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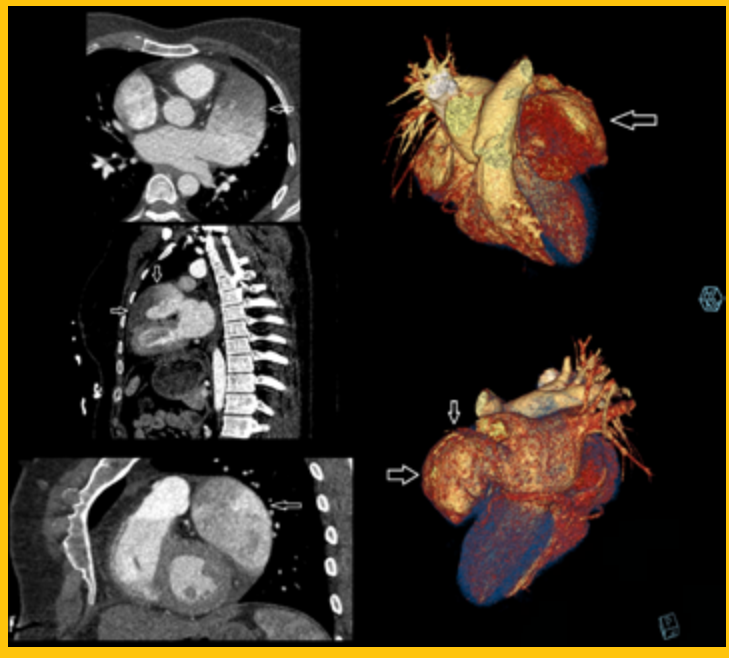

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

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Volume: 54 / Issue: 2 / Year: 2026

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

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Balloon-Expandable Versus Self-Expanding Valves in Transcatheter Aortic Valve Replacement for Patients with Left Ventricular Systolic Dysfunction

Sol Ventrikül Sistolik Disfonksiyonu Olan ve Transkateter Aort Kapak Replasmanı Yapılan Hastalarda Balon-Expandabl ve Self-Expandabl Kapakların Karşılaştırılması

ABSTRACT

Objective: Patients with severe aortic stenosis (AS) and left ventricular systolic dysfunction (LVSD) represent a particularly fragile subgroup undergoing transcatheter aortic valve replacement (TAVR). Comparative outcome data for balloon-expandable valves (BEV) and self-expanding valves (SEV) in this population remain scarce.

Method: This retrospective single-center study evaluated 246 consecutive subjects with left ventricular ejection fraction (LVEF) < 50% who underwent transfemoral TAVR between January 2015 and June 2025. Clinical, echocardiographic, and procedural characteristics were compared between BEV (n = 96) and SEV (n = 150) recipients. Long-term all-cause mortality served as the primary endpoint.

Results: Individuals treated with BEV were older (78.8 ± 7.9 vs. 75.7 ± 9.8 years; P = 0.019) and demonstrated higher EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) values (24.9 ± 6.2% vs. 22.2 ± 15.8%; P = 0.01). Periprocedural and in-hospital clinical outcomes, including mortality, vascular complications, and pacemaker requirement, were comparable between groups. SEV implantation yielded lower post-procedural transvalvular gradients (mean 7.8 ± 4.0 mmHg vs. 9.6 ± 4.1 mmHg; P = 0.001). Although crude mortality was observed more frequently among BEV patients (50.0% vs. 36.0%; P = 0.041), Kaplan–Meier survival curves showed no survival difference (log-rank P = 0.92). In multivariable Cox regression, predictors of long-term mortality included older age (hazard ratio [HR] 1.05; P = 0.007), chronic obstructive pulmonary disease (COPD) (HR: 2.64; P < 0.001), coronary artery disease (HR: 2.08; P = 0.018), lower serum albumin (HR: 0.63; P = 0.011), and lower hemoglobin (HR: 0.84; P = 0.023); valve type was not predictive.

Conclusion: In patients with LVSD undergoing TAVR, BEV and SEV provided comparable procedural and long-term outcomes. Although SEV yielded lower postoperative gradients, valve type did not affect survival. Future studies with larger samples and higher use of new-generation devices are warranted to refine valve selection in this high-risk group.

Keywords: Balloon-expandable valve, low-flow low-gradient aortic stenosis, self-expanding valve, transcatheter aortic valve implantation, transcatheter aortic valve replacement

ÖZET

Amaç: Sol ventrikül sistolik disfonksiyonu (LVSD) bulunan hastalar, transkateter aort kapak replasmanı (TAVR) uygulamalarında yüksek riskli bir alt grubu oluşturur. Bu hasta grubunda balon-expandabl (BEV) ve self-expandabl (SEV) kapakların karşılaştırmalı verileri sınırlıdır.

Yöntem: Bu çalışmada, Ocak 2015 – Haziran 2025 tarihleri arasında ejeksiyon fraksiyonu < %50 olan ve transfemoral yolla TAVR uygulanan 246 ardışık hasta retrospektif olarak analiz edilmiştir. Klinik, ekokardiyografik ve prosedürel değişkenler BEV (n = 96) ve SEV (n = 150) grupları arasında karşılaştırılmıştır. Birincil sonlanım noktası uzun dönem tüm nedenlere bağlı mortalitedir.

Bulgular: BEV grubundaki hastalar daha yaşlıydı (78.8 ± 7.9 vs. 75.7 ± 9.8, P = 0.019) ve EuroSCORE II değerleri daha yüksekti (%24,9 ± 6,2 vs. %22,2 ± 15,8; P = 0,01). Perioperatif ve hastane içi komplikasyonlar, majör vasküler olaylar ve kalıcı pacemaker ihtiyacı iki grup arasında benzerdi. SEV grubunda postoperatif transvalvüler gradiyentler daha düşüktü (ortalama 7,8 ± 4,0 mmHg vs 9,6 ± 4,1 mmHg; P = 0,001). Uzun dönem mortalite BEV grubunda daha yüksek izlense de (%50,0 vs %36,0; P = 0,041), Kaplan–Meier analizi fark göstermedi (log-rank P = 0,92). Çok değişkenli Cox regresyon analizinde ileri yaş (HR: 1,05; P = 0,007), KOAH varlığı

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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(HR: 2,64; P< 0,001), koroner arter hastalığı (HR: 2,08; P = 0,018), düşük albümin (HR: 0,63; P = 0,011) ve düşük hemoglobin (HR: 0,84; P = 0,023) uzun dönem mortalitenin bağımsız belirleyicileri olarak bulundu; kapak tipi belirleyici olarak saptanmadı.

Sonuç: LVSD hastalarında TAVR sonrası BEV ve SEV kapaklar benzer işlem başarısı ve uzun dönem sonuçlar göstermektedir. SEV kapaklar daha düşük postoperatif gradiyentler sağlasa da, kapak tipi sağkalımı etkilememektedir. Yeni nesil cihazların daha yüksek oranda kullanıldığı ileri prospektif çalışmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Balon-expandabl kapak, düşük-akım düşük-gradiyentli aort stenozu, self-expandabl kapak, transkateter aort kapak implantasyonu, transkateter aort kapak replasmanı

Transcatheter aortic valve replacement (TAVR) has become a well-established treatment option across the entire spectrum of operative risk, supported by multiple randomized and registry studies demonstrating comparable or superior outcomes in appropriately selected patients.[1–3] Among individuals with left ventricular systolic dysfunction (LVSD), particularly those with a low-flow, low-gradient (LFLG) pattern, procedural risk and long-term mortality remain substantially higher than in patients with preserved systolic function.[4–11] Nevertheless, TAVR often leads to meaningful recovery in ventricular performance and improvement in survival among patients with reduced ejection fraction.[12–14] In the report by Ludwig et al.,[15] TAVR was associated with better two-year survival than conservative medical treatment, even in patients with moderate aortic stenosis and LVSD, emphasizing its potential benefit in this high-risk population.

Balloon-expandable (BEV) and self-expanding (SEV) valves differ in design, deployment mechanics, and hemodynamic performance, which may translate into distinct procedural and clinical profiles. BEVs are generally associated with lower rates of new pacemaker implantation, moderate or severe paravalvular regurgitation (PVR), and device embolization.[16–19] In contrast, SEVs generally provide lower transvalvular gradients (reflecting superior hemodynamics due to their supra-annular design) and reduce the need for rapid pacing during deployment.[16–21] Previous studies have consistently demonstrated comparable short- and long-term mortality rates for both valve types in the overall TAVR population.[16–21] However, complications such as high-grade atrioventricular block, moderate or severe PVR, or device embolization may be less well tolerated in patients with LVSD, whereas the hemodynamic advantages of SEVs could have greater long-term relevance in this group. Despite broad experience with both platforms in general TAVR practice, evidence focusing specifically on patients with reduced ejection fraction remains scarce. Given their heightened susceptibility to adverse hemodynamic events, a clear understanding of device-related outcomes in this subset is essential. Given these mechanistic differences, valve selection may have greater clinical relevance in patients with left ventricular (LV) systolic dysfunction, who possess limited hemodynamic reserve and may be less able to tolerate complications such as paravalvular regurgitation, conduction disturbances requiring new pacemaker implantation, suboptimal valve positioning, or higher residual gradients. These device-specific features could theoretically influence myocardial afterload, ventricular recovery, and ultimately long-term mortality in this vulnerable subgroup. Therefore, this study aims to provide real-world evidence comparing the clinical outcomes of patients with LVSD who underwent TAVR for severe aortic stenosis.

ABBREVIATIONS

AKI	Acute kidney injury
AS	Aortic stenosis
BEV	Balloon-expandable valves
CAD	Coronary artery disease
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
IABP	Intra-aortic balloon pump
LFLG	Low-flow, low-gradient
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MI	Myocardial infarction
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
PVR	Paravalvular regurgitation
SAPT	Single antiplatelet therapy
SEV	Self-expanding valves
TAPSE	Tricuspid annular plane systolic excursion
TAVR	Transcatheter aortic valve replacement
VARC-3	Valve Academic Research Consortium-3

Materials and Methods

Study Population

This single-center retrospective analysis included 246 consecutive patients treated with transfemoral TAVR for severe symptomatic native aortic stenosis (AS) between January 2015 and June 2025. Patient data, including baseline clinical characteristics, comorbidities, regular medications, laboratory values, echocardiographic parameters, angiographic and procedural details, and follow-up, were retrieved from the hospital information system and patient records and then anonymized for analysis.

Eligibility required a left-ventricular ejection fraction (LVEF) below 50% prior to the procedure. Laboratory values and echocardiographic parameters were obtained at admission, and all surviving patients underwent follow-up echocardiography at 6 months after TAVR. All echocardiographic evaluations were

carried out using a Vivid E95 system (GE Vingmed Ultrasound, Milwaukee, WI, USA). Measurements were performed in accordance with the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[22] LVEF was quantified by an experienced echocardiographer using the biplane Simpson's method.

Exclusion criteria were as follows:

- Valve-in-valve TAVR (n = 8)
- TAVR performed for isolated severe aortic insufficiency (n = 5)
- Missing data (n = 11)
- Active malignancy (n = 1)
- Severe anemia (hemoglobin < 8 mg/dL) (n = 2)
- End-stage renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m^2 or chronic dialysis) (n = 8)
- Non-transfemoral access (n = 14).

After applying these strict exclusion criteria, the remaining 246 patients constituted the final study population. The study complied with the ethical standards of the Declaration of Helsinki and received approval from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: 1150, Date: 25.09.2025). All participants provided written informed consent upon hospital admission and before undergoing any invasive procedures, including permission for the scientific use of their data.

Procedural Information

All participants underwent diagnostic coronary angiography before TAVR, typically two days prior to valve implantation. Revascularization decisions were made jointly by the interventional team based on coronary anatomy and clinical presentation. A luminal narrowing ≥ 90% in vessels with a diameter ≥ 2.5 mm was considered significant and managed with percutaneous coronary intervention (PCI) when appropriate. Standard dual loading with clopidogrel 600 mg and aspirin 300 mg preceded PCI. The SYNTAX I score (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score) was calculated to quantify the anatomical complexity and severity of coronary artery disease (CAD).

Per institutional protocol, patients without an indication for long-term anticoagulation received dual antiplatelet therapy (DAPT) with aspirin 100 mg and clopidogrel 75 mg daily for three months, followed by lifelong single antiplatelet therapy (SAPT). In patients requiring oral anticoagulation, no additional antiplatelet therapy was given unless recent PCI had been performed. For patients who underwent PCI before TAVR, DAPT was continued for six months and then transitioned to SAPT in the absence of anticoagulation. Patients who required both TAVR and PCI and had an indication for oral anticoagulation received triple therapy (DAPT plus anticoagulation) for one week, followed by SAPT plus anticoagulation for up to six months post-PCI, and anticoagulation alone thereafter. All coronary angiography and PCI procedures were performed via radial arterial access.

All TAVR procedures were performed via transfemoral access. The choice of femoral access site was guided by pre-procedural computed tomography (CT) evaluation. Vascular access was obtained under combined fluoroscopic and ultrasound guidance. A 6F pigtail catheter was used for contrast injections during valve deployment. A temporary pacing lead was placed via the femoral vein in all patients before valve implantation. Standardized CT analyses were performed using the 3mensio Structural Heart software (Pie Medical Imaging, Maastricht, the Netherlands), and prosthesis sizes were determined based on these measurements. The decision regarding valve type—BEV or SEV—was made by the primary interventional cardiologist after comprehensive case evaluation. As this was a retrospective study, detailed criteria guiding the choice between BEV and SEV were not consistently documented, and device selection was primarily based on operator preference. Vascular closure was achieved with Perclose ProGlide (Abbott Vascular, Santa Clara, CA) or Angio-Seal (Terumo Corp., Tokyo, Japan) systems when feasible. Surgical repair or covered stent implantation was performed if closure failed or major vascular injury occurred.

Definitions and Outcomes

Study outcomes were determined according to the standardized definitions proposed by the Valve Academic Research Consortium-3 (VARC-3).[23] The primary endpoint of the study was all-cause mortality during long-term follow-up. Secondary clinical outcomes included in-hospital death and periprocedural events such as cardiac tamponade or rupture, myocardial infarction (MI), coronary obstruction, aortic dissection or rupture, stroke, permanent pacemaker requirement, device embolization, acute kidney injury (AKI), vascular complications, bleeding events, need for intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO), technical success, and device success. According to VARC-3 definitions, bleeding events classified as Type 2, 3, or 4 were considered major bleeding, whereas Type 1 events were considered minor bleeding.

Major vascular complications included any of the following events: aortic dissection or rupture; vascular injury, distal embolization, closure device failure, or unplanned endovascular or surgical procedures leading to mortality, major bleeding, limb or visceral ischemia, or irreversible neurologic disability. Minor vascular complications included distal embolization, vascular injury, closure device failure, or unplanned endovascular or surgical intervention not resulting in VARC type ≥ 2 bleeding, death, irreversible neurologic impairment, or limb or visceral ischemia.[23] Definitions for MI and AKI were also based on VARC-3 recommendations.

Technical success was defined as fulfillment of all the following criteria at completion of the TAVR procedure: absence of mortality; successful vascular access; successful delivery and retrieval of the delivery system; correct positioning of the valve; and absence of the need for surgery or intervention due to device-related, major vascular, or cardiac structural complications.

Device success at 30 days post-procedure was defined as the presence of technical success; absence of mortality; absence of the need for surgery or intervention due to device-, major vascular-, access-related, or cardiac structural complications; and adequate valve performance, defined as peak aortic velocity < 3 m/s, mean aortic gradient < 20 mmHg, Doppler velocity index ≥ 0.25, and less than moderate aortic regurgitation.

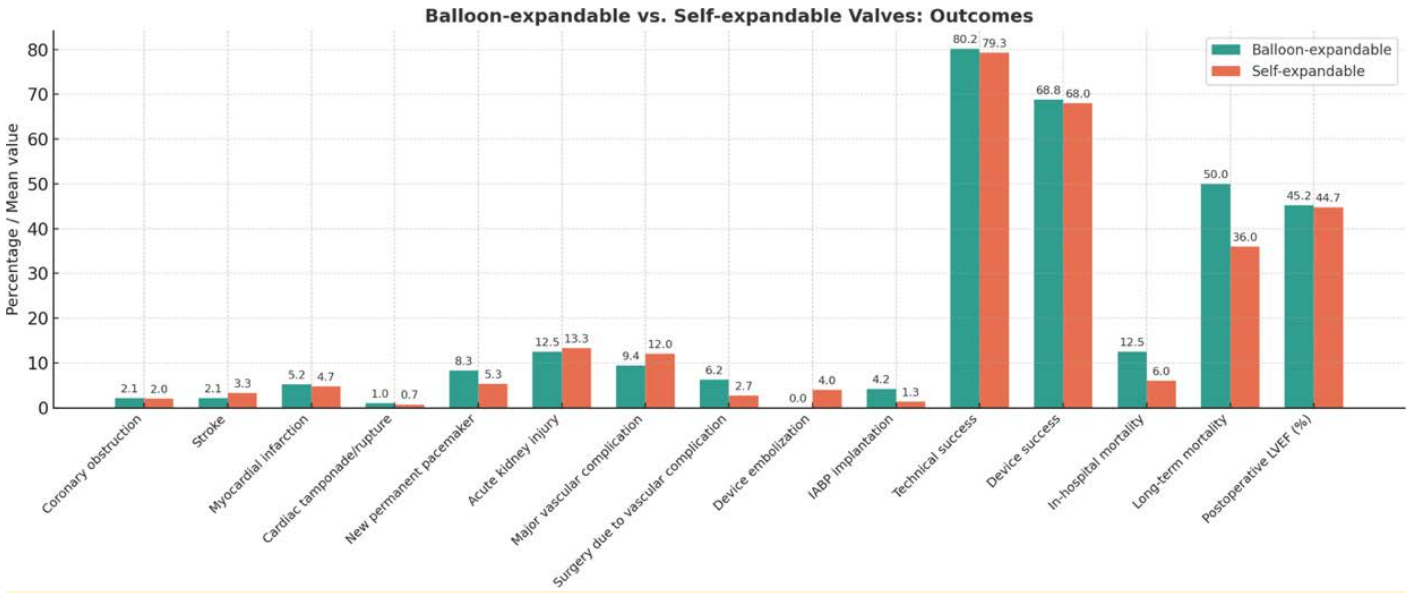

Figure 1. Comparison of perioperative and long-term outcomes between balloon-expandable valve (BEV) and self-expanding valve (SEV) groups.

All-cause mortality, the primary endpoint, was determined using a combination of the hospital electronic medical record system and direct telephone contact with patients' first-degree relatives when necessary. Periprocedural and in-hospital outcomes were obtained from the hospital information system, operative reports, and discharge summaries. Long-term clinical events were verified through scheduled outpatient clinic visits and review of electronic medical records.

Statistical Analysis

Continuous variables were tested for normality using visual histograms and the Kolmogorov–Smirnov test. Data with a normal distribution were compared using the t-test, whereas non-normally distributed variables were analyzed with the Mann–Whitney U test. Categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate. Results were expressed as mean ± standard deviation for normally distributed data and as median (interquartile range) otherwise; categorical variables were presented as counts and percentages.

Kaplan–Meier survival curves and the log-rank test were used to evaluate long-term all-cause mortality between valve groups. Predictors of mortality were assessed using Cox proportional hazards regression, employing a stepwise method for univariate and multivariate modeling. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

All analyses were performed using Python 3.11 (Python Software Foundation, Wilmington, DE, USA). A two-sided $P < 0.05$ denoted statistical significance.

Results

A total of 246 patients with LVEF < 50% underwent transfemoral TAVR and were included in the final analysis. Of these, 96 (39%) received balloon-expandable valves and 150 (61%) received self-expanding valves. Patients in the BEV group were older (78.8 ± 7.9 vs. 75.7 ± 9.8 years, P = 0.019) and had a lower body mass index (26.0 ± 3.2 kg/m² vs. 27.8 ± 4.4 kg/m², P = 0.001). The EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) was also higher in the BEV group (24.9 ± 6.2% vs. 22.2 ± 15.8%, P = 0.01). Comorbidities and medical therapy were generally comparable between groups, except for more frequent use of sodium–glucose cotransporter-2 inhibitors in the SEV group (34.0% vs. 12.5%, P < 0.001). Laboratory values did differ between groups. Detailed baseline clinical characteristics, comorbidities, follow-up medications, and laboratory values are presented in Table 1.

Among BEV recipients, 15 patients (15.6%) received newer-generation Myval™ (Meril Life Sciences Pvt. Ltd., Vapi, India), while the remainder received older-generation SAPIEN XT™ valves (Edwards Lifesciences LLC, Irvine, CA, USA). In the SEV group, 21 patients (14.0%) received newer-generation Evolut PRO™ or Evolut PRO+™ valves (Medtronic, Minneapolis, MN, USA), and the remaining patients received first-generation CoreValve™ prostheses (Medtronic, Minneapolis, MN, USA).

Preoperative echocardiographic characteristics, including LVEF, aortic maximum velocity, maximum and mean aortic gradients, aortic valve area, ascending aorta diameter, tricuspid annular plane systolic excursion (TAPSE), left atrial (LA) diameter, and pulmonary artery systolic pressure (PASP), were comparable between groups (Table 2). However, the SEV group included a higher proportion of patients with low-flow, low-gradient severe aortic stenosis (30.7% vs. 17.7%, P = 0.034) and had narrower aortic roots (2.8 ± 0.4 cm vs. 2.9 ± 2.3 cm, P = 0.011).

SYNTAX I scores derived from preprocedural coronary angiography were comparable between groups (14.7 ± 10.0 vs. 12.3 ± 11.3, P = 0.076), as were rates of PCI prior to TAVR (16.7% vs. 18.7%, P = 0.720). The SEV group required smaller sheath sizes for valve delivery (14.8 ± 1.6 mm vs. 17.5 ± 2.3 mm, P < 0.001). While rates of pre-dilation were similar (30.2% vs. 33.3%, P = 0.710), post-dilation was performed

Table 1. Comparison of baseline clinical characteristics, comorbidities, follow-up medications, and laboratory parameters between self-expanding and balloon-expandable valve groups

Variables	Balloon-expandable group (n = 96)	Self-expanding group (n = 150)	*P*
Baseline clinical characteristics and comorbidities			
Age (years)	78.8 ± 7.9	75.7 ± 9.8	0.019
Male sex	55 (57.3%)	91 (60.7%)	0.599
Body mass index (kg/m^2)	26.0 ± 3.2	27.8 ± 4.4	0.001
NYHA class	NYHA II: 25 (26.0%)	NYHA II: 27 (18.0%)	0.301
	NYHA II: 58 (60.4%)	NYHA III: 103 (68.7%)	
	NYHA IV: 13 (13.5%)	NYHA IV: 20 (13.3%)	
EuroSCORE II, (%)	24.9 ± 6.2	22.2 ± 15.8	0.01
Hypertension	86 (89.6%)	123 (82.0%)	0.105
Diabetes mellitus	40 (41.7%)	76 (50.7%)	0.168
Atrial fibrillation	33 (34.4%)	59 (39.3%)	0.433
COPD	52 (54.2%)	64 (42.7%)	0.078
Previous stroke	10 (10.4%)	6 (4.0%)	0.046
Chronic kidney disease	47 (49.0%)	68 (45.3%)	0.578
Coronary artery disease	68 (70.8%)	106 (70.7%)	0.978
Previous CABG	20 (20.8%)	31 (20.7%)	0.975
Peripheral arterial disease	5 (5.2%)	14 (9.3%)	0.237
Pre-operative pacemaker	10 (10.4%)	10 (6.7%)	0.294
Follow-up medications			
ACEi/ARB use	53 (55.2%)	83 (55.3%)	0.985
Beta-blocker use	84 (87.5%)	135 (90.0%)	0.541
SGLT-2i use	12 (12.5%)	51 (34.0%)	<0.001
Anticoagulation	25 (26.0%)	53 (35.3%)	0.127
Statin use	52 (54.2%)	77 (51.3%)	0.664
Insulin use	11 (11.5%)	23 (15.3%)	0.390
MRA use	20 (20.8%)	42 (28.0%)	0.207
ARNI use	2 (2.1%)	11 (7.3%)	0.073
Laboratory parameters			
Hemoglobin (g/dL)	11.36 ± 1.55	11.53 ± 1.86	0.446
WBC (cells/L)	(7.98 ± 3.03) × 10^3	8.13 ± 2.71 × 10^3	0.705
Platelets (cells/mcL)	(228.97 ± 89.96) × 10^3	(215.11 ± 65.21) × 10^3	0.197
Creatinine (mg/dL)	1.31 ± 0.75	1.36 ± 1.33	0.717
Glomerular filtration rate (mL/min/1.73 m^2)	65.09 ± 23.88	64.77 ± 25.72	0.919
AST (IU/L)	18.65 ± 11.33	22.87 ± 30.88	0.148
Albumin (g/dL)	4.44 ± 0.89	4.34 ± 0.71	0.444
Sodium (mEq/L)	137.22 ± 3.71	136.72 ± 11.78	0.638
Potassium (mEq/L)	4.43 ± 0.53	4.40 ± 0.50	0.762
TSH (mIU/L)	2.23 ± 2.24	2.43 ± 3.08	0.626
Total cholesterol (mg/dL)	205.02 ± 51.66	197.40 ± 47.73	0.339
LDL cholesterol (mg/dL)	125.81 ± 40.08	122.12 ± 43.03	0.543
HDL cholesterol (mg/dL)	43.06 ± 15.65	39.66 ± 10.06	0.123
Triglycerides (mg/dL)	149.72 ± 48.26	157.80 ± 52.23	0.306

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; ARNI, Angiotensin receptor–neprilysin inhibitor; AST, Aspartate aminotransferase; CABG, Coronary artery bypass graft surgery; COPD, Chronic obstructive pulmonary disease; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT-2i, Sodium–glucose cotransporter-2 inhibitor; TSH, Thyroid-stimulating hormone; WBC, White blood cell.

Table 2. Comparison of pre-operative echocardiographic parameters and angiographic characteristics between self-expanding and balloon-expandable valve groups

Variables	Balloon-expandable group (n = 96)	Self-expanding group (n = 150)	*P*
Preoperative echocardiographic parameters			
LVEF (%)	40.9 ± 9.4	40.2 ± 9.0	0.454
Aortic maximum velocity (m/s)	4.0 ± 0.7	3.9 ± 0.7	0.259
Maximum aortic gradient (mmHg)	68.2 ± 23.2	64.4 ± 22.5	0.150
Mean aortic gradient (mmHg)	44.0 ± 15.8	40.6 ± 14.7	0.085
Aortic valve area (cm^2)	0.7 ± 0.2	0.7 ± 0.2	0.738
Aortic root diameter (cm)	2.9 ± 2.3	2.8 ± 0.4	0.011
Ascending aorta diameter (cm)	3.8 ± 0.5	3.8 ± 0.4	0.890
TAPSE (cm)	1.8 ± 0.3	1.9 ± 0.3	0.211
Left atrial diameter (cm)	4.5 ± 0.6	4.5 ± 0.6	0.251
PASP (mmHg)	46.3 ± 11.8	46.7 ± 11.1	0.845
Low-flow, low-gradient severe AS	17 (17.7%)	46 (30.7%)	0.034
Aortic regurgitation	Absent: 8 (8.3%)	Absent: 34 (22.2%)	0.020
	Mild: 40 (41.7%)	Mild: 47 (31.5%)	
	Moderate: 28 (29.2%)	Moderate: 46 (30.9%)	
	Severe 20 (20.8%)	Severe: 23 (15.4%)	
Tricuspid regurgitation	Mild: 13 (13.5%)	Mild: 32 (20.8%)	0.095
	Moderate: 41 (42.7%)	Moderate: 71 (47.7%)	
	Severe: 42 (43.8%)	Severe: 47 (31.5%)	
Mitral regurgitation	Absent: 1 (1.0%)	Absent: 7 (4.0%)	0.031
	Mild: 23 (24.0%)	Mild: 41 (27.5%)	
	Moderate: 32 (33.3%)	Moderate: 64 (43.0%)	
	Severe: 40 (41.7%)	Severe: 38 (25.5%)	
Angiographic and interventional characteristics			
SYNTAX I score	14.7 ± 10.0	12.3 ± 11.3	0.076
Sheath size (mm)	17.5 ± 2.3	14.8 ± 1.6	<0.001
Pre-dilation	29 (30.2%)	50 (33.3%)	0.710
Post-dilation	6 (6.2%)	58 (38.7%)	<0.001
Valve size (mm)	26.7 ± 2.5	29.7 ± 3.5	<0.001
PCI during hospitalization	16 (16.7%)	28 (18.7%)	0.720

AS, Aortic stenosis; LVEF, Left ventricular ejection fraction; PASP, Pulmonary artery systolic pressure; PCI, Percutaneous coronary intervention; TAPSE, Tricuspid annular plane systolic excursion.

more frequently in the SEV group (38.7% vs. 6.2%, P < 0.001). Mean prosthesis diameter was larger in the SEV group (29.7 ± 3.5 mm vs. 26.7 ± 2.5 mm, P < 0.001).

The median follow-up duration for the overall cohort was 1,037 days (interquartile range (IQR): 370–1,629 days). The BEV group had a numerically longer follow-up period compared with the SEV group (1,160 [352–2,414] days vs. 962 [432–1,449] days, P = 0.09). Periprocedural and in-hospital outcomes, including coronary obstruction, stroke, myocardial infarction, cardiac tamponade or rupture, aortic dissection, permanent pacemaker implantation, acute kidney injury, major vascular complications, and in-hospital death, were comparable between groups (Table 3, Figure 1). Technical success (80.2% vs. 79.3%, P = 0.997) and device success (68.8% vs. 68.0%, P = 1.000) were also similar.

Postoperative six-month echocardiographic follow-up demonstrated comparable LVEF, PASP, LVEF recovery, left atrial diameter, and rates of moderate or severe PVR between the BEV and SEV groups (Table 3, Figure 1). However, the SEV group exhibited significantly lower postoperative transvalvular gradients, both maximal (14.3 ± 6.8 mmHg vs. 17.2 ± 7.0 mmHg, P = 0.001) and mean (7.8 ± 4.0 mmHg vs. 9.6 ± 4.1 mmHg, P = 0.001).

Long-term mortality occurred more frequently in the BEV group (50.0% vs. 36.0%, P = 0.041); however, Kaplan–Meier survival curves demonstrated no statistically significant difference between the valve groups (log-rank P = 0.92) (Figure 2).

To identify predictors of long-term all-cause mortality, stepwise univariate and multivariate Cox regression analyses

Table 3. Comparison of follow-up data and outcomes between self-expanding and balloon-expandable valve groups

Variables	Balloon-expandable group (n = 96)	Self-expanding group (n = 150)	*P*
Follow-up duration (days)	1160 (352–2414) days	962 (432–1449) days	0.09
Perioperative complications and outcomes			
Coronary obstruction	2 (2.1%)	3 (2.0%)	1.0
Stroke	2 (2.1%)	5 (3.3%)	0.855
Myocardial infarction	5 (5.2%)	7 (4.7%)	0.870
Cardiac tamponade/rupture	1 (1.0%)	1 (0.7%)	1.0
Aortic dissection	0 (0.0%)	0 (0.0%)	1.0
New permanent pacemaker	8 (8.3%)	8 (5.3%)	0.506
Acute kidney injury	12 (12.5%)	20 (13.3%)	1.0
Major vascular complication	9 (9.4%)	18 (12.0%)	0.665
Minor vascular complication	14 (14.6%)	27 (18.0%)	0.599
Surgery due to vascular complication	6 (6.2%)	4 (2.7%)	0.290
Major bleeding	9 (9.4%)	22 (14.7%)	0.306
Minor bleeding	14 (14.6%)	27 (18.0%)	0.599
Device embolization	0 (0.0%)	6 (4.0%)	0.119
IABP implantation	4 (4.2%)	2 (1.3%)	0.326
ECMO use	1 (1.0%)	0 (0.0%)	0.822
Hospitalization duration (days)	5.4 ± 3.0	5.9 ± 4.8	0.979
Technical success	77 (80.2%)	119 (79.3%)	0.997
Device success	66 (68.8%)	102 (68.0%)	1.0
In-hospital mortality	12 (12.5%)	9 (6.0%)	0.122
Long-term outcomes and control echocardiography at 6 months after TAVR			
Long-term mortality	48 (50.0%)	54 (36.0%)	0.041
Postoperative LVEF (%)	45.2 ± 10.6	44.7 ± 11.1	0.763
Postoperative LVEF change (%)	3.92 ± 5.60	4.16 ± 6.71	0.593
Moderate or severe PVL	9 (9.4%)	17 (11.3%)	0.889
Postoperative maximum aortic gradient (mmHg)	17.2 ± 7.0	14.3 ± 6.8	0.001
Postoperative mean aortic gradient (mmHg)	9.6 ± 4.1	7.8 ± 4.0	0.001
Postoperative PASP (mmHg)	41.6 ± 11.1	39.3 ± 12.0	0.136
Postoperative left atrial diameter (cm)	4.5 ± 0.5	4.5 ± 0.6	0.123

ECMO, Extracorporeal membrane oxygenation; IABP, Intra-aortic balloon pump; LVEF, Left ventricular ejection fraction; PASP, Pulmonary artery systolic pressure; PVL, Paravalvular leak.

were performed. Baseline clinical features, laboratory values, echocardiographic parameters, medications, and angiographic and procedural variables were included in the initial univariate analysis (Table 4). In univariate analysis, the following parameters predicted long-term mortality: age (HR: 1.05, 95% CI: 1.03–1.08, P < 0.001), chronic obstructive pulmonary disease (COPD) (HR: 1.72, 95% CI: 1.16–2.55, P = 0.007), chronic kidney disease (CKD) (HR: 1.68, 95% CI: 1.14–2.49, P = 0.009), lower preoperative aortic gradients, perioperative acute kidney injury (HR: 2.65, 95% CI: 1.62–4.33, P < 0.001), higher serum sodium (HR: 1.07, 95% CI: 1.02–1.13, P = 0.013), presence of coronary artery disease (HR: 1.70, 95% CI: 1.07–2.72, P = 0.025), lower serum albumin (HR: 0.74, 95% CI: 0.56–0.97, P = 0.032), lower postoperative LVEF (HR: 0.98, 95% CI: 0.96–1.00, P = 0.032), LFLG aortic stenosis (HR: 1.61, 95% CI: 1.03–2.53, P = 0.037), perioperative stroke (HR: 2.77, 95% CI: 1.02–7.56, P = 0.046), lower preoperative hemoglobin (HR: 0.89, 95% CI: 0.79–1.00, P = 0.047), and perioperative minor bleeding (HR: 1.67, 95% CI: 1.04–2.68, P = 0.034). Valve type (BEV vs. SEV) was not associated with long-term mortality.

Significant variables identified in univariate analysis, except for preoperative maximum aortic gradient (to avoid collinearity with mean gradient), were entered into the multivariate model. In multivariate Cox regression, COPD (HR: 2.64, 95% CI: 1.54–4.52, P < 0.001), age (HR: 1.05, 95% CI: 1.01–1.08, P = 0.007), lower preoperative mean aortic gradient (HR: 0.97, 95% CI: 0.94–1.00, P = 0.034), coronary artery disease (HR: 2.08, 95% CI: 1.13–3.81, P = 0.018), lower serum albumin (HR: 0.63, 95% CI: 0.44–0.90, P = 0.011), and lower preoperative hemoglobin (HR: 0.84, 95% CI: 0.72–0.98, P = 0.023) remained independent predictors of long-term mortality (Table 4, Figure 3).

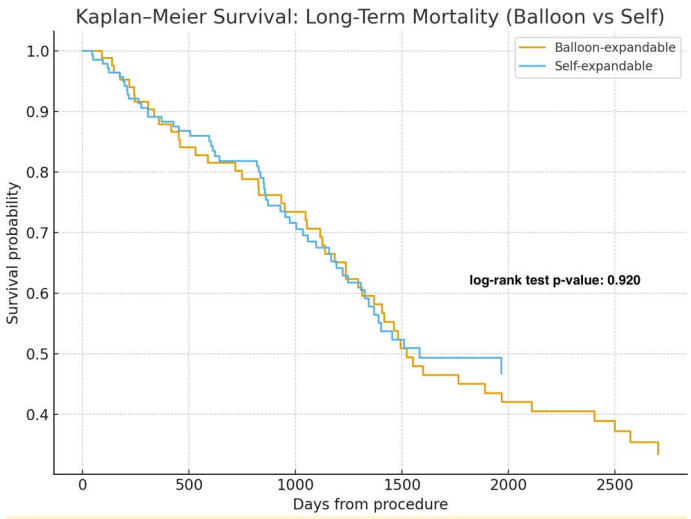

Figure 2. Kaplan–Meier curves for long-term all-cause mortality in patients undergoing transcatheter aortic valve replacement (TAVR) with balloon-expandable valves (BEV) and self-expanding valves (SEV).

In this cohort of patients with severely reduced left ventricular systolic function (LVEF < 40%) undergoing TAVR, baseline demographic and clinical characteristics were largely comparable between the balloon-expandable and self-expanding valve groups (Table 5). Age, sex distribution, comorbidities, and surgical risk scores did not differ significantly; however, patients treated with self-expanding valves had a higher body mass index (27.9 ± 3.93 kg/m^2 vs. 26.1 ± 3.20 kg/m^2, P = 0.014), a higher prevalence of SGLT-2 (sodium–glucose cotransporter-2) inhibitor use (47.4% vs. 17.5%, P = 0.003), and lower rates of prior stroke (1.3% vs. 15.0%, P = 0.006). Pre-procedural echocardiography demonstrated comparable LVEF, aortic gradients, aortic valve areas, and similar frequencies of low-flow, low-gradient severe aortic stenosis in both groups, although patients receiving balloon-expandable valves exhibited lower TAPSE values (1.66 ± 0.26 cm vs. 1.76 ± 0.21 cm, P = 0.015) and a higher prevalence of severe aortic regurgitation (30.0% vs. 10.5%, P = 0.017). Procedurally, balloon-expandable valves were associated with the use of larger sheath sizes (17.7 ± 2.20 Fr vs. 14.9 ± 1.23 Fr, P < 0.001) and smaller prosthesis diameters (27.3 ± 2.33 mm vs. 30.7 ± 3.23 mm, P < 0.001). Long-term follow-up was significantly longer in the balloon-expandable group (1575.5 [712.8–2740.3] vs. 999.0 [607.8–1406.0] days, P = 0.001). Periprocedural complication rates, including MI, stroke, acute kidney injury, vascular complications, and bleeding, were similar between groups. In-hospital mortality was higher in the balloon-expandable cohort (20.0% vs. 5.3%, P = 0.022), whereas long-term mortality did not differ significantly (47.5% vs. 39.5%, P = 0.526). Device and technical success rates were comparable between the two valve types (Table 5). Kaplan–Meier analysis also showed comparable survival probabilities between the two groups, with a log-rank p-value of 0.453 (Figure 4).

In the multivariate Cox regression analysis model for the prediction of long-term mortality in patients with advanced

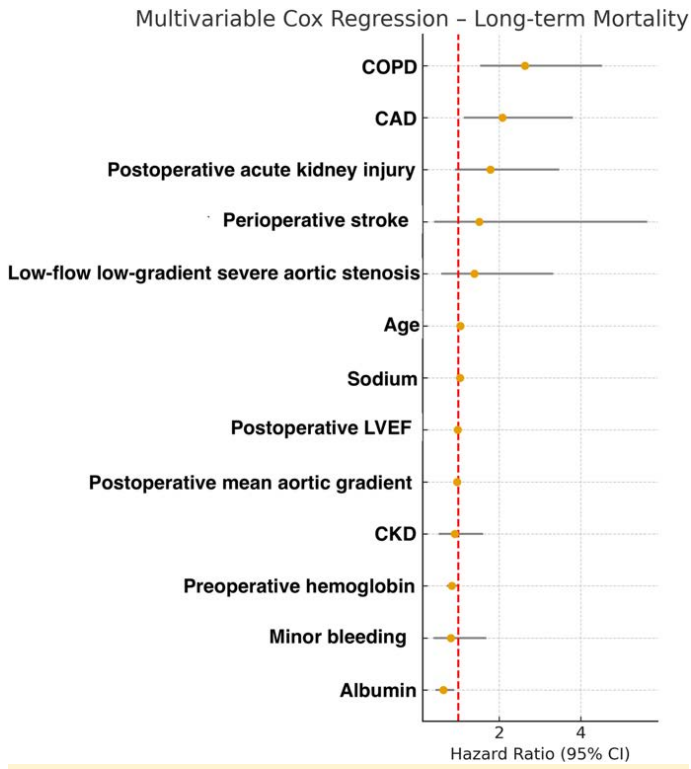

Figure 3. Forest plot showing independent predictors of long-term all-cause mortality following transcatheter aortic valve replacement (TAVR) in patients with reduced left ventricular ejection fraction.

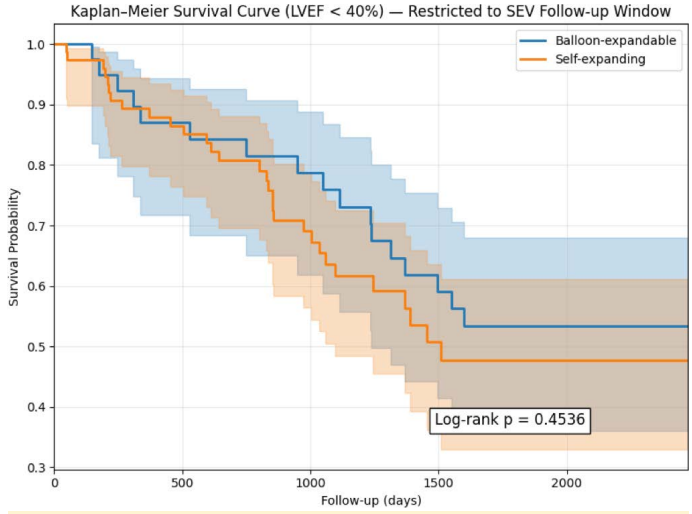

Figure 4. Kaplan–Meier survival curves in advanced heart failure patients (left ventricular ejection fraction [LVEF] < 40%) undergoing transcatheter aortic valve replacement (TAVR) with balloon-expandable valves (BEV) and self-expanding valves (SEV).

heart failure (LVEF < 40%) and severe aortic stenosis, COPD (HR: 1.91; 95% CI: 1.03–3.57; P = 0.041) and mean postoperative aortic gradient (HR: 0.97 per 1 mmHg; 95% CI: 0.94–0.99; P = 0.011) emerged as independent predictors (Table 6). Age, coronary artery disease, and valve type (BEV vs. SEV) were not significantly associated with long-term mortality (Table 6).

Table 4. Univariate and multivariate Cox regression analyses for the prediction of long-term mortality

Variables	Univariate Cox Regression Analysis			Multivariate Cox Regression Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (per 1 year)	1.05	1.03-1.08	**<0.001**	1.05	1.01-1.08	**0.007**
Male sex	0.99	0.67-1.47	0.951			
BEV vs. SEV	0.92	0.62-1.37	0.690			
COPD	1.72	1.16-2.55	**0.007**	2.64	1.54-4.52	**<0.001**
Chronic kidney disease	1.68	1.14-2.49	**0.009**	0.91	0.52-1.61	0.755
Preoperative maximum aortic gradient (per 1 mmHg)	0.99	0.98-1.00	**0.006**			
Preoperative mean aortic gradient (per 1 mmHg)	0.98	0.96-0.99	**0.002**	0.97	0.94-1.00	**0.034**
Perioperative AKI	2.65	1.62-4.33	**<0.001**	1.78	0.92-3.47	0.088
Sodium (per 1 mEq/L)	1.07	1.02-1.13	**0.013**	1.04	0.97-1.12	0.286
Coronary artery disease	1.70	1.07-2.72	**0.025**	2.08	1.13-3.81	**0.018**
Albumin (per 1 g/dL)	0.74	0.56-0.97	**0.032**	0.63	0.44-0.90	**0.011**
Postoperative LVEF (per 1%)	0.98	0.96-1.00	**0.032**	0.99	0.96-1.01	0.319
Low-flow, low-gradient aortic stenosis	1.61	1.03-2.53	**0.037**	1.39	0.58-3.33	0.456
Perioperative stroke	2.77	1.02-7.56	**0.046**	1.51	0.41-5.63	0.538
Preoperative hemoglobin (per 1 g/dL)	0.89	0.79-1.00	**0.047**	0.84	0.72-0.98	**0.023**
Perioperative minor bleeding	1.67	1.04-2.68	**0.034**	0.81	0.39-1.69	0.580
Total cholesterol (per 1 mg/dL)	1.00	0.99-1.00	0.073			
LDL cholesterol (per 1 mg/dL)	1.00	0.99-1.00	0.073			
Preoperative creatinine (per 1 mg/dL)	1.13	0.96-1.32	0.135			
Potassium (per 1 mEq/L)	0.76	0.50-1.13	0.176			
AST (per 1 IU/L)	1.01	1.00-1.01	0.190			
TSH (per 1 mIU/L)	0.93	0.83-1.04	0.195			
Body mass index (per 1 kg/m2)	0.96	0.91-1.01	0.079			
NYHA class III-IV	1.39	0.95-2.04	0.090			
Presence of device success	1.52	0.93-2.51	0.097			
Presence of technical success	1.33	0.71-2.50	0.366			
Preoperative LVEF (per 1%)	0.99	0.97-1.01	0.210			
Preoperative TAPSE (per 1 cm)	0.56	0.26-1.21	0.139			
Preoperative aortic root diameter (per 1 cm)	0.90	0.70-1.16	0.419			
Preoperative AVA (per 1 cm^2)	1.29	0.39-4.27	0.672			
Preoperative moderate or severe AR	0.99	0.81-1.21	0.927			
Postoperative moderate or severe MR	1.30	0.98-1.72	0.069			
Postoperative PASP (per 1 mmHg)	1.01	1.00-1.03	0.102			
Postoperative maximum aortic gradient (per 1 mmHg)	0.98	0.95-1.01	0.213			
Postoperative mean aortic gradient (per 1 mmHg)	0.95	0.90-1.01	0.105			
Beta-blocker use	0.64	0.36-1.12	0.117			
Insulin use	1.43	0.85-2.41	0.177			
SGLT-2i use	0.95	0.58-1.56	0.840			
Anticoagulation	1.06	0.69-1.61	0.793			
ARNI use	1.15	0.47-2.83	0.760			
MRA use	0.97	0.61-1.54	0.887			
ACEi/ARB use	1.12	0.76-1.66	0.574			
Statin use	0.88	0.60-1.30	0.535			
Diabetes mellitus	1.12	0.76-1.65	0.576			
Peripheral arterial disease	1.73	0.87-3.44	0.119			
CABG	1.14	0.72-1.82	0.573			
Hypertension	0.87	0.52-1.47	0.602			
Atrial fibrillation	1.10	0.74-1.65	0.636			
Previous stroke	1.14	0.53-2.47	0.733			
Postoperative pacemaker implantation	1.85	0.86-4.00	0.118			
Perioperative major vascular complication	0.69	0.32-1.49	0.348			
EuroSCORE II (per 1%)	1.01	1.00-1.03	0.141			
Moderate or severe PVL	0.73	0.35-1.51	0.396			
Major bleeding	0.83	0.43-1.60	0.576			
SYNTAX I score (per 1 increase)	1.00	0.97-1.02	0.841			

ACEi, Angiotensin-converting enzyme inhibitor; AKI: Acute kidney injury; AR, Aortic regurgitation; ARB, Angiotensin II receptor blocker; ARNI, Angiotensin receptor–neprilysin inhibitor; AST, Aspartate aminotransferase; AVA, Aortic valve area; BEV, Balloon-expandable valve; CABG, Coronary artery bypass graft surgery; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; HR, Hazard ratio; LDL, Low-density lipoprotein; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PASP, Pulmonary artery systolic pressure; PVL, Paravalvular leak; SEV, Self-expanding valve; SGLT-2i, Sodium–glucose cotransporter-2 inhibitor; TAPSE, Tricuspid annular plane systolic excursion; TSH, Thyroid-stimulating hormone.

Table 5. Comparison of balloon-expandable and self-expanding valves in patients with severely reduced ejection fraction (LVEF < 40%) and severe aortic stenosis

Variables	Balloon-expandable valve (n = 40)	Self-expanding valve (n = 76)	*P*
Baseline clinical characteristics and comorbidities			
Age (years)	77.9 ± 8.55	74.6 ± 11.50	0.176
Male sex	29 (72.5%)	53/76 (69.7%)	0.923
Body mass index (kg/m^2)	26.1 ± 3.20	27.9 ± 3.93	0.014
EuroSCORE II	25.5 ± 6.82	25.8 ± 17.75	0.298
Hypertension	35 (87.5%)	64 (84.2%)	0.841
Diabetes mellitus	20 (50.0%)	46 (60.5%)	0.373
Atrial fibrillation	14 (35.0%)	30 (39.5%)	0.787
COPD	24 (60.0%)	32 (42.1%)	0.101
Pre-operative pacemaker	4 (10.0%)	6 (7.9%)	0.735
Previous stroke	6 (15.0%)	1 (1.3%)	0.006
Chronic kidney disease	26 (65.0%)	40 (52.6%)	0.280
Coronary artery disease	26 (65.0%)	59 (77.6%)	0.215
Coronary artery bypass grafting	7 (17.5%)	20 (26.3%)	0.403
SYNTAX score	14.8 ± 10.40	13.4 ± 12.01	0.498
Peripheral arterial disease	3 (7.5%)	10 (13.2%)	0.538
Medications			
ACEi/ARB use	21 (52.5%)	41 (53.9%)	1.000
ARNI use	2 (5.0%)	9 (11.8%)	0.326
ß-blocker use	35 (87.5%)	72 (94.7%)	0.272
MRA use	12 (30.0%)	31 (40.8%)	0.347
SGLT-2 inhibitor use	7 (17.5%)	36 (47.4%)	0.003
Insulin use	6 (15.0%)	15 (19.7%)	0.707
Anticoagulation use	11 (27.5%)	27 (35.5%)	0.505
Statin use	22 (55.0%)	36 (47.4%)	0.558
Pre-operative echocardiographic data			
Low-flow, low-gradient severe aortic stenosis	17 (42.5%)	38 (50.0%)	0.566
Pre-operative LVEF (%)	31.0 ± 5.77	32.6 ± 5.77	0.131
Pre-operative maximum aortic gradient (mmHg)	55.5 ± 18.97	57.1 ± 19.53	0.674
Pre-operative mean aortic gradient (mmHg)	35.9 ± 12.47	36.2 ± 12.66	0.900
Pre-operative aortic valve area (cm^2)	0.78 ± 0.22	0.74 ± 0.15	0.387
Pre-operative PASP (mmHg)	46.1 ± 12.27	48.0 ± 11.40	0.386
Pre-operative TAPSE (cm)	1.66 ± 0.26	1.76 ± 0.21	0.015
Pre-operative aortic root diameter (cm)	2.74 ± 0.65	2.78 ± 0.39	0.149
Severe aortic regurgitation	12 (30.0%)	8 (10.5%)	0.017
Pre-Operative Laboratory Values			
Sheath size (Fr)	17.7 ± 2.20	14.9 ± 1.23	<0.001
Hemoglobin (g/dL)	11.5 ± 1.69	11.42 ± 1.92	0.830
Creatinine (mg/dL)	1.36 ± 0.64	1.34 ± 0.83	0.470
AST (IU/L)	21.8 ± 9.21	28.99 ± 24.86	0.110
Procedural Data & Postoperative Outcomes			
Valve size (mm)	27.3 ± 2.33	30.7 ± 3.23	<0.001
Sheath size (Fr)	17.7 ± 2.20	14.9 ± 1.23	<0.001
Hospitalization duration (days)	5.6 ± 3.38	6.3 ± 4.30	0.612

Table 5 (cont). Comparison of balloon-expandable and self-expanding valves in patients with severely reduced ejection fraction (LVEF < 40%) and severe aortic stenosis

Variables	Balloon-expandable valve (n = 40)	Self-expanding valve (n = 76)	*P*
Long-term follow-up duration (days)	1575.5 (712.75–2740.25)	999.0 (607.75–1406.0)	0.001
Periprocedural MI	1 (2.5%)	2 (2.6%)	1.000
Periprocedural stroke	1 (2.5%)	3 (3.9%)	1.000
Postoperative acute kidney injury	7 (17.5%)	10 (13.2%)	0.725
Major vascular complication	4 (10.0%)	12 (15.8%)	0.564
Minor vascular complication	4 (10.0%)	7 (9.2%)	1.000
Major bleeding	4 (10.0%)	14 (18.4%)	0.357
Coronary obstruction	1 (2.5%)	1 (1.3%)	1.000
Device embolization	0 (0%)	1 (1.3%)	1.000
IABP/ECMO use	3 (7.5%)	1 (1.3%)	0.118
Surgery due to peripheral complication	3 (7.5%)	3 (3.9%)	0.414
New permanent pacemaker implantation	3 (7.5%)	3 (3.9%)	0.414
Postoperative maximum aortic gradient (mmHg)	15.8 ± 7.73	13.4 ± 6.45	0.083
Postoperative mean aortic gradient (mmHg)	8.76 ± 3.98	7.25 ± 3.95	0.033
Postoperative LVEF (%)	35.1 ± 8.04	36.6 ± 8.93	0.457
Postprocedural LVEF change (%)	4.24 ± 6.44	3.58 ± 7.44	0.916
Postoperative PASP (mmHg)	41.9 ± 11.13	40.9 ± 12.59	0.586
Device success	26 (65.0%)	53 (69.7%)	0.756
Technical success	31 (77.5%)	61 (80.3%)	0.914
Severe mitral regurgitation	9 (22.5%)	16 (21.1%)	1.000
Severe tricuspid regurgitation	2 (5.0%)	9 (11.8%)	0.326
Moderate–severe PVL	3 (9.1%)	8 (11.8%)	1.000
In-hospital mortality	8 (20.0%)	4 (5.3%)	0.022
Long-term mortality	19 (47.5%)	30 (39.5%)	0.526

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; ARNI, Angiotensin receptor–neprilysin inhibitor; AST, Aspartate aminotransferase; COPD, Chronic obstructive pulmonary disease; ECMO, Extracorporeal membrane oxygenation; IABP, Intra-aortic balloon pump; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; MRA, Mineralocorticoid receptor antagonist; PASP, Pulmonary artery systolic pressure; PVL, Paravalvular leak; SGLT-2i, Sodium–glucose cotransporter-2 inhibitor; TAPSE, Tricuspid annular plane systolic excursion.

Table 6. Multivariate Cox regression analysis for the prediction of long-term mortality in patients with advanced heart failure (LVEF < 40%)

Covariate	HR	95% CI	*P*
Age	1.011	0.981–1.043	0.468
COPD	1.914	1.027–3.568	0.041
CAD	1.278	0.619–2.640	0.507
BEV vs. SEV	0.655	0.348–1.233	0.190
Mean aortic gradient (per 1 mmHg)	0.968	0.943–0.993	0.011

BEV, Balloon-expandable valve; CAD, Coronary artery disease; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; HR, Hazard ratio, LVEF, Left ventricular ejection fraction; SEV, Self-expanding valve.

Discussion

Reduced LVEF has consistently been linked to poorer outcomes after TAVR, including increased risks of in-hospital and long-term death as well as adverse cardiac events.[4–11] Within this group, patients exhibiting the low-flow, low-gradient phenotype experience the most unfavorable prognosis, with mortality exceeding that of both paradoxical low-gradient and high-gradient subtypes.[8–11] Given the increased hemodynamic vulnerability of patients with LVSD, complications such as paravalvular leak, arrhythmia, cardiac tamponade, hypotension, acute kidney injury, bleeding, and prosthetic valve dysfunction may be less well tolerated. Consequently, determining whether valve design or functional differences influence outcomes carries particular clinical relevance in this vulnerable population.

Previous studies comparing SEVs and BEVs have primarily focused on outcomes such as PVR, high-grade atrioventricular block, recapturability, and postprocedural hemodynamics. The CHOICE trial (Comparison of Balloon-Expandable Versus Self-Expanding Transcatheter Aortic Valve Implantation) demonstrated higher device success with BEVs, driven by lower rates of more-than-mild PVR and new permanent pacemaker implantation in the overall TAVR population.[16] Conversely, the SOLVE-TAVI trial (Comparison of Second-Generation Self-Expandable Versus Balloon-Expandable Valves and General Versus Local Anesthesia in Transcatheter

Aortic Valve Implantation)—comparing newer-generation systems—found no meaningful differences between valve types regarding mortality, PVR, or pacemaker implantation.[17] The extended follow-up of CHOICE similarly demonstrated that five-year all-cause mortality and clinically significant PVR rates were comparable, although SEVs maintained lower residual gradients.[20] Similarly, the SMART trial (Comparison of Self-Expanding Versus Balloon-Expandable Valves in Patients With Small Aortic Annuli Undergoing Transcatheter Aortic Valve Replacement), which focused on TAVR in patients with small aortic annuli, showed that SEVs provided lower transvalvular gradients and less bioprosthetic valve dysfunction, with comparable new pacemaker rates.[21] Despite these findings, most pivotal trials have not specifically analyzed outcomes in patients with reduced LVEF, and data in this subgroup remain limited. Considering the distinct hemodynamic and procedural profiles of BEVs and SEVs, evaluating their comparative performance in patients with LVSD is crucial for optimizing valve selection and improving long-term outcomes.

Mustafa et al.[24] compared SEVs and BEVs among patients with LVEF ≤ 40% and found similar early outcomes, pacemaker rates, long-term survival, and quality-of-life measures at one year. In that study, BEVs were associated with higher transvalvular gradients, whereas SEVs showed higher rates of PVR. Evidence from studies with longer follow-up durations has been limited until recently. Nakase et al.[25] analyzed five-year follow-up in a similar population (TAVR patients with LVEF < 50%) and observed higher all-cause mortality in the SEV group, whereas device success, PVR severity, pacemaker implantation, and cardiovascular mortality at one and five years were comparable. Notably, the BEV group demonstrated higher mean transvalvular gradients. However, as this study also had a retrospective design, residual confounding and selection bias may have influenced the observed differences in long-term mortality. In the present study, with a median follow-up approaching three years, the SEV group demonstrated significantly lower postoperative transvalvular gradients and numerically lower long-term mortality. Nonetheless, these differences likely reflect baseline disparities—specifically, the older age and higher EuroSCORE II values observed in the BEV group—rather than an intrinsic difference in valve performance. In the Cox regression analyses, valve type did not emerge as an independent determinant of long-term mortality, and Kaplan–Meier analysis similarly demonstrated no survival difference between BEV and SEV recipients.

Determinants of long-term mortality among patients with reduced ejection fraction undergoing TAVR are not fully defined. Ludwig et al.[5] identified male sex, COPD, stroke volume index, pulmonary hypertension, atrial fibrillation, and non-transfemoral access as independent one-year predictors, though laboratory, procedural, and imaging parameters were not incorporated. However, that analysis did not include comprehensive clinical or procedural variables such as laboratory data, detailed echocardiographic parameters, or angiographic findings. In the TOPAS-TAVI registry (True or Pseudo Severe Aortic Stenosis–Transcatheter Aortic Valve Implantation registry),[12] COPD and lower hemoglobin levels independently predicted long-term mortality after a median follow-up of 21 months in patients with low-flow, low-gradient aortic stenosis. The present study expands upon these findings with a more comprehensive dataset and a longer observation period. Consistent with prior findings, COPD and lower hemoglobin levels independently predicted long-term mortality. Additionally, advanced age, the presence of coronary artery disease, and reduced serum albumin were significant contributors. Notably, lower preoperative mean aortic gradients were also linked to higher mortality, aligning with existing evidence that LFLG severe aortic stenosis confers an adverse prognosis. These results highlight that even among patients with reduced ejection fraction, lower preprocedural gradients continue to serve as a marker of adverse clinical outcomes after TAVR.

In patients with severe LV dysfunction (LVEF < 40%) undergoing TAVR, our findings demonstrate that balloon-expandable and self-expanding valves yield broadly comparable clinical outcomes, despite notable baseline and procedural differences. The balloon-expandable group presented with slightly more advanced right ventricular dysfunction—as reflected by lower TAPSE—and a higher prevalence of concomitant severe aortic regurgitation, suggesting a potentially more complex hemodynamic substrate. Additionally, larger sheath requirements and smaller prosthesis diameters reflect known design distinctions between platforms. Despite these differences, early periprocedural events—including stroke, MI, acute kidney injury, and vascular complications—were similar across both groups, reinforcing the procedural safety of modern TAVR devices even in high-risk, low-ejection fraction (EF) populations. An important consideration when interpreting the higher in-hospital mortality observed in the balloon-expandable cohort is the temporal distribution of cases. Because the earliest procedures in our program were primarily performed with balloon-expandable valves, it is plausible that the learning curve may have contributed to the increased early mortality signal in this group. As operator and institutional experience grew, procedural refinement and complication management likely improved, which may explain the subsequently lower in-hospital mortality rates observed in later cases. This pattern suggests that at least part of the early mortality difference may be attributable to procedural maturation rather than intrinsic device-related risk. Taken together, long-term mortality, device success, and technical performance were comparable between groups, indicating that both valve types can be effectively used in patients with severely impaired systolic function. These results support individualized valve selection based not only on anatomical suitability but also on operator preference and center experience, as both platforms demonstrated acceptable safety and durability in this challenging patient subset. Matta et al.[26] reported improved long-term survival in patients with advanced heart failure and severe aortic stenosis who underwent SEV implantation compared with those receiving BEV, attributing this difference to lower postoperative transvalvular gradients. However, their study included a relatively small sample size and a retrospective design, making it susceptible to confounding and unmeasured bias. While our analysis demonstrated comparable long-term mortality outcomes between valve types, further prospective

and randomized clinical trials are needed before definitive conclusions can be drawn.

Limitations

Several limitations should be considered. First, this study was a single-center, retrospective investigation, which may restrict the generalizability of its findings. Second, computed tomography–based anatomical data were not available, precluding detailed evaluation of annular geometry, valve sizing, and calcification burden. Third, the proportion of newer-generation devices was relatively low, and outcomes with contemporary valve systems may differ. Fourth, because detailed documentation of the specific causes of death was not consistently available, we were unable to differentiate cardiovascular from non-cardiovascular mortality, which may limit the mechanistic interpretation of our findings. Finally, although EuroSCORE II and age differed statistically between groups in the overall patient cohort, the numerical differences were modest and unlikely to have introduced a clinically meaningful imbalance; nevertheless, residual confounding related to baseline risk cannot be entirely excluded, and unmeasured confounders inherent to the retrospective design may also be present. Therefore, prospective multicenter studies with higher representation of current-generation valve platforms are warranted to confirm these observations in patients with reduced systolic function.

Conclusion

In patients with impaired left ventricular systolic function undergoing TAVR, BEV and SEV systems demonstrated comparable procedural success and long-term outcomes. Although self-expanding valves provided lower postoperative gradients, valve type did not independently predict mortality. Instead, older age, COPD, coronary artery disease, lower preoperative mean aortic gradient, and reduced hemoglobin and albumin levels predicted long-term mortality. Valve selection may therefore rely more on anatomical suitability and operator preference than on differences in survival.

Ethics Committee Approval: Ethics committee approval was obtained from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: 1150, Date: 25.09.2025).

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

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

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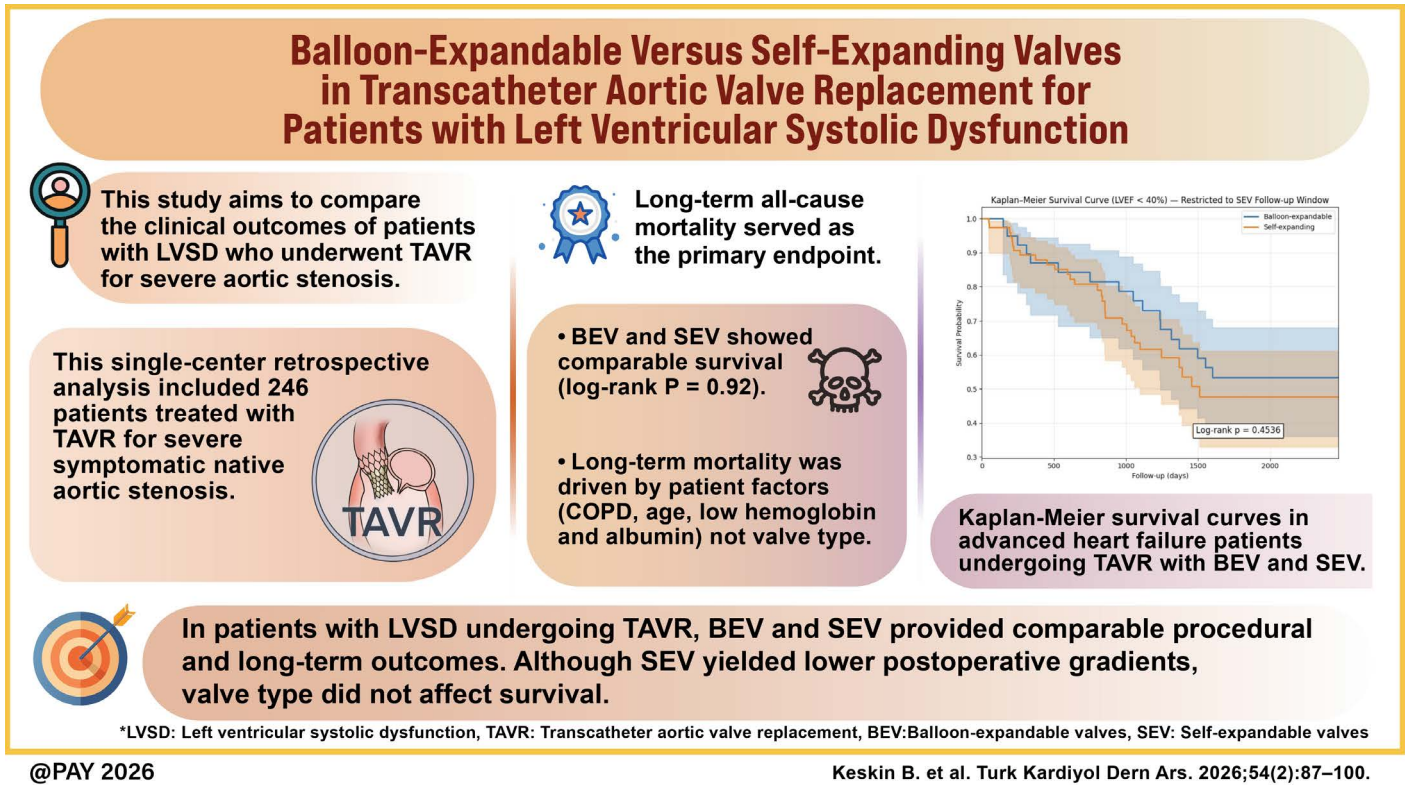

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Lipoprotein(a) and Cumulative Low-Density Lipoprotein Cholesterol as Predictors of Coronary Artery Disease in Statin-Naïve Elderly Individuals with Hyperlipidemia

Statin-Naif Yaşlı Bireylerde Koroner Arter Hastalığı Öngördürücüsü Olarak Lipoprotein(a) ve Kümülatif LDL Kolesterol

ABSTRACT

Objective: Advanced age is a well-recognized risk factor for atherosclerotic cardiovascular disease (ASCVD). Given the ongoing debate regarding the initiation of statin therapy in elderly individuals, identifying those with underlying coronary artery disease (CAD) who may benefit from lipid-lowering treatment is essential. This study aimed to identify predictors of CAD in statin-naïve adults aged ≥ 70 years with elevated low-density lipoprotein cholesterol (LDL-C), with particular emphasis on risk assessment, cumulative LDL-C burden, and lipoprotein(a) [Lp(a)] levels.

Method: The analysis included consecutive patients aged ≥ 70 years with LDL-C ≥ 160 mg/dL, available Lp(a) measurements, no prior history of ASCVD or diabetes, who underwent evaluation for CAD by coronary imaging or functional stress testing. Global ASCVD risk was estimated using the Systematic Coronary Risk Estimation 2–Older Persons (SCORE2-OP) and the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) risk scores.

Results: A total of 202 patients were included (mean age 76 years; 68.3% female). CAD was diagnosed in 30.7% of participants. In multivariable analysis, male sex (odds ratio [OR]: 2.109), Lp(a) level (OR: 1.012 per mg/dL), and cumulative LDL-C (OR: 1.155 per g/dL) were independently associated with CAD. The highest CAD prevalence was observed among individuals with cumulative LDL-C ≥ 14 g/dL and Lp(a) ≥ 50 mg/dL. While the SCORE2-OP algorithm failed to predict CAD, the SAFEHEART risk score was significantly associated with CAD.

Conclusion: In statin-naïve elderly individuals with elevated LDL-C levels, male sex, cumulative LDL-C exposure, and high Lp(a) levels were independently associated with CAD. These findings underscore the potential utility of incorporating cumulative LDL-C and Lp(a) into risk stratification for older adults.

Keywords: Cardiovascular risk stratification, cumulative low-density lipoprotein cholesterol, elderly, primary prevention, Spanish Familial Hypercholesterolemia Cohort Study risk score, statin-naïve, Systematic Coronary Risk Estimation 2–Older Persons

ÖZET

Amaç: İleri yaş, aterosklerotik kardiyovasküler hastalık (ASKVH) riskinde artış ile ilişkilidir. Yaşlı bireylerde statin tedavisinin başlatılmasına yönelik süregelen tartışmalar göz önünde bulundurulduğunda, koroner arter hastalığı (KAH) bulunan ve lipid düşürücü tedaviden fayda görebilecek kişilerin belirlenmesi önemlidir. Bu çalışmanın amacı, statin kullanmayan, LDL-kolesterol (LDL-C) düzeyi yüksek ve ≥70 yaş bireylerde KAH öngördürücülerini belirlemek; özellikle risk değerlendirmesinde kümülatif LDL-C ve lipoprotein(a) [Lp(a)] düzeylerinin rolünü incelemektir.

Yöntem: Analize, LDL-C ≥ 160 mg/dL olan, Lp(a) ölçümü mevcut, daha önce ASKVH veya diyabet öyküsü bulunmayan ve koroner görüntüleme ya da fonksiyonel stres testleri ile KAH açısından değerlendirilen ardışık ≥ 70 yaş hastalar dahil edilmiştir. Global ASKVH riski, SCORE2-OP ve SAFEHEART risk skorları kullanılarak hesaplanmıştır.

Bulgular: Toplam 202 hasta çalışmaya dahil edilmiştir (ortalama yaş: 76 yıl, %68,3 kadın). Katılımcıların %30,7'sinde KAH saptanmıştır. Çok değişkenli analizde erkek cinsiyet (OR: 2,109), Lp(a) düzeyi (OR: 1,012, mg/dL başına) ve kümülatif LDL-C (OR: 1,155, g/dL başına) KAH ile bağımsız olarak ilişkili bulunmuştur. KAH prevalansı, kümülatif LDL-C ≥ 14 g/dL ve Lp(a) ≥ 50 mg/dL olan bireylerde en yüksekti. SCORE2-OP algoritması KAH'ı öngörememişken, SAFEHEART risk skoru KAH ile anlamlı ilişkili bulunmuştur.

ORIGINAL ARTICLE
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Sonuç: Statin kullanmayan yaşlı bireylerde yüksek LDL-C düzeyi varlığında, erkek cinsiyet, artmış kümülatif LDL-C maruziyeti ve yüksek Lp(a) düzeyleri KAH ile bağımsız olarak ilişkili bulunmuştur. Bu sonuçlar, yaşlı bireylerde risk sınıflamasında kümülatif LDL-C ve Lp(a) ölçümlerinin kullanılmasının potansiyel değerini vurgulamaktadır.

Anahtar Kelimeler: Kardiyovasküler risk sınıflaması, kümülatif düşük yoğunluklu lipoprotein kolesterol, yaşlı, birincil korunma, İspanyol Ailevi Hiperkolesterolemi Kohort Çalışması, statin-naif, Sistematik Koroner Risk Tahmini 2 – Yaşlı Kişiler

Atherosclerotic cardiovascular disease (ASCVD) continues to be the leading cause of death worldwide. Elevated levels of low-density lipoprotein cholesterol (LDL-C), a major modifiable risk factor, play a pivotal role in the development of atherosclerotic cardiovascular disease and are strongly associated with increased cardiovascular risk.[1]

Low-density lipoprotein cholesterol reduction remains the cornerstone of ASCVD prevention.[2] In individuals without established ASCVD, diabetes, or familial hypercholesterolemia (FH), LDL-C targets are determined based on overall cardiovascular risk. For risk estimation, current American College of Cardiology (ACC) guidelines recommend the ASCVD risk estimator for individuals aged 40–75 years, while European guidelines recommend the Systematic Coronary Risk Estimation 2 (SCORE2) for individuals aged 40–70 years and the Systematic Coronary Risk Estimation 2–Older Persons (SCORE2-OP) for individuals aged ≥ 70 years.[3,4] However, although elderly individuals are frequently classified as high risk, they often receive weaker recommendations for statin therapy due to concerns about polypharmacy, frailty, and limited evidence of mortality benefit.[4]

Cumulative LDL-C exposure, reflecting both the level and duration of LDL-C elevation, is a recognized driver of atherosclerosis and may better predict ASCVD than a single LDL-C measurement.[5] However, interindividual differences exist: some older adults develop ASCVD despite high LDL-C levels, while others with FH may remain disease-free.[6] This variability may be influenced by additional risk modifiers such as lipoprotein(a) [Lp(a)], a genetically determined, highly atherogenic lipoprotein structurally similar to LDL-C.[7,8] Unlike LDL-C, Lp(a) levels are not significantly reduced by statins or other conventional lipid-lowering therapies. Currently, ASCVD prevention in individuals with elevated Lp(a) relies primarily on intensive LDL-C reduction, due to the lack of approved therapies specifically targeting Lp(a).[4]

This study aimed to identify individuals at higher ASCVD risk and to determine key predictors of ASCVD in statin-naïve older adults, with a particular focus on Lp(a) and cumulative LDL-C exposure. By identifying those at increased risk within this population, we sought to clarify which elderly individuals with high LDL-C are most likely to benefit from lipid-lowering therapy.

ABBREVIATIONS

ACC	American College of Cardiology
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body Mass Index
BP	Blood pressure
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CRP	C-reactive protein
CVD	Cardiovascular disease
ESC	European Society of Cardiology
FH	Familial hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MDRD	Modification of Diet in Renal Disease
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study
SBP	Systolic blood pressure
SCORE2-OP	Systematic Coronary Risk Estimation 2–Older Persons
WHO	World Health Organization

Materials and Methods

Study Approval

This retrospective study was approved by the Ethics Committee of Koç University (Approval Number: 2022.467.IRB1.184, Date: 23.12.2022), and conducted in accordance with the Declaration of Helsinki. The study was conducted using anonymized data obtained under the hospital's routine institutional research consent.

Study Design and Population

Data were collected from patients who visited the cardiology outpatient clinic of a tertiary university hospital between December 2020 and December 2023. Patients aged 70 years and older were consecutively screened for eligibility. Inclusion criteria were: (1) no prior history of ASCVD; (2) undergoing diagnostic testing for coronary artery disease (CAD), including coronary computed tomography angiography (CCTA), conventional coronary angiography, myocardial perfusion scintigraphy (MPS), or stress echocardiography; (3) statin-naïve status; (4) LDL-C levels ≥ 160 mg/dL; and (5) availability of Lp(a) measurements. An LDL-C threshold of ≥ 160 mg/dL was chosen to identify elderly individuals with markedly elevated LDL-C levels, consistent with European Society of Cardiology (ESC) guideline statements indicating that this level increases the probability of familial hypercholesterolemia.[9]

Exclusion criteria included known ASCVD, diabetes mellitus, active or prior malignancy, liver failure, renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), chronic inflammatory disease, acute infection or inflammation [defined by leukocytosis, C-reactive protein (CRP) > 10 mg/L, fever, or recent antibiotic use), and hypothyroidism. The flowchart outlining the inclusion of the study population is presented in Figure 1.

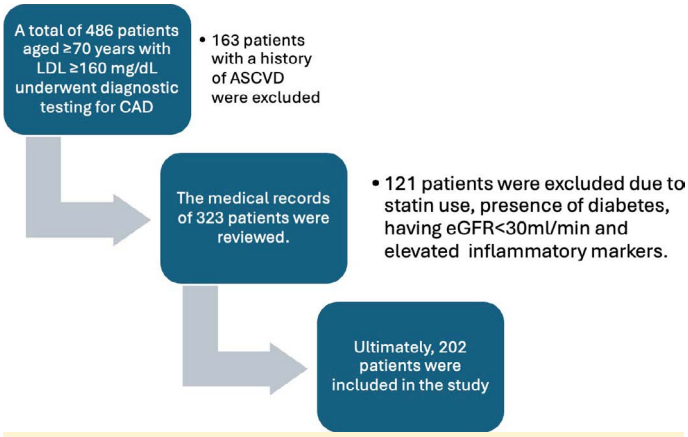

Figure 1. Flowchart of the study population inclusion.

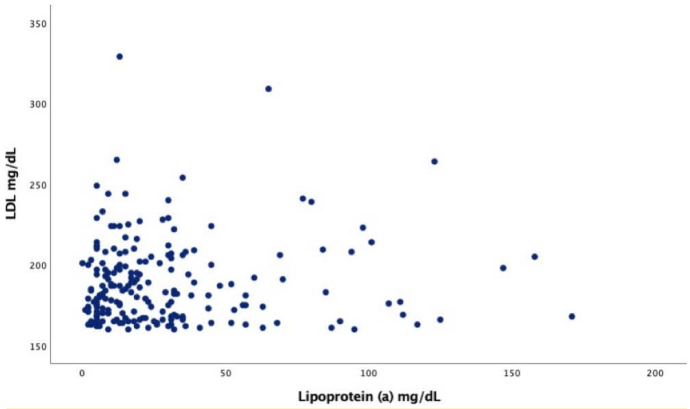

Figure 2. Distribution of LDL-C and Lp(a) in the study population.

Data Collection and Definitions

Demographic and clinical data were recorded, including sex, age, Body Mass Index (BMI), systolic blood pressure (SBP), and smoking status. Laboratory parameters included serum creatinine, estimated glomerular filtration rate calculated using the MDRD (Modification of Diet in Renal Disease) formula (eGFR), LDL-C measured with a direct assay, triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C), glucose, hemoglobin A1c (HbA1c), and Lp(a).

Cumulative LDL-C exposure was calculated by multiplying the LDL-C level (mg/dL) by age (years) and expressed in grams per deciliter (g/dL). Lp(a) levels were measured using the Roche Cobas Tina-quant Lipoprotein(a) Gen 2 assay via an immunoturbidimetric method in an accredited local laboratory.

Hypertension was defined as a previous diagnosis or office SBP ≥ 140 mmHg and/or diastolic blood pressure (BP) ≥ 90 mmHg on two separate occasions. Diabetes mellitus—an exclusion criterion—was defined as a known diagnosis, fasting glucose > 126 mg/dL, or HbA1c > 6.5%. ASCVD was defined as a history of CAD, coronary revascularization, cerebrovascular disease, or peripheral artery disease. CAD was diagnosed based on > 50% stenosis in epicardial coronary arteries (detected by invasive or computed tomography [CT] angiography) or the presence of myocardial ischemia on functional testing.

The SCORE2-OP risk score (for high-risk countries) and the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk equation scores were calculated using baseline data obtained prior to CAD diagnosis.[10,11] SCORE2-OP is a cardiovascular risk prediction tool specifically designed for older adults (≥ 70 years). It estimates the 10-year risk of ASCVD based on key variables including sex, age, SBP, smoking status, and non-high density lipoprotein cholesterol levels. The SAFEHEART risk equation is designed to estimate the 5- and 10-year ASCVD incidence in individuals with familial hypercholesterolemia.[11] It was developed using data from the Spanish SAFEHEART registry, a large, prospective cohort of patients with heterozygous FH. The equation incorporates key clinical predictors, including sex, age, history of ASCVD, smoking status, BMI, LDL-C, and Lp(a) levels (Appendix Data).

The cohort was stratified based on the median cumulative LDL-C value (14 g/dL) and Lp(a) cutoffs of < 30 mg/dL, 30–49 mg/dL, and ≥ 50 mg/dL to assess CAD risk stratification according to cumulative LDL-C and Lp(a) levels.

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 9.4.1 (GraphPad Software, San Diego, CA, USA). Normality of distributions was assessed using the Shapiro–Wilk test. Quantitative variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables as proportions. Between-group differences were examined using the chi-square or Fisher's exact test for categorical data and Student's t test or Mann–Whitney U test for continuous data, as appropriate. Univariate and multivariate logistic regression analyses were performed to determine associations between risk factors and CAD. A multivariate logistic regression model predicting CAD was developed based on variables that were significant in univariate analysis. Additionally, two further models were constructed: one incorporating the variables included in the SCORE2-OP algorithm and another incorporating both SCORE2-OP variables and Lp(a). A p-value < 0.05 was considered statistically significant. Bland-Altman analysis was conducted and presented in Appendix Figure 1 to assess agreement between the SCORE2-OP and SAFEHEART scores.

Results

The study included 202 elderly patients with a mean age of 75.9 ± 5.0 years; 68.3% were female. According to the Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia, 43.6% of the cohort was classified as possible FH and 5.4% as probable FH. The mean LDL-C level was 188.43 ± 26.32 mg/dL, while the median Lp(a) level was 18 mg/dL (Q1–Q3: 8–35 mg/dL) (Figure 2). Evaluation for CAD included coronary angiography in 43.6% of patients, MPS in 31.2%, CCTA in 19.3%, and stress echocardiography in 5.9%. Overall, 30.7% (n = 62) of patients were diagnosed with CAD.

Patients with CAD were more likely to be male (46.8% vs. 25.0%, P = 0.002), had lower HDL-C levels [52 mg/dL (Q1-Q3: 43–62.25) vs. 58 mg/dL (Q1-Q3: 50–69.75), P = 0.003],

Table 1. Baseline characteristics of the study population

Variables	CAD (-) (n = 140)	CAD (+) (n = 62)	*P*
Demographic variables			
Sex (female), n (%)	105 (75)	33 (53.2)	**0.002**
Age (mean ± SD)	75.49 ± 4.94	76.79 ± 5.00	0.088
BMI, kg/m^2 (mean ± SD)	27.29 ± 5.49	28.57 ± 4.00	0.154
Current smokers, n (%)	28 (20%)	18 (29%)	0.224
Hypertension, n (%)	97 (69.3%)	42 (68.9%)	0.951
SBP, mmHg (mean ± SD)	135.82 ± 19.88	133.07 ± 16.40	0.379
SCORE2-OP, % (mean ± SD)	30.69 ± 12.06	33.03 ± 11.17	0.195
SAFEHEART score, 5 years, % (median, Q1-Q3)*	0.94 (0.87-2.12)	2.09 (0.94-2.62)	**0.001**
SAFEHEART score, 10 years, % (median, Q1-Q3)*	1.99 (1.86-4.49)	4.42 (1.99-5.52)	**0.001**
Medications, n (%)			
Antiplatelet therapy	38 (27.10)	19 (30.64)	0.349
Beta-blockers	42 (30.00)	22 (35.48)	0.513
RAS blockers	77 (55.00)	28 (48.38)	0.260
Biochemical analysis			
eGFR, ml/min/1.73 m^2 (mean ± SD)	72.73 ± 35.37	69.84 ± 22.20	0.559
Glucose (mean ± SD)	104.89 ± 11.05	106.66 ± 11.59	0.153
HbA1C (mean ± SD)	5.76 ± 0.40	5.91 ± 2.32	0.087
Total cholesterol, mg/dL (mean ± SD)	260.84 ± 27.13	262.27 ± 40.74	0.770
HDL-C, mg/dL (median, Q1-Q3)*	58 (50-69.75)	52 (43-62.25)	**0.003**
LDL-C, mg/dL (mean ± SD)	186.19 ± 21.19	193.39 ± 34.98	0.073
Triglycerides, mg/dL (median, Q1-Q3)*	142 (105.25-191.25)	158 (119.25-206.25)	0.091
Non-HDL cholesterol (mean ± SD)	200.37 ± 27.10	208.02 ± 41.20	0.123
hsCRP, mg/L (median, Q1-Q3)*	2.8 (1.2-6.45)	3.1 (1.2-8.05)	0.168
Lp(a), mg/dL (median, Q1-Q3)*	17 (6-32.75)	19.5 (12-47.25)	**0.017**
Cumulative LDL, g/dL (mean ± SD)	14.18 ± 1.90	15.59 ± 2.7	**<0.001**

BMI, Body mass index; CAD, Coronary artery disease; eGFR, Estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; hsCRP, High-sensitivity C-reactive protein; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); SBP, Systolic blood pressure. *Continuous variables not normally distributed are presented as median (Q1–Q3), and nonparametric statistical tests were applied due to the absence of normal distribution.

higher cumulative LDL-C exposure (14.06 ± 1.97 g/dL vs. 15.59 ± 2.7 g/dL, P <0.001), and elevated Lp(a) levels [19.5 mg/dL (Q1-Q3: 12–47.25) vs. 17 mg/dL (Q1-Q3: 6–32.75), P = 0.017] (Table 1).

SCORE2-OP scores did not differ significantly between the CAD and non-CAD groups; however, nearly all participants were classified as having a very high 10-year ASCVD risk according to SCORE2-OP, except for two individuals with an estimated risk below 15%. In contrast, the SAFEHEART risk score was significantly higher in patients with CAD for both 5-year risk estimation [0.94 (IQR: 0.87–2.12) vs. 2.09 (IQR: 0.94–2.62), P = 0.001] and 10-year risk estimation [1.99 (IQR: 1.86–4.49) vs. 4.42 (IQR: 1.99–5.52), P = 0.001] (Figure 3).

In univariate logistic regression analysis, male sex (odds ratio [OR]: 2.636, 95% confidence interval [CI]: 1.406–4.493, P = 0.003), lower HDL-C levels (OR: 0.973, 95% CI: 0.953–0.994, P = 0.013), and higher Lp(a) levels (OR: 1.012, 95% CI: 1.003–1.021, P = 0.009) were significantly associated with

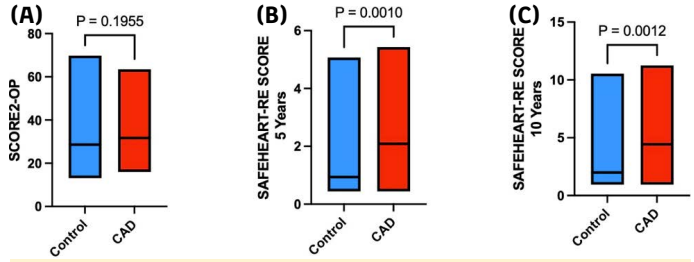

Figure 3. Comparison of risk scores between patients diagnosed with CAD and those without CAD. (A) Comparison of SCORE2-OP between groups. (B) Comparison of SAFEHEART risk score for 5-year risk prediction between groups. (C) Comparison of SAFEHEART risk score for 10-year risk prediction between groups.

CAD. The SCORE2-OP algorithm was not predictive of CAD (OR: 1.017, 95% CI: 0.992–1.042, P = 0.196), whereas the SAFEHEART score was predictive (OR: 1.605, 95%CI:1.130-1.209, P = 0.001).

Table 2. Predictors of CAD (Model 1)

Variables	OR	95% CI	*P*
Male sex	2.109	1.070–4.160	**0.031**
Lp(a)	1.012	1.002–1.022	**0.023**
HDL-C	0.978	0.956–1.001	0.060
Cumulative LDL	1.155	1.009–1.322	**0.037**

CAD, Coronary artery disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); OR, Odds ratios; CI, Confidence interval.

Multivariable analysis included all variables that were significant in univariate analysis. Independent predictors of CAD were male sex (OR: 2.109, 95% CI: 1.070-4.160, P = 0.031), Lp(a) (OR: 1.012, 95% CI: 1.002-1.022, P = 0.023), and cumulative LDL-C (OR: 1.155, 95% CI: 1.009-1.322, P = 0.037). The protective association of HDL-C with lower CAD risk did not reach statistical significance (OR: 0.978, 95% CI: 0.956-1.001, P = 0.060) (Table 2). In this model, the interaction terms for Lp(a) and sex (OR: 1.003, 95% CI: 0.983–1.023, P = 0.760) and for cumulative LDL-C and sex (OR: 1.078, 95% CI: 0.810–1.433, P = 0.607) were not statistically significant.

Coronary artery disease incidence increased with both higher cumulative LDL-C and elevated Lp(a) levels. Among patients with cumulative LDL-C ≥ 14 g/dL, CAD was diagnosed in 57% of those with Lp(a) ≥ 50 mg/dL, 45% with Lp(a) between 30 and 49 mg/dL, and 27% with Lp(a) < 30 mg/dL. In comparison, among those with cumulative LDL-C < 14 g/dL, CAD incidence was 45%, 27.8%, and 25%, respectively (Figure 4). A cumulative LDL-C level ≥ 14 g/dL combined with Lp(a) ≥ 30 mg/dL was an independent predictor of CAD (OR: 2.730, 95% CI: 1.286–5.810), with an even greater risk observed in patients with Lp(a) ≥ 50 mg/dL (OR : 3.309; 95% CI: 1.096–9.986).

Although SCORE2-OP was not predictive in our cohort, a model incorporating SCORE2-OP variables identified male sex as an independent predictor of CAD (OR: 2.747, 95% CI: 1.428–5.284, P = 0.002). When Lp(a) was added, it also emerged as an independent predictor (OR: 1.011, 95% CI: 1.001–1.020, P = 0.034), alongside male sex (OR: 2.586, 95% CI: 1.329–5.033, P = 0.005) (Table 3). In the multivariable logistic regression analysis using SAFEHEART-related variables, male sex and Lp(a) were independently associated with the presence of ASCVD (OR: 4.35, 95% CI: 1.91–9.89, P < 0.001; and OR: 1.01, 95% CI: 1.00–1.03, P = 0.026, respectively) (Appendix Table 1).

Discussion

Our study demonstrated that in statin-naïve individuals aged ≥ 70 years with elevated LDL-C levels, the presence of CAD was associated with greater cumulative LDL-C exposure, higher Lp(a) levels, lower HDL-C levels, and male sex. Multivariate analysis identified cumulative LDL-C, Lp(a), and male sex as independent predictors of CAD. Notably, the highest incidence of CAD was observed among individuals with both cumulative LDL-C > 14 g/dL and Lp(a) ≥ 50 mg/dL. While the SCORE2-OP algorithm did not effectively discriminate risk in this elderly cohort, the SAFEHEART risk score was significantly associated with CAD, supporting its potential utility in this population.

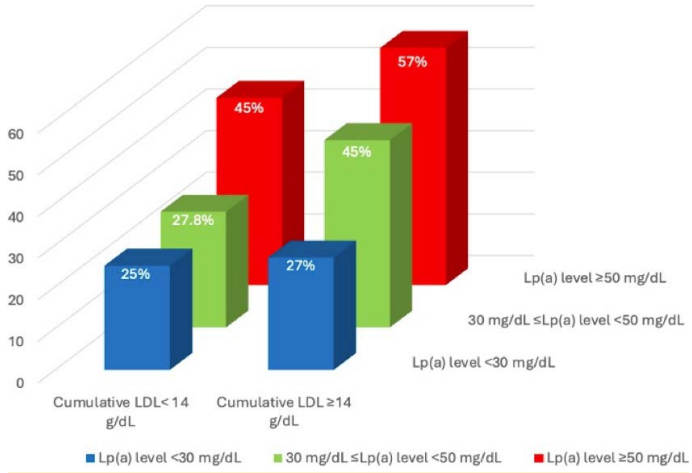

Figure 4. Incidence of CAD according to cumulative LDL-C and Lp(a) levels.

Table 3. Predictors of CAD (Model 2 with SCORE2-OP variables)

Variables	OR	95% CI	*P*
Age	1.052	0.980–1.1120	0.108
Male sex	2.737	1.431–5.235	**0.002**
Smoking	1.634	0.803–3.326	0.175
Systolic blood pressure	1.005	0.988–1.022	0.540
Non-HDL-C	1.007	0.998–1.017	0.148
After inclusion of Lp(a)			
Age	1.055	0.991–1.124	0.095
Male sex	2.586	1.329–5.033	**0.005**
Smoking	1.479	0.716–3.059	0.291
Systolic blood pressure	1.004	0.987–1.021	0.662
Non-HDL-C	1.007	0.997–1.017	0.155
Lp(a)	1.011	1.001–1.020	**0.034**

CAD, Coronary artery disease; HDL-C, High-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); SCORE2-OP, Systematic Coronary Risk Estimation 2-Older Persons; OR, Odds ratios; CI, Confidence interval.

It is well known that some elderly individuals are spared from ASCVD despite having very high LDL-C levels. In the Spanish SAFEHEART cohort, Pérez de Isla et al.[12] demonstrated that female patients with FH who had lower Lp(a) levels and higher HDL-C levels may be protected from CAD. Although this study did not specifically focus on patients with FH, due to the high LDL-C levels, 43.6% of the cohort was classified as possible FH and 5.4% as probable FH according to the Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia.[13] In our statin-naïve study group, cumulative LDL-C demonstrated high predictive value for CAD. Prolonged exposure to elevated LDL-C levels in these patients is similar to that seen in individuals with FH, who are subjected to lifelong high LDL-C concentrations.[14] Our findings are consistent with those of the SAFEHEART cohort, which highlighted the protective effects of female sex and low Lp(a) levels in elderly patients with high LDL-C levels.

Lipoprotein(a) is a genetically determined, proatherogenic, and prothrombotic lipoprotein composed of apolipoprotein B and apolipoprotein(a).[7,15] Lp(a) levels remain largely unchanged across the lifespan, although an increase is often observed in women following the menopausal transition.[16,17] The median Lp(a) level in our cohort (18 mg/dL) was higher than the estimated national average in the Turkish population (12–16 mg/dL), likely reflecting the high proportion of postmenopausal women in the study.[18] Consistent with previous studies, elevated Lp(a) levels in our cohort were associated with CAD and retained their independent predictive value following multivariable adjustment.[19,20]

At present, no approved pharmacologic therapies specifically target Lp(a) reduction. Therefore, management of patients with elevated Lp(a) focuses on optimizing modifiable risk factors, with particular emphasis on LDL-C reduction.[3,4,21] Nevertheless, the role of LDL-C-lowering treatment in elderly patients remains controversial, and it is still debated which individuals in this age group benefit most from statins. Statin therapy in older individuals is inconsistently recommended in national guidelines. The ESC Prevention Guidelines provide only a weak recommendation for statin therapy in individuals over 70 years of age, even for those classified as at very high risk.[4] Similarly, the ACC Prevention Guideline offers limited clarity regarding preventive treatment in this population.[3]

As the population continues to age, uncertainties surrounding ASCVD prevention and treatment strategies in older individuals have become increasingly prominent, partly due to their underrepresentation in clinical trials. The higher incidence of non-cardiac mortality and the presence of competing risks further complicate cardiovascular risk evaluation in the elderly population.[22,23] Existing clinical studies indicate that statins reduce ASCVD events in elderly individuals to a similar extent as in younger patients.[24] However, in the ASPREE trial (Aspirin in Reducing Events in the Elderly), a U-shaped relationship between LDL-C levels and mortality was observed, raising concerns about potential harm at very low LDL-C levels in older individuals.[25,26] These contradictory findings, combined with the lack of strong evidence demonstrating a clear mortality benefit, as well as concerns related to polypharmacy and frailty, limit the strength of recommendations for statin therapy in the elderly. Therefore, the use of risk scores and identification of specific parameters to help select elderly individuals most likely to benefit from treatment are important.

To address this issue, the SCORE2-OP risk prediction algorithm was developed by the SCORE2-OP Working Group for four different geographical regions with varying cardiovascular disease (CVD) prevalence and risk levels, as defined by the World Health Organization (WHO).[10] According to this model, a 10-year cardiovascular risk above 15% is classified as very high risk, and the latest ESC prevention guidelines recommend the use of SCORE2-OP for risk estimation in individuals aged 70 years and older.[4] However, particularly in risk algorithms developed for high-risk countries, the majority of individuals aged 70 years and above are classified as very high risk, as age itself is a major risk enhancer. In our study population, drawn from a high-risk country, nearly all patients, except for two, were categorized as very high risk, despite approximately 70% of participants being free of obstructive CAD. The superiority of the SAFEHEART risk score over SCORE2-OP in our cohort suggests that including additional clinical and lipid-related parameters, such as Lp(a), may improve CVD risk prediction in elderly individuals with elevated LDL-C levels.

An additional distinction between the two risk scores relates to the characteristics of their derivation cohorts. The SCORE2-OP algorithm was developed based on data from the CONOR study (Cohort of Norway), which included Norwegian individuals and a diverse group of immigrants residing in Norway, populations exposed to relatively uniform healthcare systems and environmental influences.[27] In contrast, the SAFEHEART registry is based on a Spanish cohort.[11] Given that both our study population and the SAFEHEART cohort are Mediterranean, they may share common dietary patterns, cultural habits, and lifestyle characteristics, enhancing the applicability of the SAFEHEART score in our setting. Second, baseline lipid profiles also differ across cohorts. The mean LDL-C level in our population more closely resembled that of the SAFEHEART cohort (177.8 mg/dL) than that of the SCORE2-OP population, which reported a non-HDL cholesterol level of 189.5 mg/dL.[10,11] Finally, the SCORE2-OP calculator tends to classify nearly all elderly individuals in high-risk countries into the very high-risk category. This broad classification may diminish its discriminative power.

Strengths and Limitations

This study has several noteworthy strengths. It addresses a critical gap in the literature by focusing on primary prevention in statin-naïve elderly individuals with elevated LDL-C levels, a population frequently underrepresented in clinical research and guideline development. The use of cumulative LDL-C as a risk marker, rather than relying on a single-point measurement, provides a more comprehensive assessment of lifelong exposure and may improve individualized risk stratification. The incorporation and comparative evaluation of multiple risk prediction models, including SCORE2-OP and SAFEHEART, offer additional insights into risk assessment in this specific elderly cohort. Importantly, the real-world nature of the study population, consisting of elderly individuals for whom guidelines are often unclear and treatment decisions are particularly challenging, enhances the clinical relevance of the findings.

However, the study also has limitations. The retrospective, single-center design of the study and its modest sample size may restrict the extent to which these findings can be generalized. The lack of longitudinal follow-up precludes assessment of long-term outcomes such as incident ASCVD events or mortality, limiting the ability to evaluate the prognostic impact of cumulative LDL-C and Lp(a) levels.

A key source of selection bias arises from the study population: most participants were referred to a cardiology outpatient clinic and underwent advanced diagnostic testing (e.g., coronary CT angiography, invasive angiography, or myocardial perfusion imaging) due to suspected CAD. As a result, the cohort likely represents a higher-risk, symptomatic, or physician-referred group rather than a community-based elderly population. This introduces the possibility of Berkson-type bias, which may further restrict the applicability of the findings to the broader elderly population with elevated LDL-C levels. The use of multiple diagnostic modalities (invasive angiography, CCTA, and functional stress testing) may have introduced variability in CAD

detection, particularly given the known limitations of CCTA in elderly individuals with severe coronary calcification; therefore, some degree of diagnostic misclassification cannot be excluded. Moreover, the absence of obstructive CAD may not be sufficient to exclude a substantial 10-year cardiovascular event risk.

Although interaction terms between sex and both Lp(a) and cumulative LDL-C were statistically insignificant, the predominance of female participants may have influenced the observed associations, thereby limiting the generalizability of the results to elderly men. In addition, cumulative LDL-C exposure was estimated by multiplying a single LDL-C measurement by age, which may not accurately reflect true lifetime exposure, especially given that LDL-C levels tend to rise with age. This approach may have led to a modest overestimation of cumulative LDL-C burden.

Lp(a) levels were reported in milligrams per deciliter (mg/dL) rather than nanomoles per liter (nmol/L), which limits comparability across studies due to interindividual variability in Lp(a) particle size. Furthermore, genetic testing for FH or specific LPA variants was not performed, leaving the contribution of monogenic or polygenic lipid disorders to elevated LDL-C and Lp(a) levels uncharacterized.

Conclusion

Among elderly individuals aged ≥ 70 years with elevated LDL-C levels, male sex, greater cumulative LDL-C exposure, and higher Lp(a) concentrations emerged as independent correlates of CAD. In particular, individuals with cumulative LDL-C ≥ 14 g/dL and Lp(a) ≥ 30 mg/dL may represent a subgroup of elderly patients who would derive the greatest benefit from statin therapy, despite current uncertainties and weaker recommendations in clinical guidelines. In this context, the SAFEHEART risk score demonstrated superior discriminatory ability compared to SCORE2-OP and may offer a more appropriate tool for risk stratification in elderly patients with substantial lipid burden. If confirmed in larger prospective cohorts, this risk score may provide an alternative approach to risk stratification among elderly individuals with elevated LDL-C levels.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Koç University (Approval Number: 2022.467.IRB1.184, Date: 23.12.2022).

Informed Consent: Informed consent was not required due to the retrospective nature of this study.

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Predictive Value of the Naples Prognostic Score for 30-Day Mortality and Major Adverse Cardiovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis

İleri Aort Darlığı Nedeniyle Transkateter Aort Kapak İmplantasyonu Uygulanan Hastalarda 30 Günlük Mortalite ve Majör Kardiyovasküler Olaylar için Naples Prognostik Skorunun Prediktif Değeri

ABSTRACT

Objective: Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of severe aortic stenosis; however, early mortality risk stratification remains challenging. The Naples Prognostic Score (NPS), which integrates inflammatory and nutritional markers, has shown promise in cardiovascular disease prognosis. This study investigated the relationship between preprocedural NPS and 30-day mortality in patients undergoing TAVI.

Method: This retrospective, single-center study analyzed 308 patients aged ≥ 65 years who underwent elective transfemoral TAVI between August 2012 and December 2022. NPS was calculated using the neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, serum albumin, and total cholesterol levels. Patients were stratified into low NPS (0-2) and high NPS (3-4) groups. The primary endpoint was 30-day all-cause mortality.

Results: The mean age was 79.81 ± 7.68 years, and 54.9% patients were female. The high NPS group comprised 191 patients (62.0%), while 117 patients (38.0%) were in the low NPS group. Thirty-day mortality was significantly higher in patients with high NPS (16.8% vs. 4.3%, P < 0.001), representing nearly a four-fold increased risk. NPS demonstrated good discriminative ability for mortality prediction (area under the curve: 0.692, 95% confidence interval: 0.611-0.774, P < 0.001), performing comparably to established surgical risk scores. Independent predictors of mortality included age (odds ratio [OR] 1.067, P = 0.039), neutrophil-to-lymphocyte ratio (OR 1.062, P = 0.048), and pulmonary artery pressure (OR 1.039, P = 0.006).

Conclusion: The Naples Prognostic Score is a significant predictor of early mortality following TAVI and offers a simple, readily available tool for preoperative risk stratification. Patients with high NPS may benefit from enhanced perioperative monitoring and targeted interventions.

Keywords: Mortality, Naples prognostic score, risk stratification, transcatheter aortic valve implantation

ÖZET

Amaç: Transkateter aort kapak implantasyonu (TAVI), ileri aort darlığı tedavisinde devrim niteliğinde bir gelişme olsa da, erken mortalite riskinin sınıflandırılması hala tartışmalıdır. Enflamatuar ve nutrisyonel belirteçleri bir araya getiren Naples Prognostik Skoru (NPS), kardiyovasküler hastalıkların prognozunda umut vaat etmektedir. Bu çalışma, TAVI hastalarında işlem öncesi NPS ile 30 günlük mortalite arasındaki ilişkiyi araştırmıştır.

Yöntem: Bu retrospektif, tek merkezli çalışma, Ağustos 2012 ile Aralık 2022 arasında elektif transfemoral TAVI uygulanan 65 yaş ve üzeri 308 hastayı analiz etmiştir. NPS, nötrofil-lenfosit oranı, lenfosit-monosit oranı, serum albümin ve toplam kolesterol düzeyleri kullanılarak hesaplanmıştır. Hastalar düşük NPS (0-2) ve yüksek NPS (3-4) gruplarına ayrıldı. Birincil sonlanım noktası 30 günlük tüm nedenlere bağlı mortalite idi.

Bulgular: Ortalama yaş 79,81±7,68 idi ve hastaların %54,9'u kadındı. Yüksek NPS grubu 191 hastadan (62,0%) oluşurken, düşük NPS grubu 117 hastadan (38,0%) oluşuyordu. 30 günlük mortalite, yüksek NPS hastalarında anlamlı olarak daha yüksekti (16,8% vs 4,3%, P < 0,001), bu da yaklaşık dört kat daha yüksek risk anlamına geliyordu. NPS, mortalite tahmini için iyi bir ayırt edici özelliğe sahipti (AUC 0,692, %95 CI 0,611-0,774, P < 0,001) ve mevcut cerrahi risk

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KLİNİK ÇALIŞMA

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skorlarıyla karşılaştırılabilir bir performans sergiledi. Mortalitenin bağımsız belirleyicileri arasında yaş (OR 1,067, P = 0,039), nötrofil-lenfosit oranı (OR 1,062, P = 0,048) ve pulmoner arter basıncı (OR 1,039, P = 0,006) yer aldı.

Sonuç: NPS, TAVI sonrası erken mortalitenin önemli bir belirleyicisi olarak kullanılabilir ve ameliyat öncesi risk sınıflandırması için basit ve kolayca elde edilebilir bir yöntem olabilir. NPS değeri yüksek olan hastalara, perioperatif takip ve hedefe yönelik müdahale şarttır.

Anahtar Kelimeler: Mortalite, Naples prognostik skoru, risk sınıflandırması, transkateter aort kapak implantasyonu

Valvular aortic stenosis (AS) is a progressive, degenerative valve disorder characterized by narrowing of the aortic valve orifice, resulting in obstruction of left ventricular outflow, increased myocardial workload, compensatory hypertrophy, and eventual left ventricular dysfunction. Over time, this hemodynamic burden leads to reduced exercise tolerance, overt heart failure, and an increased risk of mortality. Symptomatic severe AS, if left untreated, carries a dismal prognosis, with survival often measured in months to a few years, depending on symptom severity and ventricular function.[1]

The prevalence of AS rises sharply with advancing age. Population-based studies report a prevalence ranging from 0.2% to 9.8%, with markedly higher rates among individuals aged ≥ 80 years compared to those aged 50–59 years, making age one of the strongest risk factors for disease occurrence.[2]

Over the past two decades, transcatheter aortic valve implantation (TAVI) has revolutionized the management of severe, symptomatic AS, particularly in patients considered at high or prohibitive surgical risk for conventional surgical aortic valve replacement (SAVR). Initially developed as an alternative for inoperable patients, TAVI has evolved into a well-established therapeutic option, supported by large randomized trials and registry data demonstrating comparable or superior outcomes to SAVR in selected patient populations. Its indications have expanded to include intermediate- and low-risk groups.[3-5]

Early mortality, commonly defined as death within 30 days after the procedure, remains a key endpoint in TAVI research. It reflects procedural safety, influences hospital quality benchmarks, and provides a foundation for developing risk stratification tools. Several clinical, echocardiographic, and procedural parameters, including advanced age, comorbidities, baseline biomarkers, and intraprocedural complications, have been linked to early mortality after TAVI.[6,7] While established surgical risk models such as the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), as well as TAVI-specific risk scores, offer some prognostic value, their predictive accuracy and applicability in contemporary practice remain suboptimal.[8,9] Therefore, identifying simple, readily available perioperative markers for risk prediction remains an important clinical priority.

The Naples Prognostic Score (NPS) is a recently proposed composite index that integrates inflammatory and nutritional status and is calculated from the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), serum albumin, and total cholesterol levels. Originally validated in oncology settings, NPS has demonstrated stronger prognostic utility than individual inflammatory markers in predicting survival across various malignancies.[10,11] More recently, its prognostic relevance has been investigated in cardiovascular diseases, including acute pulmonary embolism, heart failure, ST-segment elevation myocardial infarction, and TAVI.[12-15] However, data on its role in predicting early mortality following TAVI remain limited.

This study aimed to investigate the relationship between preprocedural NPS and 30-day mortality in patients undergoing TAVI, with the goal of assessing its potential utility as a simple and clinically accessible prognostic tool.

ABBREVIATIONS

AS	Aortic stenosis
CT	Computed tomography
DAPT	Dual antiplatelet therapy
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LMR	Lymphocyte-to-monocyte ratio
LVEF	Left ventricular ejection fraction
NLR	Neutrophil-to-lymphocyte ratio
NPS	Naples Prognostic Score
PCI	Percutaneous coronary intervention
SAVR	Surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	Transcatheter aortic valve implantation
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VARC	Valve Academic Research Consortium
VIF	Variance inflation factor

Materials and Methods

Study Design and Population

This retrospective, observational study analyzed adult patients aged 65 years or older who underwent AS confirmed by multidisciplinary heart team evaluation and had anatomic suitability for transfemoral access, with complete preprocedural and postprocedural clinical data available. Patients with preprocedural cardiogenic shock, documented hepatic dysfunction, emergency procedures, or non-transfemoral access routes were excluded to minimize confounding factors that could impact NPS and short-term outcomes, while ensuring patient safety and data validity.

Pre-Procedural Evaluation

A comprehensive preprocedural assessment was conducted for all patients to determine eligibility, identify procedural risks, and optimize intervention planning. All patients underwent systematic transthoracic echocardiography (TTE) to assess the severity of AS, including aortic valve area and mean and peak gradients; presence and grade of aortic regurgitation; left ventricular ejection fraction (LVEF) and segmental wall motion; aortic valve morphology and calcification severity; and annular dimensions for prosthesis sizing. Invasive coronary angiography was performed in all patients to identify significant obstructive coronary artery disease (≥ 70% stenosis) and determine the necessity for concomitant percutaneous coronary intervention (PCI) to optimize myocardial perfusion prior to TAVI.

Multidetector computed tomography (CT) angiography provided assessment of the vascular access route, including vessel caliber, tortuosity, and atherosclerotic burden, along with detailed evaluation of aortic root anatomy and annular measurements for optimization of prosthesis sizing and stratification of procedural complication risk. Perioperative risk was quantified using validated scoring systems, including EuroSCORE II and the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality score, supplemented by comprehensive risk evaluation that included frailty assessment using validated tools, renal function evaluation through estimated glomerular filtration rate, pulmonary function assessment via spirometry or clinical evaluation, and cognitive assessment where indicated.

TAVI Procedure Protocol

All procedures were performed under general anesthesia or monitored conscious sedation based on patient hemodynamic status, comorbidities, and multidisciplinary team recommendations, with continuous hemodynamic monitoring and transesophageal echocardiography (TEE) guidance employed when clinically indicated. Primary vascular access was established via the common femoral artery using percutaneous or surgical cut-down techniques, with placement of an 18–22 French introducer sheath under fluoroscopic guidance and contralateral arterial access for hemodynamic support when required.

Catheter-mounted bioprosthetic valves, either balloon-expandable or self-expanding, were selected based on anatomic considerations and navigated to the aortic annulus under real-time fluoroscopic and echocardiographic guidance. Valve deployment was achieved through balloon inflation or self-expansion according to valve type, with multiple fluoroscopic projections used to ensure optimal coaxial alignment within the native annulus. Immediate post-deployment assessment included evaluation of valve function using TTE or TEE, measurement of transvalvular pressure gradients, assessment for paravalvular regurgitation, and repeat coronary angiography in selected cases to confirm ostial patency.

Post-Procedural Management

Following the procedure, patients were transferred to the cardiac intensive care unit (ICU) or high-dependency unit for 24–48 hours of continuous monitoring, including hemodynamic surveillance, continuous telemetry for arrhythmia detection (particularly conduction abnormalities), neurologic assessments for detection of cerebrovascular events, and regular pain assessments using standardized scoring systems. Post-procedural antiplatelet management included dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for a minimum of six months, with individualized anticoagulation regimens for patients with atrial fibrillation or other indications and therapy modifications based on bleeding risk assessment. Multimodal analgesia protocols were implemented, with regular pain score documentation and pharmacologic adjustments balanced between adequate analgesia and early complication detection.

Data Collection and Naples Prognostic Score

Patient information was obtained from electronic medical records and included demographics such as age, sex, and body mass index; comorbidities including diabetes mellitus, chronic kidney disease, coronary artery disease, atrial fibrillation, and peripheral arterial disease; laboratory parameters including complete blood count and comprehensive metabolic panel; echocardiographic measurements including LVEF, aortic valve area, and transvalvular gradients; and procedural data including contrast volume, fluoroscopy time, and procedural duration.

The Naples Prognostic Score was calculated using four components, each scored as 0 or 1 point: neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, total cholesterol level, and serum albumin concentration. In accordance with prior studies validating the prognostic utility of the NPS, patients were categorized into low NPS (0–2) and high NPS (3–4) groups. This binary stratification has been consistently used to differentiate patients with preserved versus impaired inflammatory–nutritional status and has demonstrated prognostic significance in cardiovascular and non-cardiovascular cohorts.[12,16] All laboratory values were obtained within 48 hours prior to the TAVI procedure using standardized laboratory protocols.

Outcome Definitions

The primary endpoint was all-cause mortality within 30 days following percutaneous TAVI. Secondary endpoints included procedural myocardial infarction, defined according to the Fourth Universal Definition of Myocardial Infarction; new permanent pacemaker implantation required due to conduction abnormalities; stroke, defined as an acute neurologic deficit lasting more than 24 hours with imaging confirmation; major bleeding classified according to Valve Academic Research Consortium (VARC) criteria; and vascular complications categorized according to VARC-2 definitions. All outcomes were adjudicated by independent reviewers blinded to NPS values and followed standardized institutional protocols for event classification.

Ethics Approval and Compliance Statement

The research followed the ethical guidelines specified in the Declaration of Helsinki. There was no utilization of artificial intelligence (AI)-powered tools such as large language models (LLMs), chatbots, or image generators, in developing this article. The study received approval from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: 249, Date: 06.03.2025). Given the retrospective design and use of de-identified clinical data, the ethics committee waived the requirement for informed consent.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of quantile-quantile plots. Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Patients were stratified into low NPS and high NPS groups for comparative analysis.

Between-group comparisons were performed using Student's t-test for normally distributed continuous data, the Mann-Whitney U test for non-normally distributed data, and the chi-square test or Fisher's exact test for categorical variables when expected cell counts were less than 5. For variables presented as median (IQR), the Mann-Whitney U test was systematically applied to ensure appropriate nonparametric comparison.

Cox proportional hazards regression was performed to identify independent predictors of 30-day mortality. Variable selection for multivariable analysis followed a systematic approach combining clinical relevance and statistical screening. Candidate predictors were first evaluated in univariable logistic regression, with variables achieving $P < 0.20$ considered for inclusion in multivariable models based on established recommendations for confounder identification. Clinical relevance was determined through literature review and multidisciplinary team consensus, prioritizing variables with established prognostic significance in TAVI outcomes, including demographic factors (age, sex), comorbidities (diabetes, chronic kidney disease, coronary artery disease), cardiac function parameters (LVEF, pulmonary artery pressure), and procedural characteristics.

Prior to multivariable modeling, multicollinearity assessment was performed using variance inflation factor (VIF) analysis, with VIF > 5 indicating problematic collinearity and VIF > 10 indicating severe multicollinearity requiring variable exclusion. Given the theoretical overlap between individual inflammatory markers (NLR, LMR), nutritional parameters (albumin, total cholesterol), and composite scores incorporating these components (Naples Score, STS Score, EuroSCORE), separate multivariable models were constructed.

Variables with VIF > 5 were sequentially removed from the models, prioritizing retention of variables with stronger univariable associations and greater clinical interpretability. Final models were constructed using backward stepwise selection with a retention threshold of $P < 0.05$, and model performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve. Sensitivity analyses were performed to assess model stability across different variable selection approaches.

Receiver operating characteristic analysis was performed to evaluate the discriminatory ability of NPS for predicting 30-day mortality, calculate the area under the curve with 95% confidence intervals, and compare predictive performance with established risk scores, including EuroSCORE II and the STS score. Missing data was handled using complete-case analysis, with sensitivity analyses performed when missing data exceeded 5%. Statistical significance was set at a p-value < 0.05 (two-tailed), confidence intervals were calculated at the 95% level for all estimates, and all analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY) and R version 4.3.0.

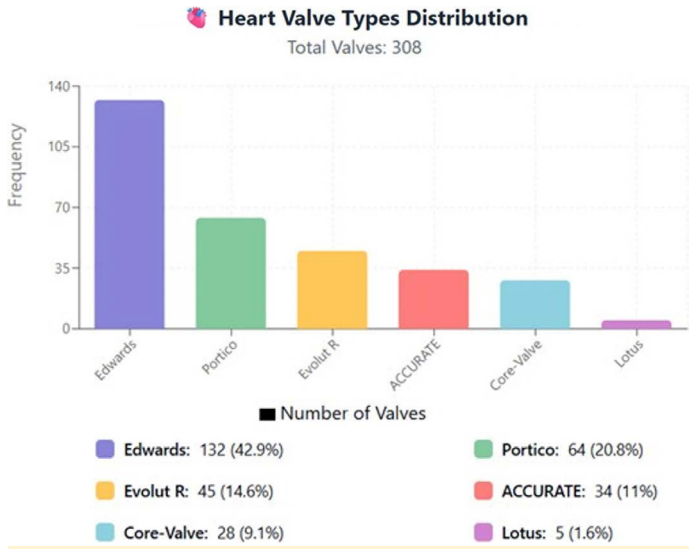


Figure 1. Distribution of transcatheter aortic valve types in the study population.

Results

A total of 308 patients undergoing TAVI were included, with a mean age of 79.81 ± 7.68 years; 169 patients (54.9%) were female. Major comorbidities included hypertension in 250 patients (81.2%), coronary artery disease in 226 patients (73.4%), diabetes mellitus in 128 patients (41.6%), and chronic obstructive pulmonary disease (COPD) in 65 patients (21.1%). Previous cardiac surgery was present in 101 patients (32.8%), and pre-TAVI coronary stents were noted in 43 patients (14.0%).

Edwards valves were the most frequently used (132 valves, 42.9%), followed by Portico (64 valves, 20.8%), Evolut R (45 valves, 14.6%), ACCURATE (34 valves, 11.0%), CoreValve (28 valves, 9.1%), and Lotus (5 valves, 1.6%) (Figure 1).

Baseline laboratory values showed a mean albumin level of 3.39 ± 0.69 g/dL and hemoglobin of 11.52 ± 1.64 g/dL. Creatinine demonstrated a non-normal distribution, with a median of 0.96 mg/dL (IQR: 0.78-1.28). Lipid profiles revealed a total cholesterol level of 171.44 ± 51.76 mg/dL, high-density lipoprotein (HDL) cholesterol of 41.82 ± 13.48 mg/dL, and low-density lipoprotein (LDL) cholesterol of 104.54 ± 41.40 mg/dL. Triglycerides showed a median of 113 mg/dL (IQR: 84-157).

Complete blood count parameters included a white blood cell count of 7.89 ± 2.54 $\times 10^3/\mu L$, with differential counts showing neutrophils at 5.36 ± 2.87 $\times 10^3/\mu L$, lymphocytes at 1.58 ± 0.78 $\times 10^3/\mu L$, and monocytes at 0.68 ± 0.31 $\times 10^3/\mu L$. Inflammatory markers demonstrated non-normal distributions, with a median NLR of 3.12 (IQR: 2.24-4.89) and a median LMR of 2.67 (IQR: 1.85-4.12).

The mean NPS was 2.74 ± 1.01, distributed as Score 0 (1.6%), Score 1 (10.7%), Score 2 (25.6%), Score 3 (36.0%), and Score 4 (26.0%). Patients were categorized into Group 1 (Naples Score 0-2, n = 117, 38.0%) and Group 2 (Naples Score 3-4, n = 191,

Table 1. Baseline characteristics of the study population

Patient characteristic	Values	Patient characteristic	Values
Demographics		Score 2	79 (25.6)
Age (years), mean ± SD	79.81 ± 7.68	Score 3	111 (36.0)
Female sex, n (%)	169 (54.9)	Score 4	80 (26.0)
Comorbidities		Category 1 (0–2)	117 (38.0)
Hypertension, n (%)	250 (81.2)	Category 2 (3–4)	191 (62.0)
Diabetes mellitus, n (%)	128 (41.6)	STS score, mean ± SD	7.06 ± 5.60
Coronary artery disease, n (%)	226 (73.4)	Logistic EuroSCORE, mean ± SD	20.40 ± 12.82
Smoking, n (%)	39 (12.7)	Rhythm and conduction	
Pulmonary arterial hypertension, n (%)	25 (8.1)	Pre-TAVI sinus rhythm, n (%)	212 (68.8)
COPD, n (%)	65 (21.1)	Atrial fibrillation (pre-procedure), n (%)	87 (28.2)
Previous cardiac surgery, n (%)	101 (32.8)	AV block (pre-procedure), n (%)	7 (2.3)
Pre-TAVI coronary stent, n (%)	43 (14.0)	Echocardiographic parameters	
Laboratory values		Left atrium (mm), mean ± SD	44.70 ± 7.49
Albumin (g/dL), mean ± SD	3.39 ± 0.69	LVEF (%), mean ± SD	50.58 ± 11.25
Lactate (mmol/L), mean ± SD	1.59 ± 1.94	Aortic valve area (cm^2), mean ± SD	0.72 ± 0.13
Total cholesterol (mg/dL), mean ± SD	171.44 ± 51.76	Mean gradient (mmHg), mean ± SD	49.71 ± 13.50
Triglycerides (mg/dL), mean ± SD	120.82 ± 64.76	Maximum velocity (m/s), mean ± SD	4.41 ± 0.56
HDL cholesterol (mg/dL), mean ± SD	41.82 ± 13.48	Ascending aorta (mm), mean ± SD	35.68 ± 4.41
LDL cholesterol (mg/dL), mean ± SD	104.54 ± 41.40	TEE aortic annulus (mm), mean ± SD	24.75 ± 3.67
Hemoglobin, pre-procedure (g/dL), mean ± SD	11.52 ± 1.64	Mitral stenosis, n (%)	
Hematocrit, pre-procedure (%), mean ± SD	34.90 ± 4.75	None	290 (94.2)
MPV, pre-procedure (fL), mean ± SD	9.03 ± 1.56	Mild	14 (4.5)
Neutrophil count ($\times10^3$/μL), mean ± SD	5.41 ± 5.49	Moderate	4 (1.3)
Lymphocyte count ($\times10^3$/μL), mean ± SD	1.58 ± 0.81	Mitral regurgitation, n (%)	
Monocyte count ($\times10^3$/μL), mean ± SD	0.85 ± 3.41	None/trivial, n (%)	48 (15.6)
Platelet count, pre-procedure ($\times10^3$/μL), mean ± SD	225.74 ± 70.06	Mild, n (%)	114 (37.0)
LMR, mean ± SD	3.23 ± 2.78	Moderate, n (%)	113 (36.7)
NLR, mean ± SD	4.36 ± 5.60	Severe, n (%)	33 (10.7)
Creatinine (mg/dL), mean ± SD	1.14 ± 0.75	Aortic regurgitation, n (%)	
INR, mean ± SD	1.27 ± 0.58	None/trivial, n (%)	94 (30.5)
Risk scores		Mild, n (%)	121 (39.3)
Naples score, mean ± SD	2.74 ± 1.01	Moderate, n (%)	68 (22.1)
Score 0	5 (1.6)	Severe, n (%)	25 (8.1)
Score 1	33 (10.7)		

Continuous variables are presented as mean ± standard deviation, and categorical variables as number (percentage). COPD, Chronic obstructive pulmonary disease; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; LMR, Lymphocyte-to-monocyte ratio; LVEF, Left ventricular ejection fraction; MPV, Mean platelet volume; NLR, Neutrophil-to-lymphocyte ratio; STS, Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation; TEE, Transesophageal echocardiography.

62.0%). The mean STS score was 7.06 ± 5.60, and the logistic EuroSCORE was 20.40 ± 12.82. Table 1 presents comprehensive baseline characteristics.

Comparative Analysis Between Naples Score Groups

Demographic analysis showed no significant difference in age (78.97 ± 7.85 vs. 80.32 ± 7.55 years, P = 0.134); however, Group 1 had a higher proportion of female patients (73 patients, 62.4% vs. 96 patients, 50.3%). Comorbidity distribution was generally similar between groups, with coronary artery disease slightly more prevalent in Group 1 (93 patients, 79.5% vs. 133 patients, 69.6%, P = 0.052).

Group 2 patients demonstrated significantly more compromised nutritional and inflammatory status compared to Group 1. Albumin levels were markedly lower in Group 2 (3.22 ± 0.61

Table 2. Pre-procedural patient characteristics stratified by Naples Prognostic Score in patients undergoing TAVI

Variables	Group 1 (n = 117)	Group 2 (n = 191)	Total (n = 308)	*P*
Demographics				
Age, years	78.97 ± 7.85	80.32 ± 7.55	79.82 ± 7.67	0.134
Female sex, n (%)	73 (62.4)	96 (50.3)	169 (54.9)	0.115
Comorbidities				
Hypertension, n (%)	94 (80.3)	156 (81.7)	250 (81.2)	0.172
Diabetes mellitus, n (%)	51 (43.6)	77 (40.3)	128 (41.6)	0.456
Coronary artery disease, n (%)	93 (79.5)	133 (69.6)	226 (73.4)	0.052
Smoking, n (%)	16 (13.7)	23 (12.0)	39 (12.7)	0.072
Pulmonary arterial hypertension, n (%)	13 (11.1)	12 (6.3)	25 (8.1)	0.065
COPD, n (%)	19 (16.2)	46 (24.1)	65 (21.1)	0.742
Previous cardiac surgery, n (%)	41 (35.0)	60 (31.4)	101 (32.8)	0.145
Laboratory values				
Albumin, g/dL	3.66 ± 0.73	3.22 ± 0.61	3.38 ± 0.68	<0.001
Lactate, mmol/L	1.44 ± 1.39	1.69 ± 2.21	1.59 ± 1.94	0.277
Total cholesterol, mg/dL	199.25 ± 52.44	154.40 ± 43.39	171.16 ± 49.73	<0.001
Triglycerides, mg/dL	140.65 ± 82.94	108.67 ± 46.76	120.73 ± 63.09	<0.001
HDL cholesterol, mg/dL	45.15 ± 13.67	39.79 ± 12.98	41.83 ± 13.47	0.001
LDL cholesterol, mg/dL	124.28 ± 43.11	92.45 ± 35.33	104.85 ± 40.63	<0.001
Creatinine, mg/dL	1.09 ± 0.49	1.17 ± 0.87	1.14 ± 0.75	0.349
Hemoglobin (pre-procedure), g/dL	11.71 ± 1.52	11.41 ± 1.71	11.53 ± 1.64	0.111
Hematocrit (pre-procedure), %	35.20 ± 4.59	34.71 ± 4.84	34.90 ± 4.75	0.376
Platelet count (pre-procedure), $\times 10^3/\mu L$	217.03 ± 58.99	231.08 ± 75.70	225.77 ± 69.73	0.088
Lymphocyte count, $\times 10^3/\mu L$	1.99 ± 1.01	1.34 ± 0.52	1.59 ± 0.77	<0.001
Neutrophil count, $\times 10^3/\mu L$	4.19 ± 1.81	6.15 ± 6.73	5.40 ± 5.36	0.002
Monocyte count, $\times 10^3/\mu L$	1.22 ± 5.52	0.63 ± 0.26	0.86 ± 3.59	0.143
Inflammatory markers				
LMR (lymphocyte-to-monocyte ratio)	4.65 ± 3.93	2.35 ± 1.04	3.26 ± 2.75	<0.001
NLR (neutrophil-to-lymphocyte ratio)	2.33 ± 1.07	5.61 ± 6.77	4.35 ± 5.45	<0.001
Echocardiographic parameters				
LVEF, %	51.48 ± 10.76	50.03 ± 11.53	50.60 ± 11.25	0,272
Aortic valve area, cm^2	0.72 ± 0.12	0.72 ± 0.13	0.72 ± 0.13	0.951
Mean gradient, mmHg	51.07 ± 12.94	48.88 ± 13.80	49.70 ± 13.49	0.169
Peak velocity, m/s	4.43 ± 0.54	4.39 ± 0.58	4.41 ± 0.56	0.637
Risk scores				
STS score	6.94 ± 5.47	7.13 ± 5.70	7.06 ± 5.60	0.778
Logistic EuroSCORE	19.80 ± 12.48	20.77 ± 13.04	20.39 ± 12.81	0.523
Rhythm disorders				
Pre-TAVI sinus rhythm, n (%)	96 (82.1)	116 (60.7)	212 (68.8)	<0.001
Atrial fibrillation (pre-procedure), n (%)	20 (17.1)	67 (35.1)	87 (28.2)	<0.001
AV block (pre-procedure), n (%)	2 (1.7)	5 (2.6)	7 (2.3)	0.242

AV, Atrial ventricular; COPD, Chronic obstructive pulmonary disease; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; LMR, Lymphocyte-to-monocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; STS, Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation.

vs. 3.66 ± 0.73 g/dL, P < 0.001). Lipid metabolism parameters also differed significantly, with Group 2 showing lower total cholesterol (154.40 ± 43.39 vs. 199.25 ± 52.44 mg/dL, P < 0.001), lower HDL cholesterol (39.79 ± 12.98 vs. 45.15 ± 13.67 mg/dL, P = 0.001), and lower LDL cholesterol (92.45 ± 35.33 vs. 124.28 ± 43.11 mg/dL, P < 0.001). Triglyceride levels were also significantly lower in Group 2 (108.67 ± 46.76 vs. 140.65 ± 82.94 mg/dL, P < 0.001).

Group 2 patients exhibited significantly elevated systemic inflammation compared to Group 1. White blood cell count was higher in Group 2 (8.21 ± 2.67 vs. 7.38 ± 2.25 $\times 10^3/\mu L$, P = 0.006). Differential counts showed significantly higher neutrophil counts in Group 2 (6.15 ± 3.15 vs. 4.19 ± 1.81 $\times 10^3/\mu L$, P = 0.002) and significantly lower lymphocyte counts (1.34 ± 0.52 vs. 1.99 ± 1.02 $\times 10^3/\mu L$, P < 0.001). Monocyte counts were also significantly higher in Group 2 (0.74 ± 0.34 vs. 0.58 ± 0.24 $\times 10^3/\mu L$, P < 0.001).

Given the non-normal distribution of inflammatory ratios, these are reported as median (IQR). The NLR was markedly higher in Group 2 [median 4.58 (IQR: 3.21–7.12) vs. 2.15 (IQR: 1.68–2.89), P < 0.001], while the LMR was significantly lower in Group 2 [median 1.82 (IQR: 1.34–2.67) vs. 3.84 (IQR: 2.89–5.43), P < 0.001]. These differences represent the defining characteristics separating the two Naples Score groups.

Echocardiographic parameters showed no significant differences between groups in LVEF (50.03 ± 11.53% vs. 51.48 ± 10.76%, P = 0.272), aortic valve area (0.72 ± 0.13 vs. 0.72 ± 0.12 cm^2, P = 0.951), or mean gradient (48.88 ± 13.80 vs. 51.07 ± 12.94 mmHg, P = 0.169). However, pulmonary artery pressure was significantly higher in Group 2 (46.76 ± 14.70 vs. 43.43 ± 12.48 mmHg, P = 0.042). Rhythm disorders differed significantly between groups, with Group 1 showing a higher prevalence of pre-TAVI sinus rhythm (96 patients, 82.1% vs. 116 patients, 60.7%, P < 0.001) and Group 2 demonstrating higher rates of pre-procedural atrial fibrillation (67 patients, 35.1% vs. 20 patients, 17.1%, P < 0.001). Table 2 presents the detailed comparison between Naples Score Group 1 and Group 2.

Procedural Characteristics and Immediate Post-Procedural Changes

The majority of procedures were performed via percutaneous closure (259 patients, 84.1%), with surgical closure in 48 patients (15.6%). Hospital length of stay showed a non-normal distribution, with a median of 5 days (IQR: 3–7 days), and no significant difference between Naples Score groups [Group 1: 5 days (IQR: 3–6) vs. Group 2: 5 days (IQR: 3–8), P = 0.156]. Immediate post-procedural hemodynamics demonstrated effective valve function, with a post-procedural maximum gradient of 17.10 ± 5.45 mmHg, representing a substantial reduction from pre-procedural values.

Vascular complications showed varied patterns between Naples Score groups, reflecting different pathophysiological mechanisms. Pseudoaneurysm occurred more frequently in Group 2 (11 patients, 5.8% vs. 4 patients, 3.4%, P = 0.341), as did hematoma formation (22 patients, 11.5% vs. 3 patients, 2.6%, P = 0.005). Conversely, femoral dissection was significantly more common in Group 1 (9 patients, 7.7% vs. 5 patients, 2.6%, P = 0.014).

The higher rate of femoral dissection in the low NPS group, despite their better overall outcomes, likely reflects procedural or anatomical factors independent of inflammatory-nutritional status. Femoral dissection may be related to vascular calcification patterns, vessel tortuosity, or technical aspects of access rather than systemic inflammation. Importantly, femoral dissections in this cohort were generally managed successfully without contributing significantly to mortality, whereas hemorrhagic complications (pseudoaneurysm, hematoma) associated with high NPS carried greater clinical consequences, potentially explaining the differential mortality between groups despite this isolated finding.

Table 3. Procedural characteristics and immediate post-procedural changes

Procedural and post-procedural parameter	Values
Procedure approach	
Percutaneous closure, n (%)	259 (84.1)
Surgical closure, n (%)	48 (15.6)
Hospitalization	
Length of hospital stay (days), mean ± SD	6.11 ± 5.72
Immediate post-procedural hemodynamics	
Post-procedural maximum gradient (mmHg), mean ± SD	17.10 ± 5.45
Post-procedural hematological changes	
Hemoglobin after procedure (g/dL), mean ± SD	10.00 ± 1.57
Hemoglobin difference, mean ± SD	1.52 ± 1.46
Hematocrit after procedure (%), mean ± SD	30.12 ± 4.87
Platelet count after procedure ($\times 10^3/\mu L$), mean ± SD	177.01 ± 72.41
Creatinine after procedure (mg/dL), mean ± SD	1.18 ± 0.75
Rhythm and conduction complications	
New atrial fibrillation, n (%)	85 (27.6)
New AV block requiring pacemaker implantation, n (%)	33 (10.7)
Procedural complications	
Procedural failure, n (%)	7 (2.3)
Second valve implantation required, n (%)	6 (1.9)
Vascular complications	
Any bleeding, n (%)	106 (34.4)
Minor bleeding, n (%)	66 (21.4)
Major bleeding, n (%)	36 (11.7)
Life-threatening bleeding, n (%)	16 (5.2)
Pseudoaneurysm, n (%)	15 (4.9)
Hematoma, n (%)	25 (8.1)
Femoral dissection, n (%)	14 (4.5)
Valve-related complications	
Valve stenosis, n (%)	19 (6.2)
Overall complications	
Major complications, n (%)	51 (16.6)
Minor complications, n (%)	31 (10.1)
Early clinical outcomes	
Stroke, n (%)	7 (2.3)
In-hospital mortality, n (%)	37 (12.0)
Acute kidney injury, n (%)	33 (10.7)
Rehospitalization, n (%)	30 (9.7)

SD: Standard deviation.

Table 4. Pre-and post-procedural changes in clinical and laboratory variables

Variables	Mean difference	SE	95% CI (lower)	95% CI (upper)	*P*
AF (before - after)	0.006	0.015	-0.024	0.036	**0.671**
AV block (before - after)	-0.084	0.018	-0.121	-0.048	**<0.001**
Hemoglobin (before - after)	1.518	0.083	1.355	1.681	**<0.001**
Hematocrit (before - after)	4.773	0.257	4.267	5.278	**<0.001**
Platelet count (before - after)	48.736	4.034	40.798	56.674	**<0.001**
Creatinine (before - after)	-0.045	0.028	-0.099	0.010	**0.109**

AF, Atrial fibrillation; AV, Atrial ventricular; CI, Confidence interval; SE, Standard error.

Significant hematological changes occurred following the procedure. Hemoglobin levels decreased from 11.52 ± 1.64 to 10.00 ± 1.57 g/dL (mean difference 1.518 g/dL, 95% confidence interval [CI]: 1.355–1.681, P < 0.001). Hematocrit similarly decreased from 34.90 ± 4.75% to 30.12 ± 4.87% (mean difference 4.773%, 95% CI: 4.267–5.278, P < 0.001). Platelet count decreased from 225.74 ± 70.06 to 177.01 ± 72.41 $\times 10^3$/μL (mean difference 48.736 $\times 10^3$/μL, 95% CI: 40.798–56.674, P < 0.001). Post-procedural creatinine levels showed minimal change (1.14 ± 0.75 to 1.18 ± 0.75 mg/dL, P = 0.109).

New rhythm complications developed post-procedurally, with new atrial fibrillation occurring in 85 patients (27.6%) and new atrioventricular (AV) block requiring pacemaker implantation in 33 patients (10.7%). Paired analysis showed a significant increase in AV block incidence (mean difference: -0.084, 95% CI: -0.121 to -0.048, P < 0.001), while changes in atrial fibrillation incidence were not statistically significant (P = 0.671). Tables 3 and 4 detail the procedural parameters and post-procedural changes.

Clinical Complications and Adverse Outcomes

Overall bleeding complications occurred in 106 patients (34.4%), with similar rates between Group 1 and Group 2 (39 patients, 33.3% vs. 67 patients, 35.1%). However, the severity distribution differed, with Group 2 experiencing higher rates of life-threatening bleeding (13 patients, 6.8% vs. 3 patients, 2.6%) and major bleeding (26 patients, 13.6% vs. 10 patients, 8.5%). Vascular complications showed varied patterns between groups. Pseudoaneurysm occurred more frequently in Group 2 (11 patients, 5.8% vs. 4 patients, 3.4%), as did hematoma formation (22 patients, 11.5% vs. 3 patients, 2.6%). Conversely, femoral dissection was more common in Group 1 (9 patients, 7.7% vs. 5 patients, 2.6%).

Procedural failure occurred in 7 patients (2.3%) overall, with similar rates between groups (2 patients, 1.7% in Group 1 vs. 5 patients, 2.6% in Group 2). Second valve implantation was required in 6 patients (1.9%). Stroke occurred in 7 patients (2.3%), predominantly in Group 2 (6 patients, 3.1% vs. 1 patient, 0.9%). Rehospitalization rates were similar between groups (13 patients, 11.1% in Group 1 vs. 17 patients, 8.9% in Group 2).

In-hospital mortality occurred in 37 patients (12.0% overall), with a striking difference between Naples Score groups. Group 1 experienced mortality in 5 patients (4.3%), whereas Group 2 had significantly higher mortality in 32 patients (16.8%), representing a nearly fourfold increase in risk. Table 5 provides a comprehensive analysis of complications and clinical outcomes stratified by Naples Score groups.

Table 5. Comparison of complications and clinical outcomes between Group 1 and Group 2

Complication	Group 1 (n = 117) n (%)	Group 2 (n = 191) n (%)	*P*
Bleeding complications			
Any bleeding	39 (33.3)	67 (35.1)	0.344
Minor bleeding	27 (23.1)	39 (20.4)	0.214
Major bleeding	10 (8.5)	26 (13.6)	0.117
Life-threatening bleeding	3 (2.6)	13 (6.8)	0.016
Vascular complications			
Pseudoaneurysm	4 (3.4)	11 (5.8)	0.015
Hematoma	3 (2.6)	22 (11.5)	0.025
Femoral dissection	9 (7.7)	5 (2.6)	0.014
Procedural complications			
Closure failure	2 (1.7)	5 (2.6)	0.723
Second valve implantation required	2 (1.7)	4 (2.1)	0.619
Clinical outcomes			
Stroke	1 (0.9)	6 (3.1)	0.023
Rehospitalization	13 (11.1)	17 (8.9)	0.309
Mortality	5 (4.3)	32 (16.8)	0.012
Major complications	17 (14.5)	34 (17.8)	0.116
Minor complications	12 (10.3)	19 (9.9)	0.311

Predictors of Mortality and Major Adverse Cardiovascular Events (MACE)

Independent predictors of in-hospital mortality included age (odds ratio [OR]: 1.067, 95% CI: 1.003–1.135, P = 0.039), indicating that each additional year of age increased mortality risk by 6.7%. The NLR also emerged as a significant predictor (OR: 1.062, 95% CI: 1.001–1.126, P = 0.048), with each unit increase associated with a 6.2% higher mortality risk. Pulmonary artery pressure was independently predictive (OR: 1.039, 95% CI: 1.011–1.068, P = 0.006), with each mmHg increase conferring a 3.9% higher mortality risk (Table 6).

Overall, major adverse cardiovascular events occurred in 85 patients (27.6% of the total cohort). Group 1 experienced MACE in 27 patients (23.1%), whereas Group 2 had MACE in 58 patients (30.4%), representing a 32% relative increase in MACE risk. Male sex showed a protective effect (OR: 0.340, 95% CI: 0.119–0.969, P = 0.044), reducing MACE risk by 66%. Pre-TAVI

Table 6. Independent predictors of 30-day mortality and major adverse cardiovascular events after transcatheter aortic valve implantation

Variables	30-day mortality			MACE		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Sex (male vs. female)	0.738	0.319–1.709	0.478	**0.340**	**0.119–0.969**	**0.044**
Age	**1.067**	**1.003–1.135**	**0.039**	1.027	0.963–1.096	0.418
LMR	1.108	0.963–1.274	0.153	0.800	0.558–1.146	0.224
NLR	**1.062**	**1.001–1.126**	**0.048**	0.834	0.627–1.109	0.212
Hypertension	1.014	0.332–3.094	0.981	1.004	0.292–3.456	0.995
Diabetes mellitus	1.653	0.696–3.923	0.254	1.935	0.758–4.943	0.168
CAD	1.169	0.444–3.078	0.751	1.494	0.476–4.693	0.491
COPD	0.781	0.280–2.177	0.636	1.597	0.585–4.365	0.361
Previous cardiac surgery	0.520	0.164–1.644	0.265	2.186	0.756–6.322	0.149
Pre-TAVI sinus rhythm	0.981	0.407–2.364	0.965	**0.295**	**0.112–0.776**	**0.013**
Pre-procedure Hgb	0.892	0.701–1.133	0.348	0.837	0.610–1.149	0.271
Creatinine	1.400	0.931–2.106	0.106	1.280	0.771–2.128	0.340
Mean gradient	0.989	0.959–1.021	0.502	**0.946**	**0.907–0.987**	**0.010**
PAP	**1.039**	**1.011–1.068**	**0.006**	0.989	0.954–1.026	0.549

CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; LMR, Lymphocyte-to-monocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; TAVI, Transcatheter aortic valve implantation; PAP, Pulmonary artery pressure; MACE, Major adverse cardiovascular events.

sinus rhythm was also protective (OR: 0.295, 95% CI: 0.112–0.776, P = 0.013), reducing MACE risk by 70.5%. Mean gradient demonstrated a protective effect (OR: 0.946, 95% CI: 0.907–0.987, P = 0.010), with each mmHg increase associated with a 5.4% reduction in MACE risk (Table 6).

ROC Analysis for 30-Day Mortality Prediction

ROC curve analysis was performed using the continuous Naples Score (range: 0–4) as the predictor variable for 30-day all-cause mortality. The Naples Score demonstrated good discriminative ability, with an area under the curve (AUC) of 0.692 (standard error: 0.042, 95% CI: 0.611–0.774, P < 0.001). The optimal cut-off value was identified as a Naples Score ≥ 2.5, yielding a sensitivity of 86.5% (95% CI: 71.2–95.5%) and a specificity of 47.6% (95% CI: 41.7–53.5%), with a positive predictive value of 16.8% and a negative predictive value of 96.6%.

For comparison, established surgical risk scores showed the following performance: the STS score achieved an AUC of 0.559 (95% CI: 0.486–0.633, P = 0.107; not statistically significant) with an optimal cut-off of 7.5% (sensitivity: 54.1%, specificity: 60.4%), and the logistic EuroSCORE demonstrated an AUC of 0.559 (95% CI: 0.488–0.631, P = 0.107; not statistically significant) with an optimal cut-off of 18.5% (sensitivity: 59.5%, specificity: 54.2%). The superior AUC and statistical significance of the Naples Score suggest better discriminative performance compared to traditional risk scores in our TAVI cohort (Figure 2).

ROC Analysis for MACE Prediction

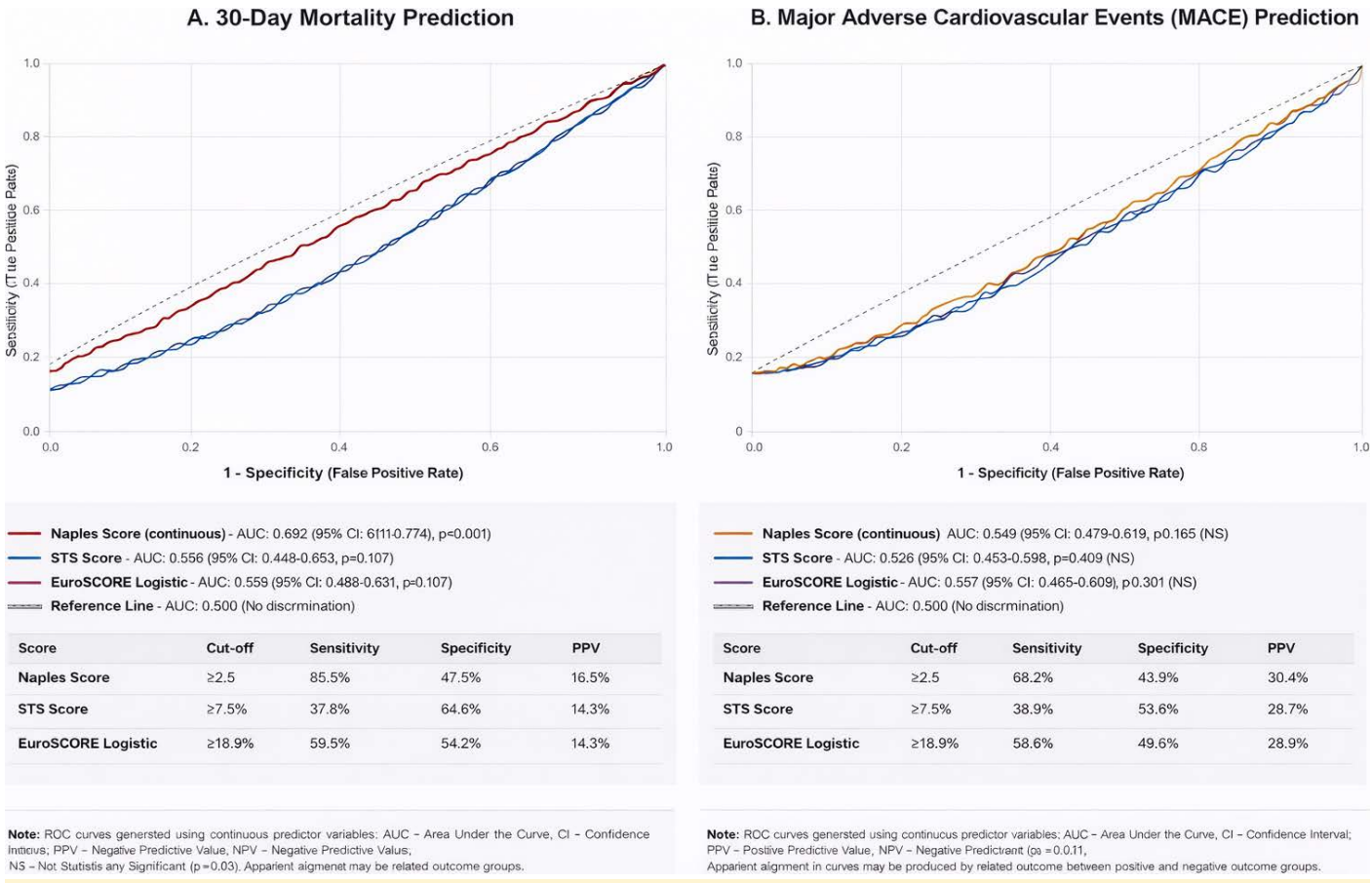
ROC analysis using the continuous Naples Score for MACE prediction demonstrated limited discriminative ability, with an AUC of 0.549 (standard error: 0.036, 95% CI: 0.479–0.619, P = 0.185), which did not reach statistical significance. The optimal cut-off value of Naples Score ≥ 2.5 yielded a sensitivity of 68.2% (95% CI: 57.4–77.8%) and a specificity of 43.9% (95% CI: 37.5–50.5%), with a positive predictive value of 30.4% and a negative predictive value of 79.5%.

Similarly, traditional risk scores showed comparable modest performance for MACE prediction: the STS score (AUC: 0.526, 95% CI: 0.453–0.598, P = 0.460) and the logistic EuroSCORE (AUC: 0.537, 95% CI: 0.465–0.609, P = 0.301), neither of which reached statistical significance. The limited discriminative ability of all scores for MACE prediction likely reflects the heterogeneous nature of composite endpoints and the multifactorial etiology of various adverse cardiovascular events (Figure 2).

Discussion

This study represents one of the largest single-center investigations evaluating the prognostic utility of the NPS in predicting early mortality following TAVI. Our findings demonstrate that the NPS, which incorporates inflammatory and nutritional parameters, serves as a significant predictor of 30-day mortality in patients undergoing TAVI, with those in the high NPS group (scores 3–4) experiencing a nearly fourfold increase in mortality risk compared to patients in the low NPS group (scores 0–2).

The utility of the NPS in cardiovascular disease has been increasingly recognized, with recent studies demonstrating its prognostic value across various cardiac conditions.[10] Our results align with emerging evidence supporting the role of combined inflammatory-nutritional indices in predicting cardiovascular outcomes. The observed mortality rates of 4.3% in the low NPS group versus 16.8% in the high NPS group underscore the clinical relevance of this scoring system for



Score	Cut-off	Sensitivity	Specificity	PPV
Naples Score	≥2.5	85.5%	47.5%	16.5%
STS Score	≥7.5%	37.8%	64.6%	14.3%
EuroSCORE Logistic	≥18.9%	59.5%	54.2%	14.3%

Score	Cut-off	Sensitivity	Specificity	PPV
Naples Score	≥2.5	68.2%	43.9%	30.4%
STS Score	≥7.5%	38.9%	53.6%	28.7%
EuroSCORE Logistic	≥18.9%	58.6%	49.6%	28.9%

Note: ROC curves generated using continuous predictor variables: AUC – Area Under the Curve, CI – Confidence Intervals; PPV – Negative Predictive Value, NPV – Negative Predictive Value; NS – Not Statistis any Significant (p =0.03). Apparient aigmenet may be related outcome groups.

Note: ROC curves generated using continuous predictor variables: AUC – Area Under the Curve, CI – Confidence Interval; PPV – Positive Predictive Value, NPV – Negative Predictrant (pa =0.0.11, Apparent alignment in curves may be produced by related outcome between positive and negative outcome groups.

Figure 2. Receiver operating characteristic curves demonstrating the performance of the Naples Score in predicting mortality and major adverse cardiovascular events (MACE).

risk stratification in TAVI patients. The ROC analysis provided important insight into the discriminative performance of the Naples Score across different outcomes. For prediction of 30-day mortality, the Naples Score demonstrated statistically significant discriminative ability (AUC: 0.692, P < 0.001), with high sensitivity (86.5%) but modest specificity (47.6%) at the optimal cut-off value of ≥ 2.5. Notably, the Naples Score outperformed both the STS score and the logistic EuroSCORE, neither of which achieved statistical significance in our cohort (both AUC: 0.559, P = 0.107). This superior performance may reflect the Naples Score's ability to capture acute inflammatory and nutritional status, which may be more relevant for early post-procedural outcomes than traditional surgical risk models designed for broader patient populations. However, the Naples Score demonstrated limited discriminative ability for MACE prediction (AUC: 0.549, P = 0.185), performing similarly to traditional risk scores. This differential performance underscores an important distinction: while inflammatory-nutritional status strongly influences early mortality risk, the heterogeneous nature of MACE—encompassing myocardial infarction, stroke, bleeding complications, and vascular events—likely requires a multidimensional risk assessment incorporating procedural, anatomical, and patient-specific factors beyond inflammation and nutrition alone.[17,18] The modest specificity of the Naples Score for mortality prediction (47.6%) suggests that while it effectively identifies high-risk patients, approximately half of low-risk patients would be misclassified, limiting its utility as a standalone decision-making tool but supporting its role as part of a comprehensive risk assessment.[19,20]

The prognostic utility of the NPS likely reflects the complex interplay between systemic inflammation, nutritional status, and cardiovascular outcomes. Patients with elevated NPS demonstrated significantly higher NLRs and lower LMRs, indicating heightened systemic inflammation and impaired immune function. This inflammatory milieu has been associated with increased procedural complications, impaired wound healing, and enhanced thrombotic risk following cardiac interventions.[21,22] The nutritional component of the NPS, reflected by lower albumin and cholesterol levels in the high NPS group, suggests compromised metabolic status and reduced physiological reserve. Hypoalbuminemia, in particular, has been consistently associated with poor outcomes in cardiac surgery and interventional procedures, reflecting not only nutritional deficiency but also underlying inflammatory processes and reduced oncotic pressure that may compromise hemodynamic stability.[23,24]

Interestingly, our study revealed comparable discriminative performance between the NPS and established surgical risk scores (STS score and logistic EuroSCORE) for predicting early mortality, with all achieving similar AUC values around 0.55-0.56. This finding suggests that simple inflammatory-nutritional

markers may provide prognostic information comparable to complex, multivariable risk prediction models. The practical advantage of the NPS lies in its simplicity and the routine availability of its components in standard preoperative laboratory panels, potentially making it a more accessible tool for real-time risk assessment.[5,25] The modest performance of all risk scores in our cohort may reflect the evolving nature of TAVI patient populations and procedural techniques. As TAVI indications have expanded to lower-risk patients and procedural outcomes have improved, traditional risk models developed for higher-risk surgical populations may require recalibration or supplementation with novel biomarkers.[4,26]

While the NPS demonstrated significant utility in predicting early mortality, its performance in predicting major adverse cardiovascular events was more limited. This differential performance may reflect the heterogeneous nature of MACE endpoints, which encompass various complications with distinct pathophysiological mechanisms. The protective effects observed for male sex, sinus rhythm, and higher mean gradients in MACE prediction suggest that procedural and anatomical factors may be more relevant for composite endpoints than inflammatory-nutritional status alone.[17,18] The integration of the NPS into clinical practice could enhance preoperative risk assessment and patient counseling. Patients with high NPS scores might benefit from enhanced perioperative monitoring, optimized nutritional support, and potentially modified procedural approaches. Furthermore, identification of high-risk patients through the NPS could facilitate targeted interventions to improve nutritional status and reduce systemic inflammation before elective procedures.[27,28]

The observed association between high NPS and increased rates of life-threatening bleeding and vascular complications suggests that these patients may require modified anticoagulation strategies and enhanced vascular access site management. Such risk-stratified approaches could potentially improve procedural outcomes and reduce complications in high-risk subgroups.[29,30]

Limitations

Several limitations warrant consideration when interpreting our results. The retrospective, single-center design limits generalizability and introduces potential selection bias. The exclusion of patients with non-transfemoral access routes, while reducing confounding, may limit the applicability of our findings to the broader TAVI population. Additionally, the relatively short 30-day follow-up period, while clinically relevant for early mortality assessment, does not capture longer-term prognostic implications of elevated NPS.

The moderate sample size, while adequate for primary endpoint analysis, may have limited power to detect associations with less frequent complications. Furthermore, the study period spanning more than a decade encompasses significant evolution in TAVI techniques, device technology, and patient selection criteria, potentially introducing temporal confounding factors.

Our ROC analysis revealed modest AUC values for MACE prediction, indicating limited discriminative ability for composite endpoints. This limitation highlights that inflammatory-nutritional markers alone may be insufficient for predicting the heterogeneous array of complications encompassed by MACE, and that multidimensional risk models incorporating anatomical, procedural, and clinical factors may be necessary for comprehensive risk stratification.

Conclusion

This single-center retrospective study of 308 patients demonstrates that the NPS serves as a significant predictor of 30-day mortality following TAVI, with patients having high NPS scores (3-4) experiencing a nearly fourfold increase in mortality risk compared to those with low NPS scores (0-2). The NPS achieved good discriminative ability for mortality prediction (AUC: 0.692, $P < 0.001$), performing comparably to established surgical risk scores while offering the advantages of simplicity and routine laboratory availability through its incorporation of NLR, LMR, serum albumin, and total cholesterol levels. These findings suggest that preoperative NPS assessment could enhance risk stratification, patient counseling, and perioperative management strategies in patients undergoing TAVI, with high-risk individuals potentially benefiting from targeted interventions, including nutritional optimization and enhanced monitoring protocols. Future multicenter, prospective studies are warranted to validate these findings and to investigate whether interventions designed to modify NPS components can improve clinical outcomes in this growing patient population.

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Informed Consent: Given the retrospective design and use of de-identified clinical data, the ethics committee waived the requirement for informed consent.

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Baseline Clinical Characteristics of Patients from the Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye Study

Türkiye'de Gerçek Yaşam Şartlarında Edoksaban Tedavisinin Atriyal Fibrilasyon Hastalarında Güvenliliğinin Değerlendirilmesi Çalışması Hastalarının Temel Klinik Özellikleri

ABSTRACT

Objective: A post-authorization safety study with a prospective design focusing on the safety of edoxaban treatment in Türkiye has not yet been conducted. The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye (ETAF-TR) study was designed to evaluate the safety and effectiveness of edoxaban treatment in atrial fibrillation (AF). The baseline results of the ETAF-TR study describe the demographic, clinical, and laboratory characteristics of the study population.

Method: The ETAF-TR study (NCT04594915) is a prospective, national, multicenter, observational, post-authorization safety study conducted in 50 outpatient cardiology clinics.

Results: Overall, 1,053 patients with AF treated with edoxaban for stroke prevention were enrolled in the study between August 2020 and May 2022. The mean age of the study population was 70.1 ± 11.3 years, and 59.0% of the patients were female. Mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category) and HAS-BLED scores (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, Labile INR, Elderly, Drugs/alcohol) were 3.5 and 1.6, respectively. Of the 1,053 patients, 843 (80.1%) received standard-dose edoxaban and 210 (19.9%) received reduced-dose edoxaban. Of the 1,053 patients, 38 (3.6%) had off-label use of edoxaban therapy. Among the remaining 1,015 patients, 834 (82.2%) received an appropriate dose of edoxaban and 181 (17.8%) received an inappropriate dose of edoxaban according to the Summary of Product Characteristics (SmPC) criteria.

Conclusion: Edoxaban has been used in a wide spectrum of patients with AF in daily routine practice, with good overall adherence to the SmPC. As the largest national pharmacovigilance study to date, the ETAF-TR study will provide detailed insight into the safety of edoxaban treatment.

Keywords: Atrial fibrillation, edoxaban, stroke, systemic embolism, bleeding, real-world data

ÖZET

Amaç: Türkiye'de edoksaban tedavisinin güvenliliğini araştıran ileri dönük bir ruhsatlandırma sonrası güvenlik çalışması henüz gerçekleştirilmemiştir. Türkiye'de gerçek yaşam şartlarında edoksaban tedavisinin atriyal fibrilasyon hastalarında güvenliliğinin değerlendirilmesi (ETAF-TR) çalışması, edoksaban tedavisinin atriyal fibrilasyon hastalarında güvenliliğini ve etkinliğini değerlendirmek üzere tasarlanmıştır. ETAF-TR çalışmasının bu sonuçları, çalışma popülasyonunun demografik, klinik ve laboratuvar özelliklerini açıklamaktadır.

Yöntem: ETAF-TR çalışması (NCT04594915), 50 kardiyoloji kliniğinde yürütülen prospektif, ulusal, çok merkezli, gözlemsel, ruhsatlandırma sonrası güvenlik çalışmasıdır.

Bulgular: Çalışmaya, Ağustos 2020 ile Mayıs 2022 tarihleri arasında inme profilaksisi amacıyla edoksaban tedavisi alan 1,053 atriyal fibrilasyon hastası dahil edildi. Çalışma grubunun yaş ortalaması 70.1±11.3 olup hastaların %59.0'ı kadındı. Ortalama CHA_2DS_2-VASc ve HAS-BLED skorları sırasıyla 3.5 ve 1.6 idi. Çalışmadaki 1,053 hastanın 843'ü (%80,1) standart doz edoksaban tedavisi alırken, 210'u (%19,9) azaltılmış doz edoksaban tedavisi aldı. Çalışma popülasyonunun %3,6'sında endikasyon dışı edoksaban kullanımı vardı. Geriye kalan 1015 hastadan 834'ü (%82,2) kısa ürün bilgisine göre uygun doz edoksaban tedavisi alırken, 181'i (%17,8) uygun olmayan dozda edoksaban tedavisi alıyordu.

ORIGINAL ARTICLE
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Sonuç: Edoksaban tedavisi, günlük rutin uygulamada atriyal fibrilasyon hastalarının büyük bir bölümünde uygun doz tercihi ile kullanılmaktadır. Bugüne kadarki en büyük ulusal farmakovijilans çalışması olan ETAF-TR çalışması, edoksaban tedavisinin güvenliliğine dair ayrıntılı bilgi sağlayacaktır.

Anahtar Kelimeler: Atriyal fibrilasyon, kanama, edoksaban, gerçek yaşam verisi, inme, sistemik embolizm

Atrial fibrillation (AF) is a significant public health problem, with a global prevalence of 60 million patients in 2019.[1] Prevalence and incidence are expected to increase due to population aging, comorbidity burden, technological evolution in detecting AF, and growing public awareness. The European Society of Cardiology guideline proposes the AF-CARE (Atrial Fibrillation, C: Comorbidity and risk factor management, A: Anticoagulation/Avoid stroke, R: Rate control, E: Early rhythm control) framework to achieve optimal care for these patients.[2] The AF-CARE framework encompasses several key elements, including management of comorbidities, prevention of stroke and systemic embolism, control of heart rate and rhythm, reduction of symptoms, and dynamic reassessment of patients. Oral anticoagulant therapy, comprising direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), is the cornerstone of stroke and systemic embolism prevention in atrial fibrillation (SSPAF).[2] Randomized controlled trials and post-marketing data have demonstrated that DOACs are at least as effective as VKAs for SSPAF and have a more favorable safety profile for major bleeding.[2] Therefore, current European and American guidelines recommend the prescription of DOACs in preference to VKAs in patients with AF.[2,3]

Edoxaban, a direct and reversible inhibitor of Factor Xa, was approved by regulatory authorities for stroke and systemic embolism prevention in Europe in 2015. Since November 2016, edoxaban has been eligible for reimbursement by the Social Security Institution of Türkiye, the primary payer institution in the country. Although randomized controlled trials of DOACs have higher internal validity, they also employ strict, well-defined inclusion and exclusion criteria that limit the generalizability of their results to the overall patient population. Post-authorization safety studies are needed to evaluate the effectiveness and safety of a treatment in real-world clinical settings.

Edoxaban Treatment in Routine Clinical Practice for Patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) is an observational safety study of edoxaban treatment in clinical practice.[4] The study was designed to evaluate the safety and effectiveness of edoxaban in real-world settings. ETNA-AF-Europe was conducted in 10 European countries, and

ABBREVIATIONS

AF	Atrial fibrillation
AF-CARE	Atrial Fibrillation, C: Comorbidity and risk factor management, A: Anticoagulation/Avoid stroke, R: Rate control, E: Early rhythm control
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRNM	Clinically relevant nonmajor bleeding
DOAC	Direct oral anticoagulant
EHRA	European Heart Rhythm Association
ETAF-TR	Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Türkiye
ETNA-AF-Europe	Edoxaban Treatment in Routine Clinical Practice for Patients with Atrial Fibrillation in Europe
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, Labile INR, Elderly, Drugs/alcohol
SmPC	Summary of Product Characteristics
SSPAF	Stroke and systemic embolism prevention in atrial fibrillation
VKA	Vitamin K antagonist

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unselected patients with AF treated with edoxaban were enrolled. The four-year follow-up results of the ETNA-AF-Europe study corroborate the long-term efficacy and safety of edoxaban, aligning with findings from the respective randomized controlled trial.[5] Although ETNA-AF-Europe is a large-scale, prospective, post-authorization safety study, it was not conducted in Türkiye. Furthermore, the potential for distinctive clinical, demographic, and pharmacogenetic attributes among Turkish patients, the differing healthcare infrastructure, and varying reimbursement requirements may limit the applicability of ETNA-AF-Europe findings to routine clinical practice in Türkiye. Notably, edoxaban has been available for marketing since 2016, yet there is a lack of post-marketing data on its safety and efficacy in the Turkish population.

The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye (ETAF-TR) study is designed to evaluate the safety and effectiveness of edoxaban treatment in patients with AF in real-life practice. The baseline analysis of the ETAF-TR study aims to describe the demographic and clinical characteristics of Turkish patients with AF receiving edoxaban treatment, to define adherence to dosing patterns for edoxaban according to the summary of product characteristics (SmPC), and to compare these characteristics with those of patients enrolled in the Edoxaban versus Warfarin in Patients with Atrial Fibrillation (ENGAGE AF-TIMI 48) trial[6] and the ETNA-AF-Europe study.[4]

Materials and Methods

Design

The design of ETAF-TR has been previously published.[7] The ETAF-TR study is a prospective, national, multicenter, observational, post-authorization safety study conducted in 50 outpatient cardiology clinics with varying health provider characteristics. Study sites were selected according to the health provider subgroup projection based on the Health Statistics Yearbook 2016 to improve external validity.[8] The ETAF-TR study protocol and other study-related documents were developed in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practice. Study documents were approved by Dokuz Eylül University Clinical Research Ethics Committee (Approval Number: 2020/04-01, Protocol Number: 513-SBKAEK, Date: 12.03.2020), and the Pharmaceuticals and Medical Devices Administration of Türkiye (TITCK) in March 2020. The ETAF-TR study is registered at www.clinicaltrials.gov (NCT04594915).

Study Population

All patients with AF treated with edoxaban, except those with mechanical heart valves and/or moderate-to-severe mitral stenosis, and patients aged < 18 years, were eligible to participate in the study if they provided written informed consent. Patients treated with edoxaban for deep vein thrombosis and/or pulmonary embolism and patients simultaneously participating in any other clinical trial were not included in the ETAF-TR study. The diagnosis of AF and decisions regarding the dosing pattern of edoxaban treatment were not within the remit of the present project and were under the responsibility of the attending physician.

Enrolment and Follow-up: The screening and enrolment period was planned for six months, and the first patient was enrolled in August 2020. As with other clinical studies, the study experienced challenges due to the coronavirus disease 2019 (COVID-19) pandemic, and the enrolment process was therefore completed in May 2022. The study population was followed for a 12-month period with interim visits [at 3 months ± 15 days after enrolment (visit 1), 6 ± 1 months after enrolment (visit 2), and 12 ± 2 months after enrolment (visit 3)].

Data Collection: Patients' baseline demographic and clinical characteristics were obtained at enrolment. The baseline data comprised demographics, comorbidities, AF-related information, stroke risk profile assessed by the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age ≥ 65 years, sex category) score, bleeding risk profile assessed by HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR, elderly, drug/alcohol usage) score, and basic laboratory tests. Data were documented in standardized electronic case report forms. The sponsor (Daiichi Sankyo Türkiye) and a contracted research organization (Ethic CRO) devised a data management and study quality control plan. The quality control mechanisms comprised data credibility checks and data monitoring, and onsite monitoring was performed at all study sites.

Dosing Patterns of Edoxaban: Study participants were classified as receiving a standard dose of edoxaban (60 mg once daily) or a reduced dose of edoxaban (30 mg once daily). The criteria proposed by the SmPC for edoxaban were used to determine the appropriate dose selection. According to the SmPC, patients with moderate or severe renal impairment (creatinine clearance 15–50 mL/min), low body weight (< 60 kg), or concomitant use of P-glycoprotein inhibitors such as cyclosporine, dronedarone, erythromycin, or ketoconazole are recommended to receive edoxaban 30 mg once daily. After adjustment of dosing patterns, the study participants were classified as follows: (I) appropriate dose of edoxaban (using an appropriate standard dose of edoxaban or an appropriately reduced dose in compliance with the dose reduction criteria of the SmPC); (II) inappropriate low dose of edoxaban (undertreatment = using a reduced dose of edoxaban without meeting the dose reduction criteria of the SmPC); and (III) inappropriate high dose of edoxaban (overtreatment = using a standard dose of edoxaban despite meeting the dose reduction criteria of the SmPC). Off-label usage was defined as edoxaban use in patients with any of the following: lower stroke risk (i.e., CHA_2DS_2–VASc score of 0 for male and 1 for female patients), creatinine clearance (CrCl) < 15 mL/min, or mitral valve area < 1.5 cm^2 or a mechanical prosthetic valve. Following the exclusion of patients who had received the medication for an off-label purpose, dosage appropriateness ratios were calculated.

Comparison with the ENGAGE-AF-TIMI 48 and ETNA-AF-Europe Studies: The baseline demographic and clinical characteristics of patients enrolled in the ENGAGE-AF-TIMI 48 and ETNA-AF-Europe studies were used as external comparators to the baseline data collected in ETAF-TR. This was done to gain a deeper understanding of how the use of edoxaban in routine clinical practice reflects the trial setting (external validation) in which edoxaban was tested.

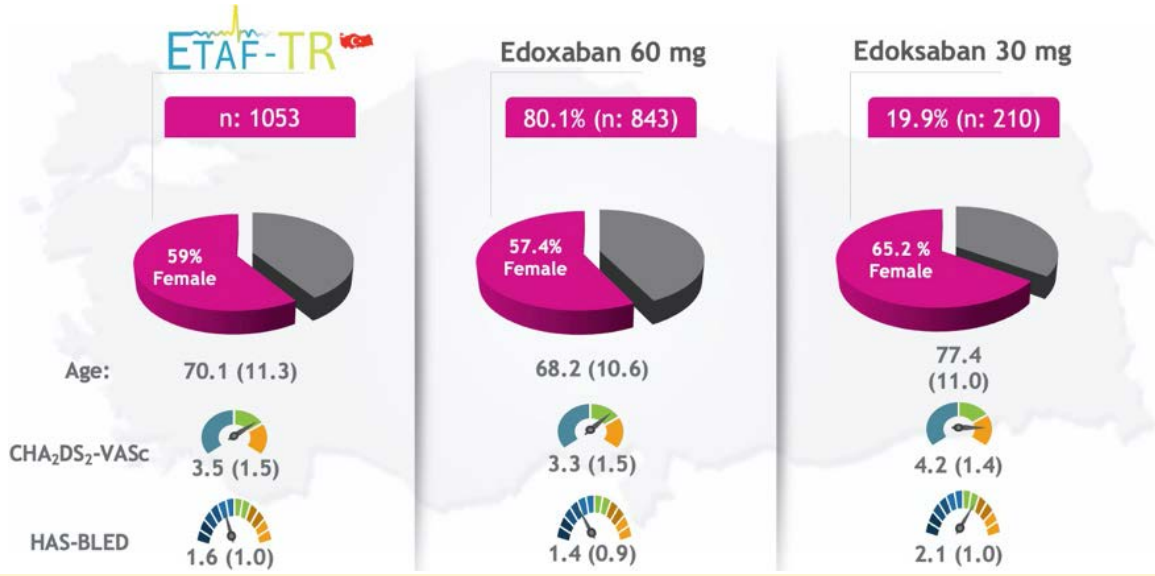

Figure 1. Baseline demographic and clinical characteristics of the ETAF-TR study population according to the edoxaban 60 mg once daily (o.d.) and 30 mg o.d. groups.

Statistical Analysis: Demographic data were summarized using descriptive statistics (n, mean, standard deviation (SD), minimum, maximum, median, and interquartile range (IQR)) and proportional distributions (n and %) according to the data type. Categorical variables were presented as the number and percentage (%) of patients in each category. Continuous variables were presented using the number of missing data, mean, SD, median, IQR, minimum, and maximum values. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). Various statistical tests were employed to evaluate screening visit characteristics, including the t-test, Wilcoxon rank-sum test, Analysis of Variance (ANOVA), and Kruskal–Wallis test, to analyze scores on the continuous scale across multiple groups. A chi-square or Fisher exact test was used for categorical variables. The primary outcome of the ETAF-TR study is any overt bleeding [consisting of significant bleeding or clinically relevant nonmajor bleeding (CRNM), or any bleeding that does not meet this definition but is considered overt bleeding by the participating physician)]. The rates of any overt bleeding were 10.68% per year in the low-dose edoxaban arm of the ENGAGE-TIMI 48 trial and 14.15% per year in the high-dose edoxaban arm of the ENGAGE-TIMI 48 trial. Based on these results, the minimum sample size was calculated as 708 patients with a 95% confidence interval (CI), using a two-sided precision value of 0.05 for the primary endpoint rate of 12.41% per year. When a rate of 14% was considered for the same primary endpoint, the minimum sample size was calculated as at least 780 patients with 95% CI, again using a two-sided precision value of 0.05. Although the initial sample size was calculated as 858, assuming a 10% dropout rate during the one-year follow-up, the dropout rate was updated to 35% with a protocol amendment due to disruptions in patient follow-up during the COVID-19 pandemic. Accordingly, 1,053 patients were enrolled to ensure the reliability of the estimation of the primary outcome.

Results

Overall, 1,053 patients with AF treated with edoxaban for stroke prevention were enrolled in the study between August 2020 and May 2022. Demographic and clinical characteristics of the study population according to the edoxaban 60 mg once daily (o.d.) and 30 mg o.d. groups are summarized in Table 1 and Figure 1. The mean age of the study population was 70.1 ± 11.3 years (37% were ≥ 75 years) and 621 (59.0%) of the patients were female. The mean body mass index was 29.1 ± 5.4 kg/m^2, and 105 (10.0%) of the study participants had low body weight (< 60 kg).

Regarding the AF pattern, most patients (57.1%) had permanent AF, 29.5% had paroxysmal AF, and 13.4% had persistent or long-standing persistent AF. The mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74 years, Sex category) and HAS-BLED scores (Hypertension, Abnormal renal/liver function, Stroke, Bleeding predisposition, Labile INR, Elderly, Drugs/alcohol) were 3.5 ± 1.5 and 1.6 ± 1.0, respectively, as reported by the study investigators. Among the study population, 12 (1.1%) patients had a CHA_2DS_2–VASc score of 0, and 81 (7.7%) had a CHA_2DS_2–VASc score of 1. Overall, 36 (3.4%) patients had lower stroke risk (i.e., CHA_2DS_2–VASc score of 0 for male and 1 for female patients). In total, 7.0% of the study population had a history of cardioversion, and only 2.0% had undergone an AF ablation procedure. Hypertension was the most common cardiovascular comorbidity (76.9%), followed by heart failure (29.0%) and diabetes (26.8%). The rates of patients with a previous ischemic stroke, transient ischemic attack, systemic embolism, and myocardial infarction were 10.6%, 2.8%, 0.5%, and 12.8%, respectively. A history of major bleeding was present in 1.7% of patients, and 1.3% had a history of gastrointestinal bleeding. Forty patients (3.8%) had history of cancer, and 118 patients (11.8%) were taking concomitant antiplatelet therapy. The mean creatinine clearance was 80 ± 31 mL/min, calculated using the Cockroft-Gault equation, and 16.5% of patients had a creatinine clearance between 15–50 mL/min.

Table 1. Baseline characteristics of the ETAF–TR study population

Variables	Total (n = 1053)	Edoxaban 30 mg (n = 210, 19.9%)	Edoxaban 60 mg (n = 843, 19.9%)
Demographics			
Age, mean ± SD, years	70.1 ± 11.3	77.4 ± 11.0	68.2 ± 10.6
Age group, n (%)			
< 65 years	265 (25.2)	13 (6.2)	252 (29.9)
65–74 years	397 (37.7)	46 (21.9)	351 (41.6)
≥ 75 years	391 (37.1)	151 (71.9)	240 (28.5)
Female sex, n (%)	621 (59.0)	137 (65.2)	484 (57.4)
BMI, mean ± SD, kg/m^2	29.1 ± 5.4	27.8 (5.4)	29.4 (5.3)
Low body weight (< 60 kg), n (%)	105 (10.0)	55 (26.2)	50 (5.9)
AF-related information			
AF pattern, n (%)			
Paroxysmal	311 (29.5)	49 (23.3)	262 (31.1)
Persistent	141 (13.4)	22 (10.5)	119 (14.1)
Permanent	601 (57.1)	139 (66.2)	462 (54.8)
CHA_2DS_2-VASc score, mean ± SD	3.5 ± 1.5	4.2 ± 1.4	3.3 ± 1.5
CHA_2DS_2-VASc = 0, n (%)	12 (1.1)	0 (0.0)	12 (1.4)
CHA_2DS_2-VASc = 1, n (%)	81 (7.7)	7 (3.3)	74 (8.8)
HAS-BLED score, mean ± SD	1.6 ± 1.0	2.0 ± 1.0	1.4 ± 0.9
History of cardioversion, n (%)	74 (7.0)	14 (6.7)	68 (8.1)
History of AF ablation, n (%)	21 (2.0)	3 (1.4)	18 (2.1)
Medical history and co-morbidities			
Hypertension, n (%)	805 (76.4)	166 (79.0)	639 (75.8)
Diabetes, n (%)	282 (26.8)	56 (26.7)	226 (26.8)
Heart failure, n (%)	305 (29.0)	72 (34.3)	233 (27.6)
Myocardial infarction, n (%)	135 (12.8)	29 (13.8)	106 (12.6)
Peripheral artery disease, n (%)	33 (3.1)	8 (3.8)	23 (3.0)
History of thromboembolic events, n (%)			
Ischemic stroke	112 (10.6)	19 (9.0)	93 (11.0)
Transient ischemic attack	24 (2.8)	6 (2.9)	18 (2.1)
Systemic embolism	5 (0.5)	5 (2.4)	0 (0.0)
Pulmonary embolism	4 (0.4)	0 (0.0)	4 (0.5)
Deep vein thrombosis	8 (0.8)	1 (0.5)	7 (0.8)
History of bleeding, n (%)			
Major bleeding	18 (1.7)	6 (2.9)	12 (1.4)
CRNM bleeding	19 (1.8)	7 (3.3)	12 (1.4)
Overt bleeding	9 (0.9)	5 (2.4)	4 (0.5)
Minor bleeding	44 (4.2)	12 (5.7)	32 (3.8)
Location of previous major bleeding, n (%)			
ICH	4 (0.4)	3 (1.4)	1 (0.1)
GIS	13 (1.3)	3 (1.4)	10 (1.2)
Other	1 (0.1)	0 (0.0)	1 (0.1)
History of cancer, n (%)	40 (3.8)	8 (3.8)	32 (3.8)
Smoking (current), n (%)	71 (6.7)	6 (2.9)	65 (7.7)
Antiplatelet treatment	118 (11.8)	29 (13.8)	89 (10.6)
Laboratory data			
Serum creatinine, mean ± SD, mg/dL	0.9 ± 0.3	1.1 ± 0.4	0.9 ± 0.2
CrCl, mean ± SD, mL/min	80 ± 31	55 ± 23	86 ± 30
CrCl 15–50 mL/min, n (%)	174 (16.5)	106 (50.5)	68 (8.1)
Hemoglobin, mean ± SD, g/dL	12.9 ± 1.9	12.1 ± 1.9	13.1 ± 1.8
Platelet × 10^3, mean ± SD, per mcL	241 ± 73	234 ± 82	243 ± 70
Appropriateness of edoxaban dose			
Appropriate dose, n (%)	834 (82.2)	129 (61.4)	743 (88.1)
Inappropriate low dose, n (%)	81 (8.0)	81 (38.6)	0 (0.0)
Inappropriate high dose, n (%)	100 (9.8)	0 (0.0)	100 (11.9)
Off-label usage	38 (3.6)	3 (1.4)	35 (4.2)

AF, Atrial fibrillation; BMI, Body mass index; CHA_2DS_2-VASc, Congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age 65–74 years, sex category (female); CrCl, Creatinine clearance; CRNM, Clinically relevant non-major bleeding; GIS, Gastrointestinal system; HAS-BLED, Uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile International Normalized Ratio, elderly (age > 65 years), drugs or alcohol (1 point each) [concomitant antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse]; ICH, Intracranial hemorrhage; LAA, Left atrial appendage; SD, Standard deviation.

Table 2. Comparison of the ETAF-TR study with the ETNA-AF Europe study and the ENGAGE AF-TIMI 48 trial

Variables	ETAF-TR (n = 1,053)	ETNA-AF Europe (n = 13,092)	ENGAGE AF-TIMI 48* (n = 2,123)	P-value (ETAF-TR vs. ETNA-AF Europe)	P-value (ETAF-TR vs. ENGAGE AF-TIMI 48*)
Age, mean ± SD, years	70.1 ± 11.3	73.6 ± 9.5	72.7 ± 8.1	<0.001	<0.001
Male sex, (%)	41.0	56.6	62.4	<0.001	<0.001
CHA_2DS_2–VASc score, mean ± SD	3.5 ± 1.5	3.1 ± 1.4	4.2 ± 1.3	<0.001	<0.001
HAS–BLED score, mean ± SD	1.6 ± 1.0	2.6 ± 1.1	1.6 ± 0.9	<0.001	1.00
Hypertension, (%)	76.4	76.9	92.4	0.71	<0.001
Diabetes, (%)	26.8	21.9	39.1	0.002	<0.001
Heart failure, (%)	29.0	5.8	48.2	<0.001	<0.001
Myocardial infarction, (%)	12.8	4.3	2.9	<0.001	<0.001
Ischemic stroke, (%)	10.6	5.9	15.5	<0.001	0.08
Creatinine clearance, mean ± SD, mL/min	80 ± 31	69 ± 24	75 ± 28	<0.001	<0.001
Atrial fibrillation pattern (%)					
Paroxysmal	29.5	53.6	26.6	<0.001	0.085
Persistent	13.4	24.4	24.1	<0.001	<0.001
Permanent	57.2	19.6	49.4	<0.001	<0.001
Dosing pattern of edoxaban (%)					
Standard dose	80.1	76.3	N/A	0.006	N/A
Reduced dose	19.9	23.7	N/A	<0.001	
Appropriateness of edoxaban dose (%)					
Appropriate dose	82.2	83.2	N/A	0.188	N/A
Inappropriate high dose (overtreatment)	9.8	8.6	N/A	0.191	N/A
Inappropriate low dose (undertreatment)	8.0	7.6	N/A	0.657	N/A

*Patients enrolled in the ENGAGE AF-TIMI 48 trial from the ETNA-AF Europe study countries. CHA_2DS_2-VASc, Congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age 65–74 years, sex category (female); ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; ETAF-TR, Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in TüRkiye; ETNA-AF Europe, Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation in Europe; HAS-BLED, Uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile International Normalized Ratio, elderly (age > 65 years), drugs or alcohol (1 point each) [concomitant antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse]; SD, Standard deviation.

Of the 1,053 patients, 843 (80.1%) received standard-dose edoxaban and 210 (19.9%) received reduced-dose edoxaban. As expected, there were notable differences in the clinical characteristics of patients receiving the edoxaban 60 mg and 30 mg doses. Compared with patients receiving standard-dose edoxaban, those receiving edoxaban 30 mg were older, more likely to have low body weight, had higher CHA_2DS_2–VASc and HAS-BLED scores, were more likely to have a history of bleeding, and were more likely to receive concomitant antiplatelet therapy. The mean baseline CrCl values were 86 mL/min and 55 mL/min for the edoxaban 60 mg and 30 mg dose groups, respectively. A total of 106 (50.5%) patients in the edoxaban 30 mg group, compared to only 68 patients (8.1%) in the edoxaban 60 mg group, had a baseline CrCl of 15–50 ml/min (Table 1). Of the 1,053 patients, 38 (3.6%) had off-label edoxaban use (36 patients had lower stroke risk, i.e., CHA_2DS_2–VASc score of 0 for men and 1 for women; and two patients had significant mitral stenosis, i.e., mitral valve area < 1.5 cm^2). Among the remaining 1,015 patients, 834 (82.2%) received the appropriate dose of edoxaban, and 181 (17.8%) received an inappropriate dose of edoxaban according to the SmPC criteria. Among the 181 patients who received an inappropriate dose, 81 (8.0%) received an inappropriate low dose (undertreatment), whereas 100 (9.8%) received an inappropriate high dose (overtreatment). The prescription rate of the appropriate edoxaban dose was higher in patients receiving the 60 mg dose compared to those receiving the 30 mg dose (88.1% versus 61.4%, respectively).

The comparative analysis of the ETAF-TR study with the ETNA-AF Europe study[4] and the ENGAGE AF-TIMI 48 trial.[6] demonstrated significant differences in the clinical characteristics of enrolled patients (Table 2). The mean age of the study population was lower in the ETAF-TR study compared with the ETNA-AF Europe study and the European cohort of the ENGAGE AF-TIMI 48 trial (70.1 years versus 73.6 and 72.7 years, respectively, P-value < 0.001 for both). Although the majority of participants were male in the ETNA-AF Europe study and the European cohort of the ENGAGE AF-TIMI 48 trial (56.6% and 62.4%, respectively), the proportion of male patients was 41.0% in the ETAF-TR study (P-value < 0.001 for both).

Stroke risks profiles also differed between both studies and the phase 3 trial. The mean CHA_2DS_2–VASc score was higher in the ETAF-TR study than in the ETNA-AF Europe study, whereas it was lower than that of the European patients included in the ENGAGE AF-TIMI 48 trial (3.5 versus 3.1 and 4.2, P-value < 0.001 for both). In contrast, the HAS-BLED score was similar between the ETAF-TR study population and the European patients included in the ENGAGE AF-TIMI 48 trial (1.6 versus 1.6, P-value = 1.00); however, it was significantly lower than in the patients included in the ETNA-AF Europe study (1.6 versus 2.6, P-value < 0.001) (Table 2).

There were significant differences in the prevalence of major comorbidities between the ETAF-TR study, the ETNA-AF-Europe study, and the European cohort of the ENGAGE AF-TIMI 48 trial. Hypertension was the most common comorbidity in all cohorts. Although the prevalence of hypertension was similar between the ETAF-TR and ETNA-AF-Europe studies (76.4% versus 76.9%, respectively; P-value = 0.71), it was significantly lower than in the European cohort of the ENGAGE AF-TIMI 48 trial (76.4% and 76.9% versus 92.4%, respectively; P-value < 0.001 for both). The prevalence of diabetes, heart failure, and myocardial infarction also differed between cohorts. The proportion of patients with a history of ischemic stroke, heart failure, and diabetes was higher in the ETAF-TR study population than in the ETNA-AF-Europe cohort (10.6%, 29.0%, and 26.8% versus 5.9%, 5.8%, and 21.9%, respectively; P-value < 0.001 for both ischemic stroke and heart failure, and P-value = 0.002 for diabetes). In contrast, the prevalence of these comorbidities was lower than in the European cohort of the ENGAGE AF-TIMI 48 trial (15.5%, 48.2%, and 39.1%, respectively; P-value = 0.08 for ischemic stroke and P-value < 0.001 for both heart failure and diabetes). The prevalence of myocardial infarction in the ETAF-TR group was significantly higher than in both the ETNA-AF-Europe study and the ENGAGE AF-TIMI 48 European cohort (12.8% versus 4.3% and 2.9%, respectively; P-value < 0.001 for both) (Table 2).

The mean baseline creatinine clearance in the ETAF-TR study was significantly higher than in the ETNA-AF study and the European cohort of the ENGAGE AF-TIMI 48 trial (80 mL/m^2 versus 69 mL/m^2 and 75 mL/m^2, respectively; P-value < 0.001 for both) (Table 2).

In terms of AF pattern, there were significant differences between the cohorts. Although permanent AF was the most common pattern in both the ETAF-TR study and the European cohort of the ENGAGE AF-TIMI 48 trial, the prevalence of permanent AF was significantly higher in the ETAF-TR study (57.2% versus 49.4%, respectively, P-value < 0.001). In contrast, paroxysmal AF was the most common pattern in the ETNA-AF-Europe study (53.6%), while only a minority of patients had permanent AF (19.6%) (Table 2).

The proportions of patients receiving standard and reduced doses of edoxaban were significantly different between the ETAF-TR and ETNA-AF-Europe studies (80.1% versus 76.3% for standard dose, and 19.9% versus 23.7% for reduced dose, respectively, P = 0.008 and P < 0.005, respectively). Adherence to appropriate prescribing of edoxaban according to SmPC criteria was similar in both studies (82.2% versus 83.8%, respectively; P = 0.188) (Table 2).

Discussion

The baseline results of the ETAF-TR study provide detailed real-world data on the demographic and clinical characteristics and dosing patterns in patients with AF who are already receiving edoxaban treatment. The principal findings of this study are as follows: (I) although the majority of individuals are male in the pivotal trials of DOACs and real-world studies from Europe, 59.0% of the participants were female in the ETAF-TR study; (II) hypertension was the most common comorbidity, and permanent AF was the most common AF pattern; (III) nearly 90% of the study population had a higher stroke risk; (IV) four out of five patients were receiving a standard dose of edoxaban; (V) more than 80% of patients were receiving an appropriate dose of edoxaban according to SmPC criteria; (VI) the ETAF-TR study population was significantly younger than the European cohort of the ENGAGE AF-TIMI 48 trial and the ETNA-AF-Europe study population; (VII) the prevalence of comorbidities including diabetes, heart failure, myocardial infarction, and ischemic stroke, was significantly higher in the ETAF-TR study than in the ETNA-AF study; (VIII) the mean CHA_2DS_2–VASc score was higher than in the ETNA-AF Europe registry; and (IX) the prevalence of appropriate and inappropriate dosing patterns was broadly similar to that observed in the ETNA-AF Study.

The results of registry-based Western population studies indicate that the mean age of patients with AF is greater than 70 years.[9-11] Conversely, observational studies conducted in Türkiye have shown that the mean age of patients with AF falls between 64 and 70 years.[12,13] As observed in previous reports, the ETAF-TR study cohort exhibited a markedly younger age profile than the European cohorts enrolled in the ETNA-AF study and the ENGAGE AF-TIMI 48 trial.[4,6] Considerable differences in population age between the ETAF-TR study and the European registries may be due to differences in comorbidity burden predisposing to AF. For example, the Middle East region has the highest rates of age-adjusted ischemic heart disease incidence and prevalence among the Global Burden of Disease study regions.[14]

On the other hand, a meta-analysis focusing on the burden of cardiovascular disease risk factors in the Middle East reported a higher prevalence of hypertension, diabetes, dyslipidemia, and smoking.[15] A higher prevalence of age-adjusted ischemic heart disease and other comorbidities may be a critical factor in the development of AF in younger individuals in the ETAF-TR study. Indeed, the nearly four-fold higher prevalence of myocardial infarction in the ETAF-TR study compared with ETNA-AF Europe may reflect the ischemic heart disease burden and higher predisposition to AF development in younger patients.

A further noteworthy demographic distinction identified in the ETAF-TR study is the preponderance of female patients. While randomized controlled trials of DOACs and prior reports from Europe have indicated that more than 55% of individuals are male, this study observed that 59.0% of the study population was female.[4,6,16-18] The results of our study are consistent with those reported in previous research conducted in Türkiye. The ROTA study (Real-World Evaluation of Anticoagulant

Treatment Patterns in Patients with Atrial Fibrillation: Data from Multicenter ROTA Study) indicated that 57.4% of participants were women, which aligns with the findings of the ETAF-TR study.[19] This observed difference may be attributable to the comparatively high prevalence of metabolic syndrome, obesity, a sedentary lifestyle, and cardiovascular risk factors and diseases among Turkish women relative to the European population.[20]

The inappropriate dosing of DOACs has been linked to an increased risk of major adverse cardiovascular events. The prescription of inappropriately low doses of DOACs may increase the risk of stroke, systemic embolism, and cardiovascular hospitalization. Conversely, prescribing inappropriately high doses of DOACs may increase the risk of bleeding and all-cause mortality.[21-23] Thus, selecting an appropriate dose represents a pivotal aspect of DOAC treatments. In the ETAF-TR study, a high level of adherence to the dose selection criteria set out in the SmPC was observed, with 82.2% of participants receiving the recommended dosage. These findings are consistent with those of the ETNA-AF Europe study, in which 83.8% of patients received an appropriate dose of edoxaban.[4] Although a high proportion of participants in the ETAF-TR study received an appropriate dose, approximately one-fifth received inappropriate low or high doses of edoxaban treatment, which may increase the risk of adverse clinical events. Notably, the proportion of patients receiving an appropriate dose of edoxaban was higher among those treated with 60 mg than among those treated with 30 mg. Fear of bleeding events in elderly or frail patients without SmPC dose-reduction criteria, but with a high comorbidity burden, concomitant antiplatelet therapy, or a history of bleeding, may have been a contributing factor to the prescription of an inappropriately reduced dose of edoxaban. The European Heart Rhythm Association (EHRA) Practical Guide provides a systematic approach for reducing anticoagulant doses for each DOAC, rather than relying solely on SmPC criteria, by taking into consideration multiple patient-specific risk factors, including age, renal impairment, low body weight, hemorrhagic risk, and the concurrent use of antiplatelet agents, verapamil, diltiazem, amiodarone, or potent P-glycoprotein inhibitors.[24]

In contrast to previous observational studies, the ANATOLIA-AF study (Prevalence and Associated Factors of Inappropriate Dosing of Direct Oral Anticoagulants in Patients With Atrial Fibrillation: the ANATOLIA-AF Study) applied the criteria proposed by the EHRA for using DOACs in patients with AF in real-life settings.[25] This study reported that the proportion of patients receiving an appropriate dose of edoxaban was 72%, which is lower than in both the ETNA-AF Europe[4] and ETAF-TR studies. It should be noted that important risk factors, including age, concomitant antiplatelet use, and previous bleeding events, are not included in the SmPC of direct oral anticoagulants, which is a significant omission that warrants further investigation.

Another critical finding in the ETAF-TR study is the higher prevalence of comorbidities, including diabetes, heart failure, myocardial infarction, and ischemic stroke, compared with ETNA-AF Europe.[4] Obesity is linked with hypertension and diabetes, which together increase the risk of myocardial infarction, heart failure, and ischemic stroke. In 2019, more than 20% of people in Türkiye were obese, and the country ranks third among European countries in terms of obesity prevalence in women.[20] As indicated in the 2021 report published by the International Diabetes Federation, Türkiye has the highest prevalence of diabetes in Europe. The age-adjusted prevalence of diabetes in Europe is 7.0%. However, it is significantly higher in Türkiye, where the prevalence is 14.5% in the adult population.[26] On the other hand, the use of tobacco products represents a significant risk factor for the development of cardiovascular diseases, including myocardial infarction and ischemic stroke. Although it is well known that smoking is the single most significant avoidable health risk, the prevalence of smoking in men in Türkiye, with a rate of 42.1%, is one of the 10 highest among European countries.[20] In light of the aforementioned cardiovascular risk factors, it is unsurprising that the prevalence of myocardial infarction, ischemic stroke, and heart failure is higher in Türkiye than in European counterparts.[27] Consequently, the CHA_2DS_2-VASc score, which incorporates factors such as diabetes, heart failure, coronary artery disease, and ischemic stroke, is significantly higher in the ETAF-TR study than in the ETNA-AF Europe study, despite the younger patient population.[4] The findings of the ETAF-TR study indicate the necessity for prompt and systematic interventions targeting obesity, smoking, hypertension, and diabetes by the Ministry of Health, healthcare professionals, and non-governmental organizations in both patients with AF and the general population of Türkiye.

This study has some limitations. The ETAF-TR study is a national study and may reflect specific characteristics of the Turkish population. Therefore, extending the results to other populations may not be feasible. As noted earlier, the Social Security Institution of Türkiye is the primary payer institution within the country, and it stipulates the use of warfarin treatment before reimbursement of DOACs. Therefore, the ETAF-TR study population comprised patients with a history of warfarin use. These patients may be more aware of the significance of anticoagulant therapy and its potential adverse effects than those who have not previously undergone such treatment. Additionally, the ETAF-TR study population was limited to outpatient cardiology clinics and may not reflect all healthcare settings, such as inpatient wards or intensive care units. Although the study used limited exclusion criteria to overcome factors that limit external validation, ETAF-TR is still susceptible to several biases, such as selection bias and recall bias. However, similar population demographics such as age and sex between ETAF-TR and other recent real-life studies may reflect the all-comer nature of the study.

Conclusion

ETAF-TR is a large, national, prospective study evaluating the use of edoxaban for SSPAF. The baseline data indicate that edoxaban has been administered to a diverse patient population with appropriate dosing. The one-year results of the ETAF-TR study will provide important insights into the safety and effectiveness of edoxaban treatment in real-life settings.

Ethics Committee Approval: Ethics committee approval was obtained from Dokuz Eylül University Clinical Research Ethics Committee (Approval Number: 2020/04-01, Protocol Number: 513-SBKAEK, Date: 12.03.2020).

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

Conflict of Interest: Umut Kocabaş, M.D., has received speaker's honoraria for lectures at meetings sponsored by Daiichi-Sankyo, Bayer, Abdi İbrahim, Sanovel, and Santa Farma drug companies. Other authors have nothing to declare.

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Effect of Cytisine on Ventricular Repolarization Parameters in Healthy Smokers

Sağlıklı Sigara İçicilerinde Sitizinin Ventriküler Repolarizasyon Parametreleri Üzerine Etkisi

ABSTRACT

Objective: Cytisine is a pharmacological agent widely used for smoking cessation, acting as a partial agonist of the α4β2 nicotinic acetylcholine receptor. While varenicline, a drug with a similar mechanism of action, has been associated with electrocardiographic (ECG) alterations, to our knowledge, the effect of cytisine on ECGs has not yet been studied. This study aimed to evaluate the effects of cytisine use on electrocardiographic parameters, particularly QT, QTc, Tp-e, and the Tp-e/QTc ratio.

Method: A retrospective analysis was conducted on 110 patients who completed a 25-day cytisine regimen for smoking cessation. Patients with known cardiovascular disease, clinically significant arrhythmias, use of QT-prolonging medications, electrolyte abnormalities, or incomplete follow-up data were excluded from the analysis. Standard 12-lead ECGs and serum biochemistry were assessed before treatment and at the one-month follow-up. Statistical analyses included paired tests and correlation analysis.

Results: No statistically significant changes were observed in QT, QTc, Tp-e intervals, or the Tp-e/QTc ratio following cytisine treatment (all $P > 0.05$). A modest increase in potassium and a decrease in calcium levels were noted, though both remained within normal limits. No correlation was found between smoking exposure (pack-years) and baseline Tp-e/QTc.

Conclusion: In healthy smokers, approximately one month of cytisine treatment was not associated with statistically significant changes in QT, QTc, Tp-e, or Tp-e/QTc. These results suggest that there is no detectable short-term effect on ventricular repolarization in this population. However, further prospective, randomized, and long-term studies are warranted to confirm these findings, particularly in patients with pre-existing cardiovascular conditions.

Keywords: Arrhythmias, cytisine, electrocardiography, ventricular repolarization, ventricular tachycardia

ÖZET

Amaç: Sitizin, sigara bırakma tedavisinde yaygın olarak kullanılan ve α4β2 nikotinik asetilkolin reseptörüne parsiyel agonist olarak etki eden farmakolojik bir ajandır. Benzer etki mekanizmasına sahip vareniklinin elektrokardiyografik (EKG) değişikliklerle ilişkili olduğu bildirilmiştir. Ancak, bildiğimiz kadarıyla sitizinin EKG üzerine etkisi daha önce incelenmemiştir. Bu çalışmanın amacı, sitizin kullanımının elektrokardiyografik parametreler üzerindeki etkilerini, özellikle QT, QTc, Tp-e ve Tp-e/QTc oranını değerlendirmektir.

Yöntem: Sigara bırakma amacıyla 25 günlük sitizin tedavisini tamamlayan 110 hasta retrospektif olarak incelendi. Bilinen kardiyovasküler hastalığı, klinik olarak anlamlı aritmisi, QT'yi uzatan ilaç kullanımı, elektrolit bozukluğu veya eksik takip verisi olan hastalar analize dâhil edilmedi. Tedavi öncesinde ve 1. ay kontrolünde tüm hastaların standart 12 derivasyonlu EKG ve serum biyokimyası değerlendirildi. İstatistiksel analizlerde eşleştirilmiş testler ve korelasyon analizi kullanıldı.

Bulgular: Sitizin tedavisi sonrasında QT, QTc, Tp-e aralıkları ve Tp-e/QTc oranında istatistiksel olarak anlamlı bir değişiklik gözlenmedi (tüm $P > 0,05$). Serum potasyumunda hafif artış ve kalsiyumda azalma saptandı, ancak bu değişiklikler normal sınırlar içinde kaldı. Sigara içme yükü (paket-yıl) ile başlangıç Tp-e/QTc arasında anlamlı bir ilişki bulunmadı.

Sonuç: Sağlıklı sigara içicilerinde yaklaşık bir aylık sitizin tedavisi, QT, QTc, Tp-e veya Tp-e/QTc'de istatistiksel olarak anlamlı değişikliklerle ilişkili bulunmamıştır. Bu sonuçlar, bu popülasyonda ventriküler repolarizasyon üzerinde saptanabilir kısa dönem bir etkinin olmadığını düşündürebilir. Bununla birlikte, özellikle kardiyovasküler hastalığı bulunan bireylerde prospektif, randomize ve uzun dönemli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aritmiler, sitizin, elektrokardiyografi, ventriküler repolarizasyon, ventriküler taşikardi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Globally, cigarette smoking is still recognized as a predominant cause of avoidable morbidity and mortality.[1] Various pharmacological agents have been proven effective in smoking cessation therapy, and their use is recommended for all patients without contraindications.[2] Cytisine is a plant-based alkaloid with potent efficacy in smoking cessation treatment that exerts its effect via partial agonism at the α4β2 nicotinic acetylcholine receptor.[3] Cytisine's agonist activity is determined by both receptor activation and receptor desensitization. It binds to α4β2 receptors with higher affinity than nicotine, thereby attenuating nicotine withdrawal. It also has a competitive antagonistic effect on these receptors and partially blocks the activity of nicotine.[4] Large-scale trials have reported smoking cessation rates of around 30–50% after one month and 18–23% after six months with cytisine.[4,5] Furthermore, recent randomized controlled trials and meta-analyses have demonstrated that cytisine is more effective than placebo and nicotine replacement therapy (NRT).[6,7] In addition to its strong efficacy, cytisine has been shown to have good tolerability.[6]

Electrocardiography (ECG) is widely used in cardiology practice as a rapid and cost-effective diagnostic tool. On ECG, the QT interval, corrected QT interval (QTc), T_{peak}–T_{end} (Tp-e), and Tp-e/QTc ratio are ventricular repolarization markers used to predict the risk of arrhythmia.[8] Changes in these parameters have been closely linked to the development of ventricular arrhythmias and the occurrence of sudden cardiac death.[9] Varenicline, which shares a similar mechanism of action with cytisine, has been reported to cause alterations in ventricular repolarization parameters and may potentially increase the risk of cardiac arrhythmias.[10]

To the best of our knowledge, the impact of cytisine on electrocardiographic parameters has not previously been investigated. Therefore, the aim of our study is to evaluate the effects of cytisine use on electrocardiographic parameters, particularly QT, QTc, Tp-e, and the Tp-e/QTc ratio.

Materials and Methods

This study was designed to retrospectively evaluate changes in the QT interval, QTc, Tp-e duration, and Tp-e/QTc ratio before and after cytisine treatment in individuals who were initiated on cytisine therapy for smoking cessation. Between January 2024 and April 2025, 315 patients who presented to the smoking cessation clinic and were prescribed cytisine were screened. The following patients were excluded based on prespecified criteria:

(i) known cardiovascular disease (coronary artery disease, heart failure/cardiomyopathy, congenital heart disease, or moderate-to-severe valvular disease);

(ii) history of clinically significant arrhythmia (including atrial fibrillation, supraventricular tachycardia, or ventricular tachycardia);

(iii) concomitant use of medications known to influence ventricular repolarization (e.g., antiarrhythmics, antipsychotics, macrolides/fluoroquinolones);

(iv) known chronic kidney disease;

(v) known thyroid disease;

(vi) electrolyte imbalance at baseline and at one-month; and

ABBREVIATIONS

CI	Confidence interval
ECG	Electrocardiography
ICC	Intraclass correlation coefficient
NRT	Nicotine replacement therapy
QTc	Corrected QT interval
Tp-e	T_{peak}-T_{end}

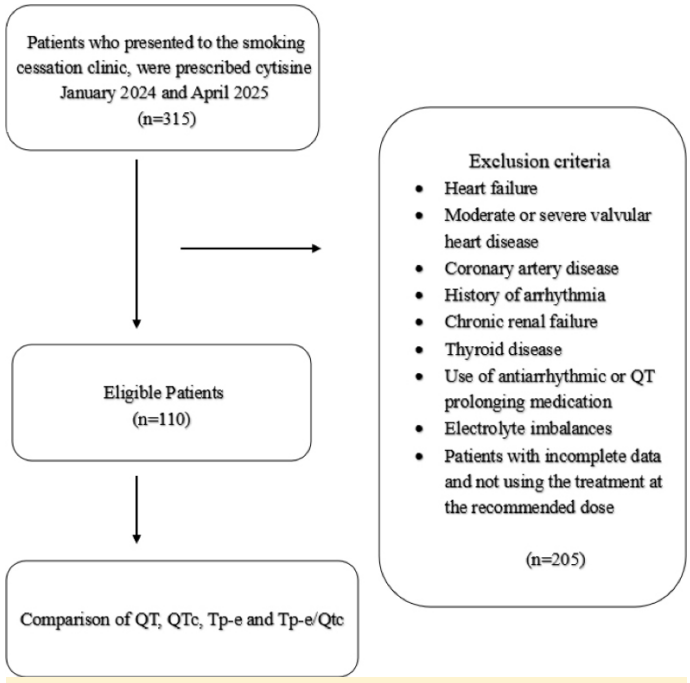

Figure 1. Flowchart of patient selection and inclusion process.

(vii) incomplete data, defined as absence of either the baseline or one-month 12-lead ECG, or ECG quality insufficient for interval measurements.

Patients who followed the manufacturer's recommended 25-day dosing schedule were included in the study.[3,11] The regimen began with one tablet every 2 hours (up to 6 tablets per day) on days 1–3, then gradually decreased: every 2.5 hours (up to 5 tablets) on days 4–12, every 3 hours (up to 4 tablets) on days 13–16, every 4–5 hours (up to 3 tablets) on days 17–20, and finally every 6 hours (up to 2 tablets) on days 21–25.

A total of 205 individuals did not meet the criteria and were excluded from the analysis, which ultimately included 110 patients. A summarized flow of the study design is presented in Figure 1.

The demographic characteristics (age, height, weight, etc.) and clinical data of the patients at the time of their initial visit to the smoking cessation clinic were obtained from the hospital's electronic medical records. We reviewed venous blood samples and standard 12-lead ECGs acquired at the initial visit and at the one-month follow-up (filter 150 Hz; paper speed 25 mm/s; amplitude 10 mm/mV). ECG measurements were performed manually on digitally archived images at a magnification of at least 400%; no automated software was used.

QT intervals were assessed from the onset of the Q wave to the termination of the T wave. QTc was derived using the Fridericia correction formula to account for heart rate variability.[12] The Tp-e interval was determined as the duration between the peak and the end of the T wave, with any U wave excluded. Tp–e intervals were measured in the precordial leads, and the Tp–e/QTc ratio was calculated accordingly. Electrocardiographic assessments were carried out by two cardiologists working independently. To assess inter- and intra-observer variability, a random sample of 40 ECGs was re-evaluated. Two cardiologists measured QTc and Tp–e independently in separate, blinded sessions. Inter-observer agreement was derived from the readings obtained in the first session, and intra-observer agreement from a repeat reading by one of the cardiologists.

Ethical Considerations

The study was approved by the Manisa Celal Bayar University Ethics Committee (Approval Number: 20.478.486/3142, Date: 11.06.2025). Written informed consent was waived due to the retrospective nature of this study. No artificial intelligence-assisted technologies, including chatbots, image generators, or large language models (LLMs), were used in this study.

Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed visually using histograms and statistically with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables with normal distribution were reported as mean ± standard deviation, whereas those not normally distributed were expressed as median with interquartile ranges. Between-group comparisons for continuous variables were conducted using the Independent Samples t-test for parametric data and the Mann-Whitney U test for non-parametric data. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square or Fisher's exact test, as appropriate. For variables with normal distribution, temporal comparisons were made using the paired t-test, whereas the Wilcoxon signed-rank test was applied to non-normally distributed variables. Correlation between smoking burden (pack-years) and baseline Tp-e/QTc was analyzed using Spearman's method. Variability was evaluated in a subset using intraclass correlation coefficients (ICC): ICC (2,1) for inter-observer variability (two-way random-effects, absolute agreement, single measures) and ICC (3,1) for intra-observer variability (two-way mixed-effects, absolute agreement, single measures). Ninety-five percent confidence intervals (CI) for ICCs were reported. Statistical significance was defined as $P < 0.05$.

Results

A total of 110 patients who met the inclusion criteria and completed a 25-day course of cytisine therapy were included in the study. The mean age of the participants was 43 ± 11 years, and 17 patients (15.4%) were female. The demographic characteristics of the study population are presented in Table 1. Laboratory and electrocardiographic parameters obtained before treatment and at the one-month follow-up were compared and summarized in Table 2. No statistically significant changes were observed in hemogram parameters, serum creatinine, or liver function tests.

Table 1. Demographic characteristics of the study population

Variables	Value
Age (years)	43 ± 11
Female sex (n, %)	17 (15.4)
BMI (kg/m^2)	24.1 ± 4.9
Smoking (pack-years)	23.4 ± 12.0

BMI, Body mass index.

Table 2. Comparison of laboratory and electrocardiographic parameters before and after cytisine treatment

	Initial	Follow-up	*P*
Leukocyte (×10^3/μL)	8.49 ± 2.31	8.46 ± 3.03	0.84
Hemoglobin (g/dL)	14.92 ± 1.60	14.86 ± 1.85	0.64
Platelet (×10^3/μL)	232 ± 43	243 ± 33	0.65
Creatinine (mg/dL)	0.92 ± 0.34	0.96 ± 0.43	0.67
AST (IU/L)	22.1 ± 6.2	22.5 ± 6.1	0.48
ALT (IU/L)	26.3 ± 7.8	26.1 ± 8.0	0.51
Na (mEq/L)	138.85 ± 15.89	136.52 ± 22.79	0.89
K (mEq/L)	4.14 ± 0.30	4.2 ± 0.41	**0.03**
Ca (mg/dl)	9.10 ± 0.40	8.8 ± 0.44	**0.02**
Mg (mg/dl)	1.97 ± 0.22	1.87 ± 0.22	0.16
Systolic BP (mmHg)	128 ± 18	130 ± 20	0.06
Diastolic BP (mmHg)	75 ± 11	76 ± 13	0.09
Heart rate	76 ± 11	77 ± 12	0.10
QT, ms	363.4 ± 25.6	364.1 ± 26.6	0.45
QTc, ms (Fridericia)	392 (21.5)	390 (29.5)	0.36
QRS, ms	94 ± 10	95 ± 9	0.52
Tp-e, ms	80 (14)	80 (15.5)	0.07
Tp-e/QTc	0.20 ± 0.03	0.20 ± 0.03	0.26

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BP, Blood pressure; Ca, Calcium; K, Potassium; Mg, Magnesium; Na, Sodium; QTc, Corrected QT interval; Tp-e, T_{peak}–T_{end}.

Among the electrolyte parameters, potassium levels showed a statistically significant increase after treatment (4.14 ± 0.30 vs. 4.20 ± 0.41 mmol/L; P = 0.03), while calcium levels significantly decreased (9.10 ± 0.40 vs. 8.80 ± 0.44 mg/dL; P = 0.02). Although systolic and diastolic blood pressure, as well as heart rate, were slightly higher at the one-month follow-up, these changes did not reach statistical significance.

Regarding electrocardiographic parameters, there were no statistically significant differences in QT, QTc, Tp-e, and Tp-e/QTc values before and after treatment (all P > 0.05).

Inter-observer variability was (ICC (2,1) 0.837, 95% CI: 0.686–0.918) for QTc and (ICC (2,1) 0.909, 95% CI: 0.869–0.959) for Tp–e. Intra-observer variability was (ICC (3,1) 0.859, 95% CI: 0.704–0.924) for QTc and (ICC (3,1) 0.917, 95% CI: 0.856–0.961) for Tp–e.

No significant correlation was observed between cumulative smoking exposure (pack-years) and baseline Tp-e/QTc ratio (Spearman's $\rho = -0.03$, P = 0.80). The correlation plot is presented in Figure 2.

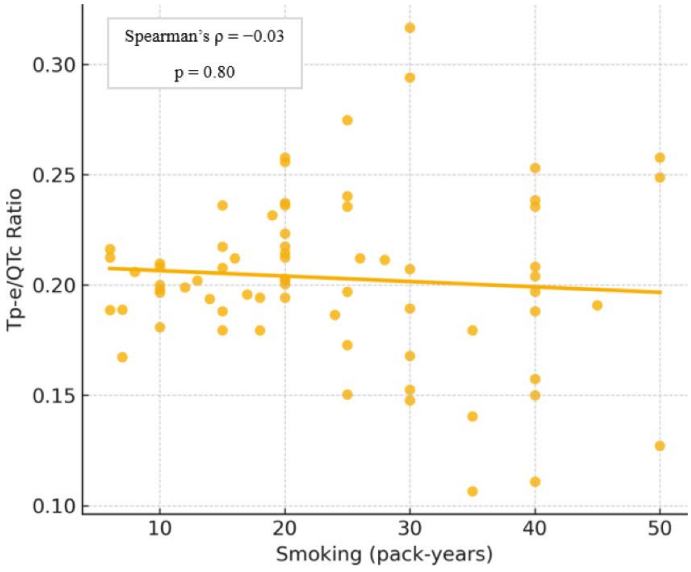

Figure 2. Correlation between cumulative smoking exposure (pack-years) and baseline Tp-e/QTc ratio.

Discussion

The main finding of our study was that no changes were observed in QT, QTc, Tp-e, and Tp-e/QTc parameters, which are important indicators of arrhythmia risk, after 25 days of cytisine treatment used for smoking cessation.

Most patients who begin smoking cessation treatment are individuals at high risk of atherosclerotic cardiovascular disease.[10] Therefore, the risk of arrhythmic side effects from a drug prescribed for this purpose is of particular importance. Varenicline, NRT, and bupropion are first-line agents in current guidelines, but there is strong evidence that varenicline is more effective than bupropion or NRT.[13] Although varenicline, which acts on the same α4β2 nicotinic acetylcholine receptors as cytisine, has been shown in several studies to influence ventricular repolarization parameters (particularly by prolonging QTc and Tp-e intervals), our findings did not demonstrate a similar effect with cytisine. For instance, in a randomized crossover trial, varenicline significantly prolonged Tp e, QTc, and Tp e/QTc (P = 0.02, P = 0.02, and P = 0.01, respectively), suggesting a potential arrhythmogenic effect.[14]

Although varenicline and cytisine have similar pharmacodynamic properties, their electrophysiological effects may differ. Both drugs reduce nicotine dependence by binding with high affinity to α4β2 nicotinic acetylcholine receptors; however, the longer half-life (approximately 24 hours) and higher receptor affinity of varenicline may lead to more pronounced effects on the central nervous system and autonomic cardiac control.[15] This may affect the vagal and sympathetic balance, causing changes in the repolarization process. Additionally, due to the renal elimination of varenicline, the potential for accumulation, especially in patients with impaired renal function, may predispose to electrocardiographic changes such as QTc prolongation.[16] Cytisine, on the other hand, exerts a more limited effect on the cardiac autonomic system due to its shorter half-life (~4.8 hours) and relatively weaker partial agonistic effect, which may explain the preservation of repolarization parameters. The mechanisms underlying the difference in arrhythmogenic safety observed in our study may therefore be attributed to these pharmacokinetic and pharmacodynamic properties.

The Tp-e interval and Tp-e/QTc ratio are recognized as sensitive indicators of transmural dispersion of repolarization and predictors of malignant ventricular arrhythmias.[17,18] Gupta et al.[9] reported that patients at increased risk of arrhythmia, including those with long or short QT syndrome and individuals with organic cardiac disease or a history of myocardial infarction, exhibited significantly higher Tp-e/QT ratios. Therefore, the stability of these markers in our study supports the cardiac safety of cytisine during early-phase smoking cessation treatment. In 2023, Livingstone-Banks et al.[5] conducted a review of 75 trials, which included data on whether there were any significant cardiac side effects associated cytisine and varenicline. In this review, although it is very valuable that the authors stated no serious cardiac side effects were observed after cytisine, ECG parameters were not evaluated. In our study, unlike others, ECG parameters were evaluated primarily.

In our study, 12-lead ECGs obtained at baseline and at one month were evaluated. As the one-month follow-up coincides with completion of the manufacturer-recommended 25-day cytisine regimen, we consider this a clinically appropriate time point to assess ventricular repolarization at the target dose. However, this interval may not capture delayed repolarization changes, which remains a limitation.

Non-adherence to medication is one of the reasons for failure in smoking cessation treatment.[19] Insufficient knowledge of adverse effects has been linked to lower adherence rates.[20] We believe that our study may help bridge this knowledge gap, thereby improving clinician and patient confidence and supporting the design of future prospective studies.

Interestingly, we noted a statistically significant increase in serum potassium and a decrease in calcium levels after treatment. These changes remained within physiological limits, but their potential impact on cardiac electrophysiology cannot be completely ruled out. Hypocalcemia is known to prolong the QT interval by delaying phase 2 of the cardiac action potential, while hyperkalemia, depending on its severity, may cause various ECG alterations.[21,22] Despite these biochemical changes, the absence of QT or Tp-e interval prolongation suggests that the electrolyte changes observed during cytisine therapy are not clinically significant in this population.

Our study is strengthened by stringent exclusion criteria and paired ECG–laboratory analyses, which minimized bias and improved validity. Still, the retrospective design, short duration of follow-up, and possible inter-observer variability in ECG interpretation represent limitations. Another limitation is that, given the limited sample size, our study may not have had sufficient power to detect subtle but clinically relevant changes in repolarization parameters; therefore, such minor differences may have remained undetected. Furthermore, the study design intentionally focused on individuals without known cardiovascular disease; consequently, the applicability of our results is confined to relatively healthy smokers. Future investigations are needed to delineate cytisine's electrophysiological safety profile in higher-

risk settings characterized by structural heart disease, impaired renal function, pre-existing arrhythmias, or polypharmacy with QT-prolonging agents.

Conclusion

Treatment with cytisine for smoking cessation did not significantly affect the QT, QTc, Tp-e, or Tp-e/QTc parameters, which may indicate a favorable short-term electrophysiological outcome. To our knowledge, this is the first study evaluating the effects of cytisine on ventricular repolarization. These findings support the use of cytisine as a safe option in smoking cessation therapy. Nevertheless, larger prospective and long-term studies are required to confirm these results and to further assess its cardiovascular safety, particularly in patients with established heart disease.

Ethics Committee Approval: Ethics committee approval was obtained from Manisa Celal Bayar University Ethics Committee (Approval Number: 20.478.486/3142, Date: 11.06.2025).

Informed Consent: Written informed consent was waived due to the retrospective nature of this study.

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

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Use of AI for Writing Assistance: No artificial intelligence-assisted technologies, including chatbots, image generators, or large language models (LLMs), were used in this study.

Author Contributions: Concept – C.C.; Design – B.Çakır; Supervision – B.Çakır; Resource – C.C., D.T.; Materials – D.T.; Data Collection and/or Processing – B.Çetinkaya; Analysis and/or Interpretation – B.Çetinkaya; Literature Review – C.C., B.Çakır; Writing – C.C., B.Çakır; Critical Review – D.T., B.Çetinkaya.

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Device Infection Imaging with Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Patients with Left Ventricular Assist Device

Sol Ventrikül Destek Cihazı Enfeksiyonlarının Flor-18 Florodeoksiglukoz Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi ile Görüntülemesi

ABSTRACT

Objective: Left ventricular assist devices (LVADs) significantly improve survival in advanced heart failure; however, infectious complications remain an important clinical challenge, with reported sepsis rates ranging from 20–40% within 1–2 years. Early and accurate identification and localization of infections—particularly at the driveline or pump—are essential for guiding treatment.

Method: We retrospectively evaluated fluorine-18 (F18) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scans of 15 patients with suspected LVAD infection. We assessed the presence and localization of infection (driveline vs. pump), its extent, and compared PET/CT findings with microbiological culture results.

Results: F18 FDG PET/CT demonstrated 100% sensitivity, 66% specificity, 92% positive predictive value, and 100% negative predictive value. Thirteen of 15 patients (87%) had positive PET/CT findings, with a mean SUV_{max} of 7.73. Infection was localized to the driveline in 10 patients and to both pump and driveline in 3. PET/CT findings were consistent with culture results, which identified *Staphylococcus aureus* and *Pseudomonas aeruginosa* as the predominant pathogens.

Conclusion: F18 FDG PET/CT is a highly sensitive, noninvasive modality for detecting and localizing LVAD infections. It aids clinicians in optimizing management strategies—such as device exchange or targeted antibiotic therapy—and may help avoid unnecessary invasive procedures. In cases of pump infection, this imaging modality supports timely interventions, including consideration for heart transplantation.

Keywords: Driveline, fluorine-18, fluorodeoxyglucose, infection, left ventricular assist device, maximum standardized uptake value, positron emission tomography/computed tomography, pump infection

ÖZET

Amaç: Sol ventrikül destek cihazları (LVAD) ileri kalp yetmezliğinde sağkalımı önemli ölçüde iyileştirir, ancak enfeksiyöz komplikasyonlar önemli bir klinik zorluk olmaya devam etmektedir ve bildirilen sepsis oranları 1-2 yıl içinde %20-40 arasında değişmektedir.Enfeksiyonların özellikle driveline veya pompa lokalizasyonlarında erken ve doğru saptanması, tedavi stratejileri açısından kritik öneme sahiptir.

Yöntem: Bu retrospektif çalışmada LVAD enfeksiyonundan şüphelenilen 15 hastanın F18 FDG PET/BT görüntüleri analiz edilmiştir. Görüntülerde enfeksiyon varlığı, lokalizasyonu (driveline vs. pompa), yayılımı değerlendirilmiş ve mikrobiyolojik kültür sonuçları ile karşılaştırılmıştır.

Bulgular: F18 FDG PET/BT, %100 duyarlılık, %66 özgüllük, %92 pozitif prediktif değer ve %100 negatif prediktif değer göstermiştir. 15 hastanın 13'ünde (%87) PET/BT pozitif bulunmuş; ortalama SUV_{max} 7,73 olarak belirlenmiştir. On hastada enfeksiyon yalnızca driveline'de, üç hastada ise hem driveline hem pompada lokalize edilmiştir. Görüntü bulguları, kültür sonuçları ile uyumlu olup, başlıca etkenler *Staphylococcus aureus* ve *Pseudomonas aeruginosa* olarak saptanmıştır.

Sonuç: F18 FDG PET/BT, LVAD enfeksiyonlarının saptanması ve lokalizasyonunda yüksek duyarlılığa sahip non-invaziv bir yöntemdir. Klinik karar süreçlerinde—örneğin cihaz değişimi veya hedefe yönelik antibiyotik tedavisi gibi—yol gösterici olabilir; özellikle pump enfeksiyonlarında gereksiz invaziv işlemleri önleyerek, kalp nakli gibi zamanlı müdahaleleri destekleyebilir.

Anahtar Kelimeler: Driveline, flor-18, florodeoksiglukoz, enfeksiyon, sol ventrikül destek cihazı, maksimum standart alım değeri, pozitron emisyon tomografisi/bilgisayarlı tomografi, pompa enfeksiyonu

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Left ventricular assist devices (LVADs) are widely used in patients with advanced heart failure as a bridging treatment for cardiac pre-transplantation. They play a critical role in disease management for this group of patients due to the shortage of donor hearts for transplantation.[1] Left ventricular assist devices significantly improve survival in advanced heart failure; however, infectious complications remain an important clinical challenge, with reported sepsis rates ranging between 20–40% within 1–2 years.[2] A left ventricular assist device is powered by a cable that passes through the skin (percutaneous driveline). The exit point of this cable from the skin (driveline exit site) provides a potential route for bacterial entry into the bloodstream. Driveline infections are the most common among LVAD-related infections. When infection spreads along the driveline to the central elements of the device and intrathoracic components (such as the cannula/tube carrying blood to the aorta and the pump), it becomes very difficult to manage and treat. This often necessitates device removal and heart transplantation. However, if the infection is peripheral or extrathoracic, antibiotic therapy and debridement may be sufficient.[3] Blood cultures, computed tomography, echocardiography, and laboratory and clinical infection findings are often insufficient for early detection and localization of infection. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F18 FDG PET/CT) has been shown to have high sensitivity in localizing infection.[4] The aim of this study is to evaluate the detection and extent of infection in patients with suspected LVAD infection using F18 FDG PET/CT.

Materials and Methods

Ethical Approval and Patient Consent

This study was approved by the Ümraniye Training and Research Hospital Scientific Research Ethics Committee (Approval Number: B.10.1.TKH.4.34.H.GP.0.01/221, Date: 10.07.2025). Written informed consent was obtained from all participants prior to their inclusion in the study. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Patient Selection

F18 PET/CT images of 15 patients (1 female and 14 males) who presented to our clinic with clinical suspicion of LVAD infection between 2019 and 2023 were evaluated retrospectively. The average age of the patients was 51 years (range: 38–65). None of the patients were receiving antibiotic therapy at the time of imaging. Patients with clinical suspicion of infection were referred to our clinic to determine the localization and extent of infection. The presence of infection was suspected based on clinical and laboratory findings.

Patient Preparation Before PET/CT Examination

Physiological glucose uptake by myocardial tissue is a limiting factor in imaging cardiac infections using F18 FDG PET/CT. A low-carbohydrate, high-fat diet is recommended for cardiac infection imaging.[5,6] All patients followed a low-carbohydrate, high-protein, and high-fat diet for 72 hours prior to the PET/CT scan.

ABBREVIATIONS

CRP	C-reactive protein
EANM	European Association of Nuclear Medicine
F18	Fluorine-18
FDG	Fluorodeoxyglucose
ISHLT	International Society for Heart and Lung Transplantation
LVAD	Left ventricular assist device
MRI	Magnetic resonance imaging
NAC	Non-attenuation corrected
NPV	Negative predictive value
OSEM	Ordered Subset Expectation Maximization
PET/CT	Oositron emission tomography/computed tomography
PPV	Positive predictive value
SUV_{max}	Maximum standardized uptake value
VAD	Ventricular assist device

PET/CT Examination

Patients' blood sugar levels were measured after fasting for at least 6 hours, and imaging was performed only if levels were below 170 mg/dl. Intravenous injection of F18 FDG was administered at a dose of 5 MBq/kg. After an uptake period of approximately 1 hour, images were acquired using a GE Discovery 600 PET/CT scanner. Low-dose CT images were obtained from the head to the mid-thigh. After CT images were obtained, PET images were acquired for each bed position for 3 minutes. Images were reconstructed using the OSEM (Ordered Subset Expectation Maximization) filter. Attenuation correction was performed with CT images, and GE's Volume Viewer software was used for reconstruction and processing.

PET/CT Image Analysis

The pump and cannula located in the intrathoracic area, as well as the surrounding intrathoracic and abdominal portions of the driveline, were visually evaluated on PET/CT images. FDG uptake higher than the physiological uptake of the liver was considered positive. Areas showing increased FDG uptake were confirmed with non-attenuation corrected (NAC) images and recorded as positive uptake. The maximum standardized uptake values (SUV_{max}) of positive involvement areas were calculated. PET metrics include regional semiquantitative indices, such as the SUV_{max}, which represents the pixel with the highest FDG uptake activity.

Definitive Diagnosis of Infection

The definitive diagnosis of LVAD infection was determined during patient follow-up based on microbiological culture results obtained from the pump and/or driveline components (Table 1). Data were accessed from the national health database (e-Nabız).

All acquisitions and evaluations were performed in accordance with the European Association of Nuclear Medicine (EANM)/EANM Research Ltd. (EARL) procedural guidelines for infection and inflammation imaging.

Results

PET/CT Findings

In 12 of 13 patients with involvement detected on PET/CT, laboratory data and infection parameters were high. The average SUV_{max} value among the 13 patients with positive findings was

Table 1. Patients' table

Patient no	Age	CRP/WBC	Culture	PET/CT	SUV_{max} values	Involvement sites in PET/CT	Clinical infection decision	Treatment	Result
1	38	30.4/4.6	+	+	8.93	Driveline	+	Antibiotic treatment	True positive
2	38	3.1/7.6	–	+	5.17	Driveline	–	Wound care, medical dressing	False positive
3	40	47,98/11.9	+	+	11.15	Driveline	+	Antibiotic treatment	True positive
4	40	19.06/9.01	–	–	–	–	–	Wound care, medical dressing	True negative
5	64	46/9.18	+	+	5.06	Driveline	+	Antibiotic treatment	True positive
6	59	191.1/12.56	+	+	7.52	Pump and driveline	Mediastinitis	Pump and driveline change	True positive
7	59	76.12/8.19	+	+	15.11	Driveline	+	Antibiotic treatment	True positive
8	62	212.0/20.07	+	+	6.0	Driveline	+	Antibiotic treatment	True positive
9	38	42.16/4.95	+	+	10.13	Pump and driveline	Mediastinitis	Pump and driveline change	True positive
10	42	32.1/11.8	+	+	2.76	Driveline	+	Antibiotic treatment	True positive
11	65	53.08/6.3	+	+	3.91	Driveline	+	Antibiotic treatment	True positive
12	53	2.6/5.7	–	–	–	–	–	Wound care, medical dressing	True negative
13	55	27.3/8.2	+	+	5.41	Driveline	+	Antibiotic treatment	True positive
14	62	36.4/9.1	+	+	3.23	Driveline	+	Antibiotic treatment	True positive
15	62	87.52/14.2	+	+	16.20	Pump and driveline	Mediastinitis	Pump and driveline change	True positive

CRP, C-reactive protein; WBC, White blood cell; PET, Positron emission tomography; CT, Computed tomography; SUV_{max}, Maximum standardized uptake value.

7.73 (range: 2.76–16.20) (Table 1). In one patient (Patient 2), infection parameters were within normal limits, but redness and fever were present at the wound site; the SUV_{max} value in this patient was 5.17 (Table 1). In 2 of 15 patients (Patients 4 and 12), no abnormal FDG uptake was detected on PET/CT (Table 1). While infection parameters were high in one of these patients and normal in the other, both patients presented with fever and discharge from the catheter. The involvement was limited to the driveline in 10 patients, while in three patients (Patients 6, 9, and 15), involvement was detected in both the pump and driveline (Table 1). The average SUV_{max} value in the 10 patients with driveline involvement was 6.67 (range: 2.76–15.11). In the three patients with both pump and driveline involvement, the average SUV_{max} value was 11.28 (range: 7.52–16.20) (Table 1).

Patients' Clinical Data

Before the PET/CT examination, the presence of infection was assessed based on clinical and laboratory findings. C-reactive protein (CRP) or white blood cell (WBC) levels were high in 13 patients (87%). Clinical findings such as fever, wound discharge, and skin redness at the driveline exit site were observed in all 15 patients (100%) (Table 1). In the microbiological evaluation of 12 patients with positive PET/CT findings, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were identified as pathogens at the driveline exit site (Table 1). Clinical and laboratory results supported the presence of LVAD infection in these 12 patients with positive PET/CT findings (Table 1). In one patient with positive PET/CT involvement (Patient 2), laboratory results were normal and no bacterial growth was observed in culture. The laboratory values of the patients with no positive uptake on PET/CT (Patients 4 and 12) were normal, and there was no growth

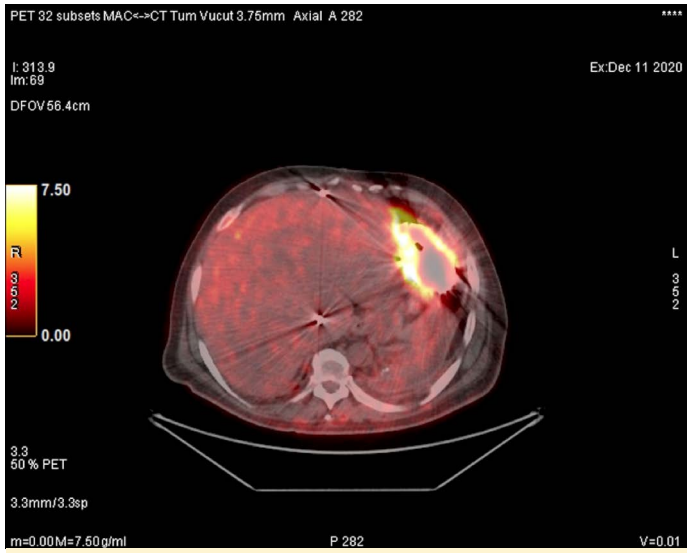

Figure 1. Focal, severe FDG uptake in favor of pump infection.

in the cultures of either patient (Table 1). PET/CT scans were performed in these patients due to clinical suspicion of infection (catheter exit site discharge).

Patient Treatment Methods

In the three patients with both LVAD pump (Figure 1) and driveline (Figure 2) involvement on PET/CT (Patients 6, 9, and 15), all components of the device were replaced. Nine patients with driveline involvement on PET/CT were treated with antibiotic therapy. After treatment, clinical and laboratory values returned

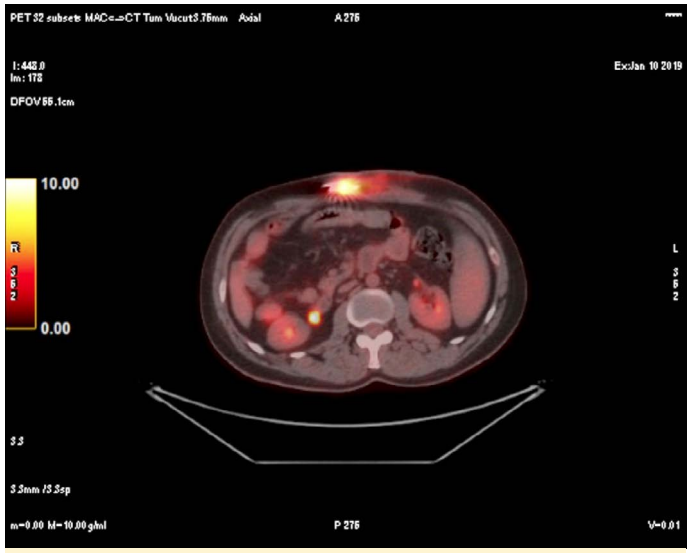

Figure 2. Focal, severe FDG uptake in favor of driveline infection.

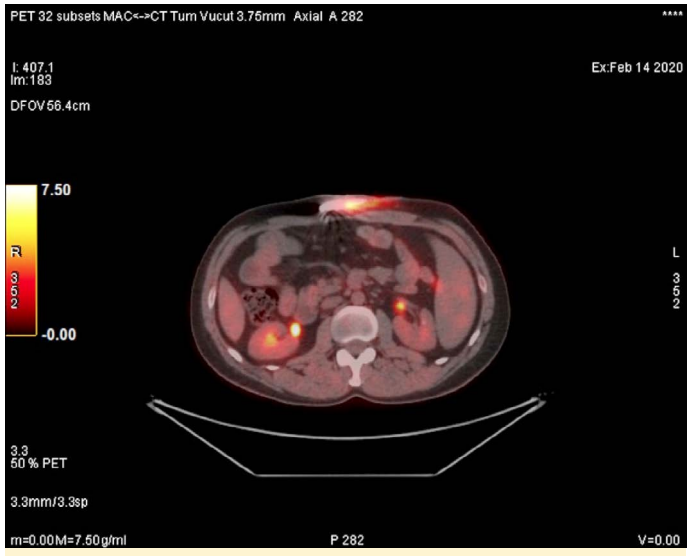

Figure 3. Relatively mild, linear false-positive FDG uptake in the driveline.

to normal, and no growth was observed in follow-up cultures. These patients were considered responsive to treatment. In one patient (Figure 3), positive uptake was detected on PET/CT, but no growth was found in microbiological cultures. In two patients with no PET/CT uptake, wound care and dressing were performed.

Statistical Values of PET/CT Findings

No statistical software was used in this study. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated manually using a confusion matrix created in Microsoft Word (Microsoft Corp., Redmond, WA, USA). These metrics were derived from the raw data obtained in the study. Among the 15 LVAD carriers evaluated, the diagnostic performance of F18 FDG PET/CT or detecting device infection was calculated as follows: sensitivity 100%, specificity 66%, PPV 92%, NPV 100%.

Discussion

According to the Infectious Diseases Council of the International Society for Heart and Lung Transplantation (ISHLT), ventricular assist device (VAD)-associated infections are classified into three categories: VAD-specific (e.g., pump pocket, cannula, driveline), VAD-associated (e.g., mediastinitis, bacteremia secondary to VAD), and non-VAD infections.[7] In our study, VAD-specific and VAD-associated infections were examined.

Early detection of infection in patients with LVADs and the specific localization of the infection are very important for patient management. As demonstrated in our study, F18 FDG PET/CT is suitable for this purpose as a test with high sensitivity and high positive and negative predictive values. If the infection has spread to central components such as the pump in LVAD carriers, device replacement is preferred. In peripheral infections such as driveline infections, medical treatment is the appropriate approach.[8]

In our study, device replacement was required in three patients in whom pump infection was detected. These LVAD exchanges were not performed solely on the basis of PET/CT findings but in conjunction with clinical, microbiological, and surgical evaluations. LVAD exchange is a high-risk procedure, and in our study, all three patients required device replacement due to progressive infection confirmed microbiologically. All patients were in good condition after replacement. Transplantation was considered but was not immediately feasible due to donor shortage and patient condition. These results are consistent with previous reports highlighting the complexity and risks associated with LVAD exchange procedures.[9]

We also prepared a flowchart (Figure 4) summarizing our institutional approach for the diagnosis and management of LVAD infections, demonstrating the role of FDG PET/CT alongside clinical, microbiological, and imaging modalities.

Moreover, detection of pump infection may be difficult with other diagnostic methods. Noninvasive detection of pump infection using F18 FDG PET/CT can protect patients from invasive procedures that require puncture.[10] F18 FDG PET/CT imaging carries an increased risk of foreign body reaction in different components, and FDG uptake in these areas can also be observed. Various semiquantitative cutoff SUV_{max} values have been determined to distinguish these involvements from true infectious involvement. In previous studies, threshold values of 4.5 for the driveline exit site, 3.1 for the subcutaneous driveline, and 5.7 for the pump have been reported.[11,12]

Since there was only one false-positive inflammatory involvement in our study, we could not determine a specific SUV_{max} threshold. However, while the average SUV_{max} value in our true-positive patients was 7.95, the SUV_{max} value in the false-positive patient was 5.17. These findings further demonstrate that inflammatory involvements are generally less focal and intense than infectious involvements. Therefore, as observed in our study, the presence of inflammatory involvement may reduce the sensitivity of F18 FDG PET/CT.

In addition, inflammatory involvements are linear and homogeneous. Although this pattern is helpful for qualitatively distinguishing inflammatory from infectious involvement, it

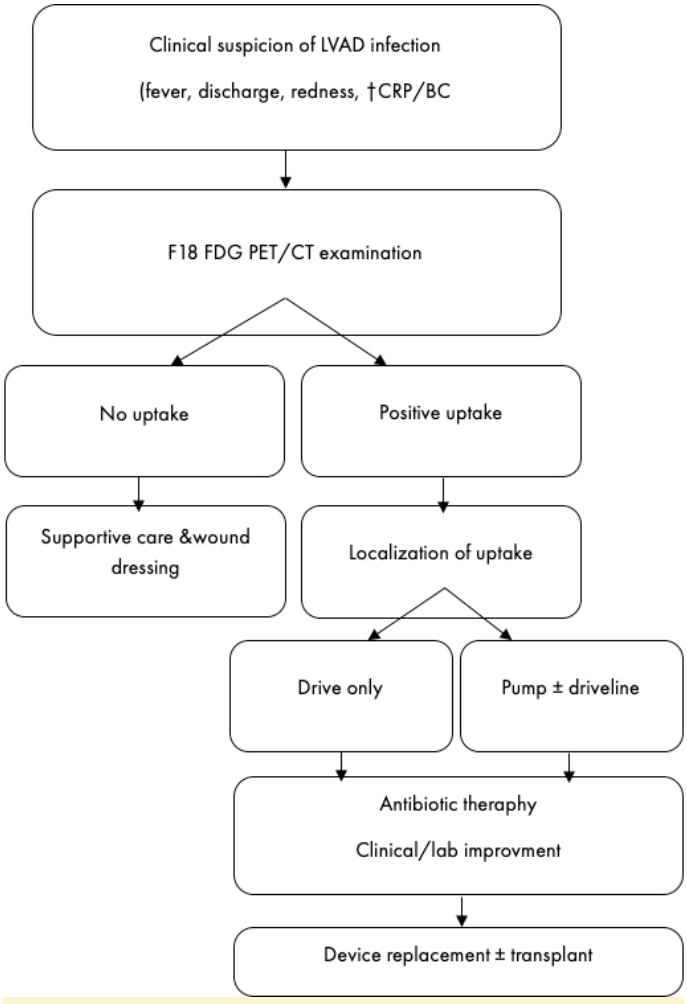

Figure 4. Flowchart: Management of LVAD Infections with F18 FDG-PET/CT.

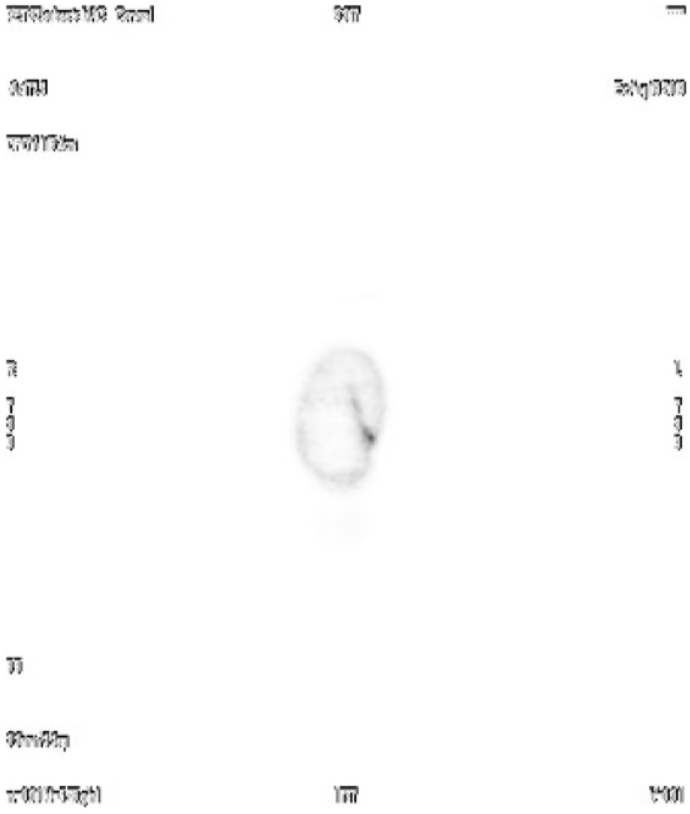

Figure 5. Slightly, linear FDG uptake in the driveline's proximal part and focal, severe distal. FDG uptake compatible with infection.

can sometimes be difficult to differentiate between the two.[13] For example, in our study, one patient (Patient 11) showed linear, mildly increased FDG uptake in the proximal part of the driveline and focal, intense FDG uptake in the distal part of the driveline (Figure 5). The patient was interpreted as PET-positive due to focal, intense involvement in the distal part, and subsequent microbiological culture demonstrated bacterial growth. Prospective studies with larger patient cohorts are needed to determine the cutoff SUV_{max} value that can be used semiquantitatively to differentiate infection from inflammatory involvement.

In addition to FDG-PET/CT, other complementary modalities such as echocardiography, conventional CT, magnetic resonance imaging (MRI), and microbiological cultures remain essential for the diagnosis and follow-up of LVAD infections. PET/CT adds particular value by providing early localization and metabolic characterization of the infection focus, which is often challenging with standard techniques.[4]

Conclusion

In conclusion, imaging with F18 FDG PET/CT is a highly sensitive modality with high positive and negative predictive values for the detection, localization, and characterization of different patterns of LVAD infections according to the causative pathogens, clinical scenarios, and distribution. The primary use of this imaging technique in LVAD infection can assist clinicians in management decisions and help identify patients who may require surgical intervention, device replacement, or emergency heart transplantation.

Ethics Committee Approval: Ethics committee approval was obtained from Ümraniye Training and Research Hospital Scientific Research Ethics Committee (Approval Number: B.10.1.TKH.4.34.H.GP.0.01/221, Date: 10.07.2025).

Informed Consent: Written informed consent was obtained from all participants prior to their inclusion in the study.

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

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Author Contributions: Concept – Y.O., B.E.A.; Design – Y.O., R.K.; Supervision – Y.O., A.T.; Materials – Y.O., A.T.; Data Collection and/or Processing – Y.O., R.K.; Analysis and/or Interpretation – Y.O., R.K.; Literature Review – Y.O., R.K.; Writing – Y.O., R.K.; Critical Review – Y.O., R.K., B.E.A.

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Central Sensitization Drives Symptom Burden in Microvascular Angina: A Cross-Sectional Case-Control Study

Mikrovasküler Anjinada Semptom Yükünde Santral Duyarlılığın Etkisi: Kesitsel Olgu-Kontrol Çalışması

ABSTRACT

Objective: Microvascular angina (MVA), a phenotype of ischemia with non obstructive coronary arteries, produces chest pain despite normal epicardial vessels. Central sensitization (CS) may amplify symptoms, but its magnitude in confirmed MVA is unclear.

Method: We conducted a single center cross sectional study. Adults with MVA undergoing coronary angiography and age- and sex matched healthy volunteers completed the Central Sensitization Inventory (CSI), Hospital Anxiety and Depression Scale (HADS), and chest pain questionnaires. MVA required documented ischemia with ≤ 50% epicardial stenosis. The primary outcome was the difference in mean CSI score; secondary outcomes were the proportion with CSI ≥ 40 and correlations between CSI, angina measures, and HADS subscores.

Results: We enrolled 200 participants; 138 (69%) were male; and the mean age was 61 ± 11 years. Mean CSI-Part A was higher in MVA versus controls (43 ± 15 vs. 19 ± 11; P < 0.001), and clinically significant CS was more prevalent (62% vs. 10%). Within MVA, CSI correlated with chest pain intensity (r = 0.58), weekly episode frequency (r = 0.46), HADS-Anxiety (r = 0.51), and HADS-Depression (r = 0.44) (all P < 0.001). In adjusted models, each 10-point increase in CSI was associated with a 0.47 standard deviation rise in pain score (β = 0.47, 95% confidence interval 0.29–0.64; P < 0.001); the model explained 39% of pain-score variance (R^2 = 0.39).

Conclusion: Central sensitization is highly prevalent and strongly linked to angina burden in MVA, supporting a heart brain contribution to symptom generation. Interventions that reduce central pain amplification may provide meaningful benefit beyond standard anti ischemic therapy.

Keywords: Central sensitization, chest pain amplification, coronary microvascular dysfunction, ischemia with non-obstructive coronary arteries, microvascular angina

ÖZET

Amaç: Obstrüktif olmayan koroner arterlerle seyreden iskeminin bir fenotipi olan mikrovasküler anjina (MVA), epikardiyal damarlar normal görünse bile göğüs ağrısına yol açabilir. Santral duyarlılık (SD) semptomları artırabilir; ancak doğrulanmış MVA'da büyüklüğü net değildir.

Yöntem: Tek merkezli, kesitsel bir çalışma yürütüldü. Koroner anjiyografi planlanan MVA'lı yetişkinler ve yaş cinsiyet uyumlu sağlıklı gönüllüler Santral Duyarlılık Envanteri'ni (SDE), Hastane Anksiyete ve Depresyon Ölçeği'ni (HAD) ve göğüs ağrısı anketlerini doldurdu. MVA tanısı, ≤ %50 epikardiyal darlık ile birlikte objektif iskemi kanıtını gerektirdi. Birincil sonlanım ortalama SDE skoru farkıydı; ikincil sonlanımlar SDE ≥ 40 prevalansı ile SDE'nin anjina ölçütleri ve HAD alt skorlarıyla korelasyonlarıydı.

Bulgular: Toplam 200 katılımcı dâhil edildi; 138'i (%69) erkekti; ortalama yaş 61 ± 11 yıldı. Ortalama SDE A skoru MVA'da kontrollere göre daha yüksekti (43 ± 15'e karşı 19 ± 11; P < 0,001); klinik olarak anlamlı SD daha sıktı (%62'ye karşı %10). MVA grubunda SDE, göğüs ağrısı şiddeti (r = 0,58), haftalık atak sıklığı (r = 0,46), HAD Anksiyete (r = 0,51) ve HAD Depresyon (r = 0,44) ile ilişkiliydi (tümü P < 0,001). Ayarlı modellerde SDE'deki her 10 puanlık artış, ağrı puanında 0,47 standart sapma artışla ilişkiliydi (β = 0,47; %95 güven aralığı 0,29–0,64; P < 0,001); model ağrı puanı varyansının %39'unu açıkladı (R^2 = 0,39).

Sonuç: SD, MVA'da yüksek prevalanslıdır ve anjina yüküyle güçlü biçimde ilişkilidir; bu durum semptom oluşumunda kalp beyin ekseninin katkısını destekler. Santral ağrı amplifikasyonunu azaltan müdahaleler, standart anti iskemik tedavinin ötesinde anlamlı yarar sağlayabilir.

Anahtar Kelimeler: Santral duyarlılık, göğüs ağrısı amplifikasyonu, koroner mikrovasküler disfonksiyon, obstrüktif olmayan koroner arterlerle iskemi, mikrovasküler anjina

ORIGINAL ARTICLE
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Microvascular angina (MVA) is now recognized as a major subgroup of ischemia with non obstructive coronary arteries (INOCA). Although epicardial coronaries appear normal, patients experience exertional or rest angina attributable to coronary microvascular dysfunction and have an elevated risk of myocardial infarction, stroke, and heart failure hospitalization.[1,2] Abnormalities in coronary flow reserve, microvascular spasm, and enhanced vasoconstrictor tone only partially explain the symptom burden; accumulating evidence implicates altered pain perception that may arise within the central nervous system.[3] Early studies in women with "cardiac syndrome X" (the historical term for MVA) demonstrated lower pain thresholds to peripheral stimuli compared with controls, suggesting a component of central pain amplification.[4]

Central sensitization (CS) is defined as an activity dependent increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, leading to amplified responses to peripheral inputs and the generation of pain hypersensitivity.[5] Originally characterized in experimental models, CS has since been shown to contribute to numerous chronic pain conditions, including visceral pain disorders that share clinical overlap with MVA (e.g., irritable bowel syndrome and fibromyalgia).[6] The Central Sensitization Inventory (CSI) is a 25 item self report questionnaire developed to screen for symptoms associated with CS; a score ≥ 40/100 is commonly used to indicate clinically significant central sensitization.[7] In a cohort of midlife women with INOCA, higher CSI scores were independently associated with greater angina burden and limited functional capacity, underscoring the relevance of CS in coronary microvascular disease.[8]

Despite these observations, the prevalence and magnitude of CS in patients with objectively confirmed microvascular angina remain poorly characterized. Understanding whether CS is heightened in MVA—and how it relates to chest pain severity, attack frequency, and psychosocial comorbidities—could reveal therapeutic targets beyond conventional anti ischemic therapy. Accordingly, this study aimed (i) to quantify central sensitization in patients with MVA using the CSI, comparing results with an age and sex matched healthy cohort, and (ii) to explore associations between CSI scores, chest pain characteristics, and anxiety–depression measures.

Materials and Methods

This single center, cross sectional study was conducted in the Cardiology Department of Selçuk University Faculty of Medicine over a six month period. Approval was obtained from the Selçuk University Faculty of Medicine Local Ethics Committee (Approval Number: 2025/177, Date: 26.03.2025), and all procedures conformed to the ethical standards of the Declaration of Helsinki. Written informed consent was secured from each participant before any study procedures were undertaken.

Participant Recruitment

Patient (Microvascular Angina) Group: Adults (≥ 18 years) presenting with chest pain or equivalent symptoms were screened consecutively at the time they were scheduled for diagnostic coronary angiography. To be included, patients had to show objective evidence of myocardial ischemia on prior non invasive testing (exercise treadmill, stress echocardiography, or myocardial perfusion scintigraphy) or invasive physiological assessment (coronary flow reserve or index of microcirculatory resistance) and demonstrate no epicardial coronary stenosis > 50% on angiography.

Healthy Control Group: Volunteers of similar age and sex distribution were recruited from staff and community advertisements. Controls had no history of cardiovascular disease, chronic pain syndromes, or regular analgesic use, and met the same consent and language requirements as patients.

Inclusion and Exclusion Criteria

Participants were eligible if they were aged 18 years or older, capable of reading Turkish, and able to understand and complete self report questionnaires. Exclusion criteria for both groups comprised: (i) significant structural heart disease (e.g., severe valvular pathology or left ventricular ejection fraction < 40%), (ii) previously diagnosed widespread chronic pain conditions such as fibromyalgia, (iii) major uncontrolled psychiatric disorders (e.g., bipolar disorder) that could compromise data reliability or informed consent, (iv) cognitive or communication impairment precluding questionnaire completion, (v) age under 18 or legal incapacity to consent, and (vi) any clinical circumstance judged by the investigators to pose safety or ethical concerns (such as recent major trauma or the immediate postoperative period). For the patient group specifically, detection of > 50% epicardial stenosis on angiography excluded the diagnosis of microvascular angina and hence study participation.

Data Collection

After consent, each participant completed the following instruments under investigator supervision in a quiet room:

1. Central Sensitization Inventory (CSI, Parts A and B): The Turkish validated version, which has proven reliability and internal consistency in chronic pain populations, was used.[9] Consistent with the original validation, we defined clinically significant central sensitization as CSI Part A ≥ 40/100—the receiver operating characteristic-derived (ROC-derived) threshold that best discriminated central sensitivity syndromes from non-patient controls (area under the curve [AUC]: 0.86; sensitivity: 81%; specificity: 75%) and which also performed well in the Turkish validation (sensitivity: 87%, specificity: 90%).[9,10] For reader convenience, open access links to the Turkish CSI instrument and the validation paper are provided in the references.[11]
2. Chest Pain Assessments: Patients reported average chest pain severity during the preceding four weeks on an eleven point numeric rating scale (0 = no pain, 10 = worst imaginable) and the mean number of pain episodes per week.

ABBREVIATIONS

CSI	Central Sensitization Inventory
HADS	Hospital Anxiety and Depression Scale
INOCA	Ischemia with non-obstructive coronary arteries
MVA	Microvascular angina
ROC-derived	Receiver operating characteristic-derived
WISE	Women's Ischemia Syndrome Evaluation

Table 1. Baseline characteristics and laboratory findings

Variable	MVA (n = 100)	Controls (n = 100)	*P*†
Age, years	61.4 ± 11.0	60.8 ± 10.5	0.56
Male sex, n (%)	70 (70)	68 (68)	0.74
BMI, kg m^{-2}	27.8 ± 3.8	27.5 ± 3.6	0.48
SBP, mmHg	114 ± 10	113 ± 11	0.44
DBP, mmHg	69 ± 7	69 ± 7	0.95
HR, min^{-1}	75 ± 14	74 ± 13	0.63
HTN, n (%)	35 (35)	32 (32)	0.66
DM, n (%)	21 (21)	19 (19)	0.72
Dyslip., n (%)	38 (38)	36 (36)	0.78
Smoking, n (%)	25 (25)	23 (23)	0.73
Obesity, n (%)	18 (18)	17 (17)	0.85
Anxiety/Dep., n (%)	15 (15)	13 (13)	0.68
Urea, mg dL^{-1}	35.0 ± 15.2	34.3 ± 14.7	0.72
Cr, mg dL^{-1}	0.90 ± 0.26	0.88 ± 0.24	0.59
Na, mmol L^{-1}	137.7 ± 3.1	137.9 ± 3.0	0.68
K, mmol L^{-1}	4.40 ± 0.39	4.38 ± 0.37	0.77
Hb, g dL^{-1}	14.0 ± 1.7	14.1 ± 1.6	0.65
WBC, 10^3 µL^{-1}	7.9 ± 2.3	7.8 ± 2.2	0.83
TC, mg dL^{-1}	189 ± 38	185 ± 35	0.47
LDL C, mg dL^{-1}	118 ± 31	116 ± 29	0.66
HDL C, mg dL^{-1}	46 ± 11	47 ± 10	0.53
TG, mg dL^{-1}	150 ± 60	148 ± 58	0.82

†: Independent t test for continuous variables; χ^2 test for categorical variables. Anxiety/Dep., History of anxiety or depression; BMI, Body mass index; Cr, Creatinine; DBP, Diastolic blood pressure; DM, Diabetes mellitus; Dyslip., Dyslipidemia; Hb, Hemoglobin; HR, Heart rate; HTN, Hypertension; K, Potassium; MVA, Microvascular angina; Na, Sodium; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WBC, White blood cell count.

3. Hospital Anxiety and Depression Scale (HADS): Separate subscores for anxiety (HADS A) and depression (HADS D) were recorded. We used the Turkish validated version; open access links to the validation citation and a publicly available Turkish HADS form are provided in the references.[12,13]
4. Clinical and Demographic Variables: Age, sex, body mass index, cardiovascular risk factors, and current medications were extracted from medical charts.

Questionnaire booklets carried only study codes; no identifying information was recorded on research forms. Completed forms were stored in a locked filing cabinet, and electronic data were entered into a password protected database accessible only to the research team. Participants were free to withdraw at any stage without consequences for clinical care.

Outcomes

The primary outcome was the difference in mean CSI score between the microvascular angina and healthy control groups. Secondary outcomes included (i) the proportion of individuals in each group with a CSI score ≥ 40 (threshold suggestive of clinically relevant central sensitization) and (ii) correlations between CSI scores and chest pain severity, pain episode frequency, and HADS subscores within the patient cohort.

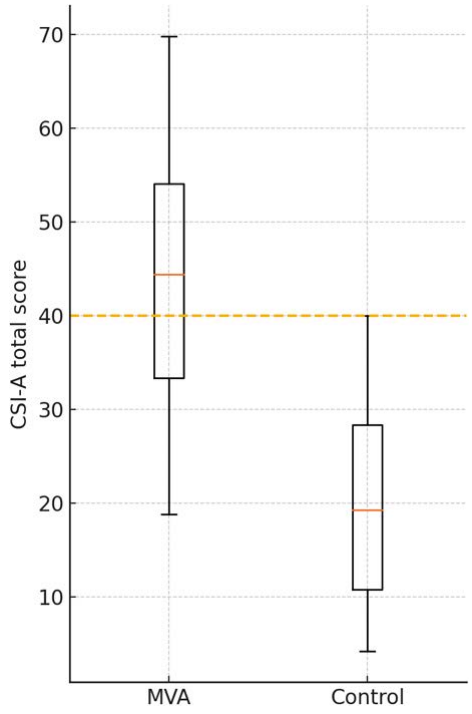

Figure 1. Markedly higher CSI A scores in microvascular angına.

Median CSI A was 44 (IQR 33–54) in the MVA group versus 19 (IQR 11–28) in controls (P < 0.001); 62 % of patients, but only 10 % of controls, scored ≥ 40 (dashed line), indicating clinically significant central sensitization.

Statistical Analysis

Continuous variables were tested for normality using the Shapiro–Wilk statistic. Between group comparisons employed independent samples t tests for normally distributed data and Mann–Whitney U tests when distributions were non normal. Categorical variables were compared with the χ^2 test. Pearson or Spearman correlation coefficients, as appropriate, quantified associations between CSI scores and clinical or psychosocial measures. Multivariable linear regression, adjusted for age, sex, and body mass index, assessed the independent relationship between CSI score and chest pain severity. A two sided P value < 0.05 denoted statistical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline demographic, clinical, and laboratory features were similar in the two study groups (Table 1). The mean age was 61 ± 11 years, and 69% of participants were male. The prevalence of traditional cardiovascular risk factors—including hypertension (35% in the microvascular angina [MVA] group vs. 32% in controls), diabetes mellitus (21% vs. 19%), dyslipidemia (38% vs. 36%), and current or former smoking (25% vs. 23%)—did not differ significantly (all P > 0.05). Body mass index, blood pressure values, heart rate, renal indices, electrolytes, full blood count, and lipid profile were likewise comparable, indicating that the two cohorts were well matched at baseline.

Despite these similarities, the burden of central sensitization diverged sharply. Mean Central Sensitization Inventory Part A

Table 2. Central sensitization outcomes

Outcome	MVA (n = 100)	Controls (n = 100)	*P*†
CSI A, mean ± SD	**43 ± 15**	19 ± 11	<0.001
CSI A ≥ 40, n (%)	**62 (62)**	10 (10)	<0.001
CSI B positive‡, n (%)	**46 (46)**	15 (15)	<0.001

†: Independent t test or χ^2 test. ‡: At least one physician diagnosed sensitization related condition. CSI A, Central Sensitization Inventory Part A total score; CSI B, Central Sensitization Inventory Part B.

Table 3. Correlation of Central Sensitization Inventory Part A scores (CSI A) with pain and psychosocial variables in patients with microvascular angina (MVA)

Variables	r	*P*
NRS pain score	0.58	<0.001
Weekly angina episodes	0.46	<0.001
HADS A	0.51	<0.001
HADS D	0.44	<0.001

HADS A, Hospital Anxiety and Depression Scale—Anxiety; HADS D, Hospital Anxiety and Depression Scale—Depression; NRS, Numeric rating scale; r, Pearson (continuous) or Spearman (count) correlation coefficient.

(CSI A) score was 43 ± 15 in the MVA cohort versus 19 ± 11 in controls (P < 0.001), and 62% of MVA patients but only 10% of controls scored ≥ 40—the established cut off for clinically relevant sensitization (Table 2). The entire score distribution was visibly shifted upward in MVA, as depicted by the side by side box plot (Figure 1). Consistent with the questionnaire findings, 46% of MVA patients reported at least one physician diagnosed sensitization related condition on CSI Part B, compared with 15% of controls (P < 0.001).

Higher CSI A scores were closely associated with symptom burden. Within the MVA group, CSI A correlated strongly with chest pain intensity on the 0–10 numeric rating scale (r = 0.58, P < 0.001) and with the weekly frequency of angina episodes (r = 0.46, P < 0.001). Significant positive correlations were also observed with anxiety (HADS A, r = 0.51) and depression (HADS D, r = 0.44) subscores (all P < 0.001) (Table 3). The scatter plot with regression line and 95% confidence band (Figure 2) visually underscores the linear relationship between CSI A and pain severity.

Multivariable linear regression confirmed central sensitization as an independent determinant of angina intensity. After adjusting for age, sex, body mass index, and hypertension, each 10 point increase in CSI A was associated with a 0.47 standard deviation rise in chest pain score (β = 0.47, 95% CI: 0.29–0.64, P < 0.001), whereas none of the conventional covariates retained statistical significance (Table 4). The model explained 39% of the variance in pain scores, highlighting the prominent contribution of central pain amplification to the symptomatic burden of microvascular angina.

Table 4. Multivariable predictors of chest pain severity in microvascular angina (MVA) (linear regression)

Predictor	β	95% CI	*P*
CSI A (per 10 pt)	0.47	0.29–0.64	<0.001
Age (per year)	0.06	–0.03–0.15	0.18
Sex (male)	–0.04	–0.30–0.22	0.75
BMI (kg m^{-2})	0.08	–0.02–0.18	0.11
HTN (yes)	0.03	–0.20–0.27	0.79

Model R^2 = 0.39, P < 0.001. β, Standardized regression coefficient; CI, Confidence interval.

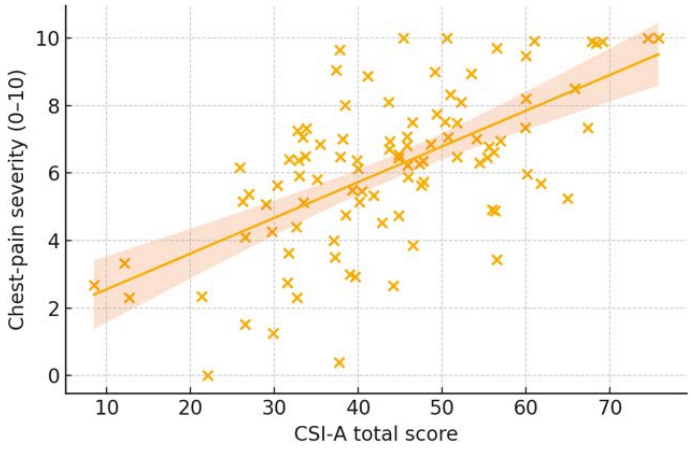

Figure 2. Central sensitization correlates with angina burden.

Higher CSI A scores were associated with greater chest pain severity in the MVA cohort (r = 0.62, P < 0.001); the shaded band denotes the 95% confidence interval for the regression line.

Discussion

Microvascular angina is rooted in structural and functional abnormalities of the coronary microcirculation—endothelial nitric oxide dysregulation, small vessel remodeling, impaired coronary flow reserve, heightened endothelin 1 activity, and microvascular spasm—all of which produce true myocardial ischemia despite angiographically normal epicardial vessels.[14] At the same time, mounting neurobiological evidence shows that repeated ischemic afferent traffic, neuroinflammation, and diminished descending inhibitory control promote central sensitization: an activity dependent amplification of nociceptive signaling in the dorsal horn, thalamus, and cortical pain matrix.[3,15,16] Once established, CS lowers somatic and visceral pain thresholds, recruits "silent" nociceptors, and couples with limbic circuits to magnify the affective dimension of pain, thereby explaining why MVA patients frequently report severe, poorly localized chest discomfort out of proportion to ischemic burden.[10]

Notably, although INOCA/MVA is more prevalent in women, our consecutive, angiography based sampling yielded a male predominant cohort (≈ 70%). This pattern likely reflects referral practices to tertiary invasive testing; however, the under representation of women is a major constraint on generalizability—particularly to Turkish women—who experience documented diagnostic delay and undertreatment.[1,2,14] Accordingly, our estimates of the association between central sensitization and angina should be interpreted with caution for women, and future studies should purposively enrich recruitment of women and be adequately powered for sex stratified analyses.

Unlike obstructive coronary artery disease, MVA offers no stenotic target for percutaneous or surgical revascularization; consequently, patients often remain symptomatic despite guideline directed anti ischemic therapy (β blockers, calcium channel blockers, nitrates).[17] Many cycle through emergency departments, stress laboratories, and catheterization suites with persistently disabling angina, highlighting an unmet need for alternative approaches. Small scale trials with ranolazine, ivabradine, and, more recently, the endothelin A antagonist zibotentan have yielded mixed or modest benefits, underscoring the therapeutic challenge.[1,17-20]

Coronary microvascular dysfunction and CS are not mutually exclusive but mutually reinforcing. Repeated subendocardial ischemia can serve as a persistent peripheral nociceptive driver that maintains central hyperexcitability, whereas CS, by amplifying spinothalamic traffic and heightening interoceptive vigilance, exaggerates the cortical representation of otherwise modest ischemic signals.[21] This interplay raises the therapeutic hypothesis that agents with proven anti sensitizing properties—serotonin–noradrenaline reuptake inhibitors such as duloxetine, gabapentinoids (gabapentin, pregabalin), and tricyclics—as well as non pharmacological modalities like cognitive behavioral therapy or mindfulness based stress reduction, could attenuate chest pain severity in MVA.[9,21-24]

Our findings accord with several recent investigations. In the Women's Ischemia Syndrome Evaluation (WISE) and in an independent INOCA cohort, higher Central Sensitization Inventory scores independently tracked with angina frequency, exercise intolerance, and diminished quality of life, mirroring the strong correlations we observed between CSI, pain intensity, and Hospital Anxiety–Depression Scale scores.[8] Functional neuroimaging studies demonstrate heightened insular and anterior cingulate activation during adenosine induced chest pain in MVA, consistent with central amplification.[25] Conversely, a large Scandinavian registry linked low pain tolerance to obstructive coronary artery disease rather than INOCA, challenging a unifying CS explanation.[26,27] Methodological heterogeneity (small sample sizes, different pain threshold protocols, female only versus mixed cohorts), and the absence of formal CS metrics in negative studies may underlie these discrepancies.

Limitations

Several caveats must be acknowledged when interpreting our findings. First, the cross sectional design precludes any inference of causality—heightened Central Sensitization Inventory scores may contribute to, result from, or simply coexist with microvascular angina; only longitudinal or interventional studies can disentangle directionality. Second, this was a single center study in a tertiary care cardiology clinic that largely serves a referral population. Consequently, disease severity, psychosocial comorbidity, and health seeking behavior may differ from those in primary care or community settings, limiting generalizability. Although INOCA/MVA is more prevalent in women, our sample was predominantly male (~70%). This likely reflects referral patterns to our tertiary, angiography based clinic, where men undergo invasive evaluation more often; however, the under representation of women is a major limitation and reduces the generalizability of our findings to the broader Turkish INOCA population. Importantly, symptomatic women are frequently diagnosed later and are less likely to receive guideline directed testing and therapy, which may perpetuate symptom burden and healthcare use. If the relationship between central sensitization and angina differs by sex, our effect estimates may also be biased. Future work should purposively enrich recruitment of women, pre specify sex stratified analyses, and be adequately powered to test sex–by–central sensitization interactions.

Third, although we screened consecutively, the sample size was modest and predominantly male (≈ 70%), whereas epidemiological data show that INOCA/MVA is more prevalent in women; sex specific mechanisms could therefore be under represented. Fourth, both central sensitization and chest pain metrics relied on self report instruments (CSI, numeric pain rating, HADS), introducing recall and reporting bias. Objective corroboration—quantitative sensory testing, functional neuroimaging, or ambulatory myocardial ischemia monitoring—was not performed and would strengthen future work.

Fifth, we excluded patients with recognized chronic pain syndromes to isolate the contribution of CS to MVA, yet this may have underestimated the real world prevalence of CS in an unselected INOCA population where fibromyalgia and irritable bowel syndrome are common. Sixth, despite multivariable adjustment, residual confounding remains possible: unmeasured factors such as sleep disturbance, autonomic dysfunction, socioeconomic stress, and antidepressant or opioid use could influence both CSI scores and angina perception.

Seventh, the control group comprised volunteer hospital staff and community respondents, raising the possibility of a "healthy worker" effect and socioeconomic mismatch relative to patients. Eighth, our diagnostic definition of MVA was based on conventional angiography plus prior non invasive or invasive evidence of ischemia; we did not perform systematic coronary flow reserve or acetylcholine testing in every participant, so a degree of physiological heterogeneity is likely. Finally, we lacked longitudinal follow up, preventing assessment of whether elevated CSI predicts downstream outcomes such as emergency department utilization, quality of life trajectories, or incident heart failure. Collectively, these limitations underscore the need for larger, multicenter, prospective studies incorporating objective neurosensory assessments and interventional trials targeting central sensitization in MVA.

Conclusion

In conclusion, our study is the first to demonstrate—using a validated Turkish version of the CSI—that clinically significant central sensitization is nearly six times more prevalent and markedly more severe in objectively confirmed MVA than in matched healthy controls, and that CS explains almost 40% of the variance in angina intensity beyond traditional cardiovascular covariates.[28] These data shift the therapeutic lens from an exclusively coronary focus to a heart–brain axis, opening avenues for trials of centrally acting analgesic and behavioral interventions in MVA. Clarifying whether attenuating CS translates into fewer emergency visits, better exercise capacity, and improved health related quality of life could substantially enrich future INOCA management guidelines and benefit a patient population that remains undertreated and often misunderstood.

Ethics Committee Approval: Ethics committee approval was obtained from Selçuk University Faculty of Medicine Local Ethics Committee (Approval Number: 2025/177, Date: 26.03.2025).

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Introducing the Digital Disparity Index: Regional Alignment Between Online Search Trends and Cardiovascular Disease Burden in Türkiye

Dijital Eşitsizlik Endeksi'nin Tanıtımı: Türkiye'de Çevrimiçi Arama Trendleri ile Kardiyovasküler Hastalık Yükü Arasındaki Bölgesel Uyum

ABSTRACT

Objective: Cardiovascular diseases are a leading health problem in Türkiye and worldwide. Digital platforms now offer ways to gauge public awareness through internet searches. This study explores how cardiovascular search trends align with regional epidemiological data in Türkiye and whether such data can indicate awareness and disease burden. Terms were chosen for clinical relevance and "related queries." Since Google Trends reports relative interest, this is noted as a limitation.

Method: Google Trends data for five terms ("coronary artery disease," "heart attack," "ischemic heart disease," "stent," "heart failure") were collected for Türkiye's seven regions and 81 provinces between January 2020 and July 2025. Term selection was based on guidelines and related queries; synonyms were not fully reviewed. Data were compared with prevalence, mortality, and disability-adjusted life years (DALYs) from national and global sources. Correlation and regression analyses assessed associations. A prototype Digital Disparity Index (DDI) combined disease burden, search activity, and socioeconomic context.

Results: Search activity correlated with epidemiological indicators, with the strongest associations in the Marmara and Aegean regions (Pearson's $r = 0.68$, $P < 0.01$). Some eastern provinces showed high burden but low search activity. Regression analysis indicated that search interest explained 46% of the variance in prevalence ($R^2 = 0.46$, $P < 0.01$). The DDI highlighted Eastern and Southeastern Anatolia as high-disparity areas.

Conclusion: Internet search data reflect awareness and cardiovascular burden in Türkiye and may support public health planning. The DDI helps identify areas where burden is high but awareness is low. Broader term inclusion, multilingual coverage, and validation with clinical outcomes are needed in future research.

Keywords: Cardiovascular diseases, information-seeking behavior, internet, infodemiology, socioeconomic factors, Türkiye

ÖZET

Amaç: Kardiyovasküler hastalıklar, Türkiye'de ve dünya çapında önde gelen bir sağlık sorunudur. Dijital platformlar artık internet aramaları yoluyla halkın farkındalığını ölçmenin yollarını sunmaktadır. Bu çalışma, kardiyovasküler arama eğilimlerinin Türkiye'deki bölgesel epidemiyolojik verilerle nasıl uyumlu olduğunu ve bu verilerin farkındalık ve hastalık yükünü gösterip göstermediğini araştırmaktadır. Terimler, klinik alaka düzeyi ve "ilgili sorgular" dikkate alınarak seçilmiştir. Google Trends göreceli ilgiyi raporladığı için, bu bir sınırlama olarak belirtilmiştir.

Yöntem: Ocak 2020 ile Temmuz 2025 arasında Türkiye'nin yedi bölgesi ve 81 ili için beş terim ("koroner arter hastalığı", "kalp krizi", "iskemik kalp hastalığı", 'stent', "kalp yetmezliği") için Google Trends verileri toplanmıştır. Seçim, kılavuzlar ve ilgili sorgulara dayalı olarak yapılmıştır; eşanlamlılar tam olarak incelenmemiştir. Veriler, ulusal ve küresel kaynaklardan elde edilen prevalans, mortalite ve sakatlık ayarlı yaşam yılları (DALY) ile karşılaştırılmıştır. Korelasyon ve regresyon analizleri ile ilişkiler değerlendirilmiştir. Bir prototip Dijital Eşitsizlik Endeksi (DDI), hastalık yükü, arama etkinliği ve sosyoekonomik bağlamı birleştirmiştir.

Bulgular: Arama aktivitesi, epidemiyolojik göstergelerle korelasyon gösterdi; en güçlü korelasyon Marmara ve Ege bölgelerinde görüldü (Pearson's $r = 0,68$, $P < 0,01$). Bazı doğu illeri yüksek yük, ancak düşük arama sayıları gösterdi. Regresyon analizi, arama ilgisinin prevalans varyansının %46'sını açıkladığını gösterdi ($R^2 = 0,46$, $P < 0,01$). DDI, Doğu ve Güneydoğu Anadolu'yu yüksek eşitsizlik alanları olarak öne çıkarmıştır.

ORIGINAL ARTICLE
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Sonuç: İnternet arama verileri, Türkiye'deki farkındalık ve kardiyovasküler yükü yansıtmakta ve halk sağlığı planlamasını destekleyebilir. DDI, yükün yüksek ancak farkındalığın düşük olduğu alanları belirlemeye yardımcı olur. Gelecekteki araştırmalarda daha geniş terimler, çok dilli kapsam ve klinik sonuçlarla doğrulama gereklidir.

Anahtar Kelimeler: Kardiyovasküler hastalıklar, bilgi arama davranışı, infodemioloji, internet, sosyoekonomik faktörler; Türkiye

Cardiovascular diseases (CVDs) remain the foremost cause of global morbidity and mortality, with Türkiye facing significant regional disparities in prevalence and outcomes. Coronary artery disease, heart failure, and related conditions account for over 35% of annual deaths nationwide, based on the most recent 2018–2023 Turkish Statistical Institute data, which indicate that circulatory system diseases caused 35.48% of all deaths in 2023.[1]

With the rapid expansion of digital technology, public health surveillance has embraced novel data sources such as internet search queries and social media activity to capture population health trends more dynamically than traditional reporting systems.[2] Google Trends, a widely accessible tool, enables the monitoring of search term frequencies over time and across regions, providing insights into public interest and awareness related to specific health conditions.[3,4]

Digital epidemiology has proven especially useful in infectious disease surveillance, with influenza-like illness and Coronavirus Disease 2019 (COVID-19) demonstrating that increases in search activity can precede confirmed case surges.[2-5] However, the application of digital search data to chronic diseases such as CVDs remains underexplored, despite the potential to track symptom awareness and information-seeking behavior in real time.[6]

Türkiye exhibits marked regional disparities in disease burden and healthcare access, making localized data essential for tailored public health interventions.[7,8] Integrating digital search data with epidemiological indicators could offer a comprehensive view of public awareness and disease prevalence, informing targeted health policies.[6]

This study aims to analyze Google Trends search data for cardiovascular-related terms across Türkiye's seven geographic regions and 81 provinces from 2020 to 2025. By correlating these digital trends with regional epidemiological data on disease prevalence, mortality, and disability-adjusted life years (DALYs), we evaluate the utility of digital epidemiology as a complementary tool for public health monitoring and strategic planning.[8,9]

Türkiye's heterogeneous digital literacy and internet penetration (ranging from 85% in Marmara to 55% in Eastern Anatolia) create unique opportunities to study how digital engagement aligns with disease burden. The findings aim to inform targeted public health strategies and assess digital data's role in CVD surveillance. Furthermore, to better characterize regional differences in digital health engagement, we introduce a novel Digital Disparity Index (DDI), which integrates search activity, socioeconomic indicators, and disease burden metrics to quantitatively identify regions where digital engagement may underestimate true health needs. We explicitly note that Google Trends reports relative interest and does not identify the "most-used" terms for a topic; our term selection therefore prioritizes clinical relevance and transparency and is treated as a study limitation.

ABBREVIATIONS

CAD	Coronary artery disease
COVID-19	Coronavirus Disease 2019
CVD	Cardiovascular disease
DDI	Digital Disparity Index
IHD	Ischemic heart disease
RSV	Relative search volume
SES	Socioeconomic status

Materials and Methods

Study Design and Setting

This ecological observational study analyzed the relationship between public digital search behavior regarding cardiovascular diseases and epidemiological burden across Türkiye's seven geographical regions and 81 provinces between 2020 and 2025.

Data Sources

1. Digital Data

Google Trends was used to extract monthly average relative search volume (RSV: 0–100) for five cardiovascular-related terms: "coronary artery disease" (CAD), "heart attack," "ischemic heart disease" (IHD), "stent," and "heart failure." A value of 100 represents the peak search interest within the specified time range and geographic region. Data were stratified by the seven regions and 81 provinces. Term selection followed a simple rule set: (i) alignment with cardiology guideline terminology, (ii) inspection of Google Trends "related queries" to avoid idiosyncratic phrasing, and (iii) preference for canonical, clinically unambiguous labels. We did not attempt to identify the "most frequently used" search terms because Google Trends does not provide absolute counts or a comprehensive ranking, and we did not include exhaustive synonyms; this is acknowledged as a limitation. Primary analyses used these five canonical terms; any additional symptom or risk-factor terms (e.g., "chest pain," "high cholesterol," "arrhythmia") are exploratory signals not included in inferential statistics and are presented descriptively when shown in Table 1 or Figures 1, 2.

Artificial intelligence (AI) assistance and reproducibility: ChatGPT was used only to generate and refactor retrieval scripts (e.g., via pytrends/gtrendsR) and to automate parameterized queries (geo = TR, time = 2020-01-01 to 2025-07-31, monthly frequency). All data pulls were executed locally by the authors; no inferential statistics or decisions were delegated to AI. Query parameters, term lists, and export settings are fully specified herein to ensure reproducibility.

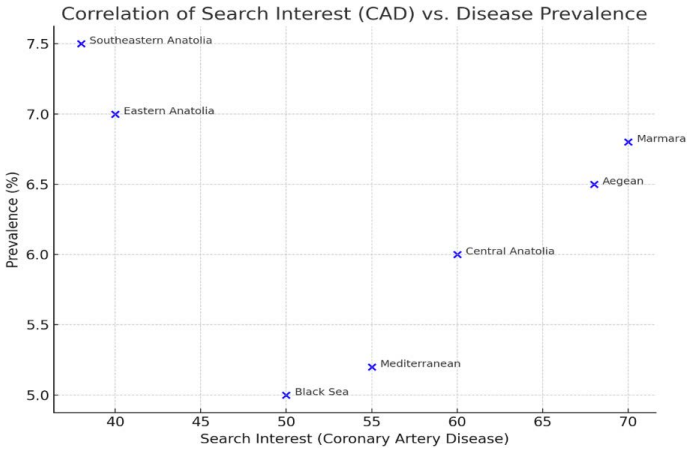

Figure 1. Correlation scatterplot of search interest vs. disease prevalence.

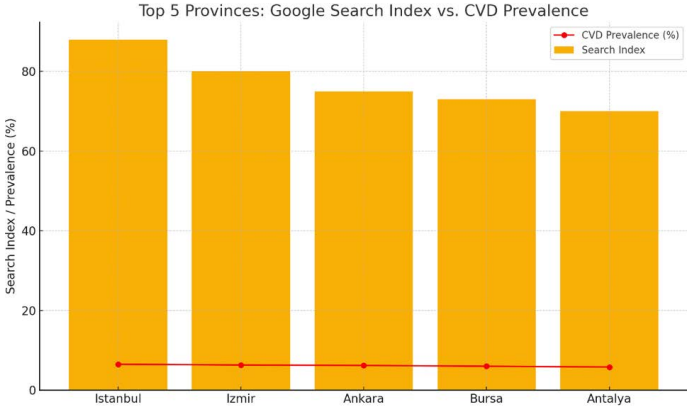

Figure 2. Comparison of Google search interest and cardiovascular disease prevalence in the top five Turkish provinces.

2. Epidemiological Data

Regional prevalence, mortality rates, and DALYs related to IHD and cardiovascular conditions were collected from the Global Burden of Disease Study, Turkish Statistical Institute (TURKSTAT) death records, the Turkish National Burden of Disease Study, and national cardiovascular surveillance reports (TEKHARF, STEPS).[1,7,10] All data were publicly available, anonymized, and aggregated; therefore, ethics review was not required.

3. Socioeconomic Covariates (for DDI Framework)

To contextualize digital engagement, the DDI incorporates socioeconomic structure using region- or province-level proxies where available (e.g., household income or poverty ratio, tertiary education share, and internet access/usage). When only regional—and not provincial—values were available, we used regional indices for the DDI demonstration and note this as a limitation.

Digital Disparity Index: Operational Definition

We define a prototype DDI that increases when disease burden is high and digital/ socioeconomic status (SES) engagement is low. Variables are z-scored at the target geography (region/province):

- Burden_z = z(mean of standardized prevalence, mortality, DALY)

Table 1. Regional distribution of Google Trends scores and cardiovascular disease metrics

Region	CAD	Heart attack	IHD	Stent	HF	Chest pain	High chol.	Arrhythmia	Heart-death	Treatments	Prevalence (%)	Mortality (per 100k)	Daly (per 100k)
Marmara	70	85	65	60	55	75	65	50	45	60	6.8	120	1800
Aegean	68	80	63	58	50	70	60	45	40	55	6.5	115	1750
Mediterranean	55	60	50	45	40	50	45	40	35	40	5.2	110	1600
Central Anatolia	60	65	55	50	45	55	50	42	38	48	6.0	118	1720
Black Sea	50	55	48	43	52	58	40	47	35	45	5.0	112	1580
Eastern Anatolia	40	45	38	35	30	35	25	30	28	30	7.0	130	1900
Southeastern Anatolia	38	40	35	32	28	30	20	25	22	28	7.5	135	1950

*RSV timeframe: Jan 2020–Jul 2025. Epidemiological metrics reflect the latest available regional/provincial sources cited in the text. "CVD mortality (search term)" denotes an RSV-based signal and was not used in primary inferential analyses. CAD, Coronary artery disease; HF, Heart failure; IHD, Ischemic heart disease. RSV denotes relative search volume (0–100). "Prevalence (%)" corresponds to IHD prevalence; "Mortality" and "DALY" represent cardiovascular disease metrics per 100k. Columns "Chest Pain," "High Chol.," "Arrhythmia," "Heart-Death," and "Treatments" reflect exploratory digital signals and were not used in primary inferential analyses.

- Search_z = z(mean RSV across the five primary terms)
- SES_z = z(composite of income and education; higher = better SES)

DDI = (Burden_z − Search_z − SES_z) / 3. A higher DDI denotes greater "digital disparity" (i.e., high burden with low search engagement and lower SES). This formula and its components are provided to enable replication and refinement in future work; weighting can be adjusted (e.g., policy-driven weights) in subsequent validations.

Statistical Analysis

All statistical analyses were performed using R (v4.2.1) and SPSS (v28, IBM Corp., Armonk, NY, USA). Descriptive statistics summarized digital search interest and epidemiological indicators. Pearson and Spearman correlations assessed associations between search volume and burden metrics; simple linear regression quantified the predictive capacity of search trends for prevalence. A two-tailed significance level of $P < 0.05$ was considered statistically significant. No AI system performed statistical computation; scripts and outputs were reviewed by two analysts for consistency.

Results

Regional Search Trends and Epidemiological Burden

Google Trends analysis revealed that the Marmara and Aegean regions consistently exhibited the highest search interest for cardiovascular terms, whereas Eastern and Southeastern Anatolia showed lower search volumes despite higher burden metrics. The highest activity appeared in Marmara (mean RSV ≈ 70 for "CAD") and the Aegean, and the lowest in Southeastern Anatolia (mean ≈ 28 for "heart failure"). Eastern provinces (e.g., Hakkâri) showed high CVD burden but low search interest (Table 1).[1,10] At the provincial level, Istanbul and Izmir demonstrated strong concordance between epidemiological burden and RSV, whereas Hakkâri and Şırnak illustrated burden–engagement mismatch.

Correlation and Regression

Significant positive correlations were observed between search interest and prevalence (Pearson's $r = 0.68$, $P < 0.01$), mortality ($r = 0.54$, $P = 0.03$), and DALYs ($r = 0.60$, $P = 0.02$). Associations were strongest in Marmara ($r = 0.68$) and the Aegean ($r = 0.62$, $P < 0.01$) and weaker in Eastern Anatolia ($r = 0.20$, $P = 0.12$). Regression models indicated that search interest explained ~46% of the variance in regional IHD prevalence ($R^2 = 0.46$, $P < 0.01$). The prototype DDI, computed with available regional SES proxies, ranked Eastern and Southeastern Anatolia as the highest-disparity areas; this aligns with the observed mismatch between burden and digital engagement.

Discussion

Our findings support the utility of Google search behaviors as indicators of CVD epidemiology in Türkiye,[6,8,9] extending digital epidemiology from infectious to chronic diseases.[2-5] Beyond internet penetration, socioeconomic structure (income, education) likely contributes to regional differences in digital engagement; the DDI explicitly integrates these factors to better characterize where digital signals underrepresent true burden.

Platform bias may influence findings, as Google-based data may not represent older adults or individuals with limited access.[6,9] The correlations suggest that online health information-seeking mirrors disease burden in well-connected regions, with acute-event terms (e.g., "heart attack") showing higher sensitivity. A more balanced emphasis on province-level signals (e.g., Hakkâri, Şırnak vs. Istanbul, Izmir) can guide targeted, local interventions rather than region-only strategies. Methodologically, we clarify how ChatGPT was used (code generation/automation only) to enhance reproducibility and transparency; all analyses and decisions were human-led.

A critical issue is the "black box" nature of some AI tools; lack of explainability can undermine trust and actionability. For public health deployment, transparent term sets, open formulas (e.g., DDI definition), and auditable pipelines should be standard.

To illustrate the potential utility of the DDI, consider a scenario in which Eastern Anatolia exhibits a high DDI score, reflecting a heavy cardiovascular burden but low digital engagement. Regional health authorities could interpret this signal as a call to prioritize awareness campaigns through traditional media (e.g., radio, television) and to deploy mobile screening units for hypertension and dyslipidemia. Conversely, a province such as Izmir with a low DDI could benefit from advanced digital interventions, such as targeted social media education or AI-driven risk calculators integrated into e-health portals. Thus, the DDI can act as a translational tool linking digital epidemiology metrics to concrete, region-specific public health actions and resource allocation.

Limitations

Unequal internet access and the ecological design constrain inference. Google Trends does not provide absolute query counts or identify the "most-used" terms; our five canonical terms were selected for clinical clarity rather than popularity ranking. We did not exhaustively test synonyms or non-Google platforms (e.g., Yandex), which may be relevant in certain locales. Digital literacy was incorporated via SES proxies at the regional level for the DDI prototype; comprehensive provincial metrics were not uniformly available. Use of ChatGPT was limited to code generation; nonetheless, potential biases in AI-assisted data handling are acknowledged and mitigated by full parameter disclosure and human verification. Future studies should employ longitudinal designs, integrate multiple platforms and multilingual terms, and use advanced learning models for nowcasting and forecasting.

Ethics Committee Approval: All data were publicly available, anonymized, and aggregated; therefore, ethics review was not required.

Informed Consent: Written informed consent was not required.

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

Funding: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: ChatGPT assisted with generating and refactoring scripts for Google Trends retrieval (e.g., pytrends/gtrendsR) and workflow automation; all data pulls and statistical analyses were executed locally by the authors, and no inferential steps were delegated to AI.

Author Contributions: Concept – H.G., A.B.D.; Design – H.G., A.B.D.; Supervision – H.G., A.B.D.; Resource – H.G., A.B.D.; Materials – H.G., A.B.D.; Data Collection and/or Processing – H.G., A.B.D.; Analysis and/or Interpretation – H.G., A.B.D.; Literature Review – H.G., A.B.D.; Writing – H.G., A.B.D.; Critical Review – H.G., A.B.D.

Peer-review: Externally peer-reviewed.

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Strain-Based Echocardiographic Evaluation of Myocardial Adaptation in Normal Pregnancy: Insights into Physiological Remodeling

Strain-Tabanlı Ekokardiyografik Değerlendirme: Normal Gebelikte Miyokardiyal Adaptasyon ve Fizyolojik Yeniden Yapılanmaya İlişkin Bulgular

ABSTRACT

Objective: The aim of this study was to investigate longitudinal changes in biventricular diastolic function and myocardial deformation during pregnancy and the early postpartum period using tissue Doppler imaging (TDI), speckle-tracking echocardiography (STE), and rotational mechanics.

Method: In this prospective observational study, 65 healthy, normotensive women with singleton pregnancies underwent echocardiography at four standardized time points: first trimester (10–12 weeks), second trimester (20–24 weeks), third trimester (36–38 weeks), and early postpartum (6–12 weeks post-delivery). Comprehensive evaluation included conventional Doppler, TDI-derived parameters, longitudinal strain rates, atrial strain, and left ventricular (LV) twist mechanics.

Results: Pregnancy was characterized by a progressive rise in cardiac output and ventricular volumes, with parallel declines in diastolic indices and atrial function. Although LV ejection fraction remained preserved, early diastolic strain rate decreased by 19% (1.59→1.29 s^{-1}, $P < 0.001$), lateral Em velocity declined by 20%, and global LV twist was reduced by 20% (17.8°→14.2°, $P = 0.002$). The mitral E/A ratio progressively decreased, while deceleration time remained prolonged postpartum (203→243 ms, $P < 0.001$). Atrial strain analysis revealed chamber-specific remodeling: left atrial conduit strain showed near recovery, whereas right atrial parameters showed only partial normalization. Collectively, these findings indicate that diastolic and torsional mechanics did not fully normalize within 6–12 weeks, suggesting heterogeneous recovery trajectories even among healthy pregnancies.

Conclusion: In healthy women, pregnancy-induced myocardial adaptation appears to involve progressive diastolic and deformation changes that may persist into the early postpartum phase. The observation of residual subclinical alterations—despite otherwise physiological remodeling—suggests that longitudinal surveillance could be valuable, even in low-risk populations. Advanced echocardiographic modalities may improve early detection and contribute to refined risk stratification in pregnancy-related cardiac adaptation.

Keywords: Diastolic function, left ventricular twist, myocardial adaptation, postpartum recovery, pregnancy, speckle-tracking echocardiography, strain rate

ÖZET

Amaç: Gebelik ve erken postpartum dönemde biventriküler diyastolik fonksiyon ile miyokardiyal deformasyon değişikliklerini doku Doppler görüntüleme (TDI), speckle-tracking ekokardiyografi (STE) ve rotasyonel mekanikler kullanarak değerlendirmek.

Yöntem: Bu prospektif gözlemsel çalışmaya, tekil gebeliği olan 65 sağlıklı ve normotansif kadın dahil edildi. Ekokardiyografik incelemeler dört standart zaman noktasında gerçekleştirildi: birinci trimester (10–12 hafta), ikinci trimester (20–24 hafta), üçüncü trimester (36–38 hafta) ve erken postpartum dönem (doğumdan 6–12 hafta sonra). Kapsamlı değerlendirme; konvansiyonel Doppler, TDI parametreleri, longitudinal strain hızları, atriyal strain ve sol ventrikül (LV) twist mekaniklerini içermekteydi.

Bulgular: Gebelik süresince kardiyak debi ve ventrikül hacimleri kademeli olarak artarken, diyastolik indeksler ve atriyal fonksiyonlarda belirgin düşüşler izlendi. LV ejeksiyon fraksiyonu korunmuş olmasına rağmen erken diyastolik strain hızı %19 azaldı (1.59→1.29 s^{-1}, $P < 0.001$), lateral Em hızı %20 düştü ve global LV twist %20 azaldı (17.8°→14.2°, $P = 0.002$). Mitral E/A oranı kademeli olarak azalırken, deselerasyon zamanı postpartum dönemde de uzamış kaldı

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(203→243 ms, P < 0.001). Atriyal strain analizinde odacığa özgü farklılıklar görüldü: sol atriyal conduit strain postpartum normale yakın seyrederken, sağ atriyal parametrelerde toparlanma belirgin olarak daha yavaş seyretti. Bu bulgular, diyastolik ve torsiyonel mekaniklerin 6–12 hafta içinde tamamen düzelmediğini ve sağlıklı gebeliklerde bile toparlanma sürecinin heterojen seyrettiğini göstermektedir.

Sonuç: Sağlıklı kadınlarda gebeliğe bağlı miyokardiyal adaptasyon, erken postpartum dönemde de sürebilen progresif diyastolik ve deformasyon değişikliklerini içermektedir. Fizyolojik yeniden yapılanmaya rağmen gözlenen subklinik değişiklikler, düşük riskli popülasyonlarda bile kardiyak fonksiyonların uzunlamasına takibinin değerli olabileceğini düşündürmektedir. İleri ekokardiyografik yöntemler, erken tanıya katkı sağlayabilir ve gebelikle ilişkili kardiyak adaptasyonda daha hassas risk sınıflamasına destek olabilir.

Anahtar Kelimeler: Diyastolik fonksiyon, sol ventrikül bükülmesi, miyokardiyal adaptasyon, postpartum iyileşme, gebelik, speckle-tracking ekokardiyografi, strain hızı

Pregnancy imposes one of the most profound physiological demands on the maternal cardiovascular system. To meet the metabolic needs of the developing fetus, cardiac output increases by 30–50%, plasma volume expands, heart rate rises, and systemic vascular resistance decreases markedly.[1–3] While these adaptations are considered physiological, the sustained hemodynamic load creates a unique environment in which subtle alterations in cardiac structure and function may occur. Increasing evidence suggests that such changes may extend into the postpartum period and potentially influence long-term cardiovascular health in women.[4–7]

The left ventricular (LV) diastolic function is particularly sensitive to fluctuations in preload and afterload. Prior studies have reported decreases in the E/A ratio, reductions in Em velocity, and prolongation of deceleration time during pregnancy.[8] However, these data are largely derived from cross-sectional designs, limiting the ability to characterize the dynamic trajectory of diastolic adaptation across pregnancy.[9] Moreover, the degree to which these alterations normalize postpartum remains incompletely defined, as systematic early postpartum evaluations are scarce.[10]

Conventional echocardiographic parameters provide important but limited insight into the complex interplay between systolic, diastolic, and torsional mechanics during pregnancy. Advanced echocardiographic modalities, such as speckle-tracking, strain rate imaging, and rotational mechanics, offer higher temporal resolution and greater sensitivity to subclinical myocardial changes, making them particularly valuable in physiological states characterized by rapidly shifting loading conditions.[11–13] Strain rate, in particular, is less preload-dependent than conventional strain and may better reflect intrinsic myocardial relaxation properties during gestation. Despite these advantages, few longitudinal studies have integrated deformation imaging, rotational mechanics, and biatrial strain in the same cohort. Additionally, atrial adaptation—a key component of ventricular filling—remains underinvestigated, especially with respect to chamber-specific remodeling patterns. Given that atrial function is highly dependent on LV relaxation and chamber compliance, a comprehensive assessment of both atria may provide additional insight into normal gestational remodeling.

ABBREVIATIONS

Ap CSR-E	Apical circumferential early diastolic strain rate
Ap RR-E	Apical early diastolic rotational rate
Ap RSR-E	Apical radial early diastolic strain rate
ASE	American Society of Echocardiography
AVC	Aortic valve closure
BMI	Body mass index
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiography
ESC	European Society of Cardiology
GLS	Global longitudinal strain
ICC	Intraclass correlation coefficient
IVRT	Isovolumic relaxation time
IVV	Isovolumic myocardial velocity
LA SR-E	Left atrial early diastolic strain rate
LSR-E	Early diastolic longitudinal strain rate
LVEDD	Left ventricular end-diastolic diameter
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
MAPSE	Mitral annular plane systolic excursion
STE	Speckle-tracking echocardiography
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging

To address these gaps, we designed a prospective, longitudinal study incorporating conventional Doppler indices, tissue Doppler imaging, strain rate parameters, and rotational mechanics to characterize physiological cardiac adaptation across pregnancy and into the early postpartum period. This integrated approach allows for a detailed evaluation of ventricular relaxation, deformation, atrial mechanics, and torsional behavior, providing a more complete understanding of maternal myocardial remodeling.

Importantly, the 2025 European Society of Cardiology (ESC) Guidelines identify pregnancy as a natural "cardiovascular stress test" that can unmask latent susceptibility to future cardiovascular disease and emphasize the importance of postpartum surveillance.[3] In this context, our study aims to clarify the temporal evolution of myocardial mechanical changes during pregnancy and to determine the degree of functional recovery within the early postpartum window, thereby contributing contemporary, guideline-aligned evidence to the growing field of pregnancy-related cardiac physiology.

Materials and Methods

Study Design and Population

This prospective, single-center study evaluated trimester-specific and postpartum cardiac changes using advanced echocardiographic modalities. Sixty-nine healthy women with uncomplicated singleton pregnancies were consecutively enrolled between January 2022 and August 2023 at a tertiary academic hospital. Four participants were excluded due to chronic hypertension. The final cohort consisted of 65 normotensive women with no prior cardiovascular, renal, pulmonary, or metabolic disease.

To ensure data consistency, only term pregnancies (≥ 37 weeks of gestation) were eligible for the final analysis; women who experienced preterm delivery were excluded by design. Additional exclusion criteria included gestational hypertension, preeclampsia, gestational diabetes, multiple gestation, fetal anomalies or growth restriction, structural heart disease, arrhythmia, and use of cardioactive medications.[5] All participants provided written informed consent, and the study was approved by Kartal Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2025/12/1196, Date: 22.07.2025) in accordance with the Declaration of Helsinki.

Echocardiographic evaluations were performed at four predefined time points: first trimester (10–12 weeks), second trimester (20–24 weeks), third trimester (36–38 weeks), and early postpartum (6–12 weeks after delivery). For each participant, gestational age at delivery and mode of delivery (vaginal vs. cesarean section) were prospectively recorded. Maternal age, body mass index (BMI), gestational weight gain, and maternal weight change postpartum were recorded at each visit.

Imaging Strategy and Rationale

To account for the dynamic hemodynamic changes of pregnancy, we focused on deformation-based measurements with higher temporal sensitivity. Strain-rate imaging was preferred because it is less preload-dependent and better reflects trimester-specific changes in myocardial relaxation. Rotational mechanics (basal and apical rotation and LV twist) were added to assess torsional adaptation, while bilateral atrial strain-rate analysis provided chamber-specific information on reservoir, conduit, and contractile function. Overall, this multimodal approach enabled a comprehensive and physiologically sensitive evaluation of cardiac remodeling during pregnancy and the early postpartum period.

Echocardiographic Acquisition and Analysis

All echocardiographic examinations were performed using a standardized protocol with a Vivid 7 ultrasound system (GE Vingmed, Norway) equipped with a 2.5-MHz phased-array transducer. Images were acquired with participants in the left lateral decubitus position, during quiet respiration, and with simultaneous electrocardiographic (ECG) gating. Harmonic imaging was used in all studies. A single experienced sonographer performed all acquisitions to minimize inter-operator variability. Offline analyses were conducted using EchoPAC PC software (GE Healthcare). All measurements were averaged over three consecutive cardiac cycles.

Left ventricular volumes were calculated using Simpson's biplane method, and left ventricular ejection fraction (LVEF) was derived accordingly. Longitudinal systolic function was assessed via mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE).[14] Due to the focus on functional assessment, we did not evaluate left ventricular mass, right ventricular dimensions, pulmonary pressures, or indexed atrial volumes in this study. The left atrial area was used as a surrogate for atrial remodeling.

Pulsed-wave Doppler was used to measure mitral and tricuspid inflow velocities (E, A, E/A ratio, and deceleration time). The Doppler sample volume (2–3 mm) was placed at the leaflet tips with an insonation angle < 15° whenever possible. Tissue Doppler imaging (TDI) was performed at a sweep speed of 100 mm/s. Early (Em) and late (Am) diastolic myocardial velocities were obtained from the septal and lateral mitral annulus using a 3–5 mm sample volume. Isovolumic relaxation time (IVRT) was measured using continuous-wave Doppler with cursor alignment toward the LV outflow tract–mitral inflow junction. Isovolumic myocardial velocity (IVV) was obtained from TDI traces during the isovolumic relaxation period.[15]

Although global longitudinal strain (GLS) is a widely used deformation parameter, we intentionally focused on strain-rate–based measurements in this study. Strain rate provides higher temporal resolution and is less influenced by preload fluctuations, which is particularly relevant in pregnancy, where loading conditions vary substantially across trimesters. To maintain methodological consistency and enhance sensitivity to dynamic hemodynamic changes, GLS was not included in the primary analysis set.

Longitudinal strain rate was measured from apical four-, two-, and three-chamber views using speckle-tracking echocardiography. Frame rates were maintained between 60 and 90 frames per second, meeting American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations, and frame-rate optimization ensured a temporal resolution-to-heart-rate ratio >0.7. Segments with suboptimal tracking were manually adjusted; persistent tracking failure resulted in segment exclusion and reacquisition when feasible. In line with guideline standards, analyses were accepted only when ≥ 12 of 16 left ventricular segments demonstrated adequate tracking quality. Key parameters included early diastolic longitudinal strain rate (LSR-E), late diastolic longitudinal strain rate (LSR-A), and systolic longitudinal strain rate (LSR-S). Atrial strain rates were obtained by tracing the atrial endocardial border, referencing end-diastole as the zero-strain point. Early and late diastolic atrial strain rates were calculated from the respective filling phases.[11,12,16]

In addition to strain-rate parameters, left atrial reservoir strain was also measured from apical four-chamber views using speckle-tracking echocardiography, and its temporal changes were evaluated as part of a supplementary analysis.

LV rotational mechanics were assessed from parasternal short-axis views at the basal level (mitral valve) and apical level (just distal to the papillary muscles). Tracking was performed ensuring clear visualization of endocardial and epicardial borders. Global

LV twist was calculated as the instantaneous difference between apical and basal rotation. Rotational rate curves were derived from the first derivative of rotational displacement, and systolic (RR-S), early diastolic (RR-E), and late diastolic (RR-A) rotational rates were quantified. Aortic valve closure (AVC) was identified using Doppler or TDI to mark end-systole.

Statistical Analysis

Data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Repeated-measures Analysis of Variance (ANOVA) or Friedman tests were used for longitudinal comparisons, with Bonferroni-corrected post hoc analyses for pairwise comparisons. Given the homogeneity of the study cohort, multivariable modeling and correlation analyses with clinical covariates were not performed.

Sample size was calculated based on an expected 15% change in Em velocity (standard deviation [SD] 2.5 cm/s), with 80% power and alpha = 0.05, yielding a requirement of 45 participants. To allow for attrition, 65 were enrolled. Complete data were available for all participants.

Intra-observer reproducibility was assessed in 20 randomly selected cases (five per time point). The same observer repeated all measurements two weeks later using the same software. Intraclass correlation coefficients (ICCs) indicated excellent reliability: > 0.90 for Doppler measures, > 0.85 for strain rate, > 0.82 for rotational mechanics, and > 0.80 for atrial strain.

A p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 26 (IBM Corp., NY, USA).

Results

Baseline Characteristics

Of the 69 women initially recruited, four were excluded due to a history of chronic hypertension. The final cohort comprised 65 healthy, normotensive pregnant women, with a mean age of 28.6 ± 5.4 years and a baseline BMI of 25.6 ± 4.1 kg/m^2. All pregnancies resulted in term deliveries (≥ 37 weeks), as preterm births were excluded by study design. The mean gestational age at delivery was 38.6 ± 1.1 weeks, and the mode of delivery included vaginal birth in 60% and cesarean section in 40% of participants. Maternal weight increased from 66 ± 9 kg in the first trimester to 75 ± 10 kg in the third trimester and decreased to 69 ± 9 kg postpartum (P < 0.001) (Table 1).

Systolic and diastolic blood pressures remained stable during early pregnancy, increased in the third trimester (systolic: 102 ± 11 to 113 ± 11 mmHg; diastolic: 65 ± 8 to 69 ± 6 mmHg), and decreased postpartum (110 ± 10 and 67 ± 5 mmHg, respectively). Mean arterial pressure followed a similar pattern (78 ± 7 → 80 ± 10 → 75 ± 8 mmHg; P < 0.001). Heart rate increased progressively during gestation from 72 ± 11 bpm in the first trimester, peaked at 81 ± 11 bpm in the third trimester, and declined to 75 ± 8 bpm after delivery, remaining slightly higher than first-trimester values (P < 0.001) (Table 1).

Changes in Left Ventricular Structure and Systolic Function

Left ventricular end-diastolic diameter (LVEDD) and end-diastolic volume (LVEDV) increased across pregnancy, peaked in the third trimester, and decreased postpartum. LVEDD increased from 4.58 ± 0.39 cm to 4.72 ± 0.40 cm in the third trimester, then decreased to 4.40 ± 0.38 cm postpartum (P < 0.001). LVEDV rose from 79.3 ± 16.9 mL to 126 ± 22.1 mL (59% increase) and declined to 98.9 ± 23.9 mL postpartum. Left ventricular end-systolic volume (LVESV) increased from 34.9 ± 9.52 mL to 53.8 ± 12.6 mL and decreased to 46.3 ± 10.2 mL postpartum (P < 0.001) (Table 1).

Left ventricular ejection fraction (LVEF) was 65.5 ± 6.3% in the first trimester and 61.5 ± 7.4% postpartum (P = 0.009). TAPSE and MAPSE values decreased in the third trimester and increased postpartum (TAPSE: 2.32 ± 0.32 → 2.31 ± 0.41 → 2.55 ± 0.28 cm; MAPSE: 1.46 ± 0.22 → 1.40 ± 0.27 → 1.53 ± 0.14 cm) (Table 1).

Left Ventricular Diastolic Function

Mitral early diastolic inflow velocity (E wave) decreased from 0.86 ± 0.16 m/s in the first trimester to 0.60 ± 0.14 m/s postpartum (P < 0.001). A-wave velocity showed a similar pattern, declining from 0.65 ± 0.15 m/s to 0.50 ± 0.16 m/s (P < 0.001). Accordingly, the E/A ratio progressively decreased throughout pregnancy. Deceleration time (DT) increased from 203 ± 41.2 ms in the first trimester to 273 ± 27.6 ms in the third trimester and remained prolonged postpartum (243 ± 15.6 ms; P < 0.001). Left atrial area also increased significantly—from 10.5 ± 2.29 cm^2 in the first trimester to 15.5 ± 2.67 cm^2 in the third trimester—and, although it partially regressed postpartum, it remained elevated at 14.6 ± 2.23 cm^2 (P < 0.001) (Figure 1).

Lateral Em velocity declined from –0.173 ± 0.03 cm/s to –0.138 ± 0.02 cm/s (P < 0.001) and remained reduced postpartum. Septal Em and Am velocities also decreased significantly across pregnancy (Em: –0.118 ± 0.03 → –0.094 ± 0.02 cm/s; Am: –0.104 ± 0.03 → –0.078 ± 0.01 cm/s; both P < 0.001). Lateral Sm similarly decreased from 0.114 ± 0.02 cm/s to 0.106 ± 0.02 cm/s postpartum (P = 0.001) (Table 1, Figure 2). Lateral, septal, and averaged E/Em ratios progressively increased throughout pregnancy, reflecting physiologic augmentation of filling pressures, and showed partial improvement during the early postpartum period (Table 1).

Septal IVV increased from 2.54 ± 1.16 ms to 4.12 ± 1.20 ms in the third trimester (P < 0.001), whereas lateral IVV remained elevated postpartum (4.20 ± 2.35 → 4.15 ± 0.94 ms; P = 0.033). Septal IVRT rose from 38.2 ± 9.54 ms in the first trimester to 42.6 ± 9.13 ms in the third trimester and decreased to 35.9 ± 7.22 ms postpartum (P < 0.001). Lateral IVRT showed a similar trend, increasing to 40.4 ± 9.96 ms in late pregnancy and regressing to 35.9 ± 7.11 ms postpartum, although this change did not reach statistical significance (P = 0.067) (Figure 3).

Right Ventricular Diastolic Function

Right ventricular diastolic indices showed clear trimester-related changes that only partially normalized postpartum. Tricuspid inflow velocities progressively declined throughout pregnancy: the E wave decreased from 0.63 ± 0.15 m/s to 0.42 ± 0.04 m/s and the A wave from 0.54 ± 0.13 m/s to 0.42 ± 0.08 m/s (both P < 0.001). In parallel, tricuspid deceleration time lengthened markedly in late pregnancy (200 ± 69.8 ms → 268 ± 29.5 ms) and remained prolonged after delivery (263 ± 20.1 ms; P < 0.001).

Table 1. Clinical characteristics and echocardiographic structural, systolic, and diastolic parameters across pregnancy and postpartum

Clinical characteristics	1st trimester	2nd trimester	3rd trimester	Postpartum	*P*
Cardiac chamber dimensions and systolic function parameters					
Weight (kg)	66 ± 9	69 ± 10	75 ± 10	69 ± 9	<0.001[a,b,c,d,f]
Systolic BP (mm Hg)	102 ± 11	100 ± 12	113 ± 11	110 ± 10	<0.001[b,c,d,e]
Diastolic BP (mm Hg)	65 ± 8	63 ± 7	69 ± 6	67 ± 5	<0.001[b,d,e]
Mean BP (mm Hg)	78 ± 7	74 ± 5	80 ± 10	75 ± 8	<0.001[a,d,f]
Heart rate (bpm)	72 ± 11	80 ± 10	81 ± 11	75 ± 8	<0.001[a,b,c,e,f]
Structural and systolic function parameters					
LV EDD (cm)	4.58 ± 0.39	4.74 ± 0.36	4.72 ± 0.40	4.40 ± 0.38	<0.001[c,e,f]
LV ESD (cm)	2.90 ± 0.36	2.97 ± 0.35	3.01 ± 0.40	2.93 ± 0.32	0.335
LV EDV (mL)	79.3 ± 16.9	108 ± 21.6	126 ± 22.1	98.9 ± 23.9	<0.001[a,b,c,d,e,f]
LV ESV (mL)	34.9 ± 9.52	47.5 ± 12.7	53.8 ± 12.6	46.3 ± 10.2	<0.001[a,b,c,d,f]
EF (%)	65.5 ± 6.29	65.5 ± 10.0	64.4 ± 7.17	61.5 ± 7.42	0.009[c,e]
TAPSE (cm)	2.32 ± 0.32	2.45 ± 0.29	2.31 ± 0.41	2.55 ± 0.28	<0.001[c,f]
MAPSE (cm)	1.46 ± 0.22	1.40 ± 0.22	1.40 ± 0.27	1.53 ± 0.14	0.002[e,f]
LA area (cm²)	10.5 ± 2.29	13.0 ± 2.27	15.5 ± 2.67	14.6 ± 2.23	<0.001[a,b,c,d,e,f]
Left ventricular (LV) diastolic function parameters					
E (m/s)	0.86 ± 0.16	0.79 ± 0.17	0.65 ± 0.14	0.60 ± 0.14	<0.001[b,c,d,e]
A (m/s)	0.65 ± 0.15	0.63 ± 0.13	0.64 ± 0.16	0.50 ± 0.16	<0.001[c,e,f]
DT (ms)	203 ± 41.2	250 ± 41.9	273 ± 27.6	243 ± 15.6	<0.001[a,b,c,d,e,f]
Lat Em (cm/s)	-0.173 ± 0.03	-0.157 ± 0.03	-0.138 ± 0.04	-0.138 ± 0.02	<0.001[b,c,d,e]
Sep Em (cm/s)	-0.118 ± 0.03	-0.106 ± 0.02	-0.086 ± 0.02	-0.094 ± 0.02	<0.001[b,c,d]
Lateral E/Em	5.20 ± 1.34	5.26 ± 1.52	5.12 ± 2.01	4.49 ± 1.33	
Septal E/Em	7.78 ± 2.18	7.83 ± 2.22	8.08 ± 2.65	6.65 ± 1.59	
Averaged E/Em	6.49 ± 1.52	6.54 ± 1.76	6.60 ± 1.88	5.57 ± 1.29	

BP, Blood pressure; EF, Ejection fraction; LA area, Left atrial area; LV EDD, Left ventricular end-diastolic diameter; LV EDV, Left ventricular end-diastolic volume; LV ESD, Left ventricular end-systolic diameter; LV ESV, Left ventricular end-systolic volume; MAPSE, Mitral annular plane systolic excursion; mean BP, Mean arterial pressure; TAPSE, Tricuspid annular plane systolic excursion. A, Late diastolic mitral inflow velocity; averaged E/Em, Mean of lateral and septal E/Em ratios; DT, Mitral E-wave deceleration time; E, Early diastolic mitral inflow velocity; lat Em, Lateral early diastolic myocardial velocity (tissue Doppler imaging); lat E/Em, Ratio of mitral E velocity to lateral Em myocardial velocity; sep Em, Septal early diastolic myocardial velocity (tissue Doppler imaging); sep E/Em, Ratio of mitral E velocity to septal Em myocardial velocity. a, First trimester vs. second trimester; b, First trimester vs. third trimester; c, First trimester vs. postpartum; d, Second trimester vs. third trimester; e, Second trimester vs. postpartum; f, Third trimester vs. postpartum.

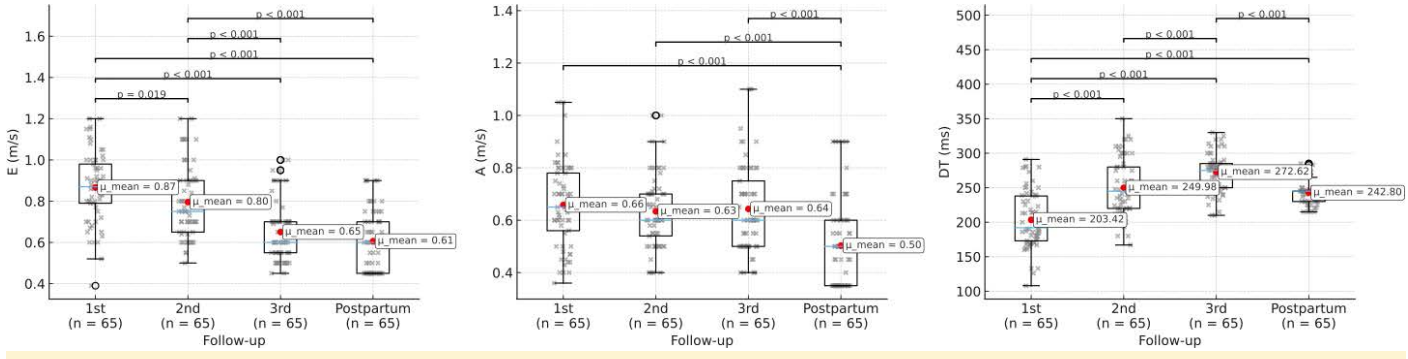

Figure 1. Longitudinal changes in E-wave, A-wave, and deceleration time (DT) across pregnancy and postpartum. Box plots illustrate temporal variations in E-wave velocity (left), A-wave velocity (middle), and deceleration time (right) measured during the first, second, and third trimesters, as well as postpartum.

Tissue Doppler findings were consistent with impaired relaxation. Right ventricular (RV) Em velocity decreased significantly to –0.123 ± 0.02 cm/s postpartum (P < 0.001), and RV Am velocity similarly declined (–0.118 ± 0.03 cm/s; P < 0.001). RV Sm initially rose slightly in mid-pregnancy but fell below baseline in the postpartum period (P < 0.001).

Isovolumic parameters also varied across pregnancy. Lateral IVRT increased from 60.8 ± 10.2 ms to 63.1 ± 8.07 ms in the third trimester and decreased to 57.3 ± 6.3 ms postpartum (P = 0.001). Lateral IVV increased from 8.07 ± 3.01 ms to 11.0 ± 2.52 ms in late pregnancy and partially decreased to 9.08 ± 1.92 ms postpartum (P < 0.001) (Figures 4, 5).

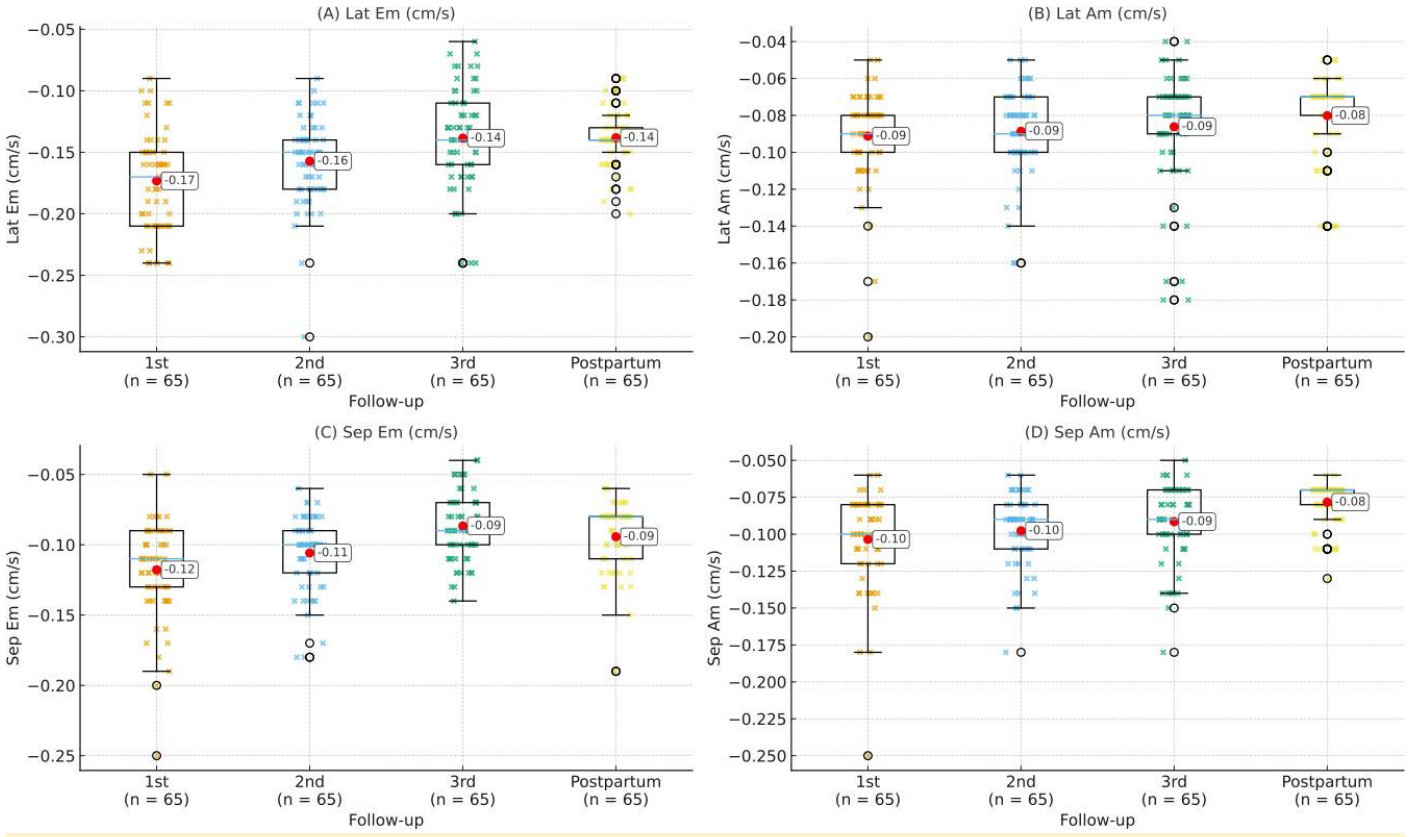

Figure 2. Longitudinal changes in tissue Doppler imaging-derived (TDI-derived) diastolic parameters across pregnancy and postpartum. Temporal changes in TDI-derived lateral and septal early diastolic velocity (Em) and atrial contraction velocity (Am) are shown. A significant decline in Em is observed throughout pregnancy and remains reduced postpartum despite normalized preload (P < 0.001). Am also progressively decreases, particularly in the septal segment (P < 0.001).

Strain Rate Parameters and Rotational Mechanics

Left Ventricular Strain Rate Analysis

Left ventricular early diastolic strain rate declined across all apical views. LSR-E decreased from 1.59 to 1.29 s^{-1} in the four-chamber view, from 1.57 to 1.36 s^{-1} in the two-chamber view, and from 1.61 to 1.09 s^{-1} in the three-chamber view (all P < 0.001). Similarly, apical circumferential early diastolic strain rate (Ap CSR-E) decreased from 2.56 to 1.91 s^{-1} (P < 0.001), whereas apical radial early diastolic strain rate (Ap RSR-E) remained stable throughout pregnancy (P = 0.587) (Table 3, Figure 6). Other basal and apical strain-rate components (e.g., Basal SR-S, Basal RSR-E, Ap CSR-A) showed smaller trimester-related variations without a uniform pattern, and their detailed values are presented in Table 3.

Rotational Mechanics

Left ventricular rotational parameters showed distinct trimester-related changes (Table 2).

Basal rotation remained stable across pregnancy and postpartum (–5.51° → –5.04°, P = 0.800), whereas apical rotation decreased from 12.4° in the first trimester to 9.16° postpartum (P = 0.002). Global LV twist declined from 17.8° to 14.2° in the postpartum period (P = 0.002). The LV systolic rotational rate (LV RR-S) decreased from 120°/s to 97.2°/s (P = 0.005), and early diastolic rotational rate (LV RR-E) declined from –119°/s to –95.5°/s (P = 0.027). Late diastolic rotational rate (LV RR-A) did not show a significant overall change (P = 0.173).

Basal systolic rotational rate (Baz RR-S) decreased from –71.3°/s to –49.7°/s (P < 0.001), while basal late diastolic rotational rate (Baz RR-A) increased from 42.5°/s to 54.3°/s (P = 0.001). Basal early diastolic rotational rate remained unchanged (Baz RR-E: 60.4°/s → 58°/s, P = 0.307). Apical early diastolic rotational rate (Ap RR-E) showed a significant change across pregnancy and postpartum (–90.9°/s → –80.5°/s, P = 0.022), whereas apical systolic and late diastolic rotational rates (Ap RR-S and Ap RR-A) did not demonstrate significant overall variation (both P > 0.05).

Atrial Strain-Rate Analysis

Left atrial early diastolic strain rate (LA SR-E) declined from –2.26 ± 0.65 s^{-1} in the first trimester to –1.85 ± 0.51 s^{-1} in the second trimester but recovered to –2.25 ± 0.65 s^{-1} postpartum (P < 0.001). Late diastolic values (LA SR-A) showed a modest temporal fluctuation across pregnancy (P = 0.020). Consistent with these changes, LA reservoir strain also varied significantly over time (Appendix Table 1).

Right atrial (RA) strain-rate values demonstrated a similar trimester-related pattern. Early diastolic strain rate (RA SR-E) decreased during pregnancy (–1.92 ± 0.75 → –2.13 ± 1.05 s^{-1}) and partially improved postpartum (–1.42 ± 0.77 s^{-1}; P < 0.001). Late diastolic RA SR-A showed a mild reduction postpartum compared with baseline (–1.62 ± 0.61 → –1.36 ± 0.54 s^{-1}; P = 0.04). In contrast, systolic strain rate (RA SR-S) progressively increased throughout pregnancy and into the postpartum period (1.85 ± 0.53 → 2.19 ± 0.48 s^{-1}; P < 0.001).

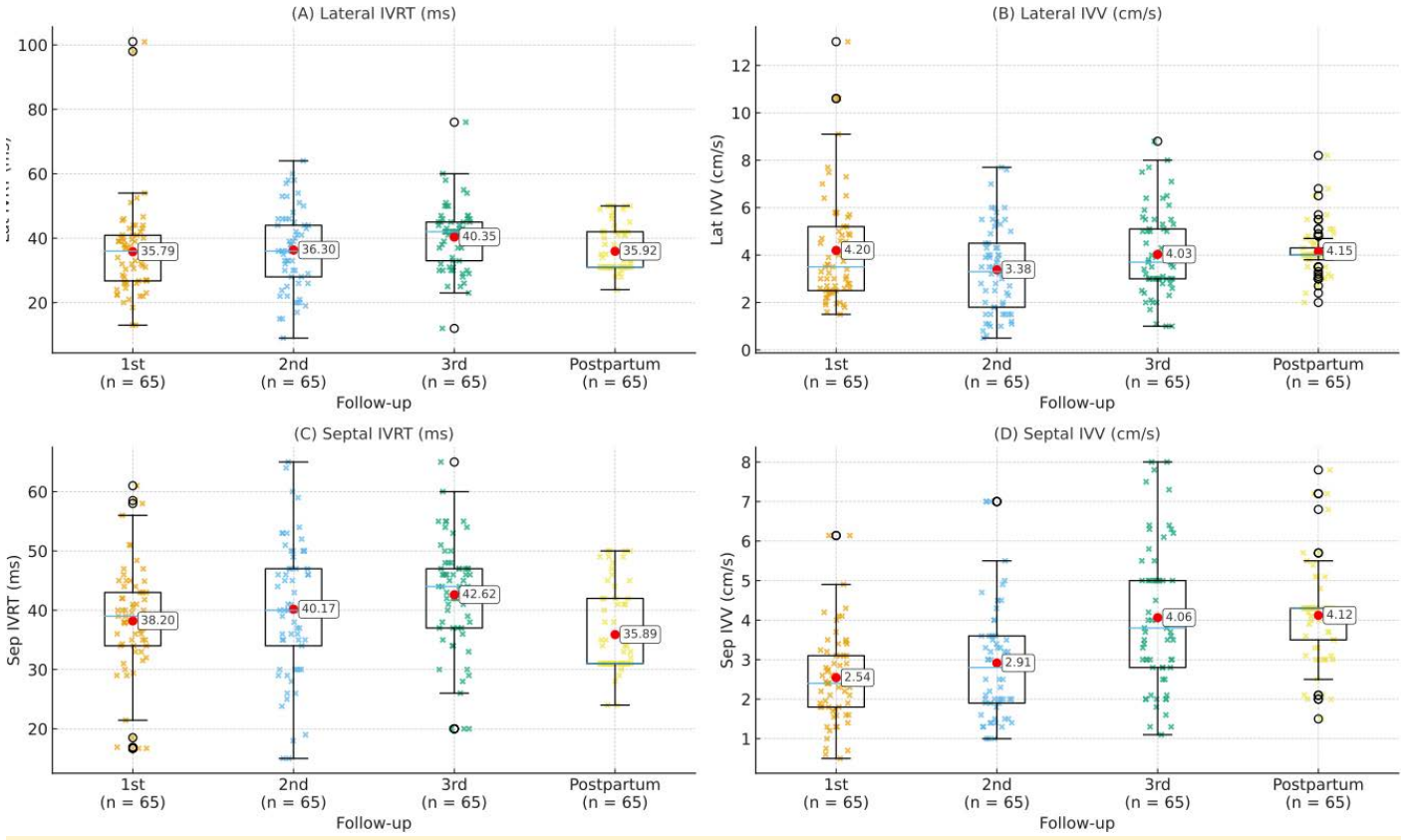

Figure 3. Longitudinal changes in isovolumetric relaxation parameters across pregnancy and postpartum. This figure illustrates changes in isovolumetric velocity (IVV) and isovolumetric relaxation time (IVRT) in the lateral and septal segments during pregnancy and postpartum.

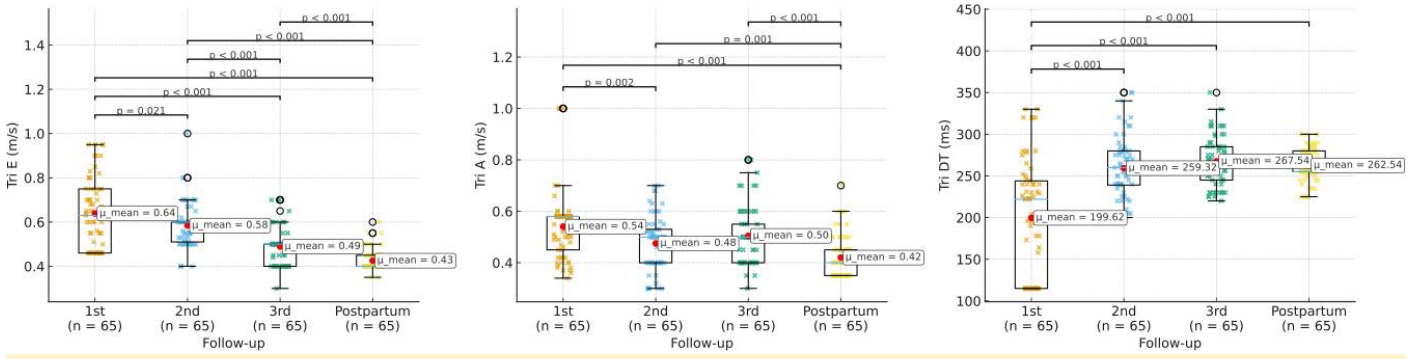

Figure 4. Longitudinal changes in tricuspid inflow parameters across pregnancy and postpartum. Temporal variations in tricuspid inflow (Tri) parameters—early diastolic velocity (Tri E), late diastolic velocity (Tri A), and deceleration time (Tri DT)—are depicted across pregnancy and postpartum.

These chamber-specific patterns are illustrated in Figure 7 (biatrial strain-rate curves) and detailed in Table 3 and Appendix Table 1.

Discussion

This prospective longitudinal study offers one of the most detailed evaluations to date of physiological cardiac adaptation during healthy pregnancy by integrating conventional Doppler, tissue Doppler imaging, strain-rate analysis, and rotational mechanics across gestation and into the early postpartum period. Unlike prior investigations that relied predominantly on cross-sectional assessments or focused primarily on LV systolic indices,[9,17] our multimodal approach enabled a chamber-specific and temporally resolved characterization of both ventricular and atrial function.

Across pregnancy, we observed progressive trimester-related alterations in several diastolic markers—including reductions in early diastolic tissue Doppler velocities (Em), early diastolic longitudinal strain rate (LSR-E), and dynamic changes in atrial strain-rate parameters—suggesting physiologic modulation of myocardial relaxation. Although LV ejection fraction remained within normal limits, a small but statistically significant decline was detected,

Table 2. Changes in rotational mechanics parameters during pregnancy and the postpartum period

Parameter	1st trimester	2nd trimester	3rd trimester	Postpartum	*P*
Rotational mechanics parameters					
Baz Rot (°)	-5.51 ± 2.77	-5.35 ± 2.50	-5.42 ± 3.15	-5.04 ± 2.90	0.800
Ap Rot (°)	12.4 ± 6.42	9.54 ± 4.96	11.1 ± 4.80	9.16 ± 4.55	0.002[a,c]
LV twist (°)	17.8 ± 6.99	14.9 ± 5.39	16.5 ± 5.88	14.2 ± 4.96	0.002[a,c]
LV RR S (°/s)	120 ± 42.5	112 ± 44	123 ± 50.4	97.2 ± 40.2	0.005[c,f]
LV RR E (°/s)	-119 ± 53.5	-99.9 ± 42.3	-106 ± 52.2	-95.5 ± 38.1	0.027[c]
LV RR A (°/s)	-83.4 ± 46.9	-68.1 ± 36.9	-79.6 ± 54	-71.5 ± 35.6	0.173
Baz RR S (°/s)	-71.3 ± 28.1	-63.6 ± 28.6	-61.7 ± 28.9	-49.7 ± 26.8	<0.001[c,e]
Baz RR E (°/s)	60.4 ± 31.7	51.9 ± 46	58.7 ± 27.5	58 ± 24.1	0.307
Baz RR A (°/s)	42.5 ± 22.6	37.3 ± 17.6	44.9 ± 28.9	54.3 ± 27.2	0.001[c,e]
Ap RR S (°/s)	79.3 ± 35.9	77.6 ± 39	87 ± 43.3	75.8 ± 25.5	0.317
Ap RR E (°/s)	-90.9 ± 53.7	-70.9 ± 37.1	-70.7 ± 43.3	-80.5 ± 43.2	0.022[b]
Ap RR A (°/s)	-68.3 ± 36.9	-56.1 ± 30.6	-69.8 ± 39	-56.4 ± 43.5	0.058

Ap RR S/E/A, Apical rotational rate during systole, early diastole, and late diastole; Baz/Ap Rot, Basal and apical rotation angle; Baz RR S/E/A, Basal rotational rate during systole, early diastole, and late diastole; LV RR S/E/A, Left ventricular rotational rate during systole, early diastole, and late diastole; LV Twist, Left ventricular twist. a, First trimester vs. second trimester; b, First trimester vs. third trimester; c, First trimester vs. postpartum; d, Second trimester vs. third trimester; e, Second trimester vs. postpartum; f, Third trimester vs. postpartum.

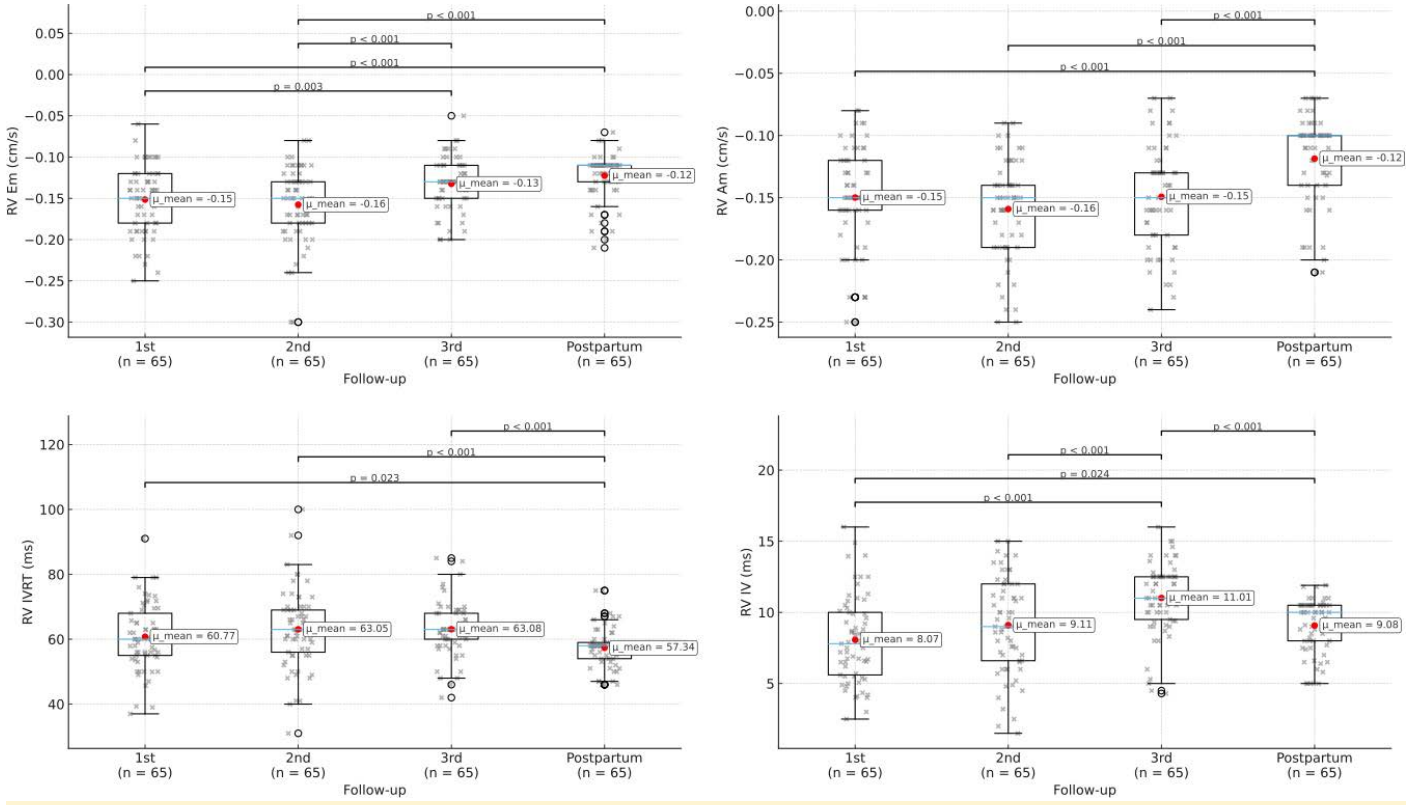

Figure 5. Longitudinal changes in tissue Doppler imaging-derived (TDI-derived) right ventricular (RV) diastolic parameters across pregnancy and postpartum. Changes in RV diastolic function assessed by TDI, including early diastolic myocardial velocity (RV Em), atrial contraction velocity (RV Am), RV lateral isovolumetric relaxation time (IVRT), and RV lateral isovolumetric velocity (IVV).

which is consistent with prior reports indicating that subtle systolic adjustments may accompany gestational remodeling. In parallel, left atrial area and deceleration time increased during pregnancy, supporting the presence of volume-related adaptive changes consistent with established physiological expectations.

Importantly, our findings demonstrate that several deformation-based diastolic and atrial indices did not fully return to first-trimester values in the early postpartum period. Rather than implying pathology, these observations indicate that mechanical recovery is heterogeneous and may extend beyond the traditional

Table 3. Changes in strain-rate parameters during pregnancy and the postpartum period

Strain rate parameters	1st trimester	2nd trimester	3rd trimester	Postpartum	*P*
Basal and apical circumferential/radial strain-rate components					
Baz SR S (s^{-1})	-1.35 ± 0.35	-1.31 ± 0.25	-1.20 ± 0.23	-1.13 ± 0.29	<0.001[b,c,e]
Baz SR E (s^{-1})	1.44 ± 0.44	1.34 ± 0.36	1.30 ± 0.56	1.37 ± 0.31	0.299
Baz SR A (s^{-1})	0.674 ± 0.33	0.635 ± 0.33	0.727 ± 0.34	0.678 ± 0.28	0.441
Baz RSR S (s^{-1})	1.72 ± 0.55	1.74 ± 0.37	1.62 ± 0.40	1.74 ± 0.37	0.319
Baz RSR E (s^{-1})	-1.88 ± 0.73	-1.72 ± 0.66	-1.46 ± 0.63	-1.58 ± 0.53	0.002[b,c]
Baz RSR A (s^{-1})	-1.11 ± 0.46	-1.22 ± 0.63	-1.41 ± 0.66	-0.97 ± 0.36	<0.001[b,f]
Ap CSR S (s^{-1})	-1.97 ± 0.78	-1.74 ± 0.51	-1.96 ± 0.74	-1.80 ± 0.32	0.085
Ap CSR E (s^{-1})	**2.56 ± 1.02**	**1.96 ± 0.82**	**1.76 ± 1.03**	**1.91 ± 0.71**	**<0.001**[a,b,c]
Ap CSR A (s^{-1})	0.914 ± 0.59	0.972 ± 0.69	1.22 ± 0.63	0.908 ± 0.56	0.015[b,f]
Ap RSR S (s^{-1})	1.39 ± 0.65	1.47 ± 0.60	1.60 ± 0.69	1.70 ± 0.52	0.026[c]
Ap RSR E (s^{-1})	-1.93 ± 0.87	-1.82 ± 0.89	-1.83 ± 0.91	-1.72 ± 0.77	0.587
Ap RSR A (s^{-1})	-0.864 ± 0.58	-0.995 ± 0.71	-1.45 ± 0.93	-1.34 ± 0.54	<0.001[b,c,d,e]
Longitudinal strain rate components (2C/3C/4C)					
LSR S 4c (s^{-1})	-1.18 ± 0.17	-1.15 ± 0.19	-1.14 ± 0.16	-1.10 ± 0.12	0.041[c]
LSR E 4c (s^{-1})	**1.59 ± 0.26**	**1.56 ± 0.26**	**1.31 ± 0.37**	**1.29 ± 0.34**	**<0.001**[b,c,d,e]
LSR A 4c (s^{-1})	0.826 ± 0.24	0.782 ± 0.18	0.772 ± 0.26	0.784 ± 0.11	0.479
LSR S 2c (s^{-1})	-1.19 ± 0.22	-1.22 ± 0.20	-1.23 ± 0.22	-1.19 ± 0.16	0.553
LSR E 2c (s^{-1})	**1.57 ± 0.42**	**1.53 ± 0.41**	**1.32 ± 0.34**	**1.36 ± 0.29**	**<0.001**[b,c,d,e]
LSR A 2c (s^{-1})	0.819 ± 0.24	0.861 ± 0.23	0.954 ± 0.27	0.878 ± 0.21	0.014[b]
LSR S 3c (s^{-1})	-1.16 ± 0.19	-1.15 ± 0.22	-1.13 ± 0.18	-1.01 ± 0.29	<0.001c, e, f
LSR E 3c (s^{-1})	**1.61 ± 0.36**	**1.45 ± 0.34**	**1.31 ± 0.39**	**1.09 ± 0.33**	**<0.001**[b,c,e,f]
LSR A 3c (s^{-1})	0.847 ± 0.25	0.704 ± 0.19	0.820 ± 0.28	0.711 ± 0.22	<0.001[a,c,d,f]
LA and RA strain rate					
LA SR S (s^{-1})	1.84 ± 0.50	1.76 ± 0.43	1.82 ± 0.65	1.81 ± 0.44	0.833
LA SR E (s^{-1})	**-2.26 ± 0.65**	**-1.85 ± 0.51**	**-1.82 ± 0.64**	**-2.25 ± 0.65**	**<0.001**[a b e f]
LA SR A (s^{-1})	**-1.89 ± 0.78**	**-1.55 ± 0.56**	**-1.89 ± 0.87**	**-1.77 ± 0.60**	**0.020**[a,d]
RA SR S (s^{-1})	1.85 ± 0.53	1.74 ± 0.46	2.06 ± 0.85	2.19 ± 0.48	<0.001c, d, e
RA SR E (s^{-1})	**-1.92 ± 0.75**	**-1.51 ± 0.53**	**-2.13 ± 1.05**	**-1.42 ± 0.77**	**<0.001**[a,c,d,e]
RA SR A (s^{-1})	**-1.62 ± 0.61**	**-1.39 ± 0.52**	**-1.57 ± 0.72**	**-1.36 ± 0.54**	**0.04**[c]

Ap CSR S/E/A, Apical circumferential strain rate (systolic, early diastolic, late diastolic); Ap RSR S/E/A, Apical radial strain rate (systolic, early diastolic, late diastolic); Baz RSR S/E/A, Basal radial strain rate (systolic, early diastolic, late diastolic); Baz SR S/E/A, Basal segment strain rate (systolic, early diastolic, late diastolic). LSR S/E/A 4c, Longitudinal strain rate in the four-chamber view (systolic, early diastolic, late diastolic); LSR S/E/A 2c, Longitudinal strain rate in the two-chamber view; LSR S/E/A 3c, Longitudinal strain rate in the three-chamber view. LA SR S/E/A, Left atrial strain rate (systolic, early diastolic, late diastolic); RA SR S/E/A, Right atrial strain rate (systolic, early diastolic, late diastolic). a, First trimester vs. second trimester; b, First trimester vs. third trimester; c, First trimester vs. postpartum; d, Second trimester vs. third trimester; e, Second trimester vs. postpartum; f, Third trimester vs. postpartum.

6–12-week interval. This aligns with recent insights highlighted in the 2025 ESC Guidelines, which describe the postpartum period as a vulnerable stage of cardiovascular adaptation,[3] and our results contribute complementary evidence by showing that even in healthy pregnancies, normalization of myocardial mechanics may follow a more protracted trajectory.

Ongoing Remodeling in the Early Postpartum Period

A notable finding of our study was that several diastolic indices did not return to first-trimester levels in the early postpartum period. Both early diastolic strain rate and lateral Em velocity remained lower than baseline, suggesting that normalization of myocardial relaxation may extend beyond the standard 6–12-week window. Although E/Em ratios (lateral, septal, and averaged) were mildly elevated compared with first-trimester measurements, all values remained within normal physiological limits, supporting the interpretation that these differences most likely reflect residual physiological adaptation rather than increased filling pressures.

These observations align with prior studies demonstrating that diastolic adjustment often continues into the postpartum period, even in uncomplicated pregnancies.[9,17] The pattern of delayed normalization observed in our cohort also mirrors trends described in hypertensive pregnancies. For instance, Muthyala

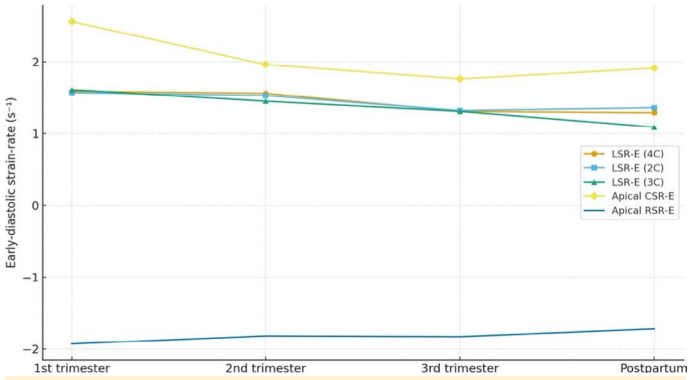

Figure 6. Early-diastolic strain-rate parameters across pregnancy and early postpartum. Line plots showing trimester-specific and postpartum changes in early diastolic strain-rate indices, including longitudinal strain rate during early diastole (LSR-E) from 4C, 2C, and 3C views, apical circumferential strain rate during early diastole (CSR-E), and apical radial strain rate during early diastole (RSR-E). Values represent mean ± standard deviation (SD).

et al.[18] in 2016 reported persistent diastolic abnormalities in a proportion of women with preeclampsia, proportional to disease severity. While our population consisted exclusively of normotensive women, the similarity in temporal recovery patterns suggests that postpartum diastolic remodeling may represent a continuum of physiological adaptation rather than a pathological extension of hypertensive pregnancy mechanisms.

Taken together, these findings indicate that cardiac recovery after pregnancy may be more gradual than traditionally assumed, supporting calls to re-examine the temporal boundaries of the "physiological" postpartum period.[4,5] Even among healthy women, subtle deviations from baseline mechanics may persist transiently, underscoring the value of sensitive imaging parameters in characterizing postpartum cardiovascular adaptation.

Rotational Mechanics and Energy Adaptation in the Postpartum Heart

Rotational mechanics findings in our cohort provide additional context for myocardial adaptation after delivery. We observed a postpartum decrease in apical rotation and global LV twist, suggesting an attenuation of the torsional augmentation that characterizes late gestation. This pattern differs from the increased twist reported by Ari et al.[19] in 2020 in late pregnancy, likely reflecting methodological differences in timing and population characteristics.

In our study, the reduction in twist was accompanied by a modest decline in LVEF and a significant decrease in apical early diastolic rotational rate (Ap RR-E). While these findings may indicate a physiological adjustment as hemodynamic load decreases after delivery, the underlying mechanisms cannot be fully determined from imaging data alone. Therefore, rather than implying intrinsic changes in fiber orientation or energetics, our results more conservatively suggest a postpartum recalibration of torsional dynamics that parallels the observed changes in diastolic function.

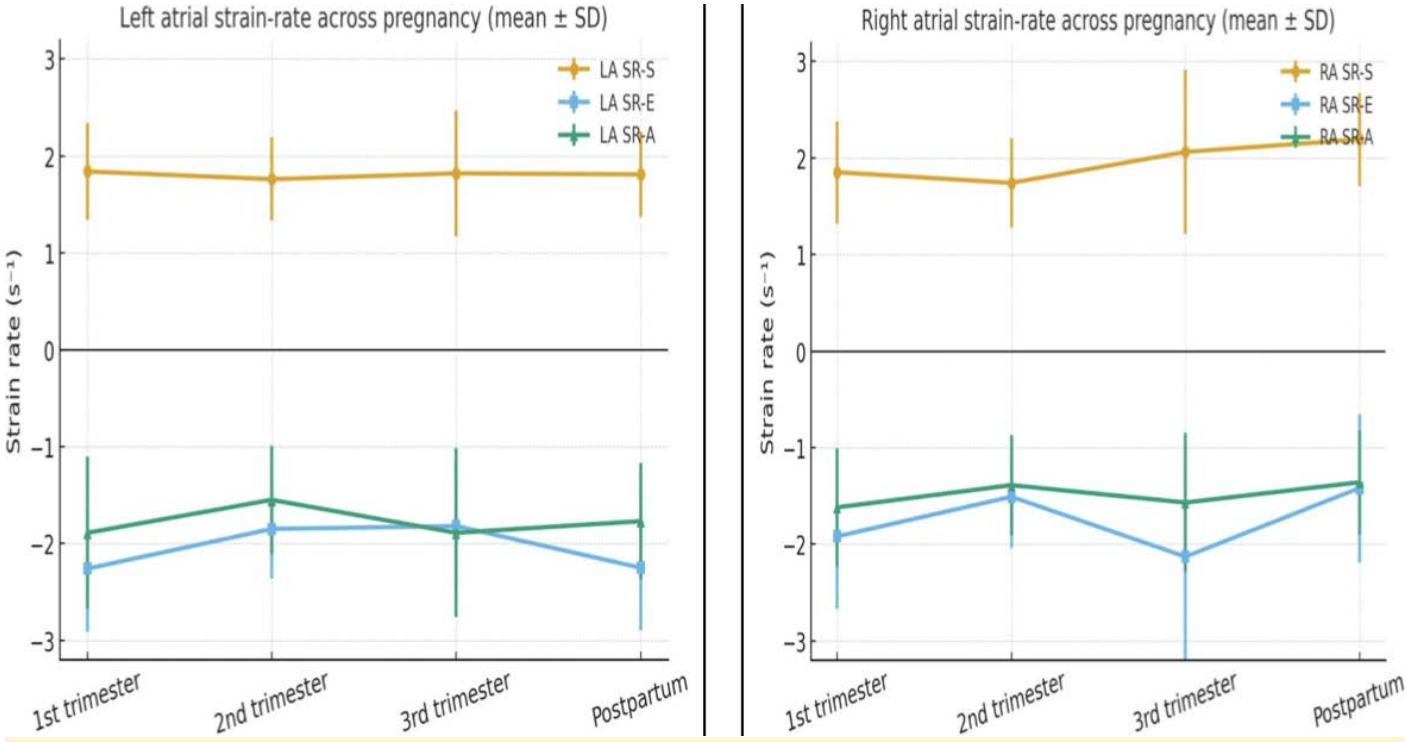

Figure 7. Left and right atrial strain-rate parameters (SR-S, SR-E, SR-A) across pregnancy and postpartum. Grouped line-plots demonstrating temporal changes in atrial systolic strain rate (SR-S), early diastolic strain rate (SR-E), and late diastolic strain rate (SR-A) for the left atrium (left panel) and right atrium (right panel). All values are shown as mean ± standard deviation (SD).

Because our postpartum follow-up was limited to 6–12 weeks, it remains unclear whether these torsional alterations fully normalize with longer recovery. Future studies with extended postpartum surveillance and integration of clinical, metabolic, and myocardial energetic markers will be essential to clarify whether reduced twist represents a transient physiological adaptation or has implications for long-term remodeling.

Biatrial Functional Adaptation Across Pregnancy and Postpartum

Our study is among the few to longitudinally evaluate both left and right atrial mechanics during pregnancy using strain-rate imaging. We identified trimester-related changes in LA and RA strain-rate parameters, with only partial normalization in the early postpartum period. These findings are consistent with Guler et al.[20] in 2024, who reported progressive increases in right atrial reservoir and contraction strain during gestation and incomplete normalization after delivery. Similarly, Song et al.[21] in 2015 and Tasar et al.[22] in 2019 documented declines in left atrial reservoir and conduit strain during pregnancy and variable recovery trajectories postpartum, with conduit function showing slower improvement. Our observations parallel these reports, demonstrating reductions in LA SR-E and SR-A during pregnancy and incomplete restoration by 6–12 weeks postpartum.

It is important to recognize that atrial reservoir and conduit strain are influenced by dynamic loading conditions, including LV base descent and end-diastolic volumes. Because full hemodynamic normalization may not occur until 3–6 months after delivery, modest deviations from baseline in our early postpartum measurements likely reflect the expected physiological recovery timeline rather than persistent dysfunction. Nonetheless, the persistence of altered atrial strain-rate indices despite improvement in preload-sensitive parameters suggests that atrial adaptation may involve intrinsic, chamber-specific remodeling processes.

These findings support the potential value of incorporating biatrial deformation indices into peripartum echocardiographic protocols to enhance phenotypic characterization and improve understanding of maternal cardiovascular adaptation.

Moreover, given that hemodynamic loading conditions during labor differ between vaginal and cesarean delivery, the mode of delivery may theoretically influence the trajectory of postpartum myocardial recovery. Although our study population was not large enough to permit adequately powered subgroup analyses, understanding whether ventricular or atrial deformation indices normalize differently according to delivery mode is an important avenue for future investigation. Larger cohorts may help clarify whether labor-related hemodynamic stress modifies early postpartum myocardial mechanics, potentially contributing to more individualized postpartum surveillance strategies.

Diagnostic Sensitivity of Advanced Echocardiographic Techniques

In our cohort, the application of strain rate imaging—characterized by superior temporal resolution and reduced preload dependency—appeared particularly valuable. Even with preserved LVEF, significant alterations in strain rate and rotational mechanics were detectable, underscoring the ability of advanced imaging to reveal subclinical myocardial changes that may remain concealed with conventional indices. These observations are in agreement with prior reports[12,23] and suggest that broader integration of deformation imaging into peripartum assessment protocols could improve the sensitivity of cardiovascular evaluation in pregnancy. While the prognostic implications of such findings require further study, our results support the potential of advanced echocardiographic modalities to complement standard measures in monitoring maternal cardiac adaptation.

Study Contributions and Methodological Considerations

This study offers several methodological contributions. First, it is among the few longitudinal investigations to apply strain rate imaging across all trimesters and into the postpartum period, thereby detecting subtle myocardial alterations not captured by conventional Doppler indices. Second, the systematic evaluation of biatrial function provided chamber-specific insights that are often overlooked in pregnancy-related cardiovascular research. Third, the demonstration of reduced postpartum twist despite preserved systolic function introduces the concept of transient physiological energy redistribution following delivery.

Collectively, these findings question the assumption that cardiovascular recovery is universally complete within 6–12 weeks postpartum. While the prognostic implications remain to be established, they suggest that extended monitoring may be warranted even in otherwise healthy pregnancies and highlight the value of advanced imaging for refining our understanding of maternal cardiac adaptation.

Limitations

Several limitations of this study should be acknowledged. First, it was conducted at a single center in a relatively homogenous cohort of healthy, low-risk pregnant women. As such, the findings may not be fully generalizable to more heterogeneous populations, including high-risk pregnancies, women with comorbid conditions, or those of advanced maternal age. Given that cardiovascular adaptation to pregnancy can vary substantially across clinical scenarios, selection bias cannot be excluded.

Second, the advanced echocardiographic parameters applied—particularly strain rate and rotational mechanics—are inherently operator dependent. Although all measurements were performed by a single experienced observer and intra-observer reproducibility was excellent (ICC > 0.85), variability related to equipment, analysis software, or operator expertise may limit the broader applicability of the protocol.

Third, postpartum assessment was confined to the early recovery phase (6–12 weeks). Our observations suggest that recovery may extend beyond this interval; therefore, studies incorporating longer follow-up, ideally beyond six months, are warranted to define the complete timeline of postpartum cardiac normalization.

Fourth, the study focused primarily on physiological adaptation mechanisms and did not include complementary measures such as biomarkers (e.g., N-terminal pro–B-type natriuretic peptide [NT-proBNP], troponin, oxidative stress markers) or clinical symptom scores. The absence of these correlates limits interpretation of the clinical and prognostic significance of the echocardiographic findings.

Finally, certain structural and hemodynamic variables—including left ventricular mass index, indexed atrial volumes, right ventricular volumes, and pulmonary artery pressures—were not assessed. Incorporating these measures might have provided a more comprehensive picture of global cardiac remodeling.

Despite these limitations, this prospective longitudinal study provides valuable insights by applying advanced echocardiographic modalities to characterize time-sensitive maternal cardiac adaptation. The findings suggest that even in low-risk pregnancies, postpartum recovery may be more protracted than traditionally assumed, and that deformation imaging can sensitively detect these subtle physiological transitions.

Conclusion

This prospective longitudinal study provides novel insights into maternal cardiac adaptation by applying advanced echocardiographic techniques across pregnancy and into the postpartum period. Despite preserved ejection fraction, subclinical alterations in strain rate, atrial function, and rotational mechanics were detected, underscoring the added diagnostic value of deformation imaging beyond conventional parameters.

The incomplete normalization of diastolic and torsional indices in the early postpartum phase suggests that cardiovascular recovery may extend beyond the traditionally accepted 6-12-week interval. These observations indicate that even in healthy pregnancies, recovery may be gradual and heterogeneous across individuals.

The 2025 ESC Guidelines on the management of cardiovascular disease and pregnancy define pregnancy as a natural cardiovascular stress test and a critical window into women's future heart health.[3] Our findings are consistent with this perspective and suggest that advanced imaging modalities may support more sensitive postpartum surveillance strategies. Such an approach could enable earlier recognition of subclinical myocardial changes and, ultimately, contribute to preventive strategies aimed at preserving long-term maternal cardiovascular health.

Ethics Committee Approval: Ethics committee approval was obtained from Kartal Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2025/12/1196, Date: 22.07.2025).

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Association of MAPH and CHA_2DS_2-VASc Scores with Left Atrial Thrombus in Atrial Fibrillation Patients Undergoing Ablation: A Comparative Evaluation

MAPH ve CHA_2DS_2-VASc Skorlarının Ablasyon Planlanan Atriyal Fibrilasyon Hastalarında Sol Atriyal Trombüs Varlığı ile İlişkisi: Karşılaştırmalı Bir Değerlendirme

ABSTRACT

Objective: This study aimed to compare the association of the MAPH score (Mean platelet volume–Age–Persistent atrial fibrillation–Hematocrit) and the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points), Vascular disease, Age 65–74 years, and Sex category (female)) with the presence of left atrial thrombus in patients undergoing atrial fibrillation ablation.

Method: This retrospective cross-sectional study included 258 consecutive patients with atrial fibrillation (AF) who underwent transesophageal echocardiography to assess thrombus status prior to ablation. Based on these findings, patients were categorized according to the presence or absence of left atrial (LA) thrombus.

Results: The mean age of the study population was 55.2 ± 11.7 years, and 53.5% of the participants were female. Patients with LA thrombus were more likely to have ongoing AF during TEE, mild mitral stenosis, elevated C-reactive protein (CRP) and international normalized ratio (INR) levels, and reduced ejection fraction. The median MAPH score was significantly higher in the thrombus group (P < 0.001). In multivariable analysis, ongoing AF (odds ratio [OR]: 3.83), anticoagulant therapy (OR: 14.95), elevated albumin (OR: 1328.5), elevated CRP (OR: 1.38), and elevated INR (OR: 9.09) were independently associated with thrombus presence. The MAPH score demonstrated superior discriminative performance compared to the CHA_2DS_2-VASc score for identifying LA thrombus (P = 0.014).

Conclusion: The MAPH score was significantly associated with LA thrombus and demonstrated superior discriminative ability compared to the CHA_2DS_2-VASc score for detecting LA thrombus. These findings suggest that the MAPH score may serve as a useful marker for identifying existing LA thrombus in patients with AF undergoing pre-procedural evaluation.

Keywords: Atrial fibrillation, left atrial thrombus, MAPH score, risk assessment

ÖZET

Amaç: Atriyal fibrilasyon ablasyonu planlanan hastalarda MAPH skoru ile CHA_2DS_2-VASc skorunun sol atriyal trombüs varlığı ile ilişkisini karşılaştırmaktır.

Yöntem: Bu retrospektif kesitsel çalışmaya, ablasyon öncesinde trombüs durumunun değerlendirilmesi amacıyla transözofageal ekokardiyografi uygulanan, ardışık 258 AF hastası dahil edilmiştir. Bu inceleme temel alınarak hastalar, sol atriyal trombüs varlığına göre gruplandırılmıştır.

Bulgular: Çalışma popülasyonunun ortalama yaşı 55.2 ± 11.7 yıl olup, katılımcıların %53.5'i kadındı. Sol atriyal trombüsü olan hastalarda TEE sırasında devam eden AF, hafif mitral stenoz, artmış CRP ve INR düzeyleri ile daha düşük ejeksiyon fraksiyonu daha sık gözlenmiştir. Medyan MAPH skoru trombüs grubunda anlamlı olarak daha yüksekti (P < 0.001). Çok değişkenli analizde devam eden AF (OR: 3.83), antikoagülan kullanımı (OR: 14.95), yüksek albümin (OR: 1328.5), yüksek CRP (OR: 1.38) ve yüksek INR (OR: 9.09) trombüsün bağımsız belirleyicileri olarak bulunmuştur. MAPH skoru, sol atriyal trombüs varlığının belirlenmesinde CHA_2DS_2-VASc skoruna göre üstün ayırt edici performans göstermiştir (P = 0.014).

Sonuç: MAPH skoru, sol atriyal trombüs varlığı ile anlamlı şekilde ilişkili olup, LA trombüsünün belirlenmesinde CHA_2DS_2-VASc skorundan daha yüksek bir ayırt edici performans sergilemiştir. Bulgular, MAPH skorunun AF hastalarında işlem öncesi değerlendirmede mevcut LA trombüsünün saptanmasında yararlı bir belirteç olabileceğini düşündürmektedir.

Anahtar Kelimeler: Atriyal fibrilasyon, sol atriyal trombüs, MAPH skoru, risk değerlendirmesi

ORIGINAL ARTICLE
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Atrial fibrillation (AF) is one of the most common sustained arrhythmias in the general population and is strongly associated with thromboembolic events. In patients with AF, thrombi most commonly form in the left atrial (LA) appendage, and evidence suggests that these patients are at risk for systemic embolism despite appropriate anticoagulant therapy. Detection of thrombus prior to therapeutic interventions is critical to ensuring procedural safety and preventing potential complications.[1,2]

Transesophageal echocardiography (TEE) is widely used to evaluate the LA and detect thrombus or dense spontaneous echocardiographic contrast (SEC). Although TEE remains the gold standard for thrombus detection due to its high sensitivity and specificity, it is a semi-invasive procedure requiring sedation, specialized equipment, and experienced operators. Therefore, complementary risk-stratification tools are valuable for identifying patients at higher risk who would benefit most from TEE.[3] The CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points), Vascular disease, Age 65–74 years, and Sex category (female)) is one of the most widely used risk stratification systems in clinical practice for estimating thromboembolic risk. In patients with AF, it is the recommended tool for assessing thromboembolic risk and guiding anticoagulant therapy.[4,5] However, because the CHA_2DS_2-VASc score is based primarily on clinical characteristics and comorbidities, its specificity and sensitivity are limited, particularly for predicting left atrial appendage thrombus (LAAT). Many researchers have therefore been prompted to investigate novel biomarkers and scoring systems to improve LAAT detection.[6]

The MAPH score (Mean platelet volume–Age–Persistent atrial fibrillation–Hematocrit), which incorporates age and blood viscosity biomarkers such as mean platelet volume (MPV), total protein, and hematocrit (Htc), was introduced relatively recently into the literature and has been shown to predict thrombus burden in various clinical contexts.[7-10] However, the utility of the MAPH score in patients with AF remains understudied. In the present study, we aimed to evaluate the association between the MAPH score and the presence of LAAT in patients scheduled for AF ablation. A secondary objective was to assess clinical, laboratory, and echocardiographic parameters potentially associated with thrombotic properties and to identify factors independently associated with LAAT in AF.

ABBREVIATIONS

AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
CRP	C-reactive protein
HCT	Hematocrit
IAS	Interatrial septum thickness
INR	International normalized ratio
LA	Left atrial
LVEDD	Left ventricular end-diastolic diameter
LYMPH	Lymphocyte count
MPV	Mean platelet volume
ROC	Receiver operating characteristic
SEC	Spontaneous echocardiographic contrast
sPAP	Systolic pulmonary artery pressure
STEMI	ST-segment elevation myocardial infarction
TEE	Transesophageal echocardiography
TSH	Thyroid-stimulating hormone
TTE	Transthoracic echocardiography

Materials and Methods

Patients and Data Collection

This cross-sectional study was conducted at the Department of Cardiology of a tertiary center. The study protocol was approved by Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: E-10840098-202.3.02-6131, Date: 15.09.2025), and was carried out in accordance with the ethical principles of the Declaration of Helsinki. All data were anonymized at the time of data recording and entry.

Patients scheduled for ablation due to AF between May 2022 and July 2024 were retrospectively screened. Of the 302 patients initially assessed, 44 were excluded for the following reasons: moderate-to-severe mitral stenosis (n = 16), prosthetic heart valves (n = 8), congenital heart disease (n = 7), prior left atrial appendage occlusion (n = 5), and hemodialysis-dependent renal failure (n = 8) (Figure 1). A total of 258 consecutive patients with non-valvular AF, defined as AF in the absence of mechanical prosthetic heart valves or moderate-to-severe mitral stenosis, either paroxysmal or persistent at presentation, were included in the analysis. The diagnosis of AF was confirmed by 12-lead surface electrocardiography (ECG) and/or 24-hour Holter monitoring.

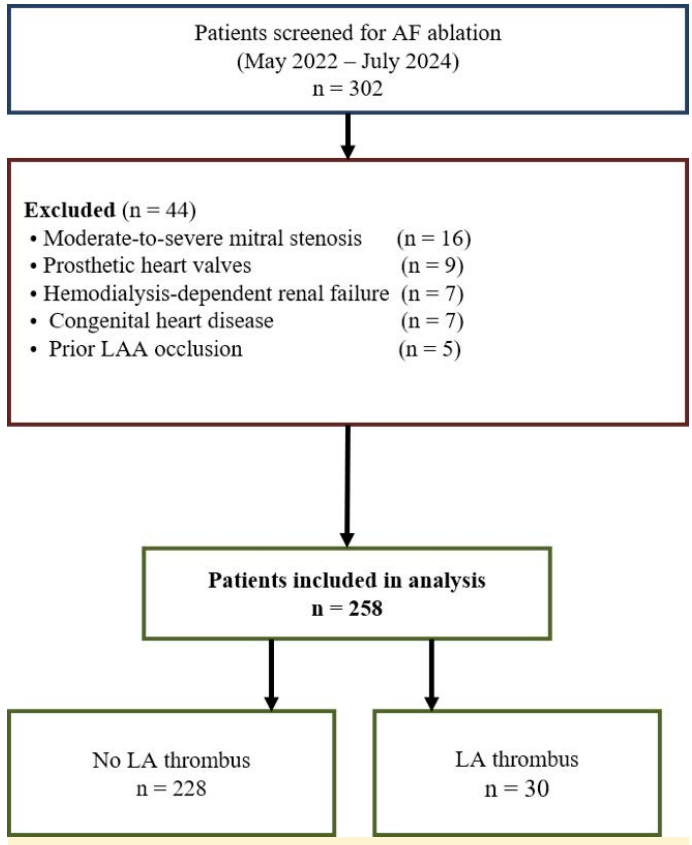

Figure 1. Patient flow diagram.

The inclusion criteria were as follows: age ≥ 18 years; availability of both transthoracic echocardiography (TTE) and TEE results performed within seven days prior to ablation; and complete clinical, laboratory, and echocardiographic data retrievable from the digital hospital records. Patients were excluded if they had moderate or severe rheumatic mitral stenosis, prosthetic heart valves, a history of congenital heart disease, prior left atrial appendage occlusion, or incomplete data. This exclusion criterion aligns with major direct oral anticoagulant trials,[11,12] which excluded only moderate-to-severe mitral stenosis and mechanical valves while including patients with other valvular diseases. In addition, patients with known active malignancies, hematologic disorders (e.g., myeloproliferative neoplasms or anemia requiring transfusion), acute infectious or inflammatory conditions at the time of blood sampling, advanced hepatic failure, or hemodialysis-dependent renal failure were excluded to minimize confounding effects on MAPH score components.

Demographic and clinical data were obtained from patient records and the electronic hospital system, including age, sex, AF type (paroxysmal, persistent, or permanent), comorbidities (hypertension, diabetes mellitus, coronary artery disease, heart failure, and history of stroke or transient ischemic attack), history of cardioversion or ablation, use of antiplatelet or anticoagulant medications (warfarin or direct oral anticoagulants), and heart rhythm at the time of TEE (AF or sinus rhythm).

The authors declare that no artificial intelligence tools were used in the conception, data analysis, drafting, or editing of this manuscript.

Sampling and Laboratory Measurements

Blood samples (collected into ethylenediaminetetraacetic acid [EDTA] and serum-separator tubes) were drawn from all patients in the morning hours (between 07:30 and 09:00) following at least 8 hours of fasting and 24–48 hours prior to TEE. Serum biochemistry and complete blood count parameters were analyzed in the hospital's central laboratory using automated analyzers. Measured parameters included albumin, C-reactive protein (CRP), international normalized ratio (INR), activated partial thromboplastin time (aPTT), thyroid-stimulating hormone (TSH), hemoglobin, hematocrit (Hct), and complete blood count indices.

Regarding anticoagulation management prior to TEE, patients receiving direct oral anticoagulants continued their medication without interruption, whereas those on warfarin were maintained on therapy with INR monitoring. Anticoagulant doses were not withheld prior to TEE, as the examination was performed under conscious sedation did not require interruption of therapeutic anticoagulation. All patients scheduled for ablation were required to have received at least three weeks of adequate anticoagulation or to have undergone TEE to exclude thrombus, in accordance with guideline recommendations.

Echocardiographic Evaluations

Transthoracic echocardiography was performed using a GE Vivid E9 system (General Electric, USA) equipped with a 3.5 MHz phased-array probe. All TTE examinations were conducted by experienced cardiologists certified in echocardiography who were blinded to thrombus status. Measurements, including left atrial diameter (parasternal long-axis view), left ventricular end-diastolic diameter (LVEDD), ejection fraction (Simpson's method), interatrial septum thickness (IAS), posterior wall thickness, and systolic pulmonary artery pressure (sPAP), were obtained in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

Transesophageal echocardiography was performed 48–72 hours prior to ablation under conscious sedation using a multiplane probe. The left atrial appendage was evaluated in at least four views (0°, 45°, 90°, and 135°), and the presence of LAAT and the severity of SEC were assessed. SEC was graded as absent, mild, moderate, or severe.[13] A thrombus was defined as a well-demarcated, echo-dense mass clearly separated from the endocardial surface and not confused with pectinate muscles or imaging artifacts. All TEE images were independently reviewed by two blinded cardiologists; in cases of disagreement, a third experienced cardiologist made the final decision. Formal inter-observer agreement statistics (e.g., Cohen's kappa) were not prospectively calculated. However, initial concordance between the two readers was high, with disagreement occurring in fewer than 5% of cases, all of which were resolved by the third adjudicator.

Score Calculation

All scoring systems were calculated individually by the investigators at the time of data collection.

The MAPH score was calculated according to its original definition,[7] based on four parameters: MPV, age, total protein level, and Hct. For each variable, a score of 1 was assigned if the value exceeded the predefined cutoff and 0 if it was below the cutoff. The total MAPH score for each individual was calculated by summing the scores of these four components. Possible scores ranged from 0 to 4, with higher values indicating greater thrombus risk.

The CHA_2DS_2-VASc score was calculated using the following criteria: congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), prior stroke or transient ischemic attack (TIA) (2 points), vascular disease (1 point), age 65–74 years (1 point), and female sex (1 point). We used the CHA_2DS_2-VASc score rather than the sex-excluded CHA_2DS_2-VA formulation because CHA_2DS_2-VASc remains the most widely adopted scoring system in clinical practice and current guidelines, thereby facilitating comparability with existing literature. Additionally, our study population included both sexes, and excluding the sex component would have reduced consistency with standard clinical workflows.

We also assessed bleeding risk using the PRECISE-DAPT score (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy). This score was calculated using an online calculator by entering age, creatinine clearance (estimated using the Cockcroft-Gault formula), hemoglobin, white blood cell count, and history of significant bleeding.

Statistical Analysis

Sample size was calculated a priori using G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany). Based on expected sensitivities of 56.3% for the MAPH score and 40.0% for the CHA_2DS_2-VASc score, with $\alpha = 0.05$ (two-tailed), power = 0.80, and a 1:1 allocation ratio, the required sample size was 232 patients (effect size $|h| = 0.332$). Accounting for 10% incomplete data, we targeted 260 patients.

Table 1. Comparison of baseline demographic, clinical, echocardiographic, and laboratory characteristics between patients with and without left atrial appendage thrombus

		Thrombus status		*P*
	Total (n=258)	**No thrombus (n=228)**	**Thrombus present (n=30)**	
Age	55.25 ± 11.67	54.90 ± 11.80	57.93 ± 10.44	0.181†
Sex				0.831§
Female	138 (53.49%)	123 (53.95%)	15 (50.00%)	
Male	120 (46.51%)	105 (46.05%)	15 (50.00%)	
Comorbidities				
Coronary artery disease	29 (11.24%)	27 (11.84%)	2 (6.67%)	0.547#
Hypertension	96 (37.21%)	89 (39.04%)	7 (23.33%)	0.141§
Hyperlipidemia	37 (14.34%)	32 (14.04%)	5 (16.67%)	0.781#
Diabetes mellitus	17 (6.59%)	16 (7.02%)	1 (3.33%)	0.702#
Heart failure	13 (5.04%)	10 (4.39%)	3 (10.00%)	0.182#
Stroke/TIA	7 (2.71%)	4 (1.75%)	3 (10.00%)	**0.036#**
AF (at the time of TEE)	45 (17.44%)	27 (11.84%)	18 (60.00%)	**<0.001§**
Type of AF				**<0.001§**
Paroxysmal	195 (75.58%)	185 (81.14%)	10 (33.33%)*	
Persistent	43 (16.67%)	32 (14.04%)	11 (36.67%)*	
Permanent	20 (7.75%)	11 (4.82%)	9 (30.00%)*	
History of prior cardioversion	31 (12.02%)	28 (12.28%)	3 (10.00%)	1.000#
Receiving anticoagulant therapy	199 (77.13%)	170 (74.56%)	29 (96.67%)	**0.013§**
Warfarin	115 (44.57%)	89 (39.04%)	26 (86.67%)*	**<0.001¶**
Dabigatran	29 (11.24%)	27 (11.84%)	2 (6.67%)	
Rivaroxaban	10 (3.88%)	10 (4.39%)	0 (0.00%)	
Apixaban	45 (17.44%)	44 (19.30%)	1 (3.33%)*	
Antiplatelet therapy	50 (19.38%)	49 (21.49%)	1 (3.33%)	**0.034§**
ASA	39 (15.12%)	38 (16.67%)	1 (3.33%)	**0.154¶**
Clopidogrel	3 (1.16%)	3 (1.32%)	0 (0.00%)	
ASA + Clopidogrel	8 (3.10%)	8 (3.51%)	0 (0.00%)	
Intervention	176 (68.22%)	171 (75.00%)	5 (16.67%)	**<0.001§**
Cryoablation	160 (62.02%)	156 (68.42%)	3 (10.00%)*	
Radiofrequency	16 (6.20%)	15 (6.58%)	2 (6.67%)	
Thromboembolism after intervention	2 (0.78%)	1 (0.44%)	1 (3.33%)	0.219#
LVEDD, mm	46.18 ± 3.29	46.30 ± 3.26	45.27 ± 3.39	0.106†
IAS, cm	1 (1–1.1)	1 (1–1.1)	1 (1–1.15)	0.100‡
Posterior wall thickness, cm	0.98 ± 0.10	0.97 ± 0.10	1.01 ± 0.08	**0.049†**
Left atrial diameter, cm	4.02 ± 0.64	3.93 ± 0.59	4.63 ± 0.68	**<0.001†**
Ejection fraction, %	60 (60–61)	60 (60–61)	59.5 (55–60)	**<0.001‡**
Mitral stenosis	63 (24.42%)	45 (19.74%)	18 (60.00%)	**<0.001§**
Mitral regurgitation	257 (99.61%)	227 (99.56%)	30 (100.00%)	1.000#
Mild	247 (95.74%)	220 (96.49%)	27 (90.00%)	0.278¶
Moderate	9 (3.49%)	6 (2.63%)	3 (10.00%)	
Severe	1 (0.39%)	1 (0.44%)	0 (0.00%)	
sPAP	30 (25–38)	30 (25–35)	42 (35–45)	**<0.001‡**
Spontaneous echo contrast				**<0.001¶**
None	180 (69.77%)	178 (78.07%)	2 (6.67%)*	
Mild	36 (13.95%)	29 (12.72%)	7 (23.33%)	
Moderate	20 (7.75%)	14 (6.14%)	6 (20.00%)*	
Dense	22 (8.53%)	7 (3.07%)	15 (50.00%)*	

Table 1 (cont). Comparison of baseline demographic, clinical, echocardiographic, and laboratory characteristics between patients with and without left atrial appendage thrombus

		Thrombus status		*P*
	Total (n=258)	**No thrombus (n=228)**	**Thrombus present (n=30)**	
Albumin	4.22 ± 0.24	4.19 ± 0.24	4.44 ± 0.16	**<0.001†**
Total protein	7.19 ± 0.57	7.16 ± 0.57	7.38 ± 0.52	0.051†
TSH	1.7 (1.3–2.3)	1.7 (1.3–2.4)	1.3 (0.91–2.1)	**0.008‡**
Hemoglobin	14.13 ± 1.34	14.06 ± 1.35	14.61 ± 1.14	**0.034†**
Hematocrit	43.39 ± 3.95	43.01 ± 3.91	46.27 ± 2.98	**<0.001†**
CRP	1.1 (0.9–2.5)	1.01 (0.75–2.1)	3.05 (1.7–6.3)	**<0.001‡**
INR	1.1 (1.01–1.35)	1.1 (1.0–1.2)	2.0 (1.2–2.11)	**<0.001‡**
aPTT	31 (29–34.4)	31 (29–33.7)	37.5 (31–43)	**<0.001‡**
PRECISE-DAPT score	11.44 ± 4.45	11.43 ± 4.48	11.50 ± 4.33	0.935†
MAPH score	2 (2–3)	2 (2–3)	3 (2–4)	**<0.001‡**
CHA2DS2-VASc score	1 (0–2)	1 (0–2)	1 (0–3)	0.692‡

Descriptive statistics are presented as mean ± standard deviation for normally distributed continuous variables, median (25^{th}–75^{th} percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. †, Student's t test; ‡, Mann-Whitney U test; §, Chi-square test; #, Fisher's exact test; ¶, Fisher-Freeman-Halton test; *, Statistically significant category among variables with three or more categories; N/A, Not applicable. Statistically significant p values are shown in bold. AF, Atrial fibrillation; aPTT, Activated partial thromboplastin time; ASA, Acetylsalicylic acid; CRP, C-reactive protein; EF, Ejection fraction; IAS, Interatrial septum; INR, International normalized ratio; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; sPAP, Systolic pulmonary artery pressure; TIA, Transient ischemic attack; TSH, Thyroid-stimulating hormone.

All analyses were conducted using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Two-tailed p-values < 0.05 were considered statistically significant. The assumption of normality was evaluated using histograms and Q-Q plots. Descriptive statistics are presented as mean ± standard deviation for normally distributed continuous variables, median (25^{th}–75^{th} percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. Normally distributed continuous variables were analyzed using Student's t-test, whereas non-normally distributed continuous variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test, Fisher's exact test, or the Fisher-Freeman-Halton test, as appropriate. The discriminative performance of the scores for identifying thrombus was evaluated using receiver operating characteristic (ROC) analysis. Optimal cutoff values for both scores were determined using Youden's index (sensitivity + specificity – 1). Comparison of area under the curve (AUC) values between the two scores was performed using the DeLong method. Multivariable logistic regression analysis was performed to identify factors independently associated with thrombus presence. Variables demonstrating statistical significance (P < 0.05) in univariate analysis were entered into the multivariable model using a forward conditional selection method. Before model construction, multicollinearity was assessed using variance inflation factors (VIF); all VIF values were below 5, indicating acceptable collinearity levels. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test.

Results

Thirty (11.6%) of the 258 patients undergoing AF ablation were found to have LAAT on TEE. Dense SEC was observed in 22 patients (8.53%). Patients with and without thrombi were similar in terms of age (57.9 ± 10.4 vs. 54.9 ± 11.8 years, P = 0.181) and sex (50.0% vs. 53.9%, P = 0.831). Clinical, echocardiographic, and laboratory parameters with group comparisons are comprehensively summarized in Table 1. Among anticoagulated patients, those with LA thrombus were more commonly treated with warfarin (76.2%) than non-vitamin K antagonist oral anticoagulants (NOACs) (11.9%), whereas the opposite pattern was observed in patients without thrombus (warfarin 35.0%, NOACs 58.4%, P < 0.001).

Patients with thrombi had a significantly higher frequency of AF at the time of evaluation (60.0% vs. 11.8%, P < 0.001) and were more likely to have persistent (36.7% vs. 14.0%) or permanent AF (30.0% vs. 4.8%) subtypes (P < 0.001). Anticoagulant treatment overall was significantly more prevalent in the thrombus group (96.7% vs. 74.6%, P = 0.013), particularly warfarin use (86.7% vs. 39.0%, P < 0.001). In contrast, apixaban was less frequently used among patients with thrombi (3.3% vs. 19.3%).

Spontaneous echo contrast was detected far more frequently in the LAAT group, with dense SEC observed in 50.0% versus 3.1% (P < 0.001). Other echocardiographic parameters also differed significantly: left atrial diameter was larger in patients with thrombi (4.63 ± 0.68 cm vs. 3.93 ± 0.59 cm, P < 0.001), systolic pulmonary artery pressure was higher (42 mmHg [interquartile range, IQR: 35–45] vs. 30 mmHg [25–35], P < 0.001), and ejection fraction was slightly lower (59.5% [55–60] vs. 60% [60–61], P < 0.001). Mitral stenosis was also significantly more prevalent in the thrombus group (60.0% vs. 19.7%, P < 0.001).

Laboratory analysis revealed significantly lower serum albumin levels in the LAAT group (4.44 ± 0.16 g/dL vs. 4.19 ± 0.24 g/dL, P < 0.001), along with higher levels of C-reactive protein (3.05 mg/L [1.7–6.3] vs. 1.01 mg/L [0.75–2.1], P < 0.001) and INR (2.0 [1.2–2.11] vs. 1.1 [1.0–1.2], P < 0.001). Hemoglobin (14.61 ± 1.14 g/dL vs. 14.06 ± 1.35 g/dL, P = 0.034) and Hct

Table 2. Discriminative performance of the MAPH and CHA_2DS_2-VASc scores for identifying left atrial appendage thrombus: receiver operating characteristic (ROC) curve analysis

	MAPH score	CHA_2DS_2-VASc score
Cutoff	>3.5	>2.5
Sensitivity	40.00%	30.00%
Specificity	89.04%	80.26%
Accuracy	83.33%	74.42%
PPV	32.43%	16.67%
NPV	91.86%	89.71%
AUC (95% CI)	0.679 (0.574–0.783)	0.478 (0.356–0.601)
P†	**0.001**	0.729
AUC difference (95% CI)		
P‡	0.200 (0.041–0.359)	
	0.014	

AUC, Area under the ROC curve; CI, Confidence interval; NPV, Negative predictive value; PPV, Positive predictive value; ROC, Receiver operating characteristic. Statistically significant p values are shown in bold; †, Significance of the AUC under the null hypothesis (H0: AUC = 0.500) for each score; ‡, Comparison of AUCs under the null hypothesis (H0: AUC difference = 0.000). Cutoff values were determined using Youden's index to maximize the sum of sensitivity and specificity.

(46.27 ± 2.98% vs. 43.01 ± 3.91%, P < 0.001) values were also significantly higher in patients with thrombi. TSH levels showed a slight but statistically significant difference, with lower values in the LAAT group (1.3 mIU/L [0.91–2.1] vs. 1.7 mIU/L [1.3–2.4], P = 0.008). Importantly, MAPH scores were significantly higher in patients with thrombi compared to those without (median 3 [IQR 2–4] vs. 2 [2–3], P < 0.001). In contrast, CHA_2DS_2-VASc scores were similar between the two groups (median 1 [0–3] vs. 1 [0–2], P = 0.692).

Because CHA_2DS_2-VASc scores did not differ significantly between groups, ROC analysis was non-significant (AUC: 0.478, 95% confidence interval [CI]: 0.356–0.601; P = 0.729). In contrast, the MAPH score demonstrated significant discriminative ability for distinguishing patients with and without thrombi, with an AUC of 0.679 (95% CI: 0.574–0.783; P = 0.001). The difference between the AUCs was statistically significant (AUC difference: 0.200 [95% CI: 0.041–0.359], P = 0.014), indicating not only significant discriminatory power but also superior performance of the MAPH score in identifying thrombus presence. At the optimal cutoff value (> 3.5), as determined by Youden's index, the MAPH

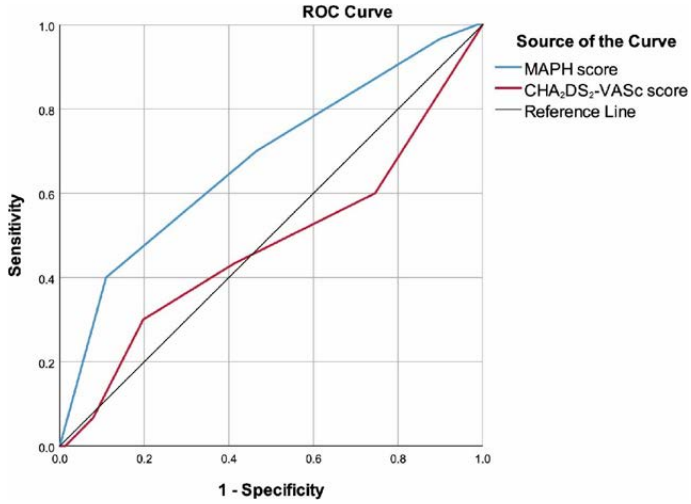

Figure 2. Receiver operating characteristic (ROC) curves of the MAPH score and the CHA_2DS_2-VASc scores for identifying left atrial appendage thrombus.

score yielded a sensitivity of 40.0%, specificity of 89.0%, and overall accuracy of 83.3%. Despite its non-significance, the discriminative performance of the CHA_2DS_2-VASc score was also evaluated. The best cutoff value was > 2.5, corresponding to a sensitivity of 30.0%, specificity of 80.3%, and accuracy of 74.4%. One subtle but important finding was that the MAPH score had a negative predictive value (NPV) of almost 92%, which was marginally higher than that of the CHA_2DS_2-VASc score (Table 2, Figure 2).

Our multivariable regression analysis identified several factors independently associated with the presence of thrombus. These included AF at the time of TEE (odds ratio [OR]: 3.834, 95% CI: 1.284–11.451; P = 0.016), anticoagulant treatment (OR: 14.954, 95% CI: 1.403–159.417; P = 0.025), high albumin levels (OR: 1328.499, 95% CI: 43.117–40933; P < 0.001), elevated CRP (OR: 1.381, 95% CI: 1.136–1.679; P = 0.001), and higher INR (OR: 9.093, 95% CI: 2.866–28.855; P < 0.001). Other variables included in the analysis, such as stroke/TIA (P = 0.695), AF type (P = 0.085), antiplatelet use (P = 0.390), posterior wall thickness (P = 0.145), left atrial diameter (P = 0.094), ejection fraction (P = 0.481), mitral stenosis (P = 0.160), sPAP (P = 0.098), TSH (P = 0.484), hemoglobin (P = 0.891), Hct (P = 0.231), aPTT (P = 0.836), and MAPH score (P = 0.146), were not independently associated with LAAT (Table 3).

Table 3. Factors independently associated with left atrial appendage thrombus: multivariable logistic regression analysis

	β coefficient	Standard error	*P*	Exp(β)	95% CI for Exp(β)	
AF present at the time of TEE	1.344	0.558	**0.016**	3.834	1.284	11.451
Anticoagulant therapy in use	2.705	1.207	**0.025**	14.954	1.403	159.417
Albumin	7.192	1.749	**<0.001**	1328.499	43.117	40933.511
CRP	0.323	0.100	**0.001**	1.381	1.136	1.679
INR	2.208	0.589	**<0.001**	9.093	2.866	28.855
Constant	-40.314	8.531	<0.001			

Nagelkerke R^2 = 0.594. Statistically significant p values are shown in bold. AUC, Area under the curve; CI, Confidence interval; CRP, C-reactive protein; Exp(β), Exponentiated beta coefficient (odds ratio); INR, International normalized ratio.

Discussion

We aimed to investigate the clinical, laboratory, and echocardiographic factors associated with LAAT in patients with AF and to determine whether the MAPH score could be used for this purpose and how it performs relative to the CHA_2DS_2-VASc score. Our findings demonstrate that inflammation (CRP), coagulation status (INR), heart rhythm at the time of imaging, and albumin levels were associated with the presence of LAAT. Although the CHA_2DS_2-VASc score is widely used for long-term thromboembolic risk stratification in cardiology, its association with existing LAAT was found to be limited. In contrast, the MAPH score showed a significantly stronger association with the presence of LAAT detected on TEE. Furthermore, our results demonstrate that LAAT is associated not only with conventional clinical risk factors but also with biochemical and rhythm-related parameters, indicating that comprehensive evaluation may improve patient risk stratification.

In our study, the prevalence of LAAT was 11.6% among patients with non-valvular AF scheduled for ablation. This finding indicates that LAAT may occur at a notable frequency even in a population receiving anticoagulant therapy. In contrast, a meta-analysis reported LAAT frequencies of 1.1% in pre-ablation TEE assessments and 4.0% in pre-cardioversion evaluations among patients with AF receiving oral anticoagulants.[14] Other series have reported LAAT prevalence ranging from 2.1% to 4.4%,[15-21] whereas some studies described rates exceeding 11% or reaching up to 15% patients with AF receiving oral anticoagulants.[22-25] This variability may be influenced by differences in patient clinical characteristics, duration and adequacy of anticoagulation, imaging modality, and study design. The relatively higher prevalence observed in our cohort may be partly explained by the greater proportion of patients in ongoing AF at the time of TEE and the overrepresentation of individuals with elevated thromboembolic risk among those referred for ablation. In addition, unlike many prior studies, our cohort included individuals who were not receiving anticoagulant therapy, which may also have contributed to the higher prevalence observed. We believe the present findings indicate the need for a multidimensional approach incorporating laboratory measurements to reliably assess LAAT presence, distinguishing the MAPH score from the CHA_2DS_2-VASc score.

An important methodological consideration is the timing of laboratory measurements relative to TEE. In our study, blood samples were obtained 24–48 hours prior to imaging. Therefore, the observed association between higher MAPH scores and LAAT presence likely reflects an ongoing thrombo-inflammatory state rather than the score's ability to predict future thrombus formation. The MAPH score should thus be interpreted primarily as a marker associated with existing thrombus at the time of evaluation, rather than as a tool for long-term thromboembolic risk prediction. It is also important to emphasize that the CHA_2DS_2-VASc and MAPH scores serve fundamentally different purposes. The CHA_2DS_2-VASc score is a validated clinical tool designed to estimate long-term stroke risk and guide anticoagulation decisions in patients with AF, incorporating demographic and comorbidity variables that reflect cumulative vascular burden. In contrast, the MAPH score is derived from contemporaneous hematological parameters that may reflect the current thrombogenic milieu. Therefore, our comparison should not be interpreted as suggesting that the MAPH score can replace the CHA_2DS_2-VASc score for long-term risk stratification. Rather, our findings indicate that the MAPH score may be more closely associated with the presence of an existing thrombus at a specific point in time, potentially complementing clinical risk assessment in the pre-procedural setting.

In our study, the presence of AF rhythm, receipt of anticoagulant therapy, elevated CRP and INR levels, and lower serum albumin concentration were independently associated with LAAT. The literature indicates that non-paroxysmal or persistent AF increases thrombus formation by impairing atrial contractility and promoting stasis. Additionally, electrocardiography-based interatrial block has been proposed as an independent marker of LAAT risk.[22,26] Structural and functional parameters, such as reduced left ventricular ejection fraction (LVEF), enlarged left atrial size, elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and reduced left atrial appendage flow, have also been identified as predictors in previous studies.[2,21,27,28] Regarding systemic inflammation, elevated neutrophil-to-lymphocyte ratio, reduced lymphocyte-to-monocyte ratio, and increased fibrinogen and bilirubin levels are notable findings. In our cohort, the associations observed with CRP and INR further support the role of inflammation on endothelial dysfunction and circulation.[29-31] The type and adequacy of anticoagulation are also important considerations, as LAAT may still occur, particularly when dosing is inappropriately reduced.[24]

The MAPH score was initially introduced as a simple tool to estimate thrombus burden in patients with ST-segment elevation myocardial infarction (STEMI).[7] Subsequent studies have demonstrated its association with coronary thrombus burden in both STEMI and non-STEMI populations.[8-10] It has also been proposed as a useful marker for distinguishing central and peripheral subtypes of pulmonary embolism, and its association with the coronary slow-flow phenomenon has been reported.[32,33] In an analysis including patients with infective endocarditis, a strong correlation was observed between higher MAPH scores and the presence of vegetations larger than 10 mm.[34] A recent study also demonstrated a relationship between the MAPH score and the presence and severity of coronary artery disease, reporting that scores above 2 were associated with coronary artery disease, whereas scores above 3 were consistent with intermediate-to-high SYNTAX scores (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score).[35] In the field of neurovascular disease, the MAPH score has been shown to aid in differentiating acute ischemic stroke from transient ischemic attack and in identifying major vessel occlusion.[36] Taken together, these findings suggest that the MAPH score is a reliable inflammation-related marker capable of reflecting thrombotic processes across various clinical conditions. Our study extends this body of evidence by demonstrating that the MAPH score is significantly associated with the presence of LAAT. This may be particularly relevant for evaluating patients at increased risk of cardioembolic stroke, especially in cases where the CHA_2DS_2-VASc score may fail to identify risks. As such, the MAPH score represents a noninvasive and easily calculated tool that appears to be especially useful as a screening marker for thrombotic risk.

On the other hand, the CHA_2DS_2-VASc score is a widely validated clinical classification system for long-term stroke risk prediction in patients with AF and has been shown in some cohorts to correlate with thromboembolic risk markers identified by TEE.[37] It has also been suggested that its predictive accuracy may be enhanced by incorporating left atrial functional parameters.[38] Nevertheless, although certain studies have demonstrated an association between CHA_2DS_2-VASc and LAAT or have supported its role in risk stratification, its predictive performance has frequently been reported as limited.[21,25,29,37,39,40] This observation is consistent with our findings. The CHA_2DS_2-VASc score was originally designed to estimate long-term stroke risk and does not incorporate variables reflecting thrombogenic mechanisms such as inflammation, coagulation activity, or viscosity. In line with this, the higher specificity and negative predictive value observed for the MAPH score in our study suggest that supplementing clinical risk scores with biomarker-based parameters may provide a more reliable approach to assessing LAAT risk.

While the MAPH score demonstrated significantly better discriminative performance than the CHA_2DS_2-VASc score in our study, we must acknowledge that both scores showed only modest ability to identify LA thrombus. The MAPH score achieved an AUC of 0.683, which, although significantly higher than that of CHA_2DS_2-VASc (AUC: 0.486), still falls short of what is generally considered strong discrimination (typically AUC > 0.7). This finding underscores an important point: although these scores may assist in risk stratification, they cannot replace TEE when definitive exclusion of thrombus is required prior to a procedure. The moderate AUC values likely reflect the complexity of thrombus formation in AF, which involves hemodynamic alterations, blood clotting tendencies, and structural cardiac changes, processes that clinical scoring systems cannot fully capture.

An important finding that warrants careful interpretation is the association between anticoagulant treatment and LA thrombus in our study. Although anticoagulant therapy emerged as an independent predictor in multivariable analysis (OR: 14.95), subgroup analysis revealed that patients with thrombus were predominantly treated with warfarin (76.2%) rather than NOACs (11.9%), whereas the opposite pattern was observed among patients without thrombus. This apparent paradox likely reflects confounding by indication: patients prescribed anticoagulants, particularly warfarin, may have had inherently higher baseline thromboembolic risk, which prompted anticoagulation in the first place. The predominance of warfarin use in the thrombus group may also indicate inadequate anticoagulation control, as suggested by the elevated INR values observed in this group, or may reflect the tendency for warfarin to be prescribed to patients with more complex clinical profiles who are not suitable candidates for NOACs. Overall, this finding highlights that the mere prescription of anticoagulant therapy does not eliminate thrombus risk, particularly when anticoagulation intensity is suboptimal or when patients have particularly high-risk features.

Our findings have several practical implications, which should be interpreted within appropriate boundaries. First, the MAPH score—calculated from routine laboratory parameters— showed a stronger association with existing LA thrombus than the CHA_2DS_2-VASc score, potentially helping to guide decisions regarding which patients warrant TEE, even when CHA_2DS_2-VASc scores are low. Second, the MAPH score incorporates markers related to blood viscosity and prothrombotic status that are not included in traditional clinical risk scores. Third, although neither score can replace TEE for definitive thrombus exclusion, integrating the MAPH score into pre-procedural assessment may enhance risk stratification. Finally, our identification of AF at the time of TEE, elevated CRP levels, and suboptimal anticoagulation as independent predictors highlights potentially modifiable elements that warrant clinical attention. The potential clinical utility of the MAPH score may be particularly relevant in patients with CHA_2DS_2-VASc scores of 0 or 1, in whom anticoagulation decisions are often uncertain and the benefit-risk balance is less clear. In this subgroup, an elevated MAPH score might prompt consideration of TEE, even when conventional risk assessment suggests low thromboembolic risk. However, beyond this specific context, the current data do not support replacing validated thromboembolic risk scores with the MAPH score for broader clinical decision-making. Prospective validation studies evaluating the incremental value of MAPH in clearly defined risk subgroups are essential before clinical implementation can be recommended.

Limitations

This study has several limitations. First, its single-center retrospective design may limit generalizability. Second, although an a priori power calculation confirmed an adequate sample size (n = 258), the class imbalance (30 vs. 228 patients) may have affected the precision of performance estimates and regression coefficients. Third, biochemical parameters were assessed at a single time point without longitudinal follow-up, and TEE examinations and laboratory tests were not performed simultaneously, introducing the possibility of temporal variation not captured by the scores. Fourth, we did not include certain variables, such as body mass index, electrolyte levels, or hepatorenal function parameters, that may influence thrombogenesis.

Fifth, we lacked data on time in therapeutic range (TTR) for warfarin users. The predominance of warfarin use in the thrombus group (76.2% vs. 35.0%) may reflect suboptimal anticoagulation control, poor adherence, or preferential selection of higher-risk patients for vitamin K antagonist therapy. Sixth, formal inter-observer agreement statistics for TEE interpretation were not calculated, although the low frequency of disagreement suggests acceptable reliability. Seventh, the extreme odds ratio observed for albumin (OR: 1328.5) warrants careful interpretation. This implausibly large effect size likely reflects statistical artifacts related to the narrow distribution of albumin values within our cohort, potential quasi-complete separation in the logistic regression model, and the relatively small number of events (n = 30). Such extreme ORs may occur when a continuous variable shows limited variance between outcome groups or when the model approaches perfect classification across certain variable ranges. Therefore, this finding should be interpreted as indicating a strong statistical association rather than a clinically meaningful magnitude of effect. Eighth, the inclusion of INR in the multivariable analysis also warrants consideration. Given the unknown TTR for warfarin users and the predominance of warfarin use in the thrombus group, elevated INR may serve as a surrogate marker of inadequate anticoagulation control or selection bias rather than a true independent risk factor. Future studies incorporating detailed anticoagulation quality metrics are needed to clarify this relationship.

Conclusion

The MAPH score demonstrated a significantly stronger association with LA thrombus compared to the CHA_2DS_2-VASc score in patients with non-valvular AF undergoing pre-procedural TEE assessment. By incorporating hematological parameters that reflect blood viscosity and prothrombotic state, the MAPH score provided improved discriminative ability for detecting existing thrombus beyond traditional clinical risk factors. Although both scores exhibited moderate overall performance, and neither can replace TEE for definitive thrombus detection, the MAPH score may help identify patients with a higher likelihood of LA thrombus who could benefit most from TEE. These findings support further investigation of MAPH scoring as a complementary screening tool in the pre-procedural thrombus evaluation of AF patients scheduled for ablation, with the caveat that prospective validation is required before clinical implementation.

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Ethanol Infusion into the Vein of Marshall Enhances Mitral Isthmus Block and Reduces Atrial Fibrillation Recurrence: A Comprehensive Meta-Analysis

Marshall Toplardamarına Etanol İnfüzyonu Mitral İstmus Blokajını Artırır ve Atriyal Fibrilasyon Nüksünü Azaltır: Kapsamlı Bir Meta-Analiz

ABSTRACT

Adjunctive vein of Marshall ethanol infusion (EIVOM) during atrial fibrillation (AF) ablation has emerged as a promising technique with the potential to significantly improve procedural outcomes. Despite the existing body of evidence, a comprehensive evaluation focusing on mitral isthmus block, AF recurrence, and procedural duration has not yet been conducted. This meta-analysis aims to rigorously assess the benefits of EIVOM combined with radiofrequency ablation (EIVOM-RF) compared with radiofrequency ablation alone (RF-only) in patients undergoing catheter ablation for AF or related arrhythmias. We systematically reviewed both randomized controlled trials and observational studies that compared EIVOM-RF with RF-only approaches, encompassing a total of 1,406 patients in the EIVOM-RF group and 1,849 in the RF-only group. The primary outcomes assessed included the rate of successful mitral isthmus ablation, recurrence of atrial arrhythmias, and overall procedure time. Patients treated with EIVOM-RF demonstrated a significantly lower likelihood of atrial arrhythmia recurrence compared to those receiving RF-only treatment. Furthermore, EIVOM-RF was associated with an impressive increase in the success rate of achieving mitral isthmus block. While total procedure time tended to be longer with EIVOM-RF, this difference was statistically significant and showed considerable variability. These findings compellingly indicate that EIVOM enhances procedural efficacy, albeit at the cost of increased procedural duration. In conclusion, EIVOM combined with RF ablation represents a transformative approach that markedly improves procedural success rates and significantly reduces arrhythmia recurrence in patients undergoing ablation for AF.

Keywords: Atrial fibrillation, catheter ablation, ethanol infusion, meta-analysis, mitral isthmus block, recurrence, vein of Marshall

ÖZET

Atriyal fibrilasyon (AF) ablasyonu sırasında ek olarak Marshall toplardamarına etanol infüzyonu, prosedür sonuçlarını önemli ölçüde iyileştirme potansiyeli olan umut verici bir teknik olarak ortaya çıkmıştır. Mevcut kanıtlara rağmen, mitral istmus bloğu, AF nüksü ve prosedür süresine odaklanan kapsamlı bir değerlendirme henüz yapılmamıştır. Bu meta-analiz, AF veya ilgili aritmiler için kateter ablasyonu geçiren hastalarda, radyofrekans ablasyonu (sadece RF) ile karşılaştırıldığında, radyofrekans ablasyonu ile kombine EIVOM'un (EIVOM-RF) faydalarını titizlikle değerlendirmeyi amaçlamaktadır. EIVOM-RF ile sadece RF yaklaşımlarını karşılaştıran randomize kontrollü çalışmalar ve gözlemsel çalışmaları sistematik olarak inceledik; EIVOM-RF grubunda toplam 1.406 hasta, sadece RF grubunda ise 1.849 hasta yer almaktaydı. Değerlendirilen birincil sonuçlar arasında başarılı mitral istmus ablasyon oranı, atriyal aritmilerin nüksetme oranı ve toplam prosedür süresi yer almaktaydı. EIVOM-RF ile tedavi edilen hastalar, sadece RF tedavisi alanlara kıyasla atriyal aritmi nüksü yaşama olasılığının önemli ölçüde daha düşük olduğunu göstermiştir. Ayrıca, EIVOM-RF, mitral istmus blokajının başarı oranında etkileyici bir artışla ilişkilendirilmiştir. EIVOM-RF ile toplam işlem süresi daha uzun olma eğilimdedir, bu fark istatistiksel olarak anlamlıdır ve belirgin değişkenlik göztermiştir. Bu bulgular, EIVOM'un işlem süresini arttırmasına rağmen işlem etkinliğini arttırdığını kesin olarak göstermektedir. Sonuç olarak, RF ablasyon ile birlikte uygulanan EIVOM, AF için ablasyon uygulanan hastalarda işlem başarı oranlarını belirgin şekilde arttıran ve aritmi nüksünü önemli ölçüde azaltan dönüşüme neden olacak bir yaklaşımdır.

Anahtar Kelimeler: Atriyal fibrilasyon, kateter ablasyonu, etanol infüzyonu, meta-analiz, mitral istmus bloğu, nüks, Marshall veni

REVIEW
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Atrial fibrillation (AF) is the most prevalent sustained arrhythmia encountered in clinical practice and is associated with substantial morbidity, including increased risks of stroke, heart failure, and reduced quality of life. Catheter ablation (CA), particularly through pulmonary vein isolation (PVI), is a well-established treatment for AF, especially in its paroxysmal form.[1] However, its efficacy in managing persistent and long-standing AF is often inadequate, primarily due to the intricate substrate and challenges in achieving lasting linear lesions, especially across the mitral isthmus (MI).[2] The vein of Marshall (VOM)—a vestigial structure involved in arrhythmogenic conduction and autonomic modulation—has emerged as an innovative therapeutic target with the potential to enhance ablation strategies.

Recent investigations have highlighted the use of ethanol infusion into the vein of Marshall (EIVOM) as a powerful adjunct to CA.[3] This approach aims to achieve robust mitral isthmus block, suppress arrhythmogenic activity, and facilitate autonomic denervation, ultimately improving long-term rhythm outcomes. Initial observational studies and the VENUS randomized trial (the Vein of Marshall Ethanol Infusion for Persistent Atrial Fibrillation) have shown promising results; however, considerable variability remains across studies in terms of patient demographics, procedural techniques, and reported outcomes.[2]

The latest meta-analysis by Ge et al.[4] synthesized data from nine studies, revealing that the combination of EIVOM with CA significantly enhances rates of mitral isthmus block and markedly reduces the recurrence of AF and atrial tachycardia (AT), while maintaining a stable profile of periprocedural complications. However, as highlighted in their findings, discrepancies in study design and methodology, limited subgroup analyses, and inconsistent reporting hinder the broader applicability and mechanistic understanding of these conclusions. Critical outcome measures, including procedural duration and subgroup performance in specific arrhythmia phenotypes (e.g., peri-mitral atrial flutter), remain inadequately explored. In the present meta-analysis, we aim to build upon prior findings by incorporating newly published studies from 2023 to 2025 and focusing on three pivotal procedural and clinical endpoints: (1) the success rate of mitral isthmus ablation, (2) the recurrence of atrial arrhythmias following the blanking period, and (3) procedure time. This comprehensive synthesis of the evolving evidence surrounding EIVOM aims to further clarify its vital role in advancing modern electrophysiology.

ABBREVIATIONS

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AT	Atrial tachycardia
BMI	Body mass index
CA	Catheter ablation
CAD	Coronary artery disease
DM	Diabetes mellitus
EIVOM-RF	Ethanol infusion into the vein of Marshall combined with radiofrequency ablation
HF	Heart failure
HTN	Hypertension
LA	Left atrial
LVEF	Left ventricular ejection fraction
MI	Mitral isthmus
PVI	Pulmonary vein isolation
RCT	Randomized controlled trial
RF-only	Radiofrequency ablation alone
VOM	Vein of Marshall

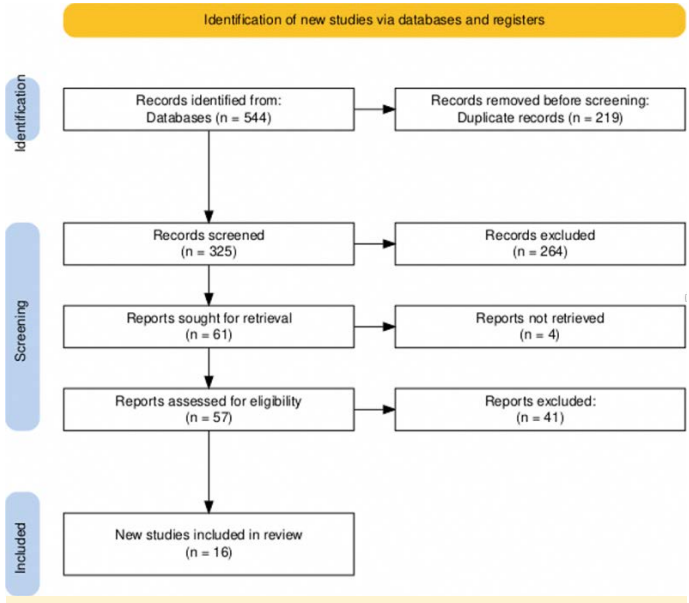

Figure 1. Flowchart of the study selection process for the meta-analysis.

Materials and Methods

Study Selection and Data Sources

A systematic review and meta-analysis were conducted to evaluate the efficacy and procedural outcomes of ethanol infusion into the vein of Marshall combined with radiofrequency ablation (EIVOM-RF) compared with radiofrequency (RF) ablation alone for the treatment of atrial arrhythmias. The study protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) (CRD420251062338). Included in the analysis were 12 multi-center and single-center retrospective studies, two prospective single-center observational studies, one prospective single-center randomized controlled trial (RCT), and one multi-center RCT (Figure 1). Follow-up durations varied, with some studies reporting no follow-up and others extending up to 70 months; however, the majority (13 studies) reported a 12-month follow-up period. The atrial tachycardia subtypes investigated included persistent AF, paroxysmal AF, non-paroxysmal/paroxysmal AF, peri-mitral atrial tachycardia, and peri-mitral flutter. In total, 3,255 patients were included across all studies, with 1,406 in the EIVOM-RF group and 1,849 in the RF-only group.

Data Extraction and Outcomes

Data extraction was conducted by two independent researchers to ensure a thorough and unbiased approach. Any disagreements were resolved through collaborative discussions to reach a unanimous consensus. Baseline characteristics extracted included critical factors such as age, sex, hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), history

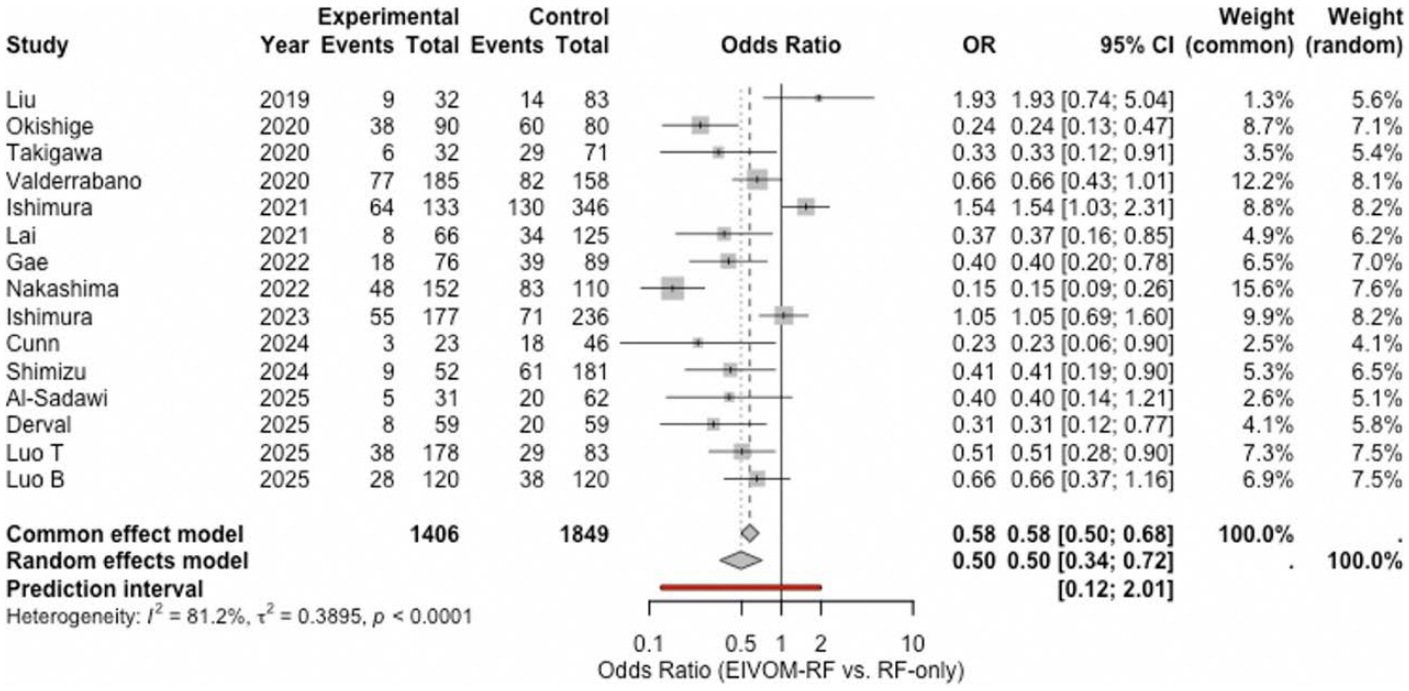

Figure 2. Forest plot of pooled effect sizes comparing vein of Marshall ethanol infusion combined with radiofrequency ablation versus radiofrequency ablation alone for atrial arrhythmia recurrence.

of stroke, heart failure (HF), CHA_2DS_2-VASc score (Congestive Heart Failure, Hypertension, Age ≥ 75 years (doubled), Diabetes Mellitus, prior Stroke or TIA (doubled), Vascular disease, Age 65–74 years, and Sex category (female)), left ventricular ejection fraction (LVEF), left atrial (LA) diameter, LA volume index, body mass index (BMI), and prior use of antiarrhythmic drugs (AADs). Key outcome measures assessed included recurrence of atrial arrhythmias (15 studies), total procedure time (12 studies), and ablation success (11 studies). Comprehensive data collection included both the EIVOM-RF and RF-only groups, with continuous variables reported as means and standard deviations (or ranges when available), while binary outcomes were presented as event counts.

Risk of Bias Assessment

Risk of bias was evaluated using the Ottawa risk of bias tool, adapted to assess the quality of both observational studies and RCTs. The domains assessed included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was rated as low, moderate, or high risk, with results summarized narratively to inform interpretation of the meta-analysis findings.

Statistical Analysis

Meta-analyses were performed using R statistical software (version 4.3.3; R Foundation for Statistical Computing) with the 'meta' and 'metafor' packages. For recurrence of atrial arrhythmias and MI ablation, binary outcomes were analyzed using the Mantel-Haenszel method for the common-effect model and the inverse variance method for the random-effects model, with odds ratios (OR) and 95% confidence intervals (CI) reported. Total procedure time, a continuous outcome, was analyzed using the inverse variance method for both models, with mean differences (MD) and 95% CI reported. The restricted maximum-likelihood estimator was used to estimate between-study variance (tau²), with Q-profile methods applied to obtain confidence intervals of tau² and tau. Heterogeneity was assessed using the I^2 statistic (low < 25%, moderate 25–75%, high > 75%) and Cochran's Q test, with a p-value < 0.10 indicating significant heterogeneity. Prediction intervals were calculated using the t-distribution to estimate the range of true effects in future studies. A continuity correction of 0.5 was applied in studies with zero cell frequencies for MI ablation. Forest plots were generated to visualize effect sizes, with weights reported for both fixed- and random-effects models.

Results

Study Characteristics

This meta-analysis integrates findings from 16 studies conducted between 2019 and 2025, encompassing data from a total of 3,255 patients (1,406 treated with EIVOM-RF and 1,849 with RF-only). The studies demonstrated considerable diversity in design, including 12 retrospective analyses (eight multi-center and four single-center), two prospective observational studies (one single-center), and both a prospective single-center RCT and a multi-center RCT. Follow-up durations varied from 0 to 70 months, with 13 studies reporting a 12-month follow-up period. AT subtypes investigated included persistent AF (the focus of 12 studies), paroxysmal AF (one study), non-paroxysmal/paroxysmal AF (two studies), peri-mitral AT (one study), and peri-mitral atrial flutter (one study). Baseline characteristics showed significant variability: patient ages ranged from 56.0 to 68.0 years, the proportion of male participants ranged from 57.3% to 90.6%, and comorbidities varied considerably, with hypertension affecting 22.4% to 87.5% of patients and diabetes mellitus affecting 4.2% to 35.0% (Appendix 1).[2,3,5-18]

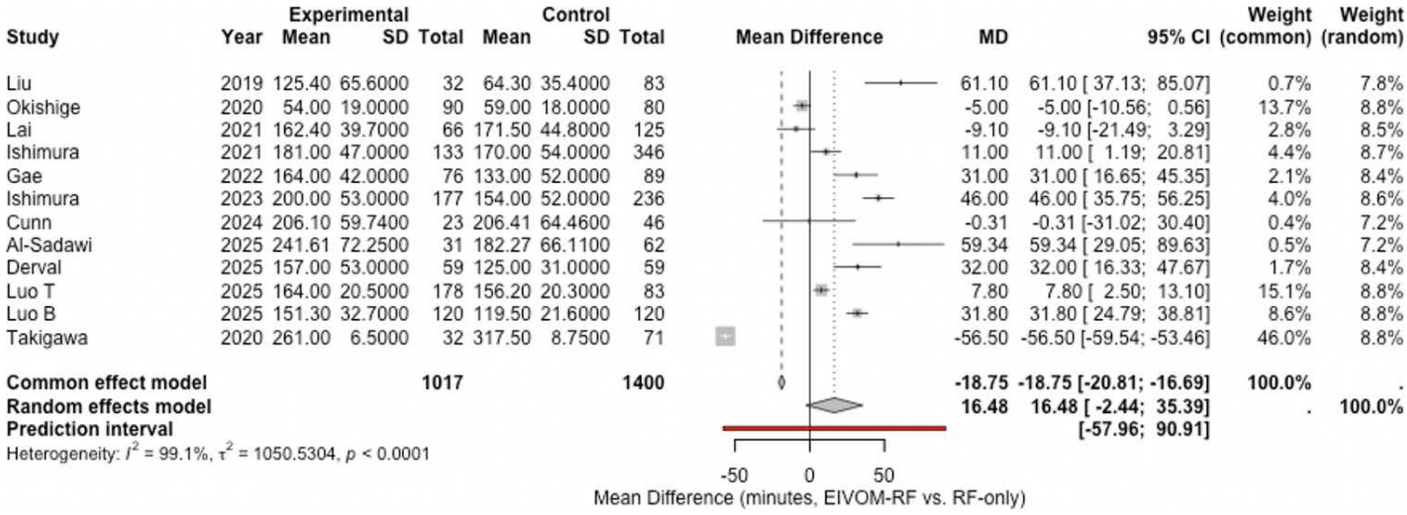

Figure 3. Forest plot of pooled effect sizes comparing vein of Marshall ethanol infusion combined with radiofrequency ablation versus radiofrequency ablation alone for total procedure time.

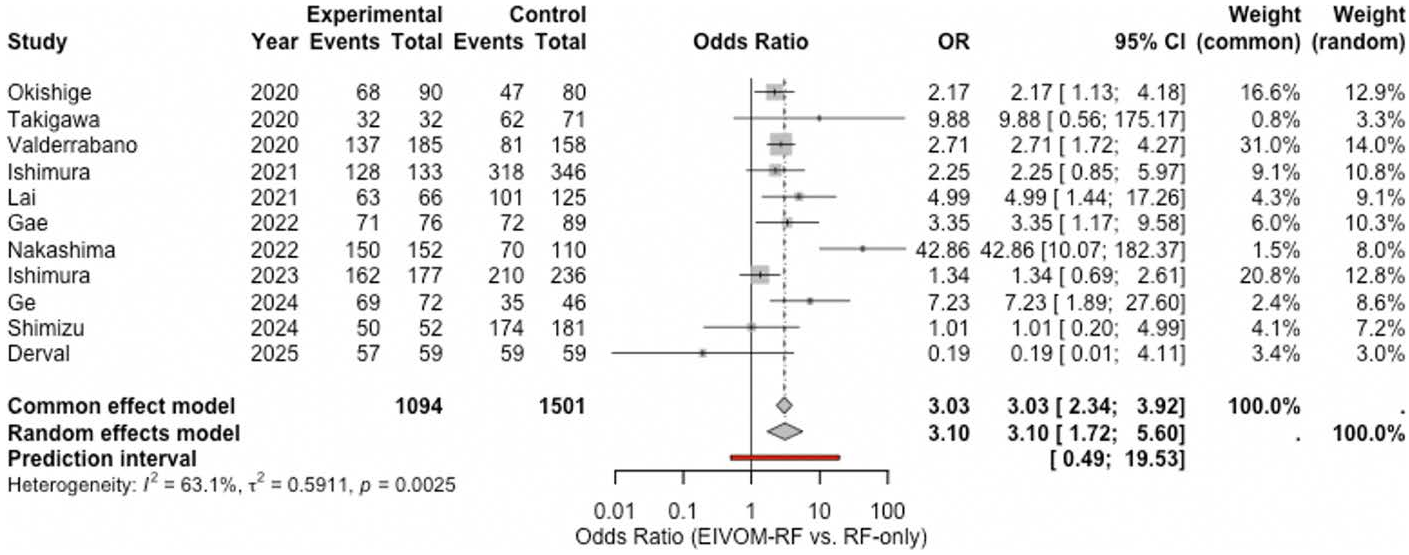

Figure 4. Forest plot of pooled effect sizes comparing vein of Marshall ethanol infusion combined with radiofrequency ablation versus radiofrequency ablation alone for mitral isthmus ablation.

Recurrence of Atrial Arrhythmias

A comprehensive analysis of 15 studies reporting recurrence of atrial arrhythmias revealed notable findings (Figure 2). The fixed-effects models demonstrated an OR of 0.5789 [95% CI: 0.4953, 0.6765], with a z-score of -6.88 and a p-value < 0.0001, indicating a significant reduction in recurrence with EIVOM-RF. The random-effects model showed an OR of 0.4954 [95% CI: 0.3423, 0.7169], with a z-score of -3.72 and a p-value of 0.0002, along a prediction interval of [0.1224, 2.0055]. High heterogeneity was observed (I^2 = 81.2% [70.1%, 88.2%], Q = 74.63, df = 14, P < 0.0001; tau^2 = 0.3895), indicating considerable variability among studies. Individual study ORs ranged from 0.1501 (Nakashima et al.[9] in 2022) to 1.9286 (Liu et al.[15] in 2019), with model weights varying significantly (common: 1.3%–15.6%, random: 4.1%–8.2%).

Total Procedure Time

Twelve studies evaluated total procedure time (Figure 3). The fixed-effects model revealed a mean difference (MD) of -18.7509 [95% CI: -20.8096, -16.6923], with a z-score of -17.85 and a highly significant p-value of < 0.0001, favoring RF-only procedures. In contrast, the random-effects model indicated a mean difference of 16.4778 [95% CI: -2.4362, 35.3919], with a z-score of 1.71 and a p-value of 0.0877, along with a wide prediction interval [-57.9551, 90.9107]. Heterogeneity among studies was extremely high (I^2 = 99.1% [98.9%, 99.3%], Q = 1,260.57, df = 11, P < 0.0001; tau^2 = 1,050.5304), underscoring the variability in the findings. Individual mean differences ranged widely, from -56.5000 in Takigawa et al.[11] in 2020 to 61.1000 in Liu et al.[15] in 2019, with study weights demonstrating variability (common: 0.4%–46.0%, random: 7.2%–8.8%).

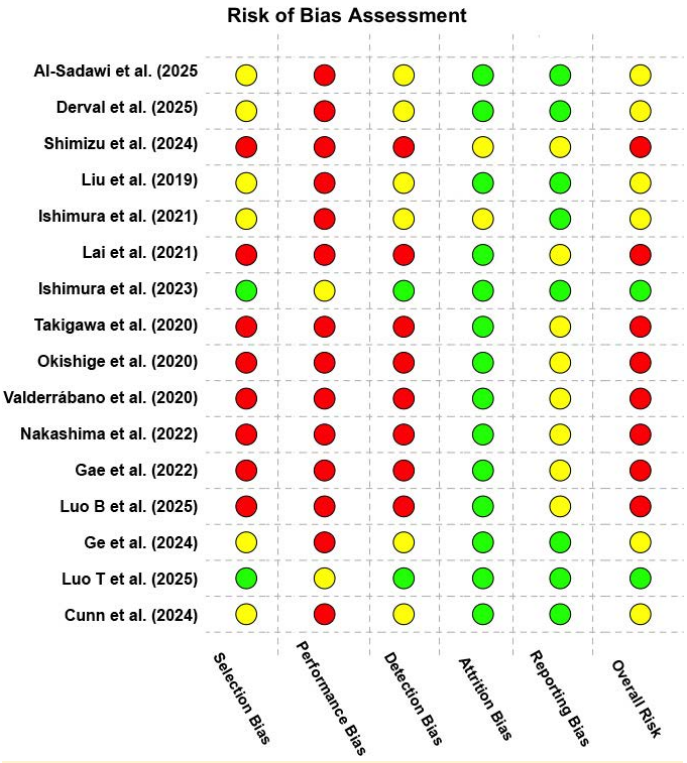

Figure 5. Risk of bias assessment using the Ottawa risk of bias tool, tailored to evaluate the quality of observational studies and randomized controlled trials.

Mitral Isthmus Ablation

A comprehensive analysis of 11 studies (k = 11, o = 2,595; o.e = 1,094, o.c = 1,501; e = 2,216) evaluated the success of MI ablation, as illustrated in Figure 4. The fixed-effects model revealed an OR of 3.0306 [95% CI: 2.3433, 3.9196], with a z-value of 8.45 and P < 0.0001, strongly favoring EIVOM-RF. Similarly, the random-effects model demonstrated an OR of 3.1020 [95% CI: 1.7198, 5.5951], with a z-value of 3.76 and P = 0.0002, underscoring the robustness of these findings, with a prediction interval of [0.4928, 19.5255]. The level of heterogeneity was moderate (I^2 = 63.1% [29.2%, 80.7%], Q = 27.07, df = 10, P = 0.0025; tau^2 = 0.5911), indicating some variability among the studies. Individual ORs ranged from 0.1933 (Derval et al.[17] in 2025) to 42.8571 (Nakashima et al.[9] in 2022), with corresponding weights varying accordingly (common: 0.8%–31.0%, random: 3.0%–14.0%).

Risk of Bias

The risk of bias assessment using the Ottawa tool showed considerable variability across the studies (Figure 5). While most retrospective studies demonstrated a moderate to high risk due to potential selection and reporting biases, the RCTs by Valderrábano[2] in 2020 and Derval et al.[17] in 2025 showed a lower risk profile. However, concerns regarding performance bias persist due to inadequate blinding. Detailed ratings and supporting information are provided in the supplementary materials.

Discussion

In clinical electrophysiology, improving outcomes for patients with non-paroxysmal AF remains a significant challenge. Despite advancements in ablation techniques, recurrence rates are still high. While PVI is foundational in AF treatment, it often proves insufficient for patients with persistent arrhythmias driven by non-pulmonary triggers and macro re-entrant circuits. One critical area that requires intervention is the mitral isthmus, where achieving a durable linear block is often technically complex.[19] Incomplete block in this region frequently leads to recurrence of arrhythmias, especially peri-mitral flutter. A promising solution to the anatomical and electrophysiological challenges encountered in standard ablation is ethanol infusion into the VOM.[20] Ethanol has the ability to reach the epicardial area of the mitral isthmus, which is typically inaccessible using endocardial radiofrequency energy. Its infusion results in chemical ablation of myocardial fibers and autonomic ganglia, facilitating substrate modification and autonomic denervation. These effects enhance lesion durability and reduce the likelihood of conduction recovery, thereby lowering the risk of arrhythmia recurrence.[21]

This meta-analysis compiles data from 16 pivotal studies involving more than 3,200 patients, providing strong evidence for the effectiveness of EIVOM as a valuable adjunct to catheter ablation for AF. Patients who received EIVOM during their ablation procedures demonstrated consistently higher rates of complete mitral isthmus block—an outcome that emerged across multiple studies. This finding suggests that the addition of ethanol effectively addresses structural barriers that hinder successful treatment. Moreover, the notable reduction in arrhythmia recurrence further underscores the clinical advantages of this innovative approach. The improved rhythm outcomes are especially significant for patients with persistent AF, for whom traditional ablation often falls short. Although a moderate increase in procedural duration was noted with EIVOM, this can be attributed to the additional steps required for cannulation and ethanol delivery. Importantly, this slight prolongation does not compromise procedural safety or overall outcomes. This trade-off appears worthwhile given the substantial improvements in lesion quality and sustained arrhythmia control. Embracing EIVOM not only enriches the ablation process but also holds the potential to transform patient outcomes in the management of atrial fibrillation.

Autonomic modulation is an important mechanism through which EIVOM enhances procedural success. The vein of Marshall contains autonomic innervation that can affect atrial refractoriness and promote AF.[22] Ablating this area not only aids in creating structural changes but also mitigates the effects of vagal triggers, helping to stabilize rhythm.[22] This dual approach highlights the growing significance of EIVOM in comprehensive substrate modification.

Mitral isthmus block is technically challenging with traditional RF ablation. In this analysis, incorporating EIVOM significantly increased the likelihood of achieving a successful mitral isthmus block by more than three times (OR = 3.10, 95% CI: 1.72–5.60), suggesting that ethanol infusion enhances lesion formation efficiency in the mitral isthmus. This improvement may stem from both mechanical and neuro-autonomic factors, including fibrotic alterations in the epicardial musculature, autonomic denervation, and better transmurality of ablation lesions. Moreover, the occurrence of atrial arrhythmias after the

blanking period was significantly lower in the EIVOM-RF group (OR = 0.50, 95% CI: 0.34–0.72), highlighting lasting rhythm control benefits. This effect persisted across different follow-up durations and arrhythmia types, affirming the strength of the outcome. However, there was considerable heterogeneity (I^2 = 81.2%), likely resulting from variations in study designs, patient characteristics, and the ablation techniques employed across studies. One concern regarding the implementation of EIVOM in ablation workflows is the potential increase in procedural burden. As expected, EIVOM-RF was associated with a trend toward longer total procedure times, with a mean difference of 16.48 minutes (95% CI: -2.44 to 35.39), although this was not statistically significant (P = 0.0877). The substantial heterogeneity in this measure (I^2 = 99.1%) could result from differences in operator experience, procedural workflow, and the technical difficulty of accessing the VOM. Nonetheless, it is crucial to consider this additional time alongside the long-term benefits of reduced recurrence rates and decreased need for repeat ablation procedures.

Our findings build on previous meta-analyses, including that by Ge et al.,[4] by incorporating more recent studies and broadening the scope of analysis. While earlier studies demonstrated the advantages of EIVOM for achieving mitral isthmus block and managing arrhythmia, our work adds further detail by including subgroup analyses and evaluating procedure time as a key endpoint. The inclusion of two RCTs, specifically the VENUS trial and the study by Derval et al.,[17] further strengthens the evidence and helps clarify causal relationships.[2,17] Notably, although the Derval et al.[17] trial did not show a benefit for mitral isthmus block, it did not significantly alter the overall effect size due to the larger supportive dataset.

The observed heterogeneity across outcomes necessitates cautious interpretation. For recurrence and procedure time, variability among studies was considerable, highlighting the influence of study design, patient demographics, and procedural techniques. The observed heterogeneity across outcomes necessitates cautious interpretation. For recurrence and procedure time, the variability among studies was considerable, underscoring the impact of study design, patient characteristics, and ablation techniques. Several of the included studies were retrospective and single-center, which may introduce selection bias and limit the applicability of the findings. Risk assessments indicated a higher risk of bias in non-randomized studies, primarily due to performance and reporting inconsistencies. However, the persistent trends across diverse studies enhance the reliability of the primary findings. Another limitation relates to inconsistencies in reporting. Not all studies uniformly detailed follow-up durations, definitions of mitral isthmus block, or methods for assessing recurrence, potentially affecting pooled estimates. Additionally, variations in post-ablation antiarrhythmic drug usage, operator expertise, and center-specific protocols could skew outcomes. The learning curve associated with EIVOM, which requires specialized skills and equipment, may also impact both success rates and procedural duration. Limited prospective data and differing follow-up methods introduce further bias. Rare complications from ethanol infusion, such as damage to the coronary sinus or surrounding structures, should also be considered. It is also important to acknowledge that the current evidence base is limited by the lack of standardized criteria for patient selection and variations in procedural techniques among studies. These methodological differences likely contribute to the observed heterogeneity and may affect the generalizability of our results. Therefore, interpretation of the present findings should remain cautious, and future investigations should focus on defining clear patient selection strategies and procedural standardization to ensure consistent outcomes. Future randomized trials with standardized methodologies are needed to refine patient selection, optimize procedural workflows, and confirm long-term safety.

Conclusion

This comprehensive and updated meta-analysis suggests that EIVOM is associated with a higher success rate of mitral isthmus ablation and a lower recurrence of atrial arrhythmias in patients undergoing CA. Although these findings indicate a potential clinical benefit, they should be interpreted with caution due to study heterogeneity and differences in patient selection and procedural strategies. Even though there is a slight increase in procedure time, the substantial benefits of enhanced rhythm control and long-lasting lesion formation make a strong case for its integration into standard clinical practice, particularly for patients with persistent AF or complex substrate. These results not only advocate for the broader adoption of EIVOM within tailored ablation strategies but also highlight the urgent need for ongoing improvements in procedural techniques and the generation of robust evidence through well-designed clinical trials.

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Suppression of Recurrent Ventricular Fibrillation Associated with J-Wave Syndrome Using Cilostazol

Silostazol Kullanılarak J-Dalga Sendromuyla İlişkili Tekrarlayan Ventriküler Fibrilasyonun Baskılanması

ABSTRACT

Survivors of sudden cardiac death (SCD) should be thoroughly evaluated for primary electrical heart diseases, including early repolarization syndrome (ERS). In some patients, early repolarization patterns may be masked by depolarization abnormalities or may appear intermittently, making diagnosis difficult. In addition to implantable cardioverter-defibrillator (ICD) implantation for secondary prevention, pharmacological agents such as quinidine and phosphodiesterase III inhibitors (e.g., cilostazol) are recommended to prevent or reduce recurrent ventricular fibrillation (VF) episodes. We present the case of a young female SCD survivor with documented VF and ICD implantation, who was admitted after Home Monitoring detected multiple short-coupled premature ventricular contraction-induced (PVC-induced) VF episodes. She was successfully treated with cilostazol.

Keywords: Cilostazol, early repolarization syndrome, ventricular fibrillation

ÖZET

Ani kardiyak ölüm (AKÖ) yaşayanları, erken repolarizasyon sendromu (ERS) dâhil olmak üzere kalbin birincil elektriksel hastalıkları açısından dikkatlice değerlendirilmelidir. Bazı hastalarda erken repolarizasyon paterni depolarizasyon veya aralıklı olarak gizlenebilir ve bu da teşhisi zorlaştırır. İkincil önleme için implante edilebilir kardiyoverter defibrilatör (ICD) implantasyonunun yanı sıra, tekrarlayan VF ataklarını önlemek veya azaltmak için kinidin ve fosfodiesteraz-III inhibitörleri (örn. silostazol) gibi farmakolojik ajanlar önerilir. Bu olguda evden izlem cihazında semptom ile uyumlu çok sayıda kısa eşleşmiş PVC kaynaklı VF atağı tespit edilen ve silostazol ile başarılı bir şekilde tedavi edilen daha öncesinde belgelenmiş VF'ye bağlı AKÖ yaşayanı olan ve ICD implante edilmiş genç bir kadın hasta sunulmuştur.

Anahtar Kelimeler: Silostazol, erken repolarizasyon sendromu, ventriküler fibrilasyon

CASE REPORT
OLGU SUNUMU

Survivors of sudden cardiac death (SCD) with documented ventricular fibrillation (VF) should be evaluated for metabolic, toxicological, structural, and channelopathy causes. Idiopathic VF is a primary electrical disease of the heart and should only be diagnosed after a thorough evaluation excludes any underlying abnormalities.[1] However, in certain primary electrical disorders such as early repolarization syndrome (ERS), electrocardiographic (ECG) findings may be intermittent. As a result, idiopathic VF may be diagnosed when no abnormalities are detected during evaluation, especially if the ECG appears normal at the time of an index event. Intermittent and long-term ECGs monitoring is therefore essential for establishing a definitive diagnosis. Implantable cardioverter-defibrillator (ICD) implantation is indicated for SCD survivors and diagnosed with idiopathic VF or ERS. Although quinidine is an effective treatment for preventing and reducing recurrent VF in both idiopathic VF and ERS, alternative pharmacologic therapies may be considered based on the specific diagnosis and underlying mechanisms. Both preclinical and clinical studies have shown that phosphodiesterase-3 inhibitors, such as cilostazol and milrinone, can reduce VF recurrences in ERS when used alongside quinidine.[1-5]

ERS is classified as a subgroup of J-wave syndromes. The underlying mechanism involves an endo-epicardial transmural electrical gradient, primarily caused by regional differences in the distribution of the transient outward current (Ito). Known

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primarily as an antithrombotic agent, cilostazol increases intracellular cyclic adenosine monophosphate (cAMP) levels and enhances the inward calcium current (ICa). It also exerts a blocking effect on Ito. These combined effects have been shown to reduce the endo-epicardial transmural electrical gradient (dispersion) and suppress phase-2 reentry-related extrasystoles and ventricular arrhythmias.[1,2,4]

Herein, we present the case of a young female SCD survivor who was initially misdiagnosed with idiopathic VF and later correctly diagnosed with ERS. Her symptomatic, frequent premature ventricular complex (PVC)-initiated VF episodes, documented on ICD records, were successfully treated with cilostazol.

Case Report

A 41-year-old female patient presented to our center with a history of brief palpitations and fainting episodes dating back to the age of 18. In 2003, she underwent a neurological evaluation for similar symptoms. Her family history was unremarkable, and she reported no use of medications or illicit drugs. She was diagnosed with probable epilepsy following electroencephalography (EEG) and was treated with various antiepileptic medications. However, she continued to experience frequent fainting spells and intermittent syncopal episodes. In January 2006, she was brought to the emergency department after an episode of fainting and loss of consciousness and was evaluated for cardiac arrest. VF was detected and successfully defibrillated, and she was resuscitated after 35 minutes of cardiopulmonary resuscitation (CPR). During hospitalization, a cardiac evaluation, including laboratory tests (electrolytes and thyroid function), 12-lead ECG, echocardiography, 24-hour Holter ECG monitoring, exercise 12-lead ECG, pharmacologic provocation with ajmaline and epinephrine, coronary angiography (with cold pressor testing), and cardiac magnetic resonance imaging (MRI), revealed no abnormalities. Toxicology screening and brain/chest computed tomography were also unremarkable. Due to her history of cardiac arrest and a diagnosis of idiopathic VF, a single-chamber ICD (VVI-ICD, with Riata Defibrillator Electrode; St Jude Medical, Sylmar, CA) was implanted prior to discharge. In 2012, externalization of the Riata defibrillator electrode was detected during a fluoroscopic examination, and the lead was extracted using a hand-powered mechanical dilator sheath. A Biotronik Lumax 340 VR-T (XL) model VVI-ICD with Home Monitoring functionality was subsequently implanted at our center (settings: basal rate 40 bpm, impedance: 646/54 Ohm, R wave: 11.3 mV, VT zone: OFF, VF zone: 200 ms). The 12-lead ECG recorded during the second implantation procedure showed normal sinus rhythm with no abnormal findings (Figure 1A).

During follow-up, no symptoms or abnormalities were observed in the Home Monitoring data. However, in 2017, the Home Monitoring system issued an alert indicating the presence of PVCs and multiple short-duration VF episodes initiated by short-coupled PVCs. Upon calling the patient for an outpatient evaluation, she reported that the episodes of brief palpitations and fainting sensations, previously experienced, had reoccurred. A 12-lead ECG obtained during this visit revealed findings consistent with ERS, a form of J-wave syndrome, which had not been present on prior ECGs. The abnormalities included ST-segment elevation in the inferolateral leads, notching in leads V_{4-6} and slurring in lead I (Figure 1B). We confirmed multiple episodes of short-coupled, PVC-induced VF (Figure 2), although the overall PVC burden was less than 1% based on ICD interrogation. However, given that the VF episodes were initiated by PVCs, we proceeded with a diagnostic electrophysiological study. No tachycardia could be induced during the procedure, and neither spontaneous nor induced PVCs were observed. Since the patient had previously been intolerant to beta-blockers, and quinidine is unavailable in our country, we initiated treatment with cilostazol at 100 mg, based on evidence from the literature. Shortly after initiating therapy, we observed a reduction and eventual complete disappearance of both the PVC frequency and the short-term VF episodes triggered by PVCs, as documented in the Home Monitoring records and ICD interrogations (Figure 3). The patient, who continued clinical and device follow-up visits at six-month intervals, reported no symptoms, ECG findings of ERS, or arrhythmic episodes during the seven-year follow-up period.

ABBREVIATIONS

cAMP	Cyclic adenosine monophosphate
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiography
EEG	Electroencephalography
ERP	Early repolarization pattern
ERS	Early repolarization syndrome
Ica	Inward calcium current
ICD	Implantable cardioverter-defibrillator
Ito	Transient outward current
MRI	Magnetic resonance imaging
PVC-induced	Premature ventricular contraction-induced
SCD	Sudden cardiac death
VF	Ventricular fibrillation

Discussion

Approximately half of all cardiovascular deaths occur as SCD, and nearly half of these patients have no prior history of cardiovascular disease.[1,6,7] In individuals under the age of 50, more than half of SCD cases are attributed to potentially hereditary electrical disorders or structural non-ischemic diseases.[8] Diagnostic tools, including a detailed personal or family history, laboratory tests, 12-lead resting or exercise ECG, Holter ECG monitoring, imaging studies (e.g., echocardiography, computed tomography, and cardiac magnetic resonance imaging), provocative testing, genetic analysis, and invasive electrophysiological studies, should be employed to investigate the underlying etiology of SCD.[1] Physicians should also review any ECG tracings from the emergency department, data from cardiovascular implantable electronic device (CIEDs) interrogation, and serial ECGs obtained during recovery to aid in the etiological evaluation of SCD survivors.[1] After the exclusion of all probable etiologies for documented VF in a SCD survivor, a diagnosis of idiopathic VF is made. In such cases, ICD implantation is recommended for secondary prevention when no reversible cause is identified.[1]

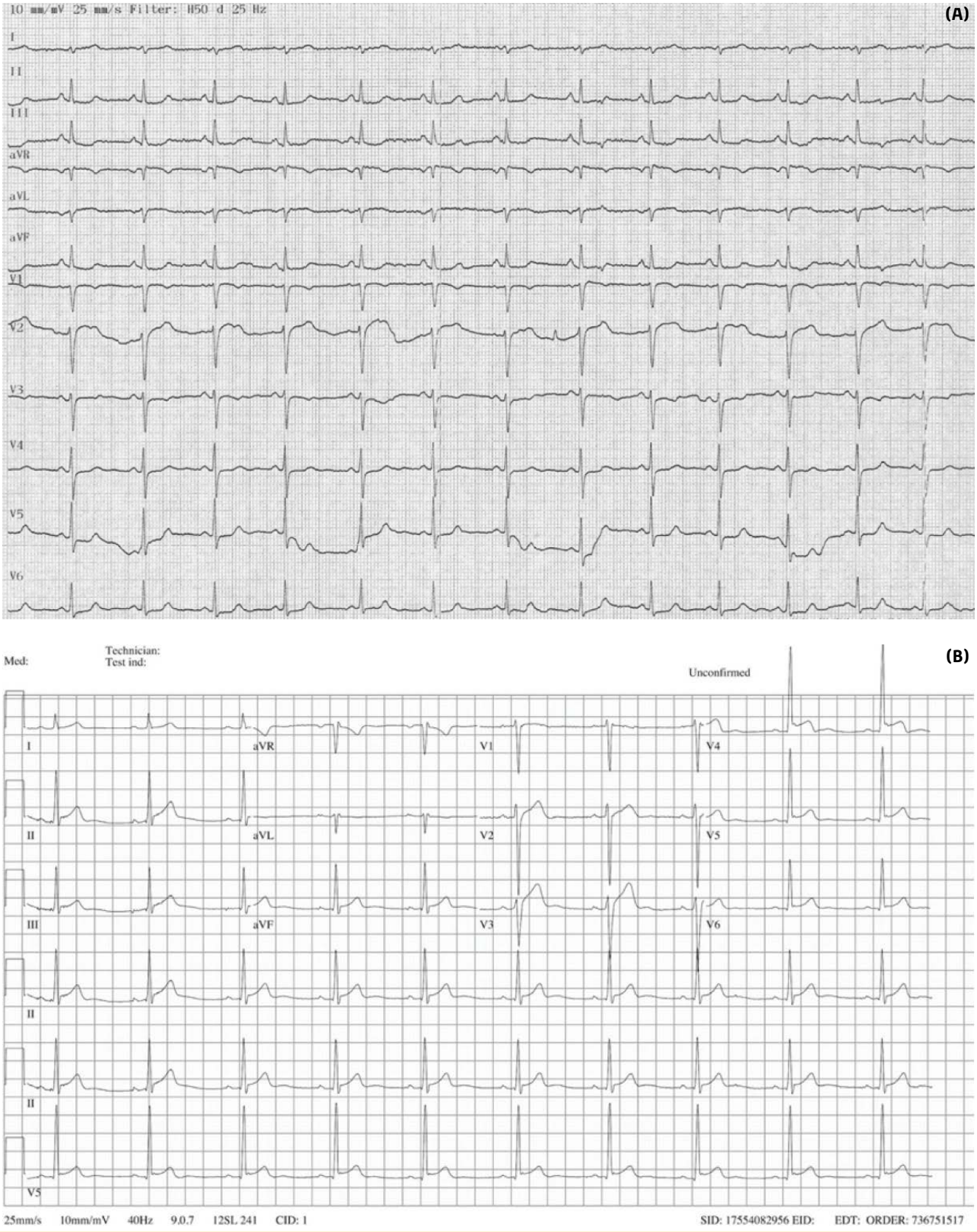

Figure 1. (A) The 12-lead electrocardiogram (ECG) obtained before implantable cardioverter-defibrillator (ICD) implantation showed normal sinus rhythm without any abnormalities suggestive of a channelopathy. (B) The 12-lead electrocardiogram (ECG) recorded during the time of ventricular fibrillation (VF) episodes, as detected by the Home Monitoring system, showed ST-segment elevations in all inferolateral leads, notching in leads V_{4-6}, and slurring in the lead I—findings consistent with early repolarization syndrome (ERS).

Guidelines also recommend the use of quinidine for long-term therapy to suppress electrical storms or recurrent ICD discharges in patients with idiopathic VF. Additionally, catheter ablation should be considered in idiopathic VF patients with recurrent episodes of VF triggered by similar PVCs, most commonly originating from the Purkinje system, especially when these episodes are resistant to antiarrhythmic medications.[1] ERS is diagnosed in patients resuscitated from VF without structural heart disease and is characterized by the presence of an early repolarization pattern (ERP), defined by:

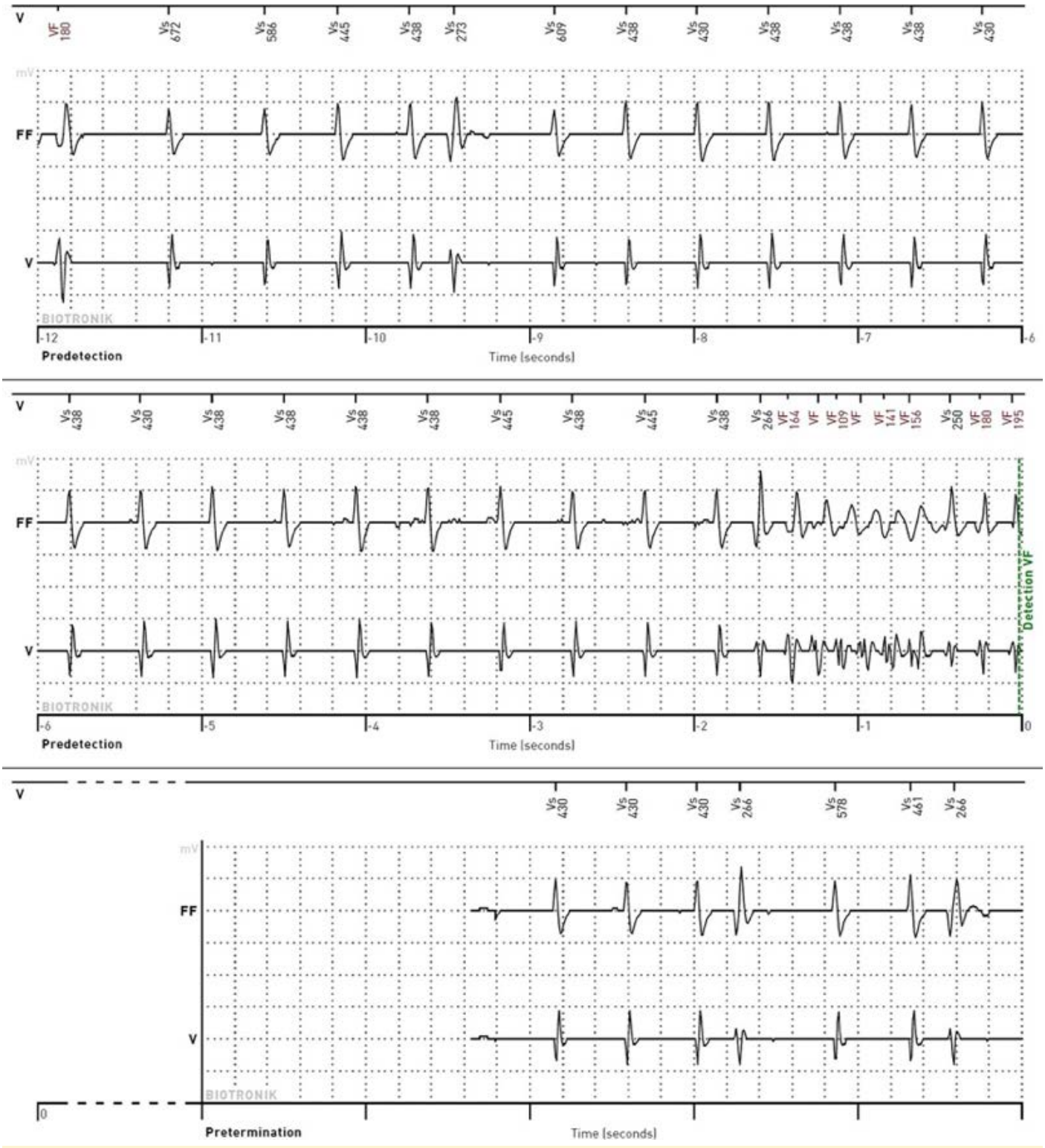

Figure 2. The Home Monitoring alert revealed multiple episodes of short-coupled premature ventricular contraction (PVC)-induced ventricular fibrillation (VF).

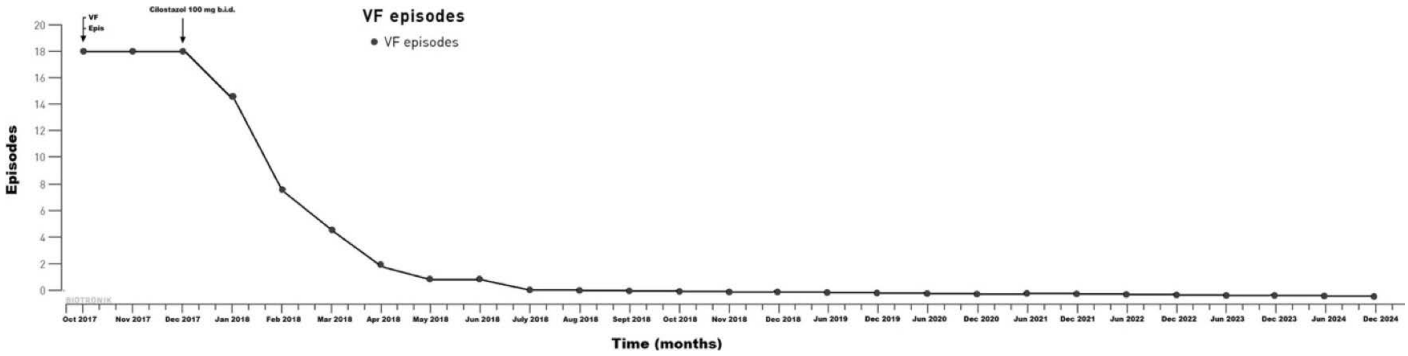

Figure 3. The short-coupled premature ventricular contraction (PVC)-induced ventricular fibrillation (VF) episodes decreased and ultimately disappeared, as shown in the Home Monitoring data and implantable cardioverter-defibrillator (ICD) interrogations, following the initiation of cilostazol 100 mg twice daily during follow-up.

1. An end QRS notch (J wave) or slur on the downslope of a prominent R wave, with or without ST-segment elevation;
2. A peak of the notch or J wave (Jp) ≥ 0.1 mV in ≥ 2 contiguous leads of the 12-lead ECG, excluding leads V1-3; and
3. A QRS duration (measured in leads without a notch or slur) of < 120 ms.[1,9]

The incidence of ERS is underestimated as a potential cause of VF and SCD due to spontaneous fluctuations in the J-wave pattern and the limited opportunity to capture arrhythmia initiation when repolarization abnormalities are at their peak. Additionally, early repolarization may be present but temporally suppressed within the depolarization phase.[10] Data on the pharmacological treatment of recurrent VF episodes in ERS are limited. In addition to quinidine and catheter ablation (in cases of PVC-induced VF), which are also used in idiopathic VF treatment, phosphodiesterase-3 inhibitors such as cilostazol and milrinone also reduce VF recurrence in ERS patients.[2] Cilostazol enhances the ICa by increasing cAMP, reverses repolarization abnormalities, and restores electrical homogeneity across the ventricular wall in ERS. It also blocks the Ito. Both of these mechanisms of cilostazol are effective in suppressing J-wave activity and reducing recurrent VF episodes.[3,9,11,12]

Although our patient had some suspicious cardiac symptoms prior to the episode of sudden cardiac arrest and VF, the condition was initially attributed to convulsions by a neurologist. As mentioned above, no abnormalities related to metabolic, toxicological, structural, or channelopathic etiologies were found in the evaluations performed after the sudden cardiac arrest and VF episode (although an ECG from that event was not available), so our initial diagnosis was idiopathic VF. Since the patient who experienced sudden cardiac arrest was diagnosed with idiopathic VF, an implantable ICD was implanted for secondary prevention. Thanks to the Home Monitoring feature of the device, we detected brief episodes of VF initiated by frequent PVCs. These episodes did not trigger therapy, as they were short in duration. This occurred during a period when the patient experienced a recurrence of symptoms similar to her previous episodes, prompting an early clinic visit. At that admission, the ECG revealed 1 mm ST-segment elevation with a slur on the downslope of the R wave in the lateral leads, and 1.5 mm ST-segment elevation in the inferior leads. Since this finding was not present on the patient's previous ECG, we considered that it was either intermittent or previously masked by depolarization abnormalities.[9,10] Furthermore, the PVCs triggering VF in our patient were short-coupled (< 350 ms), a feature reported in 6.6% of unexplained cardiac arrests in the CASPER registry (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry).[13] As a result, we revised the patient's diagnosis from idiopathic VF to ERS with short-coupled PVC-induced VF. Quinidine is the recommended pharmacological agent for reducing recurrent VF episodes in this setting. However, since quinidine was not available in our country, we initiated low-dose beta-blocker therapy, which the patient could not tolerate due to hypotension. Catheter ablation was not feasible, as no spontaneous or inducible PVCs were observed during the electrophysiological study. As an alternative, we started cilostazol at a dose of 100 mg twice daily, based on its reported effectiveness in case reports from the literature.[4,5] Shortly after initiation, the patient's symptoms resolved, and the short-term VF episodes recorded in the Home Monitoring data decreased and eventually disappeared. We have not observed any recurrence of early repolarization findings on the ECG in the patient, who has also continued regular clinic visits. She has been followed uneventfully for approximately seven years.

Conclusion

In conclusion, patients who present with sudden cardiac arrest and documented VF, and who survive as sudden cardiac death cases, should undergo comprehensive evaluation for underlying cardiac etiologies. Although a diagnosis of idiopathic VF may be made when no cause is identified, clinicians should be aware that some channelopathies may present with intermittent ECG findings and arrhythmic episodes, as observed in our patient. The Home Monitoring feature of ICD devices allows for close follow-up and facilitates early detection of previously unrecognized arrhythmic events. It also ensures timely clinical evaluation during symptomatic periods, enabling accurate diagnosis based on ECG findings. It is important to note that cilostazol, commonly used for its antithrombotic properties, may also be considered an alternative antiarrhythmic therapy to quinidine, as it effectively prevents short-term VF episodes triggered by short-coupled PVCs in patients with ERS, as seen in our patient.

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 patient.

Conflict of Interest: U.C.: Proctoring for Biotronik & Medtronic & Boston Scientific; K.A.: Proctoring for Abbott, Medtronic, Boston Scientific, Biosense Webster, and LifeTech.

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First Case of Endoscopic Resection for Left Atrial Appendage Aneurysm with Suspected Viral Myocarditis: A Multimodal Approach

Viral Miyokardit Şüphesiyle Sol Atriyal Apendiks Anevrizması İçin Endoskopik Rezeksiyon Uygulanan İlk Olgu: Multimodalite Yaklaşım

ABSTRACT

Left atrial appendage aneurysm (LAAA) is a rare cardiovascular anomaly, with fewer than 200 documented cases. It is often associated with severe complications, such as arrhythmias and thromboembolic events. Recent evidence suggests that viral infections, particularly viral myocarditis, might be an underlying cause of LAAA. We report the case of a 36-year-old woman with a history of asthma who presented with palpitations and atrial tachyarrhythmia two months after a severe upper respiratory infection. Transthoracic echocardiography revealed a large aneurysmal left atrial appendage (LAA) measuring 5.6 × 3.5 cm and a reduced left ventricular ejection fraction of 50%. Cardiac computed tomography confirmed the LAAA and revealed abnormal flow dynamics. Late gadolinium enhancement showed mid-subepicardial hyperenhancement in the posterolateral segments of the left ventricular wall, consistent with a previous myocarditis. The patient underwent a novel, minimally invasive endoscopic thoracoscopic resection of the aneurysm, guided by transesophageal echocardiography. No thrombus was present. The procedure was successfully completed with the aid of cardiopulmonary bypass. This case highlights a potential association between viral myocarditis and LAAA, while also acknowledging the possibility of a congenital and incidentally discovered aneurysm. It underscores the critical role of multimodal imaging in accurate diagnosis and management. The successful minimally invasive surgical resection and subsequent restoration of cardiac function demonstrate the effectiveness of this approach, offering a promising outlook for patients with LAAA. Clinicians should consider viral infections as potential contributors to LAAA development and advocate for early diagnosis and intervention to improve clinical outcomes.

Keywords: Arrhythmias, cardiac surgical procedures, left atrial appendage aneurysm, myocarditis

ÖZET

Sol atriyal apendiks anevrizması (LAAA), tıpta nadir görülen ve çoğunlukla tanı konulamayan bir kardiyovasküler anomalidir; literatürde bildirilen vaka sayısı 200'ün altındadır. Genellikle aritmi ve tromboembolik olaylar gibi ciddi komplikasyonlarla ilişkilidir. Son araştırmalar, özellikle viral miyokardit olmak üzere viral enfeksiyonların LAAA'nın altta yatan bir nedeni olabileceğini öne sürmektedir. Bu ilişki yeterince araştırılmamış olsa da, viral enfeksiyonlar sonrası açıklanamayan aritmiyle başvuran hastalarda dikkatli klinik değerlendirme yapılmasının önemini vurgulamaktadır. Bu yazıda, astım öyküsü olan ve ağır bir üst solunum yolu enfeksiyonundan iki ay sonra çarpıntı ve atriyal taşiaritmi şikayetleriyle başvuran 36 yaşındaki bir kadın olgu sunulmuştur. Transtorasik ekokardiyografi, 5.6 x 3.5 cm boyutlarında büyük bir anevrizmatik LAA ve sol ventrikül ejeksiyon fraksiyonunun %50 olduğu saptanmıştır. Kardiyak BT, LAAA'yı ve anormal akım dinamiklerini desteklemiştir. Gadolinyumla geç evre görüntülemede, sol ventrikül posterolateral duvar segmentlerinde orta-subepikardiyal hiperenhansman görülmüş, bu bulgular geçirilmiş miyokarditi düşündürmüştür. Hastaya, transözofageal ekokardiyografi rehberliğinde, minimal invaziv endoskopik torakoskopik anevrizma rezeksiyonu uygulanmıştır, trombüs izlenmemiştir. Cerrahi, kardiyopulmoner bypass desteğiyle başarılı şekilde gerçekleştirilmiştir. Bu olgu, viral miyokardit ile LAAA arasında potansiyel bir bağlantıyı tanımlayan ilk vaka olup, doğru tanı ve yönetimde multimodalite görüntülemenin görüntülemenin kritik rolünü ortaya koymaktadır. Minimal invaziv cerrahinin kalp fonksiyonunu yeniden kazandırmadaki başarısı, bu yaklaşımın etkinliğini göstermekte ve LAAA hastaları için umut verici bir seçenek sunmaktadır. Klinisyenler, viral enfeksiyonların LAAA gelişimindeki olası katkılarını göz önünde bulundurmalı ve daha iyi klinik sonuçlar için erken tanı ve müdahale sürecini benimsemelidir.

Anahtar Kelimeler: Aritmiler, kardiyak cerrahi prosedürler, sol atriyal apendiks anevrizması, miyokardit

CASE REPORT
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During the fourth week of embryonic development, the left atrial appendage (LAA) forms along the left wall of the left atrium (LA) and extends anterolaterally as a finger-like projection.[1,2] Its structure differs from that of the LA itself.[1] The LAA plays a minor role in LA compliance, and therefore in LA pressure and left ventricular (LV) filling pressure.[1,2] When flow velocity in the LAA decreases, such as in atrial fibrillation, mitral stenosis, or elevated LV filling pressure, thrombus formation in LAA may occur.[2]

Left atrial appendage aneurysm (LAAA) is an extremely rare cardiovascular disorder, first described by Dimond et al. in 1960.[3] To date, over 180 cases have been reported.[1] Due to its rarity, diagnosis and the establishment of standardized treatment strategies remain challenging.[4] LAAA is typically discovered incidentally during surgery, autopsy, or through cardiovascular imaging techniques such as echocardiography, cardiac computed tomography angiography (CTA), or cardiac magnetic resonance imaging (MRI).[4-6] Clinical presentations of LAAA range from asymptomatic to severe complications, including cardiac arrhythmias, heart failure, thrombotic events, compression of adjacent structures, and even sudden cardiac death.[4] Etiologically, LAAA may be congenital, arising from dysplasia of the atrial pectinate muscles or pericardial defects, or acquired, secondary to conditions such as mitral valve disease, syphilitic myocarditis, or tuberculosis.[7] Literature reports that some aneurysms are intrapericardial, leading to wall weakness, while others are extrapericardial in nature.[4,6,7] Surgical resection, often in conjunction with medical treatment, is the recommended management strategy.[4,5,8] This report aims to highlight a rare presentation of LAAA and to review relevant literature to enhance understanding of its diagnostic and treatment strategies.

ABBREVIATIONS

AF	Atrial fibrillation
AFL	Atrial flutter
AV	Atrioventricular
CPB	Cardiopulmonary bypass
CT	Computed tomography
CTA	Computed tomography angiography
ECG	Electrocardiogram
EF	Ejection fraction
LAAA	Left atrial appendage aneurysm
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVO	Left ventricular opacification
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
SSFP	Steady-state free precession
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

Case Report

A 36-year-old woman, a recent smoker with a history of asthma, presented with palpitations and dyspnea that began two months after a severe upper respiratory infection. Apart from a heart rate of 150 beats per minute, her vital signs were within normal limits. Physical examination was unremarkable. An initial electrocardiogram (ECG) revealed atrial tachyarrhythmia with a 2:1 atrioventricular (AV) block, possibly originating in the LA (Figure 1). Transthoracic echocardiography (TTE) showed a normal LV size with mildly reduced systolic function (left ventricular ejection fraction (LVEF): 50% during tachycardia), abnormal motion of the interventricular septum, normal bi-atrial volumes (left atrial volume index: 21 cc/m²; right atrial volume index: 14 cc/m²), mild mitral regurgitation (MR), and a small pericardial effusion. The apical four-chamber view of the TTE revealed a large outpouching adjacent to the lateral aspect of the LA, extending toward the lateral side of the LV. It was connected to the LA via an ostium measuring 2.4 cm, consistent with a large aneurysmal LAA measuring 5.6 × 3.5 cm (Figure 2). Communication between the LA and LAA was confirmed by color Doppler imaging, which showed to-and-fro flow through the aneurysmal ostium. The patient underwent cardiac multidetector computed tomography (CT) with prospective ECG gating and a high-pitch non-ECG-gated delayed phase at 90 seconds using the Somatom Force system (Dual Source 192×2, Siemens, Forchheim, Erlangen, Germany). Computed

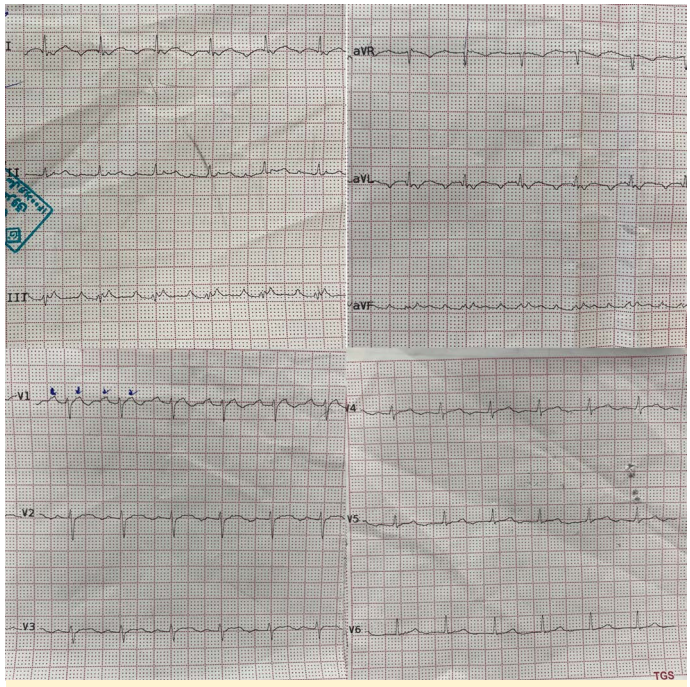

Figure 1. Electrocardiogram (ECG) showing atrial tachycardia with 2:1 atrioventricular (AV) block, characterized by a rapid atrial rhythm and alternate pulse transmission to the ventricles, originating from the left atrium.

tomography angiography (CTA) confirmed the presence of a large aneurysmal LAA with a smoky appearance at its tip. No definite clot was detected on delayed imaging (Figure 3).

Due to the patient's decreased LVEF, she was referred to the imaging department for cardiac MRI to better evaluate the myocardium and accurately measure the ejection fraction (EF). The cardiac MRI was performed using the Magnetom SOLA system (Siemens, 48 gradient channels, Forchheim, Erlangen, Germany). Calculations were conducted using CVi42 software

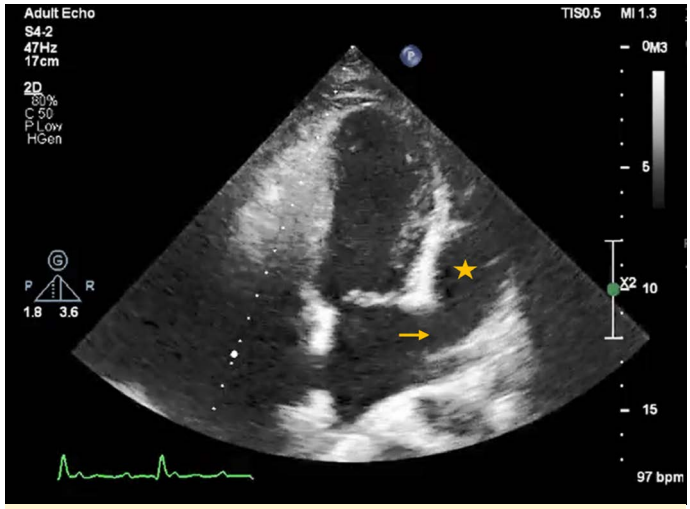

Figure 2. Off-axis apical four-chamber view on transthoracic echocardiography demonstrating a left atrial appendage (LAA) aneurysm measuring 5.6 cm × 3.5 cm (orange star), connected to the left atrium (LA) by a 2.4 cm ostium (orange arrow), during atrial tachyarrhythmia with 2:1 atrioventricular (AV) block.

(Circle Cardiovascular Imaging Inc., Calgary, Canada). The MRI confirmed a large aneurysmal LAA with a smoky appearance and no obvious filling defects. The EF was calculated using a stack of short-axis steady-state free precession (SSFP) images, which demonstrated a reduced EF. A late gadolinium enhancement (LGE) sequence was performed following intravenous administration of DOTAREM (0.2 mmol/kg; Guerbet, Paris, France). The LGE images revealed mid-subepicardial hyperenhancement in the posterolateral segments of the left ventricular wall, suggestive of a prior episode of myocarditis (Figure 4).

Given the diagnosis of left atrial appendage aneurysm and the patient's symptomatic presentation, surgical intervention was planned. Intraoperative transesophageal echocardiography (TEE) was performed prior to surgery and confirmed the TTE findings. No smoke or clot was detected within the LAAA, and the LAAA emptying velocity was measured at 31 cm/second. Under general anesthesia, the procedure was carried out using a thoracoscopic approach through a minimal incision in the left hemithorax, with cardiopulmonary bypass (CPB) support. The total Cardiopulmonary bypass time was 73 minutes. Following pericardiotomy, thoracoscopic visualization confirmed the LAAA anatomy (Figure 5). The LAA orifice was carefully closed in three layers using a non-absorbable suturing technique, and the aneurysmal tissue was then resected. No intraoperative bleeding or suture line leakage was observed. Post-resection intraoperative TEE confirmed complete excision of the LAAA, with an emptying velocity of 24 cm/second in the small remaining portion of the LAA. No thrombus was observed, and surgical margins were satisfactory. The pericardium was subsequently closed. The remainder of the procedure was completed without complications.

The patient experienced an uncomplicated recovery and was discharged in stable condition on postoperative day four. Follow-up TTE performed two weeks later demonstrated normal left ventricular function (LVEF: 55%), mild MR, and a small LAA remnant (Figure 6). Histopathological examination of the resected left atrial appendage was performed. Hematoxylin and eosin staining revealed endocardium and cardiac myocytes with mild hypertrophic changes and interstitial fibrosis (Figure 7). Serial clinical evaluations at one, three, and six months postoperatively revealed no recurrence of symptoms. The patient reported complete resolution of preoperative palpitations and maintained normal sinus rhythm on electrocardiograms throughout the follow-up period.

Discussion

The first reported case of LAAA was published by Dimond[3] in 1960 and involved surgical resection following angiographic confirmation. Initial intraoperative diagnoses, such as those by Parmley et al.[9] in 1962, were later complemented by advancements in imaging technology, including the use of I-131-labeled albumin by Godwin[10] in 19689, and further refined by echocardiographic techniques in the 1980s.[9] The advent of advanced diagnostic tools, including contrast-enhanced imaging and cardiac MRI, has led to increased detection of LAA. This, in turn, has improved our understanding of its natural history, as well as the associated morbidity and mortality.[5]

As demonstrated in case reports, LAAA can occur across a wide age range, from 28 weeks gestational age prenatally to 88 years old. However, most cases are diagnosed between the second and fourth decades of life, with approximately 25% occurring in the third decade[4,8,11] similar to the case presented in this report. This may suggest that LAA aneurysms gradually enlarge over time.[7] Some analyses also indicate a slight female predominance, with 53% of cases in women and 47% in men.[5,11]

As previously stated, LAA aneurysms are categorized into congenital and acquired types. The majority of LAAA cases (approximately 90%) are congenital anomalies, potentially resulting from dysplasia of the atrial pectinate muscles.[12] However, some authors have reported associations between LAAA and other congenital anomalies, including atrial septal defect, ventricular septal defect, anomalous pulmonary venous drainage, tricuspid atresia, Noonan syndrome, Hurler-Scheie syndrome, transposition of the great arteries, and, more rarely, mitral valve cleft.[5,7,12] Acquired LAA aneurysms may develop due to mitral valve disease, syphilitic myocarditis, or tuberculosis. Associations with viral infections, have also been reported.[4,12] In our case, evidence suggestive of prior myocarditis, such as LGE in the posterior basal segment of the LV in cardiac MRI, raises the possibility of a link to a preceding viral infection. Histopathological examination of the resected LAAA in our case revealed endocardium and cardiac myocytes with mild hypertrophic changes and interstitial fibrosis. Consistent with our findings, endocardial and myocardial fibrosis are commonly reported histopathologic features in both congenital and acquired LAAA.[5] Additionally, myocardial hypertrophy with interstitial fibrosis, similar to what we observed, has also been documented in several reported LAAA cases.[1,12] While fibrosis is a non-specific finding and can occur in various cardiac conditions, including both congenital and acquired LAAA, in the context of our patient's clinical presentation and MRI findings, it may represent a sequela of myocarditis or a pre-existing condition exacerbated by, or coincident with, the inflammatory process.

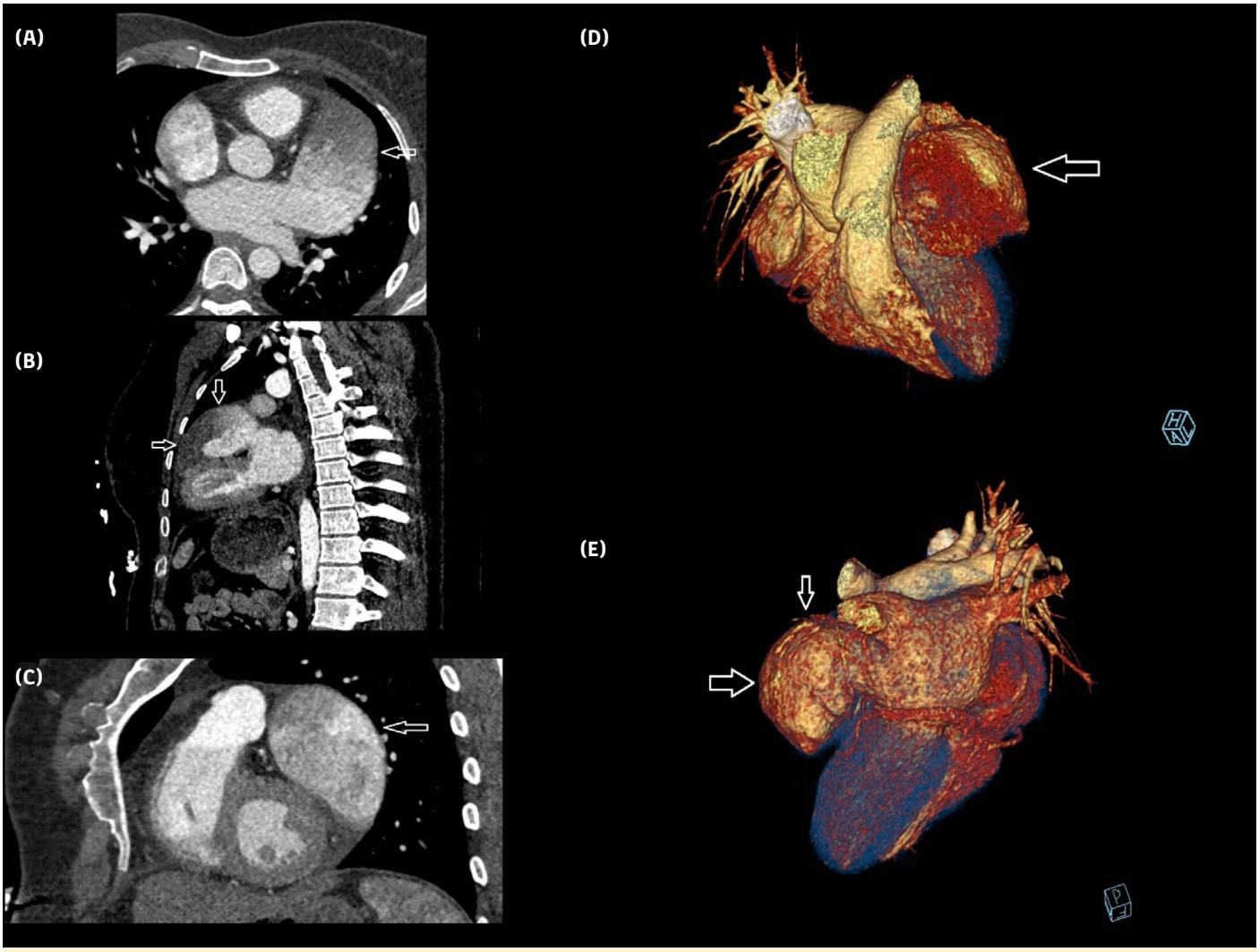

Figure 3. Cardiac multi-detector computed tomography (CT) imaging: (A, B, C) Multiplanar reconstruction (MPR) images in axial, oblique, and sagittal views reveal a markedly enlarged left atrial appendage (LAA) (white arrows). (D, E) Volume-rendered technique (VRT) reconstructions further highlight the prominent LAA (white arrows).

The literature describes a wide spectrum of clinical presentations for LAA aneurysms, ranging from asymptomatic cases discovered incidentally on chest X-ray or echocardiography to ruptured LAA aneurysms and sudden cardiac death.[13] Diagnosis can be challenging, as symptoms often result from compression of adjacent structures rather than direct cardiac dysfunction.[14] The most to least commonly reported symptoms associated with LAA aneurysms are palpitations (43%), dyspnea (22%), arrhythmias—primarily supraventricular tachyarrhythmias or atrial fibrillation (AF) (15%)—thromboembolic events such as cerebrovascular emboli (11%), chest pain (7%), and, very rarely, cough and hiccups.[14] A serious complication of LAAA is cerebrovascular embolism, which may occur due to blood stasis in the aneurysmal LAA, often as a result of AF, and sometimes is only diagnosed after a stroke.[14,15]

Despite the known predisposition of LAAA to thrombus formation, recent studies indicate that thrombus formation is not dependent on aneurysm size. Instead, it is more strongly associated with cardiac arrhythmias such as AF or flutter, neck size, and low flow velocity within the aneurysm.[4,7] The case presented in this report involved palpitations, atrial tachyarrhythmia, and a 2:1 AV block (Figure 1) following a relatively severe viral respiratory infection, a clinical presentation not previously reported in the literature. The LAA measured by intraoperative TEE prior to surgery was 31 cm/s. Notably, no thrombus was detected within the aneurysm, and there was no history of thromboembolic events.

Various imaging modalities are used to diagnose LAAA, including chest X-ray, chest CT scan, CTA, cardiac MRI, TTE, and TEE.[5,7] Among these, chest X-ray is non-specific and typically shows signs such as cardiomegaly, a mass-like silhouette, or convexity of the left atrial contour.[6,7,14] A non-contrast chest CT can reveal a left atrial mass but cannot reliably distinguish among differential diagnoses such as a left atrial diverticulum, pulmonary artery dilation, pericardial cyst, or LAAA.[5,7]

An ECG-gated CTA can help resolve these ambiguities by providing better visualization to identify the aneurysmal sac and its connection with the LAA cavity, and it may also reveal

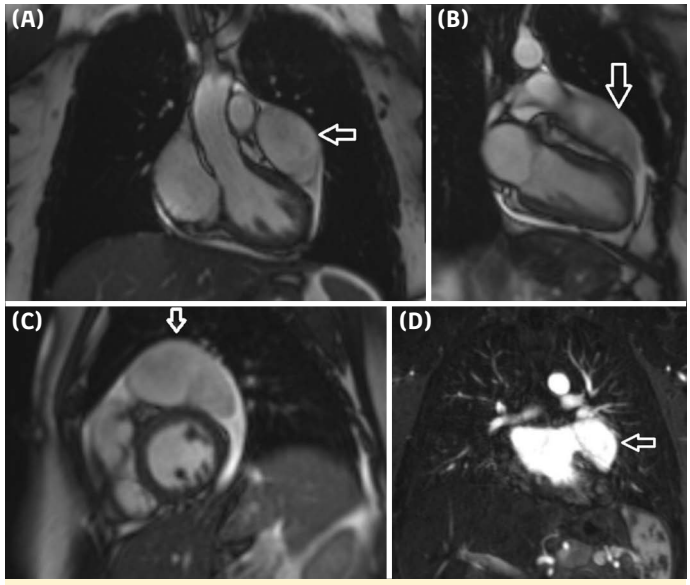

Figure 4. Cardiac magnetic resonance imaging (MRI) findings: (A) Coronal steady-state free precession (SSFP) sequence showing the enlarged left atrial appendage (LAA) (white arrow). (B) Longitudinal SSFP view of the left ventricle (LV) depicting the extensive LAA (white arrow). (C) Short-axis SSFP view confirming the presence of the large LAA (white arrow). (D)Arterial phase of magnetic resonance (MR) angiography demonstrating filling of the enlarged LAA (white arrow).

compression of adjacent structures.[5] Among all available modalities, cardiac MRI provides the highest diagnostic accuracy for LAAA, with an accuracy rate of 91%.[5] In our case, the diagnosis of LAAA was initially suggested by TTE and subsequently confirmed by both CTA and cardiac MRI (Figures 3 and 4).

Although the most accessible and cost-effective imaging modality is TTE, TEE also offers high diagnostic accuracy for LAAA (83.3%).[4,5,7] These techniques are favored for their practical utility and relatively low cost, especially when a high level of diagnostic precision is required.

The typical echocardiographic finding in LAAA is an outpouching structure originating from the LAA, with preserved continuity to the LA cavity.[5] This characteristic helps distinguish LAAA from other anomalies, as the connection between the appendage and the atrium is usually intact, even when the aneurysmal sac is significantly dilated.

Aryal et al. defined the echocardiographic dimensions of LAAA, reporting a mean orifice diameter greater than 2.7 mm, a mean length of 7.08 ± 3.03 cm, and a mean width of 9.5 ± 5.75 cm.[4] These measurements are important for diagnosing LAAA, as they help define the abnormal size and shape of the LAA. The presence of such abnormal dimensions, especially if the orifice and appendage exceed certain size thresholds, raises suspicion for an aneurysmal condition.

In terms of visualization, left ventricular opacification (LVO) is considered one of the most effective methods for assessing blood flow in the left-sided heart chambers and is especially useful for detecting thrombi. This technique improves the accuracy of

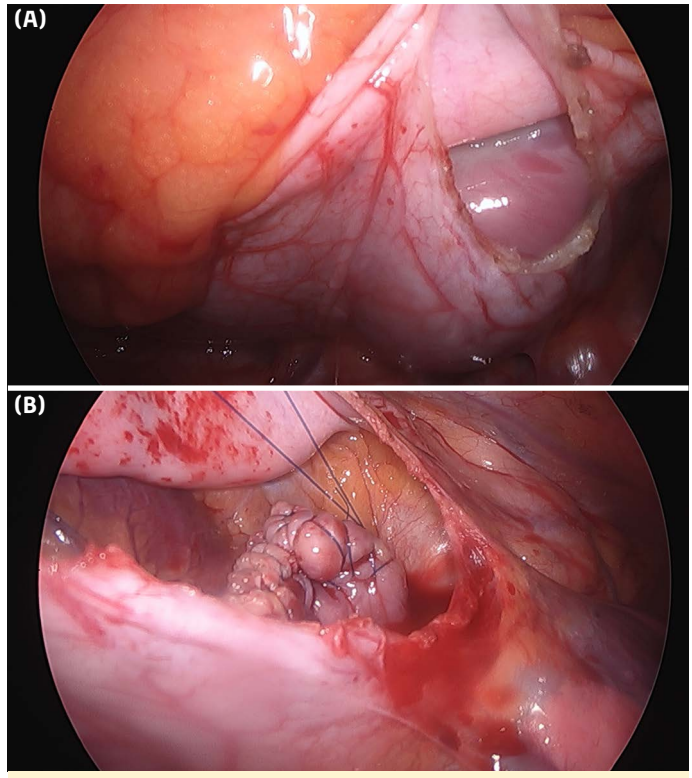

Figure 5. Endoscopic views highlighting the precise surgical technique: (A) Identification of the left atrial appendage aneurysm (LAAA) with clear anatomical delineation. (B) Post-resection image demonstrating successful removal of the aneurysm while preserving surrounding tissue integrity and ensuring optimal patient outcomes.

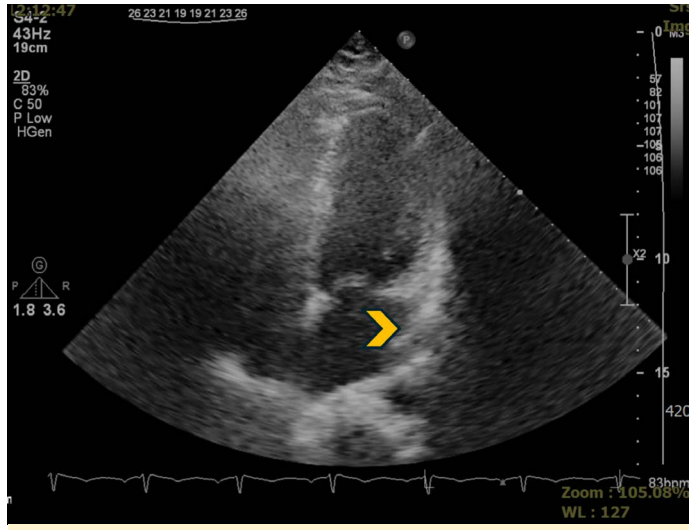

Figure 6. Off-axis apical four-chamber transthoracic echocardiography view post-surgery, showing a significant reduction in left atrial appendage (LAA) size (yellow arrowhead) in sinus rhythm.

detecting thrombotic formations, which is particularly important since LAAA is prone to thrombus development due to blood stasis in the aneurysmal sac, especially in the presence of atrial

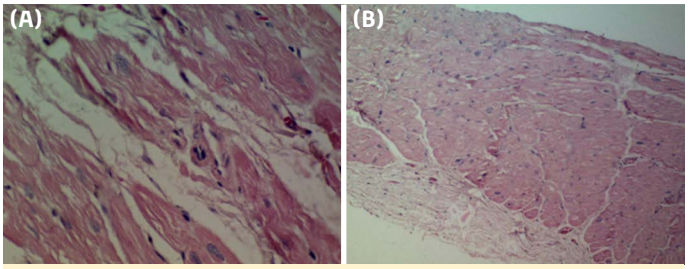

Figure 7. Microscopic findings of resected left atrial appendage tissue: Panels (A) and (B) show hematoxylin and eosin-stained sections of the resected left atrial appendage aneurysm. Histopathological analysis reveals endocardium and cardiac myocytes with mild hypertrophic changes and evidence of interstitial fibrosis.

fibrillation.[7] Contrast-enhanced echocardiography has also proven useful not only for detecting thrombi but also for guiding therapeutic decisions, such as initiating anticoagulation therapy or planning surgical intervention.[7]

As previously noted, the aneurysmal size in our reported case was 5.6 cm × 3.5 cm, with an ostial diameter of 2.4 cm. These dimensions are significant and suggest a relatively large aneurysm, potentially increasing the risk of complications such as thrombus formation, embolism, or rupture. In this case, both CT and intraoperative TEE confirmed the absence of thrombus within the LAAA prior to surgery. Monitoring the aneurysm's size and characteristics is critical, and contrast-enhanced echocardiography may offer valuable insights into both thrombus detection and flow dynamics within the aneurysmal sac.[7]

As reported in the literature, aside from symptomatic treatment, including antiarrhythmic agents and anticoagulants, there is currently no targeted medical therapy available for LAAA.[13] Most authors recommend surgical intervention, specifically aneurysmectomy, as the preferred therapeutic approach, regardless of whether the LAAA is symptomatic or asymptomatic.[5,11] A median sternotomy, with or without CPB, is the standard surgical approach commonly used for aneurysmectomy or excision of the LAA.[13] This method is particularly suitable for large aneurysms.[5]

We previously had a successful experience with median sternotomy and aneurysmectomy in a patient with a very large LAAA measuring 5.8 cm × 4.8 cm, with an orifice of 0.6 cm, at our tertiary care center.[11] However, for smaller LAA aneurysms, alternative surgical approaches may be considered, including minimally invasive endoscopic resection (Figure 5), percutaneous septal occlusion of LAAA using an occluder device, left thoracotomy with or without CPB, and the off-pump tourniquet snare technique, often performed under TEE guidance.[11]

Upon reviewing the literature, we did not find any specific size thresholds to guide the selection of a surgical method for LAAA. Therefore, based on the relatively smaller size of the LAAA in our case (5.6 cm × 3.5 cm with an ostial size of 2.4 cm), as shown in Figures 2 and 5, we opted for a minimally invasive endoscopic thoracoscopy with CPB for aneurysm resection (Figures 2 and 5). We believed that the minimally invasive thoracoscopic approach offered significant advantages for our patient, including a smaller surgical scar, potentially faster recovery, and a shorter cardiopulmonary bypass time, all contributing to greater patient comfort and potentially reduced morbidity. Beyond these advantages, it is important to emphasize that in our symptomatic patient, who presented with atrial tachyarrhythmia and a large LAAA, surgical resection was considered the most appropriate and definitive treatment. In the absence of clear guidelines on size thresholds, careful consideration of individual patient anatomy and clinical presentation is paramount in surgical planning. For symptomatic LAAA, surgical resection is frequently recommended as the definitive management strategy, as supported by the literature. Our choice of a minimally invasive approach is further supported by recent studies highlighting its benefits in appropriately selected patients, including reduced recovery times and fewer postoperative complications.[1,7]

Atrial arrhythmias such as AF, atrial flutter (AFL), and atrial tachyarrhythmias are typically managed promptly following LAAA resection. In some cases, ablation procedures are required to treat persistent arrhythmias.[16] In our case, sinus rhythm was restored after surgical resection of the LAAA, and no ablation procedure was necessary during the six-month follow-up period.

Overall, postoperative complications associated with surgical management of LAAA are low, and the prognosis is generally favorable.[12] According to published studies, 5.3% of patients who underwent surgical treatment experienced postoperative thromboembolic events, and 4% developed cardiac arrhythmias during follow-up, leading to the need for cardiac ablation. However, in one reported case, an adult patient passed away during follow-up due to carcinoma.[11]

Conclusion

Left atrial appendage aneurysm is a rare cardiovascular anomaly that presents both diagnostic and therapeutic challenges. This case of a young woman following a respiratory infection highlights the potential for atypical presentations and the effectiveness of surgical resection in managing this condition. Surgical intervention offers excellent outcomes and reinforces its role as the standard of care. Continued accumulation of case reports and further research are essential to refine diagnostic criteria and optimize management strategies for patients with LAAA.

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

Informed Consent: Informed consent was obtained from all individual participants included in the study. Participants were informed about the purpose of the study, and their consent was obtained in accordance with ethical guidelines.

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Author Contributions: Concept – S.H., Z.E.; Design – R.K., S.S.E.; Supervision – R.K., Z.E.; Resource – H.N.Z., H.F.A.; Materials – H.P.; Data Collection and/or Processing – E.T., S.M.H.; Analysis and/or Interpretation – H.P., H.N.Z.; Literature Review – S.S.E., S.M.H.; Writing – R.K., S.S.E.; Critical Review – R.K., Z.E.

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Incidentally Detected Membranous Interventricular Septal Aneurysm Resembling a Ventricular Septal Defect Occluder Device

Ventriküler Septal Defekt Oklüder Cihazına Benzeyen, Tesadüfen Tespit Edilen Membranöz Interventriküler Septal Anevrizma

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 57-year-old man was admitted to the emergency department with a diagnosis of unstable angina. Initial transthoracic echocardiography (TTE) detected a ventricular septal defect occluder device-like (VSDOD) image at the interventricular septum (IVS). However, the patient denied any history of device implantation. Coronary angiography revealed triple-vessel coronary artery disease, but the VSDOD was not observed.

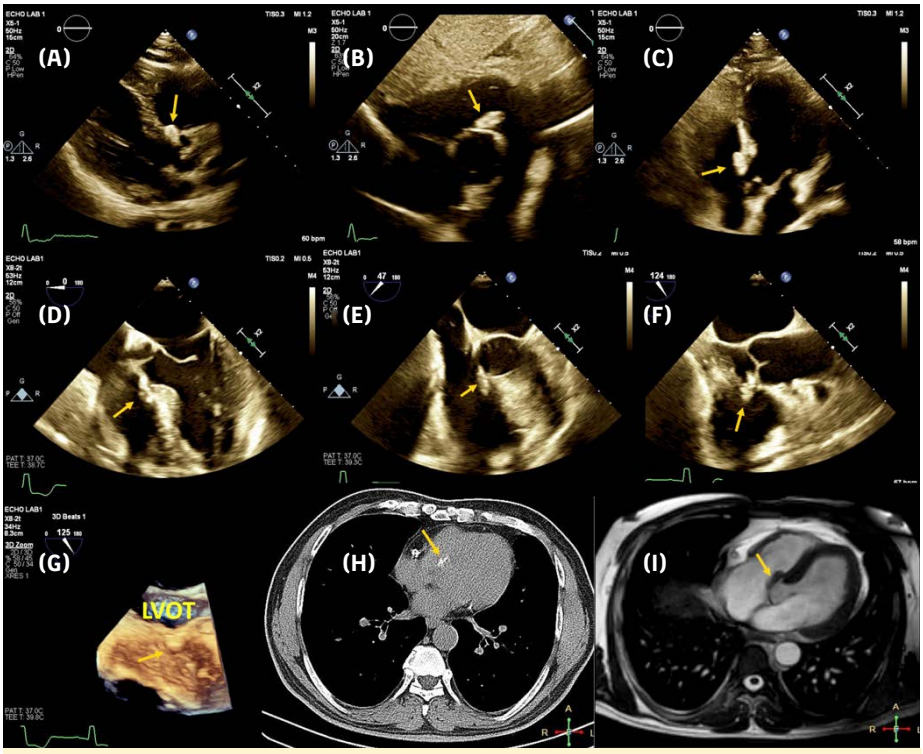

Figure 1. Densely fibrotic and/or calcified basal membrane aneurysmal septum, resembling a ventricular septal closing device (arrow) on transthoracic echocardiography views: (A) parasternal long-axis view, (B) subcostal short-axis view, (C) modified apical four-chamber view; and transesophageal echocardiography views: (D) modified upper esophageal five-chamber view, (E) modified short-axis of the aortic valve, (F) modified long-axis view of the aortic valve. (G) En face view of the densely fibrotic or calcified basal membranous aneurysmal septum (arrow) from the right ventricular side on three-dimensional transesophageal echocardiography in zoom mode. (H) Calcification in the middle of the heart (arrow) on chest computed tomography. (I) Cardiac magnetic resonance imaging identified an aneurysm of the basal interventricular septum with focal thickening and low signal intensity consistent with calcification (arrow), which was initially mistaken for a ventricular septal defect occluder on echocardiography.

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Repeat TTE and transesophageal echocardiography (TEE) showed a well-defined, non-mobile, highly echogenic mass in the shape of two disks, attached to the right ventricular (RV) side of the IVS base, resembling an Amplatzer VSDOD (Figure 1A–G, Videos 1 and 2). Due to suboptimal TTE views and artifacts such as shadowing and reverberation on TEE, visualization of all parts of the interventricular septal aneurysm (IVSA) was limited, especially in the four-chamber view. Review of the chest computed tomography scan revealed calcification in the middle of the heart (Figure 1H). Cardiac magnetic resonance imaging (CMR) identified a basal membranous IVS aneurysm (20 × 9 mm) with focal areas of thickened tissue showing low signal intensity consistent with calcification (13 mm of the IVSA wall) (Figure 1I, Video 3). The Heart Team decided that only coronary artery bypass grafting should be performed. Written informed consent was obtained from the patient. In conclusion, one echocardiographic presentation of IVSA may be a calcified mass, and additional imaging modalities help to accurately identify the underlying pathology. This case also highlights the importance of standardized medical records.

Ethics Committee Approval: This is a 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.

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

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Author Contributions: Concept – S.M., N.S.M., S.D., A.H.; Design – S.M., N.S.M., S.D., A.H.; Supervision – S.M., N.S.M., S.D., A.H.; Resource – S.M., N.S.M., S.D., A.H.; Materials – S.M., N.S.M., S.D., A.H.; Data Collection and/or Processing – S.M., N.S.M., S.D., A.H.; Analysis and/or Interpretation – S.M., N.S.M., S.D., A.H.; Literature Review – S.M., N.S.M., S.D., A.H.; Writing – S.M., N.S.M., S.D., A.H.; Critical Review – S.M., N.S.M., S.D., A.H.

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Video 1. Transthoracic echocardiography demonstrating a well-defined, highly echogenic, disk-shaped mass resembling a ventricular septal closing device at the base of the interventricular septum.

Video 2. Transesophageal echocardiography revealing a well-defined, highly echogenic, disk-shaped mass resembling a ventricular septal closing device at the base of the interventricular septum.

Video 3. Cardiac magnetic resonance imaging demonstrating an aneurysm of the basal interventricular septum with focal areas of thickening and low signal intensity indicative of calcification, initially misdiagnosed as a ventricular septal defect occluder on echocardiography.

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Transcatheter Tricuspid Valve-in-Valve Replacement in a Patient with Ebstein Anomaly

Ebstein Anomalisi Olan Bir Hastada Transkateter Triküspit Kapak-İçinde-Kapak Değişimi

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 26-year-old male patient with Ebstein anomaly was hospitalized due to New York Heart Association (NYHA) III dyspnea and syncope. He underwent tricuspid valve repair in 2006, and subsequently a bioprosthetic valve implantation was performed in 2011 due to recurrence of symptoms. Transthoracic echocardiography revealed a mean gradient of 13 mmHg and a maximum gradient of 17 mmHg across the bioprosthetic tricuspid valve, and 24-hour Holter monitoring detected transient 2:1 atrioventricular block. After Heart Team discussion, transcatheter tricuspid valve-in-valve replacement with a balloon-expandable aortic valve and surgical pacemaker implantation was decided.

After surgical epicardial lead placement, the patient was admitted to the catheterization laboratory. A stiff wire was positioned in the right pulmonary artery following right femoral transvenous access. Predilatation with a 23 × 40 mm balloon was performed at the level of the tricuspid valve, and subsequently a 30.5 mm balloon-expandable bioprosthetic aortic valve (Myval, Meril, India) was implanted (Figure 1). Right heart ventriculography showed no tricuspid regurgitation. Control echocardiography revealed significant diminution of tricuspid transvalvular velocity. The patient was event-free at the 6-month follow-up.

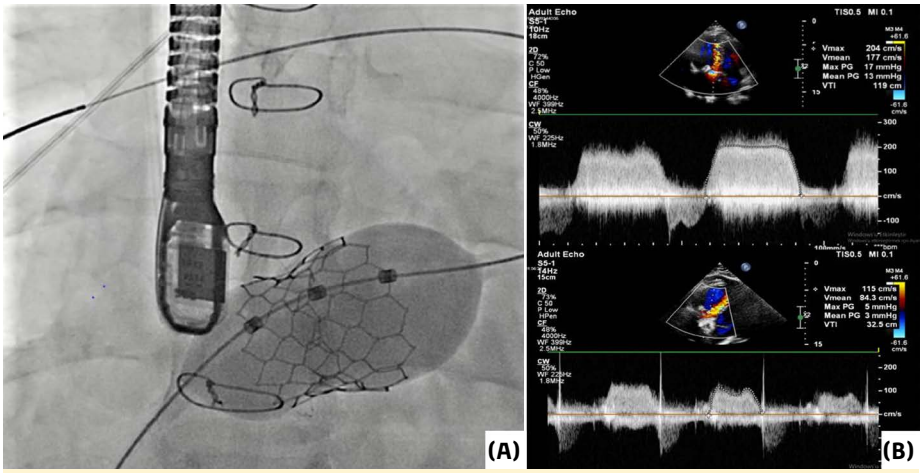

Figure 1. (A) Implantation of a balloon-expandable bioprosthetic valve. (B) Mean and maximum gradients of the tricuspid valve on echocardiography before and after the procedure.

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Electrode Detachment and Coronary Embolization from an Achieve™ Circular Mapping Catheter During Cryoballoon Ablation

Kriyobalon Ablasyonu Sırasında Achieve™ Dairesel Haritalama Kateterinden Elektrot Ayrılması ve Koroner Embolizasyon

CASE IMAGE
OLGU GÖRÜNTÜSÜ

Although the Achieve™ circular mapping catheter is central to cryoballoon-guided pulmonary vein isolation (PVI), rare mechanical failures, including spline deformation, electrode detachment, and systemic embolization can occur. Device reuse, practiced in some centers, may exacerbate cumulative structural degradation.

A 72-year-old male patient with highly symptomatic paroxysmal atrial fibrillation (AF) was referred for catheter ablation after failure of antiarrhythmic drug therapy. He had no known structural heart disease and underwent cryoballoon ablation under mild sedation with uninterrupted anticoagulation following preprocedural transesophageal echocardiography. After vascular access was obtained and a decapolar catheter was placed in the coronary sinus, systemic anticoagulation with unfractionated heparin was initiated. A standard transseptal puncture was then performed, and a 12F steerable sheath (FlexCath Advance™, Medtronic) was advanced through the septum (Figure 1A). The cryoballoon catheter (28-mm Arctic Front Advance™, Medtronic)–circular mapping catheter (20-mm reprocessed Achieve Advance™, Medtronic) assembly was advanced through the sheath, and the left upper pulmonary vein was occluded for the first freeze–thaw cycle. At this stage, a small radiodense structure was noted at the left lateral border of the cardiac silhouette (Figure 1B). A 20-mm Achieve catheter with eight electrodes was used; however, only seven electrodes were visible on fluoroscopy in multiple projections during the first application. The fifth electrode was therefore suspected to have embolized (Figure 1C). Detachment of the electrode may have occurred either during loading of the Achieve catheter into the balloon lumen or shortly after it was exposed from the balloon during catheter advancement; however, no resistance was felt during manipulation. Based on the precise stability and cyclical movement of the embolized electrode synchronized with the cardiac cycle, coronary embolization was suspected. The patient was asymptomatic, and no abnormalities were observed on electrocardiography. To prevent further foreign body or air embolization, the cryoballoon–Achieve assembly was not withdrawn. With careful and gentle catheter manipulation, the remaining pulmonary veins were successfully isolated. At the end of the ablation procedure, the assembly was withdrawn into the sheath without retracting the Achieve catheter into the balloon. Selective left coronary angiography performed immediately after ablation demonstrated the embolized electrode lodged in a small-caliber distal branch of the circumflex artery, without evidence of distal flow restriction or spasm (Figure 1D). Given the potential risk of future arterial narrowing or occlusion, a floppy guidewire was advanced into the affected branch, and a microcatheter was positioned over the guidewire adjacent to the electrode. After removal of the guidewire, a microsnare was advanced through the microcatheter in an attempt to retrieve the electrode (Figure 1E, Video 1). However, grasping was unsuccessful, and manipulation with the microsnare resulted in slight distal migration of the embolized electrode. Baseline distal Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was preserved and remained unchanged after intracoronary nitroglycerin administration. Given the small caliber of the involved vessel, the absence of ischemia, and the substantial procedural risks associated with attempted coronary retrieval, including dissection, perforation, or

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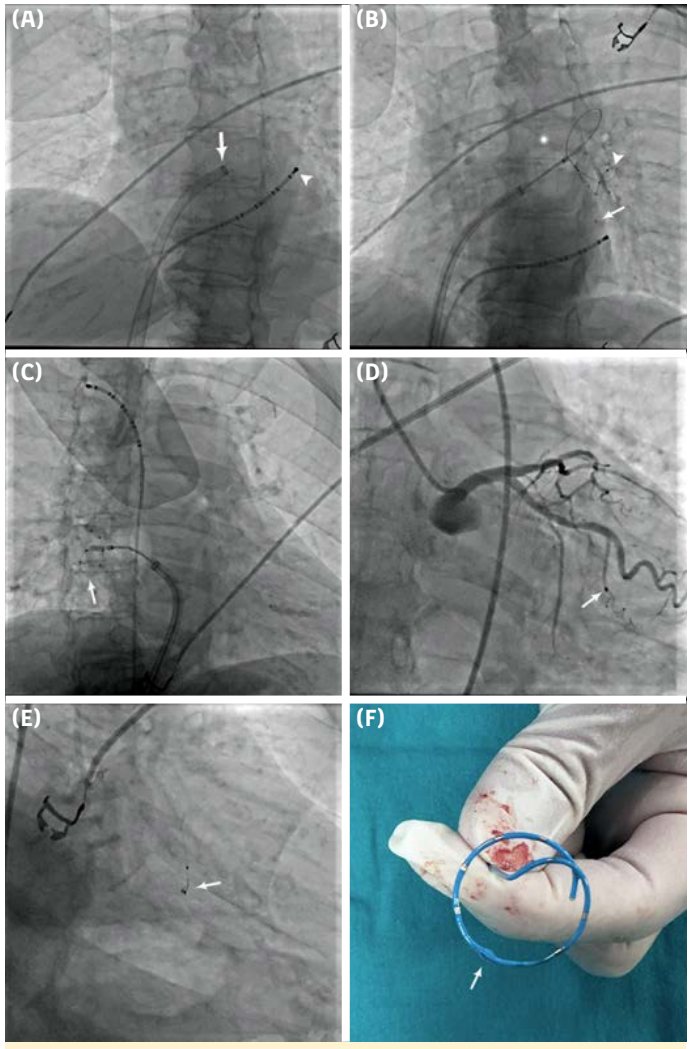

Figure 1. Fluoroscopic images demonstrating: (A) a steerable sheath (arrow) positioned in the left atrium with a decapolar catheter (arrowhead) in the coronary sinus in the left anterior oblique (LAO) view; (B) the cryoballoon (asterisk)–Achieve (arrowhead) assembly during freezing of the left superior pulmonary vein, with an embolized electrode (arrow) visible along the left border of the cardiac silhouette in the LAO view; (C) absence of the fifth electrode of the Achieve catheter (arrow) during freezing of the right inferior pulmonary vein in the right anterior oblique (RAO) view; (D) selective left coronary angiography showing the embolized electrode (arrow) lodged in a small branch of the circumflex artery without flow limitation in the RAO caudal view; (E) the microcatheter–microsnare assembly (arrow) during an attempt to grasp the embolized electrode in the RAO caudal view; and (F) the Achieve circular mapping catheter with the missing fifth electrode (arrow).

occlusion, no further retrieval attempts were undertaken. The patient remained asymptomatic, with no electrocardiographic changes immediately after the procedure or on the following day. The total procedure duration was 88 minutes, with a fluoroscopy time of 37.4 minutes. Postprocedural analysis of the damaged Achieve catheter, including gross inspection, revealed surface abrasion and loss of the detached electrode (Figure 1F, Video 2). An anticoagulation-only strategy, without antiplatelet therapy, was chosen for the patient due to the absence of symptoms, lack of flow restriction or ischemia, small vessel caliber, and the increased risk of bleeding associated with dual antithrombotic therapy. At one-month follow-up, no adverse clinical events were observed.

At our institution, one Achieve catheter is supplied for every two cryoballoon catheters, and reprocessing and reuse are performed in accordance with institutional practice to support procedural availability and resource utilization. The device used in this case had undergone two prior reprocessing and reuse cycles before the index procedure. Vacuum-based ethylene oxide sterilization was used for reprocessing of the Achieve catheter. This method provides the required sterility assurance level without exposing the device to excessive heat, moisture, or radiation, thereby preserving catheter integrity. Following sterilization, the catheter underwent visual inspection to assess potential structural damage or material degradation. No gross abnormalities in loop geometry or electrode appearance were observed; however, no microscopic or tensile integrity testing was performed. Cumulative fatigue from reprocessing and reuse weakened the structural integrity of the catheter, lowering the threshold for mechanical failure during manipulation.

At the time of the procedure, reprocessing of the Achieve catheter consisted of vacuum-based ethylene oxide sterilization followed by macroscopic visual inspection. While this ensured sterility and excluded gross defects, the present event highlighted the inability of visual inspection alone to detect cumulative microstructural fatigue resulting from repeated use. Following this case, our division restricted reprocessing to a single reuse, with mandatory device retirement thereafter, and expanded post-reprocessing quality control to include enhanced functional inspection. This inspection places specific emphasis on electrode integrity and mechanical resistance during catheter loading into the cryoballoon, advancement within and beyond the balloon, and withdrawal back into the balloon lumen during preparation. Although routine microscopic or tensile testing is impractical, these protocol changes aim to mitigate the risk of rare but potentially serious mechanical failures while balancing procedural efficiency and resource utilization.

Published data on mechanical failure of cryoballoon-compatible circular mapping catheters are limited and consist largely of case reports. Specifically regarding the Achieve catheter, fracture of the distal portion of a 20-mm Achieve catheter within a pulmonary vein during cryoballoon ablation has been reported, requiring complex retrieval techniques, including the use of advanced tools after unsuccessful snaring. This underscores that significant device disruption can occur during challenging manipulation or withdrawal from the pulmonary venous system. In another report, fracture of an Achieve catheter was recognized fluoroscopically after abnormal resistance was encountered during catheter manipulation, with a radiopaque electrode fragment visualized as embolized within the systemic circulation. The report emphasized the mechanical vulnerability of the Achieve catheter's distal electrode assembly, particularly when exposed

to repetitive torque, traction, or deformation during positioning or withdrawal from the pulmonary veins. Importantly, such failures may occur even in the absence of overt manufacturing defects and may be facilitated by cumulative mechanical stress during the procedure. Beyond Achieve™, analogous events have been reported with other circular mapping catheters, including electrode dislodgement and retention of a metallic electrode visualized fluoroscopically in the left atrium with subsequent lodging in a small vessel. These reports highlight the potential risk of systemic embolization and underscore the importance of careful inspection and fluoroscopic accounting of electrode markers when resistance or abnormal catheter behavior is encountered.

After recognition of the embolized electrode, the cryoballoon–Achieve assembly was already positioned within the left atrium. Exchanging the Achieve catheter would have required retraction into the balloon lumen and advancement of a new catheter, a maneuver considered to carry a non-negligible risk of thromboembolism or air embolization; therefore, the procedure was continued using the same Achieve catheter. The ablation was completed under heightened safety precautions, including repeated fluoroscopic assessments in multiple projections to exclude additional radiopaque fragments and continuous monitoring of the Achieve catheter, which revealed no further structural abnormalities. Catheter manipulation was minimized and performed with gentle, controlled movements, avoiding forceful advancement, excessive torque, or high-tension maneuvers. Importantly, the Achieve catheter was never retracted into the balloon lumen at any point during or after the ablation, thereby avoiding potential shear forces at the balloon–catheter interface. At the end of the procedure, the cryoballoon–Achieve assembly was withdrawn together into the FlexCath sheath.

Follow-up in the present case was limited to one month, during which the patient remained completely asymptomatic, with no electrocardiographic or echocardiographic evidence of myocardial ischemia, infarction, pericardial effusion, or other structural complications. No additional ischemia-directed functional testing or advanced cardiac imaging was performed, given the absence of symptoms, preserved ventricular function, stable electrocardiographic findings, normal echocardiographic parameters, preserved distal TIMI-3 flow on the index coronary angiogram, and the very small caliber of the involved distal circumflex branch. Nevertheless, the retained metallic intracoronary foreign body raises theoretical concerns regarding late complications, including delayed thrombotic occlusion, chronic inflammatory response, or subsequent ischemic events. The absence of long-term follow-up represents an important limitation of this report, and longer-term surveillance is warranted in similar cases to better define the natural history and optimal management strategy of such rare complications.

From a sustainability perspective, reprocessing selected devices labeled as "single use" has been proposed to reduce waste and material use in electrophysiology. Studies evaluating the life cycle of remanufactured or reprocessed electrophysiology catheters have demonstrated a lower environmental impact compared with disposal after a single use. However, these benefits depend on reprocessing being performed within standardized and validated programs. Such programs must include proper cleaning, sterilization, functional testing, and clear device identification during each reuse cycle, and must adhere to established quality systems and regulatory requirements. In the United States, reprocessed single-use devices are regulated by the Food and Drug Administration to ensure safety and effectiveness. In Europe, these practices are governed by the Medical Device Regulation.

In conclusion, this case highlights a rare but serious complication associated with the reprocessing of mapping catheters. Repeated mechanical cycling and sterilization can cause structural fatigue, increasing the risk of electrode detachment, particularly during high-tension maneuvers. Retrieval of small intracardiac metallic fragments is technically challenging. In selected cases, conservative management may be considered after careful risk–benefit assessment when the patient is clinically stable, coronary flow is preserved, and percutaneous retrieval attempts are unsuccessful.

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

Informed Consent: The patient provided written informed consent for the publication of this case report and any accompanying images. All identifiable information has been anonymized to protect patient privacy.

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Video 1. Fluoroscopic recording showing an embolized Achieve catheter electrode in a distal circumflex artery branch and an attempted retrieval using a microcatheter–microsnare assembly in the right anterior oblique (RAO) caudal view.

Video 2. Achieve circular mapping catheter with the missing fifth electrode and deformation at the site of the missing electrode.

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Interpretation of the Relationship Between CHA_2DS_2-VASc and Anxiety in Anticoagulated Patients

Antikoagülan Tedavi Gören Hastalarda CHA_2DS_2-VASc ve Anksiyete Arasındaki İlişkinin Yorumlanması

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the study entitled "*The Effects of Warfarin and Novel Oral Anticoagulants on Depression and Anxiety in Patients with Non-Valvular Atrial Fibrillation*," published by Cansel et al.[1] in the December 2025 issue of the *Archives of the Turkish Society of Cardiology*. This study significantly advances our understanding of the impact of oral anticoagulant therapy on psychiatric symptoms in patients with atrial fibrillation (AF).[1]

One point that particularly drew our attention is the relationship between the CHA_2DS_2-VASc score[2] (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack, Vascular disease, Age 65–74 years, Sex category) and anxiety levels reported in the study. In the discussion section, the authors suggest, based on correlation analysis, that higher CHA_2DS_2-VASc scores are associated with increased anxiety and depression. However, in the multivariate logistic regression analysis, the odds ratio for this variable was 0.691 (95% confidence interval: 0.538–0.883; P = 0.004), indicating an inverse relationship. We believe that the presence of a positive association in the correlation analysis but a negative association in the multivariate model warrants further clarification.

The study shows that patients in the warfarin group were older than those in the other treatment groups. As the Beck scales used in the study are based on somatic complaints, symptoms such as fatigue, insomnia, loss of appetite, and decreased energy in older people and individuals with multiple comorbidities may be a result of underlying illnesses and/or age-related frailty.[3] This may also result in scores being higher than they actually are.[4]

A higher CHA_2DS_2-VASc score usually indicates elderly patients with multiple comorbidities.[5] In the regression model, including variables that reflect the same clinical burden, such as the CHA_2DS_2-VASc score (which includes components such as age, heart failure, hypertension, diabetes mellitus, etc.), warfarin use, and depression score, may have created a suppressor effect among the variables. As these variables represent similar clinical information in different ways, the direction of the coefficients may be reversed. Thus, although the CHA_2DS_2-VASc score is positively associated with anxiety score, it may appear statistically "protective" when included in a model alongside other variables carrying the same information.

We believe that this difference should be considered as a possible model-related effect. Consequently, when constructing a statistical model, it should be borne in mind that the model's structure may lead to such directional changes. Careful consideration of this issue will improve the interpretation of the relationship between cardiovascular risk scores and psychiatric symptoms, as well as inform the design of future multivariate analyses. In this regard, the study by Cansel et al.[1] provides a valuable starting point for a more in-depth examination of the interaction between health-related risk and psychiatric symptoms.

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Reply to the Letter to the Editor: Interpretation of the Relationship Between CHA_2DS_2-VASc and Anxiety in Anticoagulated Patients

Editöre Mektup Yanıtı: Antikoagülan Tedavi Gören Hastalarda CHA_2DS_2-VASc ve Anksiyete Arasındaki İlişkinin Yorumlanması

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We would like to thank the authors[1] for their interest in our study[2] and for their constructive comments.

As noted in their correspondence, our correlation analyses demonstrated a positive association between CHA_2DS_2-VASc scores and the severity of anxiety and depressive symptoms. These analyses treated symptoms as continuous variables, reflecting a gradual increase in symptom severity.

In contrast, the multivariate logistic regression analysis modeled anxiety as a binary outcome variable (present/absent), addressing a different clinical question. In this model, the simultaneous inclusion of clinically overlapping variables—such as depression score, ejection fraction, and anticoagulant therapy—may have attenuated the independent effect of the composite risk index, CHA_2DS_2-VASc, or led to a reversal in the direction of its coefficient. This finding is consistent with the concepts of suppressor effects and overadjustment described in the literature.

Therefore, we would like to emphasize that the inverse association observed for the CHA_2DS_2-VASc score in the logistic model should not be interpreted as reflecting a true protective effect against anxiety. Our findings suggest that while the CHA_2DS_2-VASc score is associated with anxiety severity, it may not independently predict the presence of anxiety in multivariable, threshold-based models.

We believe that addressing this methodological issue will contribute to a more accurate interpretation of the relationship between cardiovascular risk scores and psychiatric symptoms.

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Enhancing Risk Stratification in Coronary Artery Ectasia: The Synergy of Inflammation and Metabolic Scores

Koroner Arter Ektazisinde Risk Stratifikasyonunu Güçlendirmek: Enflamasyon ve Metabolik Skorların Sinerjisi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the valuable study by Tunca et al.[1] investigating the role of the Pan-Immune-Inflammation Value (PIV) in the diagnosis of isolated coronary artery ectasia (CAE). The authors' demonstration within an isolated CAE group meticulously selected from a large cohort of over 17,000 patients that PIV possesses superior discriminative power compared to other inflammatory indices is a significant contribution to our understanding of the inflammatory background of the disease's pathophysiology.[2,3]

The Area Under the Curve (AUC) value of 0.674 determined for PIV in the study highlights the potential of this new biomarker; however, it also suggests that it could be supported by additional parameters to enhance diagnostic precision in clinical practice. In a multifactorial vascular pathology such as CAE, it is recognized that not only the cellular inflammatory response but also the patient's metabolic status impacts the risk profile.

In this context, a recent study by Kilic et al.[4] reported that the Intermountain Risk Score (IMRS), which includes metabolic markers such as sodium, potassium, glucose, and creatinine in addition to complete blood count parameters, is an effective risk predictor in CAE patients. Evaluating the high inflammatory burden (PIV) identified by Tunca et al.[1] in conjunction with scoring systems like IMRS, which reflect metabolic and biochemical balance, could provide an "immuno-metabolic" perspective, potentially elevating risk stratification to a stronger level.

In future studies, investigating inflammation-focused markers such as PIV in combination with holistic risk scores such as IMRS would likely increase diagnostic accuracy and offer clinicians a broader perspective in determining prognosis for this patient group.

We congratulate the authors on this insightful work.

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Reply to the Letter to the Editor: Enhancing Risk Stratification in Coronary Artery Ectasia: The Synergy of Inflammation and Metabolic Scores

Editöre Mektup Yanıtı: Koroner Arter Ektazisinde Risk Stratifikasyonunu Güçlendirmek: Enflamasyon ve Metabolik Skorların Sinerjisi

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We thank the authors[1] for their interest in our recently published article, "Pan-Immune-Inflammation Value as an Independent Indicator of Isolated Coronary Artery Ectasia",[2] and for their constructive and thoughtful comments. We appreciate their emphasis on the multifactorial nature of coronary artery ectasia (CAE) and the opportunity to further clarify the clinical implications of our findings.

As the authors rightly note, although the pan-immune-inflammation value (PIV) demonstrated the highest discriminative performance among the evaluated inflammatory indices, its diagnostic accuracy remained moderate. This finding is consistent with the complex and heterogeneous pathophysiology of CAE. As discussed in our manuscript, CAE should be considered an active vascular disorder in which inflammatory, metabolic, and hemodynamic mechanisms interact, rather than a purely anatomical or single-pathway condition.

We acknowledge the authors' reference to the Intermountain Risk Score (IMRS), which integrates metabolic and biochemical parameters in addition to hematologic indices. Combining inflammation-based markers such as PIV with comprehensive metabolic risk scores may provide a broader immunometabolic perspective. Such an approach could be particularly valuable in routine clinical practice, especially for improving risk stratification and identifying patients with a higher-risk profile.

The primary objective of our study, however, was to determine whether PIV, as a simple, inexpensive, and widely available composite inflammatory marker, is independently associated with isolated CAE. In our view, demonstrating this independent association represents an important initial step in highlighting the inflammatory component of CAE using a practical biomarker. As correctly pointed out by the authors, future studies integrating PIV with holistic risk scores such as IMRS may further enhance diagnostic performance and clinical applicability.

We thank the authors once again for their valuable contribution and for drawing attention to an important direction for future research. From our perspective, their comments add depth to the ongoing scientific discussion and support the evolving concept of combined inflammatory and metabolic risk assessment in coronary artery ectasia.

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