tedavi uyumu ile ilişkiliydi ($\chi^2 = 17,0$; $P < 0,001$). Ortalama bilgi skoru $2,8 \pm 1,3$ olup Cronbach α değeri 0,50 idi. Daha yüksek eğitim düzeyi ve kadın cinsiyet daha yüksek bilgi düzeyi ile ilişkiliyken, yaş ile bilgi düzeyi arasında ters yönlü ilişki saptandı.

Sonuç: Öz bildirilen tedavi uyumunun yüksek olmasına rağmen, AF nedeniyle antikoagülan kullanan hastalarda özellikle yan etkilere ilişkin farkındalık ve besin etkileşimleri konusunda önemli bilgi eksiklikleri bulunmaktadır. Hedefe yönelik ve sağlık okuryazarlığı düzeyini dikkate alan eğitim stratejileri, AF nedeniyle antikoagülan kullanan hastalarda ilaç güvenliğini ve klinik sonuçları iyileştirebilir.

Anahtar Kelimeler: Atrial fibrilasyon, hasta bilgisi, oral antikoagülanlar

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide and is associated with a markedly increased risk of ischemic stroke, resulting in substantial morbidity, mortality, and healthcare costs.¹ Stroke prevention with oral anticoagulants (OACs), including vitamin K antagonists and direct oral anticoagulants, is therefore a cornerstone of AF management. Contemporary European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/American College of Chest Physicians/Heart Rhythm Society (ACC/AHA/ACCP/HRS) guidelines recommend oral anticoagulation according to estimated thromboembolic risk, using validated stroke risk stratification tools such as CHA₂DS₂-VA (Congestive heart failure, Hypertension, Age ≥ 75 years [2 points], Diabetes mellitus, Stroke/transient ischemic attack/systemic thromboembolism [2 points], Vascular disease, and Age 65–74 years) in the 2024 ESC guideline and CHA₂DS₂-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years [2 points], Diabetes mellitus, Stroke/transient ischemic attack/systemic thromboembolism [2 points], Vascular disease, Age 65–74 years, and Sex category [female sex]) or an equivalent annual-risk framework in the 2023 ACC/AHA/ACCP/HRS guideline. Bleeding-risk assessment should be used to identify and address modifiable risk factors rather than to withhold indicated anticoagulation.^{2,3}

Despite these recommendations, OACs remain underused or inconsistently taken, often because patients do not fully understand the rationale for anticoagulation or how to use these medications safely. This knowledge gap is clinically important because warfarin has a narrow therapeutic window, and incorrect dosing, treatment interruption, or unsupervised discontinuation of any OAC may increase the risk of thromboembolism or major bleeding.⁴ Consequently, improving patient awareness of stroke risk, bleeding complications, and adherence requirements represents a key modifiable determinant of treatment effectiveness and clinical outcomes.⁵ Nevertheless, clinicians frequently encounter patients with AF who are unable to explain the purpose of their anticoagulant therapy or recognize its common risks.

Accordingly, the aims of this study were to (i) quantify patients' awareness of AF and anticoagulation, including treatment

ABBREVIATIONS

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AF	Atrial fibrillation
AHA	American Heart Association
AKT	Anticoagulation Knowledge Tool
DOAC	Direct oral anticoagulant
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
HRS	Heart Rhythm Society
OAC	Oral anticoagulant
QoL	Quality of life

indication, side effects, interactions, and adherence behaviors, and (ii) identify demographic and clinical factors independently associated with patient knowledge.

Materials and Methods

Study Design and Population

This cross-sectional study included patients with AF receiving oral anticoagulation therapy. Consecutive patients were recruited from the cardiology outpatient clinic of a tertiary university hospital after providing informed consent. Eligible participants were adults (≥ 18 years) with documented non-valvular AF who had been prescribed an OAC (warfarin or a direct OAC) for stroke prevention. The survey was conducted between July 1, 2024 and January 1, 2025. Patients were excluded if they were younger than 18 years or had cognitive impairment, including dementia or intellectual disability, that precluded informed consent. A total of 261 AF patients receiving OAC therapy were included in the final analysis.

Data Collection, Variables, and Endpoints

Data were collected prospectively through structured face-to-face interviews conducted by trained research physicians during routine outpatient visits. A questionnaire developed by consensus among cardiologists at our institution was used to assess patient awareness. The questionnaire was pilot-tested in 50 patients to evaluate clarity, comprehensibility, and feasibility.⁶

The survey assessed five domains using multiple-choice, yes/no, and open-ended questions (full questionnaire available in the Supplementary Material):

- Demographic characteristics: age, sex, educational level (ranging from no formal education to postgraduate education), employment status, and place of residence (urban or rural).
- Medical history: comorbid conditions, including hypertension, diabetes mellitus, prior stroke, peripheral arterial disease, and chronic kidney disease; awareness of having a cardiac rhythm disorder; and knowledge of the specific arrhythmia diagnosis (AF or atrial flutter). The CHA₂DS₂-VA score was calculated for each participant.
- Medication profile: current anticoagulant therapy (warfarin or a specific direct oral anticoagulant [DOAC] and dose), duration of treatment, previous use of anticoagulant or antithrombotic agents (e.g., prior warfarin or aspirin therapy before the current regimen), and concomitant cardiovascular medications (e.g., beta-blockers, etc.)
- Adherence and knowledge: treatment indication, medication adherence (assessed using a Morisky-type scale), receipt of information before treatment initiation, awareness of side effects, understanding of stroke risk (assessed using an open-ended question), knowledge of drug interactions or dietary restrictions, dosing frequency, and awareness of potential dose adjustments.
- Use and perception: perceived quality of life (QoL), use of medication-reminder tools, information sources, and perceived adequacy of the information received.

All responses were recorded and coded according to a predefined case report form codebook (Supplementary Material). Where applicable, dichotomous (e.g., yes/no) and multiple-choice responses were coded as categorical variables for analysis. Free-text responses were reviewed and classified according to predefined criteria. For example, patients' explanations of the effect of anticoagulant therapy on stroke risk were categorized as correct if they were consistent with stroke prevention and as incorrect if they were not.

Six-Item Composite Knowledge Score

A formative composite knowledge score was developed to quantify patients' understanding of AF and anticoagulation therapy. The score was calculated by summing the number of correct responses across key knowledge domains assessed in the survey. One point was awarded for each of the following domains: knowledge of the prescribed dosing frequency, correct identification of the indication for OAC therapy, awareness of potential side effects, awareness of the intended duration of anticoagulant therapy, awareness of potential drug interactions, and awareness of food interactions. 'Do not know' responses and missing answers were coded as incorrect (0). Scores were summed to yield a composite score ranging from 0 to 6, with higher scores indicating greater knowledge. The composite score was analyzed as a continuous outcome variable in models examining predictors of patient knowledge. The six domains (dosing frequency, treatment indication, side-effect awareness, treatment-duration awareness, drug-interaction awareness, and

food-interaction awareness) were conceptualized as formative indicators of overall anticoagulation knowledge rather than manifestations of a single latent construct. Because each domain represents a distinct clinical competency, equal weighting (1 point per domain) was chosen to maintain simplicity, facilitate clinical interpretation, and support potential bedside use. However, this approach sacrifices psychometric homogeneity, as reflected by the modest Cronbach's α of 0.50, and may not fully capture clinically meaningful differences among patients with similar total scores but different knowledge profiles.

Unlike validated instruments such as the Anticoagulation Knowledge Tool (AKT), which provides broader content coverage and formal psychometric validation for both vitamin K antagonist and direct oral anticoagulant users, our six-item score was designed as a pragmatic, survey-derived summary measure rather than a substitute for a validated knowledge instrument.⁷ Although the selected domains overlap with key areas assessed by validated tools, including treatment indication, dosing, side effects, interactions, and medication-specific precautions, the abbreviated format limits content depth and psychometric precision.

Statistical Analysis and Ethics

Descriptive statistics were used to summarize participant characteristics. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate based on their distribution. Demographic and clinical characteristics, as well as responses to knowledge and adherence items, were summarized using descriptive methods. In univariate analyses, the chi-square test was used for categorical variables, and Student's t-test or the Mann-Whitney U test was used for continuous or ordinal variables, as appropriate. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. Missing data were limited ($\leq$ 4% for all variables) and were handled using pairwise deletion. Statistical analyses were performed using IBM SPSS Statistics (version 26; IBM Corporation, Armonk, New York, USA).

Because the six-item knowledge score was approximately symmetric (mean 2.8 ± 1.3 ; median 3), it was analyzed as a continuous outcome variable. Age, sex, and educational level were selected a priori for inclusion in the primary multivariable model because they represent clinically plausible and non-overlapping demographic predictors of patient knowledge while minimizing model complexity in a modest single-center sample. Additional clinically relevant variables, including anticoagulant type, AF duration, prior counseling, and self-reported adverse events, were evaluated in exploratory analyses because of concerns regarding recall bias, category imbalance, non-random treatment allocation, and overfitting. An exploratory sensitivity analysis additionally included self-reported adverse-event history to assess whether adverse events were independently associated with the composite knowledge score.

Because this was an exploratory cross-sectional survey, no formal a priori sample size calculation was performed. However, a sample size sensitivity analysis was conducted for the six-item knowledge score. Assuming an SD of 1.2 and a two-sided α of 0.05, the final sample of 261 participants provided 80% power to detect a between-group difference of approximately 0.47

points on the 0–6 knowledge scale, corresponding to a small-to-moderate standardized effect size (Cohen *d* = 0.39).

This study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment. The protocol was approved by Ege University Medical Research Ethics Committee (Approval Number: 24–7T/71, Date: 11.07.2024).

Results

A total of 261 consecutive patients with AF receiving OAC therapy were included in the final analysis. The median age was 67 years (range, 30–92 years), and just over half of the cohort was aged ≥ 65 years. The study population was evenly distributed by sex, comprising 131 women (50.2%) and 130 men (49.8%). Educational attainment was predominantly primary school level or lower (*n* = 136, 52.1%). Most participants were retired (*n* = 181, 69.3%), consistent with the older age profile of the cohort, and resided in urban areas (*n* = 234, 89.7%). The cohort appeared relatively healthy with respect to lifestyle factors: 76.6% reported never consuming alcohol, and 65.1% had never smoked (Table 1).

Clinical comorbidities were common. Hypertension was the most prevalent comorbidity, affecting approximately two-thirds of participants. One-third of patients (*n* = 84, 32.2%) had diabetes mellitus. Peripheral arterial disease was less common (6.9%), although an additional 17.2% reported being unsure whether they had peripheral vascular disease. Chronic kidney disease was reported by 12.3% of participants.

Although AF was the indication for anticoagulation in all participants by study design, only 45 patients (17.2%) correctly identified their arrhythmia as AF or atrial flutter, including 43 patients (16.5%) who specifically named AF (Figure 1). A large majority (82.8%) reported that they did not know the type of arrhythmia they had despite receiving long-term treatment for the condition. Furthermore, 10.3% of respondents answered “No” when asked whether they had a diagnosed rhythm disorder, suggesting that a subset of patients was unaware not only of the specific diagnosis but also of the presence of an arrhythmic condition. The median CHA₂DS₂–VA score was 3 (IQR = 2) (Table 2), indicating a moderate-to-high stroke risk profile.

Approximately 36% of participants had been diagnosed with AF for more than six years (median arrhythmia duration: 36 months, IQR: 12–108 months). DOACs accounted for 72.4% of prescriptions. The distribution of anticoagulant use was as follows: rivaroxaban, 72 patients (27.6%); warfarin, 72 patients (27.6%); apixaban, 64 patients (24.5%); edoxaban, 45 patients (17.2%); and dabigatran, eight patients (3.1%) (Figure 2). The median duration of anticoagulant therapy (for AF) was 24 months (IQR: 8–60 months). The most commonly prescribed concomitant medications were beta-blockers (*n* = 168, 64.4%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) (*n* = 89, 34.1%), and diuretics (*n* = 69, 26.4%), reflecting standard AF management and treatment of associated comorbidities (Table 3). Other medications included Class I antiarrhythmic agents in 2.7% of patients and Class III antiarrhythmic agents (e.g., amiodarone) in 6.1%, indicating that rhythm-control therapy was used in only a small proportion of the cohort.

Table 1. Demographic characteristics of the study population

Characteristic	Total (<i>n</i> = 261) <i>n</i> (%)
Age (years, median)	67 (min–max: 30–92)
Female sex	131 (50.2)
Educational attainment	
No formal education	16 (6.1)
Primary school	120 (46.0)
Middle school	24 (9.2)
High school	45 (17.2)
University	54 (20.7)
Master's degree	2 (0.8)
Employment status	
Unemployed	58 (22.2)
Retired	181 (69.3)
Other	22 (8.4)
Place of residence	
Urban	234 (89.7)
Rural	27 (10.3)
Smoking status	
Current smoker	28 (10.7)
Never smoker	170 (65.1)
Former smoker	63 (24.1)
Alcohol consumption	
Current user	32 (12.3)
Never user	200 (76.6)
Former user	29 (11.1)

Min, Minimum; Max, Maximum.

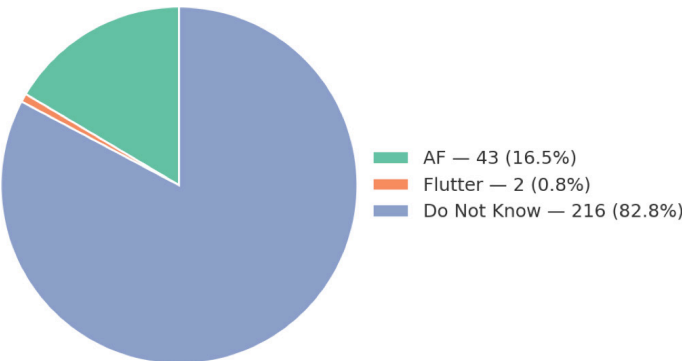


Figure 1. Patients' awareness of their arrhythmia diagnosis. Although all participants had atrial fibrillation (AF) as the indication for anticoagulation, only 16.5% correctly identified their condition as AF, whereas the majority (82.8%) reported that they did not know their arrhythmia type.

Medication Knowledge, Awareness, and Adherence Outcomes

Knowledge and Awareness

The survey revealed substantial gaps in patients' knowledge of AF and anticoagulation therapy. Although all participants were receiving anticoagulants, understanding of the indication for

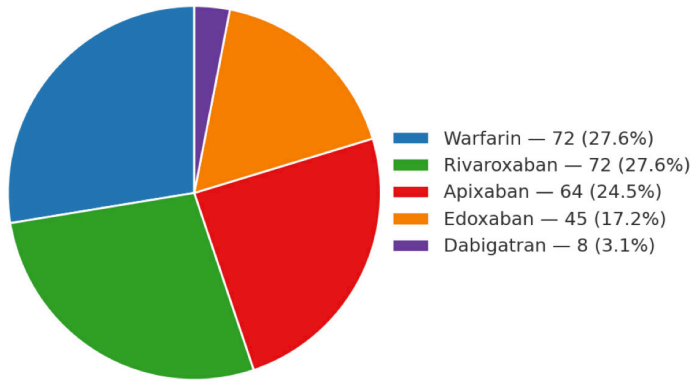


Figure 2. Distribution of oral anticoagulant use. Direct oral anticoagulants accounted for 72.4% of prescriptions. The most commonly prescribed agents were rivaroxaban (27.6%) and warfarin (27.6%), followed by apixaban (24.5%), edoxaban (17.2%), and dabigatran (3.1%).

treatment was incomplete. When asked, "What is the reason you are using a blood thinner?", 196 patients (75.1%) correctly stated that the medication was intended to prevent clot formation and thereby reduce stroke risk. However, approximately one-quarter of participants demonstrated incorrect or absent understanding of the indication for anticoagulant therapy. Specifically, 20 patients (7.7%) believed that the anticoagulant was prescribed "to correct the arrhythmia," implying that it treats atrial fibrillation itself, while five patients (1.9%) reported that its purpose was "to prevent a heart attack." Additionally, 26 patients (10.0%) stated that they did not know the reason for taking the anticoagulant. Fourteen patients (5.3%) did not answer the question.

Awareness of potential side effects was poor. Only one-third of participants (32%) reported awareness of possible anticoagulant-related adverse effects, whereas approximately 68% had no knowledge of side effects. Even among warfarin users, who require regular monitoring, fewer than half (43%) were able to identify specific side effects. Consistent with this finding, approximately 68% of patients reported that they had not been informed about side effects before starting treatment. The most frequently recognized adverse effect was bleeding, including easy bruising and mucosal bleeding. When asked about their personal experience with complications, 71.6% of participants reported no adverse effects or complications, whereas 26.8% reported bleeding-related symptoms, predominantly minor bruising or mucosal bleeding, and 1.5% reported serious adverse events. These findings should be interpreted as patient-reported historical adverse-event or complication reports rather than adjudicated treatment-emergent outcomes. Importantly, the questionnaire did not reliably distinguish whether thromboembolic events occurred before initiation of anticoagulation or during ongoing OAC therapy.

Knowledge of drug and food interactions with anticoagulants was particularly limited. Overall, 88% of participants reported no awareness of potential drug-drug interactions involving their anticoagulant, and approximately 71% were unaware of food interactions. As expected, awareness varied according to anticoagulant type. Among warfarin users, 75% reported knowledge of dietary restrictions, and 87.5% actively limited consumption of vitamin K-rich foods. In contrast, 11.6% of

Table 2. Clinical characteristics of the study population

Characteristic	Total (n = 261) n (%)
Hypertension	169 (64.8)
Diabetes mellitus	84 (32.2)
Cerebrovascular accident	46 (17.6)
Peripheral arterial disease	
Yes	18 (6.9)
No	198 (75.9)
Do not know	45 (17.2)
Renal failure	32 (12.3)
Patient-reported arrhythmia diagnosis	
Atrial fibrillation	43 (16.5)
Atrial flutter	2 (0.8)
Do not know	216 (82.8)
CHA ₂ DS ₂ -VA score (median)	3 (IQR: 2)

IQR, Interquartile range.

Table 3. Medication profile of the study population

Medication	Total (n = 261) n (%)
Oral anticoagulant therapy	
Warfarin	72 (27.6)
Rivaroxaban	72 (27.6)
Apixaban	64 (24.5)
Edoxaban	45 (17.2)
Dabigatran	8 (3.1)
ACEI/ARB	89 (34.1)
Sacubitril/valsartan	11 (4.2)
Beta-blocker	168 (64.4)
MRA	45 (17.2)
CCB	45 (17.2)
SGLT2i	36 (13.8)
Antiplatelet agent	21 (8.0)
Diuretic	69 (26.4)
Class I antiarrhythmic agent	7 (2.7)
Class III antiarrhythmic agent	16 (6.1)
Digoxin	36 (13.8)
Antidepressant	28 (10.7)
Levothyroxine	27 (10.3)
Statin	45 (17.2)
Proton pump inhibitor	47 (18.0)

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; MRA, Mineralocorticoid receptor antagonist; SGLT2i, Sodium-glucose cotransporter 2 inhibitor.

DOAC users incorrectly believed that food interactions existed, and 7.9% (15 of 189) reported unnecessarily restricting certain foods. These findings suggest that overly cautious or misguided dietary behaviors may persist in the absence of adequate patient education and provider guidance.

Understanding dose management represents another critical aspect of anticoagulation knowledge. Although nearly all patients (92.3%) correctly identified their prescribed dosing schedule (e.g., once or twice daily), virtually none could independently describe circumstances requiring dose adjustment. Overall, 98.9% reported that they did not know when anticoagulant doses should be modified and relied entirely on their physician to manage dosing. Only three patients (1%) provided any response to the open-ended question regarding dose adjustment, with varying degrees of accuracy. Consequently, almost no participants could identify clinical situations such as changes in renal function or elevated international normalized ratio (INR) values in warfarin-treated patients as potential indications for dose modification. Knowledge of the consequences of dose changes was also limited. Only 39.5% of patients recognized that reducing or omitting anticoagulant doses increases stroke risk. The remainder either did not know or provided incorrect answers, often focusing solely on reduced bleeding risk without acknowledging the associated increase in stroke risk. Similarly, only 33.7% understood that taking a higher-than-prescribed dose could increase bleeding risk. Many participants were uncertain, while some incorrectly believed that excessive dosing would increase stroke risk, suggesting confusion regarding the balance between thromboembolic protection and bleeding complications. Together, these findings highlight a limited understanding of the balance between thromboembolic protection and bleeding risk among patients receiving anticoagulant therapy.

Despite these gaps, basic awareness was generally high. Most patients (92%) knew they were taking an anticoagulant ("blood thinner"), and 90% were aware that they had a cardiac arrhythmia, even if they could not identify atrial fibrillation by name. Nevertheless, the overall findings reveal substantial deficiencies in disease- and treatment-specific knowledge.

Predictors of Knowledge Level

To identify factors associated with patient knowledge, a six-item composite knowledge score was calculated for each participant, awarding one point for each correct response regarding knowledge of the prescribed dosing frequency, correct identification of the indication for OAC therapy, awareness of potential side effects, awareness of the intended duration of anticoagulant therapy, awareness of potential drug interactions, and awareness of food interactions. Scores ranged from 0 to 6, with 0 indicating no correct answers and 6 indicating correct responses in all domains. The mean score was 2.8 ± 1.3 (median 3), and 112 participants (42.9%) scored ≤ 2, indicating substantial knowledge deficits.

Multivariable regression analysis was performed to identify independent predictors of knowledge. Age, sex, and education level were included in the primary multivariable model because they were selected a priori as key demographic predictors of patient knowledge and allowed a parsimonious approach within this modest-sized single-center cohort (Table 4). Increasing age was associated with lower knowledge scores, with each additional year corresponding to a 0.02-point decrease (P = 0.01). Men scored, on average, 0.6 points lower than women (P < 0.001), whereas each increment in educational attainment was associated with a 0.3-point increase in score (P < 0.001) (Table 4). The multivariate model explained approximately 13%

Table 4. Predictors of composite knowledge score

Variables	β (95% CI)	P
Age (per 1-year increase)	-0.020 (-0.035 to -0.004)	0.01
Male sex (vs. female)	-0.6 (-0.9 to -0.2)	<0.001
Education level (per category increase)	+0.3 (+0.2 to +0.5)	<0.001

Positive β coefficients indicate higher composite knowledge scores associated with the corresponding predictor. Model R² = 0.13; overall model P < 0.001.

of the variance in knowledge scores (R² = 0.13), suggesting that although these demographic factors contribute significantly to patient knowledge, additional unmeasured factors are also important. We also compared knowledge and medication-related behaviors between patients receiving warfarin and those receiving DOACs. In unadjusted subgroup analyses, patients treated with warfarin demonstrated higher knowledge scores than those receiving DOACs (3.57 ± 1.42 vs. 2.57 ± 1.21, P < 0.001). However, anticoagulant type was not retained in the primary multivariable model. Knowledge scores were not associated with self-reported medication adherence (Spearman ρ = -0.06, P = 0.35), likely reflecting the limited variability in adherence, as 94% of participants reported always taking their medication as prescribed. Anticoagulant type and adverse-event history were therefore treated as exploratory variables and were not included in the primary prediction model.

In an exploratory sensitivity analysis that additionally incorporated patient-reported adverse-event history, adverse-event history was not independently associated with knowledge score (β = +0.06, 95% confidence interval [CI]: -0.29 to +0.40, P = 0.75). The associations between knowledge score and age, sex, and educational level remained unchanged.

The internal consistency of the six-item knowledge index was modest (Cronbach's α = 0.50, 95% CI: 0.43-0.61). Removal of any individual item changed α by no more than 0.05, suggesting that each domain contributed unique information to the overall construct.

Adherence and Perceived Quality of Life

Despite the observed knowledge deficits, self-reported adherence was very high. Overall, 94% of patients reported "always" taking their anticoagulant as prescribed, while an additional 4% reported taking it "often" on schedule. No clinical or demographic variable was significantly associated with medication adherence. Very few participants reported non-adherence, with only 1.5% describing their adherence as "sometimes" or "rarely," and none reporting that they never took their medication as directed. Thus, based on self-report, approximately 98-99% of patients were regularly taking their OAC. High adherence rates were observed across anticoagulant types. Patients receiving warfarin were no more likely to report perfect adherence than those receiving DOACs, with no significant difference in the proportion reporting "always" taking their medication as prescribed (97% vs. 93%, P = 0.3). Consistent with these findings, 92.3% of participants correctly identified their prescribed dosing schedule (e.g., once

daily versus twice daily), whereas 7.7% were uncertain of the exact dosing frequency, which could potentially contribute to missed doses. When asked how they would manage a missed dose, the majority of patients (81%) reported that they would take the medication as soon as they remembered on the same day. We also explored the use of adherence aids and reminder strategies. Notably, two-thirds of participants (67%) reported using no specific reminder system, suggesting that medication-taking behavior was largely supported by habit, daily routine, or assistance from caregivers.

The only variable in the perception section that demonstrated a statistically significant bivariate association with adherence was the timing of anticoagulant administration in relation to meals ($\chi^2 = 17.0$, $P < 0.001$). Patients who consistently took their OAC with a meal or immediately after dinner reported no missed doses, whereas 22% of those who indicated that meal timing "did not matter" were classified as non-adherent.

Despite the knowledge deficits identified, patients generally perceived the impact of anticoagulant therapy on quality of life positively. More than half of the participants (approximately 58–60%) reported that OAC therapy had improved their overall QoL, with 13.4% describing the impact as "very positive" and 45.2% as "positive." Approximately one-third (33%) perceived no effect on their QoL, while only a small minority reported a negative impact (7.7% "negative" and 0% "very negative"). The generally favorable perception of therapy likely reflects the absence of major treatment-related complications and the belief that the benefits of stroke prevention outweigh treatment-related inconveniences. Indeed, 68% of patients reported no noticeable side effects or drawbacks. Positive perceptions were most commonly attributed to reassurance from stroke prevention and, among some warfarin-treated patients, the sense of security associated with regular monitoring. Negative perceptions were primarily related to treatment inconvenience, particularly INR monitoring requirements, or minor adverse effects such as bruising.

Among the 261 respondents, 89 patients (34.1%) reported that they had not received counseling or written information about OAC therapy at treatment initiation, while an additional 22 (8.4%) could not recall receiving such information. Overall, 42.5% of participants reported either no counseling or no recollection of counseling at treatment initiation. Consistent with this finding, nearly half (48%) considered the information provided by healthcare professionals to be insufficient. Many patients therefore sought information independently, although physicians remained the primary source of information when it was obtained.

Discussion

In this cross-sectional survey of patients with AF receiving OAC therapy, we found that although self-reported medication adherence was high, knowledge and understanding of AF and anticoagulation were often inadequate. While approximately three-quarters of patients correctly identified stroke prevention as the primary purpose of anticoagulation, substantially fewer could accurately name their arrhythmia or explain how anticoagulant therapy reduces stroke risk. Major knowledge gaps were observed in several clinically important domains, including recognition of adverse effects, awareness of drug

and food interactions, and understanding of the importance of maintaining the prescribed dosing regimen. These findings are concerning because patient knowledge is fundamental to the safe and effective long-term use of anticoagulant therapy.

One of the most notable findings was that approximately 11% of patients were unaware that they had an arrhythmia despite receiving long-term anticoagulant therapy. This suggests that some patients may be taking blood thinners without fully understanding either their diagnosis or the rationale for treatment. Alternatively, it may indicate that anticoagulant therapy is sometimes prescribed and managed without patients fully comprehending the underlying diagnosis. Patients may know that they have "an irregular heartbeat" or that they take a blood thinner for "the heart," yet remain unaware of the specific condition being treated. Such deficiencies in diagnostic understanding may limit appreciation of the benefits of therapy. Consistent with this finding, Lane et al.⁸ reported that many patients with AF have limited knowledge of both their condition and the role of anticoagulation in preventing complications. Without this understanding, patients may incorrectly perceive anticoagulants as treating symptoms or correcting the arrhythmia itself rather than preventing one of its most serious complications. This finding mirrors the general confusion observed in other studies. Similarly, the European Heart Rhythm Association (EHRA) survey found that 8% of respondents believed that the purpose of anticoagulation was to treat the arrhythmia, comparable to the 7.7% observed in our cohort.⁵ Notably, only 18% of participants in our study could independently explain how anticoagulation reduces stroke risk when asked an open-ended question. The vast majority either left the question unanswered, acknowledged that they did not know, or provided incorrect responses, highlighting substantial gaps in health literacy regarding AF and its treatment.

We also found that 42% (111 of 261) of patients reported either never receiving education about anticoagulant therapy or not recalling having received such information, while nearly half considered the information provided by healthcare professionals to be insufficient. Consequently, 60% expressed a desire for additional education regarding their anticoagulant medication. This need for further information was particularly common among patients with lower knowledge scores and among those who did not recall receiving counseling at treatment initiation. These findings highlight a significant missed opportunity in patient education. Current guidelines emphasize that initiation of OAC therapy should include discussion of the indication for treatment, expected benefits (stroke risk reduction), potential risks (bleeding), and relevant lifestyle considerations.⁵ Shared decision-making is increasingly recognized as a cornerstone of AF management, with patients expected to participate as informed partners in treatment decisions.⁵ However, our findings suggest that this goal is not consistently achieved in routine clinical practice, as many patients appeared to be passive recipients of an OAC prescription with limited understanding of its purpose. Although some counseling may have been provided but subsequently forgotten, healthcare professionals remain responsible for ensuring that patients understand the rationale, benefits, and risks of therapy.

Patients overwhelmingly identified physicians as their primary source of information about anticoagulation, with 86.2% reporting that they relied on their doctor for medication-related information. These findings underscore the central role of physicians in patient education and suggest that improvements in patient knowledge will depend largely on the quality of physician-patient communication, given the infrequent use of alternative information sources in this population.

Another notable finding was the exceptionally high self-reported adherence rate, with 94% of patients reporting that they "always" took their anticoagulant as prescribed. This observation should be interpreted cautiously. The face-to-face survey format, recruitment from a tertiary-care clinic, and inclusion of patients willing to participate may have introduced social-desirability and selection biases, resulting in overestimation of true adherence. Additionally, the predominance of older patients who were supported by family members may have contributed to the favorable adherence rates observed in our cohort. Nevertheless, these findings should be interpreted with caution, as they contrast with reports from other populations. For example, a recent analysis of U.S. Medicare beneficiaries found that only approximately 35% of patients initiating OAC therapy remained adherent after one year; adherence was associated with an approximately 40% lower risk of stroke compared with non-use.⁹ The high adherence observed in our study despite limited patient knowledge suggests that many patients may have been taking their anticoagulants primarily because of trust in their physician's recommendations rather than a detailed understanding of treatment benefits and risks. Furthermore, the absence of a significant association between knowledge and adherence, in contrast to several previous outpatient anticoagulation studies that reported modest positive correlations, likely reflects the pronounced ceiling effect created by uniformly high self-reported adherence in this tertiary-care population rather than a true lack of influence of patient knowledge on medication-taking behavior.^{10,11}

Regarding missed-dose management, it was encouraging that only one patient (0.4%) reported that they would take a double dose the following day, suggesting widespread awareness that dose doubling should be avoided. However, a substantial minority indicated that they would skip a missed dose rather than take it later on the same day, potentially resulting in periods of subtherapeutic anticoagulation and an increased risk of stroke.

Another important concern is the limited patient knowledge regarding adverse effects and bleeding-risk management associated with anticoagulant therapy. In our study, two-thirds of patients were unable to identify any potential side effects of their anticoagulant, and more than half reported never receiving information about bleeding risks. This lack of awareness is concerning because uninformed patients may either fail to recognize warning signs of serious bleeding, such as blood in the stool or urine, that require prompt medical attention, or become unnecessarily fearful after independently encountering information about bleeding risks, potentially leading to medication discontinuation without medical consultation. Knowledge deficits differed according to anticoagulant type. Patients receiving warfarin were more likely to be aware of medication-specific issues, including drug-food interactions

and the need for routine monitoring, likely reflecting the intensive education that often accompanies warfarin therapy through regular INR testing and dietary counseling. In contrast, patients prescribed DOACs may receive less reinforcement after treatment initiation. Nevertheless, substantial knowledge gaps persisted even among warfarin-treated patients. Approximately 57% were unable to identify specific side effects, and 88% of the overall cohort were unaware of potential drug interactions. Similar findings have been reported in a Brazilian primary-care study, in which 88% of patients receiving warfarin demonstrated inadequate anticoagulation knowledge.¹²

Knowledge Score

Educational attainment emerged as the strongest independent predictor of anticoagulation knowledge. In the fully adjusted model, each increase in the six-level educational scale (no formal education → primary school → middle school → high school → university → postgraduate education) was associated with a 0.3-point increase in the composite knowledge score (95% CI: 0.2-0.5, $P < 0.001$). University graduates had a mean score of 3.6 ± 1.5 , whereas participants with primary-school education had a mean score of 2.5 ± 1.3 , corresponding to a 1.1-point difference on the 0-6 scale. Knowledge gaps were particularly evident among patients with lower educational attainment. For example, only 69% of participants with primary education correctly identified stroke prevention as the purpose of anticoagulation, compared with 89% of university graduates. Similarly, only 4% of participants with primary education recognized relevant drug-drug interactions, compared with 24% of university graduates. Comparable education-related disparities have been reported elsewhere. In the EHRA patient survey, individuals without formal education demonstrated the poorest understanding of anticoagulant therapy and the lowest awareness of newer anticoagulant agents.¹³ Limited health-literacy cohorts in Brazil likewise demonstrated major deficits in warfarin knowledge and numeracy.¹² Taken together, our findings and prior evidence indicate that each increment in educational attainment is associated with a meaningful gain in patient knowledge, whereas patients with the least education remain at greatest risk of misinformation. Tailored, literacy-appropriate counseling using plain language, pictograms, and teach-back techniques may therefore be particularly useful for patients with lower educational backgrounds.

Age was inversely associated with knowledge, with older patients demonstrating lower knowledge scores. For each additional year of age, the knowledge score decreased by approximately 0.02 points (95% CI: -0.035 to -0.004, $P = 0.01$), indicating that younger patients were modestly more knowledgeable about anticoagulation. Sex was also a significant predictor: male sex was associated with lower knowledge even after adjusting for other factors. On average, men scored approximately 0.6 points lower than women (95% CI: -0.9 to -0.2, $P < 0.001$), suggesting that female patients may have had a better understanding of their therapy or may have been more engaged with medication-related education.

Together, younger age, female sex, and higher educational attainment explained a significant but modest proportion of the variance in knowledge scores (model $R^2 = 0.13$). These findings underscore the need to target older, male, and less-educated

patients for enhanced counseling, as these groups demonstrated the lowest awareness of therapy-related issues.

Knowledge profiles differed by anticoagulant type. Warfarin-treated patients demonstrated greater awareness of dietary restrictions and monitoring-related issues, likely reflecting repeated INR follow-up and more frequent counseling. However, knowledge gaps persisted even in this group, and some DOAC-treated patients reported unnecessary dietary restrictions, suggesting that warfarin-related advice may be incorrectly generalized to DOAC therapy. These findings support medication-specific counseling: warfarin users require reinforcement regarding INR monitoring and dietary consistency, whereas DOAC users should be informed that strict vitamin K restriction is generally unnecessary.

The higher knowledge score observed among warfarin-treated patients may reflect the more intensive follow-up traditionally required for vitamin K antagonist therapy, including INR monitoring, dietary counseling, and repeated patient-provider contact. This finding should be interpreted as hypothesis-generating because anticoagulant type was not randomly assigned and may reflect differences in follow-up intensity, monitoring requirements, patient selection, or prior counseling rather than a direct effect of warfarin therapy itself. Importantly, knowledge gaps persisted even among warfarin users, indicating that repeated clinical contact alone may not ensure adequate understanding.

Overall, our study adds to the growing body of evidence that patients with AF frequently have inadequate knowledge about their condition and its treatment. This aligns with observations by Li et al.,¹⁴ who reported generally inadequate knowledge and awareness of OAC therapy in a large sample of Chinese patients with AF. Similarly, Khanal et al.¹⁵ found that only 48% of Nepali patients with AF receiving OAC therapy achieved an adequate knowledge score on a formal assessment tool, indicating that more than half had substantial knowledge deficits. The consistency of these findings across diverse healthcare contexts, from Europe to Asia and the Americas, suggests that patient knowledge gaps are widespread and not limited to a single healthcare system.

Interventions to Bridge Knowledge Gaps

These findings have practical implications for routine AF care. Patient education should not be limited to a single explanation at treatment initiation; rather, it should be structured, repeated, and adapted to the patient's health-literacy level. At a minimum, counseling should cover the diagnosis of AF, the purpose of anticoagulation as stroke prevention, correct dosing, missed-dose management, bleeding warning signs, drug interactions, and medication-specific dietary issues, particularly for warfarin. Plain-language written materials, pictograms, teach-back methods, and involvement of family members or caregivers may be especially useful for older and less-educated patients.

The results also point to healthcare-system-related barriers. In busy outpatient settings, limited consultation time may reduce opportunities for detailed counseling, and DOAC-treated patients may receive less reinforcement because they do not require routine INR monitoring. Structured anticoagulation education pathways, nurse- or pharmacist-led counseling, and periodic reassessment of patient understanding may help close this gap without relying solely on physician time during routine visits.

Limitations and Strengths

This study has several limitations. First, the single-center design and modest sample size limit external validity. Because participants were recruited from a tertiary outpatient clinic, the findings may not be generalizable to rural populations, other regions of the country, primary-care settings, or healthcare systems with different sociocultural and educational characteristics. A multicenter study including different geographic regions and healthcare settings would provide a more comprehensive assessment of anticoagulation awareness in the broader population. Second, selection bias is possible because patients who agreed to participate in a face-to-face survey may have been more health-conscious or more engaged with their treatment than nonparticipants. Third, most variables, including medication adherence, prior counseling, and adverse-event history, were self-reported and therefore susceptible to recall and social-desirability bias. The very high self-reported adherence rate may therefore overestimate actual medication-taking behavior. Similarly, adverse-event reporting was based on patient reports and did not allow reliable adjudication of event timing, severity, or causal relationship with anticoagulant therapy. Finally, we did not use an objective health-literacy measure, pharmacy-refill data, pill counts, or electronic adherence monitoring.

The composite knowledge score should also be interpreted cautiously. It was designed as a pragmatic formative index of clinically relevant educational domains rather than as a formally validated psychometric scale. The score was also not formally validated against established instruments such as the Anticoagulation Knowledge Tool. Future studies should externally validate this scoring approach, assess test-retest reliability, and compare it with validated anticoagulation knowledge instruments and objective adherence metrics.

Despite these limitations, our study provides valuable insights. It included a relatively large sample for a single-center survey and used detailed face-to-face interviews to capture nuances of patient understanding that may be missed by self-administered questionnaires. Additionally, selected patient responses were cross-verified with medical records, enhancing the reliability of those data.

Conclusion

This study highlights a critical gap between the technical effectiveness of anticoagulant therapy and patients' understanding of that therapy. Although anticoagulants substantially reduce stroke risk in AF and are widely prescribed, many patients do not fully understand why they are taking these medications. This gap in awareness and knowledge may have important consequences, including improper medication use or premature discontinuation. There is a clear need to improve patient education strategies in AF care. Healthcare providers should ensure that patients are not only prescribed anticoagulants but are also given the knowledge and tools needed to use them safely and effectively. This may involve more structured counseling at treatment initiation and tailored educational materials. By improving patient knowledge and health literacy, clinicians can empower patients to become active partners in AF management, potentially enhancing adherence and medication safety. Ultimately, better-informed patients may achieve better clinical outcomes, including fewer strokes, fewer bleeding complications, and improved QoL while receiving anticoagulant therapy.

Appendix Online File: [https://jag.journalagent.com/tkd/abs_files/TKDA-23942/TKDA-23942_\(0\)_supplement.docx](https://jag.journalagent.com/tkd/abs_files/TKDA-23942/TKDA-23942_(0)_supplement.docx)

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Is Carbon Monoxide Poisoning a Potential Trigger for Spontaneous Coronary Artery Dissection? A Case Report and Review of the Literature

Karbonmonoksit Zehirlenmesi Spontan Koroner Arter Diseksiyonunu Tetikleyebilir mi? Olgu Sunumu ve Literatür Derlemesi

ABSTRACT

Spontaneous coronary artery dissection (SCAD) is a rare but potentially fatal cause of acute coronary syndrome (ACS), often associated with younger individuals and women without traditional cardiovascular risk factors. Carbon monoxide (CO) poisoning, a known cause of systemic hypoxia, has been implicated in various cardiovascular complications; however, its role in triggering SCAD remains scarcely reported. We present the case of a 55-year-old woman who developed SCAD following acute CO poisoning caused by a domestic gas leak. The patient presented with altered mental status and respiratory failure, requiring hyperbaric oxygen therapy. Following stabilization, typical anginal symptoms emerged, accompanied by rising cardiac biomarkers suggestive of myocardial injury. Coronary angiography revealed spontaneous dissections in both the distal left anterior descending artery and the distal right coronary artery without critical flow limitation. The patient was managed conservatively with medical therapy and remained asymptomatic at six-month follow-up. This case highlights the importance of considering SCAD in patients presenting with cardiac symptoms following CO poisoning and underscores the need for vigilance in atypical presentations of myocardial injury.

Keywords: Acute coronary syndrome, carbon monoxide poisoning, spontaneous coronary artery dissection

ÖZET

Spontan koroner arter diseksiyonu (SCAD), genellikle geleneksel kardiyovasküler risk faktörleri bulunmayan genç bireyler ve kadınlarla ilişkilendirilen, akut koroner sendromun (AKS) nadir ancak potansiyel olarak ölümcül bir nedenidir. Sistemik hipoksiye yol açtığı bilinen karbonmonoksit (CO) zehirlenmesi ise çeşitli kardiyovasküler komplikasyonlarla ilişkilendirilmiştir; ancak SCAD'ı tetikleyici rolü literatürde nadiren bildirilmiştir. Bu vaka raporunda ev içi doğalgaz sızıntısına bağlı akut CO zehirlenmesi sonrası SCAD gelişen 55 yaşındaki bir kadın hastayı sunmaktayız. Hasta, bilinç değişikliği ve solunum yetmezliği ile başvurdu ve hiperbarik oksijen tedavisi gereksinimi oldu. Klinik stabilizasyonun ardından tipik anjinal semptomlar ortaya çıktı ve artan kardiyak biyobelirteçler miyokardiyal hasarı düşündürdü. Koroner anjiyografide, sol ön inen arterin distal segmenti ile sağ koroner arterin distal segmentinde kritik akım kısıtlaması oluşturmeyen spontan diseksiyonlar saptandı. Hasta, medikal tedaviyle konservatif olarak izlendi ve altı aylık takipte asemptomatik kaldı. Bu olgu, CO zehirlenmesi sonrası kardiyak semptomlarla başvuran hastalarda SCAD'ın akılda tutulması gerektiğini ve miyokardiyal hasarın atipik tablolarında dikkatli değerlendirme yapılmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Akut koroner sendrom, karbonmonoksit zehirlenmesi, spontan koroner arter diseksiyonu

CASE REPORT OLGU SUNUMU

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Spontaneous coronary artery dissection (SCAD) is a rare but critical cause of acute coronary syndrome (ACS) and sudden cardiac death. It is characterized by separation of the coronary arterial wall by an intramural hematoma in the absence of atherosclerosis or external trauma.

Regardless of whether an intimal tear is present, a false lumen forms, and compression of the true lumen by the hematoma may impair coronary perfusion, potentially resulting in myocardial ischemia or infarction.¹

SCAD is more frequently observed in women and younger individuals, representing a significant cause of morbidity and mortality in these groups. Although once considered an uncommon phenomenon, recent consensus statements from the United States and Europe have highlighted that SCAD is no longer a rare entity and should be systematically investigated.^{2,3}

In younger adults, myocardial infarction may not only be explained by classical risk factors but also by a range of uncommon conditions. These include congenital or acquired structural abnormalities of the coronary arteries (such as aortic coarctation or inflammatory diseases like coronary arteritis), inherited metabolic or connective tissue disorders (for instance, familial hypercholesterolemia or hypertrophic cardiomyopathy), as well as lifestyle-related contributors, including illicit drug use—particularly cocaine and amphetamines—tobacco exposure, diabetes mellitus, psychological stress, and obesity.⁴

Despite growing knowledge about the epidemiologic, clinical, and angiographic features of SCAD, its true prevalence remains unclear. This uncertainty mainly results from underdiagnosis, which can be attributed to the low index of suspicion for ACS in young female patients—even in the presence of typical symptoms—limitations in conventional coronary angiography, and a general lack of clinical awareness. Furthermore, no high-quality, evidence-based treatment guidelines specific to SCAD currently exist; existing recommendations are largely based on expert consensus.⁵

Carbon monoxide (CO) poisoning leads to systemic hypoxia due to its 250–300 times greater affinity for hemoglobin compared to oxygen, forming carboxyhemoglobin, a highly stable complex that dissociates slowly. Although CO poisoning can affect various organ systems, its neurological and cardiac effects are particularly prominent due to the high oxygen demand of these tissues. Despite its prognostic significance, limited studies have addressed myocardial injury specifically in the context of CO poisoning.^{6,7}

Herein, we report a case of SCAD identified after acute carbon monoxide poisoning following exposure to a domestic natural gas leak.

Case Report

A 55-year-old woman with a history of hypertension and fibromyalgia contacted emergency services after experiencing severe dyspnea that woke her from sleep. Upon arrival, emergency responders noted impaired consciousness and orientation, necessitating immediate transport to the nearest healthcare facility.

On admission, her vital signs were as follows: blood pressure 117/71 mmHg, heart rate 90 bpm, oxygen saturation 95% on room air, and body temperature 36.5°C. Neurological examination revealed a Glasgow Coma Scale (GCS) score of 9, with diminished spontaneous motor responses, inappropriate verbal reactions, and localization of painful stimuli.

Other physical findings were unremarkable. Laboratory tests showed hemoglobin 11.1 g/dL, platelets $175 \times 10^3/\mu\text{L}$, creatinine 0.6 mg/dL, total cholesterol 234 mg/dL, low-density

ABBREVIATIONS

ACS	Acute coronary syndrome
CO	Carbon monoxide
COHb	Carboxyhemoglobin
ECG	Electrocardiogram
GCS	Glasgow Coma Scale
HBO	Hyperbaric oxygen therapy
IVUS	Intravascular ultrasound
LAD	Left anterior descending
NSTEMI	Non-ST elevation myocardial infarction
SCAD	Spontaneous coronary artery dissection
TIMI	Thrombolysis in myocardial infarction

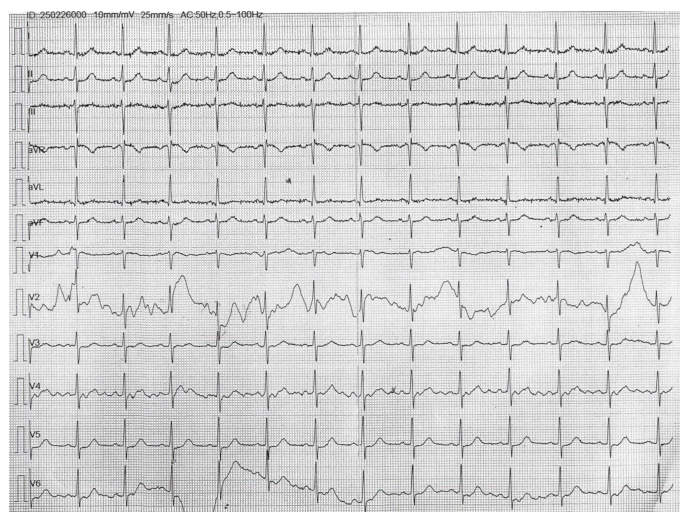


Figure 1. The patient's initial electrocardiogram (ECG) showed normal sinus rhythm.

lipoprotein 160 mg/dL, high-density lipoprotein 51.7 mg/dL, triglycerides 113.3 mg/dL, D-dimer 237 ng/mL, and creatine kinase-myocardial band 8.8 U/L. Arterial blood gas analysis revealed pH 7.56, pCO_2 28.8 mmHg, pO_2 34.1 mmHg, HCO_3^- 25.4 mmol/L, base excess 3.3 mmol/L, lactate 5.2 mmol/L, and carboxyhemoglobin (COHb) 29.9%.

The initial electrocardiogram (ECG) showed sinus rhythm (Figure 1). Given the elevated COHb levels and the patient's residence in a gas-heated home, acute carbon monoxide poisoning was suspected. The duration of CO exposure was unknown, and the patient lived alone. The National Poison Control Center was consulted, and high-flow oxygen therapy at 8 L/min was initiated per their recommendation.

The patient was transferred to our center for hyperbaric oxygen therapy (HBO) and admitted to a level 2 intensive care unit for monitoring. During transfer and initial management, she received normobaric oxygen therapy via mask for approximately two hours. Approximately three hours after initial CO exposure, the patient underwent HBO therapy at 2.4 absolute atmospheres for two hours in a multiplace chamber. Post-treatment, COHb levels decreased to 9%, allowing a transition to low-flow oxygen therapy. The patient's consciousness gradually improved, and her GCS returned to 15.

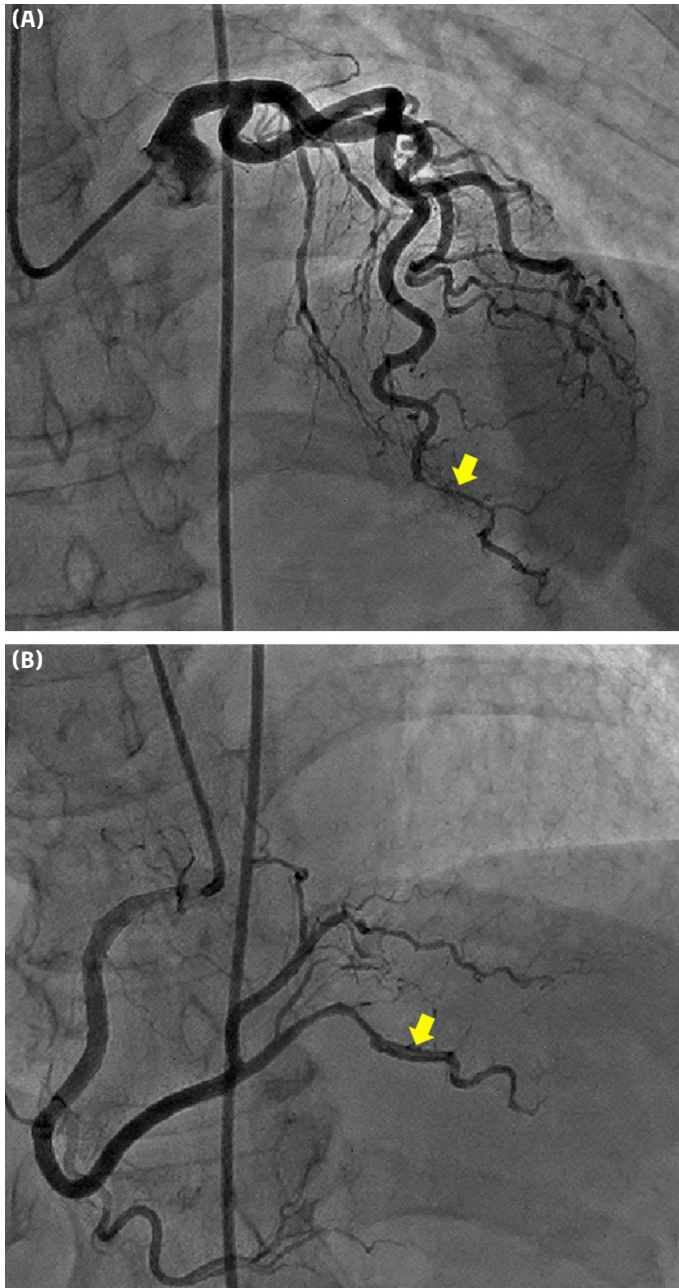


Figure 2. (A) Spontaneous coronary artery dissection (SCAD) is observed in the distal segment of the left anterior descending (LAD) artery, with luminal narrowing clearly visible. (B) A coronary artery dissection located in the posterior descending artery (PDA) branch of the right coronary artery (RCA) is observed. The image demonstrates luminal irregularity and narrowing associated with the dissection plane.

Following the restoration of consciousness, the patient reported chest pain described as pressure-like. Serial troponin I measurements revealed progressive elevation (204 → 307 → 1100 ng/L), prompting a cardiology consultation with a preliminary diagnosis of non-ST elevation myocardial infarction (NSTEMI). Echocardiography showed no regional wall motion abnormalities. After administration of a 300 mg loading dose of acetylsalicylic acid, the patient underwent coronary angiography.

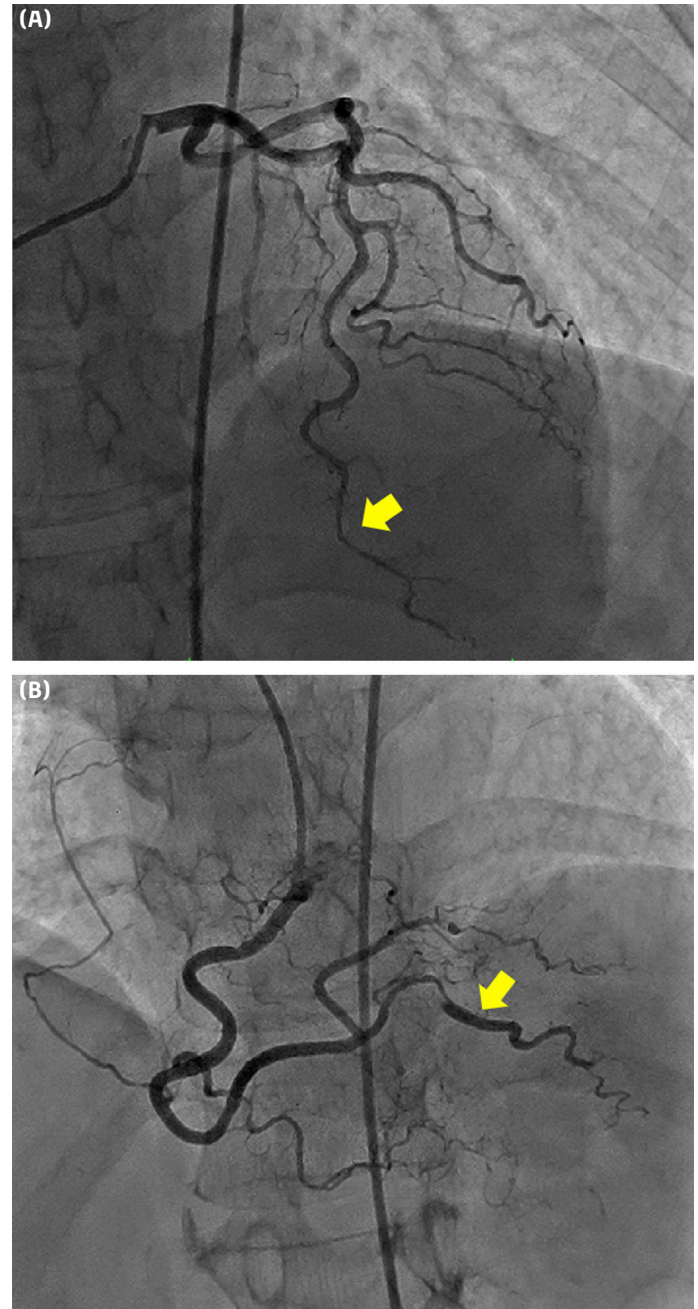


Figure 3. (A) Follow-up coronary angiography at six months demonstrates mild improvement in the luminal appearance at the dissection site in the distal left anterior descending (LAD) artery. (B) The six-month follow-up angiography demonstrates mild improvement in the luminal appearance of the posterior descending artery (PDA) segment compared with the initial image, although subtle irregularities persist.

Angiography revealed normal flow (thrombolysis in myocardial infarction [TIMI] 3 flow) in the left anterior descending (LAD) and circumflex arteries, but with a dissection in the distal LAD (Figure 2A). The distal right coronary artery (RCA) also showed dissection in the posterior descending artery branch, with preserved TIMI 3 flow (Figure 2B). No percutaneous intervention was performed; the patient was managed conservatively with a

Table 1. Carbon monoxide-induced cardiac complications: summary of reported cases (6, 7, 10, 13–18)

No	Author/year	Patient	Cardiac complication	Key findings	Treatment/outcome
1	Önal et al. ¹²	27-year-old male	ST-elevation MI	High-level CO exposure; thrombotic occlusion of PDA	Anticoagulation → complete resolution
2	Song et al. ¹³	47-year-old female	Prinzmetal angina	ST elevation + T wave inversion; normal coronaries	Vasospasm therapy; recovery
3	Küçükosman et al. ¹⁴	68-year-old female	NSTEMI	Myocardial injury; LV dysfunction	CABG; successful outcome
4	Jankowska et al. ⁹	48-year-old male	NSTEMI	Smoke/CO inhalation; elevated troponin; normal coronaries	Conservative treatment; recovery
5	Camacho et al. ⁷	56-year-old male	STEMI	RCA occlusion; COHb ~26%	PCI with stent; good recovery
6	Gao et al. ⁶	73-year-old female	NSTEMI + LV failure	Severe CO poisoning; 3-vessel disease	Oxygen + antithrombotic therapy + PCI
7	Oindi et al. ¹⁵	21-year-old pregnant female/23-year-old male	Takotsubo-like CM	CO-induced cardiomyopathy	Oxygen/HBO; supportive care
8	Kim et al. ¹⁶	47-year-old male	CO-induced cardiomyopathy + LV thrombus	Charcoal CO exposure; LV dysfunction	Supportive care; follow-up
9	Roy et al. ¹⁷	Young male	STEMI + VTE	MI + pulmonary embolism due to CO	Standard MI + PE treatment
10	Gao et al. ⁶	73-year-old female	NSTEMI	CO poisoning; dyspnea; LV dysfunction; 3-vessel disease	Oxygen + antithrombotic therapy + PCI; good recovery

CABG, Coronary artery bypass graft surgery; CM, Cardiomyopathy; CO, Carbon monoxide; HBO, Hyperbaric oxygen; LV, Left ventricle; MI, myocardial infarction; NSTEMI, Non-ST elevation myocardial infarction; PCI, Percutaneous coronary intervention; PDA, Posterior descending artery; PE, Pulmonary embolism; RCA, right coronary artery; VTE, Venous thromboembolism.

diagnosis of SCAD. During follow-up, chest pain subsided, and troponin levels decreased to 61.1 ng/L.

The patient was discharged on aspirin, atorvastatin, metoprolol, and perindopril, and remained asymptomatic at six-month follow-up with regular cardiology outpatient care. Coronary angiography performed six months later showed mild improvement in the dissection areas with no evidence of progression (Figure 3A–B).

Discussion

Acute carbon monoxide poisoning can cause not only neurological and pulmonary effects but also significant myocardial injury. More than one-third of patients with moderate-to-severe CO poisoning develop myocardial involvement within the first week. CO leads to cellular hypoxia and energy depletion through mitochondrial dysfunction, oxidative stress, and cytochrome c oxidase inhibition, resulting in anaerobic metabolism, acidosis, and apoptosis. It may also provoke coronary vasospasm, promote thrombosis, and increase platelet aggregation, thereby worsening myocardial damage.^{6,8}

When examining the potential pathophysiological mechanisms through which acute carbon monoxide exposure may predispose the arterial wall to dissection, it becomes evident that CO-induced hypoxia increases oxidative stress, triggers endothelial dysfunction, disrupts nitric-oxide-mediated vasomotor regulation, and activates inflammatory pathways. Each of these processes may contribute to weakening the structural integrity of the vessel wall. Experimental models have demonstrated that hypoxic injury can lead to smooth muscle cell necrosis, disruption of the extracellular matrix, and increased vascular permeability—changes that may facilitate the development of an intimal tear or intramural hematoma.

Additionally, the catecholamine surge and coronary vasospasm associated with acute CO poisoning may impose substantial shear stress on the arterial wall, further amplifying this vulnerability. These mechanisms align with the pathophysiological framework described by Hayes et al.,² in which underlying arteriopathy, mechanical stressors, and vascular inflammation collectively contribute to SCAD formation. Although CO-related SCAD has not been previously characterized in detail, the combined effects of hypoxia-driven oxidative injury, endothelial dysfunction, and catecholamine-mediated shear forces may create a transient weakness within the coronary arterial wall, potentially serving as a trigger for dissection in susceptible individuals.

Given the nonspecific nature of CO poisoning symptoms, cardiac biomarkers and ECG should be assessed routinely, even in the absence of chest pain. COHb measurement supports the diagnosis; however, if clinical suspicion is high, treatment should not be delayed.

Early administration of 100% oxygen is recommended in all suspected cases. Although evidence on HBO therapy remains limited, it may reduce complications and improve outcomes.⁹ HBO is particularly indicated in patients with COHb >25%, loss of consciousness, neurological deficits, cardiac ischemia, severe metabolic acidosis, or pregnancy.

As in our case, SCAD often presents with elevated troponin levels and an initial diagnosis of NSTEMI. As reported in the literature, in patients with NSTEMI and multivessel disease, immediate complete revascularization significantly reduces the rates of cardiac death, recurrent myocardial infarction, and rehospitalization compared to staged or incomplete revascularization strategies.¹⁰ However, in SCAD cases presenting with troponin elevation, the clinical course may differ, and conservative management without intervention may be sufficient.

Intravascular imaging (intravascular ultrasound or optical coherence tomography) could not be performed due to the unavailability of these modalities at the time of the procedure. This represents a limitation of our report, as intravascular imaging could have further clarified the underlying mechanism of the dissection.

An important study that exemplifies carbon monoxide-related cardiac injury in the literature is that of Cho et al.,¹¹ who conducted a prospective investigation assessing late gadolinium enhancement on cardiac magnetic resonance imaging in 104 patients with CO-induced myocardial injury, demonstrating persistent myocardial fibrosis in the majority, with implications for long-term cardiac function.

Several case reports highlight the cardiac risks associated with CO poisoning; Önal et al.¹² reported ST-elevation myocardial infarction (MI) in a 27-year-old male with no cardiovascular risk factors after high-level CO exposure. Coronary angiography revealed thrombotic occlusion of the posterior descending artery, which resolved with anticoagulation.

Song et al.¹³ described a 47-year-old woman who developed Prinzmetal's angina after CO poisoning, presenting with ST elevation and T-wave inversion but without significant coronary stenosis on angiography.

Jankowska et al.⁹ reported NSTEMI in a 48-year-old man exposed to smoke inhalation during a house fire, with ECG changes and elevated troponins despite normal coronaries.

In the case reported by Küçükosman et al.,¹⁴ NSTEMI developed following carbon monoxide poisoning, and the patient was successfully treated with coronary bypass surgery. The study emphasized that among the cardiovascular complications of CO poisoning, myocardial injury, left ventricular dysfunction, and arrhythmias are of particular significance.

The reported cases indicate that carbon monoxide exposure can trigger a wide spectrum of cardiac manifestations, including ST-elevation myocardial infarction, NSTEMI, coronary vasospasm, stress-induced cardiomyopathy, and even thrombotic events. Although the underlying mechanisms range from coronary thrombosis and vasospasm to direct myocardial toxicity, these cases collectively demonstrate a marked susceptibility of the myocardium to CO-related injury. A concise summary of the cases reported in the literature is presented in Table 1.

This case is unique because the development of SCAD following acute carbon monoxide poisoning has been reported extremely rarely in the literature, and despite the absence of atherosclerotic risk factors, angiography demonstrated a typical dissection pattern. Although the patient improved with oxygen and HBO therapy, the lack of pre-existing coronary artery disease or major risk factors, together with the angiographic confirmation of a classic dissection appearance, strongly supports the possibility that SCAD was precipitated by acute CO exposure.

Conclusion

This case underscores that carbon monoxide poisoning is not limited to its classical hypoxic effects but can trigger rare, potentially fatal cardiac events such as SCAD. The absence of significant atherosclerotic risk factors and angiographic

confirmation of dissection patterns in this patient point toward a causal relationship with CO exposure.

As an important clinical message, SCAD should be considered in the differential diagnosis of patients presenting with chest pain or elevated troponin levels following CO poisoning. In such patients, performing appropriate noninvasive assessment before proceeding with invasive interventions may help reduce the risk of misdiagnosis or unnecessary procedures.

Recognizing CO-induced SCAD may enhance our understanding of its pathophysiology and guide future management strategies.

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Informed Consent: Detailed information was given to the patient regarding the possible contribution of the case report to the literature. The patient provided written and verbal consent for publication of the case report.

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Calming the Adrenergic Storm: Mechanical Support Devices as a Life-Saving Stormbreaker in Iatrogenic Takotsubo Syndrome

İatrojenik Takotsubo Sendromunda Hayat Kurtarıcı Bir Çözüm: Adrenerjik Fırtınayı Dindiren Mekanik Destek Cihazları

ABSTRACT

Takotsubo syndrome is a cardiomyopathy characterized by transient ventricular dysfunction caused by excessive sympathetic discharge, which may potentially lead to a fatal outcome. This case report presents the successful management of a 41-year-old female patient with iatrogenic Takotsubo syndrome complicated by cardiogenic shock. The condition was triggered by the inadvertent administration of norepinephrine, which occurred due to a medication error in which it was mistaken for amiodarone because of look-alike/sound-alike packaging and name similarity. The management strategy focused on the use of mechanical support devices rather than agents that perpetuate the adrenergic discharge underlying the pathophysiology.

Keywords: Acute heart failure, arrhythmias, atrial fibrillation-flutter, cardiogenic shock, cardiomyopathy, catheter ablation, ECMO, takotsubo syndrome

ÖZET

Takotsubo Sendromu, aşırı sempatik deşarjin neden olduğu geçici ventriküler disfonksiyon ile karakterize ve potansiyel olarak ölümcül bir sonuca yol açabilen bir kardiyomiyopatidir. Bu olgu sunumu, kardiyojenik şok ile komplike olmuş iyatrojenik Takotsubo sendromu tanılı 41 yaşındaki bir kadın hastanın başarılı yönetimini sunmaktadır. Durum, paketleme ve ticari isim benzerliği nedeniyle amiodaron yerine yanlışlıkla norepinefrin uygulanması sonucu tetiklendi. Yönetim stratejisi, patofizyolojiyi tetikleyen adrenerjik deşarjı devam ettiren ajanlar yerine, mekanik destek cihazlarının kullanımına odaklanmıştır.

Anahtar Kelimeler: Akut kalp yetersizliği, aritmiler, atriyal fibrilasyon-flutter, kardiyojenik şok, kardiyomiyopati, kateter ablasyonu, ECMO, Takotsubo sendromu

Takotsubo syndrome (TTS) is a cardiomyopathy characterized by transient left ventricular dysfunction induced by emotional or physical stress. While the exact pathophysiology remains uncertain, sympathetic stimulation is frequently implicated.¹⁻⁴ The clinical spectrum ranges widely, from incidental diagnosis to cardiogenic shock. Due to its rarity, insufficient clinical experience with TTS poses challenges for both diagnosis and management. This case report highlights the successful management of an unexpected and catastrophic case of TTS.

This patient provided written consent for publication of this report.

Case Report

A 41-year-old female patient with a past medical history of paroxysmal atrial fibrillation treated with cryoballoon ablation one year prior, and an ischemic stroke, was admitted to the electrophysiology laboratory for radiofrequency ablation due to recurrent atrial fibrillation (AF). The procedure was performed under general anesthesia, with induction using propofol 200 mg, fentanyl 100 mcg, and rocuronium 50 mg, followed by maintenance with inhaled sevoflurane. Left atrial anatomy and voltage mapping were performed using the EnSite X Cardiac Mapping System

CASE REPORT OLGU SUNUMU

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(Abbott Laboratories, USA), the Advisor HD Grid Mapping Catheter (Abbott Laboratories, USA), and the TactiCath Quartz Contact Force Ablation Catheter (Abbott Laboratories, USA). Additionally, isochronal late activation mapping was performed. It was observed that all pulmonary veins were isolated except the right lower pulmonary vein. Due to partial reconnection of the right lower pulmonary vein, the anterior antral region was reisolated. Following successful isolation of the reconnected pulmonary vein, the patient experienced recurrent episodes of AF. During the procedure, direct current cardioversion (DCCV) was performed a total of eight times. The first atrial ectopic beat that initiated the recurrent AF episodes was observed to originate near the distal electrode region of the coronary sinus catheter. An empirical mitral isthmus line was created after observing normal voltage recordings forming a narrow transitional zone in the mitral isthmus region. However, as AF paroxysms continued, a possible trigger originating from the vein of Marshall was considered, and vein of Marshall alcohol ablation was planned for a separate session; therefore, the procedure was terminated.

During the awakening phase following the procedure, intravenous (IV) administration of one ampule (150 mg) of amiodarone was ordered to prevent recurrence of AF. Following the administration of amiodarone, the patient experienced sudden tachycardia and a hypertensive response, followed by profound hypotension. Blood pressure was temporarily managed with IV ephedrine. Surprisingly, ST-segment elevation was observed on the monitor (Figure 1). Transthoracic echocardiography (TTE) revealed an ejection fraction (EF) of 35% with apical ballooning

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
ARB	Angiotensin receptor blockers
DCCV	Direct current cardioversion
EF	Ejection fraction
IABP	Intra-aortic balloon pump
IV	Intravenous
LASA	Look-alike/sound-alike
LV	Left ventricular
LVOTO	Left ventricular outflow tract obstruction
RVR	Rapid ventricular response
TTE	Transthoracic echocardiography
TTS	Takotsubo syndrome
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation

and severe hypokinesia of the anterior wall of the left ventricle, consistent with Takotsubo syndrome (Video 1). Based on these findings, urgent coronary angiography was performed. However, no significant coronary artery pathology was identified to explain the clinical presentation (Figure 2). Ventriculography findings were consistent with Takotsubo cardiomyopathy (Video 2). Following the diagnosis of Takotsubo syndrome, the patient experienced rapid hemodynamic deterioration requiring escalating supportive measures. The temporal sequence of clinical events, from symptom onset to initiation of mechanical circulatory support and subsequent recovery, is summarized in Figure 3. Awakening was achieved with sugammadex and paracetamol. Neurological examination was normal. Due to

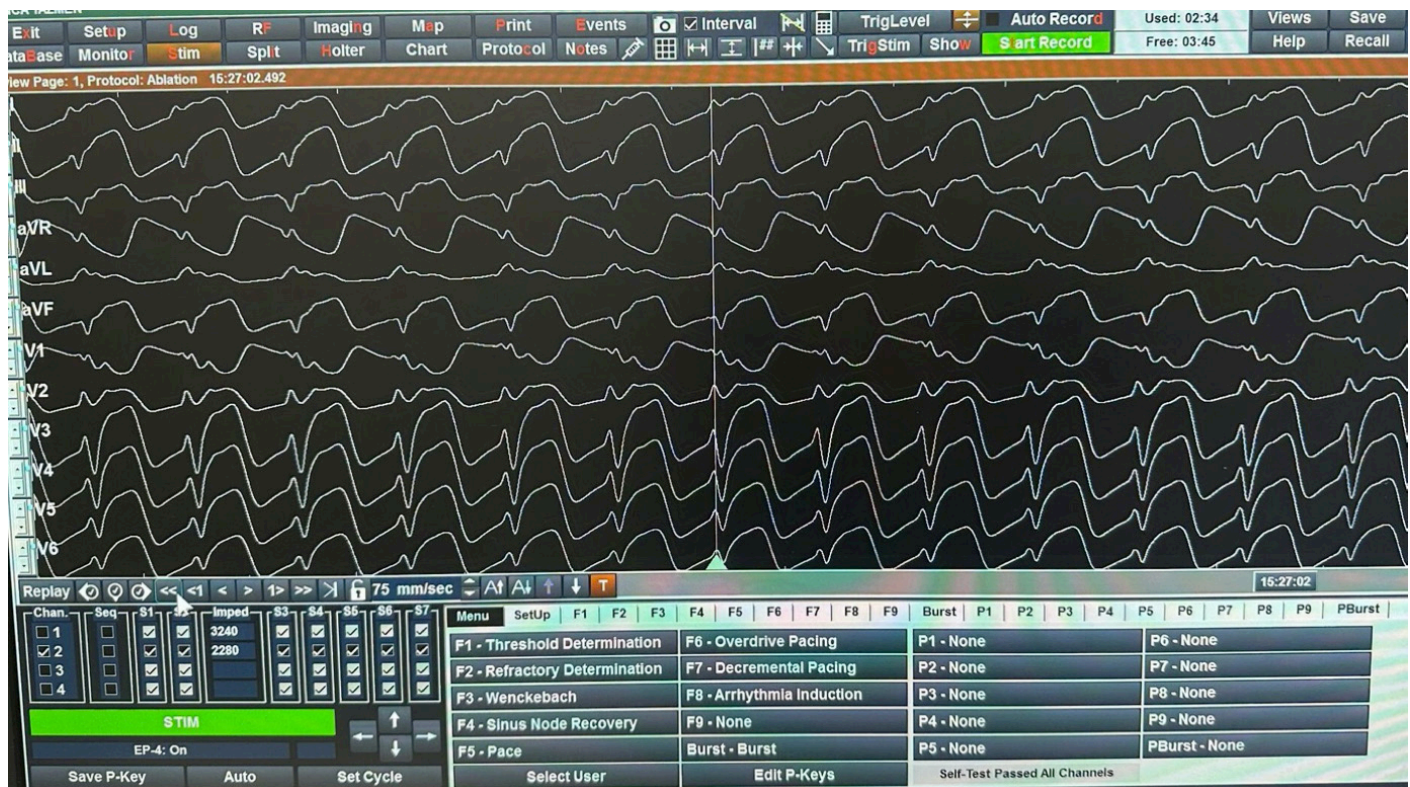


Figure 1. The monitor shows ST elevation in leads D1, D2, D3, aVF, and V2-V6, while ST depression is observed in leads aVR and V1.

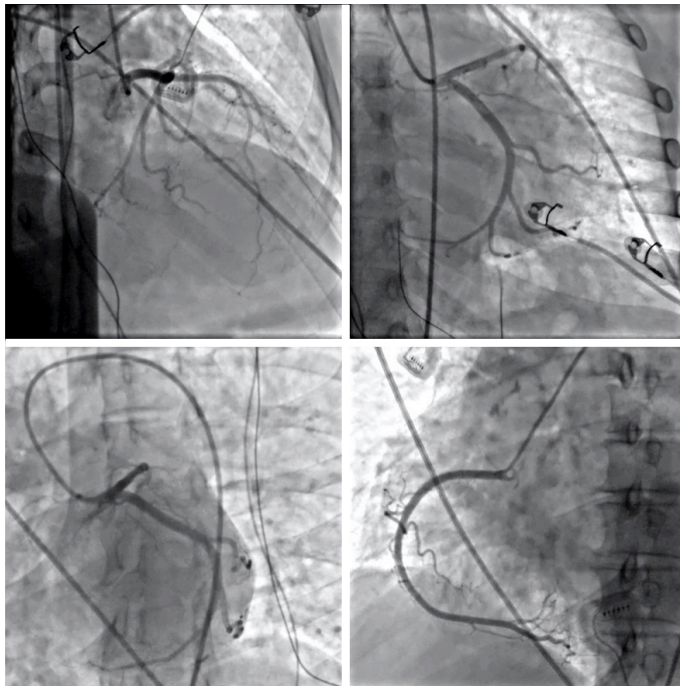


Figure 2. Coronary angiography reveals no significant obstruction in the major epicardial coronary arteries, with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow present in all vessels.

acute myocardial injury and profound hypotension, further sedation was not administered, and the patient was extubated before leaving the operating room.

The patient was transferred to the coronary intensive care unit (ICU) with an IV norepinephrine infusion. It was suspected, and later confirmed, that the nurse mistakenly administered one ampule of norepinephrine (Cardenor®) instead of amiodarone (Cordarone®). The patient, presenting with cardiogenic shock, continued to experience hypotension despite IV norepinephrine support, necessitating the initiation of IV dopamine and dobutamine infusions.

During ICU follow-up, the patient experienced recurrent rapid ventricular response (RVR-AF) and persistent hemodynamic instability. Despite two attempts at DCCV, both rhythm and rate

control were only temporarily achieved, and RVR-AF recurred. Additionally, IV digoxin failed to achieve adequate rate control. At this point, a maintenance amiodarone infusion of 37.5 mg/hour was initiated. During this period, the patient's EF dropped to 10%, and she developed noninvasive mechanical ventilator-dependent respiratory failure. The patient was subsequently intubated. To reduce catecholaminergic discharge and allow discontinuation of norepinephrine, dopamine, and dobutamine infusions, a levosimendan infusion was initiated. A bedside intra-aortic balloon pump (IABP) was implanted. Due to insufficient perfusion, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was initiated via the femoral route. Systemic anticoagulation was achieved using an unfractionated heparin infusion.

After completing 48 hours of mechanical circulatory support, the patient demonstrated spontaneous awakening, successfully self-extubated, and tolerated discontinuation of the levosimendan infusion. Despite not meeting criteria for heparin-induced thrombocytopenia, anticoagulant therapy was switched to bivalirudin due to a decline in platelet count during heparin infusion. Seventy-five hours later, with normalization of the EF to 60%, IABP and VA-ECMO support were successfully discontinued (Video 3).

The patient was monitored for an additional 48 hours without pharmacologic or mechanical hemodynamic support. As her clinical condition remained stable, the patient was discharged on day 7. At discharge, the patient was prescribed edoxaban 60 mg once daily and metoprolol 150 mg once daily. Follow-up visits at two weeks and one month were uneventful, with the EF remaining stable at 60%.

Discussion

Takotsubo syndrome was first described in the literature in a patient presenting with symptoms and electrocardiographic changes resembling acute coronary syndrome but with angiographically normal coronary arteries. Ventriculography revealed apical ballooning of the left ventricle with a narrow neck during systole.⁴

Emotional triggers such as grief, fear, panic, or even happiness are frequently reported. Physical triggers, including intracranial hemorrhage, stroke, epileptic seizures, severe respiratory or gastrointestinal illnesses, infections, endocrine disorders, and trauma, have also been documented.⁴⁻⁶

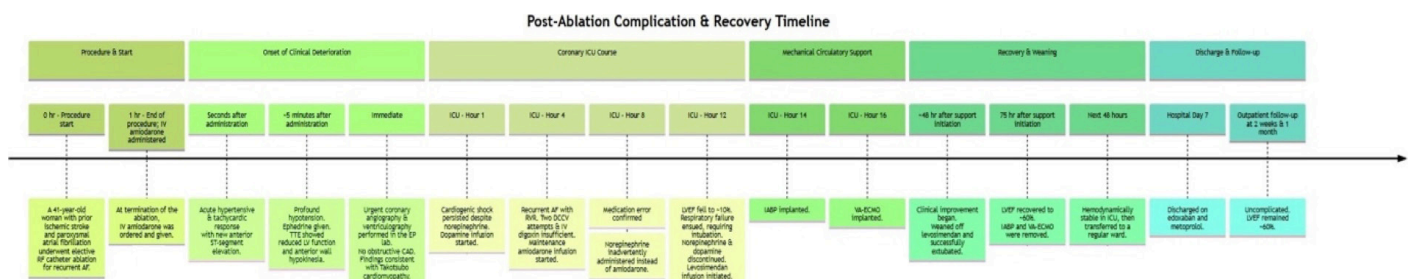


Figure 3. Timeline of the clinical course following catheter ablation, illustrating progression from inadvertent norepinephrine administration to cardiogenic shock, initiation of mechanical circulatory support, and recovery of left ventricular function.

AF, Atrial fibrillation; CAD, Coronary artery disease; DCCV, Direct current cardioversion; EF, Ejection fraction; EP lab, Electrophysiology laboratory; IABP, Intra-aortic balloon pump; ICU, Intensive care unit; TTE, Transthoracic echocardiography; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation.

Iatrogenic TTS may occur due to medications administered at appropriate doses and indications during critical clinical situations, such as anaphylaxis, or as a result of incorrect dosing or improper indications. However, consistent with pathophysiological hypotheses, the majority of cases reported in the literature involve medications that exert direct or indirect agonistic effects on the sympathoadrenergic system.⁷⁻¹⁸

In our case, the triggering factor was identified as a medication error attributable to a classic look-alike/sound-alike (LASA) phenomenon. At our institution, amiodarone is available under two interchangeable brand names (Amidovin® and Cordarone®), depending on supply. At the time of the procedure, Amidovin® was stocked in the electrophysiology laboratory medication cabinet, while norepinephrine was available under the brand name Cardenor®. During verbal communication, the request for amiodarone was interpreted as Cordarone®. However, Cordarone® was not present in the cabinet, and the visual similarity between the ampoules of Amidovin® and Cardenor®, combined with the phonetic resemblance of the brand names Cardenor® and Cordarone®, contributed to the inadvertent administration of norepinephrine instead of amiodarone.

The treatment of TTS primarily focuses on managing three key issues: 1) acute heart failure/pulmonary edema and cardiogenic shock, 2) prevention and treatment of thromboembolism, and 3) prevention and treatment of arrhythmias.^{4,19} A tailored approach based on hemodynamic profiling and assessment for left ventricular outflow tract obstruction (LVOTO) is recommended. In stable patients without LVOTO, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), along with beta-blockers, may be considered. Diuretics and nitroglycerin are appropriate for pulmonary edema but should be avoided in the presence of LVOTO due to the risk of exacerbating obstruction. When hypotension or shock is primarily driven by LVOTO, short-acting beta-blockers may be beneficial, while IABP support should be avoided. When shock is due to primary pump failure, catecholaminergic agents should be avoided whenever possible, levosimendan may be preferred, and VA-ECMO reserved for refractory cases. Anticoagulation should be considered in patients at risk of thromboembolism. Arrhythmia management includes beta-blocker use and avoidance of QT-prolonging drugs. ACE inhibitor or ARB therapy is generally continued during recovery until resolution of wall motion abnormalities. Underlying comorbid conditions should be managed according to standard clinical practice.¹⁹

In our case, specific circumstances prevented the implementation of certain literature-based recommendations in two of these fundamental areas.

First, the patient had a history of paroxysmal atrial fibrillation, and rapid ventricular response atrial fibrillation developed despite repeated electrical cardioversion following the onset of cardiogenic shock, likely related to the procedure. This condition, unresponsive to intravenous digoxin therapy, contributed to worsening hemodynamic tolerance. It also delayed the decision to implant an intra-aortic balloon pump due to a decreased likelihood of achieving optimal synchronization. Despite ongoing debate regarding the safety of antiarrhythmic agents

in TTS, amiodarone was initiated in our patient due to persistent RVR-AF causing severe hemodynamic compromise. Alternative rate- and rhythm-control strategies, including repeated electrical cardioversion and intravenous digoxin, were ineffective. Compared with other antiarrhythmic agents, amiodarone has a relatively neutral inotropic profile and is therefore considered a reasonable option in critically ill patients.²⁰⁻²² Nevertheless, amiodarone use in TTS warrants caution, as QTc prolongation has been reported in approximately 4-9% of cases and may predispose to malignant ventricular arrhythmias.^{4,19,23} In our patient, despite the necessity for high-dose amiodarone due to a lack of therapeutic alternatives, no QT-related adverse events or arrhythmic complications were observed, and only modest benefit in rate control was achieved.

Second, in our case, short-term use of norepinephrine, dopamine, and dobutamine was necessary for blood pressure regulation despite awareness of their potential to exacerbate the underlying pathophysiology. At the time of rapid clinical deterioration, the medication error had not yet been recognized, and the inadvertent administration of norepinephrine instead of amiodarone was confirmed only retrospectively. Therefore, the initial clinical approach was directed toward undifferentiated cardiogenic shock following a complex electrophysiological procedure, in accordance with institutional emergency protocols. However, due to ongoing hemodynamic instability, these agents were promptly discontinued and replaced with levosimendan, intra-aortic balloon pump support, and subsequently veno-arterial ECMO to achieve hemodynamic stabilization.

Complete clinical and echocardiographic recovery was achieved within three days. During the course of cardiogenic shock, it was observed that dobutamine and levosimendan infusions did not improve contractility in the severely affected left ventricular apex due to TTS. Despite the rapid heart rate, IABP support contributed significantly to hemodynamic stabilization, while ECMO was highly effective in maintaining systemic perfusion until contractility was restored. We believe that in patients with TTS, the use of mechanical support devices, rather than agents that trigger catecholamine release—the fundamental driver of the underlying pathophysiology—represents a highly rational approach until recovery of left ventricular (LV) function is achieved.

Case reports in the literature describe instances similar to ours, in which TTS developed following accidental administration of norepinephrine instead of other agents, inadvertent high-dose norepinephrine administration, or unavoidable use during routine procedures. In most reported cases, left ventricular function recovered with conservative management using oral heart failure therapy, occasionally supplemented by short-term mechanical support such as IABP. In contrast, in our patient, the medication error was recognized after clinical deterioration had already occurred, and the course was marked by severe cardiogenic shock requiring early escalation to advanced mechanical circulatory support. Once TTS was suspected, catecholaminergic agents were promptly discontinued and replaced with a mechanical support-based strategy. Table 1 summarizes previously reported cases and highlights differences in clinical presentation, management approaches, and outcomes.

Table 1. Reported cases of catecholamine-related Takotsubo syndrome

Author (year)	Age/sex	Comorbidities	Clinical setting/ procedure	Triggering error	Initial LVEF	Shock	Mechanical support	Treatment strategy	Recovery/ discharge time	Outcome
Sherif et al. (2016) ¹¹	76/Female	HT, DM	Rectal bleeding; post-transfusion diuretic therapy	Norepinephrine administered instead of furosemide	25–29%	No	None	Beta-blocker, ARB, MRA	Not available	LVEF 50–55% at 6 months
Chen et al (2020) ¹²	54/Male	HT, DM, HL, CAD	Hypotension during PCI	Norepinephrine overdose (100-fold dilution error)	15–20%	Yes	IABP	Beta-blocker, ARB, mechanical support	2 days/3 days	LVEF 60% at 1 week
Ioannou et al. (2023) ¹³	Young/ Female	None	Postpartum hemorrhage; hypocalcemia treatment	Norepinephrine administered instead of calcium gluconate	39%	Yes	None	Norepinephrine, dobutamine	2 days/7days	Complete recovery at 3 months
Pathangey et al. (2023) ¹⁴	47/Female	None	Contrast- enhanced CT; anaphylaxis	Intravenous norepinephrine instead of intramuscular administration	10%	Yes	None	Norepinephrine, dobutamine, vasopressin	8 hours/3 days	LVEF 60% at 6 months
Vieira et al. (2018) ¹⁵	82/Female	SLE, HT, aortic stenosis, hypothyroidism, osteoarthritis, depression	Treatment of adrenal insufficiency with shock	High-dose norepinephrine infusion (0.8 µg/kg/ min)	25%	Yes	None	Corticosteroids	5 days/11 days	Not available
Schlemmer et al. (2015) ¹⁶	48/Female	HT	Arthroscopic surgery	Epinephrine- containing saline irrigation (1 mg/L) per usual protocol	20%	Yes	None	Epinephrine infusion	—	Fatal
K. Azem et al. (2023) ¹⁷	62/Female	Idiopathic chronic lymphocytosis	Arthroscopic repair	Large-volume epinephrine- containing irrigation solution (0.33 mg/L)	30%	Yes	None	Norepinephrine, vasopressin	2 days/5 days	LVEF 65% at 3 months
Härle et al. (2010) ¹⁸	39/Female	Crohn's disease	ACTH stimulation testing	Accidental IV epinephrine (1 mg)	35%	No	None	Furosemide, beta-blocker, ACEi	Few days/6 days	Complete recovery at 10 days
Present case	41/Female	Ischemic stroke, atrial fibrillation	Radiofrequency ablation for recurrent AF	Norepinephrine administered instead of amiodarone	35%	Yes (severe)	IABP + VA-ECMO	Norepinephrine, dopamine, dobutamine → levosimendan; mechanical support devices	3 days/7 days	LVEF 60% at 2 weeks and 1 month

ACEi, Angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; ARB, Angiotensin receptor blocker; CAD, Coronary artery disease; DM, Diabetes mellitus; HL, Hyperlipidemia; HT, Hypertension; IABP, Intra-aortic balloon pump; LVEF, Left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; PCI, Percutaneous coronary intervention; SLE, Systemic lupus erythematosus; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation.

Conclusion

This case highlights a catastrophic iatrogenic TTS caused by accidental norepinephrine administration and demonstrates successful management of hemodynamic instability using mechanical circulatory support. We emphasize the importance of considering TTS in the differential diagnosis and prioritizing mechanical support over catecholaminergic agents such as norepinephrine, dopamine, and dobutamine in cardiogenic shock associated with TTS. Furthermore, preventing delays in initiating appropriate therapies, ensuring precise medication administration by nursing staff, and implementing regulatory measures to minimize confusion caused by similar drug names are critical for improving outcomes. In the literature, knowledge and experience regarding iatrogenic TTS are largely limited to case reports. One of the aims of this case report is to emphasize the need for "iatrogenic TTS" to be studied in greater detail as a distinct category and to contribute to its recognition in the literature.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the participant.

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Video 1. Transthoracic echocardiography demonstrates an ejection fraction of 35% with apical ballooning and severe hypokinesia of the mid-to-apical segments, consistent with Takotsubo syndrome.

Video 2. Ventriculography demonstrates left ventricular apical ballooning consistent with Takotsubo syndrome.

Video 3. Transthoracic echocardiography demonstrates normalization of ejection fraction.

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Inappropriate Shocks Caused by Implantable Cardioverter-Defibrillator Lead Malposition

İmplant Edilebilir Defibrilatör Elektrotunun Yanlış Yerleştirilmesinden Kaynaklanan Uygunsuz Şoklar

A 57-year-old man with ischemic cardiomyopathy underwent dual-chamber, dual-coil implantable cardioverter-defibrillator (ICD) implantation in 2016 for primary prevention of sudden cardiac death. Device programming included ventricular tachycardia detection at > 171 beats/min and ventricular fibrillation (VF) detection at > 200 beats/min. Two years later, he presented with multiple painful ICD shocks occurring over a one-week period. He was hemodynamically stable. Electrocardiography demonstrated sinus rhythm with findings consistent with prior anterior myocardial infarction. Transthoracic echocardiography revealed a dilated left ventricle with reduced systolic function (ejection fraction, 30%), and a left atrial anteroposterior diameter of 40 mm.

Device interrogation on admission demonstrated DDD mode with normal atrial sensing and pacing parameters, ventricular sensing amplitude of 2.2 mV, pacing amplitude of 3.0 V, pacing impedance of 380 Ω , absence of ventricular myocardial

CASE IMAGE OLGU GÖRÜNTÜSÜ

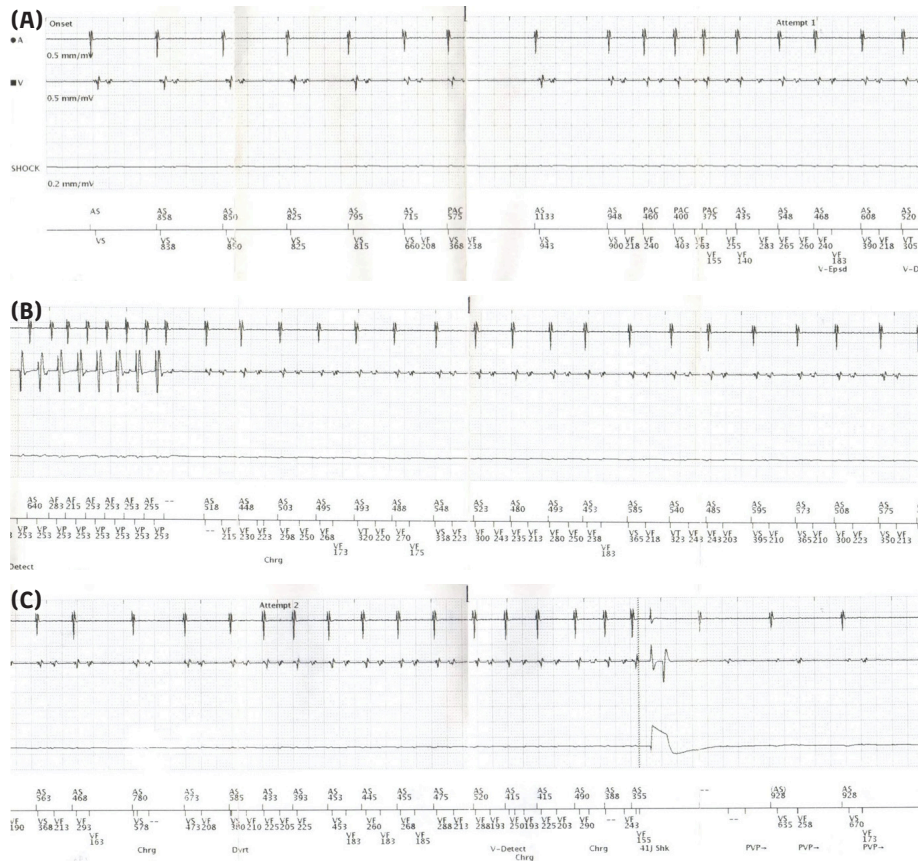


Figure 1. Intracardiac electrograms (EGMs) demonstrating irregular and rapid atrial signals misclassified as ventricular fibrillation (A). Antitachycardia pacing produced no change in the tachycardia episode (B). The recording demonstrated restoration of sinus rhythm following implantable cardioverter-defibrillator (ICD) shock delivery (C).

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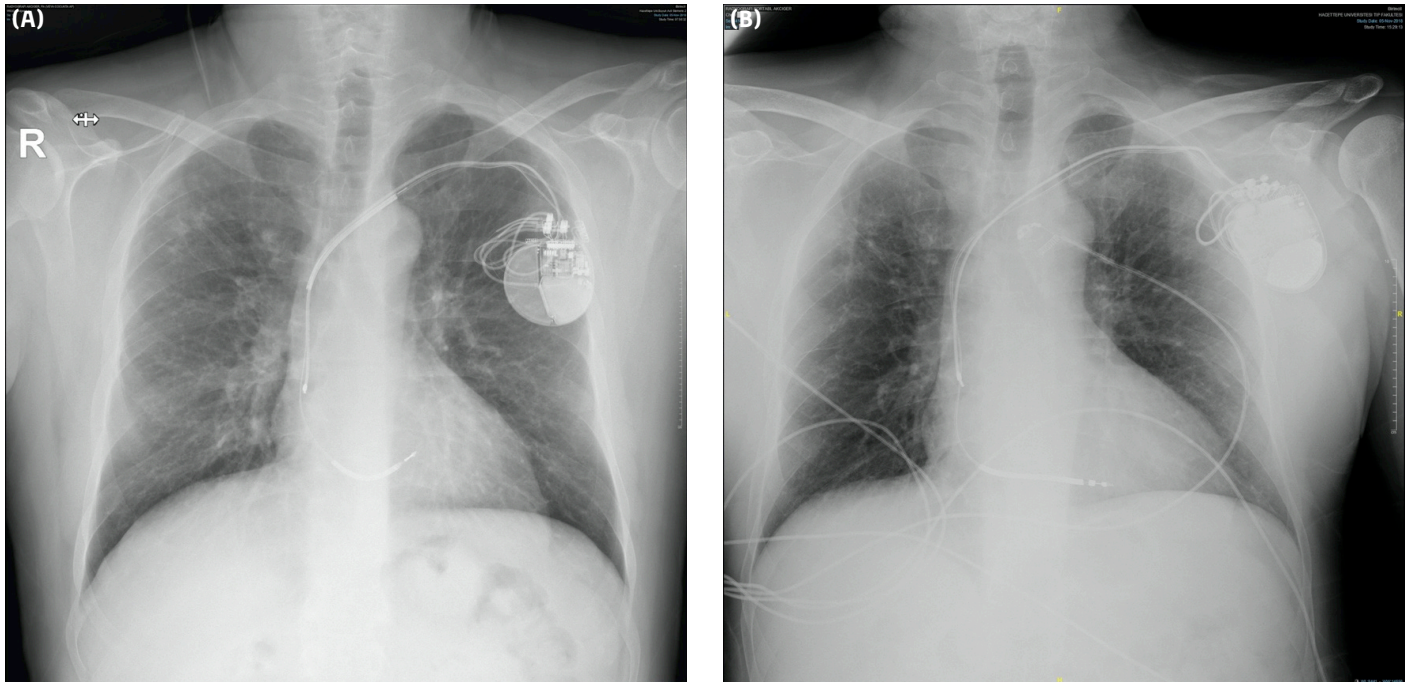


Figure 2. (A) Chest radiograph demonstrating a nonapical and abnormal posterior course of the implantable cardioverter-defibrillator (ICD) lead suggestive of coronary sinus placement. (B) Chest radiograph demonstrating right ventricular apical positioning of the ICD lead after repositioning.

capture, and multiple episodes of antitachycardia pacing and shocks classified as VF. Intracardiac electrograms showed irregular high-rate signals in both atrial and ventricular channels without organized ventricular activity. Simultaneous rhythm evaluation confirmed rapid atrial tachyarrhythmia. Double signals recorded in the ventricular channel suggested atrial oversensing, triggering inappropriate ICD therapies (Figure 1A–C). Because of the discordance between the clinical findings and device diagnosis, ICD lead position was reassessed. Chest radiography revealed an abnormal posterior and leftward course of the ICD lead, along with reduced slack of the atrial lead (Figure 2A). Fluoroscopy confirmed inadvertent placement of the ICD lead within the coronary sinus rather than the right ventricle (Supplementary Video 1). This malposition enabled sensing of atrial electrical activity from the coronary venous system. During rapid atrial tachyarrhythmia, atrial signals were misinterpreted as VF, resulting in repeated inappropriate shocks. The lead was repositioned to the right ventricular apex (Supplementary Video 2, Figure 2B), and the patient subsequently underwent successful radiofrequency ablation for atrial tachyarrhythmia. Following these interventions, no further inappropriate therapies were observed during four years of follow-up. Device interrogation demonstrated DDD mode with normal atrial sensing and pacing parameters, ventricular sensing amplitude of 6.5 mV, pacing amplitude of 2.0 V, pacing impedance of 455 Ω , and pacing threshold of 0.5 V.

Although supraventricular tachyarrhythmias are the most common cause of inappropriate ICD shocks, lead malposition represents a rare but reversible mechanism. Acceptable pacing parameters may mask incorrect positioning, resulting in sensing abnormalities and diagnostic errors. This case

highlights that clustered ICD shocks should not automatically be attributed to malignant ventricular arrhythmias. Careful device interrogation combined with imaging assessment is essential to distinguish appropriate from inappropriate therapies and to identify correctable procedural complications. Written informed consent was obtained from the patient for publication of this report.

Ethics Committee Approval: This is a single case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient for publication of this article and the accompanying images.

Conflict of Interest: UC: Proctorship for Biotronik, Medtronic, and Spectranetics.

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Video 1. Fluoroscopic right anterior oblique and left anterior oblique projections confirming inadvertent placement of the implantable cardioverter-defibrillator (ICD) lead within the coronary sinus rather than the right ventricle. The right ventricular coil extended toward the right atrium.

Video 2. Fluoroscopic right anterior oblique and left anterior oblique projections obtained after lead repositioning, confirming apical positioning of the implantable cardioverter-defibrillator (ICD) lead.

Eggshell Calcific Constrictive Pericarditis: Multimodality Diagnosis and Surgical Management

Yumurta Kabuğu Görünümünde Kalsifik Konstriktif
Perikardit: Multimodalite Tanı ve Cerrahi Yönetimi

A 53-year-old man with atrial fibrillation presented with progressive dyspnea, fatigue, abdominal distension, recurrent ascites requiring paracentesis, jugular venous distension, and peripheral edema. He had previously been diagnosed with cardiac cirrhosis. Chest radiography revealed bilateral pleural effusions and striking circumferential, eggshell-like pericardial calcification (Figure 1). Transthoracic echocardiography demonstrated a preserved left ventricular ejection fraction (60%), right-sided chamber enlargement, and annulus reversus, with septal and lateral mitral annular e' velocities of 15 and 10 cm/s, respectively. Noncontrast thoracic computed tomography demonstrated extensive near-circumferential calcified pericardial thickening with a characteristic eggshell-like morphology on axial and coronal images, measuring up to 26 mm adjacent to the left ventricle (Figure 2A and 2B).

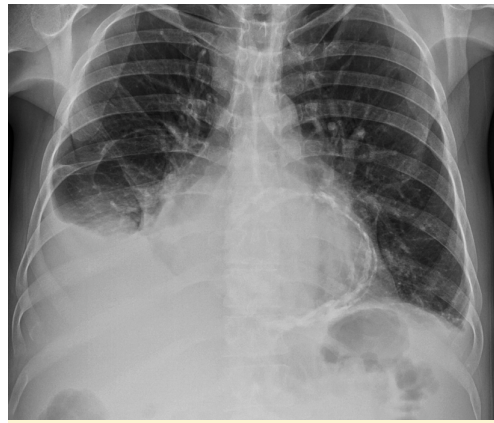


Figure 1. Chest radiograph demonstrating bilateral pleural effusions and extensive curvilinear pericardial calcification outlining the cardiac silhouette, producing an eggshell-like appearance.

Simultaneous right- and left-heart catheterization demonstrated a prominent y descent in the right atrial pressure tracing and near-equalization of ventricular end-diastolic pressures at approximately 28 mmHg, along with a dip-and-plateau pattern and discordant respiratory variation in ventricular systolic pressures, confirming constrictive physiology (Figure 3A and 3B). Fluoroscopy performed during catheterization further demonstrated extensive near-circumferential pericardial calcification surrounding the cardiac silhouette (Figure 4A).

The patient had no history of chronic kidney disease, Paget disease, tuberculosis, radiotherapy, malignancy, connective tissue disease, or another identifiable secondary cause; therefore, idiopathic calcific constrictive pericarditis was diagnosed. The patient underwent successful pericardiectomy, with extensive pericardial calcification confirmed intraoperatively (Figure 4B). The complementary use of chest radiography, echocardiography, and computed tomography enabled comprehensive assessment of the anatomical extent of calcification and its functional consequences. At 3 months, congestion and annulus reversus had regressed, liver function tests had normalized, NT-proBNP levels had significantly decreased, diuretic requirements had been reduced, and functional capacity had improved to New York Heart Association class I. This case emphasizes that extensive pericardial calcification serves as an anatomical clue, whereas the integration of multimodality imaging with invasive hemodynamic assessment establishes constrictive physiology and guides potentially curative surgery.

CASE IMAGE OLGU GÖRÜNTÜSÜ

This case was presented as an oral presentation at ESC Heart Failure 2025, held in Belgrade, Serbia, on May 17, 2025.

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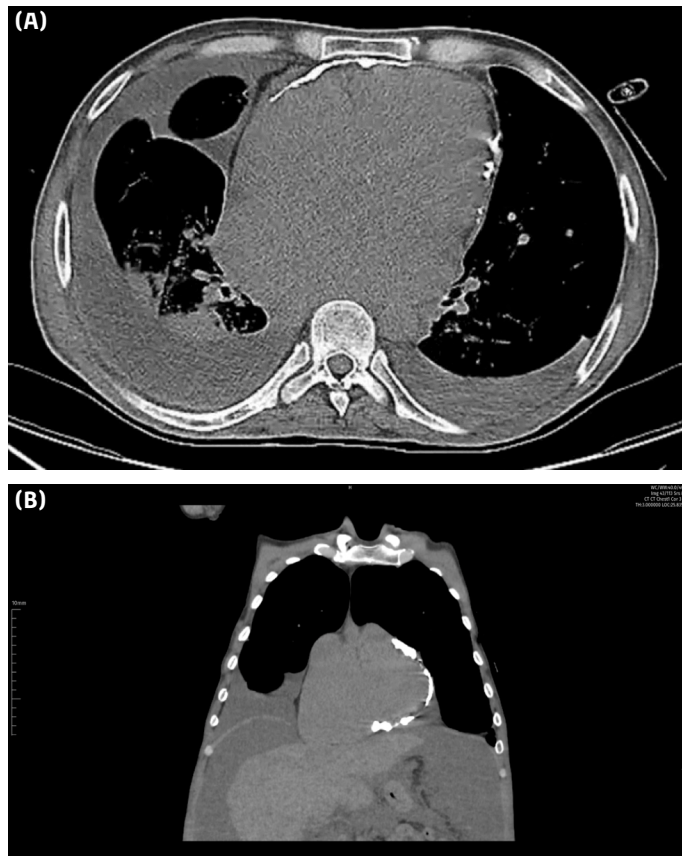


Figure 2. Noncontrast thoracic computed tomography demonstrating the characteristic eggshell-like morphology. (A) Axial noncontrast thoracic computed tomography image demonstrating extensive near-circumferential calcified pericardial thickening adjacent to the left ventricle, with a characteristic eggshell-like morphology. (B) Coronal reconstructed computed tomography image demonstrating the extensive near-circumferential distribution of pericardial calcification.

Ethics Committee Approval: This is a single case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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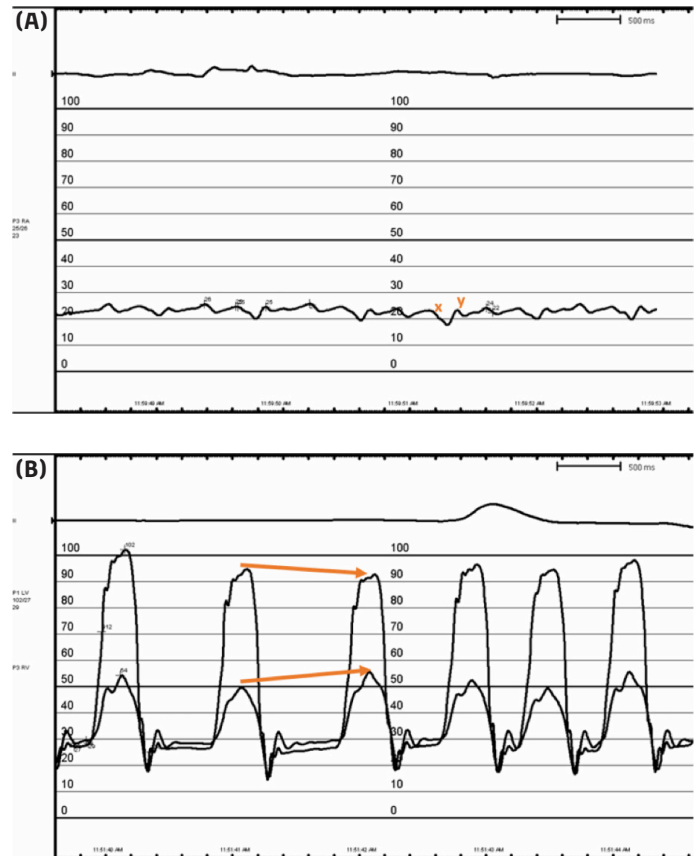


Figure 3. Invasive hemodynamic findings consistent with constrictive physiology. (A) Right atrial pressure tracing demonstrating prominent x and y descents, including a rapid y descent reflecting rapid early diastolic filling. (B) Simultaneous right- and left-ventricular pressure tracings demonstrating near-equalization of ventricular end-diastolic pressures at approximately 28 mmHg, a dip-and-plateau pattern, and discordant respiratory variation in ventricular systolic pressures.

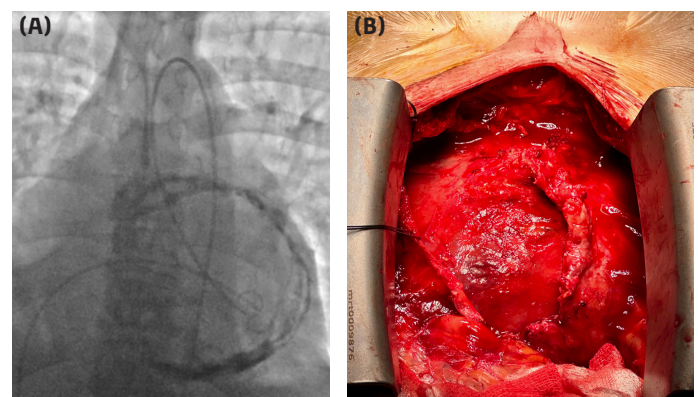


Figure 4. (A) Anteroposterior fluoroscopic projection obtained during simultaneous right- and left-heart catheterization demonstrating extensive near-circumferential pericardial calcification surrounding the cardiac silhouette. (B) Intraoperative appearance of the extensively calcified pericardium during pericardiectomy.

Beyond the Frontal QRS-T Angle: Toward Integrated Cardiovascular Phenotyping in Acute Ischemic Stroke

Frontal QRS-T Açısının Ötesinde: Akut İskemik İnmede Entegre Kardiyovasküler Fenotiplemeye Doğru

To the Editor,

We read with great interest the recent article by Usalp and Bağirtan on the prognostic value of the frontal QRS-T angle in patients with ischemic stroke.¹ The study provides valuable evidence that an increased frontal QRS-T angle is independently associated with long-term mortality, highlighting the potential utility of this simple and readily available electrocardiographic marker for risk stratification in patients with ischemic stroke. While these findings strengthen the clinical relevance of ECG-derived markers, they also provide an opportunity to explore more comprehensive approaches to cardiovascular risk stratification in ischemic stroke.

Acute ischemic stroke is not only a neurological disease but also a cardiovascular event. Cerebral ischemia can cause autonomic imbalance, increased sympathetic activity, and myocardial electrical changes. As a result, several ECG abnormalities, including atrial fibrillation, QT prolongation, P-wave abnormalities, fragmented QRS, and ventricular repolarization changes, have been associated with poor outcomes after stroke.²

In the present study, the frontal QRS-T angle emerged as an independent predictor of long-term mortality, along with age and HDL cholesterol levels.¹ The identification of both electrophysiological and metabolic predictors suggests that stroke prognosis depends on multiple biological pathways rather than on a single marker. Although the frontal QRS-T angle demonstrated independent prognostic value, the broader clinical potential of ECG may lie in the combined interpretation of multiple electrical markers rather than in a single parameter. A similar evolution has already occurred in cardiovascular risk assessment, where increasing evidence suggests that a single biomarker rarely reflects the complex mechanisms involved in cardiovascular disease. Instead, composite indices that integrate different biological pathways may provide better prognostic information. Our group has previously reported that cardiometabolic indices such as the TyG-BRI index, the BRITSH ratio, and the CTI provide additional prognostic value by integrating metabolic, inflammatory, anthropometric, and clinical variables.^{3,4} Likewise, we demonstrated that the fragmented QRS-T angle predicts long-term mortality in maintenance hemodialysis patients, supporting the value of electrocardiographic markers when interpreted within the appropriate clinical context.⁵

From this perspective, the positive findings of the present study should be viewed as an important step rather than the endpoint of ECG-based risk assessment. Instead of focusing on a single ECG marker, future studies may benefit from developing composite cardiovascular models. Such models could combine ECG findings, including the frontal QRS-T angle, QTc interval, atrial fibrillation, and P-wave duration, with metabolic indices, inflammatory biomarkers, anthropometric measures, renal function, endocrine factors, and nutritional status. Because stroke is a multifactorial disease, its prognosis is also likely determined by interactions among multiple biological pathways rather than by a single electrophysiological abnormality.

In conclusion, the study by Usalp and Bağirtan further supports the prognostic value of electrocardiographic markers in ischemic stroke. However, rather than considering the

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frontal QRS-T angle as a standalone predictor, future research should move toward integrated cardiovascular phenotyping by combining electrocardiographic findings with cardiometabolic and clinical biomarkers. Such an approach may improve risk stratification, facilitate individualized prognostic assessment, and ultimately support more personalized management strategies for patients with acute ischemic stroke.

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Reply to the Letter to the Editor: 'Beyond the Frontal QRS-T Angle: Toward Integrated Cardiovascular Phenotyping in Acute Ischemic Stroke'

Editöre Mektup Yanıtı: 'Frontal QRS-T Açısının Ötesinde: Akut İskemik İnmede Entegre Kardiyovasküler Fenotiplemeye Doğru'

To the Editor,

We thank the authors¹ for their thoughtful and insightful comments regarding our recent article on the prognostic value of the frontal QRS-T angle (FQRS-TA) in patients with ischemic stroke.² We appreciate their interest in our work and their constructive suggestions for advancing risk stratification strategies in this patient population.

We fully agree with the authors that acute ischemic stroke is not merely a neurological event but rather a complex cardiovascular phenomenon involving autonomic imbalance, increased sympathetic activity, and myocardial electrical changes.³ Their emphasis on the multifactorial nature of stroke prognosis is well taken, and we acknowledge that the identification of both electrophysiological and metabolic predictors in our study highlights the importance of considering multiple biological pathways in risk assessment.

The authors raise an important point regarding the potential limitations of focusing on a single electrocardiographic marker. We concur that composite indices incorporating different biological pathways may provide superior prognostic information compared with individual parameters. Their group's work on cardiometabolic indices such as the TyG-BRI index, BRITSH ratio, and CTI, as well as their findings regarding the fragmented QRS-T angle in hemodialysis patients, represents valuable contributions to this field.⁴⁻⁶ In our previous work, we have also investigated other electrocardiographic parameters, such as T-wave duration and the Tpeak-Tend interval, in patients undergoing cardiac resynchronization therapy, further underscoring the prognostic potential of ECG-derived markers.⁷ The evolution toward integrated cardiovascular phenotyping for cardiovascular risk assessment is indeed a promising direction for future research.

However, we would like to emphasize that our study was specifically designed to investigate the relationship between FQRS-TA and mortality in patients with ischemic stroke because this association had not previously been explored in this particular population. The frontal QRS-T angle offers several practical advantages: it can be easily calculated from a standard 12-lead ECG, does not require specialized equipment, and can be obtained rapidly at the bedside. In resource-limited settings, where advanced biomarker testing may not be readily available, such simple and cost-effective markers remain clinically valuable.

We also note that the authors' suggestion regarding composite cardiovascular models is entirely consistent with our own conclusions. In the "Limitations" section of our article, we acknowledged that our findings should be interpreted in the context of the study's retrospective, single-center design and that larger-scale studies are needed to further clarify the relationship between FQRS-TA and mortality. We explicitly stated that future research should explore these relationships more comprehensively.

The integration of electrocardiographic parameters—including FQRS-TA, QTc interval, atrial fibrillation burden, P-wave duration, and fragmented QRS—with metabolic indices, inflammatory biomarkers, anthropometric measures, renal function, and nutritional status represents a logical next step in this research area. We believe that the present

LETTER TO THE EDITOR REPLY EDİTÖRE MEKTUP YANITI

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study provides a foundation for such integrated approaches by demonstrating that a simple ECG-derived parameter can provide meaningful prognostic information that may complement other clinical and laboratory markers.

We also appreciate the authors' acknowledgment that our study further supports the prognostic value of electrocardiographic markers in ischemic stroke. We hope that our findings will encourage other researchers to build on this work and develop the comprehensive risk stratification models proposed by the authors.

In response to the specific methodological considerations raised, we would like to clarify that patients with known ischemic heart disease and heart failure were excluded based on clinical history and examination findings. However, we acknowledge that subclinical coronary artery disease may have been present in some patients, as is common in this population. This limitation, along with the retrospective nature of the study, was clearly stated in our manuscript.

Regarding the authors' suggestions for future research, we strongly support the development of composite cardiovascular models that integrate multiple ECG parameters with clinical and laboratory variables. We propose that such models should be validated in large, prospective, multicenter cohorts with long-term follow-up. Additionally, the potential utility of combining FQRS-TA with other noninvasive markers, such as echocardiographic parameters or cardiac biomarkers, warrants investigation.

We are grateful for the opportunity to respond to these valuable comments and for the authors' contribution to the ongoing discussion on cardiovascular risk stratification in ischemic stroke. Their perspective aligns well with our own vision for future research and highlights the importance of moving beyond single

biomarkers toward more comprehensive, integrated approaches to patient assessment.

In conclusion, we thank the authors of the letter for their thoughtful critique and constructive suggestions. We agree that future research should focus on developing integrated cardiovascular phenotyping approaches that combine electrocardiographic findings with cardiometabolic and clinical biomarkers to improve risk stratification and facilitate personalized management strategies for patients with acute ischemic stroke. Our study represents an initial step in this direction, and we hope that it will stimulate further investigation in this important area.

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Clinical Perspectives on Lactate in Complete Atrioventricular Block

Tam Atriyoventriküler Bloкта Laktata İlişkin Klinik Perspektifler

To the Editor,

I read the article entitled "Assessment of Lactate Levels as Prognostic and Predictive Markers in Patients with Complete Atrioventricular Block" by Cengiz et al.¹ with great interest. I congratulate the authors for addressing an important topic with limited existing literature by investigating the prognostic value of lactate levels in patients with complete atrioventricular block. The association of admission and follow-up lactate levels with adverse in-hospital clinical outcomes is of clinical interest and may provide useful information for risk stratification and future studies. Nevertheless, discussion of certain points would be beneficial for a more comprehensive evaluation of the study findings.

Regarding the study design, the adverse clinical outcome was defined as a composite endpoint comprising acute kidney injury, cardiac mortality, and the need for temporary pacemaker implantation. Although this approach increases statistical power, the clinical characteristics and underlying mechanisms of these individual components differ substantially. In particular, unlike the other endpoints, temporary pacemaker implantation is a therapeutic decision that is heavily influenced by clinical assessment, patient characteristics, and center experience.² The authors have already presented the individual components of the composite endpoint in the original article. These analyses are useful for understanding the contribution of each outcome. However, the association with lactate levels was not consistent across all components, highlighting the heterogeneity of the composite endpoint. Therefore, the composite outcome should be interpreted in consideration of the differing clinical characteristics of its individual components.

Furthermore, although the ability of lactate levels to reflect tissue hypoperfusion and reduced cardiac output is biologically plausible, lactate remains a nonspecific biomarker influenced by numerous physiological and pathological processes. Because factors such as hepatic clearance, sympathetic activation, metabolic stress, and concomitant systemic diseases can alter serum lactate levels, elevated lactate may reflect not only the severity of atrioventricular block but also the patient's overall hemodynamic and metabolic state.³ The original study excluded several important conditions that could affect lactate levels, including acute coronary syndrome, atrial fibrillation, active infection or sepsis, decompensated heart failure, the need for inotropic support, and cardiac arrest.¹ Although these exclusions may have reduced potential confounding, they cannot completely eliminate it. Therefore, residual confounding from unmeasured or incompletely assessed factors should still be considered when interpreting the association between lactate levels and clinical outcomes.

Moreover, according to current ESC guidelines, the indication for temporary pacemaker implantation is primarily based on symptoms, hemodynamic instability, and the evaluation of reversible causes.² Therefore, it is essential to determine whether lactate provides independent and additive prognostic value beyond these established clinical parameters. Establishing such additional prognostic value would help better define the clinical utility of this biomarker in routine practice.

In conclusion, this study provides useful information regarding the prognostic role of lactate in patients with complete atrioventricular block. However, the heterogeneity of the composite endpoint and the nonspecific nature of lactate should be considered. Larger, prospective, multicenter studies are needed to determine whether serial lactate measurements can improve risk stratification and guide clinical decision-making in this population.

LETTER TO THE EDITOR EDİTÖRE MEKTUP

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Reply to the Letter to the Editor: Clinical Perspectives on Lactate in Complete Atrioventricular Block

Editöre Mektup Yanıtı: Tam Atriyoventriküler Bloкта Laktata İlişkin Klinik Perspektifler

To the Editor,

We thank the authors¹ for their thoughtful comments regarding our study evaluating the prognostic value of lactate levels in patients with complete atrioventricular (AV) block.² Their observations highlight important methodological and clinical considerations and provide an opportunity to further clarify the interpretation of our findings.

We agree that the composite adverse outcome used in our study includes clinically heterogeneous components. Acute kidney injury and cardiac mortality represent adverse clinical events, whereas temporary pacemaker implantation is also influenced by symptoms, hemodynamic status, underlying etiology, and clinical judgment. Previous studies have similarly emphasized the importance of individualized pacing decisions according to the underlying conduction disorder and patient characteristics.^{3,4} For this reason, we additionally evaluated the individual components of the composite outcome. Lactate levels were significantly higher in patients who developed acute kidney injury and, particularly, in those who died. In contrast, lactate levels were not significantly different in patients requiring temporary pacing compared with those in the no-event group. However, this subgroup included only four patients, substantially limiting statistical power. Therefore, we agree that the composite outcome should be interpreted together with its individual components.

We also agree that lactate is a nonspecific biomarker and cannot be regarded solely as a direct measure of AV block-related hypoperfusion.⁵ Nevertheless, there is a plausible hemodynamic basis for the observed association. In a previous study, patients with complete AV block had significantly reduced cardiac output before pacemaker implantation despite maintaining normal mean arterial pressure through increased systemic vascular resistance.⁶ This finding is particularly relevant because it suggests that apparently preserved blood pressure does not necessarily exclude reduced systemic blood flow in complete AV block. In addition, lactate has previously been associated with acute kidney injury in patients with acute decompensated heart failure, supporting its potential role as a marker of impaired systemic perfusion in cardiovascular disease.⁷

At the same time, circulating lactate levels may be influenced by sympathetic activation, metabolic stress, hepatic clearance, renal dysfunction, and other systemic factors. To reduce major alternative causes of lactate elevation, we excluded patients with acute coronary syndrome, active infection or sepsis, decompensated heart failure, the need for inotropic support, cardiac arrest, and several other acute conditions. Nevertheless, residual confounding cannot be completely eliminated in a retrospective observational study and should be considered when interpreting our findings.

The authors also appropriately emphasize that temporary pacing is a therapeutic intervention rather than a purely biological endpoint. Temporary transvenous pacing itself is associated with potential complications, including lead-related cardiac perforation, which has also been documented in previous publications.⁷ Therefore,

LETTER TO THE EDITOR REPLY EDİTÖRE MEKTUP YANITI

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our findings should not be interpreted as suggesting that an elevated lactate level alone constitutes an indication for temporary pacing.^{8,9} Rather, serial lactate measurements may potentially complement established clinical assessments in selected patients.

Perhaps the most relevant clinical question is whether serial lactate measurements provide incremental prognostic information beyond symptoms, hemodynamic instability, reversible causes, and other established parameters. Our study was not designed to demonstrate that lactate should replace these clinical determinants. Instead, our findings suggest that elevated admission lactate levels and subsequent increases during follow-up may identify patients at higher risk despite an apparently stable initial presentation. This concept is consistent with previous observations that patients with AV block require careful follow-up even when conduction abnormalities appear reversible or initially stable.⁴

Accordingly, we consider our findings hypothesis-generating. Prospective, multicenter studies should evaluate whether serial lactate measurements provide incremental prognostic value beyond conventional clinical assessment and whether their incorporation into risk-stratification strategies improves clinical outcomes. Until such evidence is available, lactate should be considered a complementary biomarker rather than an independent determinant of temporary pacing decisions.

We thank the authors¹ again for their constructive comments, which help place our findings in an appropriate clinical and methodological context.

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Atherogenic Index of Plasma in CTO PCI: From Construct Definition to Predictive Validation

KTO PKG'de Plazmanın Aterojenik İndeksi: Yapı Tanımından Öngörüşel Doğrulamaya

To the Editor,

Güvendi Şengör and Yılmaz¹ evaluated the atherogenic index of plasma (AIP) in 197 patients undergoing percutaneous coronary intervention (PCI) for chronic total occlusion (CTO), reporting a strong inverse association between AIP and technical success and improved model discrimination after the addition of AIP to clinical and anatomical predictors. The study addresses an important question: whether a routinely available metabolic marker can complement lesion-based assessment. Two issues deserve clarification before the reported threshold or predictive performance can be translated into procedural planning.

First, the AIP construct should be clearly defined. AIP was originally defined as the log10 of the molar triglyceride (TG)-to-high-density lipoprotein cholesterol (HDL-C) ratio.^{2,3} In the present article, AIP is described as log10(TG/HDL-C), whereas lipid concentrations are reported in mg/dL, and no conversion to molar units is specified.¹ The group medians are numerically compatible with the direct use of mg/dL values: log10(141/41)=0.54 and log10(345/36)=0.98, which are close to the reported AIP medians of 0.52 and 0.95. Using mmol/L, these illustrative values become approximately 0.18 and 0.62. This conversion creates a constant shift; therefore, ranking and discrimination would remain unchanged, but absolute AIP values and the cutoff of 0.802 would not be directly transferable. More importantly, Supplementary Figure 1 depicts AIP as log(non-HDL-C/HDL-C), which represents a different construct.¹ Clarifying the calculation method, the units used, and the formula presented in the graphical abstract is therefore important for reproducibility.

Second, association should be distinguished from validated prediction. The ROC-derived cutoff, its operating characteristics, and the multivariable model were evaluated in the same cohort of 197 patients.¹ The likelihood-ratio test supports improved in-sample fit, but it does not establish out-of-sample predictive performance. Performance measured using development data is generally optimistic unless the complete modeling process is internally validated.⁴ Although a bootstrap calibration curve is presented, optimism-corrected discrimination and validation of the data-derived cutoff are not reported. Bootstrapping the full analytical pipeline, including threshold selection, followed by independent validation would provide a more robust estimate of clinical performance. Operator experience and procedural strategy, acknowledged but unavailable in the analysis, would also be important because CTO PCI success is not determined by patient biology alone.

The observed association remains clinically interesting. Standardizing the AIP definition, correcting the discrepancy in the graphical abstract, and distinguishing apparent model improvement from validated prediction would substantially strengthen the proposed role of AIP in CTO PCI planning.

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LETTER TO THE EDITOR EDİTÖRE MEKTUP

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Beyond Left Ventricular Remodeling: Reconsidering Cardiac Recovery After Bariatric Surgery

Sol Ventrikül Yeniden Şekillenmesinin Ötesinde: Bariatrik Cerrahi Sonrası Kardiyak İyileşmenin Yeniden Değerlendirilmesi

To the Editor,

The study "Structural and functional cardiac reverse remodeling following bariatric surgery: A prospective comparison of sleeve gastrectomy and Roux-en-Y gastric bypass" addresses an important clinical question.¹ The prospective comparison of sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB), examining a variety of structural and functional markers of cardiac health, is a major strength of the study. The authors provide valuable insight into the complex relationship between bariatric surgery and cardiac recovery.

However, this study has several limitations. The most important limitation is that only left ventricular (LV) remodeling was assessed, although evidence suggests a relevant role of the left atrium (LA) in heart failure with preserved ejection fraction (HFpEF) in obesity. Sorimachi et al.² previously demonstrated that although bariatric surgery leads to beneficial LV reverse remodeling and improvements in biventricular longitudinal strain, a paradoxical worsening of LA strain and increases in LA volume and estimated LA pressure were observed during significant weight loss and were associated with adverse cardiovascular outcomes such as atrial fibrillation. This implies that LA dysfunction might not be fully reversed by weight reduction and that the authors' claim of coordinated "cardiac recovery" could oversimplify the context of the left-sided cardiac remodeling response.

Another inherent limitation affecting the generalizability of the study was the exclusion of patients with poor acoustic windows, as adequate ultrasound visualization may be substantially compromised in these patients. Supariwala et al.³ found that the percentage of patients with poor acoustic windows increased with increasing obesity grade. Therefore, patients with a disproportionately higher degree of obesity were more likely to be excluded because of poor acoustic windows, potentially resulting in the underrepresentation of individuals with more severe obesity in this cohort.

Additionally, cardiac magnetic resonance (CMR) imaging has been reported to provide superior assessment of cardiac anatomy when transthoracic echocardiography (TTE) results are suboptimal in individuals with severe obesity, similar to the approach used by Michalsky et al.⁴ to assess cardiovascular remodeling outcomes after bariatric surgery in adolescents with extreme obesity. Similarly, Henry et al.⁵ used CMR to measure LV mass, the LV mass-to-LV volume ratio, and LV eccentricity before and after various bariatric surgery regimens, thereby reinforcing its potential for characterizing the process of cardiac reverse remodeling. Such inclusions would have strengthened the study endpoints and helped minimize patient selection bias arising from inadequate echocardiographic windows and the inherent measurement limitations of echocardiography.

Although the present data provide interesting findings supporting reverse cardiac remodeling following bariatric surgery, the assessment of cardiac remodeling may be complicated by both incomplete evaluation of remodeling parameters and the exclusion of patients because of inadequate imaging windows. Further assessment, including evaluation of left atrial function, more rigorous measurement of cardiac remodeling using CMR, and imaging of patients with varying degrees of obesity, could provide a more comprehensive description of cardiac remodeling after bariatric surgery. Therefore, subsequent studies should employ multiple cardiac imaging modalities and examine patients across the spectrum of obesity to confirm that the reported benefits are representative of findings across the broader population with obesity.

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