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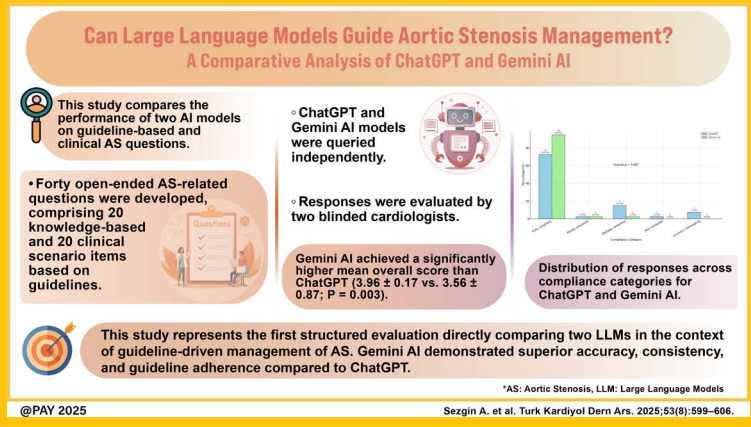

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Comparison Between Thin and Thicker Strut Stents in Patients Undergoing Primary Percutaneous Intervention for Single-Vessel Disease

Tek Damar Hastalığı Nedeniyle Primer Perkütan Girişim Uygulanan Hastalarda İnce ve Kalın Strutlu Stentlerin Karşılaştırılması

ABSTRACT

Objective: The aim of this work was to compare the safety and effectiveness of the BioMime and the thicker strut Ultimaster sirolimus-eluting stents (SESs) in patients presenting with ST-elevation myocardial infarction (STEMI) and single-vessel disease undergoing primary percutaneous coronary intervention (PCI).

Method: This prospective, single-center, non-inferiority study was carried out on 221 STEMI individuals aged 19 to 65 years, both sexes, diagnosed with STEMI. All patients were subjected to electrocardiograms, echocardiography, and clinical follow-up. Quantitative coronary angiography was done at baseline and follow-up.

Results: Post-procedure quantitative coronary angiography (QCA) demonstrated no significant differences regarding acute luminal gain and residual stenosis between the BioMime and Ultimaster groups. Binary restenosis was slightly greater in the BioMime group (7 [15.2%]) compared to the Ultimaster group (6 [13.3%], relative risk [95% confidence interval, CI]: 0.947 [0.329–2.725], P = 0.797). The variation in in-stent late lumen loss (LLL) between the groups was minimal (0.33 ± 0.3 mm in the BioMime group vs. 0.32 ± 0.4 mm in the Ultimaster group, Diff [95% CI]: 0.007 [−0.16–0.17], P = 0.935; prespecified non-inferiority = 0.024). Clinical endpoints at 30 days and 14 months, as well as patient- and device-oriented endpoints at 14 months, were not significantly different between the BioMime and Ultimaster groups. Subgroup analysis revealed a potential benefit of the Ultimaster stent in older patients (>70 years) regarding target vessel failure (TVF).

Conclusion: In primary PCI for STEMI patients, BioMime stents were non-inferior to Ultimaster stents at one-year follow-up. Further studies with longer follow-up durations are warranted to validate these results.

Keywords: Primary percutaneous coronary intervention, single-vessel disease, stents, ST-elevation myocardial infarction

ÖZET

Amaç: Bu çalışmanın amacı, ST yükselmeli miyokard enfarktüsü (STEMI) ve tek damar hastalığı olan ve primer perkütan koroner girişim (PKG) uygulanan hastalarda BioMime ve daha kalın destekli Ultimaster sirolimus salınımlı stentlerin (SES) güvenlik ve etkinliğini karşılaştırmaktır.

Yöntem: Bu prospektif, tek merkezli, non-inferiorite çalışması, STEMI tanısı almış, 19 ila 65 yaşları arasında, her iki cinsiyetten 221 STEMI hastası üzerinde yürütülmüştür. Tüm hastalara elektrokardiyogram, ekokardiyografi ve klinik takip uygulanmıştır. Başlangıçta ve takipte kantitatif koroner anjiyografi (QCA) yapılmıştır.

Bulgular: İşlem sonrası kantitatif koroner anjiyografi (QCA), BioMime ve Ultimaster grupları arasında akut lümen kazancı ve rezidüel stenoz açısından anlamlı bir fark göstermemiştir. BioMime grubunda ikili restenoz (7 [15,2%]) Ultimaster grubuna (6 [13,3%) kıyasla biraz daha fazlaydı, bağıl risk [95% güven aralığı, GA]: 0,947 [0,329–2,725], P = 0,797). Stent içi geç lümen kaybındaki (LLL) gruplar arasındaki değişim minimaldi (BioMime grubunda 0,33 ± 0,3 mm, Ultimaster grubunda 0,32 ± 0,4 mm, Fark [95% GA]: 0,007 [-0,16–0,17], P = 0,935; önceden belirlenmiş eşit etkililik = 0,024). 30. gün ve 14. aydaki klinik sonlanım noktaları ile 14. aydaki hasta ve cihaz odaklı sonlanım noktaları, BioMime ve Ultimaster grupları arasında anlamlı bir farklılık göstermemiştir. Alt grup analizi, Ultimaster stentinin yaşlı hastalarda (>70 yaş) hedef damar yetmezliği (TVF) açısından potansiyel bir fayda sağladığını ortaya koymuştur.

Sonuç: STEMI hastalarında primer PKG'de, BioMime stentleri bir yıllık takipte Ultimaster stentlerinden daha düşük performans göstermemiştir. Bu sonuçları doğrulamak için daha uzun takip süreli ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Birincil perkütan koroner girişim, tek damar hastalığı, stentler, ST-yükselmeli miyokard enfarktüsü

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Acute ST-elevation myocardial infarction (STEMI) is the most severe form of coronary artery disease and is associated with high morbidity and mortality rates.[1] Mortality from cardiovascular diseases in Egypt is among the highest both globally and regionally.[2] Drug-eluting stents (DESs) represent a significant advancement in percutaneous coronary intervention (PCI) due to their capability to inhibit neointimal proliferation, thereby reducing the requirement for repeat revascularization.[3] Nevertheless, permanent polymer DESs, especially first-generation devices, have been associated with impaired vascular healing, increasing the risk of late stent thrombosis (ST) and restenosis.[4]

To address these limitations, recent iterations of DES technology have focused on improving polymer carriers, stent platforms, and drug formulations.[5] Biodegradable polymer technology has been shown to mitigate the risks associated with older DESs, as demonstrated in trials like the MASTER trial (the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation), which reported lower ST rates with biodegradable polymer-based sirolimus-eluting stents (BP-SES) (1.9%) compared to durable polymer everolimus-eluting stents (DP-EES) (4.8%; P = 0.1).[6] Moreover, newer generations of biodegradable polymer stents have been developed, such as ultra-thin DESs (< 70 μm). These stents have demonstrated superior clinical outcomes compared to second-generation DESs,[7] offering improved flexibility, trackability, and crossability.[8] However, these benefits may occasionally compromise radial strength.[9,10] Recent meta-analyses further support the hypothesis that thinner strut DESs improve outcomes.[11] One meta-analysis demonstrated a 16% reduction in device-oriented composite endpoint (DOCE) risk (relative risk [RR]: 0.84; 95% confidence interval [CI]: 0.72–0.99) at 12 months, while another reported an 18% reduction (RR: 0.85; 95% CI: 0.76–0.96) over a mean follow-up of 2.5 years.[12]

One example of ultrathin DESs is the BioMime sirolimus-eluting stent (SES), which is made from a biodegradable polymer coated with the antiproliferative drug sirolimus and degrades within months. This is the pioneer prospective trial testing the safety and efficacy of the BioMime stent compared to the well-tested Ultimaster stent in single-vessel disease, thereby avoiding the confounding effects of other vessel stenosis in patients presenting with STEMI.

The aim of this work was to evaluate the clinical safety and effectiveness of the BioMime SES compared to the Ultimaster SES.

ABBREVIATIONS

ACS	Acute coronary syndrome
BMS	Bare-metal stents
BP-SES	Biodegradable polymer-based sirolimus-eluting stents
CD-TLR	Clinically driven target lesion revascularization
CFD	Cumulative frequency distribution
DAPT	Dual antiplatelet therapy
DESs	Drug-eluting stents
DOCE	Device-oriented composite endpoint
DP-EES	Durable polymer everolimus-eluting stents
ECG	Electrocardiography
ECHO	Echocardiography
EF	Ejection fraction
HbA1c	Hemoglobin A1c
IVUS	Intravascular ultrasound
LLL	Late lumen loss
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MLD	Minimal lumen diameter
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PNI	Prespecified non-inferiority
POCE	Patient-oriented composite endpoints
PP-EES	Permanent polymer everolimus-eluting stent
PPCI	Primary percutaneous coronary intervention
QCA	Quantitative coronary angiography
RVD	Reference vessel diameter
SES	Sirolimus-eluting stent
ST	Stent thrombosis
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
TLF	Target lesion failure
TVF	Target vessel failure
WMSI	Wall motion score index

Materials and Methods

This prospective, single-center, non-inferiority study was carried out on 221 STEMI patients aged 19 to 65 years, both sexes, diagnosed with STEMI according to the latest guidelines.[1,13] The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Ethics committee approval was obtained from Assiut University Faculty of Medicine Institutional Review Board (Approval Number: 04-2024-100305, Date: 19.10.2020).

Exclusion criteria included multisite disease, left ventricular ejection fraction (LVEF) ≤ 30%, Killip class III/IV at presentation, extreme vessel tortuosity (≥ 2 consecutive curvatures ≥ 180° in major coronary arteries),[14] severe calcification visible without cardiac motion,[15,16] and bifurcation lesions with side branch diameter > 2 mm.

The BioMime SES™ (Meril Life Sciences Pvt. Ltd., Vapi, India) features ultrathin struts (65 μm) with a cobalt-chromium platform and a unique hybrid design (open cells in the mid-segment and closed cells at the edges). The stent is coated with bioabsorbable polymers (poly-L-lactic acid and poly lactic-co-glycolic acid), which degrade within 6–9 months, and sirolimus is eluted at 1.25 μg/mm² over 30–40 days.[5,9]

Ultimaster SES® (Terumo Corporation, Tokyo, Japan) comprises a Kaname stent platform with an abluminal bioabsorbable polymer coating. Sirolimus is released at 3.9 μg/mm² until polymer degradation is completed within 3–4 months.[17,18]

Follow-Up Protocol

Participants were clinically evaluated at 1, 6, and 14 months post-procedure. Angiographic follow-up was conducted at 14 months. Echocardiography assessed left ventricular ejection fraction, wall motion score index (WMSI), and mitral regurgitation before discharge and at 14 months. Dual antiplatelet therapy (DAPT) was administered for at least one year.

Table 1. Baseline characteristics, baseline ECG, ECHO, and laboratory findings in BioMime and Ultimaster groups

	BioMime (n = 122)	Ultimaster (n = 99)	P
Age (years)	56 ± 12	54 ± 12	0.208
Gender (Male)	88 (72.1%)	77 (77.8%)	0.337
DM	30 (24.6%)	36 (36.4%)	0.057
HTN	31 (25.4%)	30 (30.3%)	0.418
Smoking	67 (54.9%)	53 (53.5%)	0.837
Dyslipidemia	90 (73.8%)	69 (69.7%)	0.503
Total ischemic time (hours)	5.7 ± 3.8	5.4 ± 3.3	0.66
Door-to-balloon (min)	36 ± 12	38 ± 11	0.175
P2Y12 inhibitors			0.294
Ticagrelor	113 (92.6%)	95 (96.0%)	
Clopidogrel	9 (7.4%)	4 (4.0%)	
GPIIb/IIIa inhibitors	33 (27.0%)	25 (25.3%)	0.763
Site of infarction			0.681
Anterior	71 (58.2%)	66 (66.7%)	
Inferior	36 (29.5%)	23 (23.2%)	
Inferior right	7 (5.7%)	4 (4.0%)	
Inferolateral	2 (1.6%)	2 (2.0%)	
Inferoposterior	5 (4.1%)	2 (2.0%)	
Posterior	1 (0.8%)	2 (2.0%)	
ST resolution	83 (68.0%)	73 (73.7)	0.355
In-hospital arrhythmias			0.725
VT	1 (0.8%)	2 (2.0%)	
VF	4 (3.3%)	1 (1.0%)	
AF	3 (2.5%)	2 (2.0%)	
CHB	2 (1.6%)	1 (1.0%)	
LVEF (%)	50 ± 8	48 ± 8	0.172
WMSI	1.43 ± 0.22	1.51 ± 0.21	**0.033***
MR			0.154
0	84 (68.9%)	71 (71.7%)	
I	28 (23.0%)	25 (25.3%)	
II	10 (8.2%)	2 (2.0%)	
III	0 (0.0%)	1 (1.0%)	
IV	0 (0.0%)	0 (0.0%)	
Troponin (ng/mL)	21 ± 22	20 ± 19	0.688

Data are presented as mean ± standard deviation (SD) or frequency (%). AF, Atrial fibrillation; CHB, Complete heart block; DM, Diabetes mellitus; GPIIb/IIIa inhibitors, Glycoprotein IIb/IIIa inhibitors; HTN, Hypertension; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; VF, Ventricular fibrillation; VT, Ventricular tachycardia; WMSI, Wall motion score index.

Table 2. Baseline lesion and procedural characteristics in BioMime and Ultimaster groups

	BioMime (n = 122)	Ultimaster (n = 99)	P
Infarct-related artery			0.636
LAD	70 (57.3%)	67 (67.7)	
LCx	9 (7.4%)	7 (7.1)	
RCA	38 (31.1%)	20 (20.2)	
Diagonal	1 (0.8%)	1 (1.0%)	
OM	2 (1.6%)	1 (1.0%)	
PDA	1 (0.8%)	2 (2.0%)	
Ramus	1 (0.8%)	1 (1.0%)	
Site of occlusion			0.789
Proximal	78 (63.9%)	66 (66.7)	
Mid	38 (31.1%)	27 (27.3)	
Distal	6 (4.9%)	6 (6.1%)	
Baseline TIMI flow			0.080
0	109 (89.3%)	76 (76.7%)	
I	7 (5.7%)	13 (13.1%)	
II	2 (1.6%)	5 (5.1%)	
III	4 (3.3%)	5 (5.1%)	
Post-procedure TIMI flow			0.179
0	1 (0.8%)	0 (0.0%)	
I	4 (3.3%)	0 (0.0%)	
II	8 (6.6%)	10 (10.1%)	
III	109 (89.3%)	89 (89.9%)	
Predilation	75 (61.5%)	72 (72.7%)	0.078
Post-dilatation	20 (16.4%)	16 (16.2%)	0.963
Stent length (mm)	32 ± 8	29 ± 7	**0.003***
Stent diameter (mm)	3.3 ± 0.4	3.2 ± 0.5	0.285
Stent diameter			**0.010***
2.25	1 (1.0%)	1 (1.0%)	
2.5	1 (1.0%)	4 (4.0%)	
2.75	8 (7.0%)	20 (20.0%)	
3.00	45 (37.0%)	26 (26.0%)	
3.5	53 (43.0%)	32 (33.0%)	
4.00	14 (11.0%)	16 (16.0%)	
Max. inflation (atm)	15 ± 2	14 ± 2	0.993

Data are presented as mean ± standard deviation (SD) or frequency (%). Diagonal, Diagonal branches of the LAD; LAD, Left anterior descending artery; LCx, Left circumflex artery; OM, Obtuse marginal; PDA, Posterior descending artery; RCA, Right coronary artery; TIMI, Thrombolysis in myocardial infarction.

Quantitative Coronary Angiography (QCA)

Angiograms were analyzed utilizing an automated edge identification system by an independent core laboratory. Paired QCA was conducted at baseline, post-procedure, and at 14-month follow-up, reporting in-stent and in-segment measurements separately.[19]

The primary clinical endpoint was target vessel failure (TVF). The secondary clinical endpoints were major adverse cardiac events (MACE), ST, and DOCE.

Sample Size Calculation

Sample size calculation was conducted using G*Power 3 software. At least 146 patients (73 in each arm) were needed to detect non-inferiority for TVF with a margin of 5% and 95% power. Allowing for a 20% dropout rate in angiographic follow-up, 221 patients were finally enrolled.

Table 3. Procedural quantitative measures at baseline, immediately post-procedure, and at one-year follow-up in BioMime and Ultimaster groups

	BioMime	Ultimaster	Difference (95% CI)	P
Baseline	N = 122	N = 99		
RVD (mm)	2.81 ± 0.4	2.80 ± 0.5	0.01 (-0.11 to 0.13)	0.853
MLD (mm)	0.78 ± 0.2	0.77 ± 0.2	0.009 (-0.06 to 0.07)	0.787
DS%	72.0 ± 7.7	72.5 ± 8.7	0.44 (-2.62 to 1.43)	0.693
Immediately post-procedure	N = 122	N = 99		
RVD (mm)	3.26 ± 0.4	3.17 ± 0.5	0.08 (-0.03 to 0.20)	0.164
MLD (mm)				
In-stent	2.60 ± 0.4	2.59 ± 0.5	0.02 (-0.11 to 0.15)	0.786
In-segment	2.35 ± 0.4	2.36 ± 0.5	-0.01 (-0.13 to 0.12)	0.874
DS %				
In-stent	20.09 ± 8.2	18.79 ± 9.7	1.29 (-1.09 to 3.68)	0.285
In-segment	27.89 ± 8.4	25.89 ± 10.2	2.01 (-0.51 to 4.51)	0.110
Acute gain (mm)				
In-stent	1.83 ± 0.4	1.82 ± 0.5	0.07 (-0.12 to 0.14)	0.895
In-segment	1.58 ± 0.4	1.59 ± 0.5	0.06 (-0.15 to 0.11)	0.769
14 months follow-up	N = 46	N = 45		
RVD (mm)	3.14 ± 0.4	3.08 ± 0.5	0.06 (-0.13 to 0.24)	0.546
MLD (mm)				
In-stent	2.32 ± 0.6	2.35 ± 0.7	-0.03 (-0.31 to 0.25)	0.874
In-segment	2.10 ± 0.6	2.13 ± 0.6	-0.03 (-0.29 to 0.24)	0.848
DS %				
In-stent	26.93 ± 14.2	24.41 ± 16.9	2.51 (-3.98 to 9.01)	0.444
In-segment	33.77 ± 13.9	30.94 ± 16.4	2.83 (-3.51 to 9.16)	0.377
LLL (mm)				
In-stent	0.33 ± 0.3	0.32 ± 0.4	0.007 (-0.16 to 0.17)	0.935
In-segment	0.29 ± 0.3	0.26 ± 0.4	0.03 (-0.13 to 0.18)	0.738
Restenosis	7 (15.2)	6 (13.3)	0.947 (0.329 to 2.725)	0.797

CI, Confidence interval; DS, Diameter stenosis; LLL, Late lumen loss; MLD, Minimal lumen diameter; RVD, Reference vessel diameter; SD, Standard deviation.

Statistical Analysis

Statistical analysis was performed using SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean ± standard deviation (SD) and compared between groups utilizing the unpaired Student's t-test. Qualitative variables were presented as frequency and percentage and analyzed using the Chi-square or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics, baseline electrocardiography (ECG), echocardiography (ECHO), except WMSI, and laboratory findings were not significantly different between the BioMime and Ultimaster groups (Table 1).

Lesion characteristics, including proximal lesion involvement, baseline thrombolysis in myocardial infarction (TIMI) flow grade, and final TIMI flow grade, were similar between the groups. Although the Ultimaster group exhibited a higher rate of pre-

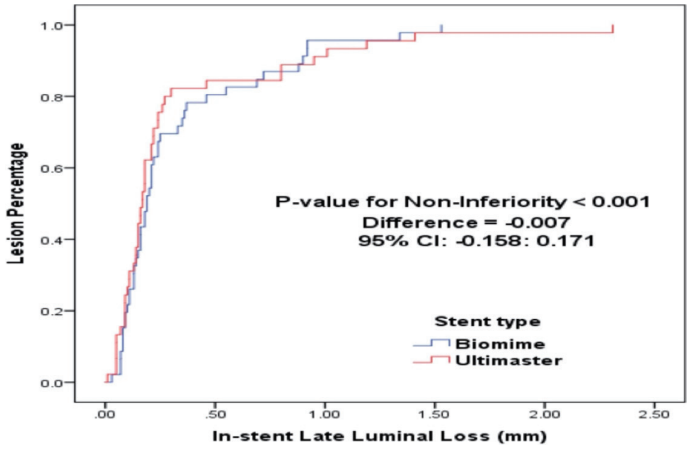

Figure 1. Cumulative frequency distribution (CFD) curves for in-stent late lumen loss (LLL) in BioMime and Ultimaster groups.

Table 4. Clinical endpoints at 30 days and at 14 months, and patient- and device-oriented endpoints at 14 months in BioMime and Ultimaster groups

	BioMime (n = 122)	Ultimaster (n = 99)	P
30 days			
All-cause death	0 (0.0%)	0 (0.0%)	–
All MI	1 (0.8)	1 (1.0%)	0.882
Stroke	0 (0.0%)	1 (1.0%)	0.266
Major bleeding	0 (0.0%)	0 (0.0%)	–
Definite stent thrombosis	1 (0.8)	1 (1.0%)	0.882
Composite	1 (1.0%)	2 (2)	0.443
14 months			
All-cause death	2 (1.6)	0 (0.0%)	0.201
Cardiac death	0 (0.0%)	0 (0.0%)	–
Undetermined death	2 (1.6%)	0 (0.0%)	0.201
Definite ST	3 (2.5%)	2 (2.0%)	0.827
MI not clearly attributable to a non-target vessel	2 (1.6%)	2 (2.0%)	0.833
Major bleeding	0 (0.0%)	1 (1.0%)	0.266
Stroke	0 (0.0%)	1 (1.0%)	0.266
Heart failure	4 (3.3%)	5 (1.0%)	0.259
CD-TLR	4 (3.3%)	5 (5.1%)	0.508
CD-TVR (including CD-TLR)	4 (3.3%)	5 (5.1%)	0.508
Total MACE	13 (10.7%)	9 (9.1%)	0.699
Target vessel failure (TVF)	8 (6.6%)	8 (8.1%)	0.664
Patient-oriented composite endpoints (POCE)			0.862
All-cause death	2 (1.6%)	0 (0.0%)	
Any stroke	0 (0.0%)	1 (1.0%)	
Any MI	7 (5.7%)	5 (5.1)	
Any revascularization	8 (6.6%)	7 (7.1%)	
Total	17 (13.9%)	13 (13.2%)	
Device-oriented composite endpoint (DOCE)			0.862
CVS death	2 (1.6%)	0 (0.0%)	
MI not clearly attributable to a non-target vessel	2 (1.6%)	2 (2.0%)	
CD-TLR	8 (6.6%)	8 (8.1%)	
Total	12 (9.8%)	10 (10.1%)	

Data are presented as frequency (%). CD-TLR, Clinically driven target lesion revascularization; CD-TVR, Clinically driven target vessel revascularization; CVS, Cardiovascular system; MACE, Major adverse cardiac events; MI, Myocardial infarction; ST, Stent thrombosis.

dilation, this difference was not statistically significant. Both groups showed no variations in post-dilation rates, maximal inflation pressure, or overall stent diameter. However, stents with a diameter ≤ 2.75 mm were more frequently used in the Ultimaster group compared to the BioMime group (25 [25%] vs. 10 [8.2%], P = 0.01). Conversely, longer stents were more commonly utilized in the BioMime group (32 ± 8 mm vs. 29 ± 7 mm, P = 0.003) (Table 2).

Pre-stenting measurements, including minimal lumen diameter (MLD), percent diameter stenosis (%DS), and reference vessel diameter (RVD), were similar between the two groups. Post-procedure QCA demonstrated no significant differences in acute luminal gain and residual stenosis between the BioMime and Ultimaster groups. At the 14-month follow-up, the in-stent MLD was slightly larger in the Ultimaster group compared to the BioMime group, but this difference was not statistically significant. Binary restenosis was slightly higher in the BioMime group (7 [15.2%]) compared to the Ultimaster group (6 [13.3%], RR [95% CI]: 0.947 [0.329–2.725], P = 0.797). The variation in in-stent late lumen loss (LLL) between the two groups was minimal (0.33 ± 0.3 mm in the BioMime group vs. 0.32 ± 0.4 mm in the Ultimaster group; difference [95% CI]: 0.007 [–0.16–0.17], P = 0.935; prespecified non-inferiority (PNI) = 0.024) (Table 3).

Cumulative frequency distribution (CFD) curves further demonstrate the non-inferiority of BioMime compared to Ultimaster stents (Figure 1).

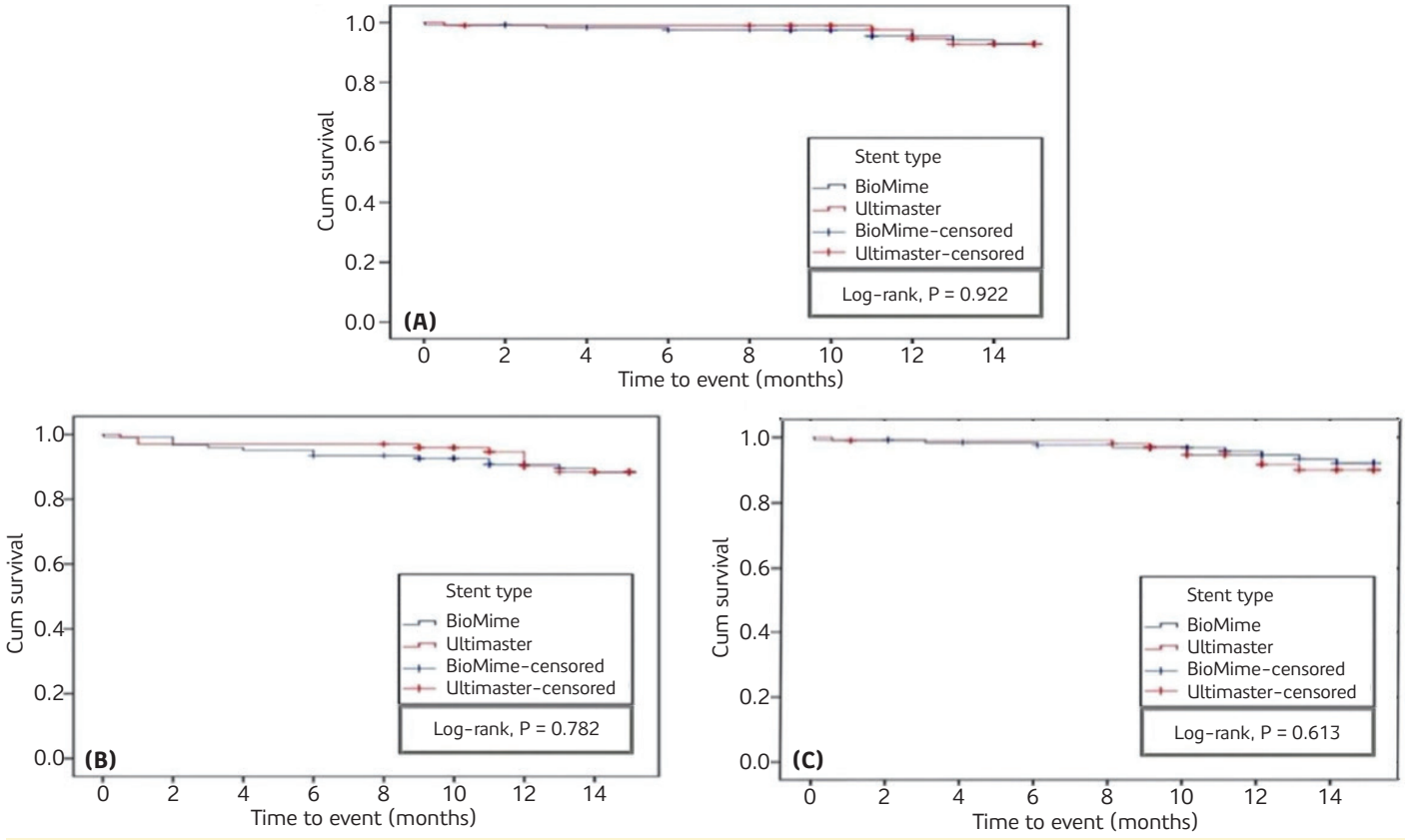

Figure 2. Kaplan–Meier cumulative event curves at 14 months in both groups: (A) target vessel failure (TVF), (B) major adverse cardiac events (MACE), and (C) myocardial infarction (MI).

Table 5. Univariate and multivariate binary logistic regression for MACE prediction

Parameter	Univariate OR (95% CI)	P	Multivariate AOR (95% CI)	P
Age (> 70)	1.010 (0.973–1.048)	0.603		
DM	0.903 (0.350–2.329)	0.833		
P2Y12 inhibitors	2.984 (0.755–11.788)	0.119		
Baseline EF	1.061 (0.997–1.133)	0.061	0.821 (0.684–0.985)	0.034
Baseline WMSI	0.039 (0.004–0.399)	0.006	0.000 (0.000–0.036)	0.003
Predilation	1.758 (0.722–4.282)	0.214		
Stent length	1.011 (0.953–1.072)	0.719		
Stent diameter (< 2.75 mm)	2.340 (0.879–6.226)	0.089	2.585 (0.938–7.122)	0.66
Stent type	0.838 (0.343–2.051)	0.699		

AOR, Adjusted odds ratio; DM, Diabetes mellitus; EF, Ejection fraction; OD, Odds ratio; TIMI, Thrombolysis in myocardial infarction; WMSI, Wall motion score index.

There were no significant differences in clinical endpoints at 30 days and 14 months, or in patient- and device-oriented endpoints at 14 months, between the BioMime and Ultimaster groups (Table 4).

Both baseline TIMI flow and ejection fraction (EF) were predictors of MACE, and the incidence of definite stent thrombosis occurred frequently in patients presenting with TIMI 0 flow (Tables 5, 6).

Kaplan–Meier survival curves for MACE-free and TVF-free survival are illustrated in Figure 2.

Subgroup analysis revealed a potential benefit of the Ultimaster stent in older patients (> 70 years) regarding TVF (Figure 3).

Discussion

This study comparing the ultrathin-strut BioMime SES with the thicker-strut Ultimaster stent in STEMI patients undergoing primary percutaneous coronary intervention (PPCI) revealed the following key findings:

Non-inferiority in clinical outcomes: At 14 months, the BioMime SES was non-inferior to the Ultimaster SES with respect to MACE and TVF.

Comparable angiographic outcomes: The BioMime SES demonstrated similar rates of LLL and restenosis compared to the Ultimaster SES.

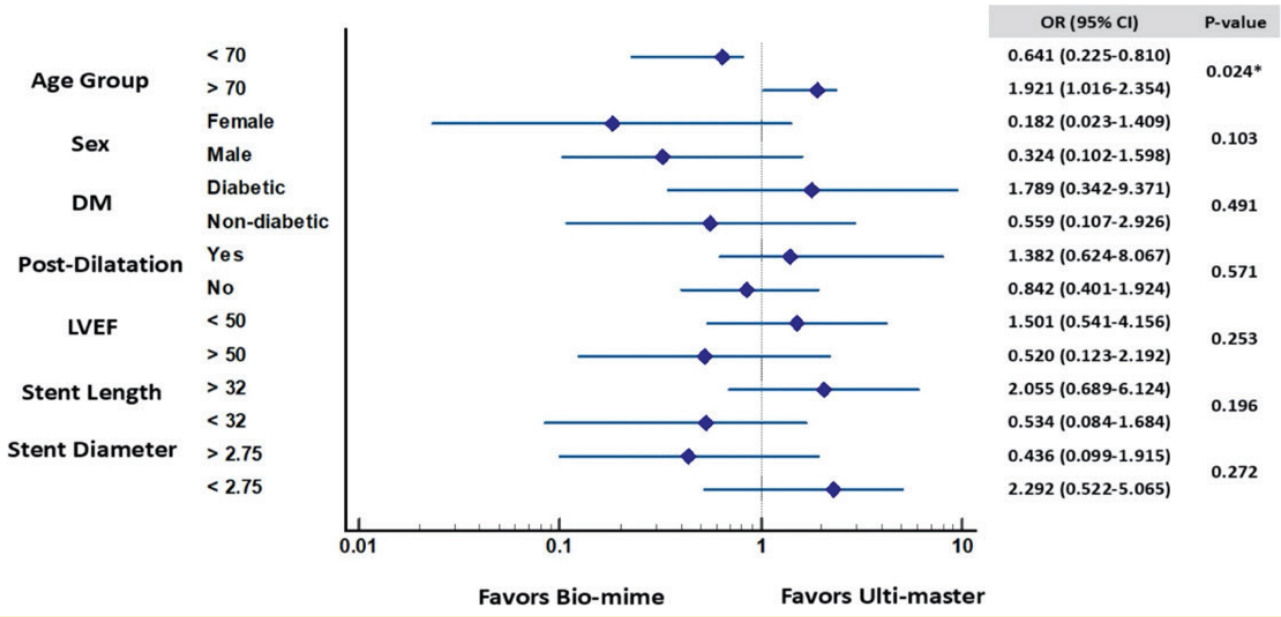

Figure 3. Subgroup interaction analysis of target vessel failure (TVF) at 14-month follow-up according to vessel size, age > 70 years, gender, diabetes mellitus, post-dilatation, maximum inflation, stent length, and stent diameter.

Similar safety profiles: Patient-oriented composite endpoints (POCE) and DOCE were statistically similar between the two groups.

BioMime was non-inferior to Ultimaster in terms of TVF (6.6% vs. 8.1%, respectively; RR: 0.818; 95% CI: 0.319–2.1; P = 0.264).[20,21] This was in agreement with the CENTURY II trial (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease), which involved high-risk acute coronary syndrome (ACS) patients and reported that BP-SESs demonstrated comparable clinical outcomes to permanent polymer everolimus-eluting stents (PP-EESs) at 24 months. The BIOSCIENCE study (Bioresorbable Polymer Versus Durable Polymer Drug-Eluting Stent in Patients With ST-Segment Elevation Myocardial Infarction) revealed reduced rates of target lesion failure (TLF) in STEMI patients treated with the Orsiro SES (ultrathin) compared to those receiving the Xience EES (3.3% vs. 8.7%, p = 0.024 at 12 months).[22,23]

The current study also showed a comparable frequency of MACE at 14 months between the BioMime and Ultimaster groups (10.7% vs. 9.1%, respectively; RR: 1.014; 95% CI: 0.498–2.065; P = 0.699). Similarly, in the meriT-IV trial (Multicenter Randomized Study of the BioMime Sirolimus-Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions), the difference in MACE rates was numerically lower but not statistically significant in the BioMime SES group compared to the Xience EES group (2.98% vs. 7.14%, respectively; p = 0.13).[5]

In our study, POCE rates were comparable between the BioMime and Ultimaster groups (13.9% vs. 13.2%, respectively; RR: 1.061; 95% CI: 0.542–2.077; P = 0.862). Likewise, the BIOSCIENCE trial comparing DP-EES in PPCI patients reported POCE rates of 8.3% vs. 9.8%, respectively (RR: 0.82; 95% CI: 0.43–1.59; P = 0.563).[23]

Table 6. Clinical endpoints at 30 days and at 14 months, and patient- and device-oriented endpoints at 14 months according to baseline TIMI flow

	TIMI 0 (n = 185)	TIMI 1-3 (n = 36)	P
MACE at 30 days	2 (1.1%)	1 (2.8%)	0.443
At 14 months follow-up			
All-cause death	2 (1.6%)	0 (0.0%)	0.201
Definite ST	5 (2.7%)	0 (0.0%)	0.023
Any MI	9 (4.9%)	3 (8.3%)	0.401
Total MACE	18 (9.7%)	4 (11.1%)	0.800
TVF	15 (8.1%)	1 (2.8%)	0.259
POCE	25 (13.5%)	5 (13.9%)	0.952
DOCE	19 (10.3%)	3 (8.3%)	0.722

Data are presented as frequency (%). DOCE, Device-oriented composite endpoint; MACE, Major adverse cardiac events; MI, Myocardial infarction; POCE, Patient-oriented endpoints; ST, Stent thrombosis.

Device-oriented composite endpoint rates in our study were also comparable between the BioMime and Ultimaster groups (9.8% vs. 10.1%, respectively; RR: 0.974; 95% CI: 0.439–2.16; P = 0.948). Similarly, in the TALENT trial (Comparison of Supraflex and Xience in a Randomized Controlled Trial), DOCE occurred in 4.9% of the Supraflex group and 5.3% of the Xience group (P for non-inferiority <0.0001).[24,25]

Regarding LLL at 14 months, our study confirmed that BioMime stents (0.34 ± 0.4 mm) were non-inferior to Ultimaster stents (0.33 ± 0.3 mm vs. 0.32 ± 0.4 mm; difference: 0.007; 95% CI: −0.16 to 0.17; P = 0.935). Similarly, the meriT-V trial demonstrated comparable but slightly lower results, with LLL values of 0.15 ± 0.27 mm in the BioMime group and 0.15 ± 0.29 mm in the Xience EES group.[5]

The rates of clinically driven target lesion revascularization (CD-TLR) in our study were 3.3% vs. 5.1% in BioMime vs. Ultimaster stents, respectively (RR: 0.649; 95% CI: 0.179–2.353; P = 0.085), consistent with previous studies. For example, the MASTER trial reported CD-TLR rates of 2.7% vs. 11.2% for BP-SES vs. bare-metal stents (BMS), respectively (P < 0.001).[18] Similarly, the meriT-V trial reported identical TLR rates for BioMime SES and Xience EES (2.38%) at nine months.[5]

Permanent polymer DES, especially first-generation devices, have been associated with impaired vascular healing, increasing the risk of late ST and restenosis.[4] Biodegradable polymer technology has been shown to mitigate these risks, as demonstrated in trials like the MASTER trial, which reported lower ST rates with BP-SES (1.9%) compared to durable polymer everolimus-eluting stents (DP-EES) (4.8%; P = 0.1).[6]

In our study, definite ST at 14 months occurred in 2.5% vs. 2% of individuals in the BioMime and Ultimaster groups, respectively (RR: 1.23; 95% CI: 0.2097–7.21; P = 0.827). A possible imbalance in lesion complexity might have contributed to the higher rate of ST in the BioMime group.

The limitations of this study included the lack of intravascular imaging techniques (e.g., intravascular ultrasound [IVUS], optical coherence tomography [OCT]) during PPCI or follow-up due to resource constraints. Moreover, about half of the patients underwent angiographic follow-up, and individuals with bifurcation lesions were not included. The absence of hemoglobin A1c (HbA1c) measurement in diabetic patients also limits the generalizability of these findings. Furthermore, non-standardized procedural techniques, such as post-dilation, were another limitation that may have affected the study results.

Conclusion

Over 14 months of follow-up, the BioMime SES was non-inferior to the Ultimaster with respect to MACE and TVF. Both stents demonstrated comparable rates of LLL, restenosis, and safety profiles. Thus, BioMime stents represent a valid treatment option for STEMI patients with single-vessel disease undergoing PPCI. Longer-term follow-up is required to assess very late risks associated with BioMime SESs.

Ethics Committee Approval: Ethics committee approval was obtained from Assiut University Faculty of Medicine Institutional Review Board (Approval Number: 04-2024-100305, Date: 19.10.2020).

Clinical Trial Registration: This study was registered at ClinicalTrials.gov (Identifier: NCT06914089).

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

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A Novel Technique to Extract Implanted Leads Using Simple Stylets and Reused Rotational Sheaths in Patients with a Cardiac Implantable Electronic Device

Kalp İçine Yerleştirilebilir Elektronik Cihazı Olan Hastalarda Basit Stiletler ve Yeniden Kullanılmış Döner Kılıflar Kullanılarak Yerleştirilmiş Elektrotların Çıkarılması İçin Yeni Bir Yöntem

ABSTRACT

Objective: Transvenous lead extraction (TLE) is used in various clinical scenarios, such as device-related infections. Mechanically powered sheaths are one of the most commonly used tools for TLE procedures. We evaluated the procedural and clinical outcomes of a novel extraction technique for chronically implanted leads in the treatment of device-related infections.

Method: The novel extraction technique utilizing standard implantation stylets, snares, reused rotational sheaths, catheters, and wires was evaluated for procedural success and clinical outcomes.

Results: A total of 12 consecutive patients with device-related infections underwent the novel TLE procedure. Complete procedural success was achieved in all patients, with a minor complication rate of 8% (one patient). No major complications or procedure-related mortality were observed. During a median follow-up period of 435 days, one patient died due to a multidrug-resistant systemic infection, one due to end-stage heart failure, and one underwent valve surgery for concomitant valve endocarditis. No cases of reinfection were reported in the study population. Additionally, this novel technique was approximately 85% less costly than the conventional standard technique using locking stylets and unused rotational sheaths.

Conclusion: In situations where unused extraction tools are unavailable or limited by reimbursement constraints, this novel TLE technique offers an effective and safe alternative.

Keywords: Extraction, infection, reused, stylets

ÖZET

Amaç: Transvenöz elektrot ekstraksiyonu (TLE), cihazla ilişkili enfeksiyonlar gibi çeşitli klinik durumlarda kullanılmaktadır. Mekanik tahrikli kılıflar, TLE prosedürlerinde yaygın olarak kullanılan araçlardandır. Bu çalışmada, cihazla ilişkili enfeksiyonların tedavisinde kronik olarak implante edilmiş elektrotların yeni bir ekstraksiyon tekniğiyle çıkarılmasının işlem ve klinik sonuçları değerlendirildi.

Yöntem: Standart implantasyon stiletleri, kementler, yeniden kullanılmış döner kılıflar, kateterler ve teller kullanılarak uygulanan yeni ekstraksiyon tekniği; işlem başarısı ve klinik sonuçlar açısından değerlendirildi.

Bulgular: Cihazla ilişkili enfeksiyonu olan toplam 12 ardışık hasta yeni TLE prosedürü ile tedavi edildi. Tüm hastalarda tam işlem başarısı elde edildi ve minör komplikasyon oranı %8 (1 hasta) olarak kaydedildi. Hiçbir majör komplikasyon veya işlemle ilişkili ölüm gözlenmedi. Medyan 435 günlük takip süresince bir hasta çok ilaca dirençli sistemik enfeksiyon nedeniyle, bir hasta son evre kalp yetmezliği nedeniyle yaşamını yitirdi; bir hasta ise ek kapak endokarditi nedeniyle kapak cerrahisi geçirdi. Çalışma grubunda hiçbir yeniden enfeksiyon vakası görülmedi. Ayrıca bu yeni tekniğin, kilitleme stiletleri ve kullanılmamış döner kılıflar içeren geleneksel standart teknikten yaklaşık %85 daha ucuz olduğu bulundu.

Sonuç: Kullanılmamış ekstraksiyon araçlarının temin edilemediği veya geri ödeme sorunlarının bulunduğu durumlarda, bu yeni TLE tekniği etkili ve güvenli bir çözüm sunabilir.

Anahtar Kelimeler: Ekstraksiyon, enfeksiyon, yeniden kullanım, stiletler

ORIGINAL ARTICLE
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Transvenous lead extraction (TLE) is essential for preventing morbidity and mortality in patients with cardiac implantable electronic device (CIED) system infections and malfunctions.[1] Mechanical-powered tools, such as rotational dilator sheaths, are commonly used for extracting CIED leads, particularly those that are chronically implanted. Two prominent types of rotational sheaths, Evolution® and TightRail™, equipped with specially designed locking stylets, have demonstrated effectiveness and safety in TLE procedures.[2-6] However, the high costs associated with these extraction tools may pose a barrier to performing transvenous extraction procedures, especially in settings where reimbursement limitations restrict the use of mechanical rotational dilator sheaths and locking stylets.

While we advocate for the extraction via the implanted vein using rotational sheaths and locking stylets as the first-line approach, in some centers, access through the femoral vein or, in selected cases, the jugular vein may be preferred for advancing extraction tools.

In this report, we present a novel technique for performing TLE via the implanted vein in patients with CIED system infections, particularly in cases where locking stylets and unused rotational sheaths are unavailable.

Materials and Methods

Study Design and Patient Selection

We conducted a single-center retrospective analysis of our lead extraction database to identify patients who underwent percutaneous lead extraction for CIED system infection using simple lead stylets and reused rotational mechanical dilator sheaths. A total of 12 patients were identified and analyzed for their clinical and procedural characteristics. The decision to use simple stylets and reused rotational sheaths for these patients was prompted by reimbursement issues, despite the fact that the standard approach in our division typically involves the use of locking stylets and unused mechanical rotational dilator sheaths from manufacturers such as Cook Medical and Spectranetics (Philips), particularly when electrodes cannot be manually extracted using simple stylets.

In cases where extraction from the implanted vein was unsuccessful, an alternative percutaneous venous approach, other than the implanted vein, was pursued as a bailout strategy. Notably, all extraction procedures in this cohort were performed due to CIED system infections; no procedures were conducted for other indications such as lead malfunction or system upgrades. Additionally, this technique was not applicable to leads with damaged or occluded lumens, or to lumenless leads, and therefore could not be used in such cases. Although the use of locking stylets with reused rotational sheaths could be a cost-saving strategy, it has not been implemented in our center due to reimbursement constraints. These limitations are important in real-world clinical practice, where lumenless leads—such as Medtronic's SelectSecure MRI SureScan Model 3830—are increasingly used in conduction system pacing, and occluded lumens may be encountered in older or chronically implanted leads due to fibrosis or calcification. Based on our institutional experience and published data, these limitations affect an estimated 10–20% of extraction candidates. In such patients, standard locking stylets cannot be inserted, precluding formation of the lead-stylet unit necessary for our novel technique. Although our current approach is not feasible in these scenarios, future iterations of the technique might explore external lead anchoring or snare-only stabilization strategies, potentially enhanced by three-dimensional imaging guidance to ensure safe traction without intraluminal support.

Consultations were conducted with local representatives of the manufacturers for both Evolution® and TightRail™ regarding the reuse of sterilized rotational sheaths. Although both companies do not recommend this practice, they indicated that, theoretically, it may be feasible.

Prior to extraction attempts, informed procedural consent was obtained from all patients. Furthermore, this retrospective study, based on our institutional database, received approval from Ankara Bilkent City Hospital No. 2 Clinical Research Ethics Committee (Approval Number: E2-24-6620, Date: 21.02.2024) before its commencement.

The reuse of single-use medical devices, such as rotational sheaths and stylets, naturally raises important safety, ethical, and regulatory concerns. While our study utilized ethylene oxide (EO) sterilization for these components, which is a widely accepted method to ensure sterility without compromising material integrity, the legal and regulatory landscape surrounding the reuse of single-use devices must be carefully addressed.

In Türkiye, the reuse of single-use medical devices is not formally regulated at the national level, and no established national guidelines or permissions explicitly authorize the practice. However, some healthcare institutions have adopted internal protocols that allow for the reuse of such devices following validated sterilization procedures, provided that the reuse is medically justified and informed consent is obtained from the patient. In our study, institutional approval was secured, and all patients gave informed consent after being made aware of the reuse of medical materials.

We acknowledge that, despite these precautions, medico-legal risks remain associated with the off-label reuse of single-use medical tools. These include potential liability in the event of adverse outcomes, even if unrelated to device sterility or integrity. It is imperative that institutions engaging in such practices ensure thorough documentation, obtain explicit patient consent, and secure ethical board oversight. We recommend that future regulatory frameworks address this issue to provide clearer guidance, particularly for resource-limited settings where such practices may be considered.

ABBREVIATIONS

CIED	Cardiac implantable electronic device
ECG	Electrocardiogram
EO	Ethylene oxide
HRS	Heart Rhythm Society
IQR	Interquartile range
NYHA	New York Heart Association
SD	Standard deviation
SVC	Superior vena cava
TLE	Transvenous lead extraction

Sterilization Method

Ethylene oxide sterilization is a vacuum-based process in which the gas penetrates the surfaces of most medical devices, ensuring contact with all accessible areas of the rotational sheath. This method delivers the required sterility assurance level without exposing the device to excessive heat, moisture, or radiation, thereby preserving the integrity of the sheath materials and ensuring the safety of the extraction procedure.

EO is an alkylating agent that disrupts the cellular metabolism and reproductive processes of microorganisms. Sterilization occurs when EO gas molecules react with cellular components via the alkylation pathway, involving the addition of alkyl groups to DNA, RNA, and proteins, ultimately destroying these microbial structures.

Regarding sterility validation, ethylene oxide sterilization was performed by a certified central sterilization unit within our hospital. This process included the use of biological indicators to verify microbial inactivation and chemical indicators to confirm adequate exposure to EO gas. Following sterilization, all devices underwent visual inspection to assess for any potential structural damage or degradation.

Extraction Procedure

All TLE procedures were conducted by a skilled device operator specializing in lead extraction (SC). Standard procedural preparations were meticulously performed and included the following: CIED interrogation, antisepsis, administration of general anesthesia, provision of oxygen and continuous saturation monitoring, establishment of arterial and venous access, availability of an on-site echocardiography machine, and creation of femoral accesses for guidewire parking in the superior vena cava (SVC) (to enable the deployment of an SVC occlusion balloon in case of potential SVC rupture during the procedure) and for electrode retraction during extraction. Additional steps included the provision of temporary pacing via the right jugular vein if necessary, administration of local anesthesia, opening of the pocket, exploration of the pulse generator, inspection of the proximal lead segments and fixation sleeves using a soft tissue dissection device, unscrewing of active-fixation leads, and cutting of the proximal lead portions. Surgical backup was available for all procedures and could intervene within less than 10 minutes if required.

In accordance with the latest expert consensus,[1] our standard protocol always begins with an attempt at simple manual traction using either a standard or locking stylet before employing specialized extraction tools. This method is particularly effective for leads with a short dwell time or those that remain mobile within the vein, such as in cases of infection. In our series, this initial approach was applied to all leads. If unsuccessful, further extraction using the novel technique described herein was then pursued.

In the initial stage of the procedure, a stiff, simple stylet, which had been previously used for left ventricular leads and was retained from prior implantation procedures, was inserted into the distal tip of the lead, unlike the procedure performed with a locking stylet. The proximal torquer portion of the stylet was then removed using lead scissors, resulting in a lead with the stylet extending outside the lead (Figure 1A).

A sterilized, reused mechanical rotational dilator sheath, either with or without an outer sheath (Evolution® or TightRail™), obtained from prior transvenous extraction procedures, was then prepared. When necessary, more than one sheath was used for upsizing.

Next, a standard goose-neck snare with its overlying guiding catheter was advanced from the proximal end of the mechanical rotational sheath through the inner lumen, eventually emerging from the sheath's tip (Figure 1B–D). The snare was then deployed from its catheter to open the loop, allowing the lead-stylet system to be introduced through the snare loop (Figure 1E, F).

After positioning the snare at the junction of the lead-stylet system, where the stylet emerged from the proximal part of the cut lead (Figure 1G), the stylet was bent over the lead in the opposite direction. Subsequently, small spirals were created from proximal to distal and from distal to proximal along the lead using a needle holder (Figure 1H, I). These small spirals were then compressed at multiple points using the needle holder (Figure 1J). Although this connection technique proved sufficient and secure in our experience, we acknowledge that this area could be considered a potential weak point in the system. An alternative approach to enhance stability could involve securing the connection with multiple non-absorbable or strong Vicryl sutures around the lead-stylet junction, including the electrode's silicone portion. However, we preferred this mechanical compression method, as it allows for a quicker setup and creates a more compact structure during extraction. In this regard, it may offer advantages over suture-based alternatives. This method is somewhat conceptually similar to the Cook Medical One-Tie compression system, which also provides mechanical locking without internal lead support.

Finally, the loop of the snare was locked in the parked position at the lead-stylet junction, effectively simulating a locking stylet and extension cable (Figure 1K).

In the second stage of the procedure, the lead-stylet system was manipulated to disengage the lead from the lateral walls of the SVC and the right atrium.[7] The lead-stylet system, once formed, was grasped from the distal portion, where the lead approaches the inferior vena cava, and pulled downward using a modified snare technique.[8] This technique involved the use of a reused steerable sheath with a 12F inner lumen (FlexCath Advance™, Medtronic), a large-loop goose-neck snare, and a standard stiff guidewire (Figure 1L).

Initially, the steerable sheath was positioned near the lead-stylet system at the point where the lead approaches the inferior vena cava. Subsequently, the snare and guidewire were advanced through the steerable sheath and passed across opposite sides of the lead (Figure 2A). The guidewire was then directed through the open loop of the snare and grasped at its stiff segment by closing the snare loop (Figure 2B, C). This formed a locked snare-guidewire system, which was pulled back to the ostium of the steerable sheath to establish a robust traction mechanism. Additionally, this system facilitated more distal torque generation during traction and counter-traction maneuvers applied simultaneously from the rotational sheath and the snare-lead-stylet system (Figure 2D).

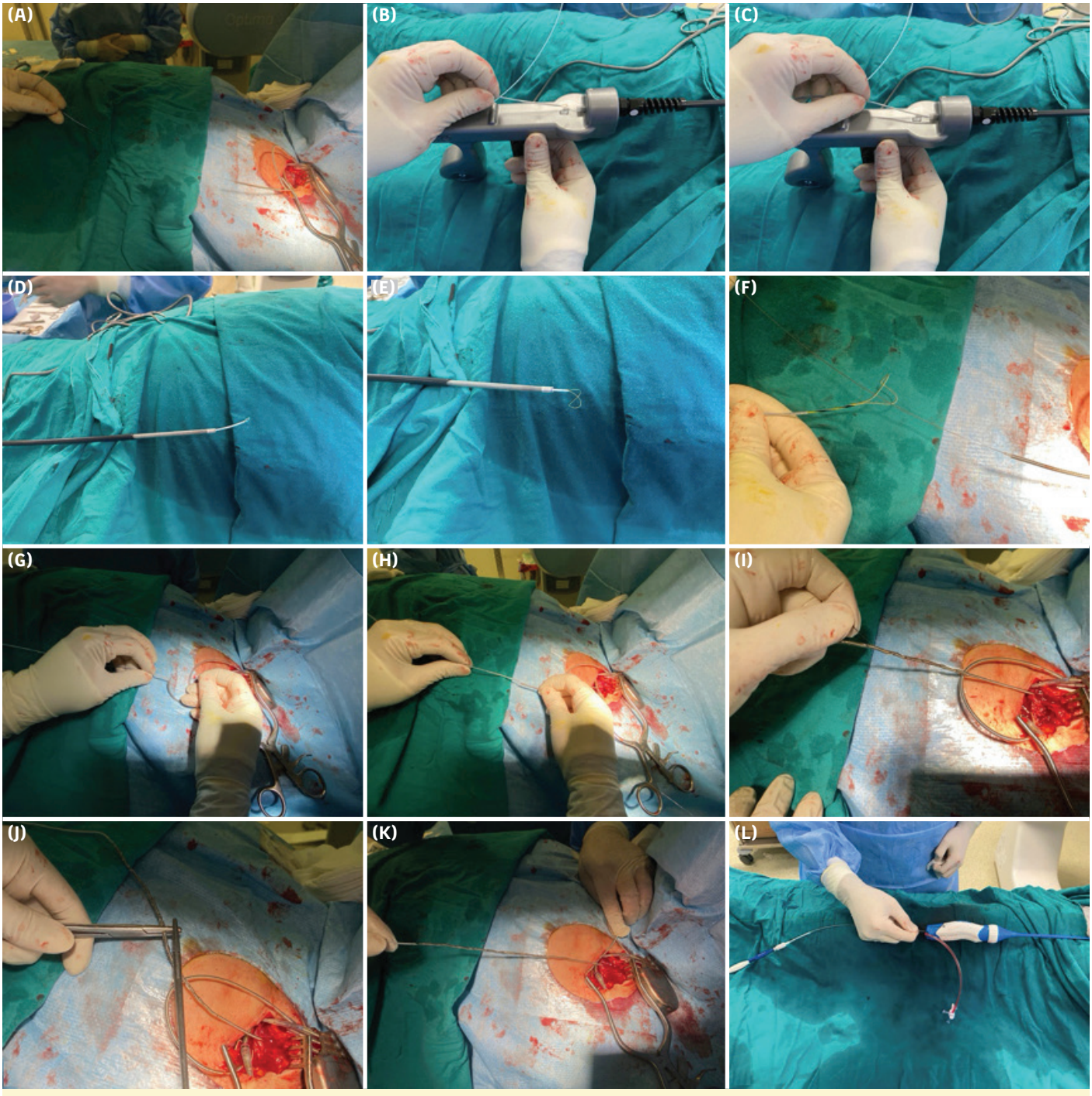

Figure 1. The lead-stylet system consists of a lead that has been cut proximally, with a long, simple implantation stylet housed inside the lead lumen (A). The snare and its guiding catheter are then advanced from the proximal hole to the distal tip of the rotational sheath (B-D). Subsequently, the snare is maneuvered from its catheter into a loop shape, and the lead-stylet system is advanced through this loop (E, F). Once advanced, the snare is positioned at the junction of the lead-stylet system, and the stylet is bent in the opposite direction (G, H). The bent stylet is then twisted over the lead in both proximal-to-distal and distal-to-proximal directions (I). After twisting, the segments are compressed using a needle holder (J). Finally, the snare is firmly closed at the lead-stylet junction using its catheter (K). Additionally, a steerable catheter with a stiff guidewire and a second snare inside it is advanced from the right femoral vein (L). These panels depict the procedure from patient 2.

In the third stage of the procedure, the rotational sheath was introduced over the snare-stylet-lead system. Traction was applied from the femoral system, and standard extraction maneuvers were performed. These included triggered rotation of the cutting blades, dissection of fibrous tissue, use of the outer sheath when necessary, and traction/countertraction movements, all continued until complete removal of the entire CIED system (Figure 2E, F).

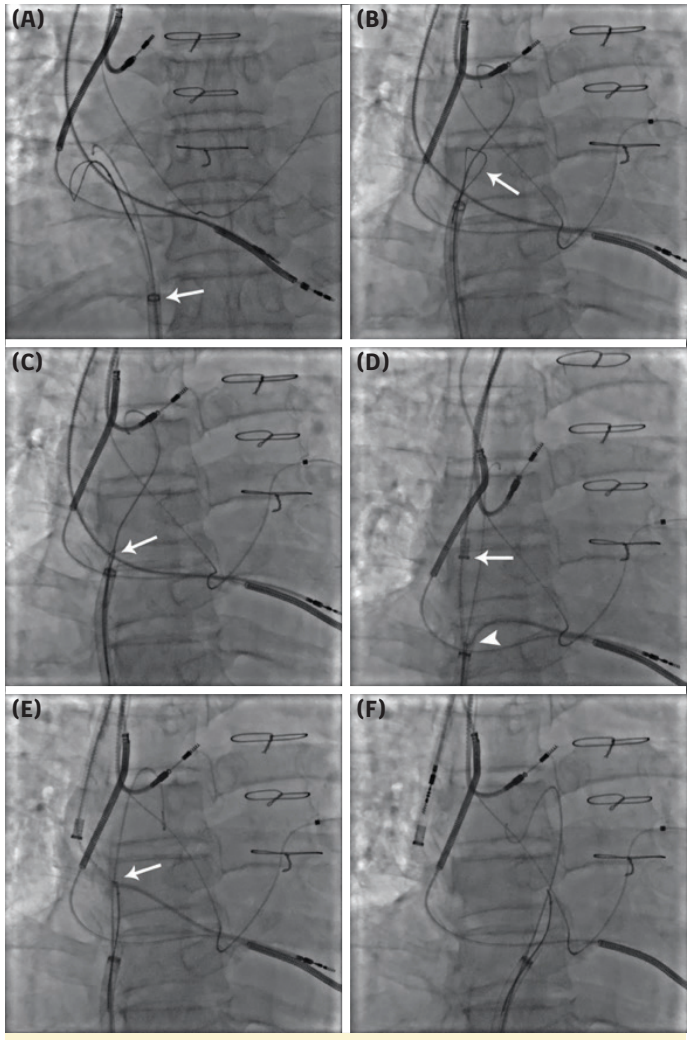

Figure 2. Through the steerable catheter (arrow), the stiff guidewire and the snare are advanced on both sides of the targeted lead (A). The guidewire is then advanced into the loop of the snare (arrow), and the snare is closed to grasp the lead-stylet system distally (arrow) (B, C). Traction is applied (arrowhead) from the catheter-snare-guidewire system to create distal locking and stability of the lead-stylet system, as well as to separate it from the vasculature during advancement of the rotational sheath (arrow) (D). The snare-guidewire system is loosened (arrow) as the rotational sheath approaches, relieving the lead-stylet system and allowing the rotational sheath to be advanced more distally, ultimately resulting in the lead removal (E, F). These panels depict the procedure from patient 2.

For a comprehensive visual demonstration of the complete extraction procedure described above, please refer to Video 1. Additionally, Video 2 provides an illustration of an additional extraction procedure.

Extraction Definitions and Follow-up

Procedural success, clinical outcomes, and complications were reported according to previously established criteria.[2] There were no instances of loss to follow-up. All patients, except one, underwent routine follow-up visits at one month and then every six months thereafter, whenever feasible. These follow-ups included clinical assessment of CIED-related symptoms, 12-lead electrocardiogram (ECG), interrogation of newly implanted CIEDs (if applicable), chest X-ray, and examination of the healed wound site.

Hospitalization outcomes and post-discharge follow-up data, including morbidity and mortality, were documented and reported.

Statistical Analysis

Baseline demographic, clinical, laboratory, and procedural characteristics of patients at the time of extraction were reported at the individual patient level. Categorical variables were presented as numbers and percentages. The Shapiro-Wilk test was used to assess the normality of distribution. Continuous variables that did not follow a normal distribution were described using the median and interquartile range (IQR), while normally distributed continuous variables were reported as mean ± standard deviation (SD). Statistical analyses were conducted using Stata®, version 16.0 (StataCorp LLC, Texas, USA).

Results

Baseline Variables

A total of 12 consecutive patients who underwent CIED extraction procedures using the novel technique for infectious indications were included in the study. The demographic, clinical, laboratory, and procedural characteristics of the patients are summarized in Appendix 1. All patients were male, with a mean age of 55 ± 20 years. The median left ventricular ejection fraction was 41% (interquartile range: 20%-60%). The indications for CIED implantation varied among patients. Half of the cases had undergone at least one prior pulse generator replacement, and one-third were found to be pacemaker-dependent. The majority of patients (58%) had a defibrillator device, and 60% of the implanted leads (n = 30) featured an active-fixation mechanism. The average lead count per patient was 2 (interquartile range: 2-3.75), including both active and abandoned leads. The mean implant duration from initial implantation was 95 ± 54 months. Pocket infection was the primary indication for extraction in 67% of cases. A 13 French rotational sheath was used in 58% of patients. Complete procedural and clinical success was achieved in all cases, with 92% of patients experiencing no complications. The mean procedure and fluoroscopy times were 130 ± 28 minutes and 23 ± 7 minutes, respectively. Positive culture results for the pocket, blood, and lead were reported in 33%, 33%, and 42% of cases, respectively.

Follow-up Data and Clinical Outcomes

The median follow-up duration was 435 days (interquartile range: 128-450 days). There were no instances of loss to follow-up, and all patients, except one, attended routine follow-up appointments at one month and then every six months thereafter. No reinfection was observed in 92% of patients during the follow-up period.

One patient with lead endocarditis and systemic infection, who had a history of drug addiction, died in the hospital due to uncontrolled systemic infection, despite achieving complete procedural success and receiving multiple broad-spectrum antimicrobials. Additionally, after successful lead extraction,

the only pediatric patient in the study underwent tricuspid valve surgery due to valve endocarditis with a large vegetation detected during follow-up. Another patient died during mid-term follow-up due to advanced heart failure.

Re-implantation strategies were individualized based on the type of extracted device, infection resolution status, and current clinical indications. According to the 2017 Heart Rhythm Society (HRS) expert consensus statement,[1] device re-implantation should ideally be deferred until complete resolution of infection, guided by negative blood cultures and clinical signs of recovery. In our cohort, re-implantation was most commonly performed via contralateral implantation sites in high-risk patients. In terms of patient-reported outcomes, symptom relief and patient satisfaction with the procedure were assessed during follow-up visits through structured in-clinic interviews. Patients reported relief from infection-related symptoms and expressed satisfaction with the treatment outcomes. Additionally, no late complications, such as lead dislodgement or recurrent bacteremia, were observed during the follow-up period, which extended up to 450 days.

When comparing the novel procedure, which utilizes sterilized implanting stylets, snares, sterilized reused catheters, and sterilized reused rotational sheaths, with the standard approach, which uses locking stylets and new rotational sheaths, it was found that the total cost related to tools used in the novel extraction technique was significantly lower than that of the standard extraction technique ($640 vs. $4,550, respectively).

Discussion

The primary finding of our study highlights the effectiveness and feasibility of this novel extraction technique, even in the absence of locking stylets and unused new rotational sheaths. This approach demonstrated high efficacy and a low complication rate in a diverse patient population with device-related infections and various types of CIEDs and leads. Furthermore, mid-term clinical follow-up showed favorable outcomes with respect to CIED-related events.

As global rates of cardiac implantable electronic device implantation continue to rise, so does the likelihood of encountering complications such as infection, venous stenosis, or electrode failure. Regardless of the specific cause of these adverse events, transvenous lead extraction has emerged as the primary approach for managing CIED-related complications in most patients with implanted devices.[9] Extraction procedures can vary widely in complexity, ranging from simple manual techniques to the use of multiple tools and combined approaches.[10] Mechanical-powered tools, such as mechanical rotational dilator sheaths, are commonly used for extracting CIED leads, particularly those that have been chronically implanted.[2-6]

However, the high costs associated with these extraction tools can present a barrier to performing TLE procedures, especially in cases where reimbursement limitations restrict access to mechanical rotational dilator sheaths and locking stylets. The estimated costs and healthcare burdens of CIED infections alone have been reported as substantial in both the United States and the United Kingdom.[11] The average cost of TLE was reported to be £10,727, increasing to £22,615 when device reimplantation was also planned.[12] Research indicates that in high-volume centers with established TLE programs, where the increased costs of the procedure are effectively reimbursed, optimal results can be achieved through the proficient utilization of various complex extraction devices.[2-6,13,14] Nevertheless, in many centers where such resources may not be readily available, there is a need to implement cost-effective and easily applicable techniques to optimize outcomes and shorten the learning curve.[15]

In our study, we demonstrated the safety and efficacy of a cost-effective extraction method that can be applied in many centers, eliminating the need for locking stylets or newly purchased, unused rotational sheaths. The average cost of TLE using our novel extraction technique was calculated to be $640. This approach holds promise as an effective and accessible solution to the challenges associated with CIED lead extraction. Although economically advantageous, the tedious sterilization and reuse of mechanically complex rotational sheaths may not be permitted in all centers. In such cases, another simple and cost-effective alternative is the use of inexpensive telescopic propylene sheaths as the first-line option.[16] The use of expensive rotational sheaths can then be reserved as a second-line strategy.

While we reported that the novel technique was approximately 85% less expensive than the conventional method, this estimate primarily reflects the direct material costs. A comprehensive cost analysis would ideally include additional factors such as staff time, training requirements, sterilization labor, and the potential costs associated with complications, safety assurance, or legal liabilities related to the reuse of medical devices. Unfortunately, such data were not systematically collected in our retrospective analysis. Nonetheless, we believe our findings provide an important starting point for highlighting the economic advantages of this technique in low-resource settings. Future studies should aim to include these indirect costs, as well as long-term clinical and economic outcomes, to enable a comprehensive cost-effectiveness analysis.

In addition to our approach, several alternative low-cost methods for transvenous lead extraction have been described in the literature, including the use of telescoping polypropylene sheaths, mechanical-only extractions, and femoral or jugular snaring techniques. These methods have also demonstrated safety and efficacy in resource-constrained environments. For instance, telescopic sheaths, which are less expensive than powered tools, have shown promising outcomes when used with a lead-locking device system, particularly under local anesthesia.[16] Similarly, mechanical-only extractions using traction and countertraction principles without powered sheaths can be effective, especially in experienced hands.[9] The femoral snaring technique, used either alone or in combination with jugular access, can serve as a bailout or primary strategy, depending on anatomical constraints and operator experience.[7,17] Compared to these methods, our technique maintains cost-efficiency while incorporating rotational sheaths to manage more complex adhesions, potentially offering a middle ground between manual traction and advanced powered tools. More comparative studies are needed to determine the optimal technique based on cost-effectiveness, safety, and procedural success.

In our series, both Evolution® and TightRail™ mechanical rotational sheaths were reused following EO sterilization. We did not observe any procedural or clinical differences attributable to the specific sheath type during the novel extraction technique. Selection between sheath types was based primarily on availability rather than performance characteristics. However, due to the small sample size, no definitive conclusions can be drawn regarding comparative performance or complication rates. In the context of clinical practice in Türkiye, two studies have directly compared the Evolution® and TightRail™ systems, highlighting their relative safety and efficacy. In the first study, the authors found no significant differences in procedural success or complication rates between the two systems.[2] Another Turkish study supported these findings, reporting that both systems are effective tools for mechanical lead extraction, with favorable safety profiles when used by experienced operators.[18] These findings support the use of either system, depending on operator preference, tool availability, and economic considerations.

Factors such as long dwell time (> 10 years), extraction of three or more leads, procedures performed in low-volume centers, the use of powered sheaths, and the femoral approach have been identified as predictors of clinical failure. Additionally, older age, procedures performed in low-volume centers, New York Heart Association (NYHA) Class III/IV heart failure, and systemic infection have been associated with higher all-cause in-hospital mortality.[10]

The risks associated with TLE must always be carefully weighed against the likelihood of procedural success. In our study, the use of a stepwise technique resulted in a procedural success rate of 100%, an uncomplicated procedure rate of 92%, and a procedure-related mortality rate of 0%. These outcomes align well with previous reports, which indicate a 96.5% success rate for lead removal and a 0.3% in-hospital mortality rate.[19]

The ability to perform a cost-effective extraction method with high success and low complication rates is crucial for healthcare teams performing TLEs in institutions with developing programs and limited extraction experience.

While the use of locking stylets during device removal procedures offers benefits, such as providing internal support to intracardiac leads, reducing fluoroscopy time, and enabling the application of distal traction force, the high cost of these specially designed tools often makes them inaccessible for many clinics. Therefore, in the initial stage of our extraction procedure, we simulated the locking stylet and extension cable using a goose-neck snare and an unused stiff simple stylet for left ventricular leads remaining from previous implantation procedures. We believe this method can be safely and effectively employed in cases where locking stylets are unavailable or cost-prohibitive.

In addition to the established efficacy of this cost-effective approach, the technique introduces novel aspects that merit further emphasis. The most innovative component is the simulated locking mechanism using a reused snare and simple stylet, which provides internal support to the lead without requiring a traditional locking stylet. Despite the technique's resourcefulness, there are procedural challenges that must be acknowledged. One significant difficulty is the successful grasping and securing of the cut lead-stylet system, particularly in the presence of dense fibrotic tissue or multiple adjacent leads. These conditions can complicate the maneuvering of the snare loop and the creation of stable spirals for traction. Care must also be taken to avoid unintended disturbance or dislodgement of other functional leads during the manipulation of extraction tools, which can be particularly challenging in patients with multiple leads or abandoned systems. These limitations underscore the importance of experienced operators and careful procedural planning.

Transvenous lead extraction procedures can be performed via either a superior or inferior approach. The effectiveness of using mechanical dilator sheaths via the superior approach has been demonstrated in numerous clinical studies.[2-6,9,13,14]

The "tandem" technique combines both superior and inferior approaches to balance the applied forces during extraction. In the second stage of our extraction procedure, the lead-stylet system was grasped from the distal portion, where the lead approaches the inferior vena cava, and pulled downward using the modified snare technique. Then, in the third stage, traction was applied from the femoral system, and standard maneuvers of the extraction procedure were performed from the superior approach until complete lead removal. Regardless of the equipment or vascular access site used, effective TLE requires control over the extraction forces. Many complications related to the central venous system can arise from an inappropriate relationship between the sheath and the vein wall geometry, or from inadequate lead support when traction is applied solely to the lead. To prevent fatal complications such as intrathoracic vascular injury, particularly SVC tears, simultaneous traction from both superior and inferior directions should be employed. This technique enhances and balances the forces applied to the targeted lead, creating a stronger rail for extraction.[20,21] Additionally, balancing the forces helps draw the lead away from the lateral walls of the SVC and right atrium, improving the geometric relationship between the vessel and the dissecting sheath, and thereby reducing the risk of SVC injury. Moreover, since most of the countertraction force is absorbed by the snare-wire-catheter system from below, the risk of damage to the right ventricle and tricuspid valve is minimized.

In a retrospective series utilizing this technique, particularly beneficial for leads with long dwell times, complete lead extraction was achieved in 96.2% of cases, with a major complication rate of 3.8%, and no reported instances of death or SVC injury.[21]

In our study, the majority of the extracted CIEDs were defibrillator devices, and 27% of all implanted leads featured a dual-coil design with a proximal coil and long dwell times. Such characteristics (long implant durations and dual-coil configurations) have been identified as predictors of increased risk for adhesion to venous and cardiac tissues. Lead-to-vessel or myocardial adhesions, along with fibrosis and calcification, represent the primary challenges encountered during TLE.

Pathological evaluation of extracted materials has shown that the adhesion process depends on both time and the presence of foreign material. Additionally, studies have demonstrated that longer indwelling times of leads are associated with higher complication rates during extraction procedures.[22,23] In our

novel technique, despite a long mean lead indwelling time, we achieved a high procedural success rate and a low complication rate. This suggests that our approach effectively addresses the challenges posed by lead adhesion and prolonged implantation, contributing to the favorable outcomes observed in our study.

It should be acknowledged that all procedures in this study were performed by a single, highly experienced operator, which may have significantly contributed to the 100% procedural success rate and low complication rate (8%). These outcomes may not be easily replicable in centers with less experience in lead extraction techniques. Therefore, operator experience likely played a major role in the observed results. To ensure broader and safer implementation of this novel extraction approach, structured training pathways—including hands-on workshops, supervised procedural mentoring, and simulation-based training—should be developed, particularly for mastering the complex maneuvers involving snare techniques.

Lastly, there are some scenarios we have not yet encountered using this novel method: non-tandem approaches; patients in whom the stylet cannot be advanced distally due to occluded or lumenless leads; and cases where catheters with a lumen smaller than 12F are used in the inferior approach. However, we believe that, theoretically, the novel lead-stylet system could also be adapted for use in these situations. Additionally, the smaller-lumen catheters mentioned earlier also offer a comparable economic advantage.[17] The primary benefit of using a large-lumen sheath is that it allows for the advancement of tools such as a snare and wire/catheter through a single sheath.

Although our study demonstrated promising results, an important limitation is the lack of a control group using conventional extraction tools, such as locking stylets and unused rotational sheaths. This absence precludes a direct comparison of procedural and safety outcomes with standard techniques. While a matched cohort or historical comparison is beyond the scope of this retrospective series, such an approach would provide more meaningful clinical context. Future studies incorporating these types of comparative analyses are warranted to strengthen the generalizability of our findings.

Limitations

This study has several limitations that should be acknowledged. First, the results were obtained from a single tertiary center with a lead extraction practice serving both local and referral patient populations. Therefore, the findings may not be generalizable to other settings with different patient demographics or varying levels of expertise in lead extraction procedures. Additionally, the small sample size and retrospective design limit the strength of the conclusions. With only 12 patients included, the statistical power of the study is inherently limited, which significantly restricts the generalizability of the results. As such, the findings presented here should be interpreted as hypothesis-generating rather than conclusive. Robust clinical conclusions cannot be drawn without further validation in larger, prospective, multicenter trials.

Although local representatives of the manufacturers have stated that the reuse of rotational sheaths and deflectable catheters may be theoretically possible, these devices were only manually and visually inspected in our study. For reused rotational sheaths, tool integrity and potential structural deformation were checked, and the functionality of the trigger mechanism, sheath body, and distal rotation system was manually assessed. For reused deflectable catheters, tool integrity and potential structural deformation were similarly evaluated, and deflection functionality was tested by manipulating the handle mechanism. However, no formal mechanical or performance testing (e.g., tensile strength or leak testing) was conducted. This constitutes a limitation, and we recommend that further validation including objective testing be considered in future studies utilizing reused equipment.

Further randomized, multicenter clinical studies with larger sample sizes are warranted to more accurately determine the success and complication rates of this novel extraction technique compared to other established TLE methods. Another limitation is the low event rate observed in transvenous lead extraction procedures in our study, which may affect the generalizability of the findings.

It is worth noting that the high success rate and low complication rate observed in our study may be attributed to the operator's expertise. Additionally, since device-related infection was the sole indication for extraction in our study, data on the efficacy of this technique for malfunctioning leads, device upgrades, and other indications are not available. Future research should aim to address these limitations and provide a more comprehensive understanding of the utility and effectiveness of this novel extraction technique.

Conclusion

Mechanical-powered tools and locking stylets are commonly used for the extraction of chronically implanted leads. However, we believe that our novel extraction technique presents a viable alternative, particularly in centers facing economic challenges. While we have suggested that this technique can be easily adopted once the learning curve is overcome and a sufficient number of procedures have been performed, we must acknowledge that this claim was not directly supported by quantitative data. Therefore, the current study should be interpreted as a preliminary, proof-of-concept evaluation. The technique may potentially be adopted following adequate operator experience and institutional familiarity, but further validation in larger, external populations is warranted. We also posit that this technique may be particularly beneficial in settings where specialized extraction tools are not readily available for TLE procedures. By offering a cost-effective and accessible solution, our technique has the potential to expand the reach of lead extraction procedures and improve patient outcomes across a variety of healthcare settings. However, given the small patient sample size in this retrospective study, the conclusion must emphasize the need for further research to assess the safety of this new procedure in a larger patient population. Therefore, future prospective studies involving larger sample sizes and multicenter collaboration are necessary to confirm the generalizability, safety, and effectiveness of this approach. Considering the extremely limited number of cases in this study, the proposed technique should be viewed as a bail-out option, applicable primarily when conventional tools are unavailable, particularly in infection-related CIED extractions.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara Bilkent City Hospital No. 2 Clinical Research Ethics Committee (Approval Number: E2-24-6620, Date: 21.02.2024).

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Video 1. Complete extraction procedure of patient 2.

Video 2. Complete extraction procedure of patient 4.

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Comparison of Propofol and Ketamine for Sedation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation

Propofol ve Ketamin'in Atriyal Fibrilasyon için Radyofrekans Ablasyonu Geçiren Hastalarda Sedasyon için Karşılaştırılması

ABSTRACT

Objective: Catheter-based ablation is now widely recognized as a beneficial therapeutic option for managing atrial fibrillation (AF). However, the extended duration and pain associated with the procedure may cause patient movements, potentially leading to disruptions in electro-anatomical mapping systems. Sedative and analgesic agents are used to prevent body movements and manage pain. This study aimed to compare the safety and effects of ketamine and propofol for deep sedation on outcomes in AF patients undergoing radiofrequency ablation.

Method: This retrospective, single-center study included 108 patients who underwent radiofrequency AF ablation under deep sedation (without intubation) in our hospital. The patients were categorized into two groups based on the anesthetic agent administered for deep sedation: the propofol group and the ketamine group. Procedure duration, success rates, and recovery times were compared.

Results: Of the 108 patients, 54 were in the propofol group and 54 were in the ketamine group. The procedure durations were similar in both groups (propofol group: 135 min (120–145) vs. ketamine group: 140 min (120–155), P = 0.803). The eye-opening time after the procedure was 275 seconds in the propofol group and 266 seconds in the ketamine group (P = 0.530). Additionally, no significant variation was detected in the initial measurements of systolic and diastolic blood pressure or heart rate.

Conclusion: There was no significant difference between the propofol group and the ketamine group in terms of outcomes. To the best of our knowledge, this is the first study to assess the efficacy of ketamine and propofol in the radiofrequency AF ablation patient group.

Keywords: Atrial fibrillation, ketamine, propofol, radiofrequency ablation

ÖZET

Amaç: Kateter bazlı ablasyon, atriyal fibrilasyonun (AF) yönetiminde faydalı bir tedavi seçeneği olarak günümüzde yaygın şekilde kabul görmektedir. Ancak, işlemin uzun sürmesi ve ağrılı olması, hastaların hareket etmesine neden olabilir; bu da elektro-anatomik haritalama sistemlerinde bozulmalara yol açabilir. Vücut hareketlerini önlemek ve ağrıyı kontrol altına almak için sedatif ve analjezik ajanlar kullanılmaktadır. Bu çalışmada, AF nedeniyle radyofrekans ablasyon uygulanan hastalarda derin sedasyon için ketamin ve propofolün güvenliği ve etkileri açısından karşılaştırılması amaçlanmıştır.

Yöntem: Bu retrospektif ve tek merkezli çalışmaya, hastanemizde derin sedasyon (entübasyon yapılmaksızın) altında radyofrekans AF ablasyonu uygulanan 108 hasta dahil edilmiştir. Hastalar, derin sedasyon için uygulanan anestezik ajana göre iki gruba ayrılmıştır: propofol grubu ve ketamin grubu. İşlem süresi, başarı oranları ve iyileşme süreleri karşılaştırılmıştır.

Bulgular: Toplam 108 hastanın 54'ü propofol grubunda, 54'ü ise ketamin grubunda yer almıştır. İşlem süreleri her iki grupta da benzer bulunmuştur (propofol grubu: 135 dk (120–145) vs. ketamin grubu: 140 dk (120–155), P = 0.803). İşlem sonrası göz açma süresi, propofol grubunda 275 saniye, ketamin grubunda ise 266 saniye olarak ölçülmüştür (P = 0.530). Ayrıca, sistolik ve diyastolik kan basıncı ile kalp atım hızının başlangıç ölçümlerinde anlamlı bir fark tespit edilmemiştir.

Sonuç: Sonuç olarak, propofol grubu ile ketamin grubu arasında sonuçlar açısından anlamlı bir fark bulunmamıştır. Bildiğimiz kadarıyla, bu çalışma ketamin ve propofolün radyofrekans AF ablasyonu uygulanan hasta grubundaki etkinliğini değerlendiren ilk çalışmadır.

Anahtar Kelimeler: Atriyal fibrilasyon, ketamin, propofol, radyofrekans ablasyon

ORIGINAL ARTICLE
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Atrial fibrillation (AF) represents the most prevalent form of atrial arrhythmia and constitutes a significant cardiovascular disease burden worldwide.[1] AF initially presents as a primary electrical disturbance, often initiated by rapid discharges originating from the pulmonary veins.[2] Radiofrequency ablation has been demonstrated to effectively treat AF by suppressing ectopic electrical impulses originating from the pulmonary veins.[3] According to the latest recommendations by the European Society of Cardiology, catheter ablation is advised as a primary therapeutic approach for rhythm management in patients presenting with paroxysmal AF.[4]

Atrial fibrillation ablation can be lengthy and painful. Therefore, administration of sedation or general anesthesia may be considered to prevent involuntary movements and manage pain.[5] A survey conducted by the European Heart Rhythm Association showed that 66% of patients undergoing pulmonary vein isolation were conscious or deeply sedated.[6] This approach may allow procedures to be performed comfortably without the need for intubation or general anesthesia. Although deep sedation with propofol is widely used in AF catheter ablation,[7] there is insufficient information in the literature regarding the use of ketamine.

Our objective was to compare the relative safety of ketamine and propofol for achieving deep sedation in patients undergoing radiofrequency ablation for atrial fibrillation.

Materials and Methods

Data Collection

This retrospective study included 108 patients who underwent radiofrequency AF ablation under deep sedation (without intubation) in our tertiary heart center. To ensure patient homogeneity, only patients who underwent pulmonary vein isolation were included, while those who received additional lesions were excluded.

The study population was divided into two groups according to the deep sedation anesthetic received: the propofol group and the ketamine group. The choice of sedative agent (propofol or ketamine) was determined according to institutional routine practice and at the discretion of the attending anesthesiologist. No randomization or predefined selection criteria were applied. Procedure duration, success rates, and recovery times were compared, ensuring that the patient groups were matched as closely as possible.

Transesophageal echocardiography was performed on all patients to exclude the presence of intracardiac thrombus, and anticoagulation therapy was continued until the day of the procedure. Regardless of the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65–74 years, Sex category), all patients were administered anticoagulation therapy for a minimum of three weeks prior to and three months following the procedure. Additionally, patients fasted for at least 12 hours before the intervention. As part of standard pre-procedural screening, patients with significantly elevated liver enzymes or known hepatic dysfunction were excluded from the study.

ABBREVIATIONS

AF	Atrial fibrillation
CI	Confidence interval
DAS	Deep analgosedation
DC	Direct current
ECG	Electrocardiogram
NOAC	Noval oral anticoagulant
RF	Radiofrequency
SaO_2	Arterial oxygen saturation
TIVA	Total intravenous anesthesia

The sedation protocol commenced 15 minutes before the intervention with intravenous doses of 2 mg midazolam and 4 mg ondansetron. The drug was administered to the propofol group as a continuous infusion with a syringe pump at a dose of 4 mg/kg/hour from the beginning of the procedure. In the ketamine group, the drug was administered as an intravenous bolus at a dose of 1 mg/kg at the beginning of the procedure. Additional ketamine boluses of 0.5 mg/kg were administered as needed throughout the procedure based on patient response and vital signs. No continuous infusion was used. The dose was titrated according to the patient's condition, anesthetic response, and changes in vital signs in both groups. All sedation procedures were administered and continuously monitored by a certified anesthesiologist throughout the intervention.

Mapping was performed in sinus rhythm. If patients were in AF at baseline, sinus rhythm was restored by direct current (DC) cardioversion. After septal puncture, the ablation catheter was introduced into the left atrium via the atrial septal puncture sheath, and three-dimensional mapping was performed. Electroanatomic mapping was obtained using the Ensite X software (Abbott Laboratories, Chicago, IL, USA) system. A radiofrequency ablation device (TactiCath by Abbott, Little Canada, Minnesota, USA) was used for the procedure. AF ablation consisted of standard techniques, including circumferential pulmonary vein isolation.[8] Radiofrequency ablation at 35 W and 45°C was performed on the antral regions of ipsilateral pulmonary vein pairs. Circumferential lesions were created until electrical isolation of each pulmonary vein from the left atrium was achieved, indicated by bidirectional conduction block. Patients who received additional left atrial lesions were excluded from the analysis.

During the procedure, anticoagulation was provided with heparin sodium to keep the patients' activated clotting time between 250–350 seconds. Oxygen was administered via a nasal cannula throughout the procedure to maintain target SaO_2 (arterial oxygen saturation) levels above 95%. Arterial blood gas levels were assessed right before and at the end of the procedure. After the procedure, patients were taken to a post-anesthesia care unit where they were monitored for electrocardiogram (ECG), blood pressure, and oxygen saturation until they regained consciousness. Procedure duration was measured from the moment of femoral puncture until the removal of the catheter.

The left ventricular ejection fraction was assessed using the modified Simpson's method, which involved measuring both the left ventricular end-diastolic volume and end-systolic volume. The clinical characteristics, comorbidities, medications used,

Table 1. Clinical baseline features of all patients categorized based on the sedative agent used: propofol or ketamine

	Propofol group (n=54)	Ketamine group (n=54)	P
Baseline characteristics			
Age, years	62 (58–68)	60 (51–68)	0.475
Male	29 (53.7)	25 (46.3)	0.441
Height (cm)	173 (165–178)	170 (163–175)	0.150
Weight (kg)	80 (75–89)	80 (75–94)	0.594
Body mass index (kg/m^2)	27.6 (24.9–30.7)	27.8 (26.0–31.5)	0.296
Smoking	14 (25.9)	17 (31.5)	0.523
Comorbidities			
Hypertension	31 (57.4)	24 (44.4)	0.178
Diabetes mellitus	13 (24.1)	12 (22.2)	0.820
Hyperlipidaemia	17 (31.5)	10 (18.5)	0.118
Coronary artery disease	6 (11.1)	9 (16.7)	0.402
Cerebrovascular accident	2 (3.7)	5 (9.3)	0.437
Congestive heart failure	6 (11.1)	8 (14.8)	0.566
Cardiac implantable electronic device	2 (3.7)	5 (9.4)	0.270
Chronic renal failure	6 (11.1)	12 (22.2)	0.118
Current medication			
Aspirin	6 (11.1)	9 (16.7)	0.402
NOAC			
Apixaban	17 (31.5)	22 (40.7)	0.316
Dabigatran	4 (7.4)	3 (5.6)	1.000
Edoxaban	10 (18.5)	8 (14.8)	0.605
Rivaroxaban	22 (40.7)	21 (38.9)	0.844
Beta-blockers	30 (55.6)	22 (40.7)	0.123
Calcium channel blocker	14 (25.9)	17 (31.5)	0.523
Ace inhibitors	31 (57.4)	24 (44.4)	0.178
Diuretics	13 (24.1)	7 (13.0)	0.135
Anti-arrhythmic agents			
Amiodarone	24 (44.4)	19 (35.2)	0.325
Dronedarone	5 (9.3)	6 (11.1)	0.750
Propafenone	14 (25.9)	9 (16.7)	0.238
Preoperative laboratory and echo findings			
Haemoglobin	13.7 (13.3–14.6)	14.1 (12.8–15.1)	0.671
Creatinine	0.86 (0.80–1.02)	0.92 (0.77–1.12)	0.518
LVEF (%)	61 (60–63)	60 (59–62)	0.111

NOAC, Non-vitamin K oral anticoagulant; LVEF, Left ventricular ejection fraction; ACE, Angiotensin-converting enzyme inhibitors.

and echocardiographic parameters of all patients were collected from patient records and electronic medical records. The study was approved by Health Sciences University Hamidiye Scientific Research Ethics Committee (Approval Number: 11/24, Date: 20.09.2024), and was conducted in full compliance with the Declaration of Helsinki.

Statistical Analysis

The participants were classified into two groups based on whether ketamine or propofol was administered during the procedure. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as medians with interquartile ranges. The Kolmogorov–Smirnov test was employed to assess the normality of continuous data distribution. Comparisons of categorical variables were performed using either the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, the Mann-Whitney U test or independent samples t-test was applied depending on data distribution.

Results

A total of 108 AF patients undergoing radiofrequency ablation were divided into two groups: those receiving propofol (n = 54) and those receiving ketamine (n = 54) for deep sedation at

Table 2. Comparison of catheter ablation procedure data with the use of propofol or ketamine for sedation

	Propofol group (n = 54)	Ketamine group (n = 54)	P
Duration of procedure (min)	135 (120–145)	140 (120–155)	0.803
Fluoroscopy time (min)	22 (19–27)	25 (20–30)	0.192
Total amount of propofol, mg	470 (400–550)		
Total amount of ketamine, mg		150 (100–300)	
Midazolam (mg)	2 (2–2)	2 (2–2)	0.304
Heparin dose (IU)	10000 (10000–12500)	12500 (10000–12500)	0.207
Time to eye opening after procedure (s)	275 (244–312)	266 (244–301)	0.530
Initial systolic blood pressure, mmHg	140 (125–154)	139 (114–146)	0.235
Initial diastolic blood pressure, mmHg	65 (57–76)	65 (58–76)	0.815
Initial heart rate, beat/minute	96 (84–110)	101 (89–114)	0.166
Initial SO_2, %	99 (99–99)	99 (99–99)	0.265
Arterial blood gas in the beginning			
pH	7.38 (7.35–7.39)	7.36 (7.36–7.38)	0.158
SO_2	99 (99–99)	99 (99–99)	0.294
PO_2	99 (89–110)	101 (96–109)	0.328
PCO_2	37 (35–37)	37 (36–38)	0.167
Lactate	1.19 (1.12–1.26)	1.14 (1.10–1.18)	0.844
Arterial blood gas in the end			
pH	7.38 (7.37–7.40)	7.38 (7.37–7.39)	0.467
SO_2	99 (99–99)	99 (99–99)	0.313
PO_2	143 (130–167)	157 (140–160)	0.071
PCO_2	39 (37–39)	39 (38–39)	0.476
Lactate	1.19 (1.12–1.26)	1.18 (1.14–1.20)	0.294

SO_2, Sulfur dioxide; pH, Potential of hydrogen; pO_2, Partial pressure of oxygen; PCO_2, Partial pressure of carbon dioxide.

the start of the procedure. The prevalence of comorbidities did not differ significantly between the groups. The patient groups showed similarity in terms of non–vitamin K antagonist oral anticoagulant (NOAC) and antiarrhythmic drug use. The left ventricular ejection fraction was 61% (60–63) in the propofol group and 60% (59–62) in the ketamine group (P = 0.111). Table 1 summarizes the baseline clinical characteristics of all patients according to use of propofol or ketamine for sedation.

The mean procedure duration was 135 (120–145) minutes in the propofol group and 140 (120–155) minutes in the ketamine group (P = 0.803) (Figure 1). The fluoroscopy durations were similar between the groups (propofol group: 22 (19–27) minutes vs. ketamine group: 25 (20–30) minutes, P = 0.192). A total of 470 (400–550) mg of propofol was used in the propofol group, while 150 (100–300) mg of ketamine was administered in the ketamine group. Following the procedure, there was no meaningful difference in eye-opening times between the groups (propofol group: 275 s (244–312) vs. ketamine group: 266 s (244–301), P = 0.530). Initial measurements of systolic and diastolic blood pressure, heart rate, and oxygen saturation showed no significant variation between the groups. Table 2 summarizes the comparison of catheter ablation procedure data with the use of propofol or ketamine for sedation. The comparison of propofol and ketamine administration based on time to eye opening is shown in Figure 2. In addition to p-values,

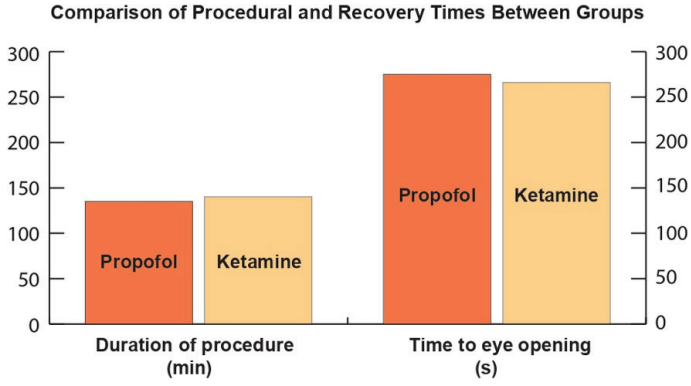

Figure 1. Comparison of procedural and recovery times in the propofol and ketamine groups.

effect sizes and confidence intervals (CI) offer deeper insight into the clinical relevance of the results. The median time to eye opening after the procedure was slightly shorter in the ketamine group (266 seconds, IQR: 244–301) compared to the propofol group (275 seconds, IQR: 244–312). Although this difference was not statistically significant (P = 0.530), the estimated effect size was small (Cohen's d ≈ 0.15), and the 95% CI for the difference ranged from −18 to +25 seconds. Similarly, the duration of the procedure was marginally longer in the ketamine

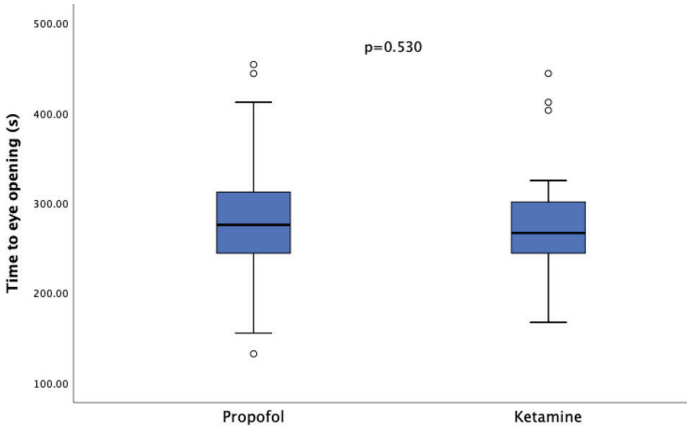

Figure 2. Comparison of propofol and ketamine administration based on time to eye opening.

group (140 minutes, IQR: 120–155) than in the propofol group (135 minutes, IQR: 120–145), with a p-value of 0.803. The effect size was negligible (Cohen's d ≈ 0.05), and the 95% CI for the median difference was -10 to +15 minutes.

Discussion

This study supports the notion that ketamine offers comparable safety and feasibility to propofol when employed for deep sedation in the context of AF ablation. To our knowledge, this is the first study in the literature to show that ketamine is safe in radiofrequency AF ablation.

While antiarrhythmic drugs are beneficial, AF ablation has now become the primary treatment approach. The electrical isolation of triggers originating from the pulmonary vein ostia or antra has become the cornerstone of AF ablation.[2] Catheter ablation is often accompanied by analgesia and sedation to manage procedural pain. Such interventions promote patient stillness, which is a critical factor for achieving catheter stability and optimal tissue contact. Currently, ablation procedures are carried out using one of three methods: general anesthesia, deep sedation, or conscious sedation. Nonetheless, a universally accepted sedation protocol has yet to be established.[9,10]

The combination of propofol with benzodiazepines is widely used for deep sedation in emergency and gastroenterological procedures.[11,12] The need for positive pressure ventilation and intubation with propofol is relatively low.[13] However, propofol's effects on hemodynamics and electrophysiology, such as hypotension and bradyarrhythmia, may limit its use during ablation procedures.[14,15] Additionally, the literature has shown that supraventricular tachycardia can be suppressed and may not be inducible during propofol anesthesia.[16,17] Heart rate and blood pressure are augmented due to ketamine-induced sympathetic nervous system stimulation.[18] Through this mechanism, ketamine has been proven effective in electrophysiological procedures performed on patients with hypotension and bradycardia.[19] Therefore, ketamine presents a viable alternative for managing patients prone to hemodynamic fluctuations and during key ablation procedures aimed at arrhythmia induction. Although not statistically significant, the slightly shorter eye-opening time observed in the ketamine group may suggest faster recovery in some patients. In high-throughput electrophysiology units, even modest improvements in recovery time may enhance procedural efficiency and patient turnover, especially in settings with limited post-anesthesia care resources.

Evidence supports the safe use of ketamine in the context of pulmonary vein isolation procedures involving pulsed field ablation.[20] However, information on the safety of ketamine use in pulmonary vein isolation with radiofrequency ablation is limited. Our study demonstrates that ketamine use may be a potential and reliable alternative in AF ablation, with similar procedure times and hemodynamic properties to propofol use. Based on the study's results, we can suggest using ketamine as an alternative medication for deep sedation in patients undergoing radiofrequency AF ablation, provided that there are no contradictions. However, we believe that our results must be confirmed in randomized controlled studies. From a clinical perspective, ketamine may offer several practical advantages in selected patients. Unlike propofol, ketamine preserves respiratory drive and cardiovascular stability, which may reduce the need for airway interventions or intensive hemodynamic monitoring. Furthermore, ketamine does not require continuous infusion equipment, potentially simplifying workflow and decreasing setup time in busy electrophysiology laboratories. In institutions where anesthesia resources are limited, ketamine may provide a cost-effective and operationally efficient alternative for deep sedation. However, its psychiatric side effects should be considered, and patient selection remains crucial.

Recent randomized data comparing sedation regimens in pulsed-field ablation procedures for AF highlight the advantages of ketamine-based deep analgosedation (DAS) over propofol-opioid protocols. A study evaluating remimazolam-ketamine DAS versus propofol-opioid DAS and total intravenous anesthesia (TIVA) demonstrated a significantly lower incidence of hypoxemia and hypotensive events in the ketamine group, underscoring its superior safety profile specifically in the context of pulsed-field ablation.[21] Although our retrospective study focused on ketamine versus propofol without opioid co-administration and found no significant difference in procedural outcomes or recovery times during radiofrequency ablation, these findings support the potential benefits of ketamine-containing sedation strategies in reducing sedation-related adverse events. Future prospective studies incorporating opioid use and airway management protocols may further clarify optimal sedation approaches to improve patient safety and comfort during various AF ablation techniques.

Our study has limitations that need to be addressed. First, the fact that our study was single-center, included a relatively small patient group, and was retrospective, limits the generalizability of our results. Unfortunately, we were not able to compare ketamine efficacy with placebo because of the design of the study. Additionally, due to the retrospective nature of the study, adverse effects—particularly psychiatric side effects associated with ketamine such as dissociation or visual disturbances—were not systematically recorded in medical files and could not be assessed. Due to the retrospective design, specific data on intra-procedural apnea episodes could not be collected or analyzed systematically. However, no advanced airway management was reported in any case based on available records.

Conclusion

The use of ketamine for deep sedation in AF ablation procedures showed no increase in sedation complications and comparable results to propofol. To the best of our knowledge, this is the first study to directly compare these two sedatives in radiofrequency AF ablation.

Ethics Committee Approval: Ethics committee approval was obtained from Health Sciences University Hamidiye Scientific Research Ethics Committee (Approval Number: 11/24, Date: 20.09.2024).

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

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The Effects of Warfarin and Novel Oral Anticoagulants on Depression and Anxiety in Patients with Non-Valvular Atrial Fibrillation

Non-Valvüler Atriyal Fibrilasyon Hastalarında Warfarin ve Yeni Nesil Oral Antikoagülan İlaçların Depresyon ve Anksiyete Üzerindeki Etkileri

ABSTRACT

Objective: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and has a detrimental impact on psychological well-being. This study aims to determine the prevalence of anxiety and depression in patients with non-valvular AF and to investigate the relationship between these psychological conditions and the treatment regimens administered.

Method: This cross-sectional study included 255 individuals diagnosed with non-valvular AF who were treated between 2021 and 2022. Psychiatric evaluation was conducted using the Beck Depression Inventory and Beck Anxiety Inventory. Multivariate regression analysis was performed to identify predictors of depression and anxiety.

Results: Of the patients included, 62 were on warfarin, 124 were on novel oral anticoagulants (NOACs), and 69 were not receiving any oral anticoagulant (OAC) therapy. Overall, 68.6% had depression and 64.7% had anxiety at a moderate or higher severity level. Although there was no notable variation in anxiety and depression scores between patients on NOACs and those not undergoing OAC treatment, the warfarin group had significantly higher scores than the other two groups. Age, anxiety, C-reactive protein (CRP) levels, and CHA_2DS_2-VASc scores (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack-Vascular disease, Age 65-74 years, Sex category) all positively correlated with the severity of depression. Anxiety, in turn, was positively associated with age, depression, and CHA_2DS_2-VASc scores, and negatively associated with ejection fraction. Regression analysis revealed a strong correlation between warfarin treatment and anxiety severity.

Conclusion: The findings of this study suggest that warfarin treatment is associated with significant psychological effects in patients with AF. Considering that comorbid psychiatric disorders are linked to unfavorable prognosis and higher mortality, the development of appropriate intervention strategies that address psychological distress as part of the treatment process may provide substantial clinical benefits.

Keywords: Anxiety, atrial fibrillation, depression, novel oral anticoagulants, warfarin

ÖZET

Amaç: Atriyal fibrilasyon (AF), kardiyak aritmilerin en sık nedeni olup psikolojik iyi oluş üzerinde olumsuz etkilere sahiptir. Bu çalışmanın amacı, non-valvüler AF hastalarında depresyon ve anksiyete prevalansını değerlendirmek ve bu psikolojik durumlar ile uygulanan tedavi rejimleri arasındaki ilişkiyi incelemektir.

Yöntem: Kesitsel nitelikteki bu çalışma, 2021-2022 yılları arasında non-valvüler AF tanısı ile tedavi gören toplam 255 hastayı kapsamaktadır. Hastaların psikolojik değerlendirmelerinde Beck Depresyon ve Beck Anksiyete Envanteri kullanılmıştır. Depresyon ve anksiyetenin belirleyicilerini tespit etmek amacıyla çok değişkenli regresyon analizi uygulanmıştır.

Bulgular: Çalışmaya dahil edilen hastaların 62'si warfarin, 124'ü yeni nesil oral antikoagülan (NOAK) kullanırken, 69'u herhangi bir oral antikoagülan (OAK) tedavisi almamaktaydı. Orta ve üstü şiddet baz alındığında, hastaların %68,6'sında depresyon, %64,7'sinde anksiyete tespit edilmiştir. NOAK kullanan hastalar ile herhangi bir OAK tedavisi almayan hastalar arasında anksiyete ve depresyon puanları açısından anlamlı bir fark bulunmazken, warfarin kullanan grupta diğer iki gruba kıyasla anlamlı derecede daha yüksek bulunmuştur. Depresyon şiddeti, yaş, anksiyete, CRP ve CHA_2DS_2-VASc puanları ile pozitif korelasyon göstermiştir. Anksiyete ise yaş, depresyon ve CHA_2DS_2-VASc skoru ile pozitif, ejeksiyon fraksiyonu ile negatif korelasyona sahipti. Regresyon analizi, warfarin tedavisinin anksiyete şiddetini öngörmede önemli faktörlerden biri olduğunu göstermiştir.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Sonuç: Çalışmamızın bulguları, warfarin kullanımının AF hastalarında belirgin psikolojik etkilere neden olduğunu ortaya koymaktadır. Eşlik eden psikiyatrik hastalıkların kötü prognoz ve artmış mortalite ile ilişkili olduğu göz önünde bulundurulduğunda, hastaların tedavi sürecinde ruhsal sıkıntılarının da ele alındığı uygun müdahale stratejilerinin geliştirilmesi önemli klinik faydalar sağlayabilir.

Anahtar Kelimeler: Anksiyete, atriyal fibrilasyon, depresyon, yeni nesil oral antikoagülanlar, warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with its prevalence increasing with age and affecting approximately 1–4% of the global population. Although AF can present with a wide range of symptoms, nearly one-third of patients may remain asymptomatic.[1,2] AF is strongly associated with increased morbidity and mortality due to heart failure, stroke, and other thromboembolic events. Compared to healthy individuals, patients with AF have a threefold higher risk of developing heart failure and a fivefold higher risk of stroke.[3,4] The rising medical costs associated with AF also contribute to its substantial socioeconomic burden.[5]

Oral anticoagulant (OAC) therapy plays a crucial role in the management of AF, primarily by reducing the risk of cardioembolic events.[6] Current guidelines recommend OAC therapy not only for patients with AF but also for all individuals with a CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack–Vascular disease, Age 65–74 years, Sex category) of ≥ 2.[7] Although vitamin K antagonists (VKAs), such as warfarin, are effective in preventing stroke, their clinical use is limited by several challenges, including food–drug interactions, a narrow therapeutic window, the need for frequent international normalized ratio (INR) monitoring, bleeding risks, and associated costs. These factors collectively contribute to reduced patient satisfaction and poor medication adherence. In contrast, novel oral anticoagulants (NOACs) have become increasingly preferred in recent years due to their predictable anticoagulant effects, lack of need for routine bleeding monitoring, and minimal drug and food interactions.[8]

Patients with AF experience depression and anxiety more frequently than the general population. Contributing factors may include reduced quality of life, functional impairment, and the direct biological effects of the underlying cardiac condition.[9] Conversely, pre-existing anxiety and depression may contribute to the development of functional somatic disorders through behavioral, pathophysiological, genetic, and iatrogenic mechanisms. These conditions can significantly impair treatment adherence and further diminish quality of life.[10] Furthermore, these mental health disorders may increase the frequency of AF episodes and elevate the risk of complications such as heart failure and mortality.[11,12] Therefore, effective prevention and management of AF requires the identification and addressing of psychosocial risk factors.

Recent studies have shown that OAC therapy can affect the psychological well-being of patients with AF, with warfarin use being particularly associated with increased symptoms of depression and anxiety.[9,13] However, these studies have often been limited by small sample sizes and have primarily focused on comparisons among patients receiving different types of oral anticoagulants, without accounting for the severity of psychiatric symptoms in individuals not receiving any anticoagulant therapy. This study aims to assess the prevalence of depression and anxiety among patients with non-valvular atrial fibrillation (NVAF) and to investigate potential associations between these psychiatric conditions and the type of anticoagulant therapy administered.

ABBREVIATIONS

AF	Atrial fibrillation
ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CHF	Congestive heart failure
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
DM	Diabetes mellitus
HGB	Hemoglobin
INR	International normalized ratio
MI	Myocardial infarction
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation
PVD	Peripheral vascular disease
TSH	Thyroid-stimulating hormone
VKA	Vitamin K antagonist

Materials and Methods

Patients and Study Protocol

This study was conducted among patients diagnosed with NVAF who attended the cardiology outpatient clinic between 2021 and 2022. Participation was entirely voluntary, and informed consent was obtained from all patients. The following exclusion criteria were applied:

- Current treatment for pulmonary embolism and/or deep vein thrombosis
- Presence of an endocrine disorder other than diabetes mellitus requiring treatment
- Active or chronic psychiatric illness
- Diagnosed dementia
- Cardiac resynchronization therapy (CRT) within the last six months
- Recent transition between warfarin and NOAC therapy within the past three months
- Major surgery or trauma within the last three months
- History of malignancy.

The CHA_2DS_2-VASc score was calculated based on the presence of the following factors, with corresponding points assigned: congestive heart failure (1), hypertension (HT) (1), age ≥ 75 years (2), diabetes mellitus (DM) (1), prior stroke or transient ischemic attack (2), vascular disease (1), age 65–74 years (1), and female sex (1). The maximum possible CHA_2DS_2-VASc score was nine points. Vascular disease was defined as a history of myocardial infarction (MI), peripheral vascular disease (PVD), or aortic plaque formation. Peripheral arterial disease was defined as at least 50% stenosis in non-coronary arteries. Left ventricular systolic dysfunction was classified as an ejection fraction ≤ 40% in patients with congestive heart failure. HT was defined as a systolic and/or diastolic blood pressure ≥ 140/90 mmHg, a previous diagnosis of HT, or the use of antihypertensive medication.[14] DM was defined as a fasting blood glucose level ≥ 126 mg/dL, a two-hour postprandial glucose level ≥ 200 mg/dL, or the use of glucose-lowering medication.[15]

Laboratory parameters, including C-reactive protein (CRP), hemoglobin (HGB), fasting blood glucose, creatinine, and thyroid-stimulating hormone (TSH), were recorded at the time of study enrollment.

Data Collection Tools

Psychiatric assessment of the participants was conducted using the Beck Depression Inventory and the Beck Anxiety Inventory.

Beck Depression Inventory (BDI)

The BDI was used to evaluate the severity of depressive symptoms in the patients. Developed by Beck in 1961,[16] the Turkish adaptation and validation study of this scale was conducted by Hisli et al.[17] The BDI comprises 21 items, each rated on a four-point Likert scale. The maximum attainable score is 63. Results are classified as follows: 0–9, no/minimal depression; 10–18, mild depression; 19–29, moderate depression; and 30–63, severe depression.[18]

Beck Anxiety Inventory (BAI)

The BAI, designed by Beck et al.,[19] assesses anxiety symptoms in individuals. This self-report scale consists of 21 items, each scored from 0 to 3. A total score between 0 and 7 reflects minimal anxiety, scores between 8 and 15 correspond to mild anxiety, scores from 16 to 25 represent moderate anxiety, and scores from 26 to 63 indicate severe anxiety. The Turkish adaptation and validation of the scale were carried out by Ulusoy et al. in 1996.[20]

Ethical approval for the study was obtained from İnonü University Non-Invasive Clinical Research Ethics Committee (Approval Number: 2021/2369, Date: 07.09.2021). The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. Throughout the preparation of this study, no artificial intelligence (AI)-driven tools, including large language models (LLMs), chatbots, or image generation technologies, were employed.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 26.0 (SPSS Inc., Chicago, IL, USA). Based on their history of oral anticoagulant use, patients were divided into three groups: (1) those not receiving anticoagulant therapy (including individuals who declined treatment upon recommendation), (2) those receiving NOACs, and (3) those receiving warfarin.

One-way analysis of variance (ANOVA) was used to compare continuous variables across groups, while the chi-square (χ^2) test was used for categorical variables. Continuous variables are presented as mean ± standard deviation (SD) and/or median (minimum–maximum), whereas categorical variables are summarized as frequencies and percentages.

Pearson correlation analysis was conducted to examine the relationship between depression and anxiety scores and clinical variables. Additionally, multiple logistic regression analysis was performed to identify independent predictors of depression and anxiety.

Results

Characteristics of the Patients

A total of 255 patients participated in the study, consisting of 133 women and 122 men. Among them, 69 patients were not on anticoagulant treatment, 124 were on NOACs, and 62 were on warfarin. Statistically significant age differences were observed across the groups ($P < 0.001$), with Group 1 (no anticoagulant) having a younger mean age (53 ± 18 years) compared to Group 2 (NOACs, 69 ± 11 years) and Group 3 (warfarin, 70 ± 10 years). Age distribution also showed significant variation (< 65, 65–75, > 75) ($P < 0.001$). Group 1 had a greater proportion of patients under 65 years, while Groups 2 and 3 included a larger proportion of patients aged 65–75 and over 75 years.

The incidence of heart failure did not differ significantly across the groups ($P = 0.335$). However, significant differences were observed in the incidence of hypertension, diabetes mellitus, and stroke, with Group 1 having fewer cases than Groups 2 and 3. Vascular disease also showed significant variation, with the lowest prevalence in Group 1 and the highest in Group 3 ($P < 0.001$).

While hemoglobin levels did not differ significantly across the groups, glucose levels exhibited significant variation ($P = 0.024$), with Group 2 demonstrating the highest mean glucose level. Similarly, creatinine levels differed significantly ($P = 0.003$). No statistically significant differences were observed in TSH levels across the groups ($P = 0.302$). Conversely, CHA_2DS_2-VASc scores varied considerably, with the highest levels recorded in Group 3 (Group 1 vs. Group 2, $P < 0.001$; Group 2 vs. Group 3, $P = 0.017$). Sociodemographic and clinical features of the patients are presented in Table 1.

Anxiety and Depression Levels of the Patients

The analysis of anxiety and depression levels among the three patient groups revealed significant differences ($P < 0.001$). Patients' BAI scores differed significantly across groups, with Group 3 having the highest mean score (27.8 ± 12.1; $P < 0.001$). No difference was found between Group 1 and Group 2 ($P = 0.889$). Additionally, the distribution of anxiety severity varied notably among the groups. A larger proportion of Group 3 patients (87.1%) experienced moderate to severe anxiety, compared to 55.6% in Group 2 and 60.9% in Group 1.

Similarly, BDI scores were highest in Group 3 (30.1 ± 9.2), followed by Group 1 (21.8 ± 10.3) and Group 2 (25.8 ± 11.4), demonstrating statistically significant differences. However,

Table 1. Demographic and clinical characteristics of the patients

Variables	Not using anticoagulant (Group 1)	Using NOACs (Group 2)	Using warfarin (Group 3)	P
Age (years), mean ± SD	53 ± 18[a]	69 ± 11[b]	70 ± 10[b]	**<0.001**
	n (%)	**n (%)**	**n (%)**	
Gender				0.394
Female	35 (50.7)	61 (49.2)	37 (59.7)	
Male	34 (49.3)	63 (50.8)	25 (40.3)	
Education				0.161
Primary	33 (47.8)	68 (54.8)	33 (53.2)	
High school	29 (42.0)	32 (25.8)	20 (32.3)	
University	7 (10.1)	24 (19.4)	9 (14.5)	
Marital status				0.604
Married	60 (87.0)	105 (84.7)	50 (80.6)	
Single/widowed	9 (13.0)	19 (15.3)	12 (19.4)	
Age group				**<0.001**
< 65 years	55 (79.7)[a]	40 (32.3)[b]	15 (24.2)[b]	
65–75 years	14 (20.3)[a]	49 (39.5)[b]	28 (45.2)[b]	
> 75 years	0 (0)[a]	35 (28.2)[b]	19 (30.8)[b]	
Heart failure				0.335
No	65 (94.2)	110 (88.7)	54 (87.1)	
Yes	4 (5.8)	14 (11.3)	8 (12.9)	
Hypertension				**<0.001**
No	49 (71.0)[a]	37 (29.8)[b]	11 (17.7)[b]	
Yes	20 (29.0)[a]	87 (70.2)[b]	51 (82.3)[b]	
Diabetes mellitus				**0.017**
No	60 (87.0)[a]	86 (69.4)[b]	43 (69.4)[b]	
Yes	9 (13.0)[a]	38 (30.6)[b]	19 (23.6)[b]	
Stroke				**0.008**
No	69 (100.0)[a]	108 (87.1)[b]	57 (91.9)[b]	
Yes	0 (0)[a]	16 (12.9)[b]	5 (8.1)[b]	
Vascular disease				**<0.001**
No	55 (79.7)[a]	65 (52.8)[b]	18 (29)[c]	
Yes	14 (20.3)[a]	59 (47.2)[b]	44 (71.0)[c]	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Ejection fraction (%)	60 ± 2.5a	55 ± 10[b]	55 ± 10b	**0.009**
Hemoglobin (g/dL)	14.1 ± 2.4	13.6 ± 2.3	13.3 ± 2.2	0.521
Glucose (mg/dL)	94 ± 46[a]	103.5 ± 34.5[b]	98 ± 41[a]	**0.024**
Creatinine (mg/dL)	0.79 ± 0.17[a]	0.88 ± 0.4[b]	0.93 ± 0.3[b]	**0.003**
Thyroid-stimulating hormone (mIU/L)	0.965 ± 1.5	1.12 ± 1.3	1.23 ± 0.4	0.302
CHA_2DS_2-VASc	1.3 ± **0.8**[a]	3.3 ± 1.0b	3.7 ± **1.2**[c]	**<0.001**
CRP (mg/dL)	0.3 ± 0.39	0.3 ± 0.4	0.3 ± 0.4	0.164

*Groups with different superscript letters (e.g., a, b, c) indicate statistically significant differences (P < 0.05). NOACs, Novel oral anticoagulants; SD, Standard deviation; CRP, C-reactive protein.

no substantial difference was observed between Group 1 and Group 2 (P = 0.102). Regarding depression severity, Group 3 once again showed a higher proportion of patients with moderate to very severe depression (85.5%) compared to Group 1 (59.4%) and Group 2 (65.3%). Conversely, the proportion of patients with none/very mild to mild depression was lowest in Group 3 (14.5%), compared with 40.6% in Group 1 and 34.7% in Group 2.

Table 2. Anxiety and depression levels of the patients

Variables	Not using anticoagulant (Group 1)	Using NOACs (Group 2)	Using warfarin (Group 3)	P
Beck anxiety score (mean ± SD)	19.4 ± 9.6[a]	20.1± 9.5[a]	27.8 ± 12.1[b]	<0.001
Anxiety severity, n (%)				<0.001
Minimal to mild	27[a] (39.1)	55[a] (44.4)	8[b] (12.9)	
Moderate to severe	42[a] (60.9)	69[a] (55.6)	54[b] (87.1)	
Beck depression score (mean ± SD)	21.8 ± 10.3[a]	25.8 ± 11.4[a]	30.1 ± 9.2[b]	<0.001
Depression severity, n (%)				<0.001
None/minimal to mild	28[a] (40.6)	43[a] (34.7)	9[b] (14.5)	
Moderate to very severe	41 (59.4)[a]	81 (65.3)[a]	53 (85.5)[b]	

*Variables are summarized as mean ± SD. Groups with different superscript letters (e.g., a, b) indicate statistically significant differences (P < 0.05).

These findings indicate that individuals on warfarin (Group 3) are more prone to elevated levels of anxiety and depression than those on NOACs (Group 2) or those not receiving anticoagulant treatment (Group 1). Table 2 presents a comprehensive comparison of anxiety and depression levels.

Correlation Between Depression and Anxiety Scores and Patient Characteristics

Correlation analysis was conducted to examine the relationship between participants' clinical variables and anxiety and depression levels (Table 3).

A positive correlation was found between anxiety and age scores (P = 0.034), depression scores (P < 0.001), creatinine levels (P = 0.021) and CHA_2DS_2-VASc score (P = 0.008), while a negative correlation was observed with ejection fraction (EF) (P < 0.001).

On the other hand, a positive correlation was found between depression scores and age (P = 0.034), anxiety scores (P < 0.001), CRP levels (P = 0.044), and CHA_2DS_2-VASc scores (P = 0.001).

Predictors of Anxiety and Depression

The multiple logistic regression results indicated that moderate and severe anxiety were predicted by warfarin use (odds ratio [OR]: 4.902; 95% confidence interval [CI] [1.928–12.461]; P = 0.001), EF (OR: 0.892; 95% CI [0.846–0.941]; P < 0.001), depression score (OR: 1.105; 95% CI [1.069–1.144]; P < 0.001), and CHA_2DS_2-VASc score (OR: 0.691; 95% CI [0.538–0.883]; P = 0.004). Depression was predicted solely by anxiety scores (OR: 1.126; 95% CI [1.081–1.173]; P < 0.001), with no other variables identified as significant predictors. The predictors determined for the variable of anxiety are presented in Table 4.

Discussion

This study investigates the prevalence of depression and anxiety in patients with NVAF and examines the relationship between these psychological conditions and the treatment regimens administered. AF predominantly affects the elderly population. In Australia, North America, and Western Europe, 70% of AF patients are over the age of 65,[21,22] and OAC therapy remains the most effective therapeutic approach for managing the condition.[14] In the present study, the mean age of AF patients was 64.08 ± 13.52 years, with 72.9% receiving oral anticoagulant therapy. It was observed that patients with higher mean age and CHA_2DS_2-VASc scores were more likely to use warfarin compared with other groups. Despite having similar efficacy and fewer side effects, warfarin was preferred over NOACs in elderly patients. This could be attributed to the relatively recent introduction of NOACs in our country[23] and/or patients' reluctance to switch from their established treatment.

The literature suggests that anxiety and depression are frequently observed in AF patients, contributing to disease progression, exacerbating symptoms, increasing the frequency of attacks, and worsening prognosis.[24–28] For instance, in a study by Thrall et al.,[29] more than one-third of AF patients were found to experience depression and anxiety. Similarly, Polikandrioti et al.[30] reported that 47.5% of AF patients exhibited anxiety symptoms, while 29.5% had depressive symptoms. Our study also revealed a high prevalence of depression and anxiety among patients. When considering moderate or higher severity cases, 68.6% met the diagnostic criteria for depression, while 64.7% met the criteria for anxiety disorder. Although these rates appear higher than those reported in previous studies, this discrepancy could be attributed to variations in the assessment scales used, cut-off values for symptom severity, sample characteristics (e.g., factors influencing psychiatric disease development such as age, gender, education level, and economic status), and cultural differences in reporting psychiatric symptoms. While our study was not designed to establish causality, it is noteworthy given the well-documented association between psychiatric comorbidities, poor prognosis, and increased mortality risk.

Previous studies have highlighted the significance of demographic variables such as age, gender, family history, and marital status in the onset and progression of psychiatric disorders.[31–33] Particularly, 10–15% of the elderly population experience clinically significant depressive symptoms that negatively impact their quality of life, with even higher rates reported among individuals with chronic illnesses.[34] Among the factors investigated in our study, age was found to be the most important demographic factor linked to increased psychiatric symptom severity; both depression and anxiety scores rose with older age. The association observed in our study aligns with earlier studies indicating that older adults could be more psychologically vulnerable.[34,35] Psychosocial stressors that frequently accompany aging could also contribute to this vulnerability, in addition to physical decline. The greater emotional burden observed in older adults may be influenced by factors such as grief, declining social support systems, transition to institutional living conditions, and perceived loss of autonomy. Furthermore, in this age group, depressive symptoms

Table 3. Correlation between anxiety and depression scores and patient characteristics

	Age	Anxiety	Depression	EF	HGB	Glucose	Creatinine	CRP	TSH	CHA_2DS_2-VASc
Age										
r	1.000	0.133*	0.133*	-0.247**	-0.224**	0.095	0.308**	-0.0061	-0.058	0.644**
P	–	**0.034**	**0.034**	**<0.001**	**<0.001**	0.132	**<0.001**	0.400	0.450	**<0.001**
Anxiety										
r	0.133*	1.000	0.430**	-0.325**	0.066	-0.008	0.145*	0.077	-0.029	0.165**
P	**0.034**	–	**<0.001**	**<0.001**	0.296	0.895	**0.021**	0.287	0.706	**0.008**
Depression										
r	0.133*	0.430**	1.000	-0.032	-0.002	-0.031	0.090	0.145*	0.050	0.204**
P	**0.034**	**<0.001**	–	0.616	0.970	0.625	0.152	**0.044**	0.510	**0.001**
EF										
r	-0.247**	-0.325**	-0.032	1.000	-0.146*	-0.128*	-0.324**	-0.169*	-0.115	-0.295**
P	**<0.001**	**<0.001**	0.616	-	**0.022**	**0.043**	**<0.001**	**0.021**	0.137	**<0.001**
HGB										
r	-0.224**	0.066	-0.002	-0.146*	1.000	0.053	0.144*	0.257**	-0.036	-0.193**
P	**<0.001**	0.296	0.970	0.022	–	0.397	0.021	**<0.001**	0.635	0.002
Glucose										
r	0.095	-0.008	-0.031	-0.128*	0.053	1.000	0.184**	0.090	0.030	0.273**
P	0.132	0.895	0.625	0.043	0.397	–	0.003	0.213	0.697	**<0.001**
Creatinine										
r	0.308**	0.145*	0.090	-0.324**	0.144*	0.184**	1.000	0.254**	0.059	0.236**
P	**<0.001**	0.021	0.152	**<0.001**	0.021	0.003	–	**<0.001**	0.437	**<0.001**
CRP										
r	-0.061	0.077	0.145*	-0.169*	0.257**	0.090	0.254**	1.000	-0.103	0.082
P	0.400	0.287	**0.044**	0.021	**<0.001**	0.213	**<0.001**	–	0.236	0.254
TSH										
r	-0.058	-0.029	0.050	-0.115	-0.036	0.030	0.059	-0.103	1.000	0.120
P	0.450	0.706	0.510	0.137	0.635	0.697	0.437	0.236	–	0.115
CHA_2DS_2-VASc										
r	0.644**	0.165**	0.204**	-0.295**	-0.193**	0.273**	0.236**	0.082	0.120	1.000
P	**<0.001**	**0.008**	**0.001**	**<0.001**	0.002	**<0.001**	**<0.001**	0.254	0.115	–

*P < 0.05, **P < 0.01. EF, Ejection fraction; HGB, Hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone.

may sometimes manifest atypically through somatic complaints such as fatigue, pain, or cognitive decline, which could lead to underdiagnosis or misdiagnosis of underlying depression. As a result, mental health assessments in the elderly, especially those with comorbid chronic diseases, may have to be conducted using more sensitive and age-specific screening tools. Developing screening and intervention strategies that address both the biological and psychosocial aspects of mental health in the aging population may help reduce the negative impact of psychiatric symptoms on their quality of life in future research.

Table 4. Results of logistic regression analysis of anxiety

Variables	OR	95% CI	P
Depression score	1.105	1.069-1.144	<0.001
Warfarin use	4.902	1.928-12.461	0.001
EF	0.892	0.846-0.941	<0.001
CHA_2DS_2-VASc score	0.691	0.538-0.883	0.004

OR, Odd ratios; CI, Confidence interval; EF, Ejection fraction.

Consistent with prior research demonstrating that disease severity exacerbates anxiety and depressive symptoms,[36] our study found that higher CHA_2DS_2-VASc scores were associated with increased depression and anxiety scores. Moreover, the CHA_2DS_2-VASc score emerged as one of the most significant independent predictors of anxiety severity. Given that this classification includes variables such as congestive heart failure (CHF), hypertension, DM, and advanced age—all of which are individually linked to psychological distress—the observed association between elevated CHA_2DS_2-VASc scores and higher psychiatric symptomatology is not unexpected. Notably, DM has been shown to double the risk of depression,[37] likely due to mechanisms involving chronic inflammation, oxidative stress, and vascular changes affecting the brain. Similarly, hypertension

has been strongly associated with increased psychological burden; studies report that up to 56% of hypertensive individuals experience anxiety, and approximately 20% exhibit clinically significant stress symptoms.[38] Therefore, the co-occurrence of these risk factors not only exacerbates disease severity but may also contribute to a diminished ability to cope with stress.[39] Furthermore, our study revealed a positive correlation between CRP levels and depression scores, supporting the hypothesis that proinflammatory cytokines—upregulated in response to stress—contribute to depressive symptoms via neuroendocrine and neurotransmitter dysregulation.[40]

Recent literature indicates that the management of AF extends beyond pathophysiological factors, highlighting the significant impact of therapeutic strategies on patients' psychological well-being and overall quality of life. For instance, Sang et al.[41] reported that implementing catheter ablation and avoiding warfarin therapy contributed substantially to improvements in depression, anxiety, and quality-of-life measures. Similarly, a study by Altiok et al.[42] found that individuals with atrial fibrillation experienced considerable limitations in daily activities and social lives due to disease-related symptoms and the burden of warfarin treatment. Moreover, more than half of the patients reported persistent anxiety stemming from fears of palpitations, gastrointestinal bleeding, or cerebral hemorrhage as potential medication side effects. Additionally, it has been demonstrated that patients capable of managing their oral anticoagulant therapy independently report higher levels of treatment satisfaction and perceive fewer daily challenges, social burdens, and treatment-related stressors.[43] Okumura et al.[8] reported that patients using NOACs experienced greater treatment satisfaction compared to those on warfarin, while Türker et al.[9] observed a significant reduction in depression scores among patients who transitioned from warfarin to dabigatran.

The findings of the present study are consistent with previous research, indicating that patients receiving warfarin therapy exhibited significantly higher depression and anxiety scores compared to the other two groups. Furthermore, warfarin use emerged as the strongest predictor of anxiety development. Although this study was not specifically designed to examine causal relationships, it is plausible that challenges inherent to warfarin therapy, such as frequent monitoring, dietary restrictions, and bleeding risk, may have contributed to these psychological outcomes. The need for frequent blood testing, strict dietary restrictions, and persistent concerns about complications such as bleeding or embolism may contribute to heightened anxiety levels among patients receiving warfarin therapy. Additionally, the necessity for regular medical check-ups and repeated visits to healthcare facilities may impose financial burdens and contribute to a loss of productivity over time, further exacerbating depressive symptoms. Moreover, the higher CHA_2DS_2-VASc scores observed in the warfarin group indicate that these patients represent a clinically higher-risk population. This suggests that the severity of psychological symptoms in this group may be influenced not only by the demands of the treatment regimen itself but also by the broader burden of the underlying disease. In contrast, NOACs may have a more favorable impact on psychological well-being, owing to their practical advantages, such as ease of administration, lack of need for frequent INR monitoring, comparable efficacy to warfarin, and lower risk of bleeding.[44] Given that comorbid anxiety and depression can negatively affect clinical outcomes, the present findings are clinically meaningful in suggesting that NOAC use may offer psychological as well as physiological benefits for patients.

Limitations

The findings from this study provide important insights into the potential effects of anticoagulant agents used for AF treatment on patients' psychological status; however, they should be interpreted cautiously in light of several limitations. First, the study utilized a single-center sample, which limits the generalizability of the findings to broader patient populations with diverse geographic, socioeconomic, and cultural characteristics. Second, the cross-sectional design precludes the ability to draw causal inferences. In particular, because patients' psychological status prior to initiating oral anticoagulant therapy was not assessed, it is unclear whether the observed levels of depression and anxiety are attributable to the treatment itself or to pre-existing psychiatric conditions. Third, key confounding variables such as socioeconomic status, psychiatric history, health literacy, and social support were not controlled for. Given their known influence on mental health, the absence of these factors may introduce uncertainty in interpreting the results. Fourth, the study did not evaluate NOACs by individual subgroups (e.g., dabigatran, rivaroxaban, apixaban), thereby overlooking potential pharmacokinetic and side-effect differences that could differentially impact psychological outcomes. Finally, it is important to consider that some patients in the NOAC group may have previously been treated with warfarin. A transition to NOAC therapy following negative experiences with warfarin could have positively biased patients' perceptions of the new treatment and their psychological responses, potentially leading to an overestimation of the benefits associated with NOACs.

Despite these constraints, the study employed validated scales to assess depression and anxiety, and the sample size was adequate for the analyses conducted. To the best of our knowledge, this is among the first studies to compare the psychological status of patients with non-valvular atrial fibrillation who are receiving anticoagulant therapy versus those who are not. As such, it provides preliminary data that may inform and guide future research in this important area.

Conclusion

This study demonstrated a high prevalence of anxiety and depression among patients with NVAF, with psychiatric symptoms particularly pronounced in those receiving warfarin therapy. The findings suggest that the type of anticoagulant therapy may significantly affect psychological status and that NOACs are better tolerated psychologically. Additionally, factors such as age, disease severity, and inflammatory response are also thought to mediate this relationship. Therefore, in the management of NVAF, attention to patients' mental health through routine psychological assessment, patient education, and psychiatric support when needed may provide significant benefits for prognosis and quality of life. A holistic, multidisciplinary approach that integrates both cardiovascular and psychological care is recommended.

Ethics Committee Approval: Ethics committee approval was obtained from İnonü University Non-Invasive Clinical Research Ethics Committee (Approval Number: 2021/2369, Date: 07.09.2021).

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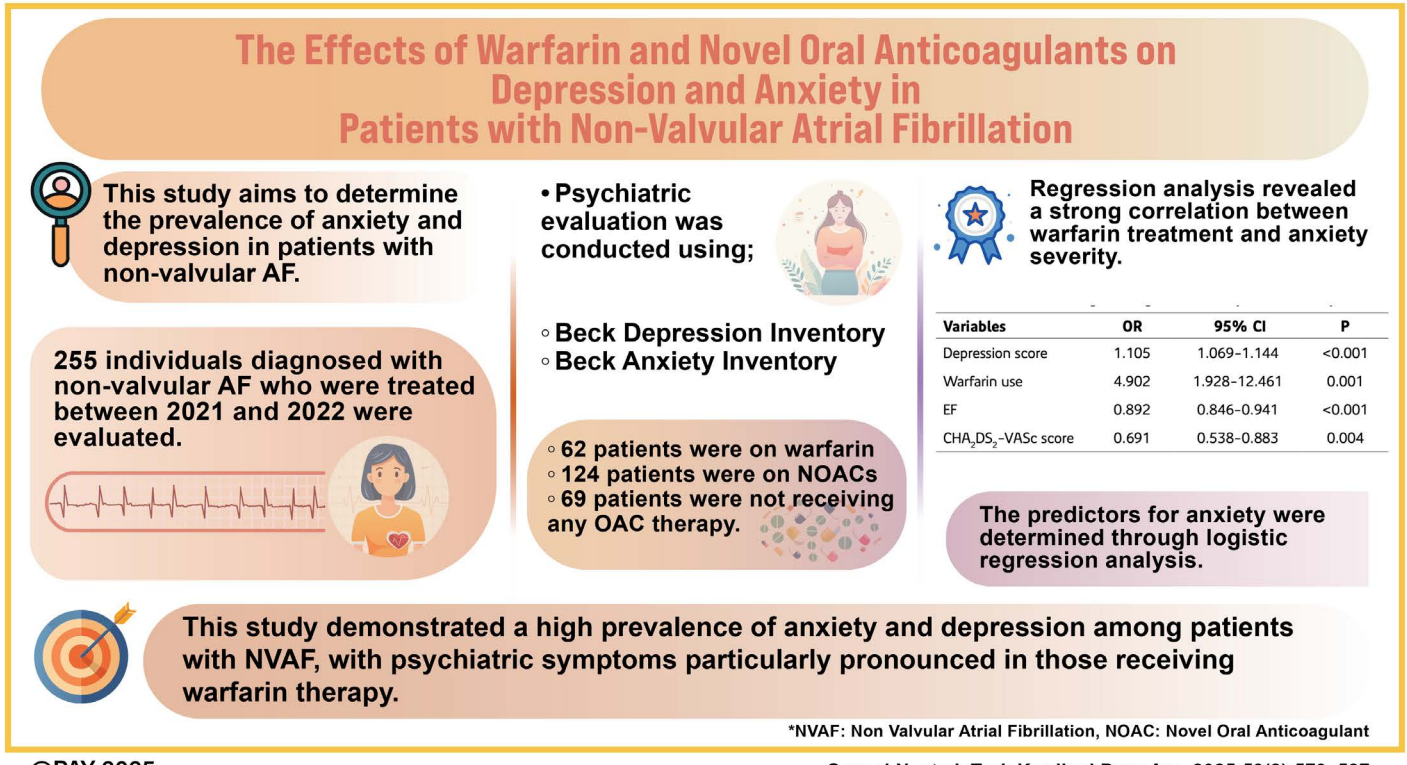

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The Relationship Between the CHA_2DS_2-VASc Score and Lesion Complexity and Long-Term Outcomes in Peripheral Arterial Disease

Periferik Arter Hastalığında CHA_2DS_2-VASc Skorunun Lezyon Karmaşıklığı ve Uzun Vadeli Sonuçlarla İlişkisi

ABSTRACT

Objective: Originally designed to evaluate stroke risk in individuals with atrial fibrillation unrelated to valvular disease, the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65–74 years, and Sex category – female) is now additionally utilized for the prognostic evaluation of cardiovascular diseases. This study aimed to evaluate the predictive role of the CHA_2DS_2-VASc score for lesion severity and long-term survival outcomes in individuals with peripheral artery disease (PAD).

Method: This retrospective analysis included 784 patients diagnosed with PAD via computed tomography (CT) angiography, consecutively enrolled from two medical centers. The CHA_2DS_2-VASc score was determined for all participants. Lesion severity was assessed according to the TASC II (Trans-Atlantic Inter-Society Consensus II) criteria, and patients were categorized into TASC-AB (simple) and TASC-CD (complex) lesion groups. Mortality data were obtained from hospital and social security records.

Results: The study included 784 patients (average age: 61.7 ± 9.9 years; 17.2% female). In the regression analysis performed to predict lesion severity, we found that the CHA_2DS_2-VASc score ($P < 0.007$) and left ventricular ejection fraction ($P = 0.009$) were independent predictors. The receiver operating characteristic (ROC) curve indicated that a CHA_2DS_2-VASc score threshold of 3.5 predicted long-term mortality with 70% sensitivity and 79% specificity ($P < 0.001$). Kaplan-Meier survival estimates indicated that patients with higher CHA_2DS_2-VASc scores had significantly lower survival rates over the 60-month follow-up period ($P < 0.001$).

Conclusion: The CHA_2DS_2-VASc score was independently associated with both lesion severity and adverse long-term outcomes in individuals with PAD.

Keywords: CHA_2DS_2-VASc score, lesion complexity, mortality, peripheral artery disease

ÖZET

Amaç: Başlangıçta kapak hastalığı ile ilişkili olmayan atriyal fibrilasyonu olan bireylerde inme riskini değerlendirmek için geliştirilen CHA_2DS_2-VASc skoru (Konjestif kalp yetmezliği, Hipertansiyon, Yaş ≥ 75, Diyabetes mellitus, daha önce inme/geçici iskemik atak/sistemik emboli, vasküler hastalık, yaş 65-74 ve cinsiyet kategorisi - kadın), günümüzde kardiyovasküler hastalıkların prognostik değerlendirmesi için de kullanılmaktadır. Bu çalışmanın amacı, periferik arter hastalığı (PAH) olan bireylerde lezyon şiddeti ve uzun dönem sağkalım sonuçları açısından CHA_2DS_2-VASc skorunun öngörücü rolünü değerlendirmektir.

Yöntem: Bu retrospektif analiz, bilgisayarlı tomografi (BT) anjiyografi ile PAH tanısı konulan ve iki tıp merkezinden ardışık olarak dahil edilen 784 hastayı içermektedir. Tüm katılımcılar için CHA_2DS_2-VASc skoru belirlendi, lezyon şiddeti TASC II kriterlerine göre değerlendirildi ve hastalar TASC-AB (basit) ve TASC-CD (kompleks) lezyon gruplarına ayrıldı. Mortalite verileri hastane ve sosyal güvenlik kayıtlarından elde edilmiştir.

Bulgular: Çalışmaya 784 hasta (ortalama yaş 61,7±9,9 yıl; %17,2 kadın) dahil edildi. Lezyon şiddetini öngörmek için yapılan regresyon analizinde, CHA_2DS_2-VASc skoru ($P < 0,007$) ve sol ventrikül ejeksiyon fraksiyonunun ($P = 0,009$) bağımsız öngörücüler olduğunu bulduk. ROC analizi, 3,5 CHA_2DS_2-VASc skoru eşiğinin uzun dönem mortaliteyi %70 duyarlılık ve %79 özgüllükle öngördüğünü göstermiştir ($P < 0,001$). Kaplan-Meier sağkalım tahminleri, daha yüksek CHA_2DS_2-VASc skorlarına sahip hastaların 60 aylık takip süresi boyunca anlamlı olarak daha düşük sağkalım oranlarına sahip olduğunu göstermiştir ($P < 0,001$).

Sonuç: CHA_2DS_2-VASc skoru, PAH'lı bireylerde hem lezyon şiddetiyle hem de olumsuz uzun dönem sonuçlarla bağımsız olarak ilişkili bulunmuştur.

Anahtar Kelimeler: CHA_2DS_2-VASc skoru, lezyon şiddeti, mortalite, periferik arter hastalığı

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Peripheral artery disease (PAD) predominantly results from atherosclerosis and manifests as a consequence of the systemic atherosclerotic process. Atherosclerosis-related risk factors, including hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), and smoking, are frequently observed in individuals with PAD.[1] PAD has been linked to elevated risks of both cardiovascular events and overall mortality. With the aging of the global population, PAD continues to be a growing clinical problem and a significant cause of adverse outcomes and deaths, despite advances in modern treatment strategies.[2]

The CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65–74 years, and Sex category – female) is a practical and easily applicable scoring system initially designed to assess the cardioembolic risk in individuals with atrial fibrillation (AF) not caused by valvular disease and to guide anticoagulation therapy decisions.[3]. The components of this scoring system—congestive heart failure (CHF), HT, stroke, advanced age, vascular disease, DM, and female sex—largely coincide with the key risk factors for PAD.[4] Initially designed as a risk assessment tool for AF, the CHA_2DS_2-VASc score has progressively been recognized for its prognostic value across various cardiovascular diseases.[5,6] It has been reported that this score can independently predict adverse outcomes, including both acute stent thrombosis and mortality, particularly in situations like stable and acute coronary artery disease (CAD).[7-13]

This study aimed to assess the predictive role of the CHA_2DS_2-VASc score, an established tool in cardiovascular risk assessment, for lesion complexity and prognosis in patients with PAD. Thus, we sought to evaluate the potential application of this scoring system in the context of PAD.

Materials and Methods

Study Methodology and Population

This observational, retrospective study, administered across two centers, included patients aged 18 to 95 years. A total of 784 consecutively selected patients with PAD who had been followed at the cardiology outpatient clinics between 2015 and 2020 were enrolled. The patients were followed for an average duration of 60 months.

Inclusion Criteria

All patients presented with symptoms of PAD, including intermittent claudication, ischemic rest pain, or non-healing ulcers. Patients who were found to have ≥ 50% luminal narrowing in the femoropopliteal or aortoiliac segments on computed tomography (CT) angiography were included in the study. These individuals subsequently underwent conventional peripheral angiographic evaluation for further assessment. Angiographic images were reviewed for lesion severity and classified into TASC-AB (simple lesions) and TASC-CD (complex lesions) groups based on the lesion classification criteria established in the TransAtlantic Inter-Society Consensus-II (TASC II), in accordance with the diagnostic and therapeutic recommendations of the European Society of Cardiology (ESC) (Figure 1).[14] Treatment strategies were determined by a specialized interventional cardiology team according to lesion complexity, patient comorbidities, and guideline-directed management protocols. The CHA_2DS_2-VASc score was calculated based on the presence of CHF, HT, age ≥65 years (with additional weighting for ≥ 75 years), DM, prior transient ischemic attack (TIA) or stroke, vascular disease (coronary or peripheral), and female gender, in accordance with established

ABBREVIATIONS

AF	Atrial fibrillation
AIP	Atherogenic index of plasma
AUC	Area under the curve
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CLTI	Critical limb-threatening ischemia
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DM	Diabetes mellitus
EF	Ejection fraction
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
GLASS	Global Limb Anatomic Staging System
HL	Hyperlipidemia
HT	Hypertension
IQR	Interquartile ranges
LVEF	Left ventricular ejection fraction
MALE	Major adverse limb events
PAD	Peripheral artery disease
ROC	Receiver operating characteristic
STEMI	ST-Elevation Myocardial Infarction
TASC II	Trans-Atlantic Inter-Society Consensus II
TIA	Transient ischemic attack
WIfI	Wound, Ischemia, and Foot Infection

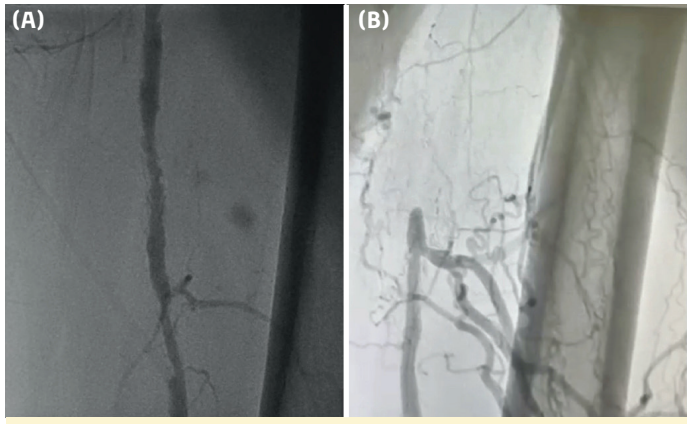

Figure 1. Angiographic images of simple and complex femoropopliteal lesions from patients included in the study. (A) Simple lesion: Angiographic image from a study patient demonstrating a short-segment, non-occlusive stenosis with preserved distal runoff in the superficial femoral artery. (B) Complex lesion: Angiographic image from another study patient showing a long-segment total occlusion of the femoropopliteal artery with extensive collateral circulation, consistent with a TASC-CD lesion. TASC-CD, TransAtlantic Inter-Society Consensus C–D

definitions.[13] Consistent with prior research, patients were categorized into two groups based on their CHA_2DS_2-VASc scores: low (< 3 points) and high (≥ 3 points). Although different threshold values (e.g., ≤ 2 and > 2) have been used in other studies,[11] we chose ≥ 3 points as the cut-off since this value has been associated with adverse cardiovascular outcomes in previous PAD-focused research. All patients had at least 1 point, as they were all affected by vascular atherosclerosis. The CHA_2DS_2-VASc score was calculated at the time of PAD diagnosis using the patients' demographic and comorbidity data as recorded in the hospital's electronic health records.

Exclusion Criteria

Individuals younger than 18 years, or those diagnosed with conditions such as familial hyperlipidemia, vasculitis, systemic inflammatory or autoimmune diseases, hematologic malignancies, end-stage heart failure (NYHA class IV), advanced chronic kidney disease (CKD) (glomerular filtration rate [GFR] < 30 mL/min/1.73 m²), severe liver diseases (e.g., cirrhosis, chronic hepatitis, hepatocellular carcinoma), Buerger's disease, those with a history of organ transplantation, patients with malignancies, and those who had recently received chemotherapy were not included in the analysis (Figure 2).

Data Collection

All demographic information regarding patient characteristics (age, gender), comorbid conditions such as DM, HT, AF, smoking, cerebrovascular diseases, CAD, HL, chronic obstructive pulmonary disease (COPD), CKD, physical condition, symptoms, clinical stages (Rutherford and Fontaine), and routine laboratory test results were extracted from hospital clinical documentation.

Blood tests were collected from the antecubital vein before the peripheral angiography, after a 12-hour fasting period in the morning, as well as following the procedure. Biochemical parameters were measured using a fully automated system (Roche Modular, Tokyo, Japan). All patients underwent transthoracic echocardiographic evaluation (Vivid S5; GE, Norway), with left ventricular ejection fraction (LVEF) calculated via the biplane Simpson's method.

Mortality Data

Death data were obtained from hospital and social security records. Patients were categorized based on survival upon completion of follow-up.

Endovascular Treatment Procedure

All procedures were conducted by a skilled team specializing in interventional cardiology, following standard protocols, including systemic heparinization. Depending on lesion characteristics, endovascular treatment involved the use of standard balloon dilation, balloons coated with antiproliferative agents, and stents with or without pharmacologic coatings. A procedure was considered successful if residual stenosis was reduced to below 20% in the absence of complications.

Clinical Outcomes

The clinical outcomes of the study included:

1. Lesion complexity, categorized as TASC-AB (simple) or TASC-CD (complex) based on the TASC II classification system;

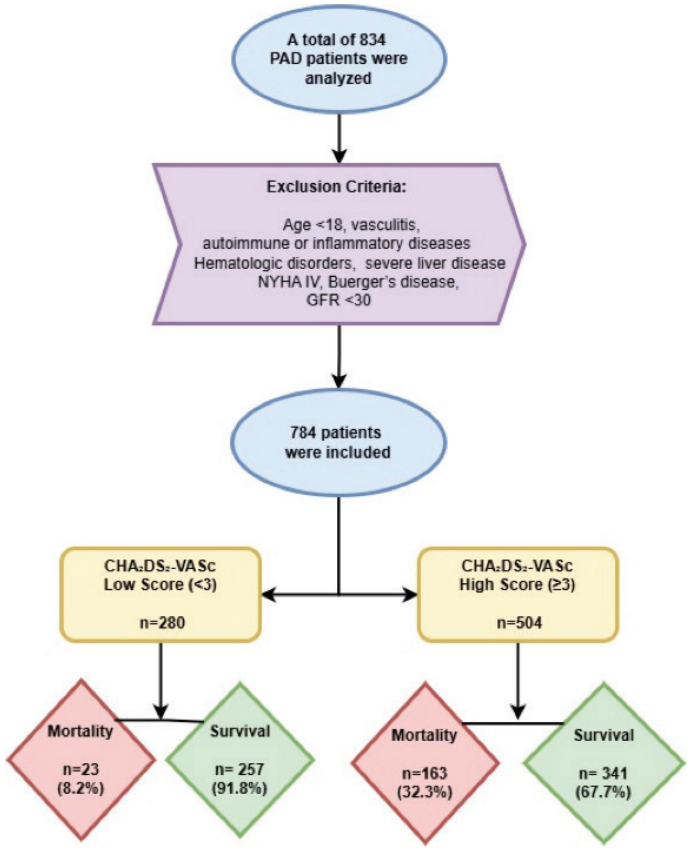

Figure 2. Study design flowchart.

2. Major amputations, defined as any limb amputation above the ankle level;
3. Minor amputations, defined as amputations at or below the ankle (e.g., toe or forefoot);
4. All-cause long-term mortality, obtained from hospital records and national social security system data.

Ethical Considerations

The study protocol was approved by Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (Approval Number: 2024-296, Date: 16.10.2024), and the research was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

SPSS version 26.0 (IBM, Chicago, USA) was employed for data analysis. Demographic and clinical variables were outlined using descriptive statistical methods. Data distribution patterns were evaluated using histograms alongside appropriate statistical normality tests. Continuous variables were analyzed using the independent samples t-test or Mann-Whitney U test, depending on the distribution pattern. Categorical data were compared using either Pearson's chi-square or Fisher's exact test, as applicable. Variables exhibiting non-normal distributions were summarized by medians and interquartile ranges (IQR). In contrast, data with normal distribution were expressed as mean ± standard deviation. Categorical data were shown as percentages (%). All statistical tests were evaluated at a significance level of

P < 0.05. Survival outcomes were analyzed using Kaplan–Meier curves, and lesion complexity was further examined through Cox regression analysis. Receiver Operating Characteristic (ROC) curve analysis was performed to assess how well the CHA_2DS_2-VASc score could predict long-term outcomes.

Results

Patient Characteristics, Laboratory Findings, and Outcome Parameters

A total of 784 participants were included in the study, with a mean age of 61.7 ± 9.9 years. Of these patients, 135 (17.2%) were female, and the CHA_2DS_2-VASc score was calculated consistently for each participant. Patients were subsequently categorized into two groups based on their scores: the low score (< 3) group (n = 280, 36%) and the high score (≥ 3) group (n = 504, 64%) (Figure 1). Table 1 presents the demographic and procedural characteristics.

Age, female gender, TASC-CD, smoking, HT, DM, CAD, left ventricular hypertrophy (LVH), procedure duration, type of treatment, and CKD (all, P < 0.001) were substantially higher in the high score group. TASC-CD lesions were markedly more frequent in individuals with higher CHA_2DS_2-VASc scores in both the aortoiliac (P = 0.002) and femoropopliteal (P = 0.007) arterial segments. Consistently, analysis based on the Rutherford and Fontaine clinical classifications—used to evaluate the symptomatic severity of PAD—revealed that patients with higher CHA_2DS_2-VASc scores were more likely to present with advanced clinical stages (P = 0.001). Moreover, patients in the high-score group had importantly elevated levels of creatinine and fasting glucose (P < 0.001), systolic (P = 0.022) and diastolic blood pressure (P = 0.021), C-reactive protein (CRP) (P = 0.036), and leukocyte count (WBC) (P = 0.043). The high-score group demonstrated lower measurements of LVEF and hemoglobin compared to those with lower scores (P < 0.001).

In addition to the primary analysis based on CHA_2DS_2-VASc score groups, further subgroup analyses were conducted to enhance the depth of the study by addressing lesion complexity and clinical outcomes. Patients were categorized according to the severity of PAD (TASC-AB and TASC-CD) and survival status (survivor and non-survivor). The clinical, laboratory, and outcome characteristics of these additional subgroups are presented in Tables 2 and 3, respectively.

Follow-Up and Surveillance

The participants were retrospectively monitored over a mean period of 60 months. The average follow-up duration was similar in both low (< 3) and high (≥ 3) CHA_2DS_2-VASc score groups. Surveillance data were collected from hospital databases and Social Security records, including outpatient follow-up visits and rehospitalizations.

Major adverse limb events (MALE) were also assessed during follow-up. A total of 35 amputations were observed among 784 patients. When stratified, 23 were minor amputations and 12 were major amputations. Overall, the incidence of amputation was significantly higher in the high-score group (P < 0.007). Specifically, the rate of major amputation was significantly elevated in this group (P = 0.006), whereas the difference in minor amputation rates did not reach statistical significance (P = 0.156) (Table 1).

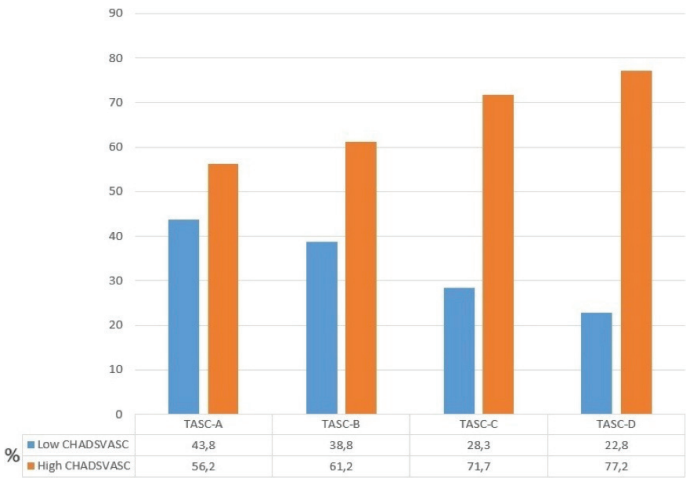

Figure 3. A bar graph showing that as lesion complexity increases, the proportion of high-scoring patients increases significantly.

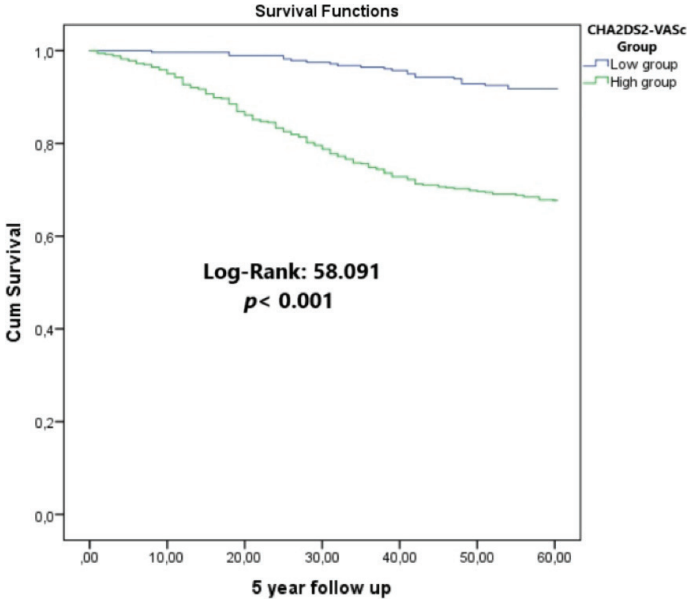

Figure 4. Kaplan–Meier survival curves demonstrating the association between CHA_2DS_2-VASc score and all-cause mortality during five-year follow-up. Patients were stratified into low and high CHA_2DS_2-VASc score groups. The high-score group exhibited significantly reduced cumulative survival (Log-rank = 58.091, P < 0.001). CHA_2DS_2-VASc score, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65–74 years, and Sex category – female.

Among the 784 patients, a total of 186 deaths were recorded during follow-up, with 163 occurring in the high CHA_2DS_2-VASc score group (P < 0.001).

Predictors of Lesion Severity

Univariate logistic regression revealed that the CHA_2DS_2-VASc score, LVEF, and CKD were considerably related to lesion severity (P

Table 1. Comparison of clinical, demographic, and outcome parameters between low and high CHA_2DS_2-VASc score groups

	All patients (n=784)	Low CHA_2DS_2-VASc score (n=280)	High CHA_2DS_2-VASc score (n=504)	P
Age, years	61.7 ± 9.9	56.5 ± 7.8	64.5 ± 9.8	**<0.001**
Gender (female), n (%)	135 (17.2)	13 (4.6)	122 (24.2)	**<0.001**
BMI, kg/m^2	26.9 ± 4.7	26.9 ± 4.7	26.9 ± 4.6	0.986
Heart rate (minute)	87.0 ± 17.9	88.2 ± 18.5	86.4 ± 17.5	0.188
Systolic blood pressure (mmHg)	129 ± 15.0	127.5 ± 14.0	130.1 ± 15.4	**0.022**
Diastolic blood pressure (mmHg)	79.7 ± 9.7	78.7 ± 9.3	80.3 ± 9.9	**0.021**
Smoking, n (%)	505 (64.7)	205 (73.5)	300 (59.9)	**<0.001**
Diabetes mellitus, n (%)	339 (43.2)	46 (16.4)	293 (58.1)	**<0.001**
Hypertension, n (%)	450 (57.4)	78 (27.9)	372 (73.8)	**<0.001**
CAD, n (%)	427 (54.5)	117 (41.8)	310 (61.5)	**<0.001**
Hyperlipidemia, n (%)	405 (51.7)	137 (48.9)	268 (53.2)	0.254
Cerebrovascular disease, n (%)	64 (8.2)	3 (1.1)	61 (12.1)	**<0.001**
CKD, n (%)	206 (26.3)	38 (13.6)	168 (33.3)	**<0.001**
LVEF, %	53.1 ± 11.1	57.9 ± 8.3	50.4 ± 11.6	**<0.001**
Creatinine, (mg/dL)	0.98 (0.82–1.20)	0.91 (0.81–1.10)	1.00 (0.84–1.23)	**<0.001**
Hemoglobin, g/L	13.48 ± 2.58	13.91 ± 2.46	13.24 ± 2.62	**<0.001**
Glucose (mg/dL)	147.4 ± 68.6	133.0 ± 64.2	154.6 ± 69.6	**<0.001**
WBC, 10^6/L	8.73 ± 1.40	8.60 ± 1.53	8.81 ± 1.32	**0.043**
Total cholesterol, mg/dL	198.3 ± 45.9	200.9 ± 46.6	196.8 ± 45.5	0.229
LDL-C, mg/dL	121.5 ± 39.4	123.4 ± 39.3	120.5 ± 39.5	0.323
HDL-C, mg/dL	38.5 ± 7.2	38.0 ± 6.9	38.8 ± 7.4	0.124
Triglyceride, mg/dL	156.5 (112.7–215.0)	161.5 (118.7–209.2)	156.0 (106.0–221.5)	0.172
CRP (mg/dL)	3.50 (1.26–9.76)	2.78 (1.08–6.46)	3.81 (1.31–11.28)	**0.036**
TASC, n (%)				**<0.001**
AB	510 (65.1)	208 (74.3)	302 (59.9)	
CD	274 (34.9)	72 (25.7)	202 (40.1)	
Aortoiliac TASC, n (%)				**0.002**
AB	250 (67.8)	100 (78.1)	150 (62.2)	
CD	119 (32.2)	28 (21.9)	91 (37.8)	
Femoro-popliteal TASC, n (%)				**0.007**
AB	260 (62.7)	108 (71.1)	152 (57.8)	
CD	155 (37.3)	44 (28.9)	111 (42.2)	
Contrast volume (mL)	162.7 ± 70.7	157.0 ± 80.9	165.8 ± 64.3	0.094
Procedure duration (min)	57.7 ± 20.8	53.3 ± 24.2	60.1 ± 18.3	**<0.001**
Rutherford, n (%)				**0.001**
1	54 (6.9)	27 (9.6)	27 (5.4)	
2	133 (17.0)	52 (18.6)	81 (16.1)	
3	362 (46.2)	142 (50.7)	220 (43.7)	
4	143 (18.2)	41 (14.6)	102 (20.2)	
5	73 (9.3)	15 (5.4)	58 (11.5)	
6	19 (2.4)	3 (1.1)	16 (3.2)	

Table 1 (cont). Comparison of clinical, demographic, and outcome parameters between low and high CHA_2DS_2-VASc score groups

	All patients (n=784)	Low CHA_2DS_2-VASc score (n=280)	High CHA_2DS_2-VASc score (n=504)	P
Fontaine, n (%)				**0.001**
I	72 (9.2)	30 (10.7)	42 (8.3)	
II	483 (61.6)	190 (67.9)	293 (58.1)	
III	144 (18.4)	45 (16.1)	99 (19.6)	
IV	85 (10.8)	15 (5.4)	70 (13.9)	
Type of treatment, n (%)				**<0.001**
Medical	122 (15.6)	23 (8.2)	99 (19.6)	
PTCA	352 (44.9)	109 (38.9)	243 (48.2)	
Stent	261 (33.3)	128 (45.7)	133 (26.4)	
Bypass	49 (6.3)	20 (7.1)	29 (5.8)	
Amputation, n (%)	35 (4.5)	5 (1.8)	30 (6.0)	**0.007**
Minor	23 (2.9)	5 (1.8)	18 (3.6)	0.156
Major	12 (1.5)	0 (0)	12 (2.4)	**0.006**
Mortality, n (%)	186 (23.7)	23 (8.2)	163 (32.3)	**<0.001**

BMI, Body Mass Index; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CRP, C-Reactive Protein; HDL-C, High-Density Lipoprotein Cholesterol (mg/dL); LDL-C, Low-Density Lipoprotein Cholesterol (mg/dL); LVEF, Left Ventricular Ejection Fraction; PTCA, Percutaneous Transluminal Coronary Angioplasty; TASC II, TransAtlantic Inter-Society Consensus-II; WBC, White Blood Cell Count (10^6/L). Data are presented as mean ± standard deviation (SD) or n (%). Statistical significance is considered at a P-value of less than 0.05.

< 0.001) (Table 2). According to the multivariate logistic regression model, the CHA_2DS_2-VASc score (odds ratio [OR] = 1.604; 95% confidence interval [CI]: 1.137–2.261; P = 0.007) and LVEF (OR = 0.982; 95% CI: 0.968–0.995; P = 0.009) were identified as independent determinants of lesion complexity (Table 4).

According to the TASC II classification, lesion complexity was evaluated according to CHA_2DS_2-VASc score groups. The proportion of high-scoring patients was found to increase significantly with greater lesion complexity (Figure 3).

Predictors of Long-Term Mortality

To determine independent predictors of long-term mortality, Cox proportional hazards regression analysis was performed. Variables that demonstrated a statistically significant association with mortality (Table 3) were included in both univariate and multivariate Cox regression models.

In the univariate Cox regression analysis, age, female sex, CHA_2DS_2-VASc score, DM, ejection fraction (EF), CAD, CKD, hemoglobin level, TASC classification, and amputation were all significantly associated with long-term mortality (all, P < 0.05). In the multivariate Cox regression model, age (hazard ratio [HR]: 1.062, 95% CI: 1.038–1.086, P < 0.001), CHA_2DS_2-VASc score (HR: 1.272, 95% CI: 1.040–1.555, P = 0.019), DM (HR: 1.589, 95% CI: 1.097–2.302, P = 0.014), lower EF (HR: 0.976, 95% CI: 0.962–0.991, P = 0.001), TASC classification (HR: 1.211, 95% CI: 1.034–1.418, P = 0.018), and amputation (HR: 2.450, 95% CI: 1.514–3.965, P < 0.001) emerged as independent predictors of long-term mortality (Table 5).

Survival Analysis

Kaplan-Meier survival analysis revealed that patients with higher CHA_2DS_2-VASc scores had significantly lower long-term survival, indicating a greater risk of all-cause mortality over the 60-month follow-up period (Log-rank = 58.091, P < 0.001) (Figure 4).

ROC Curve Analysis

Receiver operating characteristic curve analysis was conducted to evaluate the predictive performance of the CHA_2DS_2-VASc score for long-term mortality. The area under the curve (AUC) was 0.793 (95% CI: 0.755–0.832, P < 0.001), indicating good discriminative ability. The optimal cut-off value was identified as 3.5, yielding a sensitivity of 70% and a specificity of 79% (Figure 5).

Discussion

Our findings demonstrate that the CHA_2DS_2-VASc score, a widely used tool for cardiovascular risk grouping, may also serve as a practical and accessible prognostic indicator for evaluating lesion severity and predicting long-term outcomes in patients with PAD. The main findings are:

1. The CHA_2DS_2-VASc score was identified as an independent determinant of long-term mortality in patients with PAD, and higher scores were significantly associated with shorter survival times.
2. High CHA_2DS_2-VASc scores are associated with increased lesion severity in PAD.
3. Reduced LVEF was found to be an independent determinant of both lesion severity and long-term mortality.

PAD is becoming increasingly common, a trend largely driven by the rise in global life expectancy.[2] This growing prevalence has positioned PAD as a significant public health concern. In patients with PAD, advancing age was found to be an independent predictor of long-term mortality in our study, further emphasizing its prognostic importance in this high-risk population. In particular, the associated rise in major complications such as critical limb-threatening ischemia (CLTI) and limb amputations—both of which significantly impair quality of life—highlights the

Table 2. Comparison of clinical, laboratory, and outcome parameters between TASC-AB and TASC-CD groups

	All patients (n = 784)	Mild PAD (TASC-AB) (n = 510)	Severe PAD (TASC-CD) (n = 274)	P
Age, years	61.7 ± 9.9	60.7 ± 9.5	63.4 ± 10.5	**<0.001**
Gender (female), n (%)	135 (17.2)	74 (14.5)	61 (22.3)	**0.006**
BMI, kg/m^2	26.9 ± 4.7	26.8 ± 4.7	27.0 ± 4.7	0.493
CHA_2DS_2-VASc score	3.00 ± 1.25	2.75 ± 1.16	3.47 ± 1.29	**<0.001**
Heart rate (minute)	87.0 ± 17.9	86.7 ± 17.6	87.7 ± 18.3	0.429
Systolic blood pressure (mmHg)	129.2 ± 15.0	129.1 ± 14.7	129.3 ± 15.4	0.890
Diastolic blood pressure (mmHg)	79.7 ± 9.7	80.0 ± 9.6	79.2 ± 10.0	0.252
Smoking, n (%)	505 (64.7)	339 (66.7)	166 (61.0)	0.112
Diabetes mellitus, n (%)	339 (43.2)	201 (39.4)	138 (50.4)	**0.003**
Hypertension, n (%)	450 (57.4)	270 (52.9)	180 (65.7)	**0.001**
CAD, n (%)	427 (54.5)	259 (50.8)	168 (61.3)	**0.005**
Hyperlipidemia, n (%)	405 (51.7)	247 (48.4)	158 (57.7)	**0.014**
Cerebrovascular disease, n (%)	64 (8.2)	37 (7.3)	27 (9.9)	0.205
CKD, n (%)	206 (26.3)	119 (23.3)	87 (31.8)	**0.011**
LVEF, %	53.1 ± 11.1	54.2 ± 10.7	50.9 ± 11.6	**<0.001**
Creatinine, (mg/dL)	0.98 (0.82–1.20)	1.00 (0.83–1.18)	0.97 (0.82–1.28)	0.211
Hemoglobin, g/L	13.48 ± 2.58	13.53 ± 2.60	13.38 ± 2.56	0.453
Glucose (mg/dL)	147.4 ± 68.6	147.0 ± 65.1	148.0 ± 74.4	0.863
WBC, 10^6/L	8.73 ± 1.40	8.62 ± 1.29	8.93 ± 1.57	**0.003**
Total cholesterol, mg/dL	198.3 ± 45.9	197.0 ± 44.8	200.7 ± 48.0	0.279
LDL-C, mg/dL	121.5 ± 39.4	121.7 ± 38.7	121.3 ± 40.8	0.901
HDL-C, mg/dL	38.5 ± 7.2	38.0 ± 7.1	39.3 ± 7.4	**0.016**
Triglyceride, mg/dL	156 (112–215)	151 (110–215)	169 (116–223)	0.357
CRP (mg/dL)	3.50 (1.26–9.76)	3.59 (1.38–9.09)	3.34 (1.19–10.55)	0.543
Contrast volume (mL)	162.7 ± 70.7	161.2 ± 71.9	165.3 ± 68.6	0.445
Procedure duration (min)	57.7 ± 20.8	56.6 ± 21.1	59.6 ± 20.2	0.051
Rutherford, n (%)				**<0.001**
1	54 (6.9)	45 (8.8)	9 (3.3)	
2	133 (17.0)	100 (19.6)	33 (12.0)	
3	362 (46.2)	269 (52.7)	93 (33.9)	
4	143 (18.2)	57 (11.2)	86 (31.4)	
5	73 (9.3)	26 (5.1)	47 (17.2)	
6	19 (2.4)	13 (2.5)	6 (2.2)	
Fontaine, n (%)				**<0.001**
I	72 (9.2)	62 (12.2)	10 (3.6)	
II	483 (61.6)	354 (69.4)	129 (47.1)	
III	144 (18.4)	61 (12.0)	83 (30.3)	
IV	85 (10.8)	33 (6.5)	52 (19.0)	
Type of treatment, n (%)				**<0.001**
Medical	122 (15.6)	103 (20.2)	19 (6.9)	
PTCA	352 (44.9)	220 (43.1)	132 (48.2)	
Stent	261 (33.3)	165 (32.4)	96 (35.0)	
Bypass	49 (6.3)	22 (4.3)	27 (9.9)	
Amputation, n (%)	35 (4.5)	12 (2.4)	23 (8.4)	**<0.001**
Minor	23 (2.9)	11 (2.2)	12 (4.4)	0.079
Major	12 (1.5)	1 (0.2)	11 (4.0)	**<0.001**
Mortality, n (%)	186 (23.7)	86 (16.9)	100 (36.5)	**<0.001**

BMI, Body Mass Index; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CRP, C-Reactive Protein; HDL-C, High-Density Lipoprotein Cholesterol (mg/dL); LDL-C, Low-Density Lipoprotein Cholesterol (mg/dL); LVEF, Left Ventricular Ejection Fraction; PTCA, Percutaneous Transluminal Coronary Angioplasty; TASC II, TransAtlantic Inter-Society Consensus-II; WBC, White Blood Cell Count (10^6/L). Data are presented as mean ± standard deviation (SD) or n (%). Statistical significance is considered at a P-value of less than 0.05.

Table 3. Clinical, demographic, and outcome data by survival status

	All patients (n = 784)	Survivors (n = 598)	Non-survivors (n = 186)	P
Age, years	61.7 ± 9.9	59.6 ± 8.9	68.4 ± 10.1	**<0.001**
Gender (female), n (%)	135 (17.2)	76 (12.7)	59 (31.7)	**<0.001**
BMI, kg/m^2	26.9 ± 4.7	26.8 ± 4.5	27.0 ± 5.0	0.696
CHA_2DS_2-VASc score	3.00 ± 1.25	2.68 ± 1.07	4.06 ± 1.22	**<0.001**
Heart rate (minute)	87.0 ± 17.9	87.1 ± 17.8	86.6 ± 18.2	0.843
Systolic blood pressure (mmHg)	129.2 ± 15.0	129.1 ± 15.1	129.3 ± 14.5	0.878
Diastolic blood pressure (mmHg)	79.7 ± 9.7	79.5 ± 9.6	80.4 ± 10.1	0.269
Smoking, n (%)	505 (64.7)	382 (64.1)	123 (66.8)	0.494
Diabetes mellitus, n (%)	339 (43.2)	235 (39.3)	104 (55.9)	**<0.001**
Hypertension, n (%)	450 (57.4)	331 (55.4)	119 (64.0)	**0.038**
CAD, n (%)	427 (54.5)	306 (51.2)	121 (65.1)	**0.001**
Hyperlipidemia, n (%)	405 (51.7)	308 (51.5)	97 (52.2)	0.878
Cerebrovascular disease, n (%)	64 (8.2)	42 (7.0)	22 (11.8)	**0.037**
CKD, n (%)	206 (26.3)	118 (19.7)	88 (47.3)	**<0.001**
LVEF, %	53.1 ± 11.1	54.9 ± 10.0	47.3 ± 12.6	**<0.001**
Creatinine, (mg/dL)	0.98 (0.82–1.20)	0.94 (0.81–1.12)	1.13 (0.92–1.32)	**<0.001**
Hemoglobin, g/L	13.48 ± 2.58	13.64 ± 2.59	12.95 ± 2.49	**0.001**
Glucose (mg/dL)	147.4 ± 68.6	145.1 ± 68.0	153.9 ± 69.9	0.155
WBC, 106/L	8.73 ± 1.40	8.75 ± 1.42	8.69 ± 1.35	0.617
Total cholesterol, mg/dL	198.3 ± 45.9	198.0 ± 43.3	198.9 ± 45.0	0.821
LDL-C, mg/dL	121.5 ± 39.4	121.5 ± 39.8	121.5 ± 38.3	0.993
HDL-C, mg/dL	38.5 ± 7.2	38.4 ± 7.2	38.7 ± 7.2	0.599
Triglyceride, mg/dL	156 (112–215)	156 (110–210)	161 (117–224)	0.674
CRP (mg/dL)	3.50 (1.26–9.76)	2.95 (1.17–7.59)	4.70 (1.81–14.73)	**0.001**
Contrast volume (mL)	162.7 ± 70.7	161.6 ± 71.4	166.2 ± 68.6	0.437
Procedure duration (min)	57.7 ± 20.8	57.2 ± 21.2	59.2 ± 19.5	0.238
Rutherford, n (%)				**<0.001**
1	54 (6.9)	46 (7.7)	8 (4.3)	
2	133 (17.0)	117 (19.6)	16 (8.6)	
3	362 (46.2)	288 (48.2)	74 (39.8)	
4	143 (18.2)	99 (16.6)	44 (23.7)	
5	73 (9.3)	37 (6.2)	36 (19.4)	
6	19 (2.4)	11 (1.8)	8 (4.3)	
Fontaine, n (%)				**<0.001**
I	72 (9.2)	61 (10.2)	11 (5.9)	
II	483 (61.6)	393 (65.7)	90 (48.4)	
III	144 (18.4)	98 (16.4)	46 (24.7)	
IV	85 (10.8)	46 (7.7)	39 (21.0)	
Type of treatment, n (%)				**0.007**
Medical	122 (15.6)	85 (14.2)	37 (19.9)	
PTCA	352 (44.9)	257 (43.0)	95 (51.1)	
Stent	261 (33.3)	217 (36.3)	44 (23.7)	
Bypass	49 (6.3)	39 (6.5)	10 (5.4)	
TASC, n (%)				**<0.001**
AB	510 (65.1)	424 (70.9)	86 (46.2)	
CD	274 (34.9)	174 (29.1)	100 (53.8)	
Amputation, n (%)	35 (4.5)	15 (2.5)	20 (10.8)	**<0.001**
Minor	23 (2.9)	13 (2.2)	10 (5.4)	**0.024**
Major	12 (1.5)	2 (0.3)	10 (5.4)	**<0.001**

BMI, Body Mass Index; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CRP, C-Reactive Protein; HDL-C, High-Density Lipoprotein Cholesterol (mg/dL); LDL-C, Low-Density Lipoprotein Cholesterol (mg/dL); LVEF, Left Ventricular Ejection Fraction; PTCA, Percutaneous Transluminal Coronary Angioplasty; TASC II, TransAtlantic Inter-Society Consensus-II; WBC, White Blood Cell Count (10^6/L). Data are presented as mean ± standard deviation (SD) or n (%). Statistical significance is considered at a P-value of less than 0.05.

Table 4. Independent predictors of lesion severity in univariate and multivariate logistic regression analysis model

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Hemoglobin	0.979	0.925–1.036	0.453			
BMI	1.011	0.980–1.043	0.493			
CRP	0.994	0.986–1.001	0.097			
WBC	1.002	0.999–1.005	0.279			
LVEF	0.974	0.962–0.987	**<0.001**	0.982	0.968–0.995	**0.009**
Smoking	0.781	0.575–1.060	0.112			
CKD	1.529	1.102–2.120	**0.011**	1.287	0.917–1.806	0.144
Creatinine	1.029	0.877–1.208	0.725			
CHA_2DS_2-VASc group	1.932	1.401–2.666	**<0.001**	1.604	1.137–2.261	**0.007**

BMI, Body Mass Index; CI, Confidence Interval; CKD, Chronic Kidney Disease; CRP, C-Reactive Protein; LVEF, Left Ventricular Ejection Fraction; OR, Odds Ratio; WBC, White Blood Cell Count (106/L). Statistical significance is considered at a P-value of less than 0.05.

Table 5. Independent predictors of long-term mortality identified by univariate and multivariate cox regression analyses

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age	1.096	1.079–1.114	**<0.001**	**1.062**	**1.038–1.086**	**<0.001**
Gender	2.638	1.937–3.595	**<0.001**	1.258	0.881–1.797	0.207
CHA_2DS_2-VASc score	2.168	1.949–2.412	**<0.001**	1.272	1.040–1.555	**0.019**
DM	1.803	1.350–2.409	**<0.001**	1.589	1.097–2.302	**0.014**
LVEF	0.954	0.943–0.965	**<0.001**	0.976	0.962–0.991	**0.001**
CAD	1.622	1.200–2.192	**0.002**	1.137	0.830–1.557	0.424
CKD	3.027	2.269–4.038	**<0.001**	1.374	0.996–1.895	0.053
Hemoglobin	0.917	0.869–0.967	**0.001**	0.971	0.916–1.030	0.331
TASC	2.436	1.826–3.251	**<0.001**	1.211	1.034–1.418	**0.018**
Amputation	3.320	2.086–5.283	**<0.001**	2.450	1.514–3.965	**<0.001**

CAD, Coronary Artery Disease; CI, Confidence Interval; CKD, Chronic Kidney Disease; DM, Diabetes Mellitus; HR, Hazard Ratio; LVEF, Left Ventricular Ejection Fraction; TASC II, Transatlantic Inter-Society Consensus-II. Statistical significance is considered at a P-value of less than 0.05.

importance of early-stage classification and the development of effective treatment strategies. In this context, if risk stratification is performed early and high-risk patients are recognized, more effective interventions can be applied to improve the incidence and prognosis of PAD.[2,15] Although our study mainly focused on a non-invasive clinical risk score applicable to a broad PAD population, it is also important to consider advanced staging systems specifically developed for the management of CLTI. In recent years, classification systems such as WIfI (Wound, Ischemia, and Foot Infection) and GLASS (Global Limb Anatomic Staging System), supported by the European Society for Vascular Surgery (ESVS) guidelines, have been widely adopted, providing detailed anatomical and clinical risk stratification to guide revascularization strategies in CLTI patients.

Peripheral artery disease patients, particularly those classified as TASC-CD, demonstrated that higher WIfI clinical stages were associated with increased one-year amputation and mortality rates.[16] Similarly, in our study, when PAD patients were stratified according to lesion severity, those with TASC-CD lesions exhibited significantly higher rates of both amputation and long-term mortality.

These findings underscore the critical importance of evaluating wound infection and systemic comorbidities in the clinical decision-making process for TASC-CD patients. Although our study did not directly assess wound infection parameters, we believe that future research combining clinical risk scores such as CHA_2DS_2-VASc with wound-based or systemic comorbidity-based staging systems may offer a more comprehensive risk stratification for patients with advanced PAD.

With the rising prevalence of PAD, the importance given to this issue and the studies conducted have recently increased. Amputation rates also increase with the increasing incidence of PAD.[15] Interestingly, in our study, the overall rate of amputation—including among non-survivors—remained relatively low. This may be attributable to the advanced age, increased frailty, and higher burden of comorbidities in this population, which likely resulted in limited life expectancy and a greater emphasis on palliative care rather than limb salvage interventions. This has increased the use of various indices to evaluate the prognosis of PAD. Altunova et al.[17] analyzed the association between the atherogenic plasma index (AIP) and long-term consequences following endovascular treatment in patients with PAD. It was

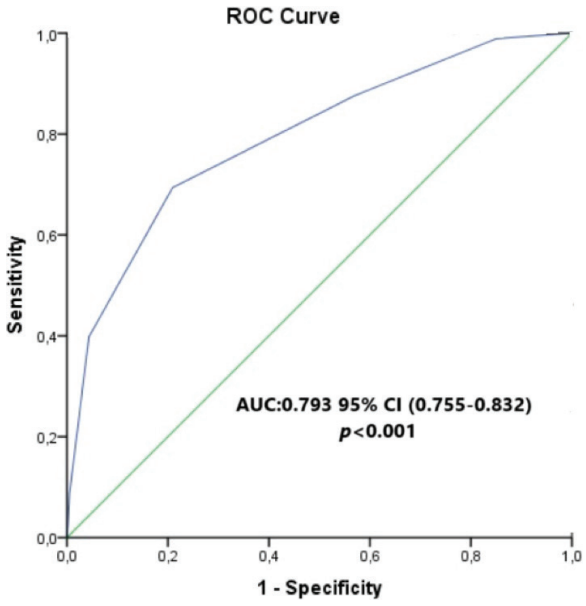

Figure 5. Receiver operating characteristic (ROC) curve demonstrating the predictive accuracy of the CHA_2DS_2-VASc score for long-term mortality. The score showed an area under the curve (AUC) of 0.793 (95% confidence interval [CI]: 0.755–0.832, P < 0.001), with an optimal cut-off value of 3.5, providing 70% sensitivity and 79% specificity. CHA_2DS_2-VASc score, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack/ systemic embolism, Vascular disease, Age 65–74 years, and Sex category – female.

observed that long-term mortality and major adverse limb events increased as the AIP value increased. In that study, a rise in AIP was also associated with higher rates of amputation, suggesting that elevated AIP levels may contribute to both limb-related complications and overall mortality. In our study as well, both a high CHA_2DS_2-VASc score (≥ 3) and the presence of amputation were identified as independent predictors of long-term mortality. Notably, amputation was more frequently observed in patients with higher CHA_2DS_2-VASc scores, further emphasizing the close association between systemic cardiovascular risk burden and adverse limb outcomes in PAD. In a study by Duran Karaduman et al.,[18] which evaluated lesion severity in PAD, the relationship between the triglyceride-glucose index and PAD lesion severity was examined. It was observed that as the index increased, PAD lesion severity also increased. Consistently, we observed that lesion complexity increased in parallel with rising CHA_2DS_2-VASc scores, and the score was identified as an independent predictor of lesion severity in multivariate logistic regression analysis. An important distinction of our study from these others is the fact that indices like these may show dynamic changes during hospital admissions and follow-ups. However, the CHA_2DS_2-VASc score does not change before and after the procedure.

Recent literature suggests a link between the CHA_2DS_2-VASc score and the extent of CAD.[19] Given that both PAD and CAD share a common pathophysiological basis—namely, atherosclerosis—our findings support that higher CHA_2DS_2-VASc scores are significantly associated with greater lesion severity in PAD as well.

The CHA_2DS_2-VASc score was originally developed to stratify stroke risk in patients with non-valvular AF.[3] However, subsequent studies have demonstrated its prognostic utility beyond AF, particularly in patients with atherosclerotic cardiovascular disease. In this context, Goto et al.[20] reported that the CHADS2 score could predict cardiovascular mortality in high-risk atherosclerotic patients, even in the absence of atrial fibrillation. Bozbay et al.[11] indicated that a CHA_2DS_2-VASc score greater than 2 was connected with adverse clinical outcomes—including low LVEF, cardiogenic shock, reinfarction, and mortality—in patients with ST-Elevation Myocardial Infarction (STEMI) undergoing percutaneous coronary revascularization. Similarly, in our study population, reduced LVEF was identified as an independent determinant of both lesion complexity and long-term mortality in patients with PAD. This parallel supports the broader applicability of a high CHA_2DS_2-VASc score in estimating unfavorable cardiovascular events across different patient populations.

One of the key advantages of the CHA_2DS_2-VASc score is its practicality. It is easy to apply at the bedside, does not require additional testing or incur extra costs, and remains stable regardless of pre- or post-procedural conditions. These features distinguish it from many other risk assessment tools. In patients with PAD, the use of the CHA_2DS_2-VASc score may support early risk stratification and subsequently aid in shaping treatment strategies. Specifically, patients with higher CHA_2DS_2-VASc scores were more likely to exhibit complex lesions according to TASC classification, potentially influencing therapeutic choices such as medical management, percutaneous transluminal angioplasty (PTCA), stenting, or surgical bypass. Furthermore, the score was identified as an independent predictor of long-term mortality in multivariate Cox regression analysis, highlighting its role in guiding clinical decision-making and demonstrating its prognostic utility during long-term follow-up in patients with PAD.

Several limitations should be considered. It is important to acknowledge that conducting the study retrospectively and within only two centers may constrain the external validity of the results. Furthermore, the relatively small cohort and the possibility of non-homogeneous patient distribution may also affect the robustness of the results. Due to the retrospective nature of the study and limitations in data availability, information regarding baseline medications could not be retrieved and was therefore not included. Additionally, although hypertension is incorporated as a binary parameter in the CHA_2DS_2-VASc score, the study design did not allow for distinguishing between controlled and uncontrolled hypertension, which may have differing prognostic implications. Propensity score matching or similar balancing techniques could not be performed, and this limitation may have introduced potential confounding related to baseline differences between groups. To confirm the prognostic findings, multicenter, long-term prospective studies with larger patient populations should be performed.

This study highlights the clinical utility of the CHA_2DS_2-VASc score in patients with PAD. Higher scores were significantly associated with increased lesion severity and reduced long-term survival. These findings indicate that the CHA_2DS_2-VASc score may serve as a practical and accessible prognostic tool in PAD, supporting risk stratification and potentially guiding treatment decisions.

Ethics Committee Approval: The study protocol has been approved by Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (Approval Number: 2024-296, Date: 16.10.2024).

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

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Can Large Language Models Guide Aortic Stenosis Management? A Comparative Analysis of ChatGPT and Gemini AI

Büyük Dil Modelleri Aort Darlığı Yönetimine Rehberlik Edebilir mi? ChatGPT ve Gemini Yapay Zekanın Karşılaştırmalı Analizi

ABSTRACT

Objective: Management of aortic stenosis (AS) requires integrating complex clinical, imaging, and risk stratification data. Large language models (LLMs) such as ChatGPT and Gemini AI have shown promise in healthcare, but their performance in valvular heart disease, particularly AS, has not been thoroughly assessed. This study systematically compared ChatGPT and Gemini AI in addressing guideline-based and clinical scenario questions related to AS.

Method: Forty open-ended AS-related questions were developed, comprising 20 knowledge-based and 20 clinical scenario items based on the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines. Both models were queried independently. Responses were evaluated by two blinded cardiologists using a structured 4-point scoring system. Composite scores were categorized, and comparisons were performed using Wilcoxon signed-rank and chi-square tests.

Results: Gemini AI achieved a significantly higher mean overall score than ChatGPT (3.96 ± 0.17 vs. 3.56 ± 0.87; P = 0.003). Fully guideline-compliant responses were more frequent with Gemini AI (95.0%) than with ChatGPT (72.5%), although the overall compliance distribution difference did not reach conventional significance (P = 0.067). Gemini AI performed more consistently across both question types. Inter-rater agreement was excellent for ChatGPT (κ = 0.94) and moderate for Gemini AI (κ = 0.66).

Conclusion: Gemini AI demonstrated superior accuracy, consistency, and guideline adherence compared to ChatGPT. While LLMs show potential as adjunctive tools in cardiovascular care, expert oversight remains essential, and further model refinement is needed before clinical integration, particularly in AS management.

Keywords: Aortic stenosis, artificial intelligence, clinical decision support, guideline adherence, large language models

ÖZET

Amaç: Aort darlığı (AD) yönetimi; karmaşık klinik, görüntüleme ve risk sınıflandırma verilerinin entegrasyonunu gerektirir. ChatGPT ve Gemini yapay zeka gibi büyük dil modelleri (LLM'ler) sağlık hizmetlerinde umut verici sonuçlar göstermiştir, ancak kapak hastalıklarında, özellikle de AD'deki performansları yeterince değerlendirilmemiştir. Bu çalışma, AD ile ilişkili kılavuz temelli ve klinik senaryo sorularında ChatGPT ile Gemini yapay zekanın sistematik olarak karşılaştırılmasını amaçlamıştır.

Yöntem: 2021 ESC/EACTS kılavuzları temel alınarak, 20 bilgi temelli ve 20 klinik senaryo sorusundan oluşan toplam 40 açık uçlu AD sorusu geliştirildi. Her iki model de bağımsız olarak sorgulandı. Yanıtlar, ikisi kardiyolog olan iki bağımsız değerlendirici tarafından körleme yöntemiyle, yapılandırılmış 4 puanlık bir sistemle puanlandı. Kompozit puanlar kategorize edildi ve karşılaştırmalar Wilcoxon işaretli sıralar testi ve ki-kare testi ile yapıldı.

Bulgular: Gemini yapay zeka, ChatGPT'ye kıyasla anlamlı derecede daha yüksek ortalama toplam puan elde etti (3,96 ± 0,17 vs. 3,56 ± 0,87; P = 0,003). Kılavuzlara tamamen uyumlu yanıtlar Gemini yapay zeka tarafından daha sık verildi (%95,0 vs. %72,5), ancak genel uyum dağılımı geleneksel anlamlılık düzeyine ulaşmadı (P = 0,067). Gemini yapay zeka her iki soru türünde de daha tutarlı performans sergiledi. Değerlendiriciler arası uyum ChatGPT için mükemmel (κ = 0,94), Gemini yapay zeka için ise orta düzeydeydi (κ = 0,66).

Sonuç: Gemini yapay zeka, doğruluk, tutarlılık ve kılavuz uyumu açısından ChatGPT'ye üstünlük göstermiştir. LLM'ler kardiyovasküler bakımda tamamlayıcı araçlar olarak potansiyel taşısa da, uzman denetimi vazgeçilmezdir ve özellikle AD yönetiminde klinik entegrasyon öncesi modellerin daha da geliştirilmesi gerekmektedir.

Anahtar Kelimeler: Aort darlığı, yapay zeka, klinik karar destek, kılavuz uyumu, büyük dil modelleri

ORIGINAL ARTICLE
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Aortic stenosis (AS) is one of the most prevalent and clinically significant valvular heart diseases, particularly affecting elderly populations in developed countries. Its burden continues to rise alongside global population aging, contributing substantially to cardiovascular morbidity and mortality. Severe AS, when left untreated, carries a poor prognosis, with survival rates as low as 50% at two years in symptomatic individuals. Early diagnosis and timely intervention—whether through surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI)—are therefore crucial for improving clinical outcomes.[1] However, determining disease severity and selecting an optimal therapeutic strategy require integrating complex clinical, imaging, and risk stratification data.

In recent years, artificial intelligence (AI) has emerged as a promising tool to support clinical decision-making in cardiology. Among AI applications, large language models (LLMs) such as ChatGPT and Gemini AI have attracted particular attention for their ability to generate human-like responses informed by extensive biomedical knowledge. These systems can interpret clinical scenarios, extract guideline-based recommendations, and assist healthcare providers in managing complex cases. Their roles in patient education, documentation support, and diagnostic guidance are expanding rapidly across various medical disciplines.[2,3]

Despite this growing interest, the reliability and clinical utility of LLMs in specialized areas such as valvular heart disease remain uncertain. AS presents unique diagnostic and therapeutic challenges, particularly in nuanced situations such as low-flow, low-gradient states or asymptomatic patients with high-risk features. Whether AI models can comprehend and apply these subtleties in alignment with current guidelines has yet to be systematically evaluated.[4]

This study aims to evaluate and compare the performance of two widely accessible AI models—ChatGPT and Gemini AI—in their ability to answer guideline-based and scenario-driven questions related to aortic stenosis. By involving expert cardiologists in the evaluation process, we assessed the models' compliance with the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) valvular heart disease guidelines[1] and explored their potential and limitations as decision-support tools in contemporary cardiology practice.

ABBREVIATIONS

AI	Artificial intelligence
AS	Aortic stenosis
EF	Ejection fraction
ESC/EACTS	European Society of Cardiology/European Association for Cardio-Thoracic Surgery
LLMs	Large language models
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation

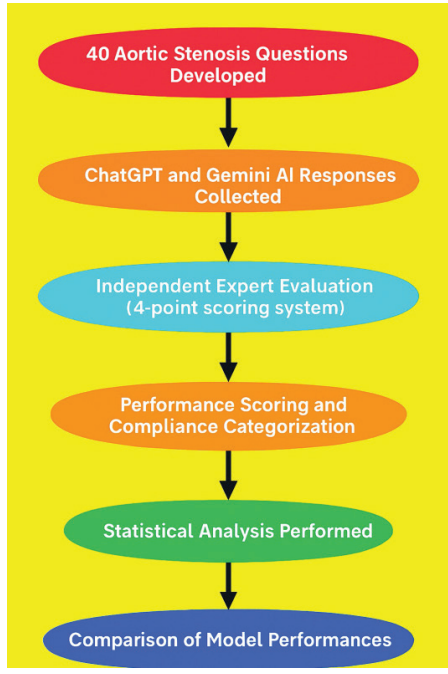

Figure 1. Flowchart summarizing the evaluation process of ChatGPT and Gemini AI models. Forty aortic stenosis-related questions were created and separately submitted to both AI models. Responses were independently assessed by blinded cardiologists using a 4-point scoring system. Compliance categorization and statistical analyses were then performed to compare each model's adherence to clinical guidelines and overall decision-making performance.

Materials and Methods

This study was conducted as a cross-sectional evaluation to assess and compare the aortic stenosis-related clinical knowledge and decision-making performance of two LLMs: ChatGPT-4 (OpenAI) and Gemini AI (Google). Specifically, we used the GPT-4-turbo model, available via ChatGPT-Plus, and the Gemini 1.5 Pro model, accessed via Google's web interface, both in May 2025. The evaluation was based on the 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease.[1] No human or animal participants were involved in this study.

The overall study workflow is summarized in Figure 1. A total of 40 open-ended questions were developed by two experienced cardiologists, comprising 20 knowledge-based items and 20 clinical scenarios (Table 1). The questions were phrased in a standardized open-ended format and independently reviewed to ensure clinical neutrality and consistency. All prompts were submitted in a zero-shot setting—without prior examples, role prompts, or chain-of-thought instructions—to eliminate prompt engineering bias. The identical questions were presented to both models in clean, isolated sessions. These questions were specifically designed to reflect the core principles of diagnosis, risk stratification, and treatment decision-making in aortic stenosis, as outlined in guideline-recommended practices.[1] The clinical scenarios were designed to simulate realistic patient cases with varying presentations, comorbidities, and surgical risks, providing a comprehensive framework for assessing the AI models' ability to reason through complex situations. Both AI models were presented with the same set of questions under standardized conditions. Each question was submitted separately to the respective model in independent sessions, using a new prompt environment to prevent memory-based carryover effects. All prompts were presented in a uniform

Table 1. Expert-assigned scores for each of the 40 questions evaluating ChatGPT and Gemini AI. Scores are shown alongside their corresponding guideline compliance category

Question no	Question type	Question text	Overall ChatGPT score	ChatGPT category	Overall Gemini score	Gemini category
1	Knowledge-based	What are the echocardiographic criteria for diagnosing severe aortic stenosis?	4.0	Fully compliant	4.0	Fully compliant
2	Knowledge-based	What are the surgical indications for asymptomatic patients with aortic stenosis?	1.0	Incorrect / Misleading	3.0	Partially compliant
3	Knowledge-based	What is the diagnostic approach in low-flow/low-gradient aortic stenosis?	3.5	Mostly compliant	4.0	Fully compliant
4	Knowledge-based	What is the STS (Society of Thoracic Surgeons) risk score, and how does it affect treatment decisions?	4.0	Fully compliant	4.0	Fully compliant
5	Knowledge-based	What are the indications for transcatheter aortic valve implantation (TAVI) in aortic stenosis?	4.0	Fully compliant	4.0	Fully compliant
6	Knowledge-based	In patients with aortic stenosis and coronary artery disease, what is the order of intervention?	4.0	Fully compliant	4.0	Fully compliant
7	Knowledge-based	What are the most common complications after transcatheter aortic valve replacement (TAVR)?	4.0	Fully compliant	4.0	Fully compliant
8	Knowledge-based	What should be done in patients with severe aortic stenosis (AS), normal ejection fraction (EF), and low gradient?	4.0	Fully compliant	4.0	Fully compliant
9	Knowledge-based	What is the recommended approach for young patients with bicuspid aortic stenosis?	4.0	Fully compliant	4.0	Fully compliant
10	Knowledge-based	Is beta-blocker therapy recommended for patients with aortic stenosis?	3.0	Partially compliant	4.0	Fully compliant
11	Knowledge-based	What are the advantages of TAVI in geriatric patients?	4.0	Fully compliant	4.0	Fully compliant
12	Knowledge-based	How should aortic stenosis be managed in patients with reduced EF?	4.0	Fully compliant	4.0	Fully compliant
13	Knowledge-based	What is the role of angiotensin-converting enzyme (ACE) inhibitors in aortic stenosis?	4.0	Fully compliant	4.0	Fully compliant
14	Knowledge-based	What does a paradoxical low-flow state mean in echocardiography?	4.0	Fully compliant	4.0	Fully compliant
15	Knowledge-based	What is the role of computed tomography (CT) in the diagnosis of aortic stenosis?	3.0	Partially compliant	4.0	Fully compliant
16	Knowledge-based	What are the non-surgical treatment options for severe AS?	4.0	Fully compliant	4.0	Fully compliant
17	Knowledge-based	When is stress echocardiography necessary in the evaluation of aortic stenosis?	4.0	Fully compliant	4.0	Fully compliant
18	Knowledge-based	How should pregnant patients with aortic stenosis be monitored and managed?	4.0	Fully compliant	4.0	Fully compliant
19	Knowledge-based	How does the calcification process develop in aortic valve biology?	4.0	Fully compliant	4.0	Fully compliant
20	Knowledge-based	What is ventriculo-arterial coupling in aortic stenosis and its prognostic significance?	4.0	Fully compliant	4.0	Fully compliant
21	Clinical scenario	What is your treatment approach for an 82-year-old patient with EF 55%, NYHA III (New York Heart Association Class III), and STS risk of 10%?	4.0	Fully compliant	4.0	Fully compliant
22	Clinical scenario	What would you recommend for a 70-year-old patient with EF 38%, aortic valve area (AVA) 0.6 cm^2, and a mean gradient of 28 mmHg?	4.0	Fully compliant	4.0	Fully compliant
23	Clinical scenario	What would you suggest for a 58-year-old asymptomatic patient with normal EF, AVA 0.75 cm^2, and Vmax 4.3 m/s?	4.0	Fully compliant	4.0	Fully compliant
24	Clinical scenario	What is your treatment choice for a 79-year-old patient with EF 60%, chronic kidney disease (CKD) stage 3, NYHA II, and STS 6.5%?	4.0	Fully compliant	4.0	Fully compliant

Table 1 (cont). Expert-assigned scores for each of the 40 questions evaluating ChatGPT and Gemini AI. Scores are shown alongside their corresponding guideline compliance category

Question no	Question type	Question text	Overall ChatGPT score	ChatGPT category	Overall Gemini score	Gemini category
25	Clinical scenario	Would you recommend further testing for a 65-year-old patient with EF 48% and a mean gradient of 32 mmHg?	4.0	Fully compliant	4.0	Fully compliant
26	Clinical scenario	What is the management plan for an 87-year-old with severe chronic obstructive pulmonary disease (COPD) and anemia, AVA 0.7 cm^2?	3.0	Partially compliant	4.0	Fully compliant
27	Clinical scenario	What is your approach for a 55-year-old patient with a congenital bicuspid valve and AVA 0.9 cm^2?	4.0	Fully compliant	4.0	Fully compliant
28	Clinical scenario	TAVI or SAVR (surgical aortic valve replacement): What would you recommend for a 60-year-old patient with EF 30% and low-gradient severe AS?	2.0	Not compliant	4.0	Fully compliant
29	Clinical scenario	How would you manage a 72-year-old patient with active malignancy and severe AS findings?	4.0	Fully compliant	4.0	Fully compliant
30	Clinical scenario	What is the next step for an 80-year-old with AVA 0.6 cm^2, a gradient of 22 mmHg, and a low stroke volume?	3.0	Partially compliant	4.0	Fully compliant
31	Clinical scenario	Surgery or TAVI: What is the best option for a 66-year-old with multivessel disease and severe AS?	3.0	Partially compliant	4.0	Fully compliant
32	Clinical scenario	Follow-up or intervention: What would you do for a 76-year-old with a high frailty score and AVA of 0.5 cm^2?	4.0	Fully compliant	4.0	Fully compliant
33	Clinical scenario	Is surgery indicated in a 59-year-old asymptomatic patient with left ventricular (LV) hypertrophy and EF 52%?	1.0	Incorrect / Misleading	4.0	Fully compliant
34	Clinical scenario	Is a patient with prior coronary artery bypass grafting (CABG) surgery at age 83 a suitable TAVI candidate?	4.0	Fully compliant	4.0	Fully compliant
35	Clinical scenario	How should combined treatment be planned for a 64-year-old with 90% left anterior descending (LAD) stenosis and severe AS?	1.0	Incorrect / Misleading	4.0	Fully compliant
36	Clinical scenario	What confirmatory test would you perform for a 70-year-old with AVA 0.8, low-flow/low-gradient AS, and EF 45%?	4.0	Fully compliant	4.0	Mostly compliant
37	Clinical scenario	Is urgent intervention needed for a 75-year-old patient with syncope despite medical therapy?	4.0	Fully compliant	4.0	Mostly compliant
38	Clinical scenario	How does chronic atrial fibrillation affect management in a 68-year-old patient with AVA 0.7?	4.0	Fully compliant	3.5	Mostly compliant
39	Clinical scenario	What is the recommendation for an 85-year-old with cognitive impairment and high surgical risk?	4.0	Fully compliant	4.0	Partially compliant
40	Clinical scenario	How should a 73-year-old patient with EF 58%, AVA 0.8, and severe diastolic dysfunction be evaluated?	3.0	Partially compliant	4.0	Fully compliant

format as plain-text, open-ended clinical questions. No system messages or role instructions were provided prior to submission. Each model received identical questions individually in a clean session without any prior conversation history. Prompt length and phrasing were standardized to maintain consistency across models and ensure a fair evaluation. Responses were recorded without editing or refinement, and all identifying data were removed to ensure objectivity. Each response was independently evaluated by two cardiologists who were blinded to the source of the answer (ChatGPT or Gemini). A structured 4-point ordinal scoring system was used:

- 4 = Fully Guideline-Compliant – Accurate, complete, and consistent with current ESC/EACTS recommendations.
- 3 = Partially Guideline-Compliant – Generally accurate but with minor omissions or incomplete details.
- 2 = Non-Compliant – Significant deviation from guideline recommendations.
- 1 = Incorrect or Misleading – Contains factual errors or potentially unsafe suggestions.

The arithmetic mean of the two reviewers' scores was calculated for each AI response to produce a composite performance metric. These mean values, which could include decimal scores (e.g., 3.5), were then grouped into interpretive performance bands to enhance clinical interpretability:

- 4.0 → Fully compliant
- 3.5–3.9 → Mostly compliant
- 3.0–3.4 → Partially compliant
- 2.0–2.9 → Not compliant
- <2.0 → Incorrect/Misleading.

Table 2. Descriptive statistics of AI scores

Model	Mean score	Median score	Standard deviation	Minimum score	Maximum score
ChatGPT	3.56	4.0	0.87	1.0	4.0
Gemini AI	3.96	4.0	0.17	3.0	4.0

AI: Artificial intelligence.

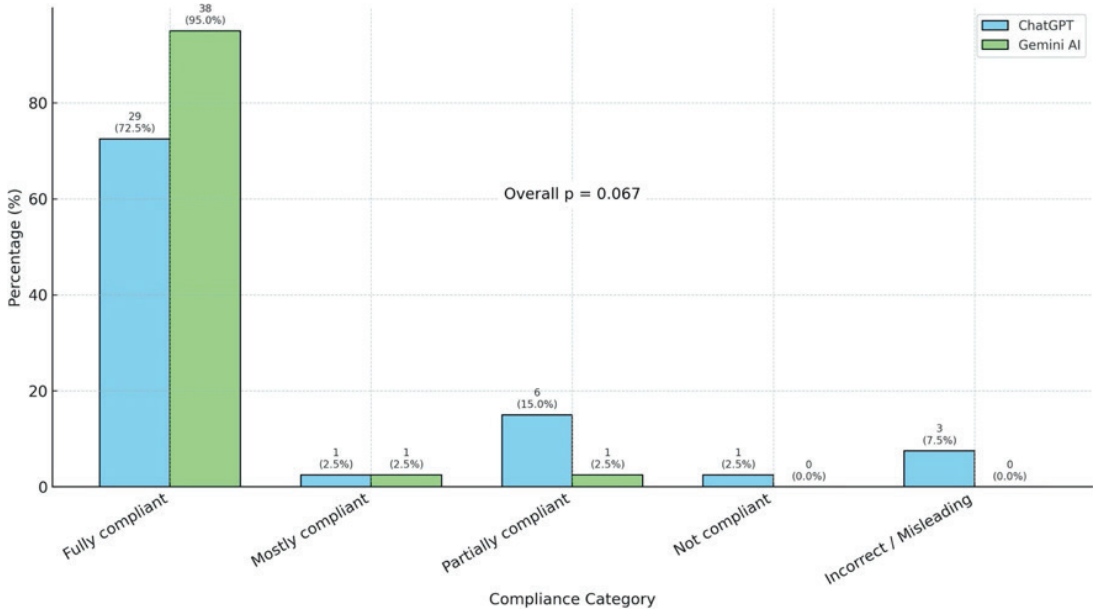

Figure 2. Distribution of responses across compliance categories for ChatGPT and Gemini AI. Fully compliant responses were significantly more frequent with Gemini AI than with ChatGPT (95.0% vs. 72.5%), while ChatGPT had higher rates of partially compliant, not compliant, and incorrect/misleading answers. Although the overall difference did not reach traditional statistical significance (overall P = 0.067, chi-square test), a numerical trend favoring Gemini AI was observed. Data are presented as both absolute counts (n) and percentages (%).

This approach aligns with scoring strategies used in recent AI evaluation studies,[2] where ordinal expert scores are averaged and mapped to descriptive categories. Such methods are widely employed to consolidate expert ratings while preserving both clinical relevance and statistical interpretability.

The study was conducted in accordance with the recommendations outlined in the Declaration of Helsinki for biomedical research involving human subjects. As it did not involve human or animal participants, patient data, or identifiable information, institutional ethics committee approval was not required. While the study focuses on evaluating the consistency of AI in the therapeutic management of AS, no artificial intelligence tools were utilized in the preparation, analysis, or writing of this manuscript.

Statistical Analysis

Descriptive statistics were calculated for each model, including the mean, median, and score distribution. The Wilcoxon signed-rank test was applied to compare the overall performance scores of ChatGPT and Gemini AI. This non-parametric test was chosen due to the ordinal nature of the scoring system (1-4) and the paired design of the data, as each model answered the same set of questions. Inter-rater agreement between the two cardiologists was measured using Cohen's kappa coefficient, with values above 0.8 interpreted as excellent agreement and values between 0.6 and 0.8 interpreted as moderate agreement. Additionally, a chi-square test was performed to compare the distribution of responses across categorical compliance levels (fully compliant, mostly compliant, partially compliant, not compliant, and incorrect/misleading) between the two AI models. All statistical analyses were two-tailed, and a p-value <0.05 was considered statistically significant. Analyses were conducted using SPSS (IBM Corp., Armonk, NY, USA) and Python (v3.10) with the matplotlib and scikit-learn libraries for figure generation and advanced modeling.

Results

Descriptive statistics of expert-assigned scores are shown in Table 2. ChatGPT had a lower average score (mean score = 3.56) and greater variability [standard deviation (SD) = 0.87] compared with Gemini AI, which achieved scores closer to the maximum (mean score = 3.96; SD = 0.17). Although both models had a median score of 4.0, the broader score range for ChatGPT suggests a higher proportion of partially compliant or incorrect responses.

Overall Compliance with Guidelines

A detailed summary of the categorical score distribution is provided in Figure 2.

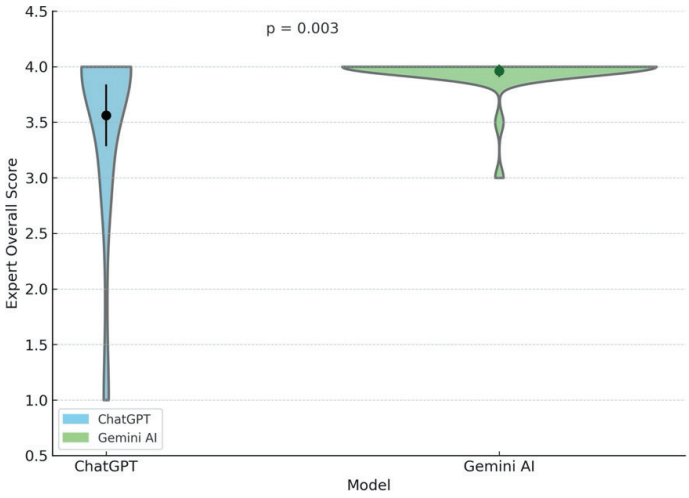

Figure 3. Violin plot showing the distribution of expert-assigned overall scores for ChatGPT and Gemini AI. Each model's distribution is displayed with mean scores (dots) and 95% confidence intervals (error bars). Gemini AI achieved a significantly higher mean overall score than ChatGPT (P = 0.003, Wilcoxon signed-rank test). Expert scores were based on a 4-point ordinal scale measuring adherence to clinical guidelines.

Among ChatGPT's 40 responses, 29 (72.5%) were classified as fully guideline-compliant, while 11 (27.5%) were categorized as partially compliant, not compliant, or incorrect. Specifically, six responses (15.0%) were partially compliant, one (2.5%) was not compliant, and three (7.5%) were considered incorrect or potentially misleading. In contrast, Gemini AI demonstrated greater consistency and a higher level of compliance. Of its 40 responses, 38 (95.0%) were fully compliant, while only two (5%) fell outside this category—one was mostly compliant and one was partially compliant. No responses from Gemini were rated as incorrect or non-compliant. Although Gemini AI demonstrated a numerically higher rate of fully compliant responses compared with ChatGPT (95.0% vs. 72.5%), the overall difference across all compliance categories did not reach statistical significance (P = 0.067, chi-square test).

Performance Across Question Types

When analyzed by question type, Gemini AI achieved full compliance in 90% of theoretical questions and 85% of clinical scenarios. ChatGPT reached full compliance in 75% of theoretical questions and 70% of clinical scenarios. ChatGPT's weaker performance in clinical questions reflected its difficulty integrating patient complexity, surgical risk assessment, and low-gradient decision-making algorithms.

Comparison of the AI Models

A Wilcoxon signed-rank test was conducted to compare the overall performance of ChatGPT and Gemini AI based on expert-assigned scores. Gemini AI achieved a significantly higher average score (3.96 ± 0.17) compared with ChatGPT (3.56 ± 0.87). The difference between the two models was statistically significant (P = 0.003), indicating that Gemini AI provided a more consistent and guideline-compliant output. The distribution of expert scores for both models is shown in Figure 3.

Inter-Rater Agreement

Cohen's kappa coefficient was used to evaluate inter-rater reliability. Agreement was excellent for ChatGPT evaluations (κ = 0.94) and moderate for Gemini AI evaluations (κ = 0.66). This apparent discrepancy likely reflects a ceiling effect: the almost unanimous high scores given to Gemini AI responses reduced kappa sensitivity despite minimal actual disagreement.

Observations on Common Errors

ChatGPT's partially or non-compliant responses were often due to vague thresholds (e.g., citing ejection fraction [EF] <50–55% instead of the guideline-defined <55%), incorrect prioritization of treatment options, or omission of specific criteria for surgical decision-making in low-flow states. In contrast, Gemini AI's rare deficiencies involved subtle oversimplifications but seldom contradicted ESC/EACTS recommendations.

Discussion

This study provides a new, structured comparison of two publicly available large language models—ChatGPT and Gemini AI—in the specific and complex clinical setting of AS management. While previous research has evaluated LLMs on general medical examinations or broad clinical scenarios,[5-7] to our knowledge, this is the first study focused exclusively on a high-stakes, guideline-driven cardiovascular condition. This targeted approach enables a detailed assessment of each model's ability to reason through real-world clinical decision-making processes.

Gemini AI demonstrated superior adherence to guidelines, achieving full compliance in 95.0% of responses compared with 72.5% for ChatGPT. Although the overall compliance rates across all categories did not reach statistical significance, the notable difference in the proportion of fully compliant responses between the models may represent a clinically meaningful advantage for Gemini AI. Notably, Gemini AI produced no responses classified as non-compliant or incorrect, whereas ChatGPT generated several partially compliant and some misleading responses. These differences were most evident in complex clinical scenarios, such as low-flow, low-gradient AS or asymptomatic high-risk patients, where knowing how to interpret hemodynamic data and stratify risk is essential. These findings suggest that while both models possess strong factual knowledge, Gemini AI may interpret clinical complexities more reliably. These results are consistent with prior studies showing that newer or more specialized LLMs outperform generalist models in clinical reasoning.[8] Our findings highlight that domain-specific complexity—such as the nuanced decision-making thresholds in AS—can reveal significant performance gaps in AI models not specifically tailored for medical tasks.

Several factors may explain the observed differences. First, Gemini AI may incorporate more current or finely tuned medical training data than ChatGPT-4. Second, Gemini's response algorithms could focus on guideline-based patterns and threshold-specific logic, thereby reducing variability and generalization errors observed in ChatGPT.[9-11] Prior research suggests that "prompt engineering" and "model alignment" strategies have a significant impact on AI performance in clinical settings.[12] Additionally, differences in how each model processes conditional decision trees—a central element in AS management—may explain the discrepancies.

Our findings reinforce the potential of LLMs as adjunctive tools in cardiovascular care, particularly in domains with stringent, evidence-based guidelines. For example, LLMs could assist in standardized case triage, preliminary risk stratification, or continuing medical education. Recent work has also demonstrated the value of LLMs in aligning with cardiology guidelines and supporting structured decision-making workflows.[13] However, the variability noted with ChatGPT underscores the ongoing need for expert oversight. In AS, where therapeutic decisions such as intervention timing critically impact survival, reliance on non-validated AI recommendations could pose safety risks. Although this study assessed performance quantitatively, it did not formally investigate how each model internally constructs its reasoning. Understanding which textual features or decision thresholds influence LLM-generated recommendations is crucial for clinician confidence. Incorporating transparent reasoning mechanisms has been shown to significantly improve user trust and facilitate model adoption in clinical contexts.[14] Future studies should consider integrating explainability frameworks—such as rationale tracing or language-based model introspection—to improve interpretability and transparency.

Given the rapid pace of development in large language models, it is important to interpret our findings as a reflection of model capabilities at a specific point in time (May 2025). Both ChatGPT and Gemini AI are evolving platforms that may undergo substantial changes in performance, reasoning strategies, and guideline adherence in future iterations. This transient nature introduces inherent challenges for reproducibility and long-term clinical reliability. Accordingly, our study should be viewed as an early-stage evaluation rather than a definitive benchmark. These dynamics have been highlighted in recent work on biomedical LLM benchmarks, where inconsistent performance across versions in zero- and few-shot settings underscores the need for ongoing, adaptive benchmarking models rather than static one-time assessments.[15] Future research should focus on developing adaptive validation frameworks that account for version changes and enable continuous performance monitoring over time. The relatively high accuracy of Gemini AI indicates that, with additional medical fine-tuning, LLMs could eventually support—or even partially automate—decision-support tools for managing valvular heart disease. However, current models are still inadequate for unsupervised clinical use, consistent with recent concerns about hallucinations, overconfidence, and factual inaccuracies.[10,16]

Recent evaluations of LLMs on medical licensing examinations have reported overall accuracies ranging from 60% to 80%.[9,10] Our findings show slightly higher compliance rates, likely due to the study's use of tightly structured, guideline-based questions rather than broad knowledge domains. Nevertheless, the drop in ChatGPT's performance for clinical scenarios echoes prior observations: LLMs often excel at knowledge recall but struggle when integration, synthesis, and nuanced judgment are required.[11,12] Building on these observations, it is crucial to emphasize the potential clinical implications of integrating AI into the management of valvular heart disease. With further refinement and external validation, LLMs could help clinicians streamline diagnostic workflows, identify high-risk patients for early intervention, and ensure adherence to evidence-based practices. However, AI outputs should be viewed as complementary rather than definitive, serving to augment, not replace clinical expertise. Collaborative models that combine AI-driven suggestions with physician oversight may ultimately provide the most balanced and safe approach to leveraging these technologies in complex cardiovascular care.

Ongoing developments in LLMs suggest that domain-specific fine-tuning ("medically aligned LLMs") and multi-modal capabilities (e.g., integration of imaging data) will be critical next steps.[4,12] Future research should evaluate LLM performance in real-time clinical simulations, across broader valvular diseases (e.g., mitral regurgitation, tricuspid valve disease), and in diverse clinical settings, including low-resource environments. Ethical considerations, such as explainability, bias minimization, and clinician-AI collaborative workflows, will also need to be addressed.[16]

Study Limitations

This study has several important limitations that warrant consideration. Although expert-based scoring provides a structured framework for evaluation, some degree of subjectivity is inevitable, even with high inter-rater agreement. The study focused exclusively on AS and did not examine model performance in other valvular pathologies such as mitral or tricuspid disease, which limits generalizability. Moreover, both ChatGPT and Gemini AI are rapidly evolving platforms; their performance may vary significantly across different versions, and the present findings reflect only the capabilities of the specific model versions available in May 2025. All interactions were conducted in English, and no assessment was made of model performance in non-English clinical settings or multicultural contexts. Another limitation relates to the artificial nature of the testing environment. The use of isolated, pre-formulated prompts does not fully replicate the dynamic, iterative decision-making processes encountered in real-world clinical practice. In particular, multimodal data inputs—such as echocardiographic images, laboratory values, or structured electronic health records—were not incorporated, potentially underestimating the complexity of actual clinical reasoning. Additionally, the impact of AI-assisted responses on clinical decision-making accuracy, workflow efficiency, or patient outcomes was not assessed. Since both models rely exclusively on textual input, their outputs are highly sensitive to prompt clarity, phrasing, and completeness, raising concerns about reproducibility and context dependence. Lastly, the study did not evaluate how clinicians with varying levels of expertise interpret or act upon AI-generated responses. Human-AI interaction dynamics, cognitive bias, and user trust are all critical factors that could affect the utility, safety, and real-world applicability of such tools. These limitations collectively underscore the importance of cautious interpretation and the continued need for rigorous validation before any clinical deployment of large language models.

Conclusion

This study represents the first structured evaluation directly comparing two LLMs—ChatGPT and Gemini AI—in the context of guideline-driven management of AS. Our findings show that while both models demonstrate substantial factual knowledge, significant variability exists in their clinical reasoning capabilities.

Gemini AI consistently provided more accurate and guideline-compliant responses, whereas ChatGPT exhibited greater variability, particularly in complex clinical scenarios that required nuanced judgment. These results underscore the critical importance of expert validation when employing AI tools in high-stakes, patient-specific decision-making. Although LLMs show promise as adjuncts in medical education and preliminary decision support, they are not yet suitable for independent clinical application, particularly in complex domains such as valvular heart disease. Until such models undergo specialized medical alignment, fine-tuning, and rigorous real-world validation, human expertise remains irreplaceable. Future developments should prioritize enhancing LLM accuracy, minimizing response variability, and improving transparency and interpretability. Ethical deployment frameworks, strong data privacy safeguards, and clinician-centered integration strategies will be essential to safely leverage AI's potential. With continued evolution and responsible implementation, AI tools may ultimately contribute to a more efficient, equitable, and evidence-based cardiovascular care system.

Ethics Committee Approval: This study did not involve human or animal participants, patient data, or identifiable information. Therefore, institutional ethics committee approval was not required.

Informed Consent: Written informed consent was not required for this study.

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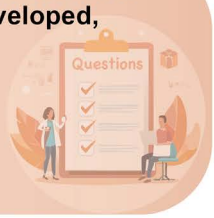
Can Large Language Models Guide Aortic Stenosis Management?

A Comparative Analysis of ChatGPT and Gemini AI

This study compares the performance of two AI models on guideline-based and clinical AS questions.

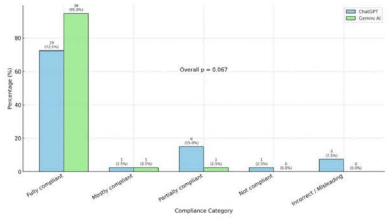
- Forty open-ended AS-related questions were developed, comprising 20 knowledge-based and 20 clinical scenario items based on guidelines.



- ChatGPT and Gemini AI models were queried independently.

- Responses were evaluated by two blinded cardiologists.

Gemini AI achieved a significantly higher mean overall score than ChatGPT (3.96 ± 0.17 vs. 3.56 ± 0.87; P = 0.003).



Distribution of responses across compliance categories for ChatGPT and Gemini AI.

This study represents the first structured evaluation directly comparing two LLMs in the context of guideline-driven management of AS. Gemini AI demonstrated superior accuracy, consistency, and guideline adherence compared to ChatGPT.

*AS: Aortic Stenosis, LLM: Large Language Models

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Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery Syndrome in Adults: A Case-Based Clinical Review

Yetişkinlerde Pulmoner Arterden Anormal Olarak Kaynaklanan Sol Koroner Arter Sendromu: Vaka Temelli Klinik İnceleme

ABSTRACT

This review provides a structured overview of ten published case reports of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) syndrome in adults, with a focus on clinical presentation, diagnostic methods, and treatment approaches. A narrative review was conducted using the PubMed database to identify English-language case reports of adult patients with ALCAPA. Ten cases were selected based on clearly reported clinical features, diagnostic methods, and treatment approach. The most common symptoms included atrial fibrillation, chest pain, dyspnea, and syncope. Surgical correction was performed in four cases, while others were managed conservatively or with medical therapy. Adult-type ALCAPA presents with variable clinical manifestations and requires individualized treatment. Timely diagnosis and appropriate management are crucial for optimal outcomes.

Keywords: ALCAPA syndrome, congenital heart diseases, sudden cardiac death

ÖZET

Bu derleme, yetişkinlerde pulmoner arterden sol koroner arterin anormal kökenli (ALCAPA) sendromuna ilişkin yayınlanmış on olgu sunumunun klinik görünüm, tanı yöntemleri ve tedavi yaklaşımlarına odaklanarak yapılandırılmış bir özetini sunmaktadır. ALCAPA'lı yetişkin hastaların İngilizce olgu sunumlarını belirlemek için PubMed veritabanı kullanılarak anlatımsal bir derleme yapılmıştır. Açıkça bildirilen klinik özellikler, tanı yöntemleri ve tedavi yaklaşımına göre on vaka seçilmiştir. En sık görülen semptomlar atriyal fibrilasyon, göğüs ağrısı, dispne ve senkop idi. Dört vakada cerrahi düzeltme yapılırken, diğer vakalar konservatif veya tıbbi tedavi ile yönetilmiştir. Yetişkin tipi ALCAPA, değişken klinik belirtilerle ortaya çıkar ve bireyselleştirilmiş tedavi gerektirir. Optimal sonuçlar için zamanında tanı ve uygun yönetim çok önemlidir.

Anahtar Kelimeler: ALCAPA sendromu, konjenital kalp hastalıkları, ani kardiyak ölüm

REVIEW
DERLEME

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Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), also known as Bland–White–Garland syndrome, is a rare but potentially life-threatening congenital coronary anomaly. Without timely surgical correction, the condition is associated with high morbidity and mortality, particularly in infancy. ALCAPA is classified into two main types based on the age and nature of presentation: the infant type, which typically manifests within the first few months of life with signs of myocardial ischemia or heart failure, and the adult type, which is less common and may remain undiagnosed until later in life.[1] ALCAPA most commonly presents as an isolated congenital coronary anomaly, although it has occasionally been associated with other structural defects, including tetralogy of Fallot, coarctation of the aorta, ventricular septal defect, and patent ductus arteriosus. The anomaly remains clinically silent during fetal life due to comparable pressures and oxygenation in the great arteries. However, after birth, the progressive decline in pulmonary artery pressure leads to insufficient coronary perfusion, resulting in myocardial ischemia. This cascade may cause left ventricular dysfunction, chamber dilation, and mitral regurgitation, ultimately manifesting as heart failure, arrhythmias, or sudden cardiac death in the absence of timely recognition and

treatment.[2,3] Echocardiography remains the most commonly used initial diagnostic tool for ALCAPA. When findings such as left ventricular dilation and dysfunction, significant mitral regurgitation, abnormal flow patterns across the interventricular septum, and right coronary artery dilatation are present, along with increased echogenicity and thickening of the endocardium, clinicians should extend their differential diagnosis beyond idiopathic endocardial fibroelastosis and idiopathic dilated cardiomyopathy (DCM). Careful assessment of the coronary artery origins is crucial to avoid misdiagnosis. The hallmark echocardiographic sign of ALCAPA is visualization of the left coronary artery arising from the pulmonary artery, with delineation of its origin, size, and course. The presence of reversed flow within the left coronary artery and a well-developed collateral network further support the diagnosis. Owing to its noninvasive nature, repeatability, affordability, and ability to visualize coronary origins, echocardiography is considered indispensable. It enables real-time assessment of hemodynamic status, early detection of subclinical myocardial dysfunction, and reliable postoperative follow-up through evaluation of cardiac size, wall motion, contractility, and strain rate. Nevertheless, digital subtraction angiography (DSA) with coronary angiography (CAG) remains the gold standard for confirming the diagnosis of ALCAPA. In neonates and infants, however, the use of contrast agents is sometimes controversial due to concerns about radiation exposure and potential allergic reactions. Noninvasive modalities such as coronary computed tomography angiography (CCTA) and magnetic resonance angiography (MRA) are increasingly employed. CCTA offers excellent spatial resolution and is particularly useful for visualizing small vessels like the coronaries, although it does not provide information on intravascular flow. MRA, on the other hand, is useful in evaluating postoperative ventricular morphology and function, particularly in suspected myocardial ischemia, although image quality may be affected by elevated heart rates.[4] The 2018 guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) recommend surgical correction of ALCAPA in all patients, regardless of age or symptoms, due to the lifelong risk of myocardial ischemia, ventricular arrhythmias, and sudden cardiac death. Surgical techniques are generally categorized into single- and dual-coronary system repairs. In the past, simple ligation of the anomalous artery—a single-coronary approach—was common, but today it is used only temporarily in critically ill infants to prevent coronary steal and allow clinical stabilization prior to definitive repair. The current surgical objective is to restore a dual coronary circulation. Techniques include direct reimplantation of the anomalous artery into the aorta (coronary button transfer), the Takeuchi procedure (intrapulmonary baffle), subclavian-to-left coronary artery anastomosis, and coronary artery bypass grafting (CABG) using venous or arterial grafts. Cardiac transplantation is reserved for patients with severe left ventricular dysfunction and refractory heart failure. The coronary button technique is preferred in infants because it offers near-physiologic perfusion with low complication rates. In adult patients, direct reimplantation may not be feasible due to the immobility or fragility of the anomalous artery, so the Takeuchi technique or CABG is typically performed. Although surgery remains the standard treatment, medications may be used adjunctively—for example, in elderly patients with high surgical risk, or in infants as preoperative support to improve cardiac function.[5]

ABBREVIATIONS

ACC	American College of Cardiology
ACEI	Angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
AHA	American Heart Association
ALCAPA	Anomalous origin of the left coronary artery from the pulmonary artery
ARBs	Angiotensin II receptor blocker
CABG	Coronary artery bypass grafting
CAG	Coronary angiography
CCTA	Coronary computed tomography angiography
CMR	Cardiac magnetic resonance
CXR	Chest radiography
DCM	Idiopathic dilated cardiomyopathy
DSA	Digital subtraction angiography
ECG	Electrocardiography
ICD	Implantable cardioverter-defibrillator
IMA	Internal mammary artery
LAD	Left anterior descending artery
LAVI	Left atrial volume index
LCA	Left coronary artery
LCx	Left circumflex artery
LMCA	Left main coronary artery
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MDCT	Multi-detector computed tomography
MPI	Stress myocardial perfusion imaging
MR	Mitral regurgitation
MRA	Magnetic resonance angiography
PA	Pulmonary artery
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
ROSC	Return of spontaneous circulation
SVG	Saphenous vein graft

Materials and Methods

A systematic search of the PubMed database was performed in June 2025. The search was restricted to case reports published in English between January 2020 and June 2025, involving adult patients (> 18 years). Pediatric and borderline cases were excluded. The following search terms were used: "ALCAPA syndrome adult" (yielding 19 records) and "Bland-White-Garland syndrome adult" (yielding 14 records). After removal of duplicates (n = 20) and exclusion based on title/abstract (n = 3), ten full-text case reports were assessed for eligibility. Only full-text, freely accessible articles were included. The selection process followed the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and is summarized in the corresponding flow diagram (Figure 1). Additional case reports were identified but excluded from the final analysis due to incomplete data or non-English full text.

Results

Ten case reports of adult patients diagnosed with ALCAPA were included in the analysis. Patient age ranged from 29 to 81 years, and the majority were female (9 out of 10). The extracted data included age, sex, clinical presentation,

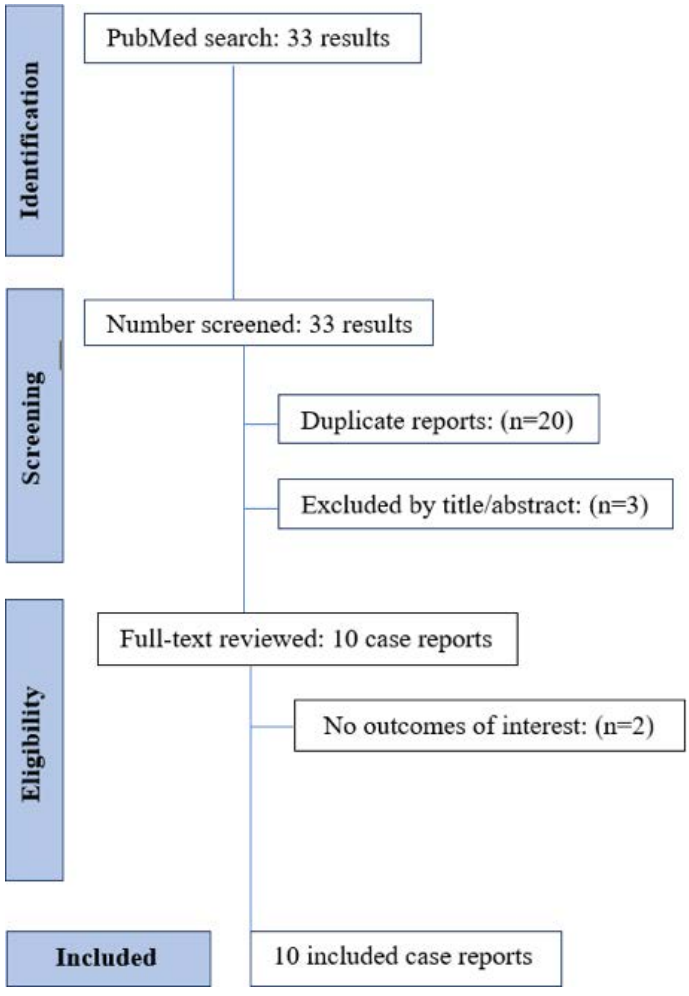

Figure 1. PRISMA flow diagram of study screening and selection.

diagnostic modalities, and treatment strategies. An overview of the key findings is presented in Table 1.[6-15]

The most commonly reported presenting symptoms included atrial fibrillation, chest pain, dyspnea, and syncope. However, a subset of patients remained asymptomatic at the time of diagnosis, with the condition detected incidentally during preoperative assessment or workup for unrelated complaints (Table 1). This highlights the potential for ALCAPA to remain clinically silent until late adulthood. Notably, three of the included cases exhibited acute and severe clinical presentations, namely acute myocardial infarction, sudden cardiac arrest, and acute heart failure, underscoring the potential of ALCAPA to present as a life-threatening emergency in adult patients (Figure 2).

In nearly all cases, transthoracic or transesophageal echocardiography, along with coronary imaging—either computed tomography angiography (CTA) or catheter-based CAG—played a central role in establishing the diagnosis. Additional modalities such as cardiac magnetic resonance imaging (MRI) and stress myocardial perfusion imaging were employed in select cases to assess myocardial viability, presence of ischemia, and the extent of collateral circulation (Figure 3, 4).

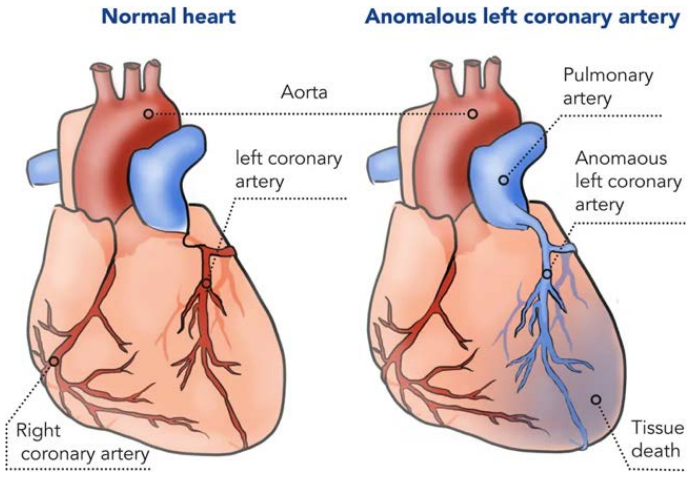

Figure 2. Schematic illustration of a normal heart and anomalous left coronary artery from the pulmonary artery (ALCAPA). Reproduced with permission under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License from Kyorin University.

Therapeutic strategies varied considerably across cases (Table 1). Four patients underwent surgical repair, most commonly direct reimplantation of the anomalous left coronary artery into the aorta, sometimes combined with grafts or concomitant valve procedures, with favorable outcomes and resolution of symptoms. Another four patients were managed conservatively, either due to adequate collateralization, absence of ischemia on stress imaging, or refusal of surgery, and all remained clinically stable on follow-up. One patient underwent percutaneous coronary intervention (PCI) with angioplasty of the left circumflex artery and was discharged in good condition. One patient died before definitive therapy could be performed.

Follow-up durations ranged from one month to three years, with generally favorable outcomes in both surgically and conservatively managed patients.

Where reported, postoperative functional outcomes demonstrated significant improvement in left ventricular function and symptom relief, whereas New York Heart Association classification was inconsistently documented across reports.

These findings underscore the clinical heterogeneity and diagnostic challenges of adult-type ALCAPA. Management must be tailored individually, based not only on symptom burden but also on myocardial viability, coronary anatomy, surgical risk, and patient preferences. Given the potential for sudden cardiac events even in minimally symptomatic individuals, early recognition and appropriate risk stratification remain crucial.

Discussion

ALCAPA is an extremely rare congenital anomaly in adults, typically diagnosed during evaluation for arrhythmia, ischemic symptoms, or incidentally. In ALCAPA, the left coronary artery originates abnormally from the pulmonary artery, resulting in perfusion of the left ventricle with desaturated blood at low pressure. Given the high oxygen demand of the left ventricle, this leads to chronic myocardial ischemia, particularly during exertion. As pulmonary

Table 1. Summary of adult anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) case reports

Author (year)	Age (years)	Sex	Clinical presentation	Diagnosis	Treatment	Follow-up duration	Long-term outcomes	NYHA functional class
Lotman et al. (2020)[6]	76	F	Asymptomatic at presentation; history of palpitations and irregular pulse (AF detected)	ECG, echocardiography, CAG, CCTA	Conservative management	3 years	Good physical condition, no adverse events	Not reported
De Stefano et al. (2024)[7]	76	F	Fever, fatigue, cognitive-motor slowing, hyposthenia of the left hemisoma	ECG, echocardiography, CXR, cranial CT, chest CT, contrast-enhanced CT with ECG	Fatal outcome prior to surgical or medical management	1 month	Death (January 2022)	Not reported
Niu et al. (2022)[8]	64	F	Paroxysmal precordial pain for 10 years, aggravated over 2 days, acute myocardial infarction	ECG, echocardiography, CCTA, aortic angiography, MDCT	Surgical correction recommended but refused; medical therapy initiated	6 months	No significant chest pain during follow-up	Not reported
Prandi et al. (2022)[9]	55	F	Syncope, ventricular fibrillation, sudden cardiac arrest, AF after ROSC	ECG, echocardiography, 24-hour ECG Holter monitoring, head CT, CCTA, cardiac catheterization, MPI, CMR, MRA	Surgical repair with direct LCA reimplantation using Hemashield grafts; ICD placement; medical therapy	3 months	Asymptomatic, no surgical complications, returned to normal activity	Not reported
Rao et al. (2022)[10]	29	F	Dyspnea, orthopnea, edema, weight gain; AF, heart failure	ECG, echocardiography, CXR, cardiac catheterization, CCTA	Conservative management	Not specified (on regular follow-up after discharge)	Stable on medical therapy, maintained sinus rhythm post-cardioversion, no urgent surgery required	Not reported
Alsamman et al. (2021)[11]	38	F	Chest pain, palpitations, diaphoresis during exercise, AF	ECG, echocardiography, CAG, cardiac catheterization, CCTA, head CT	LMCA translocation to aorta; full recovery	Short-term and ongoing tertiary center follow-up	Recovered well, no complications	Not reported
Riaz Gondal et al. (2024)[12]	81	F	Chest pain, progressive mental deterioration, bradycardia, hypotension, complete heart block	ECG, cardiac catheterization	Atropine, transcutaneous and temporary transvenous pacing, percutaneous balloon angioplasty of LCx; discharged with ACS medical therapy	Short-term follow-up until discharge	Discharged stable, no pacing needed after PCI	Not reported
Sandugash Talkhatova et al. (2023).[13]	52	F	Asymptomatic (incidentally detected during routine check-up)	ECG, echocardiography, CAG, CCTA, cardiac catheterization	Conservative management	3 months; planned follow-up every 6 months	Asymptomatic at 3 months, good exercise tolerance, no adverse events	Not reported
Tetsuya Saito et al. (2023).[14]	65	F	Palpitations, mild dyspnea, AF	ECG, echocardiography, CXR, CCTA	Surgical repair (ALCAPA repair, mitral valve repair, Cox-Maze IV, cryoablation, CABG with SVG to LAD)	1 year (regular follow-up described)	Good condition, sinus rhythm, improved LVEF (70%), reduced LAVI, mild MR, no AF recurrence	Not reported
Maaweya Jabareen et al. (2024).[15]	27	M	Shortness of breath that had gradually worsened over the past few months	ECG, echocardiography, CCTA, cardiac catheterization	Conservative management	2 years	Good condition, asymptomatic, no reported adverse events	Not reported

AF, Atrial fibrillation; CAG, Coronary angiography; CCTA, Coronary computed tomography angiography; CMR, Cardiac magnetic resonance; CT, Computed tomography; CXR, Chest radiography; ECG, Electrocardiography; ICD, Implantable cardioverter-defibrillator; LCA, Left coronary artery; MDCT, Multi-detector computed tomography; MPI, Myocardial perfusion imaging; MRA, Magnetic resonance angiography; PCI, Percutaneous coronary intervention.

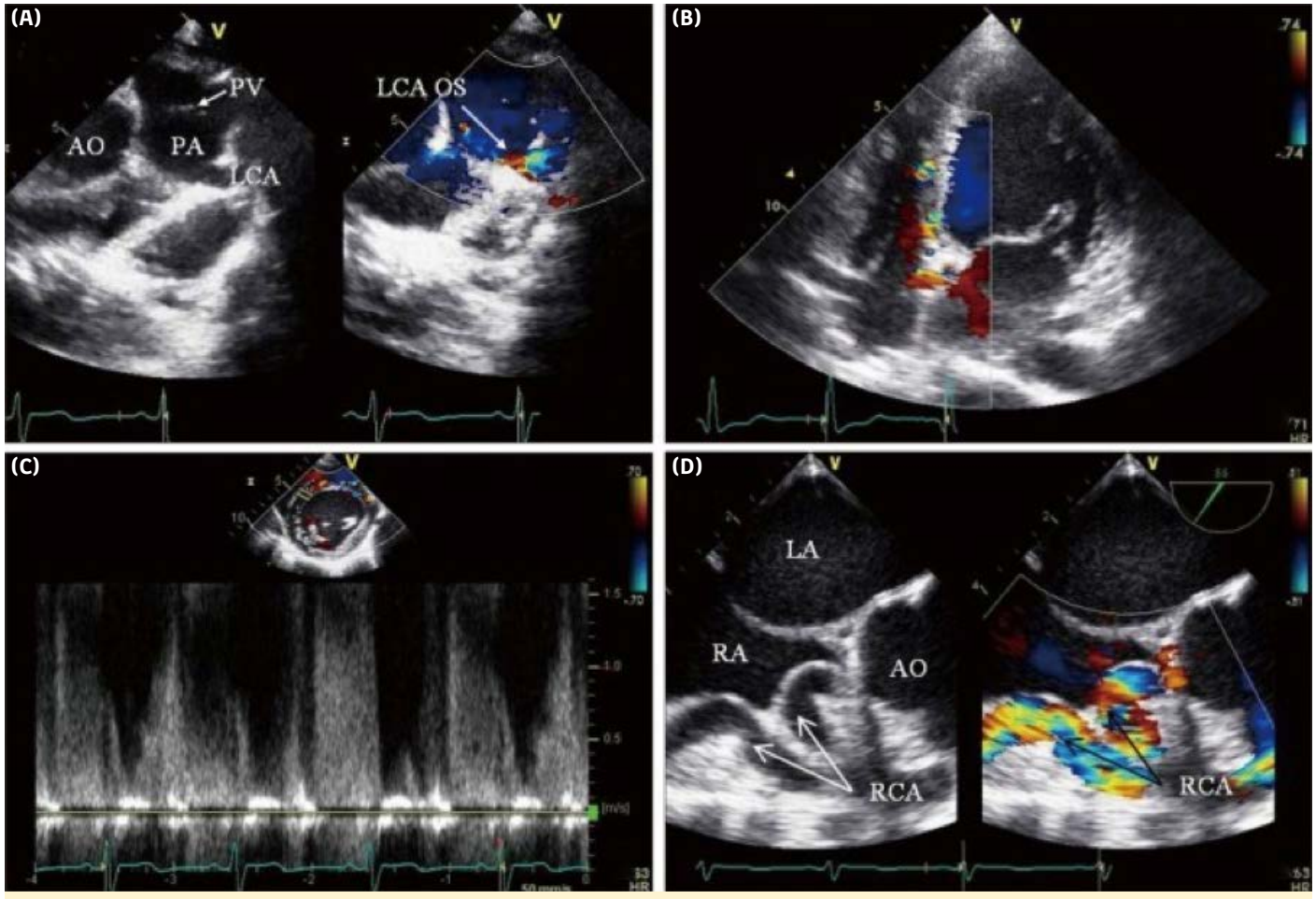

Figure 3. Transthoracic and transesophageal echocardiographic findings in a patient with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). (A) Left coronary artery (LCA) arising from the main pulmonary artery (PA); (B) color Doppler showing abundant septal collateral flow; (C) retrograde filling of the left anterior descending artery (LAD) on Doppler; (D) markedly dilated and tortuous right coronary artery (RCA). Reproduced from Kim BH, Park YW, Hong SP, et al. Anomalous origin of the left coronary artery from the pulmonary artery initially visualized by echocardiography and multidetector computed tomography coronary angiography. *J Cardiovasc Ultrasound*. 2012;20(4):197-200. Under the Creative Commons Attribution Non-Commercial License (CC BY-NC 3.0).

vascular resistance falls after birth, blood flow from the left coronary artery is diverted into the pulmonary artery, a process known as the coronary steal phenomenon, which further aggravates ischemia. Collateral circulation from the right coronary artery to the left coronary artery may partially compensate and allow survival into adulthood, but it rarely provides adequate myocardial perfusion. Consequently, progressive myocardial damage, infarction of the anterolateral left ventricular wall, and congestive heart failure may develop. Even in patients with extensive collaterals, the condition carries a risk of serious complications, including arrhythmias, angina, syncope, and sudden cardiac death. The clinical variability in adult patients with ALCAPA largely depends on the extent and adequacy of collateral circulation between the right and left coronary arteries. Patients with well-developed collaterals may maintain sufficient myocardial perfusion to remain asymptomatic, sometimes for decades. In contrast, when collaterals are insufficient, myocardial ischemia develops, leading to angina, arrhythmias, heart failure, or even sudden cardiac arrest. Additional factors such as left ventricular remodeling, the severity of the coronary steal phenomenon, and the presence of associated valvular dysfunction (e.g., mitral regurgitation secondary to papillary muscle ischemia) further contribute to symptom development. This pathophysiological spectrum explains why some adults are incidentally diagnosed during routine evaluation, while others present with life-threatening complications.[16]

While conventional coronary angiography with digital subtraction angiography has historically been regarded as the gold standard for diagnosing ALCAPA, its invasive nature and associated risks (ionizing radiation, contrast reactions) limit its use, particularly in infants. In contrast, modern multimodal imaging techniques provide complementary strengths (Figure 5):

1. CCTA offers high spatial resolution and direct visualization of the anomalous origin and collateral circulation. Its sensitivity for anatomic definition makes it invaluable for preoperative planning, though it cannot evaluate dynamic intravascular flow.
2. MRA provides functional assessment, including left ventricular morphology, myocardial ischemia, and viability, without radiation exposure. However, image quality can be affected by patient motion and high heart rates.

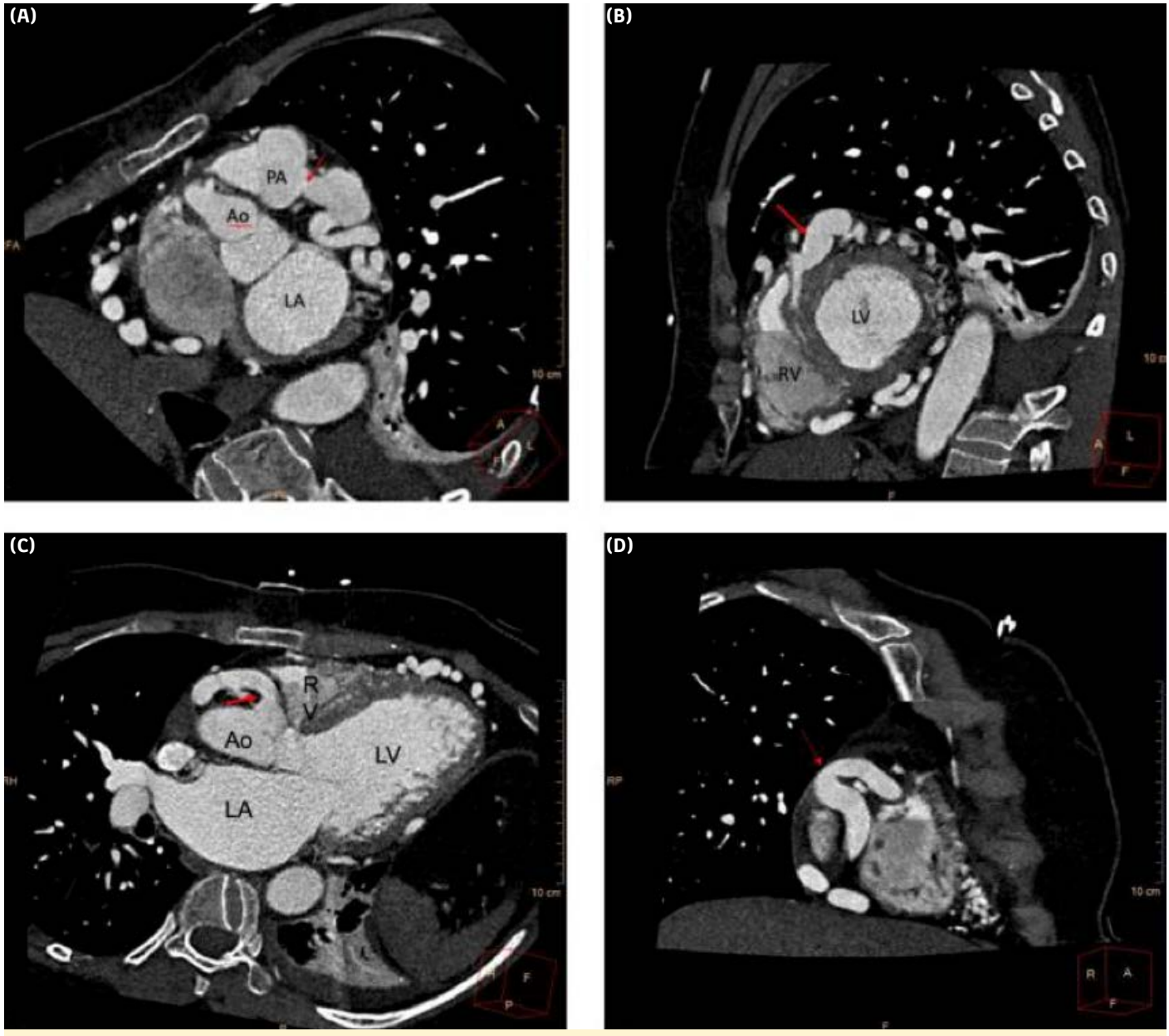

Figure 4. Coronary computed tomography angiography (CCTA) showing: (A) anomalous origin of the left coronary artery (red arrow) from the pulmonary artery (PA); (B) ectatic and tortuous left coronary artery (LCA) (red arrow); (C) normal origin of the right coronary artery (RCA, red arrow) from the right coronary sinus; and (D) diffusely ectatic coronary vasculature. Reproduced with permission from Prandi FR, Zaidi AN, LaRocca G, et al. Sudden Cardiac Arrest in an Adult with Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA): Case Report. *Int J Environ Res Public Health*. 2022;(3):1554. Licensed under Creative Commons Attribution (CC BY) 4.0 International License.

3. Conventional angiography remains superior in evaluating coronary steal physiology and offers the possibility of interventional treatment.

Therefore, combining modalities maximizes diagnostic accuracy: CCTA for structural definition, MRA for functional and viability data, and CAG for hemodynamic evaluation and therapeutic decision-making. This integrated approach improves both preoperative assessment and postoperative follow-up.[17]

The 2018 American Heart Association and American College of Cardiology guidelines recommend surgical correction of ALCAPA in all patients, regardless of age or symptoms, due to the lifelong risk of myocardial ischemia, malignant arrhythmias, and sudden cardiac death. The overarching goal of surgery is to re-establish a dual coronary system and ensure adequate myocardial perfusion. Surgical approaches include:

- Direct reimplantation of the left coronary artery (LCA) into the aorta (coronary button transfer): the gold standard, restoring near-physiologic circulation with excellent long-term outcomes.
- Two-flap technique: a modification of reimplantation used when the LCA is too short to reach the aorta without tension.

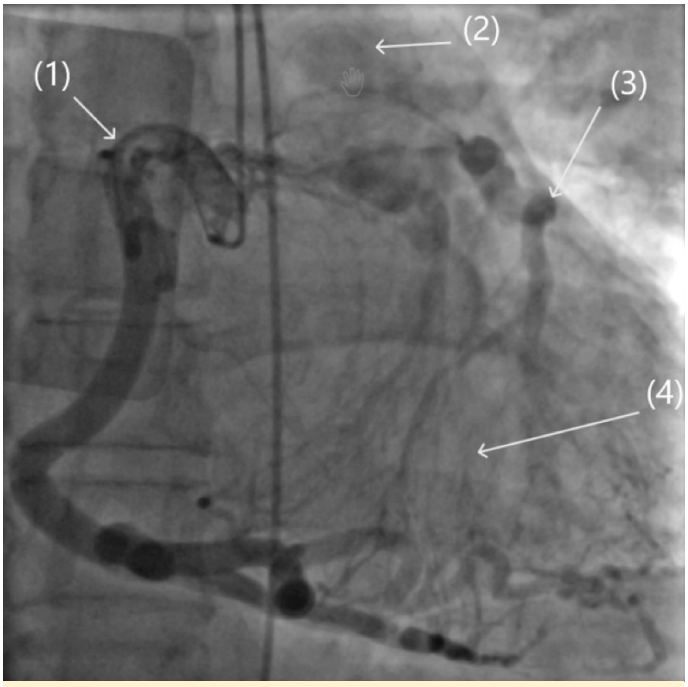

Figure 5. Coronary angiography demonstrating a markedly dilated right coronary artery (1), extensive collateral circulation (4), retrograde filling of the left anterior descending artery (3), and contrast runoff into the pulmonary trunk (2). Reproduced from Urban T, Grundmann S, Klein F, Wengenmayer T, Müller-Peltzer K, Busch HJ. First diagnosis of ALCAPA syndrome in adulthood: a rare cause of cardiac arrest. *Inn Med (Heidelb)*. 2025;66(1):124–128. German, under the terms of the Creative Commons Attribution (CC BY 4.0) license.

- Takeuchi procedure (intrapulmonary baffle repair): creating an aortopulmonary window and baffle between the aorta and anomalous LCA; most common in pediatric patients but also used in adults.
- Coronary artery bypass grafting: using a saphenous vein graft (SVG) or internal mammary artery (IMA), generally reserved for older adults or when reimplantation is technically not feasible.

Adjunctive procedures include mitral valve repair for regurgitation, Cox-Maze IV or cryoablation for atrial fibrillation, and implantable cardioverter-defibrillator (ICD) implantation in patients with malignant arrhythmias. Cardiac transplantation is considered in patients with severe, irreversible left ventricular (LV) dysfunction and refractory heart failure.

Surgical repair is preferred in the vast majority of patients, including asymptomatic individuals, because of the lifelong risk of ischemia and sudden death. Younger and symptomatic patients (angina, arrhythmia, syncope, heart failure) almost invariably require surgery.

Conservative management may be considered in carefully selected adults with extensive collateral circulation, preserved LV function, no demonstrable ischemia on functional testing, or in those with prohibitive surgical risk (e.g., advanced age, significant comorbidities). In such cases, therapy typically includes beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), antiarrhythmic drugs, and anticoagulation/antiplatelet agents. Close clinical and imaging surveillance is mandatory.

PCI has only a limited role, used primarily to treat coexisting obstructive coronary artery disease rather than the anomaly itself.

In summary, corrective surgery remains the gold standard, whereas conservative therapy is reserved for exceptional situations in which the risks of surgery outweigh the potential benefits.[5]

In the largest published review of 151 adult cases of ALCAPA, the mean age at diagnosis was 41 years, with the oldest patient being 83 years old. The majority (66%) presented with angina, dyspnea, palpitations, or fatigue, while 17% presented with malignant arrhythmias, syncope, or sudden cardiac death, and 14% were incidentally diagnosed. Notably, 12% of cases were identified only at autopsy, and most patients underwent surgical correction during their clinical course.[18]

In contrast, the present review of ten adult cases demonstrated an older age range (29–81 years, with a median above that reported in larger cohorts) and a predominance of female patients (9 out of 10). Clinical presentation was heterogeneous, ranging from incidental detection to life-threatening events such as acute myocardial infarction, cardiac arrest, or acute heart failure. While four patients underwent surgical repair and four were managed conservatively, one underwent PCI and one died before definitive treatment. These findings highlight that, despite the limited sample size, the spectrum of presentation and treatment strategies mirrors those of larger series, though with proportionally higher representation of conservatively managed patients.

Importantly, even after surgical repair, adult ALCAPA patients remain at risk for adverse events, including myocardial ischemia, arrhythmias, and sudden cardiac death, underscoring the need for long-term follow-up and cardiac surveillance.

Current literature on adult ALCAPA is limited to isolated case reports and small case series. Prospective data are lacking, and there are no standardized recommendations for long-term surveillance strategies in adult patients. Consequently, the choice between surgical and conservative management is largely individualized, depending on institutional expertise and patient-specific risk profiles. Future multicenter registries and prospective studies are needed to define optimal treatment algorithms and follow-up protocols for this rare but potentially lethal condition.

Clinical Implications

Early recognition of ALCAPA syndrome in adulthood remains crucial, as delayed diagnosis is associated with progressive myocardial ischemia, ventricular dysfunction, and a high risk of sudden cardiac death. Echocardiography, CCTA, and CAG are the key diagnostic modalities that allow timely identification of the anomaly. Once diagnosed, surgical correction should be prioritized, as conservative management carries substantial risks and is rarely appropriate outside of selected asymptomatic cases with preserved ventricular function. Given the lack of standardized long-term follow-up strategies, clinicians should remain vigilant in surveillance of postoperative patients. Future multicenter registries and prospective studies are needed to establish evidence-based recommendations for adult ALCAPA management.

Conclusion

ALCAPA syndrome is a rare but serious congenital coronary anomaly with variable clinical presentations. Long-term follow-up and heightened clinical awareness are essential for timely diagnosis and optimal management.

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Diagnosis of Loeffler Endocarditis in a Patient with a Cerebrovascular Event

Serebrovasküler Olay Yaşayan bir Olguda Loeffler Endokarditi Tanısı

ABSTRACT

Cardiac embolic origin is a significant etiological factor in patients presenting with stroke. Thrombi located in the left ventricle may result from various underlying causes. This case report examines a thrombus located in the left ventricular apex of a 76-year-old female patient and presents a comprehensive analysis of the clinical findings, laboratory results, and multimodality imaging techniques used. Furthermore, this report provides a detailed summary of the diagnostic approach to Loeffler endocarditis, a rare but important differential diagnosis.

Keywords: Echocardiography, endocarditis, stroke

ÖZET

İnme hastalarında kardiyak embolik köken önemli bir etyolojik nedendir. Sol ventrikül yerleşimli trombüsler farklı nedenlere bağlı oluşabilmektedir. Bu olguda 76 yaşında bir kadın hastanın sol ventrikül apeksinde yerleşimli bir trombüse klinik, laboratuvar ve özellikle farklı görüntüleme yöntemleri ışığında yaklaşılmış ve hastamız üzerinden nadir görülen Loeffler endokardit tanısına yaklaşım özetlenmiştir.

Anahtar Kelimeler: Ekokardiyografi, endokardit, inme

CASE REPORT
OLGU SUNUMU

Loeffler endocarditis (LE) is a clinical condition caused by rare hypereosinophilic syndromes characterized by persistent eosinophilic infiltration into various tissues. It was first described by W. Loeffler in 1936.[1] Patients may present with nonspecific symptoms such as fatigue, fever, weight loss, and cough, or may develop severe complications such as stroke, heart failure, or malignant arrhythmias. In this case report, we present a patient diagnosed with LE during an evaluation for stroke.

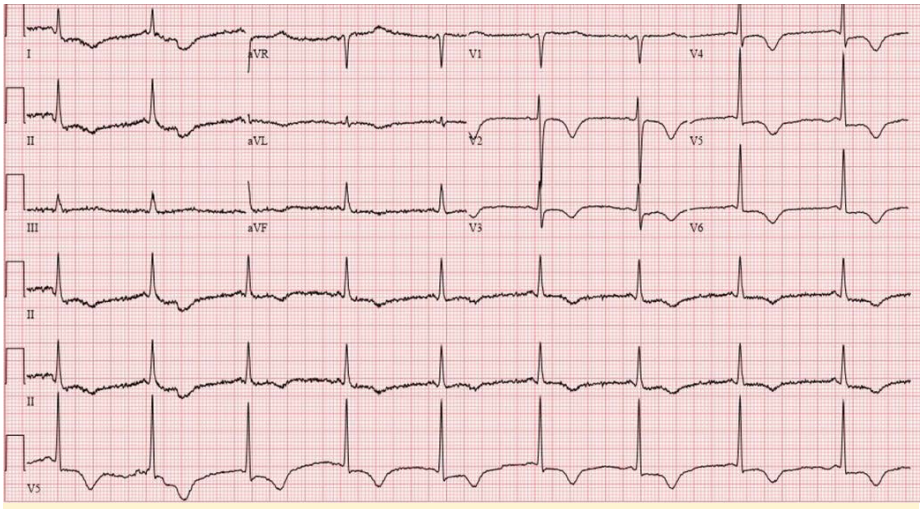

Figure 1. Twelve-lead surface electrocardiography showing diffuse T-wave inversion at admission.

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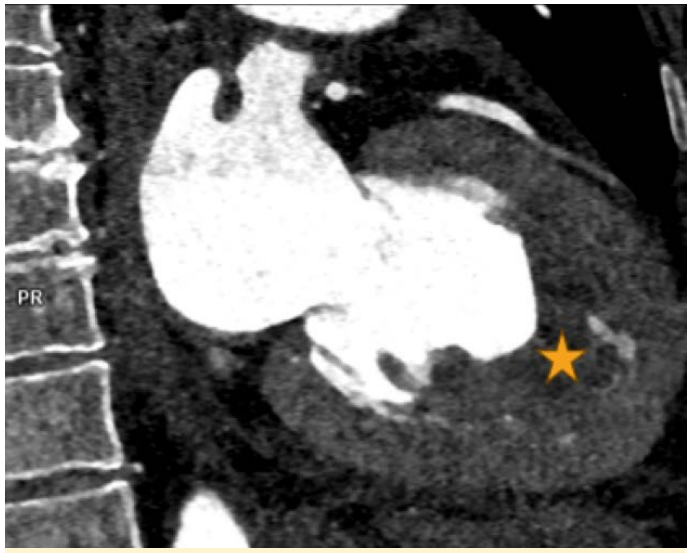

Figure 2. Coronal section image from cardiac computed tomography showing a filling defect (indicated by a star) at the left ventricular apex.

ABBREVIATIONS

AHA	American Heart Association
CCT	Cardiac computed tomography
CMR	Cardiac magnetic resonance imaging
CT	Computed tomography
HCM	Hypertrophic cardiomyopathy
LE	Loeffler endocarditis
LV	Left ventricle
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonist

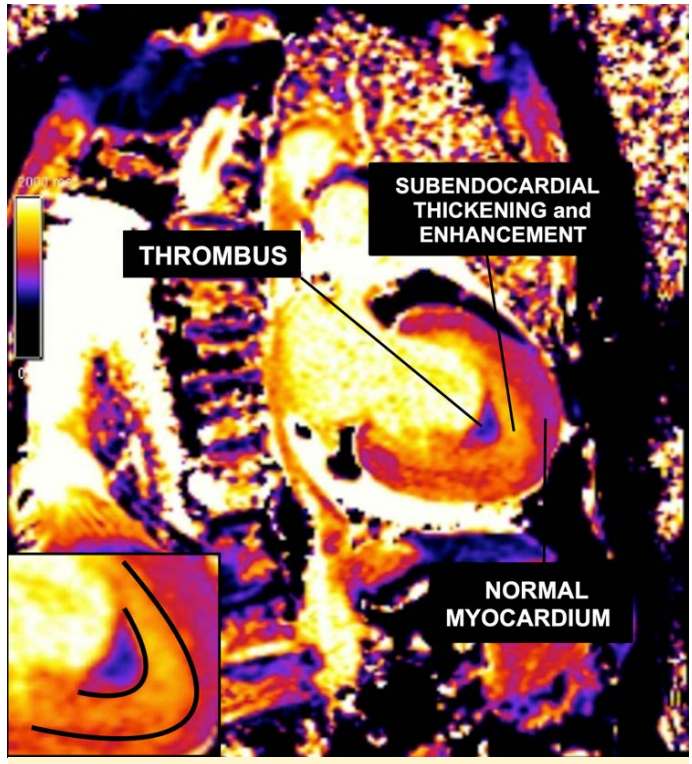

Figure 3. Cardiac magnetic resonance imaging demonstrating the "double V" sign (magnified area at the bottom left) at the ventricular apex. This sign is characterized by a three-layered appearance from the outer to the inner wall, consisting of normal myocardium, a thickened and contrast-enhanced subendocardium, and an overlying thrombus.

Case Report

A 76-year-old female patient with a history of diabetes mellitus, hypertension, and allergic asthma presented with cardiac chest pain. Due to elevated cardiac biomarkers and diffuse T-wave inversions on a 12-lead surface electrocardiogram (Figure 1), coronary angiography was performed. However, no critical stenosis was observed in the coronary arteries.

Following the coronary angiography, the patient complained of weakness in the left lower and upper extremities, along with disorientation. Computed tomography (CT) angiography showed no evidence of an acute intracranial event or major vascular occlusion. However, cranial magnetic resonance imaging revealed acute-to-subacute infarct foci of predominantly embolic origin in the bilateral internal carotid artery border zones of the cerebral and cerebellar cortical-subcortical regions. Intravenous unfractionated heparin therapy was initiated. No rhythm abnormalities were detected during 24-hour Holter monitoring. Transthoracic echocardiography (TTE) revealed an ejection fraction of 45%, with hypokinesia in the apical, apical lateral, and apical septal walls. Additionally, a well-circumscribed iso- to hypoechogenic mass was observed in the apex, appearing as a filling defect (Videos 1-2). Based on echocardiographic findings, apical hypertrophic cardiomyopathy and Takotsubo syndrome were considered in the differential diagnosis. Further TTE findings included a septal e′ of 7 cm/sec, lateral e′ of 10 cm/sec, E/e′ ratio of 21, a left atrial volume index of 41 mL/m^2, and a peak tricuspid regurgitation velocity of 2.7 m/sec, indicative of severe diastolic dysfunction. Subsequently, the patient underwent cardiac computed tomography (CCT), which revealed a lobulated filling defect in the left ventricular apex, along with dyskinesia of the surrounding apical segments (Figure 2). Cardiac magnetic resonance imaging (CMRI) was then performed and demonstrated a characteristic 'double V' sign at the ventricular apex. The sign consisted of a three-layered structure comprising normal myocardium, thickened and contrast-enhanced subendocardium, and an overlying thrombus at the apex (Video 3, Figure 3). The findings were considered suggestive of LE. Given the presence of nasal polyposis, late-onset asthma, and eosinophilia (1881/μL), the patient was referred to the Rheumatology department. To confirm the diagnosis, endomyocardial biopsy and bone marrow aspiration were recommended; however, the patient declined due to the associated risks. Following further evaluation, eosinophilic granulomatosis with polyangiitis was considered, and steroid therapy was initiated. The patient's eosinophil levels normalized during follow-up. The patient was discharged with a Glasgow Coma Scale score of 15, following improvement in left-sided weakness during neurological follow-up. At discharge, treatment included a vitamin K antagonist (VKA), metoprolol, and an angiotensin-converting enzyme inhibitor.

Discussion

The mechanisms underlying stroke in cases of LE are not yet fully understood. However, several contributing factors have been proposed, including embolization from intracardiac thrombi, primary eosinophilic involvement of the central nervous system, and microthromboembolisms resulting from inflammation of the vascular tree within the central nervous system.1 From a cardiological perspective, LE can affect all three layers of the heart: endocardium, myocardium, and pericardium. Consequently, it can lead to valvular heart disease, restrictive cardiomyopathy, and pericarditis.[2] Pathologically, myocardial fibrosis and collagen deposition occur due to fibroblast proliferation, resulting in a stiffer myocardium and ventricular diastolic dysfunction. Additionally, cytokines released from eosinophil granules activate platelets and promote thrombus formation.[3] In this case, we presented an instance of LE causing thrombus formation within the left ventricle (LV). TTE findings initially suggested apical hypertrophic cardiomyopathy (HCM) and Takotsubo syndrome. However, cardiac magnetic resonance imaging (CMR) is the diagnostic tool of choice in cases of uncertainty, as it can demonstrate endocardial involvement and thrombus formation, even in the early stages of the disease.[4] Furthermore, studies have shown that CMR is effective in the differential diagnosis of LV apical HCM and apical masses.[5] LE-related thrombus differs from LV apical thrombus occurring after myocardial infarction, due to the absence of myocardial thinning and transmural contrast enhancement, as well as the the characteristic 'shell-like' structure surrounding the thrombus.[6] Diastolic dysfunction in our patient was another finding supporting the diagnosis of LE.[7] In a previously reported case, a patient presented with dyspnea, orthopnea, and fatigue; TTE revealed diastolic dysfunction and a thrombus at the LV apex. CMR confirmed the thrombus at the LV apex, and bone marrow aspiration showed 25% eosinophils, leading to a diagnosis of LE.[8]

In the present case, multidisciplinary imaging findings supported that the cerebral embolic event originated from the left ventricular apical thrombus. Although cardiac imaging is an essential diagnostic step in clarifying the etiology, endomyocardial biopsy is the gold standard for diagnosing Loeffler endocarditis.[9] Endocardial biopsy and bone marrow aspiration were recommended to the patient; however, she declined due to the associated risks. The high sensitivity and specificity of cardiac magnetic resonance imaging (MRI) make it a valuable tool in distinguishing LE from other types of cardiomyopathies.[10]

A review of the literature indicates that most patients with LE and thrombus are treated with steroids and VKAs as anticoagulant therapy. Approximately 43% of patients demonstrated complete resolution of intracardiac thrombus during follow-up, with no additional thromboembolic events.[3] In the same study, mortality was found to be higher among patients who did not receive anticoagulation therapy and those with concomitant heart failure. Clinical guidelines, including those from the American Heart Association (AHA) and American Stroke Association (ASA) Stroke guidelines, recommend anticoagulant therapy for at least three months in the presence of an intracardiac thrombus.[11-15] Our patient had experienced a stroke, and due to the presence of an intracardiac thrombus, was discharged with VKA therapy. Additionally, the patient responded well to steroid treatment and showed neurological improvement. Although LE is a rare condition, it can be diagnosed through clinical, laboratory, and imaging findings, with CMRI playing a particularly important role in the differential diagnosis. The most critical aspect of managing these patients is addressing the underlying cause of hypereosinophilia, optimizing heart failure treatment according to ejection fraction, and initiating anticoagulant therapy in cases where thrombus is present.[16]

Conclusion

Although rare, Loeffler endocarditis should be considered and suspected by cardiologists, particularly in patients undergoing evaluation for stroke. An elevated eosinophil count may serve as an important laboratory clue. In this case, we presented a diagnostically challenging example of LE and aimed to emphasize the critical role of cardiac imaging in identifying cardiac etiologies in patients presenting with stroke.

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 for the publication of this case report.

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

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

Peer-review: Externally peer-reviewed.

Video 1. Transthoracic echocardiography (apical long-axis view) showing a well-circumscribed, iso- to hypoechogenic mass in the apical region of the left ventricle, appearing as a filling defect, along with mild pericardial effusion.

Video 2. Transthoracic echocardiography (apical four-chamber view) showing a well-circumscribed, iso- to hypoechogenic mass in the apical region of the left ventricle, appearing as a filling defect.

Video 3. Coronal cine image from cardiac magnetic resonance imaging showing left ventricular apical akinesia and an apical thrombus.

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A Rare Anatomical Variant: Cryoballoon Ablation of an Accessory Pulmonary Vein Originating from the Left Atrial Roof – A Case Report

Nadir Bir Anatomik Varyant: Sol Atriyal Roof'tan Kaynaklanan Aksesuar Pulmoner Venin Kriyobalon Ablasyonu: Bir Olgu Sunumu

ABSTRACT

We performed cryoballoon ablation on a 61-year-old female patient with recurrent paroxysmal atrial fibrillation. Pre-procedural contrast-enhanced computed tomography (CT) angiography, used to assess the patient's pulmonary vein anatomy, revealed an accessory pulmonary vein originating from the left atrial roof. Cryoballoon ablation was successfully applied to this accessory vein, which represents a rare anatomical variant not commonly described in the literature.

Keywords: Accessory pulmonary vein, cryoballoon ablation, computed tomography

ÖZET

61 yaşındaki kadın hastaya tekrarlayan paroksismal atriyal fibrilasyon nedeniyle kriyobalon ablasyonu uygulandı. Kriyobalon ablasyon işleminden önce hastanın pulmoner ven anatomisini görüntülemek için çekilen kontrastlı bilgisayarlı tomografi anjiyografide, sol atriyal rooftan çıkan bir aksesuar pulmoner ven saptandı. Literatürde nadir görülen bu aksesuar vene ilk kez kriyobalon ablasyonu başarıyla gerçekleştirildi.

Anahtar Kelimeler: Aksesuar pulmoner ven, kriyobalon ablasyon, bilgisayarlı tomografi anjiyografi

CASE REPORT
OLGU SUNUMU

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Cryoballoon ablation (CA) as a first-line treatment has been shown to be more effective than drug therapy in preventing the recurrence of atrial arrhythmias in patients with paroxysmal atrial fibrillation (PAF).[1] The fundamental principle of CA is the isolation of the pulmonary veins (PVs). In approximately 60% of individuals, four distinct PV ostia are observed. The most common anatomical variations include a left common PV trunk and a right middle PV.[2] Pulmonary vein anatomy is highly variable; therefore, noninvasive imaging of individual PV structures prior to ablation is essential. Contrast-enhanced computed tomography (CT) angiography, magnetic resonance imaging (MRI), and transesophageal echocardiography (TEE) are commonly used for this purpose.[3]

This case report presents the first documented instance in the literature of CA targeting a PV originating from the left atrial roof, an extremely rare anatomical variation in left atrial PV configuration.

Case Report

A 61-year-old female patient was admitted to our hospital with symptoms of palpitations and dyspnea that had started 10 hours earlier. The patient's medical history included chronic hypertension (HT) and a thrombosis in the right leg that had occurred one year prior. The electrocardiogram (ECG) revealed atrial fibrillation (AF). On physical examination, the patient had a heart rate of 136 beats per minute and a blood pressure of 120/70 mmHg. The respiratory rate was 18 breaths per minute, oxygen saturation was 95%, and body temperature was 37°C. Laboratory results, including complete blood count, serum biochemistry, thyroid function tests, and cardiac biomarkers, were

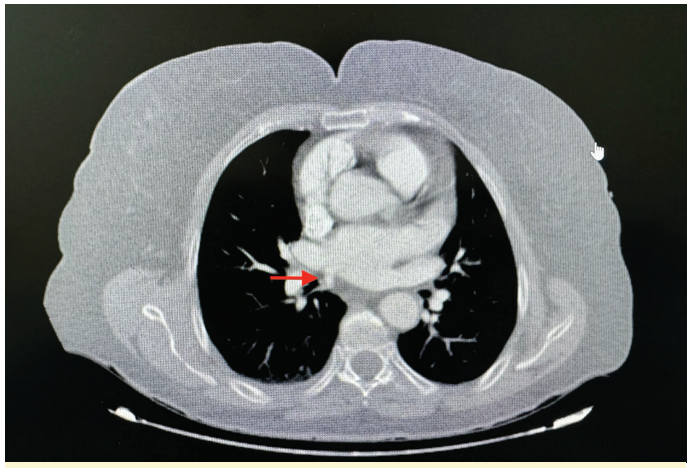

Figure 1. Contrast-enhanced computed tomography angiography image.

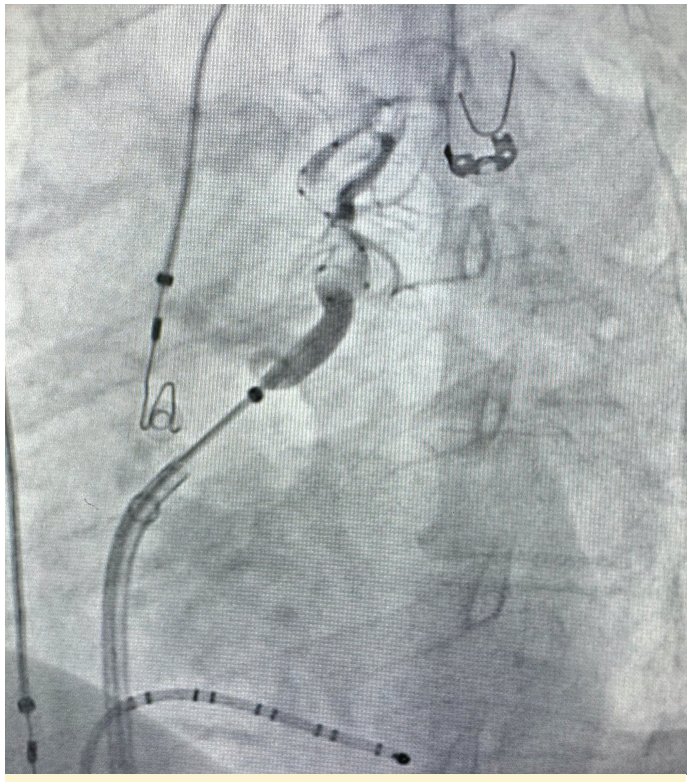

Figure 2. Cryoballoon ablation of the accessory pulmonary vein.

within normal limits. Transthoracic echocardiogram (TTE) showed an ejection fraction (EF) of 60%, normal valve structures, normal cardiac dimensions, and only mild mitral insufficiency. Sinus rhythm was restored with medical cardioversion following a 600 mg loading dose of propafenone. Anticoagulation and beta-blockers were initiated as part of the therapeutic regimen for rate control. Over the subsequent four months, the patient experienced two additional episodes of AF, leading to the decision to proceed with CA for the management of PAF. Pre-procedural contrast-enhanced CT angiography of the left atrium and PVs revealed, in addition to the right upper and lower PVs draining the right lung and the left upper and lower PVs draining the left lung, an accessory PV draining the apical-posterior segment of the right upper lobe. This vein entered the left atrium independently via a 4 mm trunk (Figure 1). After the necessary preparations, the patient was taken to the operating room, and CA was initiated. Cryoballoon ablation (POLARx; Boston Scientific) was performed in the following order: left upper PV, left lower PV, right upper PV, and right lower PV. Subsequently, the accessory vein located on the roof of the left atrium was identified and successfully ablated (Figure 2). Following confirmation of PV occlusion after contrast injection in all PVs, including the accessory PV, CA was performed using a freeze-thaw cycle of 240 seconds, creating a single lesion in each PV and achieving temperatures below -50°C. Post-ablation, it was confirmed that all PV potentials captured by the Achieve mapping catheter were eliminated. Electrical isolation of all PVs was verified using both entry and exit block maneuvers, and the procedure was successfully completed without complications. The patient underwent follow-up evaluations at 1, 3, and 6 months post-procedure. During these visits, ECGs demonstrated sinus rhythm, and the patient reported no symptoms. Continued anticoagulant and beta-blocker therapy, along with regular cardiology follow-up, was recommended.

ABBREVIATIONS

AF	Atrial fibrillation
CT	Computed tomography
ECG	Electrocardiogram
EF	Ejection fraction
HT	Hypertension
MRI	Magnetic resonance imaging
PAF	Paroxysmal atrial fibrillation
PVs	Pulmonary veins
TEE	Transesophageal echocardiography

Conclusion

Given the frequent occurrence of anatomical variations in PV structures, a comprehensive pre-procedural evaluation of PV anatomy may be essential to ensure the efficacy of the cryoballoon ablation procedure.

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 for the publication of relevant medical history, ECGs, procedural images, and laboratory results.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.K., Design – M.İ.H.; Supervision – K.G.; Resource – M.Ö.; Materials – M.Ö.; Data Collection and/or Processing – M.Ö.; Analysis and/or Interpretation – M.İ.H.; Literature Review – K.K.; Writing – K.K.; Critical Review – K.G.

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Conflict of Interest: The authors declare no conflicts of interest relevant to this manuscript.

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A Case of Coronary Artery Rupture Caused by Negative Vessel Remodeling

Negatif Damar Yeniden Şekillenmesinin Neden Olduğu Bir Koroner Arter Rüptürü Olgusu

ABSTRACT

Coronary artery rupture is a rare but potentially fatal complication of coronary procedures. This case report describes a 63-year-old male patient with coronary atherosclerotic heart disease who presented with typical symptoms. However, echocardiography, myocardial injury markers, and electrocardiograms did not indicate an acute myocardial infarction. Coronary angiography (CAG) revealed lesions in two vessels, requiring intervention. During the procedure, a coronary artery rupture occurred. Intravascular ultrasound (IVUS) revealed negative vessel remodeling in the affected arteries. Coronary artery rupture is uncommon in clinical practice and is primarily documented in case reports. Due to the limited information available on its management, early detection and timely treatment are essential.

Keywords: Coronary artery rupture, interventional cardiology, negative vessel remodeling

ÖZET

Koroner arter rüptürü, koroner prosedürlerin nadir ancak potansiyel olarak ölümcül bir komplikasyonudur. Bu olgu sunumunda, tipik semptomlarla başvuran koroner aterosklerotik kalp hastalığı olan 63 yaşında bir erkek hasta bildirilmiştir. Ekokardiyografi, miyokardiyal hasar belirteçleri ve elektrokardiyogramlar akut miyokard enfarktüsünü göstermemiştir. Koroner anjiyografide (KAG), iki damarda müdahale gerektiren lezyonlar saptanmıştır. İşlem sırasında bir koroner arter rüptürü meydana gelmiştir. İntravasküler ultrason (IVUS), etkilenen arterlerde negatif damar yeniden şekillenmesini göstermiştir. Koroner arter rüptürü klinik pratikte nadir görülür ve öncelikle olgu sunumlarında belgelenmiştir. Yönetimi hakkında sınırlı bilgi bulunması nedeniyle erken teşhis ve zamanında tedavi esastır.

Anahtar Kelimeler: Koroner arter rüptürü, girişimsel kardiyoloji, negatif damar yeniden şekillenmesi

CASE REPORT
OLGU SUNUMU

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Coronary artery rupture (CAR) refers to the extravasation of contrast agent or blood from the coronary arteries during or after coronary interventional procedures. The diagnosis of coronary artery rupture is primarily made through angiography and echocardiography. The presence of contrast agent outside the vascular lumen on angiography, or the detection of pericardial effusion on echocardiography, suggests the occurrence of coronary artery rupture. Although rare, it is a potentially fatal complication during coronary artery procedures.[1,2] Studies have reported an increasing incidence, ranging from 0.1% to 0.82%, with a mortality rate between 7% and 19%.[3-6] The incidence of major adverse cardiovascular events (MACE) associated with CAR is also high. Coronary artery rupture most commonly occurs in large vessels, where lesions tend to be complex and the prognosis is often poor. Negative remodeling of the coronary artery is considered one of the key factors contributing to coronary artery rupture. This article presents a case of CAR caused by negative remodeling of the coronary artery.

Case Report

A 63-year-old male patient had a history of hypertension for over five years (peak blood pressure: 180/80 mmHg), managed with Levamlodipine Besylate Tablets. During the same period, he was also diagnosed with diabetes mellitus, which was irregularly treated with metformin and without routine glucose monitoring. Four months prior to admission, he began experiencing chest tightness and pain following

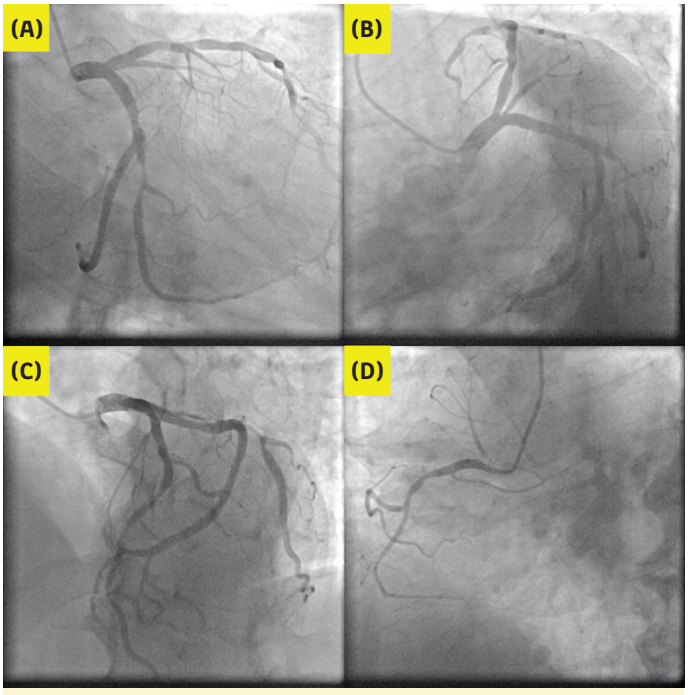

Figure 1. (A–C) Left anterior descending artery (LAD) and left circumflex artery (LCX) coronary angiographic images. (D) Right coronary artery (RCA) coronary angiographic image.

physical activity. The discomfort, localized to the mid-to-lower sternum, lasted for several minutes and was relieved by rest. The episodes were not accompanied by palpitations, dyspnea, or radiating to the shoulders or back. He had previously been admitted to a local county hospital, where he was diagnosed with coronary atherosclerotic heart disease, but no further treatment was provided. His symptoms worsened one week before the current admission. On physical examination, his blood pressure was 152/92 mmHg, and his heart rate was 102 beats per minute. Cardiac auscultation was normal, and there was no peripheral edema. Laboratory and imaging findings are summarized in Table 1.

ABBREVIATIONS

AS%	Area stenosis percentage
BNP	B-type natriuretic peptide
CAG	Coronary angiography
CAR	Coronary artery rupture
CHD	Coronary heart disease
cTn-T	High-sensitivity cardiac troponin-T
ECG	Electrocardiogram
EF	Ejection fraction
IVSD	Interventricular septal thickness at end-diastole
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LAS	Left atrium size
LCX	Left circumflex artery
LDL	Low-density lipoprotein
LM	Left main trunk
LVD	Left ventricular diastolic dimension
MACE	Major adverse cardiovascular events
MLA	Minimal lumen area
PA	Pulmonary artery
PCI	Percutaneous coronary intervention
RAS	Right atrium size
RCA	Right coronary artery
RVD	Right ventricular diastolic dimension

In light of the patient's symptoms, clinical signs, and ancillary test results, coronary heart disease was strongly suspected. The patient was started on secondary prevention medications for coronary heart disease, along with antihypertensive therapy. Coronary angiography was performed, and the subsequent treatment plan was developed based on its findings.

Given the patient's long-standing history of hypertension and diabetes, as well as the poor baseline condition of the blood vessels, an intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) was selected to allow for a clearer and more accurate assessment of the intravascular environment. An extra backup (EBU) 3.5 guide catheter was advanced through the radial artery to the opening of the left coronary artery. The

Table 1. Summary of Laboratory and Imaging Findings

Examination	Result	Normal Reference Value
cTn-T	20.63 ng/L	<14 ng/L
BNP	100 ng/L	<125 ng/L
TC	3.64 mmol/L	<5.2 mmol/L
LDL	2.43 mmol/L	<3.15 mmol/L
Random Blood Glucose	9.3 mmol/L	<11.1 mmol/L
ECG	Sinus tachycardia	
Cardiac Ultrasound	Left heart enlargement; aortic valve irritation; mild mitral regurgitation; mild tricuspid regurgitation.	
CAG	Conclusion: Severe stenosis in the middle and distal segments of the left anterior descending artery and the distal segment of the left circumflex artery.	
	The proximal LAD exhibited 30% stenosis, while the middle and distal segments showed up to 90% stenosis, with a maximum stenosis of 90%, as shown in Figure 1A-C. The distal LCX also demonstrated 90% stenosis (Figure 1A-C). The RCA appeared unremarkable, with no significant stenosis (Figure 1D).	

BNP, B-Type Natriuretic Peptide; CAG, Coronary Angiography; cTn-T, High-Sensitivity Cardiac Troponin-T; ECG, Electrocardiogram; LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery; LDL, Low-Density Lipoprotein; RCA, Right Coronary Artery; TC, Total Cholesterol.

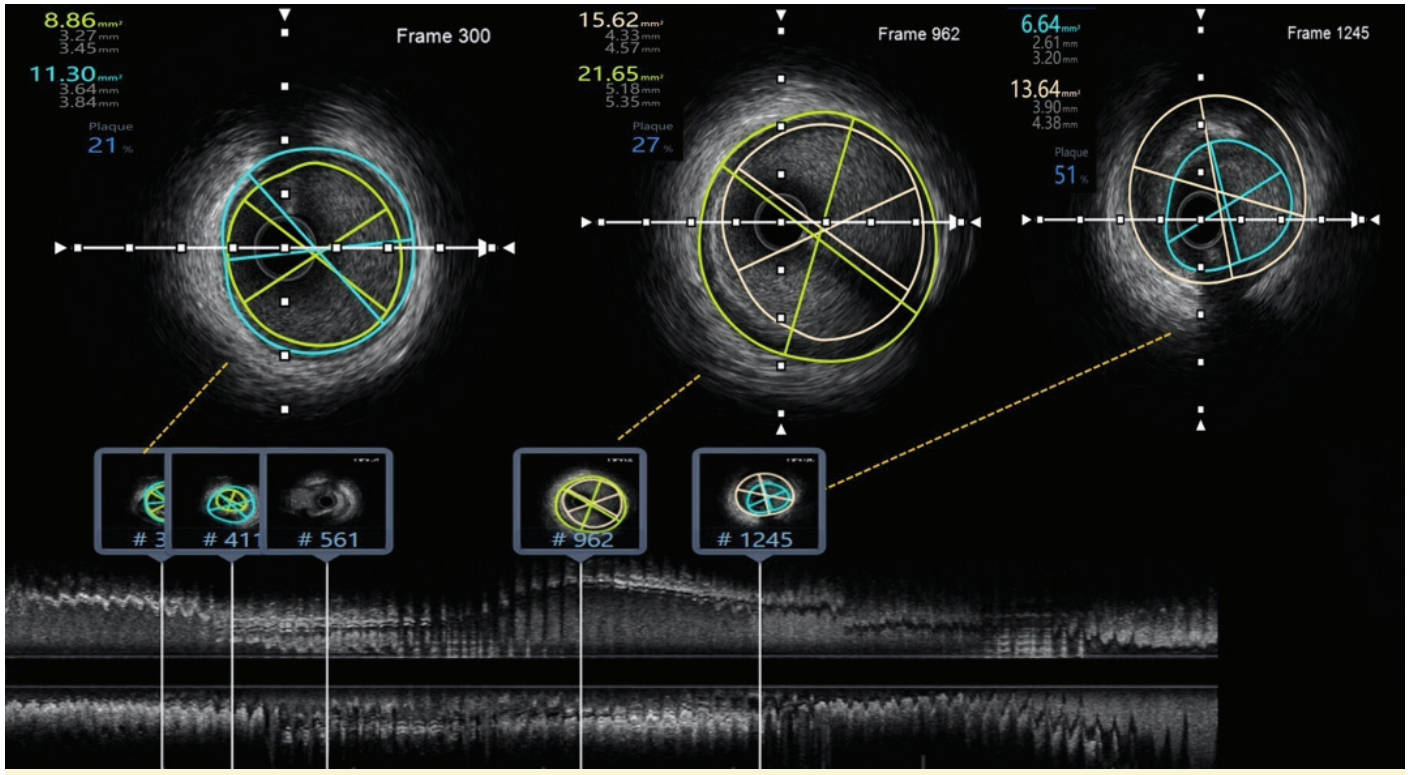

Figure 2. Preoperative examination findings of the left circumflex artery (LCX).

Runthrough guidewire was then navigated through the lesion into the distal left anterior descending (LAD) artery, while the Sion guidewire was directed through the lesion into the distal left circumflex (LCX) artery. Subsequently, IVUS examinations of both the LAD and LCX arteries were performed individually. The IVUS revealed mixed fibrocalcific plaques with distal calcified nodules and negative remodeling in the LCX (minimal lumen area [MLA] 2.38 mm^2; area stenosis [AS%] 77%), and fibrotic plaques in the LAD (MLA 2.99 mm^2, AS% 68%) (Figure 2).

Based on the IVUS findings, interventional treatment was initiated for the LAD lesions. The lesions were first dilated using a 2.5 × 20 mm balloon, followed by the implantation of two drug-eluting stents (3.0 × 29 mm and 3.5 × 29 mm) in the distal and proximal segments of the LAD, respectively. A 3.5 × 15 mm non-compliant balloon was then used to further expand and shape the stents and their junction.

For the LCX lesion, a 3.0 × 10 mm cutting balloon was used for dilation at a pressure of 10–12 atm (Figure 3A). This was followed by the deployment of a 3.5 × 21 mm drug-eluting stent at 10 atm pressure in the LCX lesion (Figure 3B). Angiography revealed contrast extravasation consistent with an Ellis III coronary perforation (red arrow, Figure 3C). To prevent adverse events such as pericardial tamponade, myocardial infarction, or stroke, immediate intervention was undertaken. A 3.5 × 15 mm non-compliant balloon was first used to seal the proximal LCX. Subsequently, an Abbott 3.5 × 19 mm covered stent was implanted at the site of the rupture in the LCX (Figure 3D). However, follow-up angiography showed persistent contrast extravasation. Given the severity of the rupture and the inadequate response to balloon occlusion, a self-made 3.5 × 12 mm covered stent was deployed (Figure 3E). No extravasation of contrast medium was observed upon re-examination with angiography (Figure 3F).

The operation was successful, and the patient reported no discomfort. During the procedure, two drug-eluting stents were implanted in the LAD lesions, while one drug-eluting stent, one covered stent, and one self-made covered stent were implanted in the LCX lesions.

Discussion

The cause of the patient's LCX rupture is believed to be related to negative remodeling of the vessel and the selection of an oversized stent during the procedure, as illustrated in Figure 4. Coronary remodeling refers to the compensatory thickening of coronary lesion segments in response to the progression of coronary artery disease, helping to preserve blood flow in affected arteries.[7] The degree of coronary artery remodeling is quantified by the Remodeling Index (RI), defined as the ratio of the minimal vessel area within the lesion to the average vessel area of the reference segments located proximally and distally to the lesion. When the Remodeling Index is less than 0.95, it is classified as negative vascular remodeling.[8,9] Negative remodeling is typically characterized by severe stenosis, smaller plaque burden, and more stable plaque features. These lesions are often the result of plaque healing and intimal repair following earlier rupture.[10] As coronary atherosclerosis progresses to its later stages, the deposition of calcium salts and intimal fibrosis within plaques further exacerbates luminal narrowing, leading to altered hemodynamics. In a case report of Ellis III coronary artery perforation following PCI by Watabe et al.,[11] a review of IVUS and optical coherence

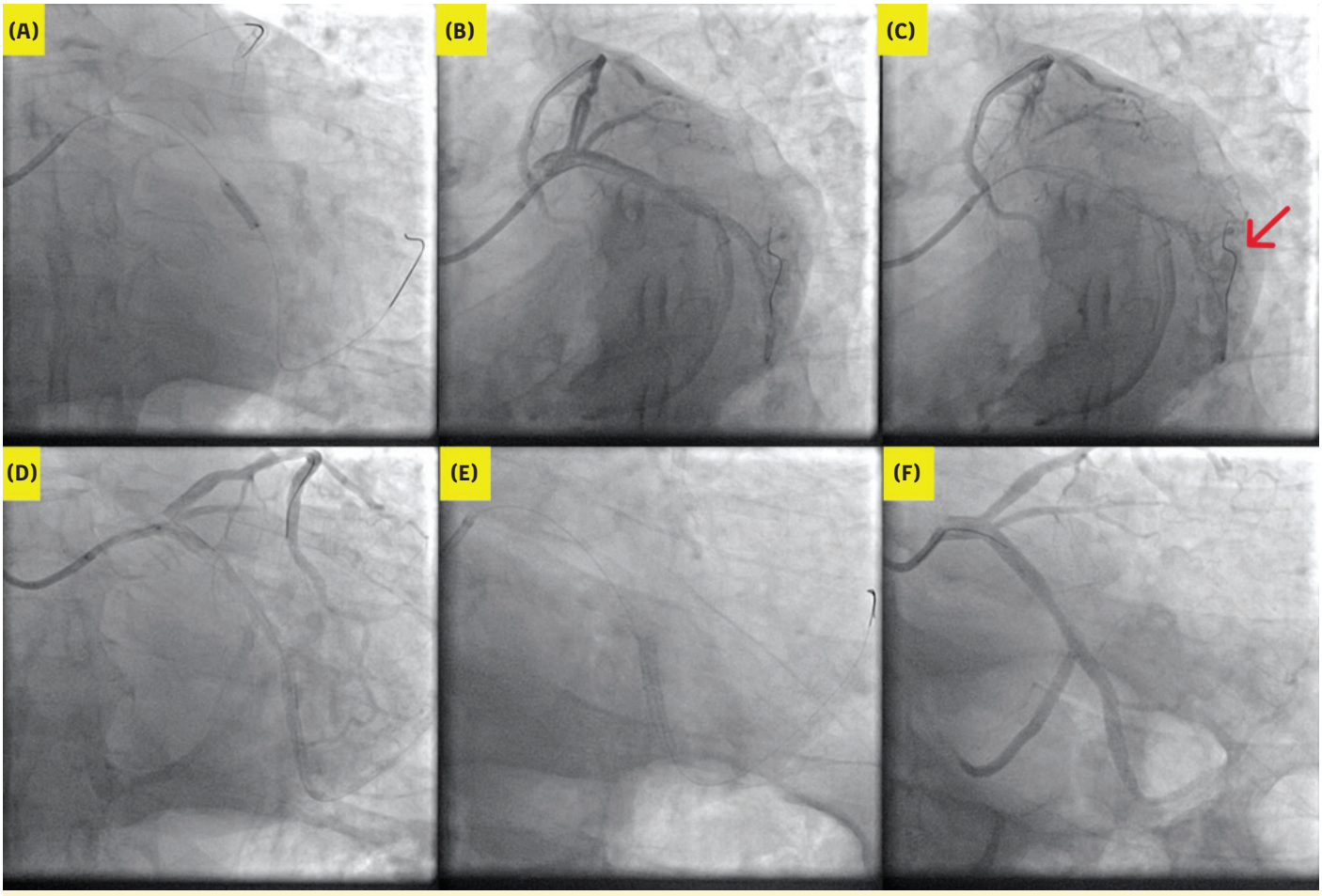

Figure 3. (A) 3.0 × 10 mm cutting balloon dilation in the left circumflex artery (LCX) lesion. (B) Implantation of a 3.5 × 21 mm drug-eluting stent. (C) Contrast medium extravasation at the LCX stent implantation site (red arrow). (D) Implantation of a 3.5 × 19 mm covered stent. (E) Implantation of a 3.5 × 12 mm self-made covered stent. (F) Final angiographic image.

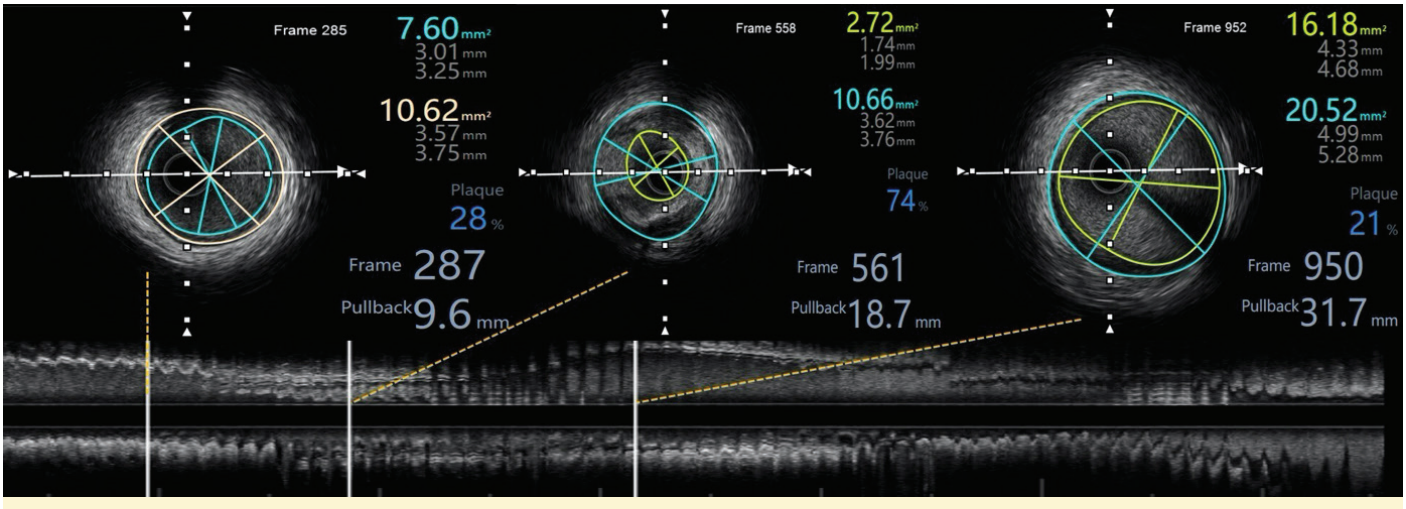

Figure 4. Remodeling Index (RI) = 10.66 / (10.62 + 20.52) = 0.68, which is less than 0.95, indicating negative vascular remodeling.

tomography (OCT) findings revealed focal negative remodeling and eccentric plaques with superficial intimal calcification in the culprit vessels. In another case involving a type III perforation of the mid-left anterior descending coronary artery after stent implantation, OCT imaging demonstrated focal negative remodeling, which may have contributed to the coronary artery rupture.[12] IVUS evidence also highlights the vulnerability of these lesions to external elastic membrane (EEM) and adventitial overstretch during dilation.

Based on these cases, special attention should be given to coronary arteries exhibiting negative remodeling. The symmetry and characteristics of the plaque should be carefully evaluated. Prior to balloon dilation and/or microcatheter advancement, multi-angle projections should be used to confirm that the guidewire is positioned within the lumen. Intravascular imaging should be utilized appropriately to determine vessel size, lesion length, and plaque type. Balloon and stent sizes should be selected with consideration of the external elastic membrane of the remodeled vessel. Reducing pressure and minimizing the use of stents and balloons can help further reduce vascular injury caused by the procedure. In cases of severe CAR, a covered stent is typically effective for sealing perforations in large vessels, especially in arteries with a diameter greater than 2.5 mm and without major branches.[13]

Conclusion

Coronary artery rupture is a potentially fatal complication that requires prompt diagnosis and effective intervention. Medical personnel may consider the impact of negative remodeling in coronary interventional therapy, as illustrated by this case. However, this report represents a single case and is not broadly generalizable. Further research is needed to expand knowledge in this area, enabling more patients with complex coronary heart disease to avoid such complications or receive timely treatment, ultimately improving clinical outcomes.

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 the patient for the publication of this case and the accompanying images.

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

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A Challenging Case of Transvenous Lead Extraction Using a Mechanical Dilator Sheath via Combined Subclavian and Femoral Vein Approaches

Kombine Subklavyen ve Femoral Ven Yaklaşımları ile Mekanik Dilatör Kılıfı Kullanılarak Zorlu Transvenöz Elektrot Çıkarma İşlemi Vakası

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 26-year-old male patient presented to the emergency department with complaints of palpitations followed by fainting. His medical history included aortic coarctation surgery in 1996, mitral valve replacement surgery in 2005, and left pectoral implantable cardioverter-defibrillator (ICD) implantation in 2010 following cardiac arrest. Additionally, a new dual-coil single-chamber ventricular demand pacing implantable cardioverter-defibrillator (VVI-ICD) was implanted in the right pectoral region in 2011, leaving the previously implanted lead in place due to a lead fracture (Figure 1A). He also underwent atrial tachycardia ablation in 2021 and 2022. His vital signs were stable at presentation. Electrocardiography (ECG) showed sinus rhythm (77 bpm). Echocardiography revealed a left ventricular ejection fraction (LVEF) of 35%, normal mechanical mitral valve function, moderate tricuspid regurgitation, and a systolic pulmonary artery pressure (sPAP) of 50 mmHg. ICD interrogation revealed a battery life of 2.94 V (elective replacement indicator [ERI]: 2.63 V), basal rate of 50 bpm, ventricular tachycardia (VT)/ventricular fibrillation (VF) zones at 162/194 bpm, ventricular lead pacing amplitude of 2.0 V, ventricular lead sensing amplitude of 14.8 mV, pacing impedance of 625 ohms, pacing threshold of 1.0 V, and shock impedance of 33/59 ohms. It was observed that the patient had regular tachycardia with altered intracardiac ventricular signal morphology at a rate of 231 bpm. However, despite the ICD detecting the tachycardia and indicating a shock signal, the patient did not receive any therapy (marked as OJ, with a warning for shock impedance of < 20 ohms). Considering the possibility of high-voltage coil insulation breach, implantation of a new ICD system (both lead and battery) was planned after transvenous lead extraction (TLE). Extraction of the first ICD lead, implanted 12 years earlier via the left subclavian vein, was not considered. Upper extremity venography prior to the procedure revealed venous occlusion at the right subclavian vein level. A dual-coil ICD electrode, implanted 11 years ago in the right pectoral region, was released from the battery pocket. Removal was attempted using an EZ1 locking stylet and a 13F TightRail (Spectranetics, Philips) mechanical dilator sheath (Figure 1B). However, this was unsuccessful, and the electrode fractured. The broken proximal end of the electrode was captured. Using a BullDog Lead Extender (Cook Medical), the 13F TightRail mechanical dilator sheath was advanced over the electrode to the tip, but the electrode could not be removed (Figure 1C-E). A 20F short sheath was then placed in the femoral vein. A direct femoral snare-only attempt was performed after capturing the fractured lead tip in the inferior vena cava (IVC). However, due to firm adhesions along the lead body and coil, retrieval could not be completed using the snare alone. The tip of the ICD electrode was then pulled distally from the IVC using a Marinr radiofrequency (RF) ablation catheter and a 20-mm standard GooseNeck snare (Figure 1F-G). The ICD lead was then successfully and uneventfully removed from the femoral tract using a 13F TightRail mechanical dilator sheath over the snare (Figure 1H-J, Supplementary Video 1). Left-sided non-selective (Figure 1K) and selective (Figure 1L) venography revealed venous occlusion at both the subclavian and brachiocephalic vein levels. A new ICD lead was therefore placed via the right subclavian vein in a separate session (Figure 2).

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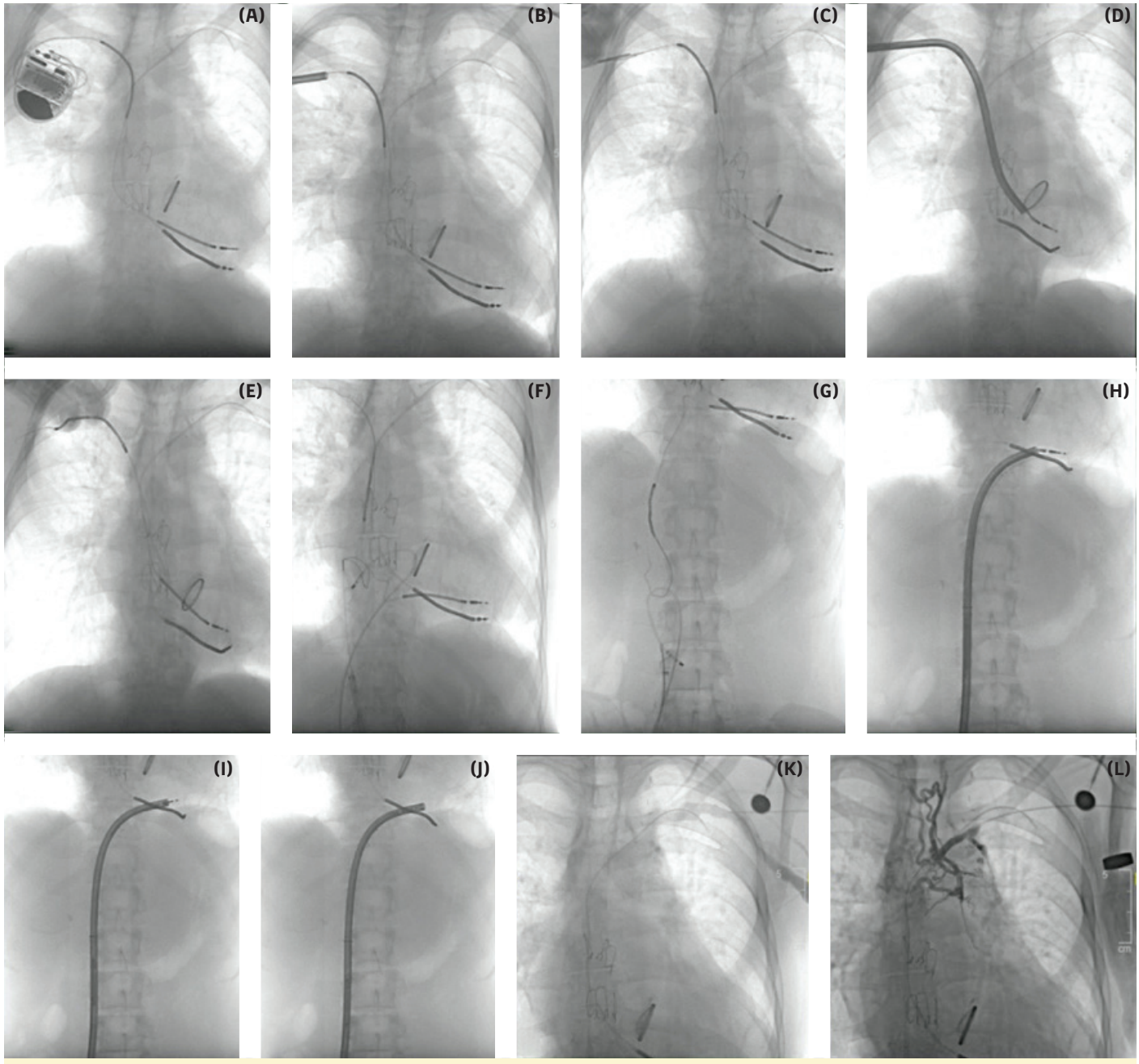

Figure 1. (A) The figure shows a right-sided dual-coil ventricular demand pacing with implantable cardioverter-defibrillator (VVI-ICD) lead and an abandoned left-sided single-coil VVI-ICD lead. (B) A 13F TightRail mechanical dilator sheath was used with the help of an EZ1 locking stylet from the subclavian access. (C-D-E) The lead was fractured, and the BullDog Lead Extender was used as a novel railway for the mechanical dilator sheath. The railway was fractured, and the procedure failed from the subclavian access. (F-G) The tip of the ICD electrode was pulled distally from the inferior vena cava (IVC) using a Marinr radiofrequency (RF) ablation catheter and a 20-mm standard GooseNeck snare. (H-I-J) The ICD lead was then successfully and uneventfully removed from the femoral tract using a 13F TightRail mechanical dilator sheath over the snare. Left-sided non-selective (K) and selective (L) venography also revealed venous occlusion at the subclavian and brachiocephalic vein levels.

Femoral extraction of transvenous leads using snares and large sheaths is a well-documented strategy, often employed when subclavian approaches fail. Previous reports have highlighted the utility of femoral snares in complex cases. However, to our knowledge, advancement of a mechanical dilator sheath via the femoral route to achieve successful extraction has been rarely described. This technique provided a unique alternative when both subclavian dissection and snare-only femoral attempts were unsuccessful. In situations with multiple challenging factors, as in our patient, such as young age, longer dwell time, dual-coil ICD leads, venous occlusion, and prior abandoned leads, the ability to use the TightRail sheath femorally may represent an important addition to the extraction toolkit. Therefore, an additional femoral approach

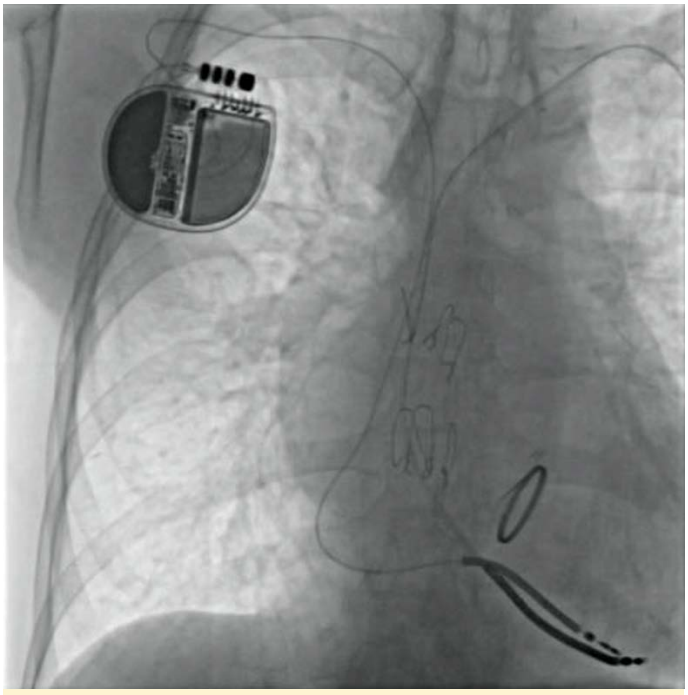

Figure 2. The figure shows the new right-sided implantable cardioverter-defibrillator (ICD) lead implantation.

was required, and we demonstrated that the mechanical dilator sheath can also be used successfully via the femoral approach, not only snares or telescoping sheaths as described in most previous reports. We propose that the success of this approach is not solely due to the greater exerted force, but rather to the altered traction vector achieved by the femoral route, which provides more favorable alignment along the lead body and reduces counterforces at adhesion sites. This vector advantage, combined with the sheath's ability to dissect fibrotic adhesions, facilitated complete removal.

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

Informed Consent: Written and verbal informed consent was obtained from the patient.

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: This article did not utilize artificial intelligence (AI)-assisted technologies.

Author Contributions: Concept – U.C., C.M., A.H.A., E.B.K., K.A.; Design – U.C., C.M., A.H.A., E.B.K., K.A.; Supervision – U.C., A.H.A., E.B.K., K.A.; Data Collection and/or Processing – U.C., C.M., A.H.A., E.B.K., K.A.; Analysis and/or Interpretation – U.C., C.M., A.H.A., E.B.K., K.A.; Literature Review – U.C., C.M., A.H.A.; Writing – U.C., C.M.; Critical Review – U.C., C.M., A.H.A., E.B.K., K.A.

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Video 1. The video displays all details of the transvenous lead extraction (TLE) procedure.

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The Incremental Diagnostic Value of Computed Tomography Attenuation in the Differential Diagnosis of Malignant Pericardial Effusion: A Retrospective Observational Study

Bilgisayarlı Tomografi Attenüasyonunun Malign Perikardiyal Efüzyonun Ayırıcı Tanısındaki Artımlı Tanısal Değeri: Retrospektif Gözlemsel Bir Çalışma

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the valuable study by İnan et al.,[1] published in the *Archives of Turkish Society of Cardiology,* which investigated the value of computed tomography (CT) attenuation in the differential diagnosis of malignant pericardial effusion (MPE). The authors deserve commendation for addressing a topic of high clinical importance. However, I would like to draw attention to certain methodological limitations underlying the use of CT attenuation as a standalone biomarker.

The main finding of the study is that CT attenuation is an independent predictor of MPE.[1] However, the most significant weakness of this biomarker is the absence of a universally accepted Hounsfield Unit (HU) threshold in the literature. The proposed cutoff value of 16.45 HU by İnan et al.[1] conflicts with other studies. For instance, one study reported a much lower threshold of 4.7 HU for exudative pericardial effusions.[2] This inconsistency, combined with technical variability arising from different CT scanners and protocols, severely limits the generalizability of a single HU value.[3] Furthermore, the study's retrospective design and the selected patient population from a tertiary care center may have artificially inflated the diagnostic accuracy of the results.

The most critical diagnostic challenge is distinguishing MPE from non-malignant effusions in the "gray zone," which can exhibit similarly high attenuation values, such as tuberculous or hemorrhagic pericarditis. It has been demonstrated that HU values in this "gray zone" overlap significantly, weakening the standalone discriminatory power of attenuation.[4]

I believe the future of MPE diagnosis lies in the integration of a multiparametric approach, moving beyond reliance on a single parameter. Instead of a crude measure like the mean HU value, more sophisticated models are needed, such as:

1. Advanced Imaging Analysis: Radiomics and texture analysis offer superior potential for distinguishing malignant effusions by capturing their intrinsic heterogeneity, differentiating them from inflammatory effusions, which may have similar attenuation values but are more homogeneous.
2. Liquid Biomarkers and Pathology: Given the known limitations of cytology, methods such as immunohistochemistry (IHC) are crucial for confirming the malignant origin of atypical cells in pericardial fluid and determining their cell lineage.[5]

In conclusion, while the study by İnan et al.[1] has initiated an important discussion, I argue that the use of CT attenuation, in its current state, is premature for routine clinical implementation. Progress in this field will be achieved through multiparametric studies that are prospectively designed, standardized, and integrate radiomics with advanced pathological analyses.

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Reply to the Letter to the Editor: "Incremental Diagnostic Value of Computed Tomography Attenuation in Differentiating Malignant Pericardial Effusion"

Editöre Mektuba Yanıt: "Bilgisayarlı Tomografi Attenüasyonunun Malign Perikardiyal Efüzyonun Ayırıcı Tanısındaki Artımlı Tanısal Değeri: Retrospektif Gözlemsel Bir Çalışma"

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We would like to thank the authors for their interest in our study and for their valuable contributions.[1] We appreciate the opportunity to further clarify certain methodological aspects and elaborate on the clinical implications of our findings.

Firstly, as the authors have also indicated, a universally accepted Hounsfield Unit (HU) threshold for differentiating malignant pericardial effusions has not yet been established in the literature. The cut-off value of 16.45 HU identified in this study was derived not only through ROC analysis but also through evaluations based on cytologically or histopathologically confirmed cases. Thus, it was specifically tailored to our dedicated patient population. Throughout the imaging protocol, standard CT parameters were used, and circular region-of-interest (ROI) measurements were taken from three distinct anatomical levels to minimize interobserver variability. In studies such as that of Çetin et al.,[2] which reported a lower HU threshold, the focus was on distinguishing between exudative and transudative effusions. In contrast, the primary aim of our study was to differentiate between malignant and non-malignant effusions—a more complex area of clinical practice. Therefore, a wider distribution and greater overlap in HU values is to be expected. Indeed, our study showed greater methodological similarity to that of Nakamura et al.,[3] particularly in terms of CT measurement techniques and the classification of patients based on the presence or absence of malignancy. This similarity may explain why the threshold value we identified is more consistent with their results. Moreover, unlike other studies that classified patients solely based on biochemical findings, our study employed cytological diagnosis for classification, and the HU cut-off was established accordingly. This approach enhanced the diagnostic reliability of our model. Although concerns regarding the use of different CT scanners and protocols are valid, we remain hopeful that these issues—similar to those encountered in differentiating pannus from thrombus in prosthetic heart valves or in assessing calcium scores—can be overcome through future multicenter prospective studies.[4] Nevertheless, as we have elaborated in the "Limitations" section of our study, technical differences in imaging parameters, the inherent sensitivity limitations of cytological analysis of pericardial fluid, and the biochemical variability arising from different underlying etiologies of effusion are all factors that may inevitably affect the generalizability of the HU cut-off value we proposed and should be taken into account when interpreting the results.

Secondly, we are aware of the limitations inherent in the retrospective and single-center design of our study, and we have explicitly acknowledged these in the limitations section. However, our study reflects real-world clinical practice in a tertiary referral center with a high prevalence of advanced-stage malignancy. The high diagnostic performance of CT attenuation observed in our findings may reflect the characteristics

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of this particular patient population. We believe that the findings of our study should be interpreted not as universally applicable values but rather as preliminary data that provide a foundation for future multicenter prospective investigations.

Thirdly, non-malignant effusions, such as tuberculosis or hemorrhagic effusions, were another significant issue in this patient group. These effusions may present with high HU values. In our cohort, the prevalence of tuberculosis (3%) and hemorrhagic effusion was low, and HU values in these cases did not exceed 20 HU. Furthermore, CT attenuation was not evaluated in isolation in our analysis. Rather, it was incorporated into a comprehensive multiparametric model (Model 2), which demonstrated significantly superior diagnostic performance compared to the model based solely on clinical and laboratory parameters (Model 1).

Fourthly, the studies and emerging data on the potential applications of advanced techniques such as radiomics, texture analysis, and immunohistochemistry are both promising and exciting.[5] These approaches indeed offer promise in improving diagnostic sensitivity and specificity for MPE. However, their current implementation in clinical practice is limited by cost, accessibility, and technical requirements. In the future, such methods may prove transformative for this patient population. The main contribution of our study lies in proposing HU measurement as a simple, accessible, and reproducible parameter that can be readily integrated into routine diagnostic workflows until more advanced technologies become widely available.

In conclusion, it is gratifying that this academic contribution has laid the groundwork for scientific debate and encouraged research in the field. While we agree that CT attenuation should not be considered a standalone diagnostic tool, our findings indicate that it offers significant incremental value when incorporated into multiparametric diagnostic models. We believe that future prospective studies integrating radiomics and molecular biomarkers will further refine diagnostic accuracy and advance the field of pericardial disease evaluation.

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Revisiting Iron Deficiency in Heart Failure: The Prognostic Value of Type 1 Iron Deficiency

Kalp Yetmezliğinde Demir Eksikliğini Yeniden Ele Almak: Tip 1 Demir Eksikliğinin Prognostik Değeri

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the article by Çolluoğlu et al.,[1] titled "*Beyond the Guidelines: The Critical Role of Type 1 Iron Deficiency in Predicting Mortality in Patients with Heart Failure*," published in the April 2025 issue of the *Archives of the Turkish Society of Cardiology*. The authors provide compelling evidence that Type 1 iron deficiency (ID), defined as transferrin saturation (TSAT) ≤ 15–16% with anemia, is an independent predictor of one-year all-cause mortality in patients with heart failure (HF), unlike Type 2 or Type 3 ID or guideline-defined ID. This study highlights the need to refine ID classification to better identify high-risk HF patients.

The findings challenge the reliance on guideline-defined ID criteria, which primarily focus on ferritin and TSAT levels extrapolated from non-HF populations.[2] The higher mortality rate in Type 1 ID patients (38.3%) compared to those with Type 2 or Type 3 ID (22.7%) or guideline-defined ID (26.0%) underscores the prognostic value of this novel classification. We agree that Type 1 ID, reflecting reduced systemic iron availability, may better capture the iron demands of cardiomyocytes, as supported by the significant hazard ratios in both unadjusted (hazard ratio [HR]: 2.289, $P < 0.001$) and adjusted (HR: 1.543, $P = 0.020$) Cox regression analyses.[1]

However, I would like to raise a point for discussion. The study notes that patients with Type 1 ID had higher B-type natriuretic peptide (BNP) levels and lower estimated glomerular filtration rate (eGFR), suggesting more severe HF.[1] Could the increased mortality risk associated with Type 1 ID partly reflect an advanced disease state rather than ID alone? Including New York Heart Association (NYHA) class data, as acknowledged in the study's limitations, could have clarified this relationship.[3] Additionally, exploring hepcidin levels, which mediate functional ID by sequestering iron in HF, could further validate the mechanistic pathways proposed by Weber et al.[4,5] The absence of NYHA functional class data in the study by Çolluoğlu et al.[1] limits the ability to fully discern whether the elevated mortality risk in Type 1 ID patients is solely attributable to ID or reflects more advanced heart failure. Given that higher NYHA classes (III–IV) are associated with worse prognosis, their inclusion could have clarified whether the observed 38.3% mortality rate in Type 1 ID patients was partly driven by greater disease severity, as suggested by their higher BNP levels and lower eGFR. Incorporating NYHA class data in future studies could enhance the precision of risk stratification and strengthen the prognostic specificity of Type 1 ID in HF.

I commend the authors for their rigorous methodology and for emphasizing the potential of intravenous iron supplementation as a therapeutic strategy. Their findings advocate for revising ID diagnostic criteria in HF to improve risk stratification and patient outcomes. I look forward to future studies validating these results in larger, multicenter cohorts, and I believe these considerations may further strengthen future research on this topic.

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The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death

Ani Kardiyak Ölüm Riski Düşük Hipertrofik Kardiyomiyopati Hastalarında Uzun Vadeli Mortalite Belirleyicileri

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with interest the recent article by Kalenderoğlu et al.,[1] entitled Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death. I would like to congratulate the authors on addressing an important and under-researched clinical issue by investigating long-term mortality predictors in patients with hypertrophic cardiomyopathy (HCM) who are considered to be at low risk according to current guidelines.

Identifying advanced age, cerebrovascular accident, and elevated neutrophil count as independent predictors of long-term mortality in patients with an HCM Risk-sudden cardiac death (SCD) score of less than 4% highlights the limitations of the HCM Risk-SCD model. This study emphasizes the need to integrate additional clinical and laboratory parameters into HCM risk models, especially for patients with an HCM Risk-SCD score below 4%.

However, I would like to respectfully offer a few points for your consideration:

As the primary endpoint was all-cause mortality, the results would have been more clearly interpreted if a competing risk analysis had distinguished between cardiovascular and non-cardiovascular causes of death. Given the advanced average age of the study population, such an analysis would clarify whether the identified predictors reflect cardiac-specific risk or systemic vulnerability in general. Additionally, 34% of the study population had coronary artery disease and 19% had undergone revascularization, both of which increase the risk of sudden and non-sudden cardiac death independent of the underlying disease. It is therefore difficult to attribute the increased all-cause mortality risk solely to HCM without a control group. Furthermore, a comparison between patients who experienced long-term mortality and those who survived could add valuable data for the study. An event-based subgroup analysis could provide a clearer understanding of which variables truly differentiate high-risk individuals within this ostensibly low-risk group.

While identifying neutrophil count as an independent risk factor, the reported median neutrophil values across the three groups were within or only slightly above the upper limit of normal. As neutrophil count is a non-specific inflammatory marker, it would be valuable to know whether potential confounders such as subclinical infection, smoking status, or chronic inflammatory conditions were considered or adjusted for in the analysis. Furthermore, in a disease in which chronic low-grade inflammation plays a pathophysiological role, including additional inflammatory markers such as C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR) would have provided a more comprehensive assessment of the inflammatory burden and its prognostic significance. Incorporating cardiac magnetic resonance imaging (MRI) data, such as myocardial fibrosis quantification and late gadolinium enhancement, would also likely provide additional prognostic information in this population. Future studies investigating the added value of cardiac magnetic resonance-derived (CMR-derived) fibrosis burden in patients with a low HCM Risk-SCD score could substantially improve long-term risk stratification.

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The prevalence of atrial fibrillation (AF) in the study cohort was also substantial, ranging from 20% to 32% across tertiles. Similarly, coronary artery disease (CAD) was present in approximately one-third of the population. Both conditions are well established as risk factors for adverse outcomes in hypertrophic cardiomyopathy, including thromboembolic events, heart failure, and mortality.[2-4] However, neither AF nor CAD was included or reported in the univariable or multivariable analyses presented in Table 3. Given their known prognostic importance, particularly in an older HCM population, this information would meaningfully enhance the interpretation of the study's findings.

As the study is retrospective and single-center, its nature may limit the generalizability of the results to different populations. To increase the validity and reliability of the findings, prospective studies should include patient groups from different geographic regions and with different clinical characteristics.

In conclusion, Kalenderoğlu et al. have made a meaningful contribution to our understanding of long-term risk in patients with HCM who have low HCM Risk-SCD scores. I once again congratulate the authors and believe that addressing these points would further enhance the clinical applicability and robustness of their findings.

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Commentary on 'The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death': A Call for Multidimensional Risk Stratification

'Ani Kalp Ölümü Riski Düşük Hipertrofik Kardiyomiyopati Hastalarında Uzun Dönemli Ölüm Tahmin Edicileri' Hakkında Yorum: Çok Boyutlu Risk Sınıflandırması Çağrısı

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the recent publication by Kalenderoğlu et al.,[1] which provides crucial insights into the prognostic landscape of hypertrophic cardiomyopathy (HCM), specifically among patients classified as low risk for sudden cardiac death (SCD) based on HCM Risk-SCD scores. Importantly, we recognize that the primary endpoint of the study was all-cause mortality, not SCD itself; thus, any extrapolation to SCD risk modeling must be viewed as hypothesis-generating rather than definitive. Their study challenges the long-held clinical notion that low-risk HCM patients represent a uniformly benign population and highlights the need for refined risk stratification.

The authors identified advanced age, history of cerebrovascular accident, and elevated neutrophil count as independent predictors of long-term mortality, despite a baseline HCM Risk-SCD score < 4%. While neutrophil count reached statistical significance in multivariable analysis, the tertile-based comparisons showed no significant difference (P = 0.129). This discrepancy suggests that neutrophil count may exert its prognostic effect as a continuous variable, only becoming apparent after adjustment for confounders. Such nuances are critical for interpreting the role of inflammation in HCM.

We also emphasize that elevated neutrophil counts can arise from secondary causes such as acute infection, corticosteroid use, or hematologic disorders. Without systematically controlling for these factors, integration of neutrophil count into clinical risk scores may face challenges in translation to routine practice.

Moreover, the study's strength lies in its long-term, real-world follow-up. Nonetheless, several limitations must be acknowledged: the absence of cause-specific mortality data prevents distinguishing arrhythmic from non-arrhythmic deaths; lack of cardiac magnetic resonance imaging (MRI) precludes fibrosis quantification; omission of genetic testing leaves hereditary risk unexplored; and the absence of long-term rhythm monitoring limits insights into atrial fibrillation burden.[2] Recommendations for modifying risk models should therefore be framed in light of these constraints.

Particularly innovative is the identification of neutrophil count as an independent predictor of mortality—a finding that links systemic inflammation with both arrhythmic and non-arrhythmic pathways of disease progression. While the neutrophil-to-lymphocyte ratio has been previously correlated with adverse outcomes in HCM,[3] this is one of the first studies to isolate neutrophil count as a stand-alone marker in a low-risk cohort. We agree with the authors that this opens the door to exploring anti-inflammatory therapies (e.g., colchicine, interleukin-1 beta [IL-1β] blockade), but we stress that such proposals remain speculative and should be explicitly regarded as hypothesis-generating until tested in dedicated trials.

To build upon the valuable foundation laid by Kalenderoğlu et al.,[1] we suggest the following multidimensional future research pathways:

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1. Inflammatory Biomarker Integration: Investigating composite markers such as neutrophil extracellular traps (NETs), high-sensitivity C-reactive protein, and interleukin-6 may elucidate causal pathways linking inflammation to myocardial fibrosis and mortality in HCM.[4]
2. Machine Learning Models: Incorporating variables such as clinical features, frailty markers, echocardiographic data, atrial fibrillation burden, laboratory markers (including neutrophils), and cardiac magnetic resonance (CMR)-derived fibrosis into artificial intelligence (AI)-based prognostic tools—with attention to algorithm selection, training/validation schemes, and external validation—could yield individualized mortality predictions.
3. Holistic Risk Frameworks: Future scoring systems should include markers of frailty, systemic inflammation, and cerebrovascular risk, especially in elderly patients, who may fall outside the scope of traditional SCD-focused guidelines.
4. Longitudinal Imaging Correlates: The absence of cardiac MRI data in the present study limits interpretation of myocardial fibrosis burden. Future prospective cohorts should integrate late gadolinium enhancement quantification, T1 mapping, and strain imaging.
5. Therapeutic Implications: Future interventional studies should investigate whether modulation of inflammatory pathways can impact mortality or arrhythmic events in HCM, while recognizing that current evidence remains preliminary.

In conclusion, Kalenderoğlu et al. have provided important evidence that low-risk HCM patients are not a homogeneous group. Their study highlights predictors of all-cause mortality—advanced age, cerebrovascular history, and elevated neutrophils—that may not directly equate to SCD risk but nonetheless deserve consideration in future multidimensional risk models. Framing these findings as hypothesis-generating, we believe this work will catalyze more nuanced and personalized approaches to HCM management.

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

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Reply to the Letter to the Editor: Commentary on 'The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death': A Call for Multidimensional Risk Stratification

Editöre Mektup Yanıtı: 'Ani Kalp Ölümü Riski Düşük Hipertrofik Kardiyomiyopati Hastalarında Uzun Dönemli Ölüm Tahmin Edicileri' Hakkında Yorum: Çok Boyutlu Risk Sınıflandırması Çağrısı

LETTER TO THE EDITOR REPLY
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To the Editor,

We appreciate the insightful feedback[1] on our recently published study entitled "The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death," from the authors of the letter.[2] We acknowledge their interest in our work and welcome the opportunity to elucidate several topics.

Our primary endpoint was long-term all-cause mortality, rather than sudden cardiac death (SCD) alone. We emphasize that our findings should be interpreted as hypothesis-generating and not as definitive evidence that would alter current guideline-based SCD risk stratification strategies.

We agree with the authors' observation regarding the inconsistency between tertile-based studies and multivariable models. Indeed, the predictive impact of neutrophil count is more significant when treated as a continuous variable, indicating that minor increases in inflammatory load may cumulatively affect long-term outcomes.

As emphasized in the comments and corroborated by current studies, we note that inflammation is associated with myocardial fibrosis, atrial arrhythmogenesis, and adverse outcomes in hypertrophic cardiomyopathy.[3-5] Furthermore, we concur that secondary causes of leukocytosis, such as infection, corticosteroid treatment, or hematologic abnormalities, should be carefully evaluated.

We also reiterate that the absence of systematic cardiac magnetic resonance imaging (MRI), genetic testing, and long-term rhythm monitoring represents significant limitations of our study. We believe that forthcoming multicenter, prospective studies involving larger and more diverse cohorts will enhance the development of comprehensive risk stratification frameworks to more effectively identify high-risk individuals within the HCM population deemed "low risk."

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